

CHAPTER 1

OXIDATIVE CLEAVAGE OF FURANS

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INTRODUCTION

The furan ring plays important roles in many areas of chemistry and biology.^{1–6} This oxygen-containing heterocyclic ring system is a component of a variety of natural product structures, such as those found in pheromone **1** from the beetle *Galerucella clamariensis*,⁷ epothilone macrolides exemplified by **2**,^{8,9} and marine products like bipinnatin J (**3**).^{10–12} The furan ring is also embedded within the backbones of substances that have a broad range of biological activities, including insecticides (resmethrin¹³ (**4**)), therapeutic drugs (ranitidine¹⁴ (**5**), a histamine H₂-receptor antagonist), antibiotics (cefuroxime¹⁵ (**6**) from the cephalosporin family), and antihypertensives (prazosin¹⁶ (**7**)).

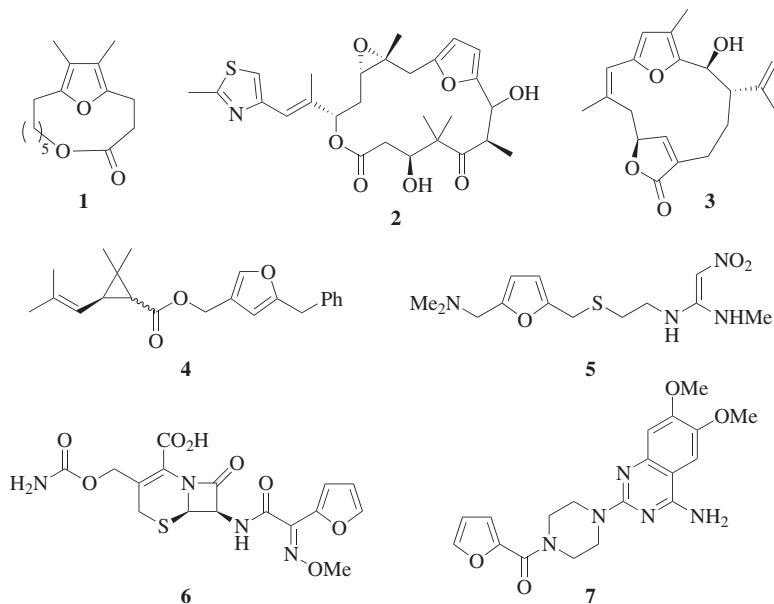
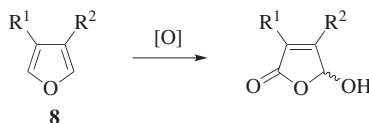


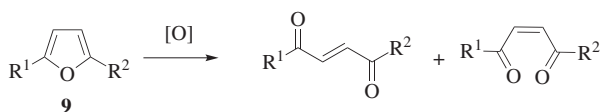
Figure 1. The furan ring system as a component of natural products and therapeutically active substances.

No discussion of furan chemistry would be complete without mentioning the intense efforts that have been directed at employing this heterocycle as a synthetic equivalent of a variety of four-carbon synthons. Owing to the presence of unsaturated carbons and an oxygen atom, furans have been used as starting materials for the production of polyhydroxylated compounds^{17–19} and a number of natural products.^{20,21} In the presence of different oxidizing agents²² including bromine, chromium(VI) reagents, hydrogen peroxide, dioxiranes, and metal oxides, the furan ring is transformed to a variety of four-carbon, carbonyl-containing substances such as 1,4-dicarbonyl compounds.^{23,24} One of the earliest examples of a process of this type involves oxidation of furan with vanadium pentoxide in the presence of air to generate maleic acid.²⁵ Several reviews have appeared describing photooxidation reactions of furans²⁶ and benzofurans,²⁷ as well as applications of furans in the synthesis of natural products²⁸ and multifunctional compounds.²⁹ Furan oxidation using peracids has also been reviewed.³⁰

In many instances, oxidative cleavage reactions of furans produce molecular frameworks that contain functionality suitable for accessing a diverse range of organic compounds. Whereas 3,4-disubstituted furans **8** react to form butenolides under oxidative conditions (Scheme 1), their 2,5-disubstituted analogs **9** undergo oxidation reactions that afford corresponding 1,4-diketoalkenes (Scheme 2). In addition, depending on the nature of the oxidizing conditions used, C2 unsubstituted furans are transformed to 4-oxoalkenals ($R^2 = H$) or 4-oxoalkenoic acids ($R^2 = OH$).

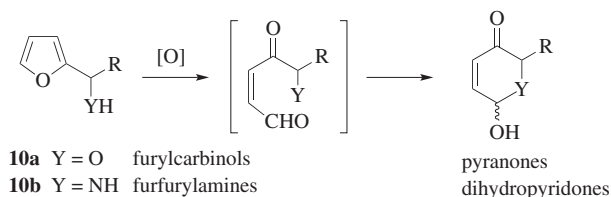


Scheme 1

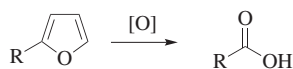


Scheme 2

Furylcarbinols **10a** (Y = O) constitute a special case as the intermediate α,β -unsaturated aldehydes generated by oxidation undergo in situ cyclization to produce pyranones (Achmatowicz reaction) (Scheme 3), which have been employed as key intermediates in the synthesis of higher sugars.^{31,32} A similar reaction, taking place upon oxidation of furfurylamines **10b** (Y = NH), has been used in the preparation of iminosugars.^{33,34} Finally, because complete oxidation of furans generates the corresponding carboxylic acids, this oxygen heterocycle can be viewed as a protected form of a carboxylic acid moiety (Scheme 4).



Scheme 3

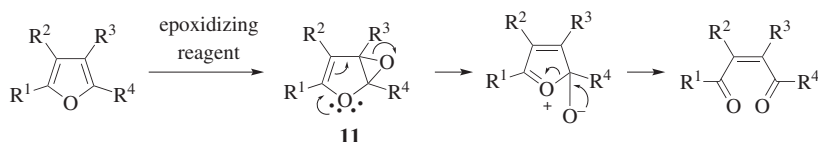


Scheme 4

MECHANISM AND STEREOCHEMISTRY

Some of the common oxidants employed for transforming furans into 1,4-dicarbonyl derivatives²⁴ are characterized by the presence of an electrophilic oxygen atom that is capable of acting as an epoxidizing agent. These oxidants include *m*-CPBA³⁵ and other peracids,³⁶ magnesium monoperoxyphthalate,³⁷ dimethyldioxirane,³⁸ oxaziridines,³⁹ and *tert*-butyl hydroperoxide (TBHP) in the presence of catalysts like VO(acac)₂,⁴⁰ Mo(CO)₆,⁴¹ or Ti(IV) complexes.⁴² It is

reasonable to assume that the first step in the oxidation reactions promoted by these reagents involves epoxidation of one of the double bonds of the furan ring system or related isobenzofurans³⁸ to form intermediate **11** (Scheme 5).⁴³ Importantly, initial formation of an intermediate epoxide in these processes has been demonstrated by using ¹⁸O-labeled substrates.⁴⁴ Ring opening of intermediate **11**, which can be catalyzed by acids,⁴⁵ produces the 1,4-dicarbonyl product.⁴⁶ This mechanism is consistent with the observation that the corresponding *cis* isomers of the unsaturated 1,4-dicarbonyl products are generated in all cases. Moreover, the results of ¹⁸O labeling studies demonstrate that the initial epoxidation process occurs preferentially on the more substituted double bond in the furan ring.⁴⁴

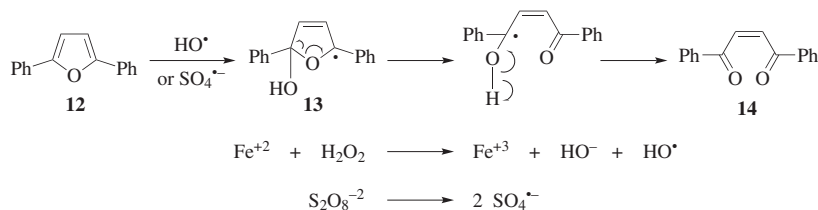


Scheme 5

Oxidations with Hydrogen Peroxide

Additives. Oxidation reactions of furan derivatives with hydrogen peroxide have been carried out in the presence of a variety of promoters including sulfuric acid,⁴⁷ titanium(IV) silicalite,⁴⁸ methyltrioxorhenium,⁴⁹ sodium molybdate,⁵⁰ vanadyl sulfate,⁵¹ and those described in the following sub-sections.

Iron(II) (Fenton's Reagent). Oxidation of 2,5-diphenylfuran (**12**) with hydrogen peroxide in the presence of Fe(II) (Fenton's reagent) to produce 1,4-diketone **14** takes place by a pathway involving addition of the in situ formed hydroxyl radical to the furan C2 position (Scheme 6).⁵² The intermediate **13** generated in this manner can also be formed by treating furans with peroxydisulfate, which decomposes spontaneously in solution to form sulfate radical anions. Addition of a hydroxyl radical to furans has been studied using density functional theory (DFT) calculations. The results of these studies suggest that a pre-reactive hydrogen-bonded complex of furan and the hydroxyl radical is formed prior to addition yielding **13**.⁵³



Scheme 6

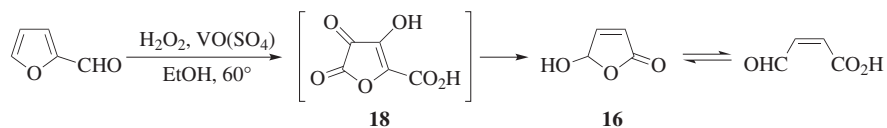
c1ccoc1 $\xrightarrow{\text{HO}^\bullet}$ Oc1ccoc1[CH2] $\xrightarrow{\text{HO}^\bullet}$ Oc1cc(O)c(O)c1 $\xrightarrow[\text{-H}_2\text{O}]{\text{HO}^\bullet}$ Oc1cc(O)c(O)c1[CH2] $\xrightarrow[\text{-H}_2\text{O}]{\text{HO}^\bullet}$ O=C1C=CC(=O)O1 $\xrightarrow[\text{-H}_2\text{O}]{\text{HO}^\bullet}$ O=C1C=CC(=O)O1[CH2] $\xrightarrow[\text{-H}_2\text{O}]{\text{HO}^\bullet}$ O=C1C=CC(=O)O1 $\xrightleftharpoons{\text{H}_2\text{O}}$ OC(=O)/C=C/C(=O)O

15

16

17

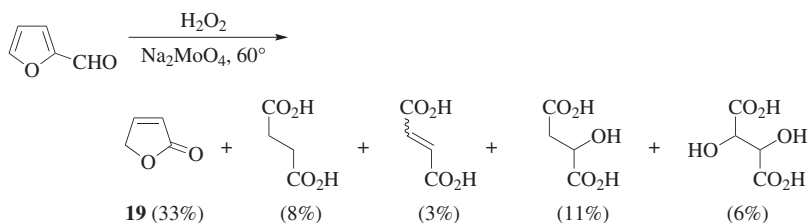
Oxidation of furfural with aqueous hydrogen peroxide in the presence of vanadyl sulfate and ethanol yields (Z)-4-oxobut-2-enoic acid (Scheme 8). Vanadyl sulfate exists in aqueous hydrogen peroxide as vanadium(V) peroxy complexes, which are the species responsible for the oxidation process. The proposal that this reaction proceeds through the intermediacy of keto lactone **18** is supported by isolation and full spectroscopic characterization of an ester derivative of **18**.⁵⁸ Although a mechanism for formation of **18** from furfural and for its transformation to malic acid has not been offered, the pathway to **18** does not involve the intermediacy of furoic acid.



Oxidation of furan in the gas phase at 300° in air, and in the presence of a vanadium–molybdenum–phosphorus catalyst on low-porosity corundum, to form maleic anhydride is proposed to take place through the generation of furyl radicals

on the surface of the catalyst.⁵⁹ This process is presumed to involve an initial electrophilic attack of the catalyst at C2 of the furan ring,⁶⁰ based on the results of infrared spectroscopic studies on the interaction between furan and the catalyst support.⁶¹ Both the gas-phase oxidation of furans on vanadium catalysts and their liquid-phase oxidation on heterogeneous oxides, such as Ag_2O and $\text{Ag}_2\text{O}/\text{CuO}$, have been reviewed.⁶²

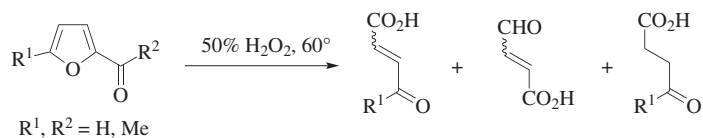
Molybdenum(VI), Chromium(VI), and Niobium Salts. The oxidation reaction of furfural with hydrogen peroxide in the presence of a catalytic amount of sodium molybdate, a source of Mo(VI), yields 2(5H)furanone (**19**) via a pathway that is thought to involve a molybdenum peroxide. Tartaric, malic, fumaric, and succinic acids are also formed as minor products in this process (Scheme 9).⁶³ Similar results are observed when this oxidation is conducted in the presence of potassium bichromate as a source of Cr(VI),⁶⁴ and $\text{Nb}(\text{OAc})_2$ and Nb_2O_5 as sources of Nb(II) and Nb(V), respectively.⁶⁵ The conversion of 2(5H)furanone (**19**) into succinic acid under the reaction conditions has been demonstrated to take place in reactions performed at different pH values.⁶⁶



Scheme 9

Spectroscopic studies, carried out on a Mo/Ti/O catalyst, have demonstrated that furan exhibits two adsorption modes on the surface of the catalyst,⁶⁷ and that the Mo=O bond in the catalyst does not play a role in the formation of maleic anhydride.

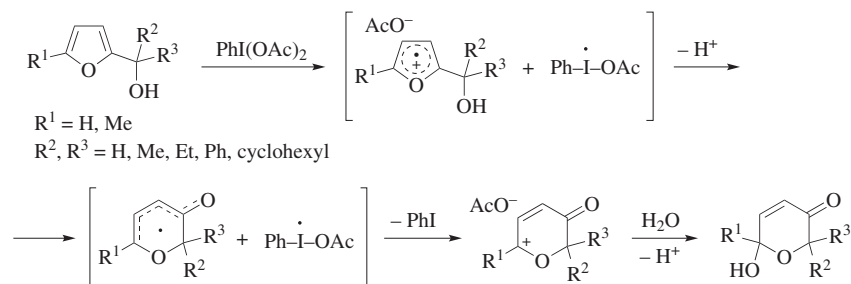
No Additives. Oxidations of furylketones and furfurals with hydrogen peroxide in the absence of additives have been studied.⁶⁸ Both furylketones and aldehydes undergo the same type reaction to give 1,4-dicarbonyl compounds (Scheme 10).



Scheme 10

Oxidations with Hypervalent Iodine Reagents

Cation radicals, similar to those produced in electrolysis and strong acid promoted reactions,⁶⁹ have been proposed to serve as intermediates in oxidation reactions of furan derivatives with $\text{PhI}(\text{OAc})_2$ (Scheme 11),⁷⁰ and radical intermediates have been detected by using EPR spectroscopy. The addition of salts such as $\text{Mg}(\text{ClO}_4)_2$ or KBF_4 enhance the efficiency of the oxidation process.

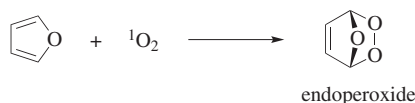


Scheme 11

Similar observations have come from studies of oxidation reactions of 9-furyl naphtho[2,3-*b*]furans with magnesium monoperoxyphthalate (MMPP) and pyridinium chlorochromate (PCC). The results of cyclic voltammometric studies suggest that these processes proceed through the intermediacy of 9-furyl naphtho[2,3-*b*]furan radical cations.⁷¹

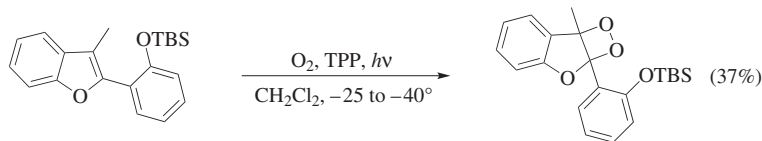
Photooxygenations with Singlet Oxygen

Furan derivatives react with singlet dioxygen through a formal [4 + 2] cycloaddition pathway to form ozonides (also called endoperoxides) that decompose in different ways depending on the reaction and work-up conditions.⁷² Although several mechanistic pathways are possible for the formation of ozonides in these reactions, the results of kinetic experiments confirm that a concerted cycloaddition route is followed (Scheme 12).²⁶



Scheme 12

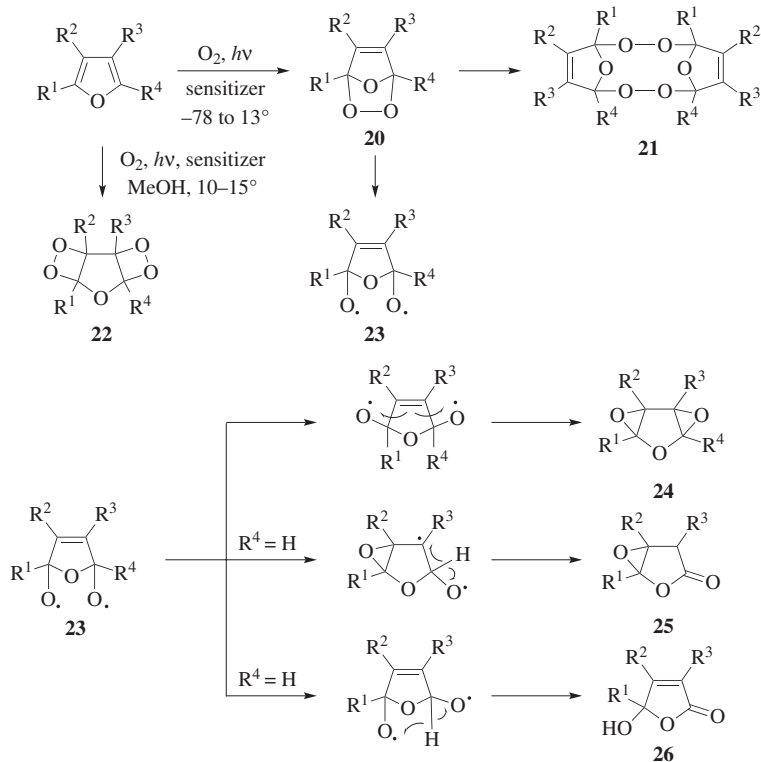
Singlet oxygen is usually formed through triplet energy transfer from a photosensitizer such as rose bengal, methylene blue, or tetraphenylporphyrin (TPP). When benzofuran derivatives are used as substrates for the photooxidation reactions, the corresponding dioxetanes are formed through [2 + 2] cycloaddition of molecular oxygen with the furan double bond (Scheme 13).⁷³



Scheme 13

The use of pyrene as photosensitizer and solar or ultraviolet light irradiation for photooxidation of 1,3-diphenylisobenzofuran in aqueous dodecyltrimethylammonium chloride has been investigated.^{74,75} In these reactions, chemical methods have been used to form singlet oxygen, such as those involving hydrogen peroxide with several reagents including PIFA ($\text{PhI}(\text{OCOCF}_3)_2$)⁷⁶ and heterogeneous catalysts containing MoO_4^- .⁷⁷ Other methods include generation of singlet dioxygen from fragmentation of monoactivated 1,1-dihydroperoxides.⁷⁸

Ozonides **20** are typically produced in photooxidations of furans when irradiation is carried out in the presence of typical sensitizers, in solvents such as CCl_4 , CFCl_3 , CH_2Cl_2 , benzene, acetone, or acetonitrile,⁷⁹ and at temperatures of -78 to 13° (Scheme 14). In some instances, these reactions occur even in the absence of

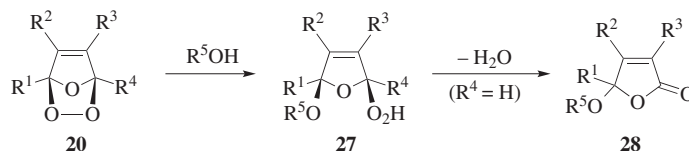


Scheme 14

sensitizers.⁸⁰ Photolysis of oxygen-saturated solutions of furan rings in the presence of the imidazolium-bound sensitizers provides the corresponding butenolides.⁸¹ In addition, the use of rose bengal, either polymer-supported or immobilized on wool,⁸² produces identical results. Under these conditions the ozonides **20** can be isolated at -15° and can be stored for several days. Bis-dioxetanes **22** have also been observed as products.⁸³ Ozonides **20** are observed to dimerize slowly to form bis-peroxide **21** in CCl_4 and CFCl_3 and more rapidly in 2:1 benzene/petroleum ether, and spontaneously and quantitatively at $55\text{--}60^\circ$ in CCl_4 .⁷⁹ Homolytic cleavage of the O–O bond in ozonides **20** produces biradical intermediates **23**,⁸⁴ which can form mono- and bis-epoxy derivatives **24** and **25** through epoxycyclization, followed by 1,2-hydrogen atom shifts when $\text{R}^4 = \text{H}$. In addition, biradical intermediates **23** can form 4-hydroxybutenolides **26** as a result of 1,4-hydrogen migration.

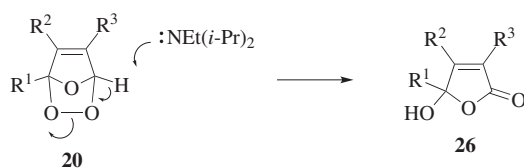
The distribution of products formed in photooxidation reactions is highly dependent on the substitution pattern of the furan derivatives and the reaction conditions. For example, whereas epoxylactones **25** and 4-hydroxybutenolides **26** are generated in the oxidation reactions of furans in benzene,⁸⁰ diepoxy derivatives **24** are also produced in reactions run in dichloromethane.⁸⁵ In some cases, mixtures of **24** and the corresponding 1,4-dioxoalkenes are also observed,⁸⁶ and when substituents are present that can exert neighboring-group effects other products are formed.⁸⁷

Addition of primary and secondary alcohols to ozonides results in the formation of the corresponding alkoxyhydroperoxides **27**,⁸⁸ via a nucleophilic addition reaction that takes place stereoselectively to give *cis* OR⁵ and OOH stereoisomers as a consequence of H-bonding between the incoming alcohol and displaced peroxy group (Scheme 15).⁷⁹ When a hydrogen is present at the hydroperoxide substituted carbon, **27** undergoes dehydration to form 4-alkoxybutenolides **28**.⁸⁰ As a result of these processes, hydroperoxides are formed when the singlet oxygen oxidation reactions of furans are carried out in alcohol solvents.⁷⁹ Moreover, depending on the work-up conditions employed, 4-alkoxy or 4-hydroxybutenolides are obtained as products of these reactions.



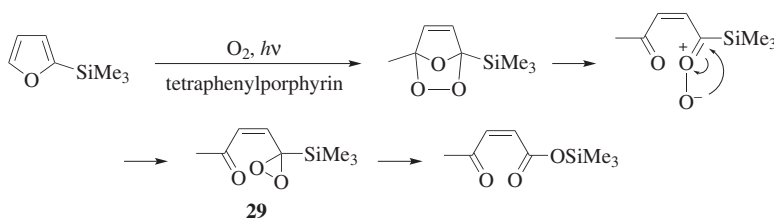
Scheme 15

Ozonides also participate in other non-radical processes. For example, the formation of 4-hydroxybutenolides from ozonides **20** ($\text{R}^4 = \text{H}$) can also be promoted by the action of bases such as diisopropylethylamine, which facilitates abstraction of the proton at C2 (Scheme 16).⁸⁹ This type of reaction can also be carried out in ionic liquids, the best results being obtained when chloride serves as the counter anion. Lower yields (11–16%) are obtained when the ionic liquids are associated with tetrafluoroborate, methyl sulfate, and lactate anions.⁹⁰



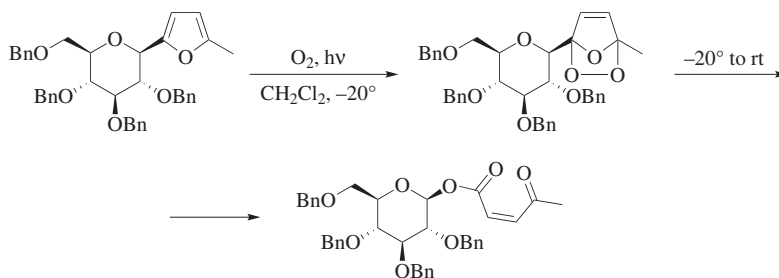
Scheme 16

Photooxygenation reactions of furan can generate 1,4-dioxoalkenes, which are believed to form through a pathway involving a sila-Baeyer–Villiger rearrangement of dioxirane intermediate **29** (Scheme 17).⁹¹



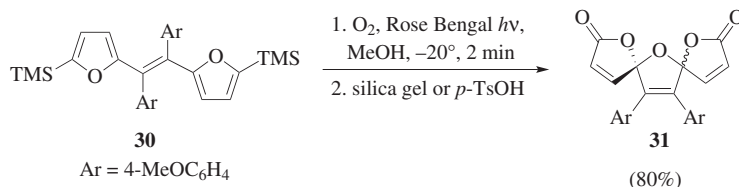
Scheme 17

Formation of 1,4-dioxoalkenes has also been rationalized by invoking a concerted mechanism involving 1,2-migration of the C2 substituent to the peroxide.⁹² This type of process is often observed in photooxidation reactions of glycosylfurans,^{86,93} indicating that the nature of the C2 furan substituent strongly influences the nature of the pathway followed in reactions of intermediate ozonides (Scheme 18).⁹⁴



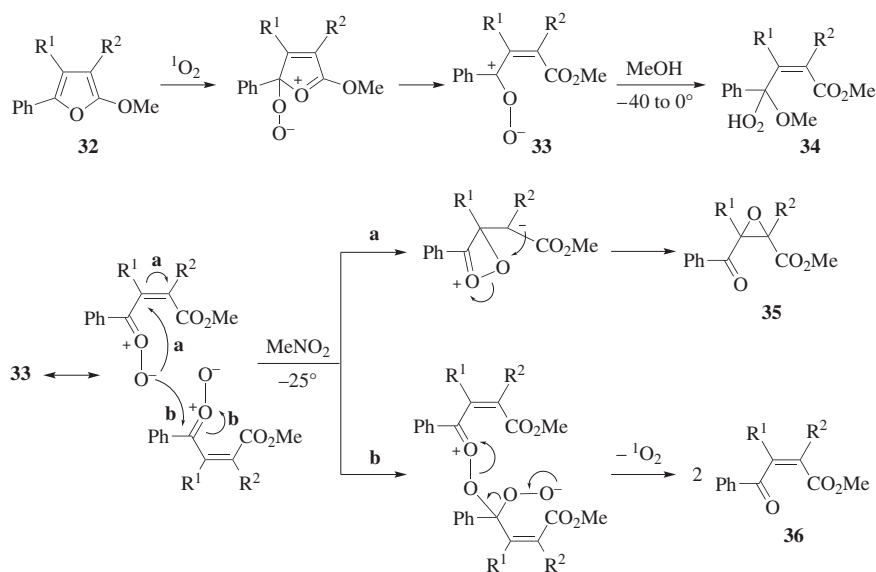
Scheme 18

In dimeric furans such as **30**, ozonide ring opening results in the formation of spirotutenolides **31** (Scheme 19).^{95,96}



Scheme 19

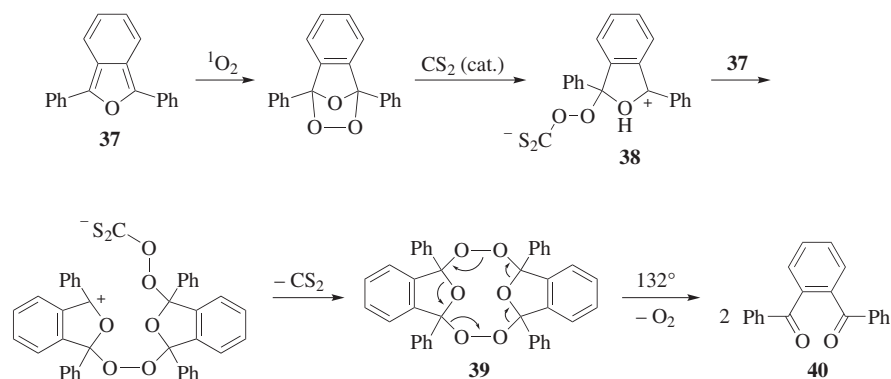
Direct photooxygenation of 2-methoxy-5-phenyl furans **32** at -40 to 0° in MeOH yields α -methoxyhydroperoxides **34**, whose formation is proposed to take place through a carbonyl oxide intermediate **33** rather than via an ozonide followed by trapping with methanol (Scheme 20).^{88,97} When these reactions are conducted in nitromethane, mixtures of epoxides **35** and 1,4-dioxoalkenes **36** are produced.⁸⁸ The formation of epoxides **35** can be rationalized by invoking a mechanistic route involving intramolecular Michael addition of the ylide oxygen atom to the double bond. In contrast, formation of dicarbonyl products **36** are believed to occur by dimerization of intermediate **33**. These processes serve as evidence for carbonyl oxide participation in sensitized photooxygenation reactions of furan derivatives.



Scheme 20

Photooxidations of furan and its 2- and 3-methyl derivatives in the presence of nitrous acid has been investigated using proton transfer reaction mass spectrometry. 1,4-Dicarbonyl compounds, the main products produced in the reaction, are formed by a radical process beginning with attack by a hydroxyl radical.⁹⁸ Carbon disulfide catalyzes dimerization of the ozonide derived from photooxygenation

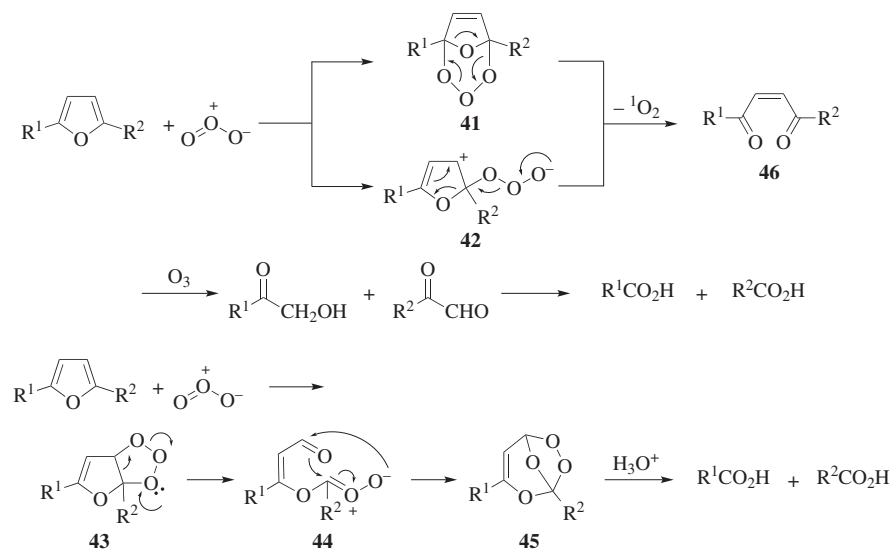
of 2,5-diphenylbenzoisofuran (**37**), a process that takes place via carbocationic intermediate **38**. The dimer **39** is then transformed to diketone **40** upon prolonged heating in chlorobenzene at 132° (Scheme 21).⁹⁹



Scheme 21

Oxidations with Ozone

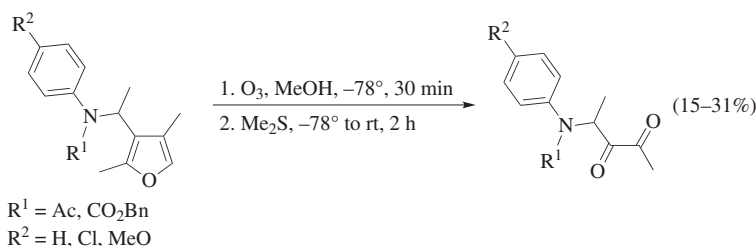
Reactions of furans with ozone may proceed by the formation of bicyclic intermediates **41** that are similar to the ozonide formed by cycloadditions with singlet oxygen.¹⁰⁰ Fragmentation of **41** may lead to the corresponding 1,4-dicarbonyl derivatives **46** (Scheme 22). An alternative mechanism involves electrophilic addition of ozone to the reactive α -position of the furan ring, leading to generation of zwitterionic



Scheme 22

intermediates **42**, which also can rearrange to generate the dicarbonyl compounds with loss of singlet oxygen.¹⁰¹

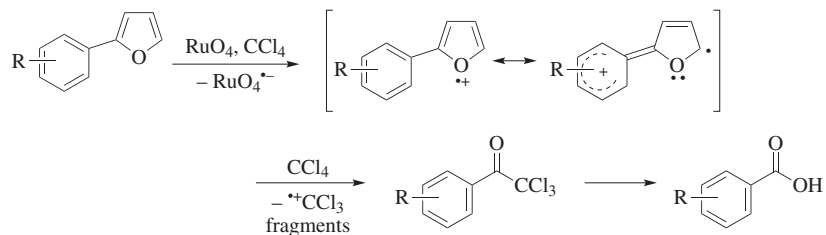
Ozone can also add to the double bond of the furan ring to give unstable primary ozonides **43**, which decompose through a cycloreversion process to give carbonyl ylide intermediates **44**. Intramolecular cycloaddition yields the more stable secondary ozonides **45**, which upon hydrolysis provide the corresponding carboxylic acids. The formation of intermediates **43–45** is in agreement with the Criegee mechanism suggested for ozonolysis of alkenes,¹⁰² which has been further explored using ¹⁷O spectroscopy¹⁰³ and confirmed experimentally.^{104–106} Although hydrolysis of **45** can produce carboxylic acids, this reaction pathway is not the exclusive mechanism for carboxylic acid production.¹⁰⁷ It has also been proposed that the ozonization reaction first forms 1,4-dienones that undergo a second ozonization in which the double bond is cleaved, generating α -keto aldehydes,¹⁰⁸ which undergo further oxidation to form carboxylic acids. Indeed, glyoxal and methylglyoxal are observed products in ozonolysis reactions of furan and 2,5-dimethylfuran, respectively,¹⁰⁹ and 1,2-diketones are generated in ozonolysis reactions of tri- and tetrasubstituted furans (Scheme 23).¹¹⁰ In some instances the two-step process involving 1,4-diketone formation and further oxidation can be accomplished in a sequential manner.¹⁰⁷ Finally, oxidations of furans to form carboxylic acids can be performed using ozone followed by dimethyl sulfide work-up,¹¹¹ a reaction that takes place through the same rearrangement process described above for endoperoxides.



Scheme 23

Oxidations with Ruthenium Tetroxide

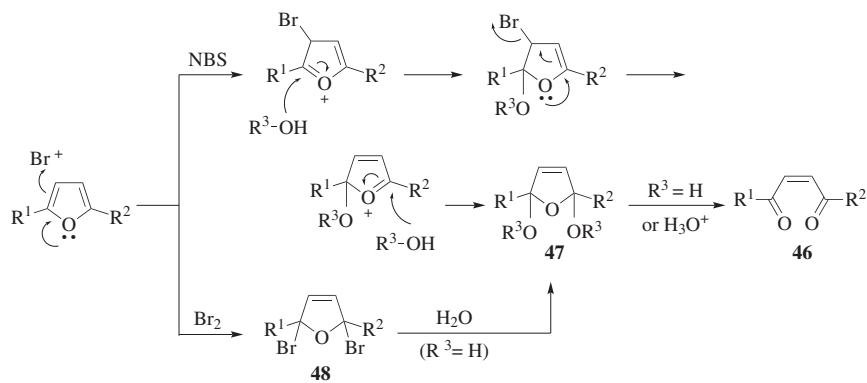
Ruthenium tetroxide is a strong oxidant that can be formed in situ by oxidation of a ruthenium(III) or (IV) compound such as RuCl_3 or RuO_2 ,¹¹² usually using NaIO_4 ¹¹³ or other oxidants including KIO_4 , NaClO , NaBrO_3 , $\text{Ce}(\text{SO}_4)_2$, Oxone[®], or H_5IO_6 .¹¹⁴ The participation of free-radical intermediates in oxidations of aryl-furans with ruthenium tetroxide has been demonstrated using EPR spectroscopy (Scheme 24).¹¹⁵ The results of a study based on furan adsorption on ruthenium at 80 K indicates that abstraction of oxygen by the furan ring takes place through the formation of a metallocycle-like intermediate.¹¹⁶ The use of CCl_4 as the solvent is crucial for the success of this process owing to its promotion of the formation of intermediates that are precursors of the carboxylic acids. Moreover, due to the high reactivity of ruthenium tetroxide it must be used in halogenated organic solvents.¹¹⁷



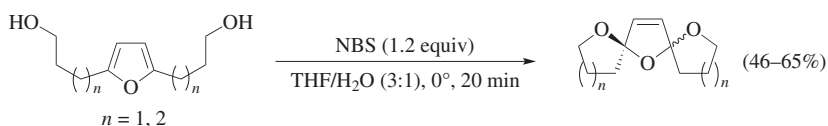
Scheme 24

Oxidations with *N*-Bromosuccinimide and Related Reagents

N-Bromosuccinimide serves as a source of bromonium ions, which undergo electrophilic addition to the furan ring. 2,5-Dialkoxydihydrofurans **47** ($\text{R}^3 \neq \text{H}$) or 1,4-dioxoalkenes **46** are generated when either alcohols or water, respectively, are used as solvents for the reaction. A similar mechanism is possible for transformations of furan derivatives to 1,4-dicarbonyl compounds by the action of bromine in water or methanol, although the formation of 2,5-dibromo-2,5-dihydrofurans **48** as intermediates has also been postulated.¹¹⁸ In the latter mechanism, **48** is converted into the 2,5-dihydroxy derivative **47** ($\text{R}^3 = \text{H}$), which upon dehydration forms the 1,4-dicarbonyl compound **46** (Scheme 25).¹¹⁹ Reactions of compounds containing hydroxy groups provide spiro derivatives through intramolecular addition (Scheme 26).¹²⁰

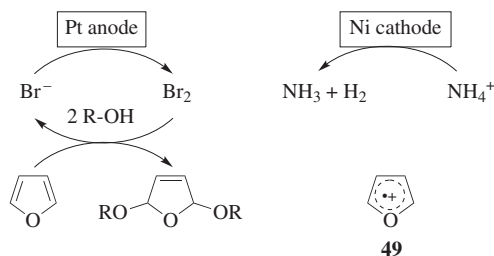


Scheme 25



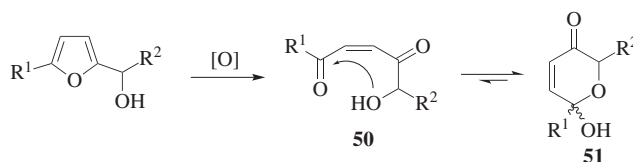
Scheme 26

Bromine can be generated in situ by electrochemical oxidation of salts such as NH_4Br .¹²¹ Under these conditions, the reactions are cleaner and may involve the formation of tribromide anion (Br_3^-) (Scheme 27), an anion that has a similar redox potential to bromine. The radical cation **49** usually reacts with methanol.



Scheme 27

In the special case of furfuryl alcohols, initial oxidation leads to the production of 1,4-dicarbonyl derivatives **50**, which then undergo intramolecular addition of the hydroxy group to furnish the corresponding 6-hydroxy-2*H*-pyran-3(6*H*)-ones **51** through the well-known Achmatowicz reaction (Scheme 28).³¹ A similar mechanistic pathway operates in reactions of furfurylamines, which yield 6-hydroxy-2*H*-pyrimidin-3(6*H*)-ones by the aza-Achmatowicz reaction.^{33,34} It should be noted that isomers **50** and **51** exist in an equilibrium in which the cyclic isomer **51** is usually favored.



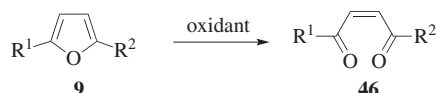
Scheme 28

SCOPE AND LIMITATIONS

Synthesis of 1,4-Dicarbonyl Compounds

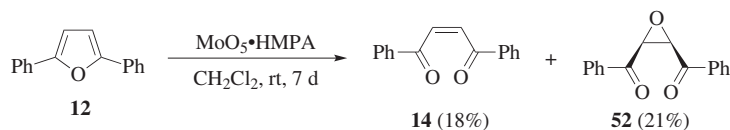
1,4-Dioxoalkenes. 2,5-Disubstituted furans can be transformed to *cis* 1,4-dioxoalkenes utilizing a wide variety of reagents (Scheme 29).²⁴ In the first half of the 19th century, the first examples of oxidation reactions of di-, tri-¹²² and tetrasubstituted¹²³ furan derivatives with nitric acid were described.¹²⁴ The procedure was also applied to oxidations of furans containing hydroxy functions in their side chains.¹²⁵ More recently, oxidation of triphenylfurans has been promoted by using milder conditions consisting of a stoichiometric amount of ammonium

nitrate in refluxing 80% aqueous acetic acid.¹²⁶ These conditions have also been applied to the synthesis of 3-(2*H*)-furanones that have antitumor activities.¹²⁷ During the same period, oxidations of furan with air in the presence of various catalysts, including vanadium pentoxide, were developed²⁵ as were oxidations of 1,3-diphenylisobenzofurans with chromic acid.¹²⁸



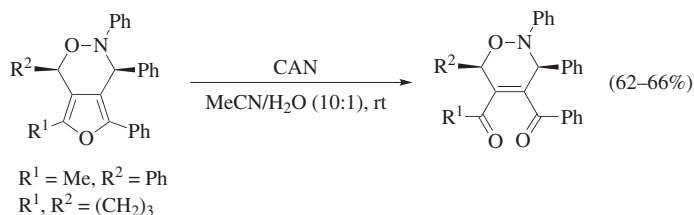
Scheme 29

Metal Oxidants. The oxidation of 2,5-diarylfurans to *cis* unsaturated 1,4-diketones by the action of lead tetraacetate in chloroform was first studied in detail in 1957.¹²⁹ Low to moderate product yields attend these processes and some degree of substituent dependence is observed. 2,5-Diphenylfuran (**12**) is oxidized using MoO₅•HMPA to afford a mixture of *cis*-1,4-diphenyl-2-butene-1,4-dione (**14**) and *cis*-2,3-epoxy-1,4-diphenylbutane-1,4-dione (**52**) in 18% and 21% yields, respectively (Scheme 30).¹³⁰ Under the same conditions, benzo[*b*]furan reacts to yield a mixture of 2-hydroxy-3(2*H*)-benzofuranone (18%), 2(3*H*)-benzofuranone (7%), and salicylaldehyde (12%) with 15% of recovered starting material, rendering the process of limited synthetic utility.



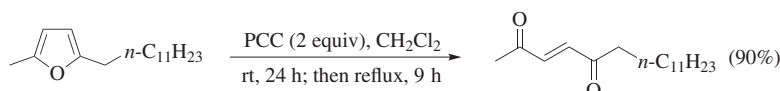
Scheme 30

Metal-promoted oxidations are also possible using ceric ammonium nitrate (CAN),¹³¹ but even though these reactions can be carried out in the presence of benzyl ethers they occur in low yields.¹³² On the other hand, the compatibility of this method with the presence of N–O bonds leads to its application to the synthesis of 1,4-dienones in 62–66% yields (Scheme 31).¹³³



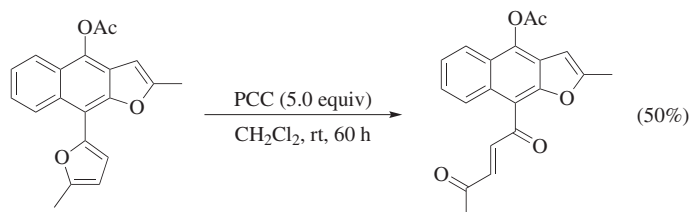
Scheme 31

2-Methyl-5-(2-pyrrolyl)furans react with CAN at low temperatures to afford *trans* 1,4-dicarbonyl derivatives. However, application of the same conditions to reactions of various 3-(2-pyrrolyl)furans leads to formation of products containing coupled furan rings.¹³⁴ In contrast, the use of pyridinium chlorochromate (PCC) for oxidations of alkyl furans produces *trans* 1,4-dienones (Scheme 32).¹³⁵

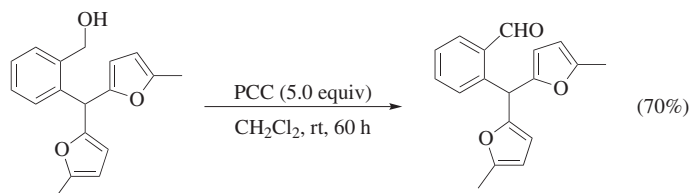


Scheme 32

By using PCC, it is possible to carry out selective oxidation of a furan ring in the presence of a benzofuran moiety (Scheme 33).¹³⁶ However, when a primary hydroxyl group is present, an aldehyde is selectively formed without oxidative cleavage of the heterocycle (Scheme 34). The reactivity of furans with Cr(VI) oxidants depends to a great extent on the reaction conditions. In some cases, it is possible to oxidize the side chain of furyl derivatives without altering the furan ring by carrying out the reaction using pyridinium dichromate (PDC) in organic solvents such as dichloromethane at 55° for 2 hours.¹³⁷



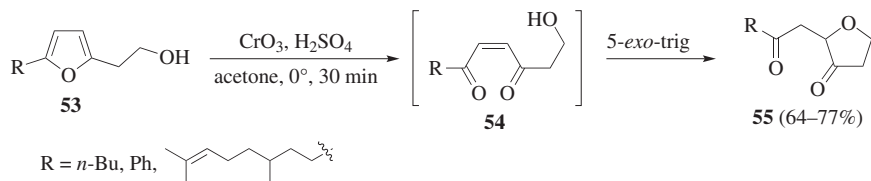
Scheme 33



Scheme 34

In contrast, oxidation of furanyl alcohols **53** with Jones reagent in acetone at 0° affords keto tetrahydrofurans **55**, through the intermediacy of 1,4-dicarbonyl compounds **54** (Scheme 35).¹³⁸ The formation of **55** takes place by 5-*exo*-trig cyclization

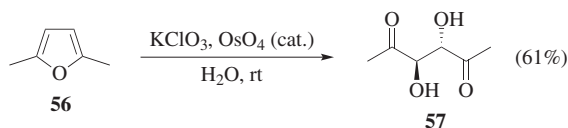
involving the hydroxy group in the side chain. However, 1,4-dicarbonyl compounds **54** are the isolated product when oxidation is carried out using magnesium monoperoxyphthalate (MMPP).



Scheme 35

Indeed, the use of MMPP in oxidation of 2,5-dialkylfurans leads to high yields of *cis* enediones. These reactions take place in less than 1 hour at room temperature, with isomerization to form the *trans* enediones occurring after 2 hours at reflux.¹³⁹ This process cannot be used to oxidize substrates that contain electron-withdrawing groups directly attached to the furan ring.

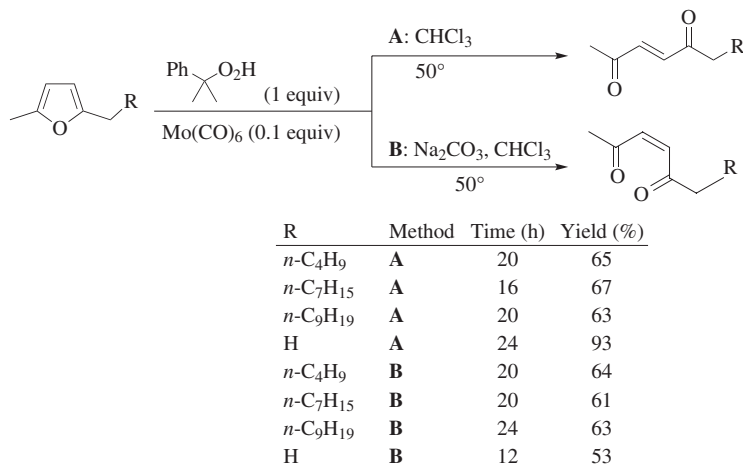
The potassium chlorate/osmium tetroxide oxidizing system is capable of transforming 2,5-dimethylfuran (**56**) into *erythro*-3,4-dihydroxyhexane-2,5-dione (**57**) in 61% yield (Scheme 36).¹⁴⁰ Similarly, this method can be applied to enantiomerically pure compounds and it tolerates amine protecting groups such as Cbz.¹⁴¹



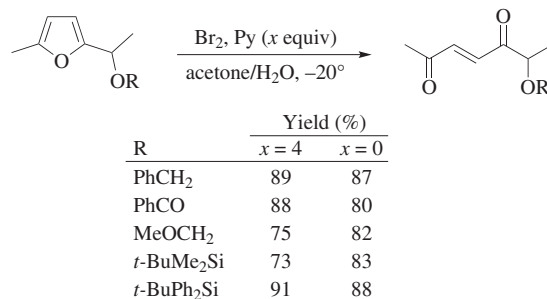
Scheme 36

The use of peroxides in combination with metal catalysts is an effective oxidation strategy to ensure high degrees of conversions of furans to their oxidation products. Hydrogen peroxide in the presence of methyltrioxorhenium can be used to convert substituted furans to *cis* 1,4-dioxoalkenes in high yields.⁴⁹ Moreover, the reaction can be carried out using the safer urea/hydrogen peroxide complex (UHP). Cumyl hydroperoxide in the presence of Mo(CO)₆ also promotes oxidation reactions that generate *trans* 1,4-dioxoalkenes. Notably, if the reaction is carried out in the presence of sodium carbonate, *cis* isomers are obtained (Scheme 37).⁴¹ Presumably, the presence of the base neutralizes the acid formed during the reaction, thus, preventing acid-catalyzed isomerization of the *cis* isomers to the more stable *trans* isomers.

Bromine. Oxidation of furans with bromine in aqueous medium under either acidic or basic conditions produces *trans* 1,4-dioxoalkenes in good yields.^{118,142} The method is compatible with furans containing acetals¹⁴³ as well as protecting groups like benzoyl esters, and benzyl and silyl ethers (Scheme 38).²¹

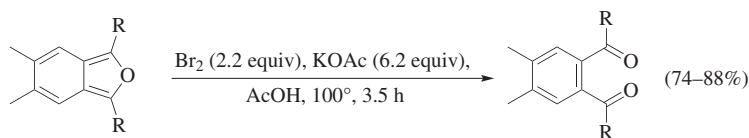


Scheme 37



Scheme 38

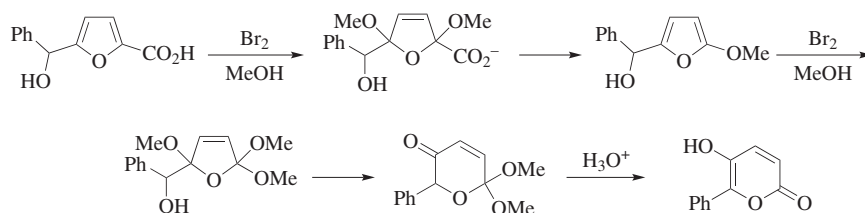
It is also possible to carry out the bromine-promoted oxidation reactions in the presence of acetic acid. When methanol is used as a solvent the formation of *trans* 1,4-dioxoalkenes takes place through intermediate 2,5-dimethoxyfurans, which are hydrolyzed in situ.¹⁴⁴ The same conditions can be applied to dihydrobenzo[*c*]furan derivatives to produce substituted diacylbenzenes (Scheme 39).¹⁴⁵



R = Ph, 4-MeC₆H₄, 2,5-Me₂C₆H₃, 2,4,6-Me₃C₆H₂, 4-*t*-BuC₆H₄,
4-MeOC₆H₄, 4-ClC₆H₄, 3-O₂N-4-MeOC₆H₃, 3-Br-4-MeOC₆H₃, 2-thienyl

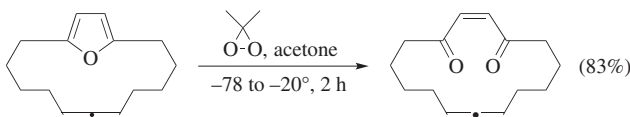
Scheme 39

In the oxidation of 2-furoic acids with bromine, however, 5-hydroxy-2*H*-pyran-2-ones are generated by an oxidative decarboxylation–ring expansion sequence (Scheme 40).¹⁴⁶



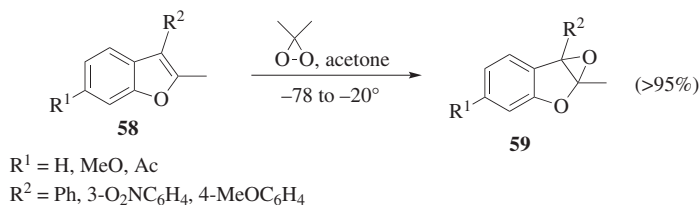
Scheme 40

Dimethyldioxirane. Dimethyldioxirane (DMDO) reacts with substituted furans to form *cis* 1,4-dioxoalkenes in excellent yields.⁴³ This process can be carried out on furans containing allene moieties¹⁴⁷ and deactivated double bonds (Scheme 41).¹⁴⁸



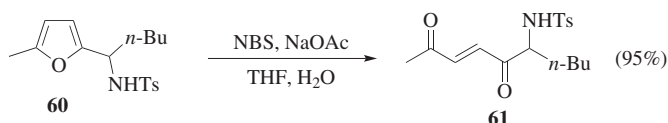
Scheme 41

In DMDO-promoted reactions of 4-oxo-2-amidotetrahydrobenzofurans, 4-oxo-2-oxazolines are formed as a consequence of the participation of the amide group in ring opening of the intermediate epoxide.¹⁴⁹ Similar reactions, occurring through intermediate epoxyfurans, have been described for 2,5-dimethylfuran containing an oxaziridine moiety.³⁹ By carrying out reactions of benzofuran derivatives **58** at low temperature, it is possible to isolate labile intermediate epoxides **59** (Scheme 42).⁴⁶ Depending on the substituents, either furan epoxides or quinone methides can be observed by ^1H NMR spectroscopy.³⁸



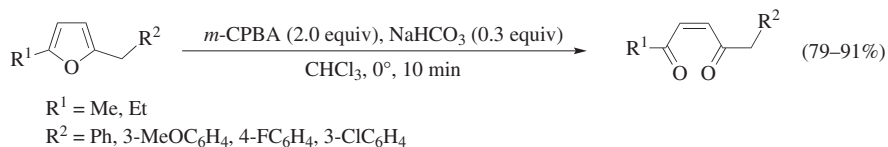
Scheme 42

N-Bromosuccinimide. Oxidation of 2,5-disubstituted furans with *N*-bromosuccinimide in basic medium affords *trans* 1,4-dioxoalkenes in good yields.¹⁵⁰ This process is compatible with various functional groups,¹⁵¹ including MOM and TBS protecting groups,¹⁵² and enables the generation of libraries of small molecules.¹⁵³ In some cases *trans* 1,4-dioxoalkenes such as **61** are formed even when furfuryl amines, such as **60** (Scheme 43)¹⁵⁴ that are known to furnish the corresponding piperidones through the aza-Achmatowicz reaction, are used as substrates (see below).



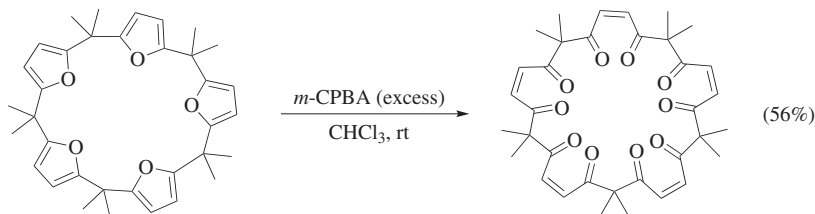
Scheme 43

m-Chloroperoxybenzoic Acid. Peracids, such as *m*-CPBA, react with substituted furans³⁰ to produce *cis* 1,4-dialkenes in good yields and without simultaneous production of *trans* isomers,⁴⁵ although in some instances minor amounts of the *trans* isomers are observed even when the reaction is carried out at 0°. ¹⁵⁵ The reaction can be performed at ambient temperature in dichloromethane with furans bearing both alkyl and aryl substituents (Scheme 44).¹⁵⁶ The use of an excess of the peracid, however, can lead to formation of over-oxidized byproducts.⁴⁴



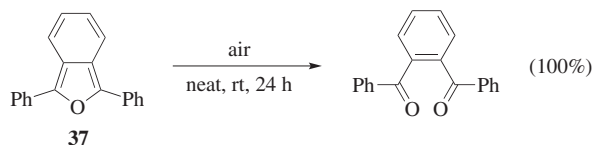
Scheme 44

Oxidation reactions of furans with *m*-CPBA are compatible with the presence of double bonds¹⁵⁷ including dienes, as well as protecting groups such as cyclic^{158,159} and acyclic¹⁶⁰ acetals, esters,¹⁶¹ and benzyl ethers.¹⁶² The reactions of 1,3-diarylbenzo[*c*]furans with *m*-CPBA at room temperature lead to the formation of 1,2-diaroylbenzenes in good to excellent yields.¹⁶³ When two furan units are present in the same molecule, it is possible to oxidize only one ring by using one equivalent of the peracid.¹⁶⁴ On the other hand, when an excess of *m*-CPBA is employed, oxidations of all heterocyclic nuclei in the molecule take place (Scheme 45).¹⁶⁵ Sequential oxidation of different furan rings is also possible.¹⁶⁶ Finally, oxidation of the furan ring with *m*-CPBA followed by catalytic hydrogenation can be used as an alternative method to hydrolyze the heterocycle.¹⁶⁷



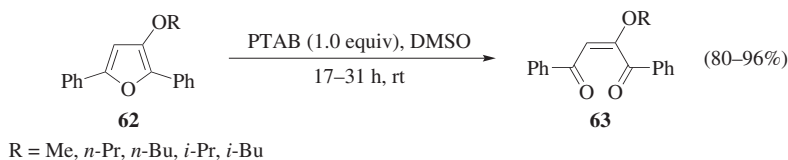
Scheme 45

Other Oxidants. Exposure to air or oxygen for several hours^{168–170} is suitable for transforming isobenzofurans to *o*-dibenzoylbenzenes (Scheme 46). The reaction also takes place in the presence of Lewis acids and on silica gel.¹⁷¹ This method has been utilized in the synthesis of steroids¹⁷² and terpenes.¹⁷³ The laccase-catalyzed ring opening of 2,5-dialkylfurans using air as an oxidant provides (*Z*)- or (*E*)-3-hexene-2,5-diones depending on the mediator employed: with TEMPO the (*Z*)-isomer is formed, while a combination of TEMPO and violuric acid gives the (*E*)-isomer.¹⁷⁴



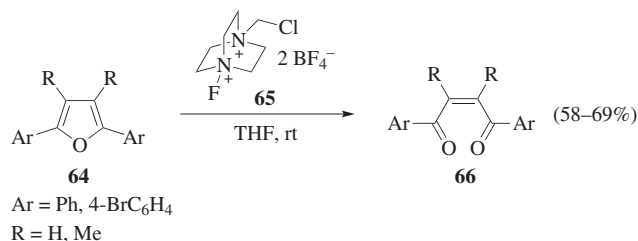
Scheme 46

3-Alkoxy-2,5-diphenylfurans **62** are converted to *cis* 1,4-dienones **63** upon treatment with phenyltrimethylammonium bromide (PTAB) in DMSO at room temperature (Scheme 47).¹⁷⁵ These oxidations can also be carried out using DDQ instead of PTAB as the oxidant but competitive formation of 3-(2*H*)-furanones is observed.¹⁷⁶ The latter compounds are also formed in reactions promoted by PTAB when an additional substituent is present at C4 of the furan ring, a consequence of steric effects that favor cleavage of the ether functional group.



Scheme 47

Oxidations of 2,5-diarylfurans **64** also occur using the N–F reagent Selectfluor[®] (**65**) to generate the corresponding *cis* enediones **66** along with trace quantities of the *trans* isomer in good yields (Scheme 48).¹⁷⁷

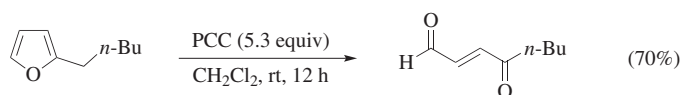


Scheme 48

Electrochemical oxidation of bis(2-furyl)benzene via a two-electron transfer mechanism gives a diketone, which upon further two-electron oxidation furnishes the corresponding tetraketone.⁶⁹

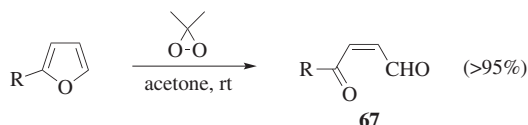
4-Oxoalkenals. In principle, the same reactions of 2,5-disubstituted furans leading to 1,4-dioxoalkenes might be applicable to transforming furans that do not contain substituents at C5 to 4-oxoalkenals. However, the formation of an aldehyde under oxidizing conditions makes it necessary to carefully select the oxidant to avoid over-oxidations. Nevertheless, several examples of reactions of this type, occurring on some simple substrates, have been described.

Pyridinium Chlorochromate (PCC). Among the reagents reported to cleave 2-substituted furans into 4-oxoalkenals, PCC is quite effective for providing *trans* isomers in acceptable yields (60–70%) (Scheme 49).¹⁷⁸



Scheme 49

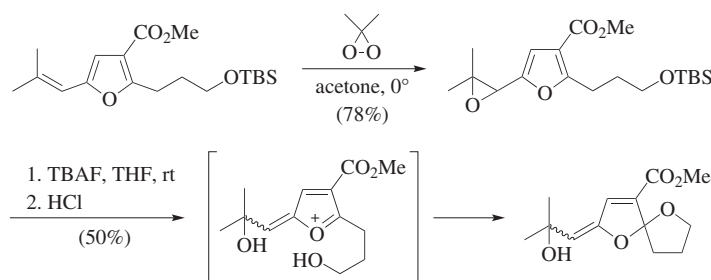
Dimethyldioxirane. Dimethyldioxirane can convert 5-unsubstituted furans bearing ester moieties to *cis* 4-oxoalkenes.¹⁷⁹ Notably, under these conditions, it is also possible to obtain unstable compounds, such as *cis* 4-oxo-2-pentenals **67** (R = H) (Scheme 50).⁴³



R = H, Me, AcOCH₂, (MeO)₂CH, Me₂(TMSO)C, PhthHNCH₂

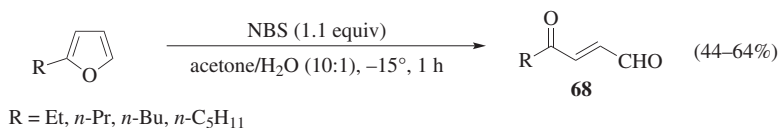
Scheme 50

DMDO also serves as an oxidant for reactions of furan derivatives that contain alkene substituents. However, in reactions of deactivated furans bearing electron-withdrawing substituents, the double bond is epoxidized preferentially without oxidation of the heterocyclic ring (Scheme 51).¹⁸⁰ As a result, it is possible to achieve high chemoselectivity between double bonds and furan rings based on activation and deactivation of the heterocycle towards oxidation.



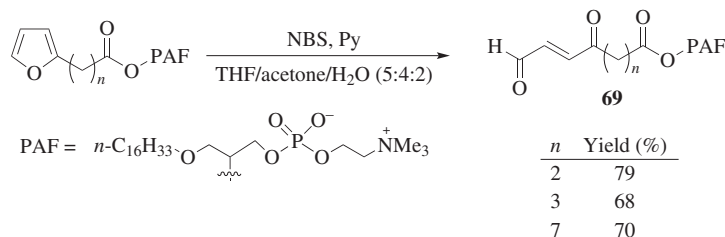
Scheme 51

N-Bromosuccinimide. The use of bromine in pyridine has also been reported to oxidize 2-substituted furans,¹⁸¹ albeit with some limitations.¹⁸² In contrast, a reasonably broad array of furans undergo oxidation with NBS in pyridine to yield *trans* 4-oxoalkenals. Substrates containing different protecting groups (such as MOM-acetals¹⁸³) and other functional groups (such as free hydroxyl groups and esters,¹⁸⁴ the 4-methoxyphenyl group,¹⁸⁵ silyl ethers,¹⁸² and double bonds¹⁸⁶) are compatible with these oxidation conditions, but in some cases mixtures of (*E*)/(*Z*) isomers are formed.¹⁸⁷ The use of NBS in 10:1 acetone/water with 2-alkylfurans also provides *trans* 4-oxoalkenals **68** (Scheme 52).¹⁸⁸



Scheme 52

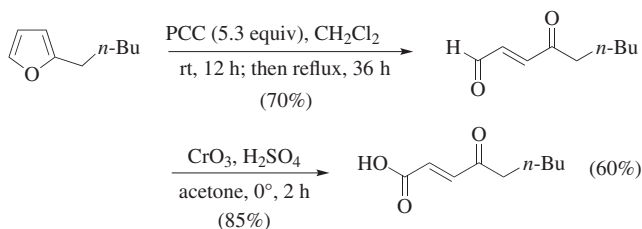
A variety of bioactive phospholipids have been synthesized by using oxidation reactions of furans that form a 4-oxoalkenal unit as a key step. In these cases, oxidations have been carried out using NBS in the presence of pyridine in 5:4:2 THF/acetone/H₂O at -20°C to generate the corresponding *trans* 4-oxoalkenals **69** in 68–80% yields without oxidation of the sensitive aldehyde group (Scheme 53).¹⁸⁹ Notably, the same aldehydes do not survive when the reactions are carried out using *m*-CPBA,¹⁹⁰ although the formation of a *cis* 4-oxoalkenal from a 2,3-fused furan derivative has been reported.¹⁹¹



Scheme 53

The same NBS procedure is used to prepare several targets bearing the typical phosphatidylcholine unit, which survives under the reaction conditions.^{192,193} Identical reaction conditions are applied to simpler 2-alkylfurans to obtain the corresponding aliphatic 4-oxo-2-alkenals.¹⁹⁴

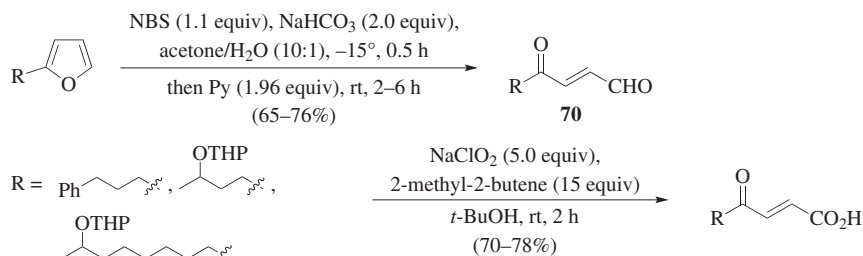
4-Oxoalkenoic Acids and Derivatives. As described above, oxidations of substituted furans with a variety of reagents invariably leads to formation of either 1,4-dioxoalkenes or 4-oxoalkenals, depending on the number and position of the substituents. In some cases, further in situ oxidation of a formed aldehyde function is possible under the reaction conditions,¹⁹⁵ but mixtures of compounds at different levels of oxidation are usually obtained.¹⁹⁶ Consequently, direct, clean oxidations to generate 4-oxoalkenoic acids are a difficult objective in this area. Some exceptions are found in *m*-CPBA promoted oxidations of fused furan derivatives, in which the use of 2 equivalents of the oxidant produces the corresponding *cis* 4-oxoalkenoic acids,¹⁹¹ although in low yield.¹⁹⁷ Instead, it is usually preferable to transform 2-substituted furans into 4-oxoalkenoic acids by utilizing a two-step sequential oxidation process. Sometimes the intermediate aldehyde is isolated but most often the second oxidation step is carried out in a one-pot procedure. Jones' reagent in combination with PCC is found to be convenient for this purpose,¹⁷⁹ as exemplified by the oxidation of 2-pentylfuran to the antibiotic (*E*)-4-oxonon-2-enoic acid in 60% overall yield (Scheme 54).¹⁷⁸



Scheme 54

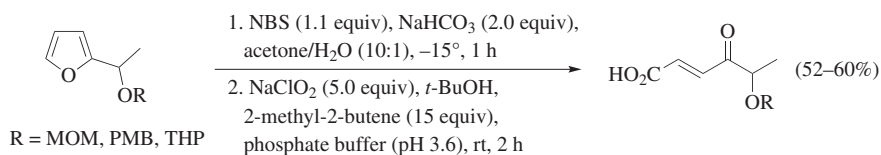
The most popular combination of reagents for this purpose employs sodium chlorite in the presence of an excess of 2-methyl-2-butene as chlorine scavenger as

the second oxidant, which follows initial furan ring cleavage promoted by NBS in an aqueous medium.¹⁹⁸ The use of an excess of 2-methyl-2-butene leads in some cases to quantitative yields in the second oxidation step,¹⁸⁶ but resorcinol can also be used as an additive in reactions carried out in an NaH_2PO_4 buffer solution.¹⁸³ A weak base such as pyridine or sodium bicarbonate is used as a scavenger of HBr generated in the reaction.¹⁹⁹ Under these conditions, furan cleavage is complete within 2 hours at -15° , but further reaction at ambient temperature is needed to isomerize the initially obtained *cis* dicarbonyl compound to the *trans* enal **70** (Scheme 55).¹⁸²



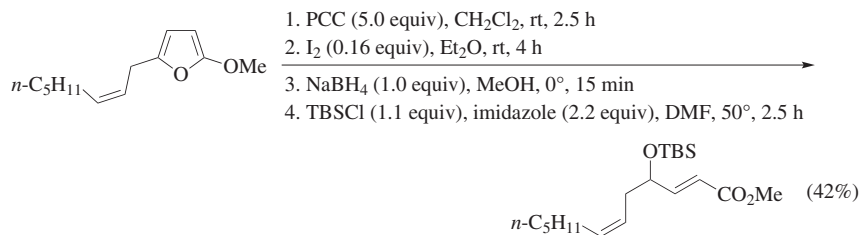
Scheme 55

From a synthetic point of view, the use of two different oxidation conditions avoids prolonged reaction times and expands the array of functionalities that can be tolerated in this transformation. For example, the oxidation reaction conditions described above are compatible with furans that contain MOM acetals¹⁸⁴ and 4-methoxybenzyl protecting groups (Scheme 56).¹⁸⁵ The versatility of the method has been demonstrated by its use in the preparation of bioactive phospholipids.¹⁹³

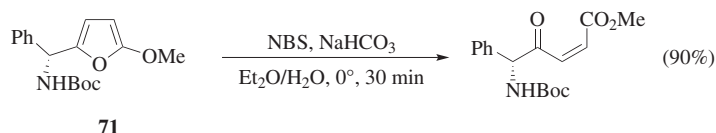


Scheme 56

Oxidation of 2-alkoxy-5-substituted furans serves as a direct method to prepare 4-oxoalkenoates. The oxidizing agent is the same as that used for 2,5-disubstituted furans, and ester products are formed in one step. Thus, both PCC (Scheme 57)²⁰⁰ and NBS (Scheme 58)²⁰¹ are used for oxidation of 2-alkoxy-5-substituted furans, the latter being an effective choice for enantiomerically pure *N*-protected furfurylamines such as **71**.²⁰²

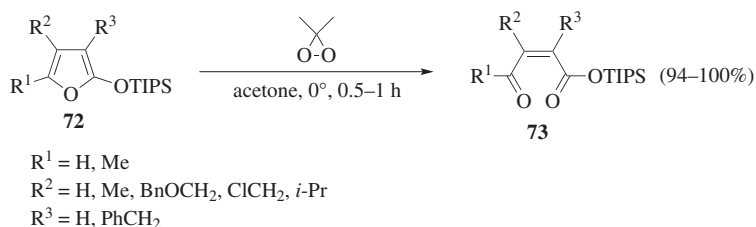


Scheme 57



Scheme 58

In a similar manner DMDO has been used to oxidize 2-siloxyfurans **72** to silyl esters **73** in high yields (Scheme 59).²⁰³ As with 2,5-disubstituted furans, oxidations using NBS provide *trans* isomers while those promoted by dimethyldioxirane furnish *cis* isomers.



Scheme 59

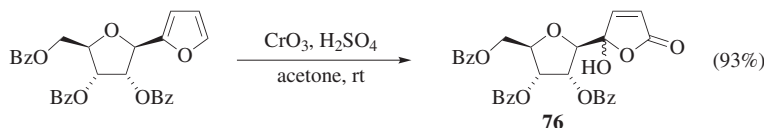
This process has been extended to PCC oxidations of 2-methylthiofurans to produce thiocarboxylates,²⁰⁴ but longer reaction times (up to 24 hours) are needed and mixtures of *cis* and *trans* isomers are obtained.²⁰⁵

γ -Hydroxybutenolides. The *cis* 4-oxoalkenoic acids **74** exist in equilibrium with the corresponding γ -hydroxybutenolides **75** (ring tautomers) (Scheme 60),²⁰⁶ but under acidic conditions γ -hydroxybutenolides are the only tautomers observed.



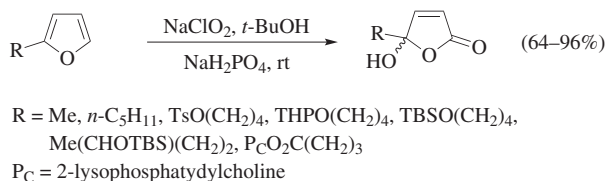
Scheme 60

Thus, by forming 4-oxoalkenoic acids oxidatively in situ and selecting favorable reaction conditions, pH, substituents, and work-up conditions, the corresponding γ-hydroxybutenolides can be produced cleanly. For example, γ-hydroxybutenolides are obtained from 2-siloxyfurans by treatment with DMDO²⁰⁷ followed by acid-catalyzed hydrolysis of the initially formed silyl-4-oxoalkenoate.²⁰³ The conversion of 2-unsubstituted furans directly into γ-hydroxybutenolides is carried out by employing the same oxidizing agents used in the transformation of 2,5-disubstituted furans to 1,4-dioxoalkenes. A good example of this method is found in the chromic acid induced synthesis of butenolides **76** in the preparation of *C*-nucleosides (Scheme 61).²⁰⁸



Scheme 61

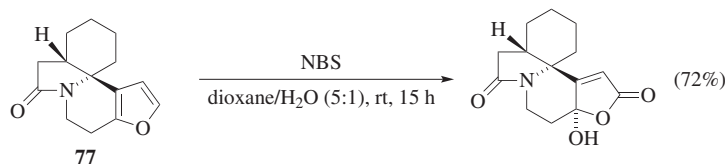
In a similar fashion, the formation of a butenolide has been reported to occur by reaction of magnesium monoperoxyphthalate (MMPP) with a 2,3,4-trisubstituted furan.²⁰⁹ Nitrous acid has also been used for this purpose, but the yields are generally lower.²¹⁰ Oxidations of 2-alkylfurans using sodium chlorite under slightly acidic aqueous conditions furnish γ-hydroxybutenolides in high yields (Scheme 62).²¹¹ These reaction conditions are compatible with the presence of several acid-sensitive protecting groups and can be employed to carry out reactions of substrates possessing free hydroxy groups.²¹²



Scheme 62

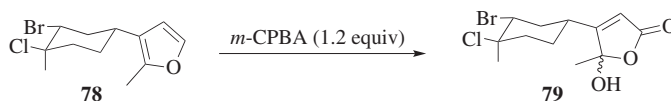
Some success has been achieved in preparing γ-hydroxybutenolides by using an excess of NBS in an aqueous medium,²¹³ as exemplified by the reaction of the

polycyclic substrate **77** (Scheme 63),²¹⁴ which produces an advanced intermediate in the synthesis of *Erythrina* alkaloids. A similar result is obtained in studies targeted at tetra-*nor*-terpenoids where NBS in methanol along with microwave irradiation is employed to promote the key oxidation process.²¹⁵



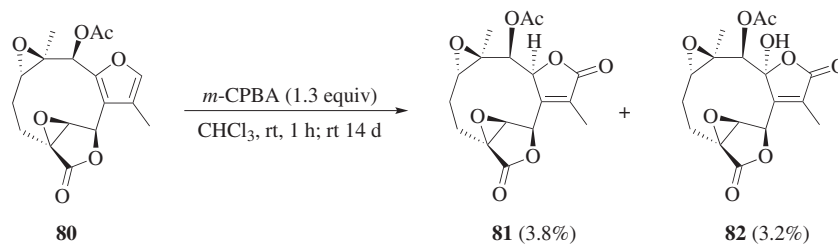
Scheme 63

m-CPBA is an ideal reagent for oxidation of the terpenoid-derived dihalide **78**, producing butenolide **79** in a study aimed at establishing the absolute configuration of the natural product (Scheme 64).²¹⁶



Scheme 64

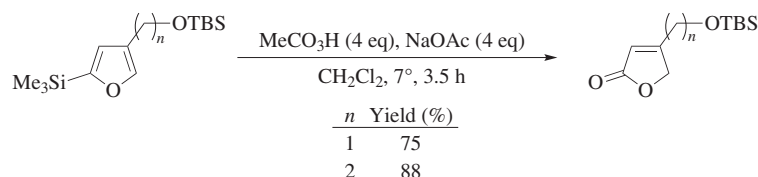
In other cases, such as in the *m*-CPBA induced oxidation of zeylanidine (**80**), mixtures of the expected lactone **81** and the γ -hydroxybutyrolactone **82** are obtained (Scheme 65).²¹⁷ However, a glucosyl butenolide is formed in 70% yield under very similar conditions,¹⁶¹ which have also been employed in a reaction sequence used to confirm the absolute configuration of glaucescenolide, a natural γ -hydroxybutyrolactone.²¹⁸



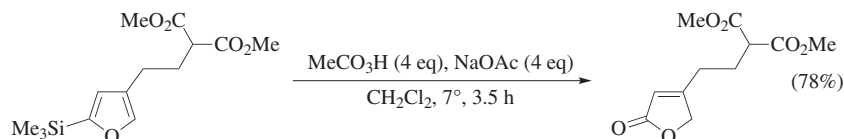
Scheme 65

Reactions of 3-(silyloxyalkyl)- and 3-bis(methoxycarbonyl)propyl-2-trimethylsilyl furans with peracetic acid yield the corresponding butenolides (Schemes 66 & 67).²¹⁹

3-Alkenyl-2-trimethylsilylfurans react under these conditions to form butenolides almost exclusively if the alkene is less than trisubstituted.²²⁰

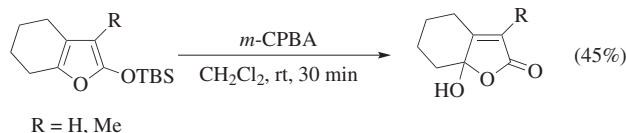


Scheme 66



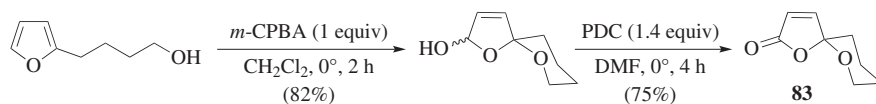
Scheme 67

On the other hand, oxidations of 2-siloxyfuran derivatives with *m*-CPBA lead to generation of γ -hydroxybutyrolactones through a pathway involving concomitant desilylation at C2 of the furan ring (Scheme 68),²²¹ a process that does not take place when DMDO is employed as oxidant.²⁰³ Reactions of 3,4-unsubstituted 5-alkyl-2-siloxyfurans produce silyl 4-oxoalkenoates in up to 11% yield. These oxoalkenoates can be converted to the expected γ -hydroxybutyrolactones upon treatment with dilute HCl in THF. The reaction can also be performed with enantiomerically pure substrates.²²²



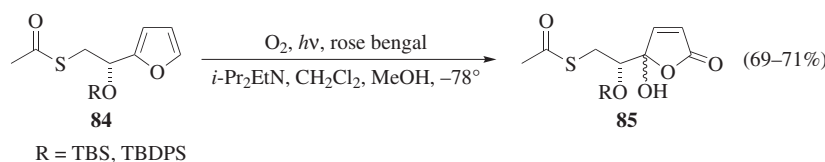
Scheme 68

When hydroxy substituents are present in furan side-chains, oxidations with *m*-CPBA yield lactols and a second oxidation step with PDC is required to obtain the corresponding lactones. This sequence is exemplified in the reaction of 4-(furan-2-yl)butan-1-ol from which 1,6-dioxaspiro[4,4]dec-3-en-2-one (**83**) is obtained (Scheme 69).²²³



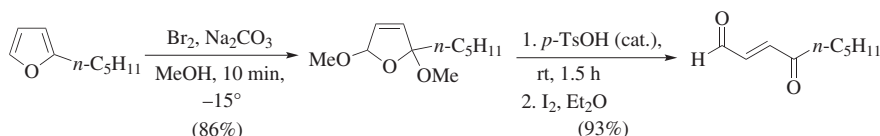
Scheme 69

Similarly, photooxygenation of an enantiomerically pure furan derivative bearing a hydroxyl group at the γ -position, followed by treatment with acetic anhydride in pyridine, leads to formation of a 2.7:1 mixture of epimeric γ -spiroketal- γ -lactones.²²⁴ Photooxygenation of siloxy derivatives **84** using rose bengal as a sensitizer affords γ -hydroxybutenolides **85** in good yields (Scheme 70).²²⁵



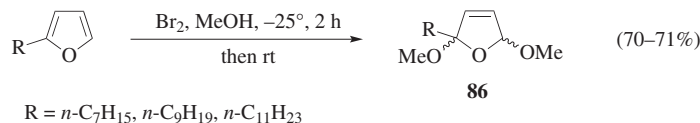
Scheme 70

2,5-Dialkoxy-2,5-dihydrofurans. *Bromine in Methanol.* Oxidation of furan derivatives in alcohol-containing solvents (methanol in most cases) is an excellent method for preparing protected 1,4-dicarbonyl derivatives in the form of 2,5-dialkoxy-2,5-dihydrofurans. Indeed, the main interest of these compounds resides in the fact that they are masked 1,4-dioxoalkenes that can be liberated by treatment with 2 N HCl,²²⁶ HCl in THF/ H_2O ,²²⁷ or catalytic amounts of 4-toluenesulfonic acid (Scheme 71).²²⁸ Careful hydrolysis under mild conditions (0.005 M H_2SO_4) leads to partial hydrolysis of the bis-acetal moiety.^{229,230}



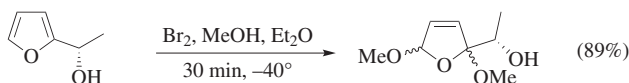
Scheme 71

Oxidations with bromine in methanol serve as efficient methods for converting 2-substituted furans to 2,5-dimethoxy-2,5-dihydrofurans **86** (Scheme 72) in processes known as the Clauson–Kaas reaction.^{231,232} In addition, a variety of alcohols such as ethanol, n -propanol, and n -butanol can be employed in place of methanol without reducing the yield, and dichloromethane^{233–235} and diethyl ether²³⁶ can be used as cosolvents.²³⁷



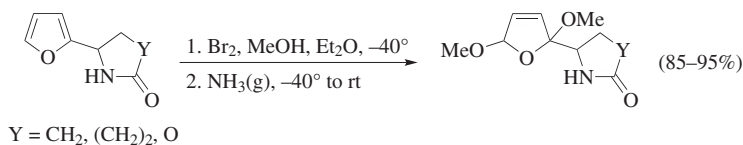
Scheme 72

The oxidation reaction of furfuryl alcohol using bromine in methanol produces a very useful synthetic intermediate, 2,5-dimethoxy-2-hydroxymethyl-2,5-dihydrofuran.^{238,239} Also, racemic^{240,241} and enantiopure forms (Scheme 73)^{242,243} of methyl furfuryl alcohol undergo bromine-promoted oxidation in methanol containing diethyl ether as the cosolvent.²⁴⁴



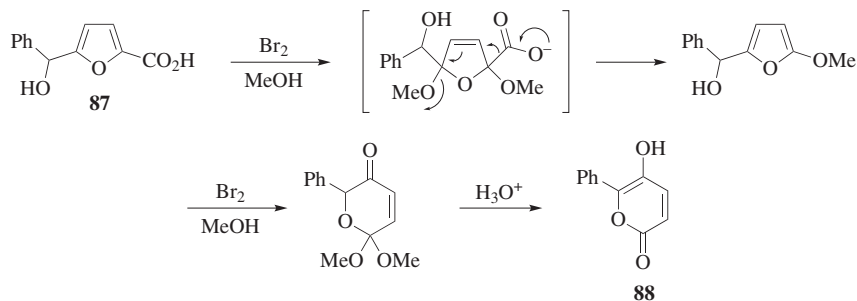
Scheme 73

The same type of reaction can be carried out with a variety of substrates including substituted²²⁶ and unsubstituted *N*-phthaloyl²⁴⁵ and *N*-acyl furfuryl amines (Scheme 74).²⁴⁶ In all cases, the process is fully compatible with common protecting groups, such as benzyl ethers,³² esters,^{247,248} phosphonates²⁴⁹ and acetals.²⁵⁰ In general, 1:1 mixtures of stereoisomers are obtained.²⁵¹ In addition, the presence of substituents on the furan ring does not affect the reaction and thus 2,5-disubstituted²⁵² and 3,4-disubstituted furans can be employed as substrates.²⁵³



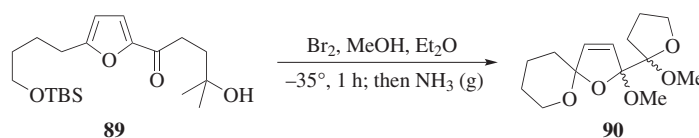
Scheme 74

Treatment of 5-(α -hydroxybenzyl)furoic acid (**87**) with bromine in methanol under basic conditions results in a reaction that occurs with concomitant decarboxylation. A second oxidation step in this process produces 5-hydroxy-2-pyranone **88**, through a rearrangement promoted by the hydroxyl group in the intermediate (Scheme 75).¹⁴⁶



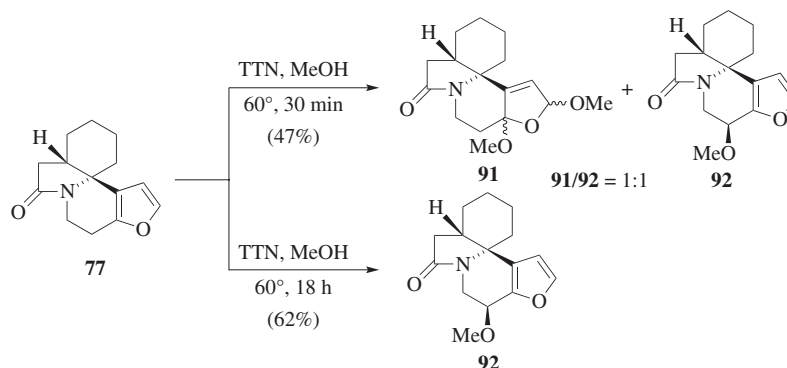
Scheme 75

Oxidation of furan **89** using bromine in methanol with diethyl ether as a cosolvent and at low temperature, followed by treatment with ammonia leads to formation of the 2,5-dialkyl-2,5-dioxy-2,5-dihydrofuran derivative **90**. Under these conditions, the TBS protecting group does not survive and its loss yields an alcohol that promotes formation of the spirocyclic ketal **90** (Scheme 76).²⁵⁴



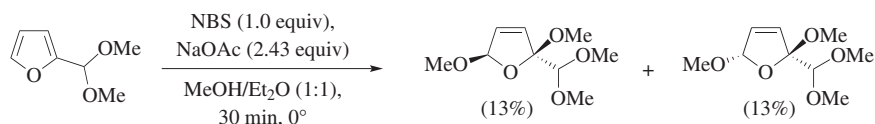
Scheme 76

In contrast to the oxidation described above, treatment of furan **77** with thallium trinitrate (TTN) leads to production of **91** in 47% yield as a 1:1 mixture of isomers along with 50% of recovery of the starting material (Scheme 77). Prolonged oxidation (18 h) of **77** under the same conditions affords **92** as a single product in 62% yield, suggesting that **92** is formed by a secondary reaction of **91**.²⁵⁵



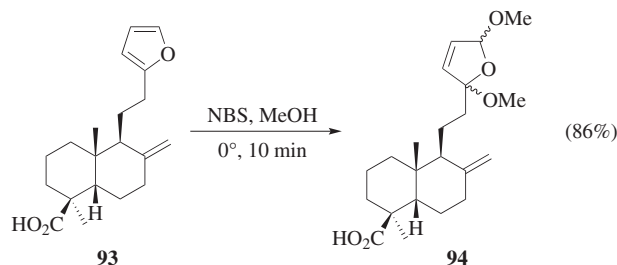
Scheme 77

N-Bromosuccinimide. Treatment of furfural dimethyl acetal with NBS in 1:1 methanol/diethyl ether in the presence of sodium acetate leads to formation of the corresponding dimethoxy derivative as a 1:1 mixture of isomers in 26% yield (Scheme 78).²⁵⁶



Scheme 78

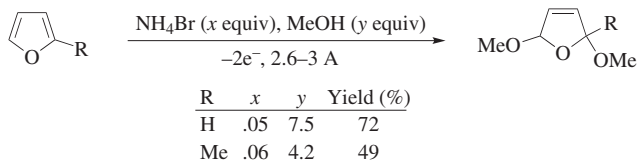
Enantiomerically enriched furan derivative **93** subjected to these conditions produces an approximately 1:1 mixture of stereoisomeric 2,5-dimethoxy dihydrofurans **94** (Scheme 79).²⁵⁷ Analogous reactions take place under electrochemical or chemical (bromine in methanol) oxidation conditions.^{258,259}



Scheme 79

Oxidations of 3-substituted and 3,4-disubstituted furans with NBS in ethanol provide 2,5-diethoxy dihydrofurans in essentially quantitative yields by reactions that are tolerant of a variety of substituents on the furan ring and appended functional groups.²⁶⁰ The hydroxyl moiety participating in formation of the acetal functional group can be from the alcohol solvent or from the same molecule. In the latter case, spiro compounds are generated in a manner that is similar to oxidations with bromine in methanol illustrated above.¹²⁰

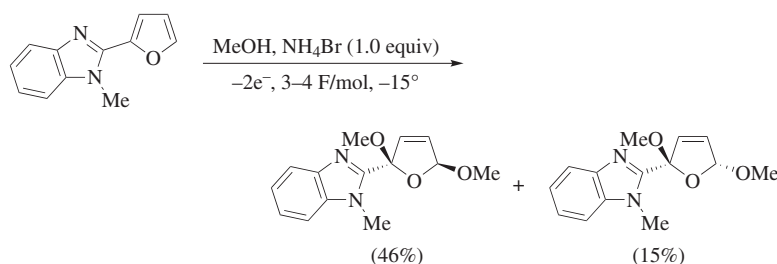
Electrochemical Oxidation. Electrochemical oxidation of furans in the presence of an alcohol is one of the first and most used methods for preparing 2,5-dialkoxy-2,5-dihydrofurans. The reaction was initially reported in 1952 by Clauson-Kaas, who described the electrochemical dimethoxylation of several 2-substituted furans^{261,262} Electrolytic oxidations of furan and 2-methylfuran with ammonium bromide as the electrolyte and in methanol as the solvent are carried out by using an electrolysis cell consisting of a hollow brass cylindrical cathode and a hollow graphite cylindrical anode. The average current employed is 2.6 A, with an average temperature of 12°. Under these conditions the products are formed in 72% and 49% yields, respectively, on a multigram scale (0.25–0.36 mol of starting materials) (Scheme 80).²⁶³ Other electrolytes such as sodium bromide²⁶⁴ can also be employed in these processes.



Scheme 80

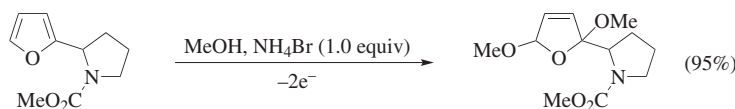
Electrolytic methoxylation has been carried out with *N*-benzoyl furfurylamine²⁶⁵ and polyfunctionalized furans using a similar protocol, showing the compatibility

of the method with ester and acetal groups.²⁶⁶ Some anomalous oxidation products have been observed in electrochemical oxidations of 2,5-dialkylfurans in acetic acid, but the expected 2,5-dimethoxy-2,5-dihydrofurans are obtained when the reactions are performed in methanol.²⁶⁷ The presence of aromatic or other conjugated 2-substituents causes formation of anomalous products that either have dimeric structures or are structures in which one methoxy group is introduced into the furan ring.²⁶⁸ In spite of these issues, electrochemical oxidations of 2-(2-benzimidazolyl)furans proceed in the anticipated manner (Scheme 81).²⁶⁹ If aromatic and heteroaromatic substituents are not conjugated with the furan ring, oxidation proceeds to give the corresponding 2,5-dialkoxy-2,5-dihydrofuran derivatives.²⁷⁰



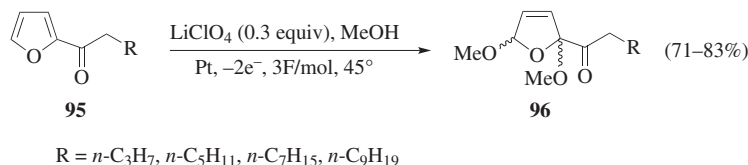
Scheme 81

Dihydrofuryl pyrrolidines and piperidines have been prepared in high chemical yields using electrochemical oxidations (Scheme 82).²⁷¹ The reactions tolerate oxygen-containing functionality and, more interestingly, can be carried out on 100 g scales to give the products in very high yields.²⁷²



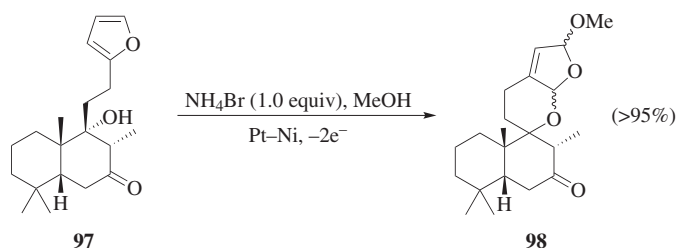
Scheme 82

It is not always necessary to apply the theoretical amount of electricity in order to bring reactions to completion. For example, by using tetraethylammonium perchlorate in methanol, 3-substituted-2,4-dimethylfurans have been oxidized to generate the corresponding 3-substituted-2,4-dimethyl-2,5-dimethoxy-2,5-dihydrofurans in high yields after passing only 2.78 F/mol of electricity through the solution.²⁷³ Similarly, electrochemical oxidations of furanyl ketones **95** in methanol using lithium perchlorate as the electrolyte, platinum electrodes, and 3 F/mol of electricity afford the corresponding dihydrofuran derivatives **96** in high yields (Scheme 83).²⁷⁴



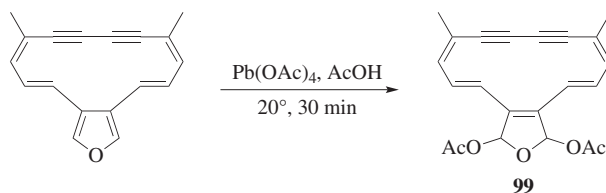
Scheme 83

Electrochemical oxidation of the natural product hispanolone (**97**) using the typical system comprised of ammonium bromide, methanol, a platinum anode, and a nickel cathode affords the spiro-tetracyclic compound **98** in high yield (Scheme 84). This reaction can be extended to several similar compounds.¹²¹



Scheme 84

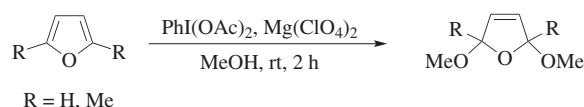
Other Oxidants. Other oxidizing agents such as lead tetraacetate have been employed in oxidations of a furan that forms a functionalized macrocycle en route to preparation of annulenes. Because these reactions are conducted in acetic acid, the corresponding 2,5-diacetoxy dihydrofurans **99** are produced (Scheme 85).^{275,276}



Scheme 85

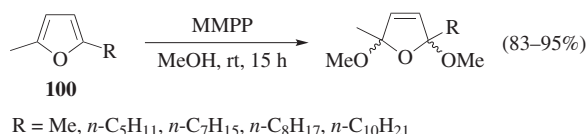
2,5-Diethoxy-2,5-dihydrofurans are generated by oxidation of 2,5-disubstituted furans with hydrogen peroxide in aqueous ethanol in the presence of a catalytic amount of vanadyl sulfate. The reactions are conducted at 20° , but the products are isolated in only 12% yields.²⁷⁷ Oxidations of furan and 2,5-dimethylfuran with

Dess–Martin periodinane in the presence of magnesium perchlorate in methanol leads to formation of 2,5-dimethoxydihydrofurans (Scheme 86).⁷⁰



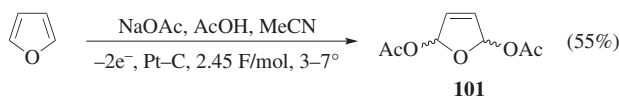
Scheme 86

Similarly, if the reagent used in this process is magnesium monoperoxyphthalate (MMPP), excellent yields accompany oxidations of 5-substituted-2-methylfurans **100**, a reaction that has been demonstrated to take place through intermediate 1,4-dienones (Scheme 87).³⁷



Scheme 87

Oxidation of 2-furoic acid leads to formation of methyl 4,4-dimethoxybutanoate in 77% yield through a pathway involving decarboxylation and secondary oxidation of the intermediate 2,5-dialkoxy-2,5-dihydrofuran.²⁷⁸ Anodic oxidation of furan can also be carried out in acetic acid (or in a mixture of acetic acid and acetonitrile) using sodium acetate and 2.45 F/mol of electricity to afford 2,5-diacetoxy-2,5-dihydrofuran (**101**) in 55% yield (Scheme 88).²⁷⁹

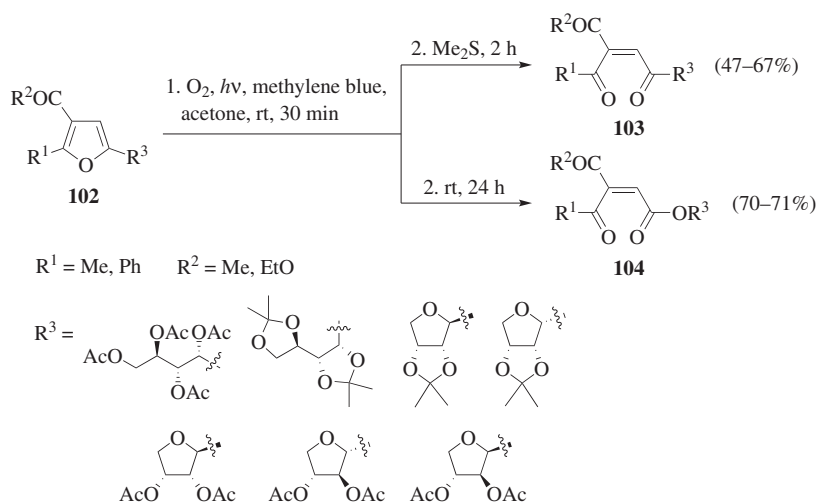


Scheme 88

Photooxygenation with Singlet Oxygen

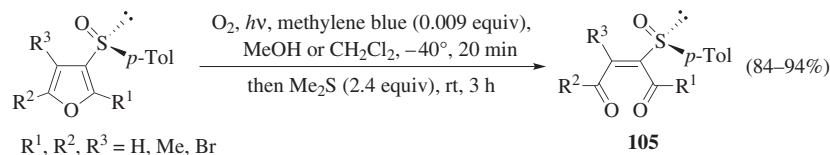
Photooxygenation reactions of furans with singlet dioxygen have been extensively studied^{26,27,72,280} and analyzed in detail²⁸¹ with regard to their substituent dependence,^{282,283} intermediates formed,^{88,284,285} solvent effects,²⁸⁶ and optimized reaction conditions.^{287–289} Consequently, even though mixtures of products are often formed in these processes,^{79,92,99} useful procedures for preparing 1,4-dicarbonyl compounds²⁹⁰ and related derivatives such as butenolides²⁹¹ have emanated from these studies.²⁸

Glycosyl furans **102** have been transformed using singlet oxygen mediated photooxygenation reactions through the corresponding endoperoxides to afford 1,4-dicarbonyl products (Scheme 89).²⁹² This process can be extended to furans bearing a hexose moiety⁹³ and a methoxycarbonyl function at the C5 position.⁸⁶ Formation of 1,4-dioxoalkenes **103** in these reactions is promoted by reaction of dimethyl sulfide with the intermediate endoperoxide. If dimethyl sulfide is not added to the reaction mixture after 1 mol of molecular oxygen is consumed, keto esters **104** are mainly generated by Baeyer–Villiger-type rearrangement of the intermediate endoperoxides.^{94,292} Moreover, *cis* isomers of the products are transformed to the more stable *trans* isomers upon silica gel chromatography.²⁹³ This same behavior has been observed for other substrates,²⁹⁴ confirming that 2,5-disubstituted furans can undergo rearrangement reactions that generate esters upon photooxygenation at low temperature and followed by warming the reaction mixture.²⁹⁵ Starting from 2-methoxyfurans, functionalized methyl *cis* 4-oxo-2-alkenoates can be prepared in a one-pot procedure by photooxygenation in methanol.²⁹⁶ Singlet oxygen promoted photooxygenations afford both types of compounds chemoselectively depending on the reaction conditions employed. Moreover, these reactions can be carried out on furans that contain esters and acetals, and it is likely that the process will tolerate most other protecting and functional groups as well.⁸⁷



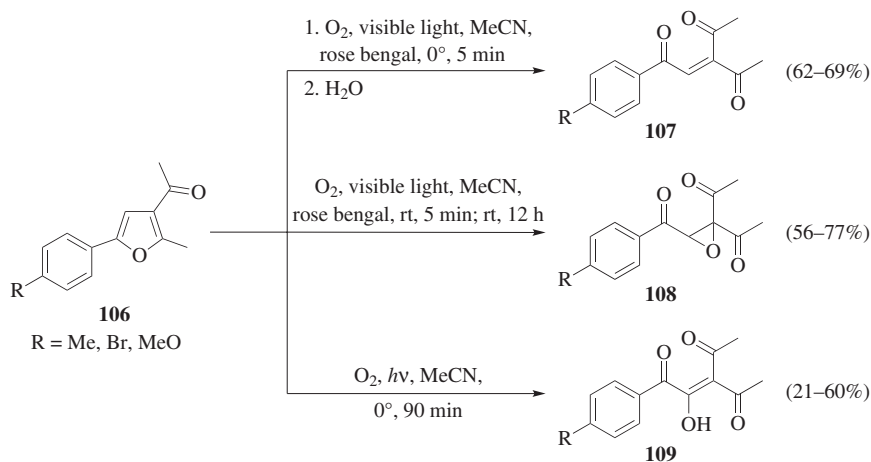
Scheme 89

Enantiomerically pure 1,4-dicarbonyl-2-(4-tolylsulfinyl)-2-alkenes **105** are generated by photooxygenation of the corresponding furans using methylene blue as sensitizer followed by treatment with dimethyl sulfide. Both methanol and dichloromethane can be used as solvents for these reactions and enantiomeric purities of the substrates are preserved in the products of the reactions (Scheme 90).²⁹⁷



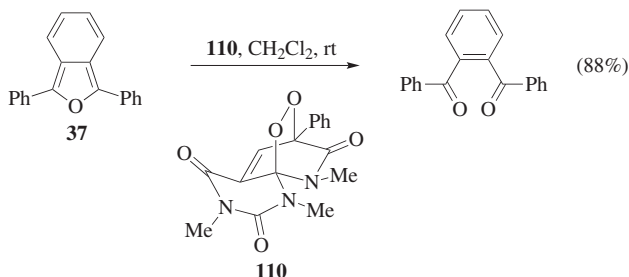
Scheme 90

Because of the mildness of the conditions used for these reactions, most functional groups remain intact. Direct photooxygenations of 3-acetyl-5-aryl-2-methylfurans **106** in acetonitrile in the presence of dry air and rose bengal yield 3-acetyl-1-aryl-2-pentene-1,4-diones **107** after aqueous work-up.²⁹⁸ If the reaction mixture is kept at room temperature, epoxides **108** are obtained instead. The epoxides are also generated by base treatment of the intermediate hydroperoxy-dihydrofurans.²⁹⁹ Several reaction conditions have been evaluated to bring about selective formation of either epoxides or 1,4-dioxoalkenes.³⁰⁰ Direct UV light irradiation of the furans in the absence of additive was observed to promote formation of 3-acetyl-2-hydroxy-2-pentene-1,4-diones **109** (Scheme 91).²⁹⁸



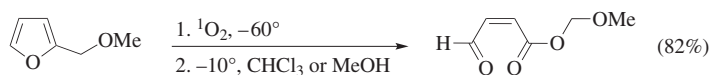
Scheme 91

Isobenzofurans undergo similar singlet oxygen promoted reactions. For example, 1,3-diphenylisobenzofuran undergoes photooxidation to form 1,2-dibenzoylbenzene in quantitative yield.³⁰¹ However, if norbornene is present in the reaction mixture as the solution containing the intermediate endoperoxide is warmed, the yield of the 1,2-dibenzoyl product decreases to 73%, and norbornene epoxide is observed as a byproduct.³⁰² Higher yields and more selective reactions take place when reactions of 1,3-diphenylisobenzofuran are conducted using singlet oxygen generated from chemical precursors, in particular the pteridin-2,4,7-trione-6,8'-endoperoxide (**110**) (Scheme 92).³⁰³



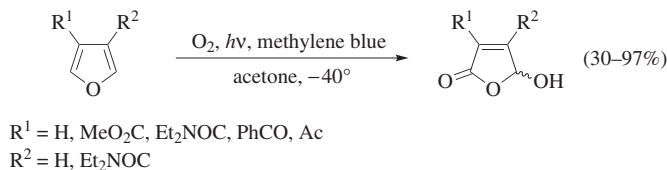
Scheme 92

Photooxygenation reactions of furan derivatives aimed at the preparation of 4-oxoalkenals have not yet been explored in detail, but in one of the few examples studied, a high yield of the product is observed (Scheme 93),³⁰⁴ suggesting that similar substrates can undergo these transformations.



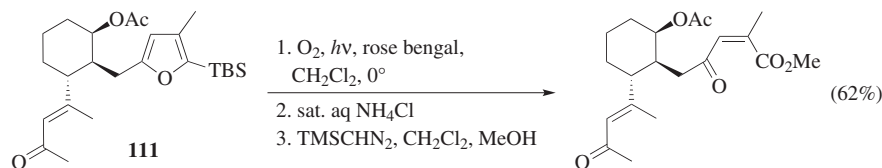
Scheme 93

Although γ -hydroxybutenolides are generated in photooxygenation reactions of furans carried out under a variety of conditions, these processes often produce side products. In some cases the low chemical yields are not caused by the reaction itself but by the instability of the products. Among those reactions that take place in high yields, and therefore are practical, are the conversions of 3,4-disubstituted furans to γ -hydroxybutenolides promoted by photooxygenation in acetone (Scheme 94).²⁹¹



Scheme 94

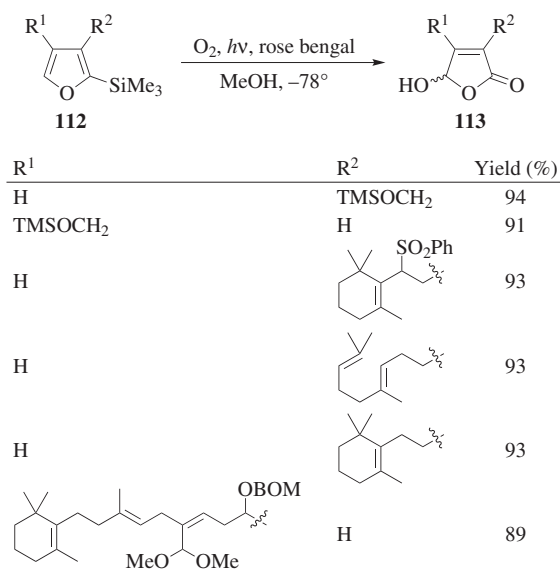
4-Oxoalkenoates are formed in photooxygenation reactions of 2-silyl-substituted furans, exemplified by **111** (Scheme 95).³⁰⁵ Performing these photooxygenations in methanol generates butenolides directly.³⁰⁶ Silyl esters resulting from these processes are quantitatively converted into γ -hydroxybutenolides by methanolysis.⁹¹



Scheme 95

In addition to the examples presented above, others exist in which photooxidations of simple furan substrates take place with moderately high efficiencies. The substrates for these processes, including isobenzofuran,⁷⁶ 2-benzimidazolylfuran,³⁰⁷ 2,5-diarylfurans,³⁰⁸ fused furans,³⁰⁹ and macrocyclic furan-containing compounds,³¹⁰ all react to generate the corresponding 4-oxoalkenoates.

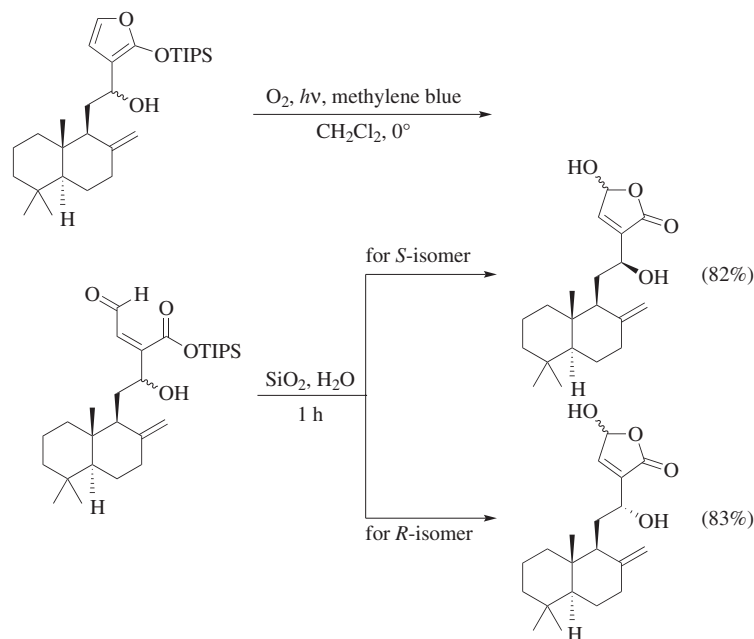
2-(Trimethylsilyl)furans **112** react to form γ -hydroxybutenolides **113** in very high yields upon exposure to singlet oxygen (from rose bengal sensitization) for a few minutes at ambient,³⁰⁶ low (-17°),³¹¹ and very low (-78°) temperatures.^{312,313} Identical results are observed when methylene blue is used as the photosensitizer.³¹⁴ Moreover, this process can be made compatible with substrates that contain alkene moieties by properly adjusting the flow rate of oxygen and concentration of substrates (Scheme 96).^{315,316} Notably, reactions of substrates that do not contain trimethylsilyl groups take place in lower yields and longer reaction times are needed for completion.



Scheme 96

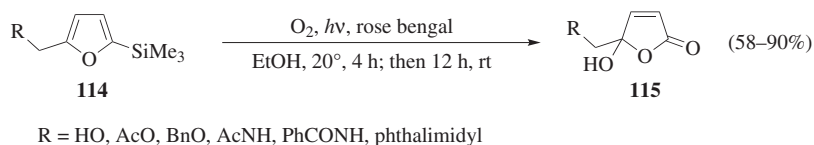
Photooxidation reactions of 2-*tert*-butyldimethylsilyl-substituted furans can be promoted by using tetraphenylporphyrin as a photosensitizer,³¹⁷ conditions in which

the presence of several functional groups such as acetals are tolerated.^{318,319} When a triisopropylsilyl group is present at C2 of the furan ring, the open-chain 4-oxosilyl alkenoate is generated, although the γ -hydroxybutenolide can be formed by in situ hydrolysis of the silyl ester (Scheme 97).³²⁰



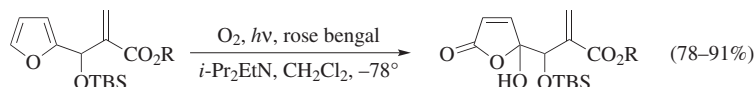
Scheme 97

It is likely that the same pathway is followed in the reactions of 2-trimethylsilylfurans, but the higher lability of the trimethylsilyl group prevents isolation of the silyl ester.³²¹ Similarly, a 4-oxo(*tert*-butyldimethylsilyl)alkenoate is produced from the corresponding 2-*tert*-butyldimethylsilyl furan derivative and the silyl ester group can be transformed in situ into a methyl ester by desilylation with TBAF in the presence of methyl iodide.³²² Site selectivity can also be achieved by introducing a formyl group instead of the trimethylsilyl group at C2, but mixtures of butenolides and 4-oxoalkenoates are obtained in some cases.³²³ In contrast, photooxidation reactions of 5-substituted-2-silylfurans **114** in ethanol generate γ -hydroxybutenolides **115** in high yields (Scheme 98).³²⁴ Similar reactions of 5-glycosylfurans produce glycosyl-butenolides in high yields.³²⁵



Scheme 98

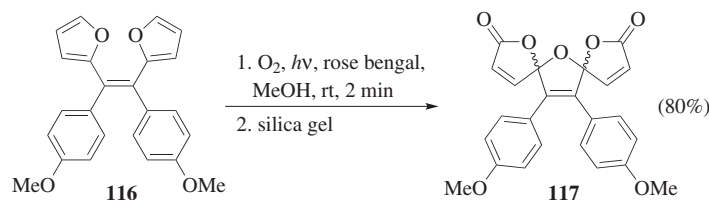
Reactions of 3-alkylfurans with singlet oxygen (generated by irradiation of polymer-bound rose bengal in the presence of molecular oxygen at -78°) in the presence of a hindered base yields 3-alkyl-4-hydroxybutenolides in moderate to high yields.³²⁶ The site-selective formation of only γ -hydroxybutenolides in these processes is a consequence of the fact that, at low temperatures, base-catalyzed decomposition of the intermediate endoperoxides is favored over thermal decomposition. The use of a hindered base is crucial for ensuring site-selective removal of the hydrogen at C1 on the endoperoxide.³²⁷ Hydroxyl groups in the substrate must be protected to avoid undesired fragmentation reactions (Scheme 99).⁸⁹ Bi- and polycyclic fused furans also undergo site-selective formation of butenolides owing to the steric restraints imposed by the substituents.⁸⁰ Fragmentation processes may also result in unexpected butenolides.⁸⁵



R = Me, Et, *n*-Bu, dodecyl, benzyl, cinnamyl, allyl, chloroethyl

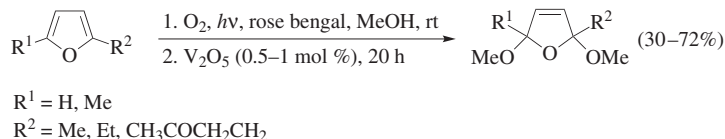
Scheme 99

Bis-spirobutenolides can be prepared by photooxygenation of bis-furans, exemplified by 1,2-difurylalkene **116**, in methanol followed by silica gel treatment. The process consists of a cascade sequence in which a double photooxygenation of **116** is followed by dehydration and spirocyclization to yield bis-spiroketal **117** (Scheme 100).⁹⁶ Formation of highly substituted bis-spirobutenolides is possible using photooxygenation of difuryl compounds, which undergo sequential additions of singlet oxygen to afford diendoperoxides that form the final products.⁹⁵



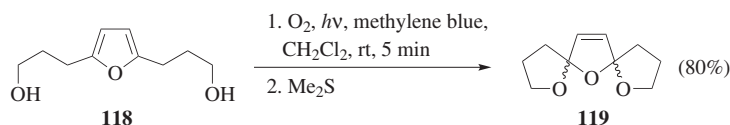
Scheme 100

Photooxygenation reactions of 2,5-disubstituted furans in methanol, followed by treatment with a catalytic amount of vanadium pentoxide, produce 2,5-dimethoxy-2,5-dihydrofurans as mixtures of *cis/trans* isomers (Scheme 101).³²⁸ The formation of 2,5-dialkoxy-2,5-dihydrofurans can also take place by controlled addition of alcohols to endoperoxides formed in situ through photooxygenation of furans in alcoholic medium, and in the presence of triphenylphosphine.³²⁹ Similarly, 2,5-diethoxy-2,5-dihydrofurans are generated by photooxygenations of these substrates in an ethanol/acetone mixture. However, in this solvent system the reaction affords up to seven products, considerably limiting its synthetic utility.⁹²



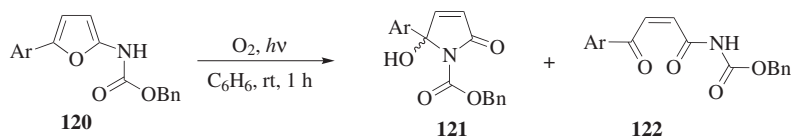
Scheme 101

Photooxidation reactions of 2,5-disubstituted furans take place more cleanly when hydroxyl groups are present in the side chains. For example, furan **118** is converted into **119** in a one-pot, singlet oxygen-mediated, cascade process (Scheme 102).³³⁰ The use of dimethyl sulfide is crucial for promoting reduction and ketalization of the intermediate spirocyclic hydroperoxide formed in this process by cleavage of the initially formed endoperoxide through intramolecular attack of a hydroxyl group. With unsymmetrical bis-spiroketal, induction of the second ketalization step by acid treatment is sometimes needed.



Scheme 102

2-Furylcarbamates **120** are transformed to 5-hydroxy-3-pyrrolin-2-ones **121** by irradiation in the presence of oxygen. The initially formed products **121** are in equilibrium with the corresponding *cis* γ -keto amides **122**. The results of a ^1H NMR study show that the presence of electron-withdrawing nitro groups in the aromatic ring linked at C5 of the furan ring stabilize the pyrrolinone isomer **121** (Scheme 103).³³¹ The process has been extended to 5-(alkoxymethyl)furyl carbamates, which react to

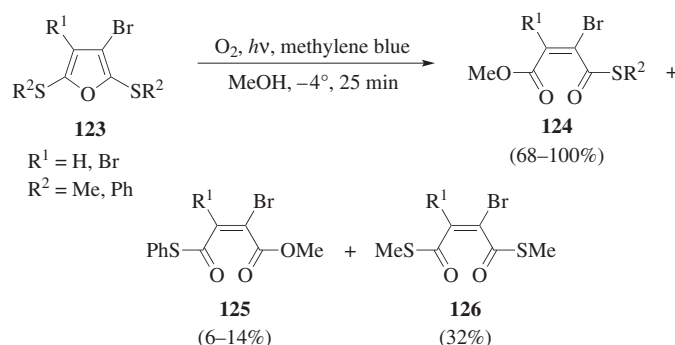


Ar	121 + 122 Yield (%)	121/122
Ph	41	81:19
4-MeOC ₆ H ₄	42	50:50
4-MeC ₆ H ₄	34	67:33
4-ClC ₆ H ₄	36	88:12
4-O ₂ NC ₆ H ₄	77	100:0
3-MeOC ₆ H ₄	32	87:13
3-ClC ₆ H ₄	36	92:8
3-O ₂ NC ₆ H ₄	41	100:0
2-MeC ₆ H ₄	16	20:80
2-ClC ₆ H ₄	35	89:11

Scheme 103

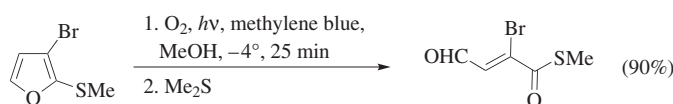
form products that generally show a marked preference for existence as pyrrolinone tautomers.³³²

Methylene blue sensitized photooxygenations of 3-bromo-2,5-bis(thio)furans **123** lead to the formation of *O,S*-thiomaleates **124** in high yields (Scheme 104).³³³ The thioester moiety in the products is formed predominantly at the site adjacent to the bromine substituent, although the alternative thiomaleates **125** are obtained to some extent and the bis-thioesters **126** are obtained in one case (for $R^1 = H$, $R^2 = Me$). Finally, this reaction is not affected by the addition of reducing agents such as dimethyl sulfide, thiourea, and triphenylphosphine.



Scheme 104

The photooxidation reaction of 3-bromo-2-(methylthio)furan yields (*E*)-2-bromo-4-oxobutenethioate as the only product (Scheme 105).³³³ In contrast, reaction of the 2,3-bis(thio)furan analog gives a γ -thiobutyrolactone in high yield.

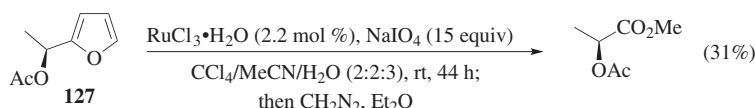


Scheme 105

Oxidations to Carboxylic Acids

Oxidations with Ruthenium Tetroxide. Complete oxidation of the furan ring of 2-substituted furan derivatives results in the formation of carboxylic acids. This transformation can be accomplished using a variety of oxidizing reagents, among which ruthenium tetroxide is the most common. Since its first introduction as an organic oxidant³³⁴ the ability of ruthenium tetroxide to oxidize arenes has been demonstrated.^{115,335} An improved procedure for the oxidation of phenyl groups, in which acetonitrile is used as solvent,³³⁶ was successfully applied to the oxidation of furans and other heterocycles.¹¹³ The optimal procedure to generate ruthenium

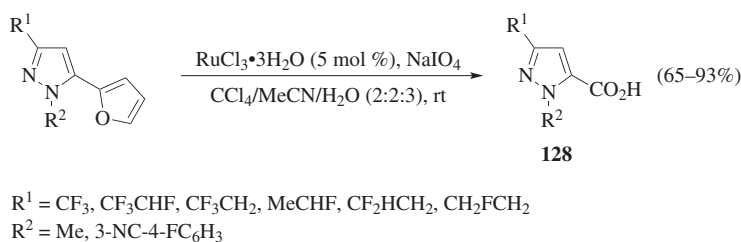
tetroxide involves the use of a catalytic amount (2.2 mol %) of ruthenium(III) chloride in the presence of an excess (4–30 equivalents) of sodium periodate with a 2:2:3 mixture of carbon tetrachloride/acetonitrile/water as the solvent. Under these conditions oxidation of the enantiomerically pure furan derivative **127** takes place without loss of enantiomeric purity, although in only 31% yield (Scheme 106).¹¹³



Scheme 106

These reaction conditions are tolerated by an extensive array of hydroxyl, protecting groups including alkyl,³³⁷ benzyl,³³⁸ and silyl³³⁹ ethers, acetals,³⁴⁰ and esters.^{113,337} The use of ruthenium(III) chloride to generate ruthenium tetroxide is also possible in the presence of various nitrogen protecting groups including trifluoroacetyl,³⁴¹ benzyl,³⁴¹ 4-methoxybenzyl,³³⁸ tosyl,³⁴² phosphinoyl,³⁴³ and carbamates including *tert*-butoxycarbonyl^{344,345} and benzyloxycarbonyl derivatives.³⁴⁶ Interestingly, the oxidation reaction is also compatible with labile *N,O*-acetals.^{347,348} Most of the transformations probed have employed enantiomerically pure compounds, thus demonstrating that the oxidation protocol is extremely useful in asymmetric synthesis.

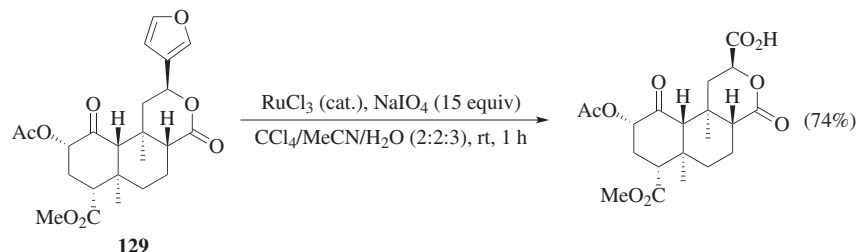
Oxidations of furans with ruthenium(III) chloride in the presence of sodium periodate is chemoselective with respect to other aromatic heterocyclic nuclei, such as the pyrazole ring,³⁴⁹ making the method applicable to the preparation of a variety of fluorinated pyrazole derivatives **128** (Scheme 107).^{350,351}



Scheme 107

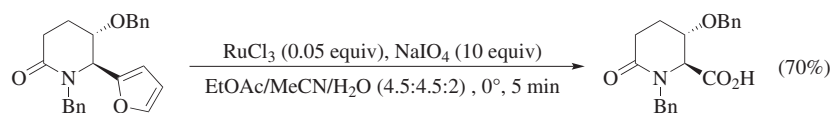
Similarly, 2-furylpyrazolines are transformed into 2-carboxypyrazolines using this oxidant. In these cases, while the reaction conditions are tolerated by *N*-benzoyl groups, the *N*-trifluoroacetyl group is lost during the oxidation reaction.³⁵²

Oxidation of the furan ring to a carboxylic acid functionality also takes place with 3-substituted furans. For example, salvinorin (**129**), isolated from *S. divinorum*,³⁵³ is readily oxidized to the corresponding carboxylic acid in 74% yield (Scheme 108).²³³



Scheme 108

Although a 2:2:3 carbon tetrachloride/acetonitrile/water mixture is commonly used as the solvent for ruthenium tetroxide oxidations of furans, the reaction can also be successfully carried out in other solvents. For example, a combination of 5 mol % of ruthenium(III) chloride in 1:1 acetonitrile/water can be used for this purpose.³⁵⁴ Although replacement of carbon tetrachloride by dichloromethane increases reaction times up to 2 hours,³⁴² high yields are obtained.³⁵⁵ A 1:1:1 acetonitrile/dichloromethane/water mixture has been employed in efficient (up to 90%) oxidations of 2-furan derivatives containing spiroketal units.^{356,357} Other solvent combinations can be employed for this process, as exemplified by oxidation of the sugar-containing *N*-sulfonyl furfurylamines in 1:0.04:0.7 water/dichloromethane/acetonitrile,³⁵⁸ but reaction times up to 1.5 h are needed for oxidations that are carried out in 2:2:3 acetonitrile/ethyl acetate/water at room temperature.³⁴⁸ In contrast, in 4.5:4.5:2 acetonitrile/ethyl acetate/water the same reaction only requires 5 min at 0° for completion (Scheme 109).³⁵⁹

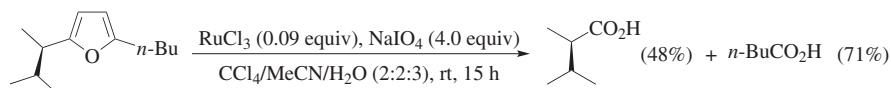


Scheme 109

High yields are also observed in ruthenium tetroxide promoted furan oxidations carried out in a biphasic system comprised of 1:1 ethyl acetate/water. These conditions, which make the reactions slightly exothermic, can be applied to the oxidation of 2,3-disubstituted furans.³⁶⁰ The reaction is efficient when different ratios of the solvents are employed (for example, from 3:1:4 to 0:1:1 hexane/ethyl acetate/water and in 2:2:3 carbon tetrachloride/methanol/water). Even though ideal results are obtained when these reactions are run in the most versatile solvent system comprised of 1:3:4 hexane/ethyl acetate/water, substantial variations are observed for different substrates. As a consequence, no one set of optimized conditions can be prescribed for this process.

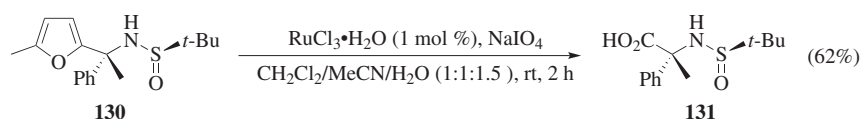
Oxidations of 2,5-disubstituted furans with catalytic amounts of ruthenium(III) chloride in the presence of an excess of sodium periodate afford the corresponding carboxylic acids in which one of the side-chains is lost.³⁵⁴ When the C2 and C5

positions are occupied by similar alkyl chains, mixtures of products are produced (Scheme 110).³⁶¹ For example, with 2-methyl-5-substituted furans, the carboxylic acid is obtained along with acetic acid.



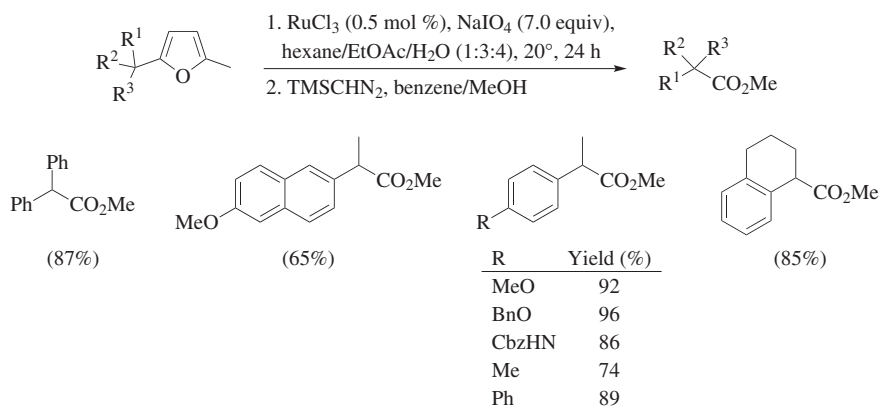
Scheme 110

Oxidation of 5-methyl-*N*-sulfonyl furfurylamine **130** utilizing this oxidant leads to formation of the *N*-sulfinyl amino acid **131** in 62–69% yield (Scheme 111).³⁴² Similarly, 5-(methoxycarbonyl)-*N*-acetyl furfurylamines provide *N*-acetyl- α -amino acids in good yields.³⁶²



Scheme 111

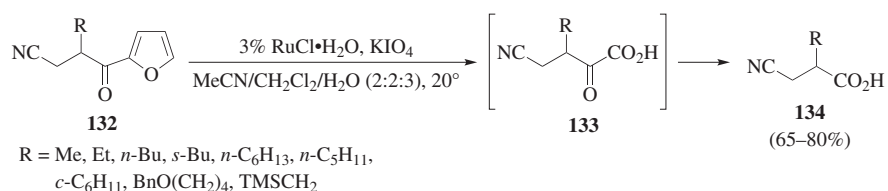
The regioselective nature of oxidations of 2-arylmethyl-5-methylfurans has been explored in detailed studies probing the effects of solvents and number of equivalents of sodium periodate. In 1:3:4 hexane/ethyl acetate/water with 0.5 mol % of ruthenium(III) chloride and 7.0 equivalents of sodium periodate, the furan ring in the 2,5-disubstituted substrates is oxidized selectively on the side not containing phenyl or naphthyl substituents (Scheme 112).³⁶³



Scheme 112

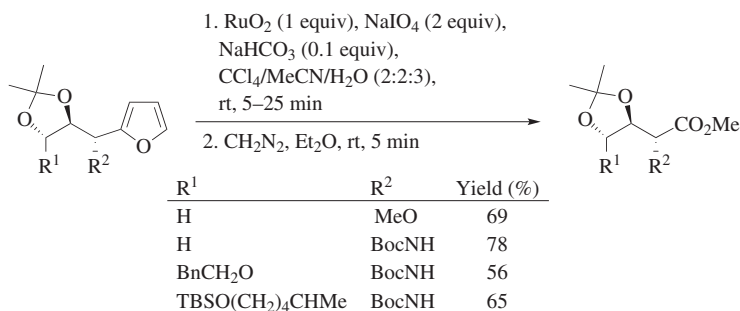
In addition, enantiomerically pure 2-methoxyfurans are oxidized without loss of enantiomeric purity.³⁶⁴ Sodium periodate can be replaced as the primary oxidant

in this process by periodic acid. Under the latter conditions (RuCl_3 , H_5IO_6 , 2:2:3 carbon tetrachloride/acetonitrile/water, 10 minutes, room temperature) *N*-benzyl and *N*-benzyloxycarbonyl protecting groups are not affected.³⁶⁵ An interesting decarboxylative oxidation reaction takes place when the furanyl ketones **132** are oxidized with ruthenium(III) chloride in the presence of potassium periodate. In this process, the initially formed pyruvic acid derivatives **133** undergo secondary oxidative decarboxylation to form acids **134** (Scheme 113).³⁶⁶



Scheme 113

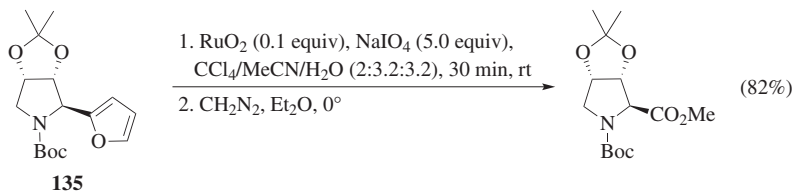
Ruthenium tetroxide can also be generated using ruthenium(IV) oxide and sodium periodate. No particular differences are observed in efficiencies when reactions are promoted using ruthenium(III) chloride or ruthenium(IV) oxide as the source of ruthenium, although the latter reagent has traditionally been utilized in carbohydrate chemistry^{367–370} where a variety of protecting groups are employed. Indeed, oxidations using either ruthenium(IV) oxide or ruthenium(III) chloride are fully compatible with silyl,³⁶⁸ benzyl, and allyl ethers,³⁶⁹ and MOM acetals.³⁷¹ Isopropylidene acetals also tolerate typical oxidation conditions as do both oxygen³⁷² and nitrogen³⁷³ functionalities (Scheme 114),^{370,374,375} and *N,O*-acetals.³⁷⁶



Scheme 114

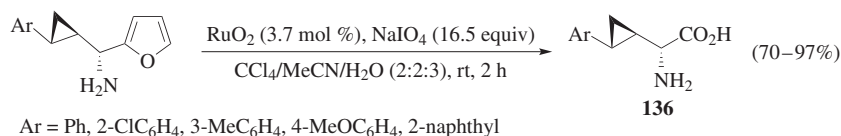
As with ruthenium(III) chloride, oxidative cleavage employing ruthenium(IV) oxide can be performed in the presence of amino groups, monoprotected as carbamates,^{373–375} tosylamines,^{376,377} and benzamides,^{378,379} as employed in an expeditious synthesis of amino acids from furfurylamines.³⁸⁰ *N*-Hydroxy amino

acids are also prepared using this method because the N–O bond is not affected by the reaction conditions.³⁸¹ Cyclic amino acids can be prepared from the corresponding 5-furyl-*N*-Boc-2-pyrrolidinones³⁸² and 2-furyl-*N*-Boc-2-pyrrolidines **135** (Scheme 115).³⁸³



Scheme 115

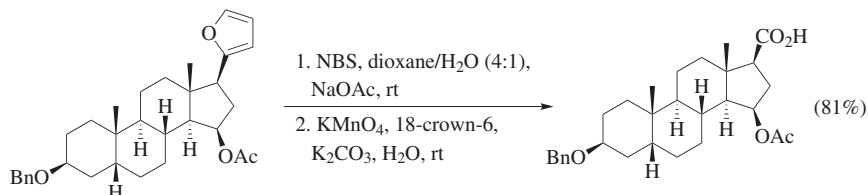
The use of ruthenium(IV) oxide enables chemoselective oxidations of the furan ring in the presence of other aromatic rings.³⁸⁴ Notably, free amino groups can sometimes survive the reaction conditions as exemplified by the formation of amino acids **136** in high yields (Scheme 116).³⁸⁵



Scheme 116

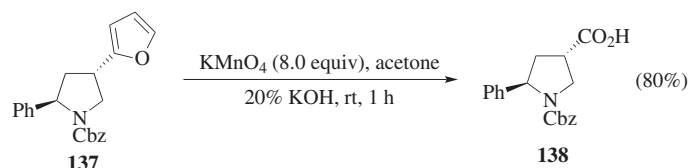
In summary, oxidative cleavage reactions of furans with ruthenium tetroxide does not depend on the method of generation of the oxidant, and either ruthenium(III) chloride or ruthenium(IV) oxide can be used for this purpose. In addition, several solvent systems can be employed, lending flexibility when substrate solubility is an issue. No matter what reaction conditions are used, the process displays excellent compatibility with a great variety of oxygen and nitrogen protecting groups, making this a method of high synthetic utility.

Oxidations with Potassium Permanganate. Potassium permanganate is an alternative oxidant that can be employed in furan ring cleavage reactions. This oxidant is generally useful for the oxidation of heterocyclic compounds.³⁸⁶ The combination of NBS in dioxane/water followed by in situ oxidation with a catalytic amount of potassium permanganate in the presence of an excess of sodium periodate has been employed to transform a steroidal furan derivative into the corresponding carboxylic acid (Scheme 117).³⁸⁷



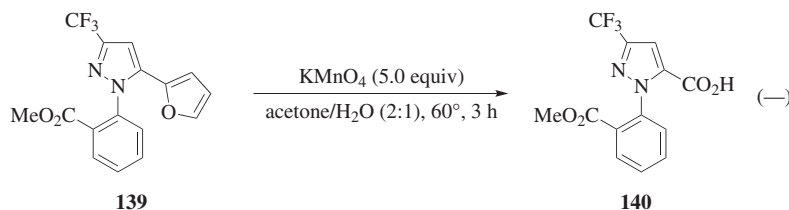
Scheme 117

Arylfurans are converted into benzoic acid derivatives by the action of potassium permanganate in *tert*-butanol/water at reflux for several hours.³⁸⁸ Milder conditions (room temperature, 1 hour) are sufficient for converting enantiomerically pure *N*-Cbz-2-phenyl-4-(2-furyl)pyrrolidine (**137**) into the corresponding β -proline derivative **138** (Scheme 118).³⁸⁹



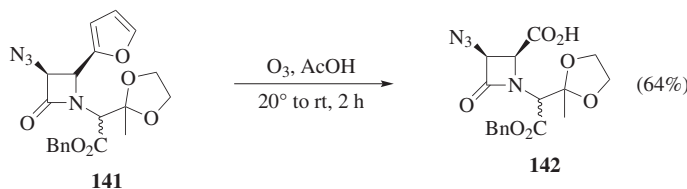
Scheme 118

The oxidizing power of potassium permanganate prevents its use with substrates bearing sensitive functional groups even when catalytic amounts of oxidant and controlled reaction conditions are utilized. Nevertheless, this oxidant is useful in the oxidation of 3-(2-furyl)pyrazolyl derivatives of biological importance. For example, an excess of potassium permanganate promotes oxidation of pyrazole **139** to the corresponding carboxylic acid **140** in high yield (Scheme 119).³⁹⁰ Finally, potassium permanganate is compatible with aromatic rings containing different functional groups such as azides,³⁹¹ nitrile,³⁹² and ester moieties.³⁹³



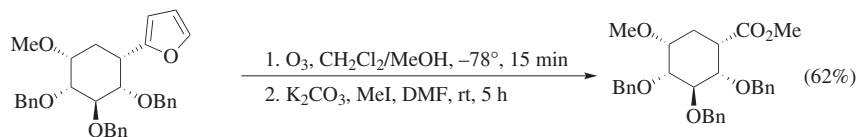
Scheme 119

Oxidations with Ozone. The process of oxidizing furans to give carboxylic acids by the action of ozone has been known for more than 50 years.^{100,101} No systematic studies have been performed on this process but numerous examples illustrate its high synthetic utility. For example, oxidation of the highly functionalized β -lactam **141** to produce carboxylic acid **142** takes place smoothly by treatment with a stream of ozone in acetic acid at room temperature (Scheme 120).³⁹⁴



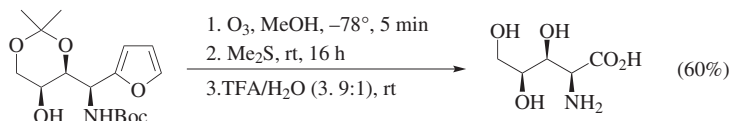
Scheme 120

Ozone-induced oxidations can be carried out in anhydrous methanol³⁹⁵ at -30° and in dichloromethane/methanol at -78° . The carboxylic acid is isolated by simply warming the reaction mixture to room temperature and evaporating the solvent. In general, the methyl ester is formed in situ by treatment with diazomethane, trimethylsilyldiazomethane, or methyl iodide in a basic medium (Scheme 121).³⁹⁶ The mildness of these reaction conditions, including a simple work-up procedure, has contributed to the popularity of furan oxidations through ozonolysis in carbohydrate chemistry.³⁹⁷ A variety of protecting groups (acetals, benzyl, esters, ethers, etc.) may be present³⁹⁸ in the substrate without being affected by the ozonolysis conditions.³⁹⁹



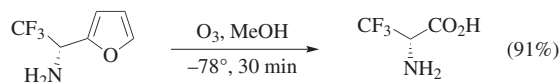
Scheme 121

In a similar fashion, warming the reaction mixture to room temperature after ozonolysis at -78° can be followed by treatment with triphenylphosphine^{400,401} or dimethyl sulfide¹¹¹ to promote decomposition of the ozonide. Unprotected hydroxyl groups are preserved under these reaction conditions. Several stereoisomers of 4-hydroxyleucine are obtained from the corresponding *N*-Boc-1-(2-furyl)-1,3-amino alcohols using this technique.⁴⁰² The ozonolysis of the furan ring is also possible in the presence of free amino and hydroxyl groups,^{403,404} although in one example only a 30% yield was obtained.⁴⁰⁵ Ozone oxidations can also be carried out on substrates possessing labile 1,3-acetonides.^{400,406} This procedure is particularly convenient when other acid-labile groups are present because it is possible to carry out an in situ deprotection step subsequent to the oxidation (Scheme 122).⁴⁰⁷



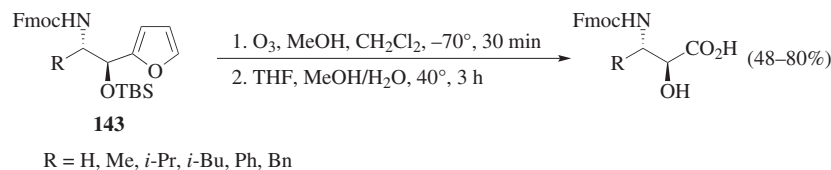
Scheme 122

Ozonolysis of furans in dichloromethane at low temperature permits preservation of the integrity of amino protecting groups, such as *N*-Boc,^{408,409} *N*-Cbz,⁴¹⁰ *N*-Fmoc,^{411,412} *N*-benzoyl,³⁷⁹ cyclic carbamates,⁴¹³ and lactams.⁴¹⁴ Interestingly, this oxidation is also compatible with the presence of free amino groups, as demonstrated by the process shown in Scheme 123.^{385,415}



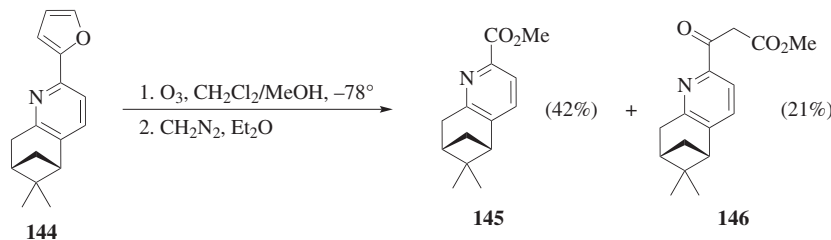
Scheme 123

On the other hand, partial cleavage of a *tert*-butyldimethylsilyl group is observed in the ozonolysis of **143** caused by migration of the silyl group to the newly formed carboxylic acid moiety.⁴¹¹ For this reason, a one-pot deprotection is carried out to yield *N*-protected α -hydroxy- β -amino acids in high yields (Scheme 124).⁴¹²



Scheme 124

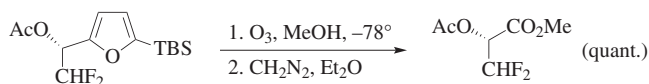
Ozone-promoted oxidation of 2-furylpyridine **144** forms nicotinic acid **145**, although this process is accompanied by formation of the incompletely oxidized by-product **146** (Scheme 125).⁴¹⁶



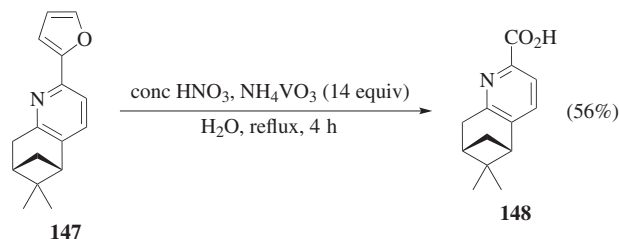
Scheme 125

$$\text{Structure 1} \xrightarrow[\text{2. H}_2\text{O}_2, \text{CH}_2\text{Cl}_2/\text{MeOH,}]{\text{1. O}_3, \text{CH}_2\text{Cl}_2/\text{MeOH, } -78^\circ} \text{Structure 2} \quad (77\%)$$

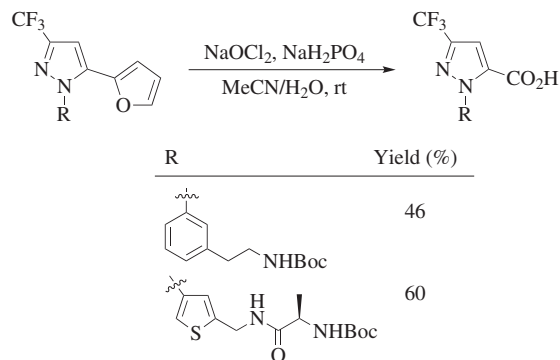
Ozonolysis reactions of chiral furans containing C2 silyl groups take place with complete preservation of enantiomeric purity (Scheme 127).⁴²⁰ In contrast, whereas 2-acyl furans yield mixtures of the expected keto acid and the corresponding decarboxylated derivatives,⁴²¹ 2-methyl-5-(trifluoromethylcarbonyl)furan reacts with ozone to form the α -keto ester in good yield.⁴²²



Oxidations with Other Oxidants. Oxidation reactions of furans to generate carboxylic acids can be performed using photooxidation in methanol, but low yields are common in these reactions.³⁰⁷ To avoid this problem, oxidations of the substrates exemplified by **147** can be carried out using nitric acid in the presence of ammonium vanadate (Scheme 128).⁴²³ Under these conditions, carboxylic acid **148** is formed as the only product in 56% yield.



2-Pyrazolylfuran derivatives have been oxidized using sodium chlorite under conditions that do not affect several functional groups, including benzene⁴²⁴ and heteroaromatic ring systems like thiophenes (Scheme 129).⁴²⁵

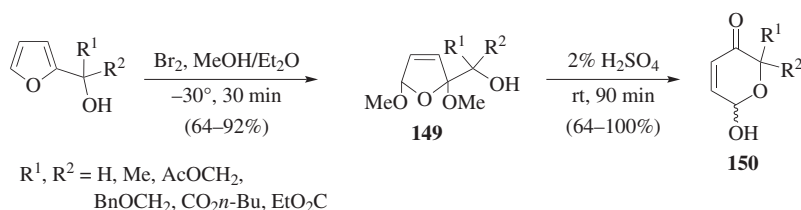


Scheme 129

The Achmatowicz Reaction

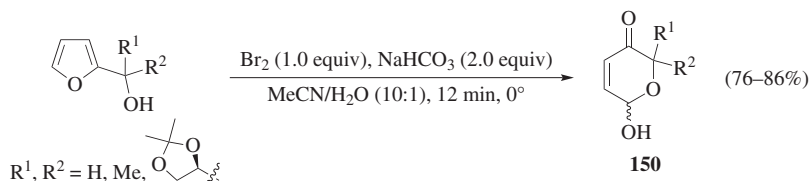
The Achmatowicz reaction, the oxidative conversion of furfuryl alcohols to 6-hydroxy-2H-pyran-2-ones, can be achieved with substrates bearing multiple substituents on side chains and the furan ring. Thus, the synthetic utility of this method is determined by availability of methods for oxidizing the furan ring. In this process, oxidation generates the corresponding 1,4-dicarbonyl compound that undergoes in situ cyclization involving the hydroxy group at the α -position.

Bromine in Methanol. The original procedure reported by Achmatowicz³¹ involves oxidation of a furan derivative using bromine in methanol to give a dimethoxy dihydrofuran **149**. Acid hydrolysis of **149** then produces the rearranged 2H-pyran-2-one **150** (Scheme 130).^{426,427}



Scheme 130

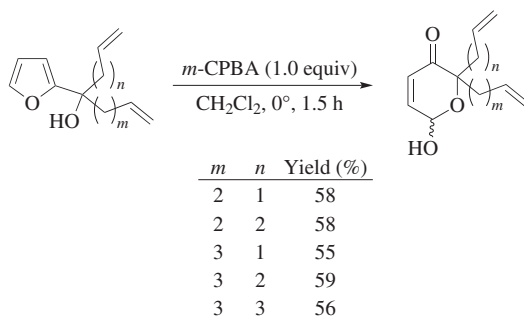
The reaction involving bromine also proceeds at -78° and the hydrolysis can be performed using 10% aqueous sulfuric acid at room temperature.⁴²⁸ The overall transformation can be accomplished in one pot by treating the furfuryl alcohol with a stoichiometric amount of bromine in a solvent containing a few equivalents of water (Scheme 131).⁴²⁹



Scheme 131

Solvents have little influence on the reaction and, as a result, both protic (alcohols and carboxylic acids) and aprotic (diethyl ether, dioxane, acetone, acetonitrile, DMF) solvents can be used. In all cases, reactions take place at 0° and are complete in less than 2 minutes, typically generating products in essentially quantitative yields. When tetrahydrofuran/water serves as the solvent and reactions are performed at 5°, the yields are lower.⁴³⁰ Moreover, the resulting epimeric mixtures of products can be silylated in situ using *tert*-butyldimethylsilyl chloride to form a chromatographically separable mixture (3:1) of α - and β -epimers at C2. The undesired β -epimer can be readily separated and recycled by sequential deprotection/protection to give the α -epimer in 67% overall yield after two recycles.⁴³¹

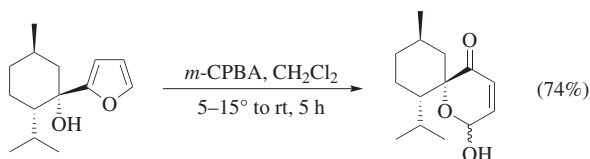
***m*-Chloroperoxybenzoic Acid.** Oxidations of furfuryl alcohols with peroxyacetic acid or *m*-CPBA produce the corresponding 6-hydroxy-2*H*-pyran-3(6*H*)-ones in one step and without the need for a secondary hydrolysis step.^{432,433} This reaction is general for a variety of furans containing alkyl and aryl substituents as side chains.^{434–437} In a similar fashion, substrates with steroid side chains are smoothly oxidized by *m*-CPBA⁴³⁸ utilizing several reaction protocols.^{439,440} With simple furfuryl alcohols, reactions are nearly always carried out in dichloromethane at 0°, are complete within 1 hour, and produce products in high yields as mixtures of isomers.^{441–445} Highly substituted substrates require reaction times of up to 12 hours.⁴⁴⁶ The oxidation procedure is compatible with substrates containing double bonds (Scheme 132),^{310,447,448} and a furan substrate in which an epoxide is present reacts to give the product in 94% yield.⁴⁴⁹ High yields also attend reactions of substrates containing several protecting groups such as TBS and benzyl ethers.^{444,450}



Scheme 132

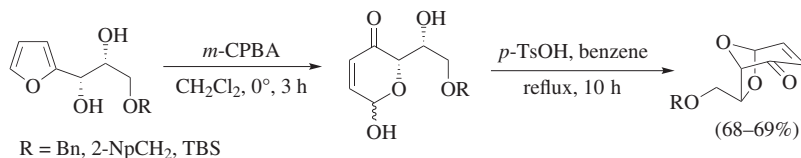
β -Phosphinoyl furfuryl alcohols are also oxidized in high⁴⁵¹ to moderate chemical yields.⁴⁵²

In general, substitution on the furan ring does not affect the yield of the reaction. In addition, the process takes place smoothly with more diverse substrates to generate highly substituted 2*H*-pyran-3(6*H*)-ones.^{442,453} Cyclic tertiary furyl carbinols can also be easily oxidized using *m*-CPBA to form spiro derivatives (Scheme 133).^{452,454,455}



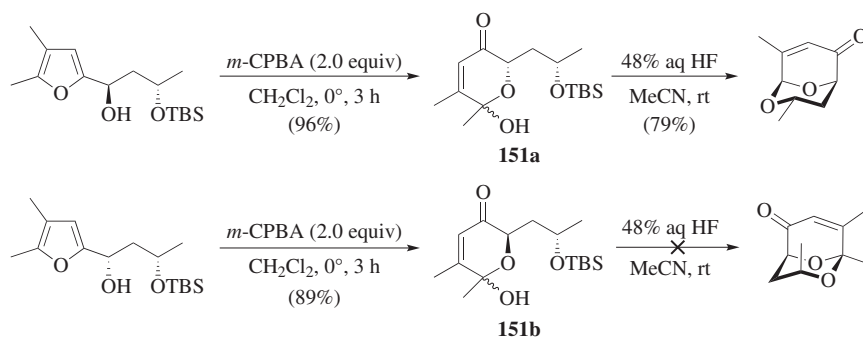
Scheme 133

With furans possessing a hydroxyl group on a side chain, it is possible to induce formation of a bicyclic product by prolonged acid treatment following the oxidation step (Scheme 134).^{456,457} In reactions of enantiomerically pure substrates that generate new stereocenters, high levels of diastereoselectivity are observed.^{458,459} 4,5-Disubstituted furans give products such as **151a** and **b**. Only **151a**, derived from the corresponding *anti* adduct, forms the corresponding hemiacetal. No reaction is observed for **151b** as a consequence of unfavorable 1,3-diaxial interactions in the final product (Scheme 135).⁴⁵³



R = Bn, 2-NpCH₂, TBS

Scheme 134

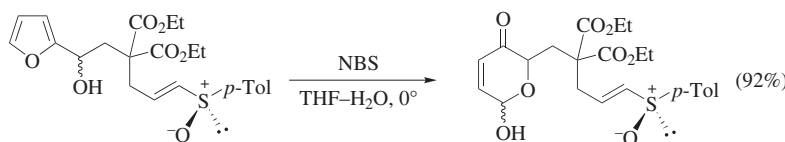


151a

151b

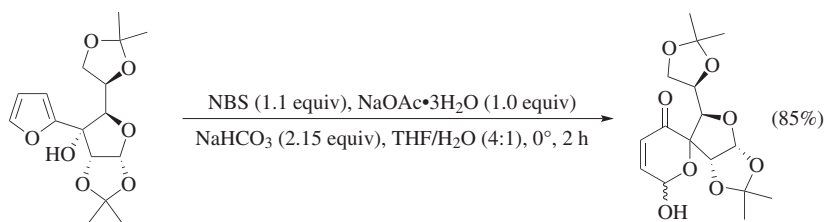
Scheme 135

***N*-Bromosuccinimide.** Furfuryl alcohols react rapidly with *N*-bromosuccinimide in the presence of water to produce 6-hydroxy-2*H*-pyran-3(6*H*)-ones in high yields.⁴³⁵ *N*-Bromosuccinimide in 4:1 tetrahydrofuran/water effects oxidations of a variety of furfuryl alcohols. The typical reaction conditions employed for these processes⁴⁶⁰ are compatible with hydroxyl protecting groups including acetals,^{461,462} silyl ethers,^{463–469} and esters,^{470–472} as well as typical carbamates^{473–475} that are used as amine protecting groups (Scheme 136).



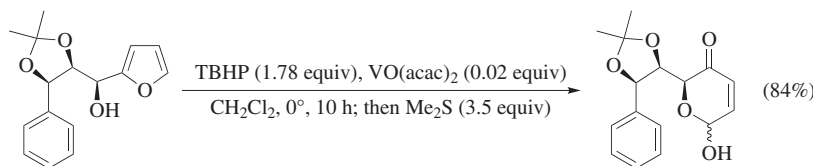
Scheme 136

Double^{476–478} and triple⁴⁷⁹ bonds are also compatible with furan oxidation using *N*-bromosuccinimide. Moreover, the method has been applied to solid-phase synthesis of compound libraries.^{151,480} In one case, selective acylation of the resulting mixture of hemiacetals formed at low (-78°) temperature results in a dr >20:1.⁴⁸¹ NBS oxidation of a furanyl sugar at room temperature gives a 1:1 mixture of anomers. Spiro compounds can also be produced using this process if there is an appropriate substituent on the side chain⁴⁸² or on the furan ring⁴⁸³ (Scheme 137).



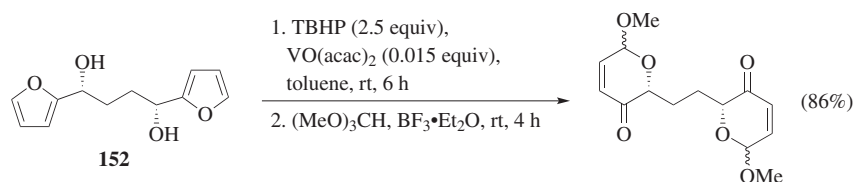
Scheme 137

***tert*-Butyl Hydroperoxide.** *tert*-Butyl hydroperoxide (TBHP) and a catalytic amount of vanadyl diacetylacetonate serve as another oxidizing system for transforming furfuryl alcohols into 6-hydroxy-2*H*-pyran-3(6*H*)-ones.^{484,485} A proposed mechanism for this process involves initial epoxidation of a double bond of the furan ring followed by vanadium-promoted epoxide ring opening and rearrangement to form the final products via a *cis* 1,4-dicarbonyl intermediate.⁴⁸⁶ These conditions enable oxidation of a furan ring in the presence of a labile acetonide group (Scheme 138).^{487–493} Several types of furan derivatives, including aliphatic and aromatic derivatives, can be effectively oxidized using these conditions.^{494–499}



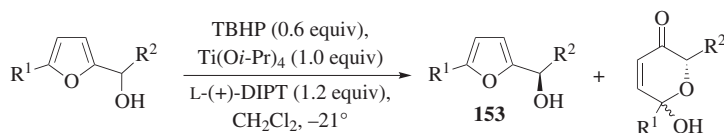
Scheme 138

When other oxidizable groups are present in the substrate, the use of lower temperatures results in a greater degree of chemoselectivity.^{10,500–502} In addition, under the reaction conditions, double bonds,^{503–506} including dienes⁵⁰⁷ and allenes, remain unreactive.⁵⁰⁸ Implementation of these reaction conditions along with the inclusion of acetic anhydride in the reaction mixture enables the conversion of furan substrates to mixtures of 6-acetoxy epimers.⁵⁰⁹ Similarly, in situ methylation with methyl orthoformate in the presence of boron trifluoride etherate can be used to generate 6-methoxy derivatives.^{40,510} The procedure has been applied in two-directional syntheses starting with bis-furan derivatives such as **152** (Scheme 139).^{511,512}



Scheme 139

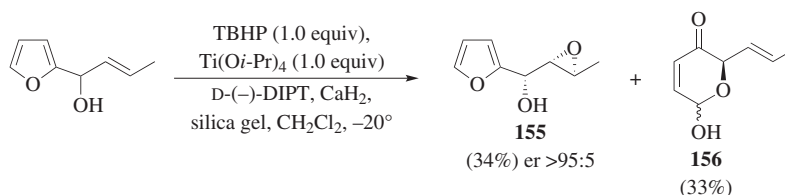
Replacement of the vanadium catalyst with 10 mol % of titanium isopropoxide and 15 mol % of D- or L-tartrate enables catalytic, asymmetric, kinetic resolution of racemic furfuryl alcohols.⁵¹³ Various enantiomerically enriched 2-furlylcarbinols **153** have been prepared in addition to 6-hydroxy-2*H*-pyran-2-ones **154** using stoichiometric amounts of both titanium isopropoxide and L-(+)-diisopropyl tartrate (DIPT).⁵¹⁴ Under these conditions excellent enantioselectivities are observed except for the reaction of the *tert*-butyl derivative (Scheme 140).



R ¹	R ²	Time (h)	153 Yield (%)	153 er	154 Yield (%)
H	Me	24	32	>95:5	53
H	<i>n</i> -C ₅ H ₁₁	25	42	>95:5	53
H	<i>i</i> -Pr	25	39	>95:5	55
H	<i>t</i> -Bu	40	41	58:42	58
H	Ph	40	42	>99:1	44
Me	<i>n</i> -C ₅ H ₁₁	6	45	>95:5	55

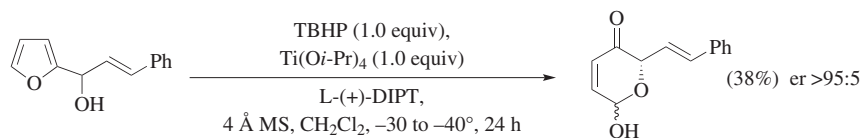
Scheme 140

When an excess of *tert*-butyl hydroperoxide is employed, higher product yields are obtained by carrying out the reaction in the presence of 5–10 mol % of calcium hydride and 10–15 mol % of silica gel.⁵¹⁵ The kinetic resolution process is applicable to substrates containing double bonds since only the furan ring is oxidized.^{516,517} However, it is possible to adjust the reaction conditions so that both resolution and epoxidation of the double bond occur. For example, whereas oxidation of a furfuryl alcohol with 0.5 equivalents of *tert*-butyl hydroperoxide produces only a 4% yield of the epoxidation product **155**, using 1.0 equivalent of oxidant increases the yield of **155** to 34% without affecting the degree of enantioselectivity (Scheme 141).⁵¹⁸



Scheme 141

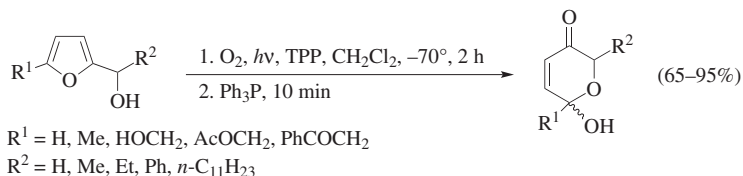
Kinetic resolution based synthesis of enantiomerically pure 2-alkenyl-6-hydroxypyran-3-ones such as **156** can be carried out under reaction conditions in which the double bond is not altered, followed by a second conventional oxidation (*tert*-butylhydroperoxide/vanadyl acetylacetonate) of the resolved alkenyl furfuryl alcohol.^{476,519} High levels of enantioselectivity are realized using 20 mol % of titanium isopropoxide/L-(+)-diisopropyl tartrate, although under these conditions only the resolved furfuryl alcohol is recovered from the reaction mixture.⁵²⁰ In contrast, catalytic conditions (10 mol % of titanium isopropoxide and 15 mol % of L-(-)-diisopropyl tartrate) at -40° enable isolation of the enantiomerically enriched (er 97:3) 6-hydroxypyran-3-one in moderate yield (31%) as a 69:31 mixture of epimers.⁵²¹ These conditions are applicable to sequential kinetic resolution of difuryl derivatives⁵²² and desymmetrization of *meso* compounds.⁵²³ By executing the reaction at -40° in the presence of molecular sieves, alkenyl pyranones are obtained with high levels of enantioselectivity (Scheme 142).⁵²⁴



Scheme 142

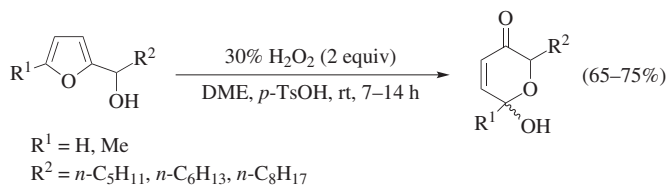
Photooxygenation. The photooxygenation reactions of alkenyl furfuryl alcohols, which produce 6-hydroxypyran-3-ones in high yields,⁵²⁵ are generally carried out

using either rose bengal, TPP, or methylene blue as sensitizers (Scheme 143).⁵²⁶ Irradiation is typically followed by treatment of the product mixture with an excess of triphenylphosphine or dimethyl sulfide.^{527,528} These reaction conditions are also compatible with the presence of double bonds in the molecule.⁵²⁹



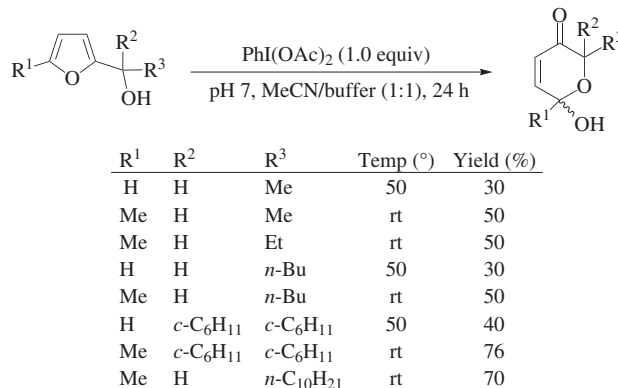
Scheme 143

Hydrogen Peroxide. Treatment of furfuryl alcohols with hydrogen peroxide in the presence of *p*-toluenesulfonic acid (PTSA) affords furfuryl hydroperoxides, which in the presence of excess oxidant (2.0 equivalents) give rise to 2,6-disubstituted 6-hydroxy-2*H*-pyran-3(6*H*)-ones (Scheme 144).⁵³⁰ The formation of these products results from two sequential oxidations of the starting materials.⁵³¹ On the other hand, by using hydrogen peroxide in the presence of titanium silicalite 1 (TS-1) in acetonitrile as a solvent, 6-hydroxy-3-pyranones are generated through the intermediacy of dicarbonyl derivatives formed via the conventional Achmatowicz reaction mechanism.⁴⁸ Oxidations of 5-methyl-substituted furfuryl alcohols proceed in low yields (20%) in marked contrast to oxidations of 5-unsubstituted compounds (80–93%).



Scheme 144

Other Oxidants. The Achmatowicz reaction of furylcarbinols promoted by dimethyldioxirane is compatible with the presence of double bonds.⁵³² The use of hypervalent iodine reagents can also be used to transform these substances into 6-hydroxy-3-pyranones, as exemplified by the iodosobenzene diacetate (IBDA)-induced formation of the hydroxy-2*H*-pyran-3(6*H*)-ones shown in Scheme 145.⁵³³



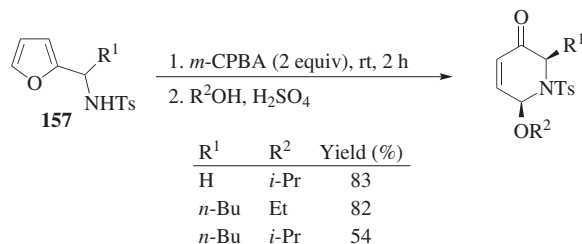
Scheme 145

Other oxidants capable of promoting formation of 6-hydroxy-3-pyranones from furfuryl alcohols include pyridinium chlorochromate (PCC)⁵³⁴ and sodium chlorite.⁵³⁵ Electrochemical oxidation is also effective for this purpose.⁵³⁶

The Aza-Achmatowicz Reaction

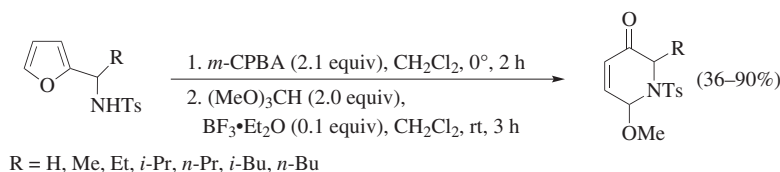
Oxidation of furfuryl amines affords the corresponding 6-hydroxy-1,2-dihydropyridin-3(6*H*)-ones, provided that the nitrogen is properly substituted. Since the resulting heterocycle contains a potentially labile hemiaminal group, the presence of electron-withdrawing groups on nitrogen is needed to increase stability of the dihydropyridinone ring system. As a consequence, the so-called aza-Achmatowicz reaction³³ is limited to furfuryl amides, sulfonamides, and carbamates. This condition does not limit the synthetic utility of the process, whose products are widely applicable as building blocks in the preparation of a great variety of nitrogen-containing compounds. Solid-phase techniques have also been applied for carrying out this reaction.⁵³⁷

***m*-Chloroperoxybenzoic Acid.** Treatment of *N*-tosyl furfurylamines **157** with *m*-CPBA in dichloromethane for 2 hours at room temperature yields 2,6-dihydro-1*H*-pyridin-3-ones as single diastereomers.⁵³⁸ These substances are often unstable and therefore are treated with an alcohol in the presence of a catalytic amount of sulfuric acid (Scheme 146)⁵³⁸ or cerium(IV) salts⁵³⁹ to give the corresponding alkoxy derivatives.



Scheme 146

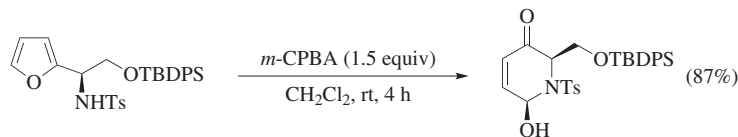
The hydroxyl groups in these products can be converted into ethers by treatment with methyl^{540,541} or ethyl^{542,543} orthoformate in the presence of boron trifluoride etherate (Scheme 147). These reaction conditions are fully compatible with the presence of other protecting groups, including silyl ethers,^{541,544,545} esters,⁵⁴⁶ and acetals.⁵⁴⁷ An alternative to the protection of the hydroxyl group is an in situ oxidation to form the corresponding lactams.⁴³⁷



Scheme 147

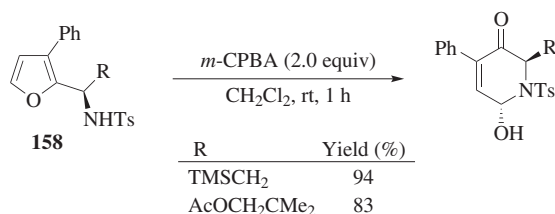
The stabilities of 6-hydroxy-2,6-dihydro-1*H*-pyridin-3-ones are strongly substituent dependent. Some of these substances are sufficiently stable to be purified using column chromatography on silica gel,⁵⁴⁸ and to be stored at room temperature.⁵⁴⁹ When alkyl substituents are present at C2 of the furan, in situ protection of the hydroxy group is advisable,^{550–552} although these compounds can be purified by using silica gel pretreated with a phosphate buffer.⁴⁰⁵

Trans isomers of 6-methoxy-2-methyl-1-tosyl-1,6-dihydro-2*H*-pyridin-3-ones are formed preferentially in these processes, but the *cis* isomers can be generated as a consequence of the A^{1,3}-strain involving the tosyl group, which forces the methoxy and the methyl groups to adopt pseudoaxial orientations.^{553,554} Indeed, even in products containing bulkier groups on the ring, such as a dioxolane ring⁵⁵⁵ or a *tert*-butyldiphenylsiloxy group,⁵⁵⁶ *cis* isomers predominate (Scheme 148).



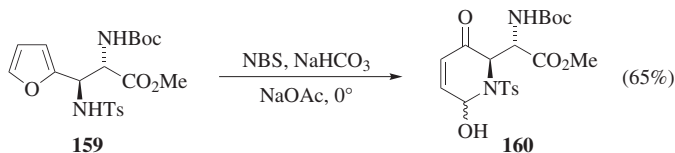
Scheme 148

Thus, reactions of enantiomerically pure phenyl furfuryl-*N*-tosylamines **158** produce 4-phenyl *trans* isomers in very high yields (Scheme 149).⁵⁵⁷



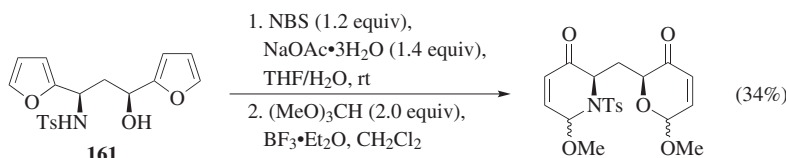
Scheme 149

***N*-Bromosuccinimide.** Treatment of racemic *N*-tosyl-furylglycinol with *N*-bromosuccinimide at 0° for 4 hours yields 83% of the oxidized product *trans*-*N*-tosyl-2-hydroxymethyl-6-hydroxy-1,2-dihydropyridin-3(6*H*)-one.⁵⁵⁸ A mixture of *N*-bromosuccinimide, sodium bicarbonate, and sodium acetate has been employed to oxidize diamino acid **159** to produce the dihydropyridone **160** in 65% yield (Scheme 150).⁵⁵⁹ Actually, a 5:1 mixture of **160** and its side chain epimer is obtained, indicating that some epimerization of the α-amino group takes place in this process. However, in a manner that is similar to that described above, the *cis* isomers of 6-methoxy-2-methyl-1-tosyl-1,6-dihydro-2*H*-pyridin-3-ones are formed as a consequence of the A^{1,3}-strain of the tosyl group, which forces the methoxy and methyl groups to adopt pseudoaxial orientations.^{553,554} Even with bulkier groups like a dioxolane ring⁵⁵⁵ or a *tert*-butyldiphenylsiloxy group,⁵⁵⁶ the formation of the *cis* isomers predominates. In addition to *N*-tosyl furfurylamines, *N*-benzyloxycarbonyl derivatives can be used as substrates in these reactions,⁵⁶⁰ which produce mixtures of *cis* and *trans* isomers even when bulky substituents are present.⁵⁶¹ If an excess of *N*-bromosuccinimide is used, further oxidation occurs to produce pyridines.¹⁵⁴



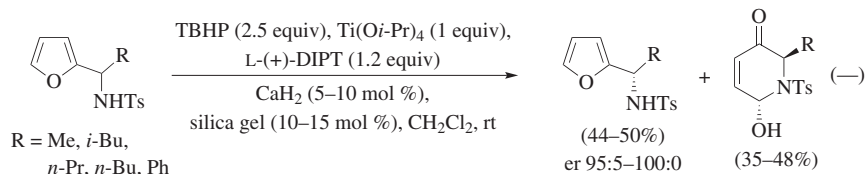
Scheme 150

As previously discussed (Scheme 147), in situ formation of the corresponding methoxy derivatives can take place by secondary reactions with trimethyl orthoformate in the presence of boron trifluoride etherate.⁵⁶² With the difurfuryl alcohol derivative **161**, *N*-bromosuccinimide promotes simultaneous Achmatowicz reactions on both furan moieties, which serves as a critical step in the synthesis of disaccharide mimetics (Scheme 151).⁵⁶³ The same transformation takes place with the corresponding *anti* isomer of **161**.



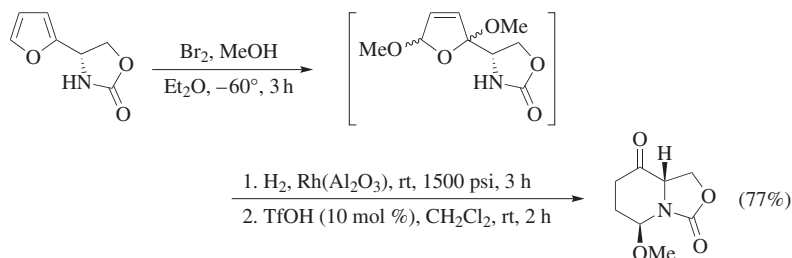
Scheme 151

***tert*-Butyl Hydroperoxide.** Oxidations of furfuryl alcohols using the modified Sharpless asymmetric epoxidation reagent can also be used for preparing enantiomerically enriched furfuryl amides by way of a kinetic resolution.⁵¹⁵ In general, up to three days are needed for the reaction to go to completion.⁵⁶⁴ With *N*-tosylfurfuryl amines, the (*S*) enantiomer is slower-reacting when L-(+)-diisopropyl tartrate is employed and, thus, (6*R*)-dihydropyridones are obtained in enantiomerically pure form (Scheme 152).⁵⁶⁵ Using the enantiomeric D-(+)-diisopropyl tartrate causes the (*R*)-enantiomer to be slower-reacting.⁵⁶⁶ The efficiency of this kinetic resolution process is not affected by the presence of isolated double bonds, which are not oxidized.⁴²



Scheme 152

Bromine in Methanol. A variety of furfuryl amines bearing sulfone or carbonyl groups on the nitrogen atom are oxidized to give dimethoxy dihydrofurans by the action of bromine in methanol. Cyclization of these compounds occurs to form 3-piperidinones under acidic conditions after catalytic hydrogenation of the (*Z*) double bond (Scheme 153).²⁴⁶ The procedure is applicable to cyclic substrates, furnishing 3,8-dioxoindolizidines^{567,568} and carbacephems precursors.³³

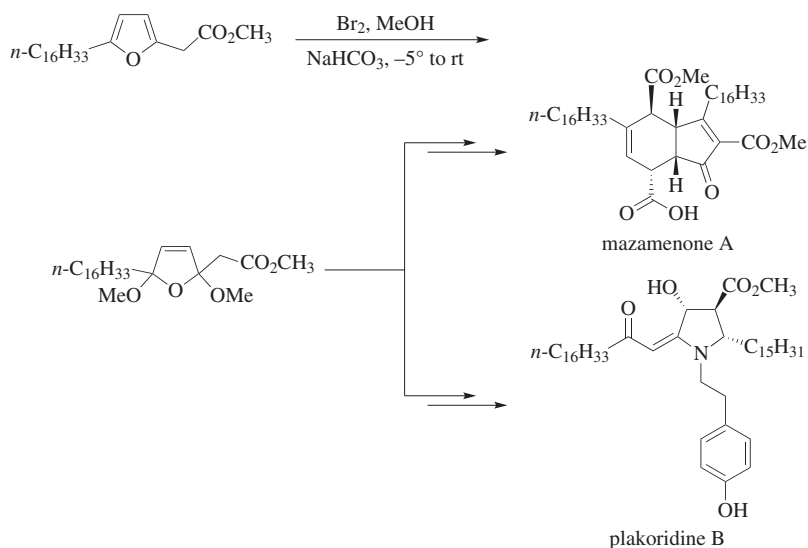


Scheme 153

APPLICATIONS TO SYNTHESIS

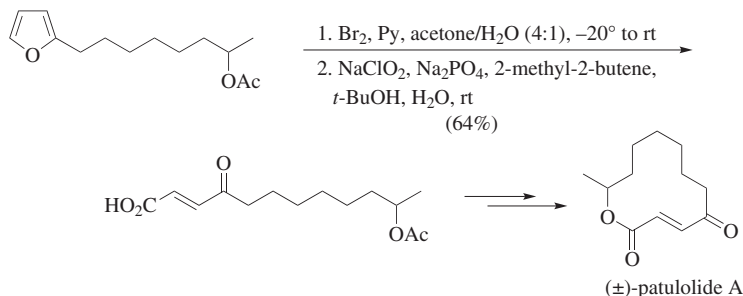
Synthesis of 1,4-Dioxo Compounds

The scope and synthetic potential of employing the furan ring as a C_4 synthon has been amply demonstrated in a number of synthetic studies. All of the possible transformations of this heterocycle into 1,4-dicarbonyl compounds have been employed in routes for the total synthesis of a variety of substances. For example, efficient routes using bromine in methanol oxidations have been developed to prepare a host of alkaloids²⁴⁸ and marine natural products of biological interest such as mazaminones^{251,252} and plakoridines^{229,230} (Scheme 154).



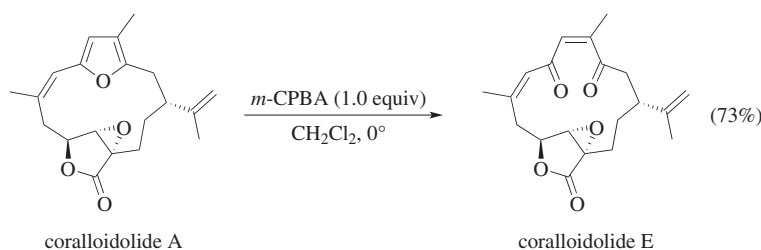
Scheme 154

Reactions of furans with bromine in other solvents have also been applied to the synthesis of the macrocyclic lactones tylonolide¹⁴² and patulolide (Scheme 155).¹⁸¹



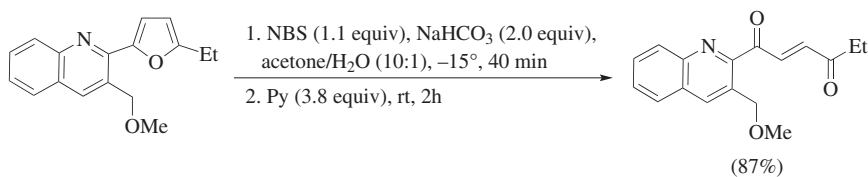
Scheme 155

Preparation of the latter target was also accomplished by employing a *m*-CPBA oxidation of a furan derivative.¹⁹⁷ Indeed, the use of *m*-CPBA has been extended to the synthesis of diverse targets such as aphidicolin,^{158,159} endesmanolides,¹⁹¹ and coralloidolide E (Scheme 156).¹⁵⁷



Scheme 156

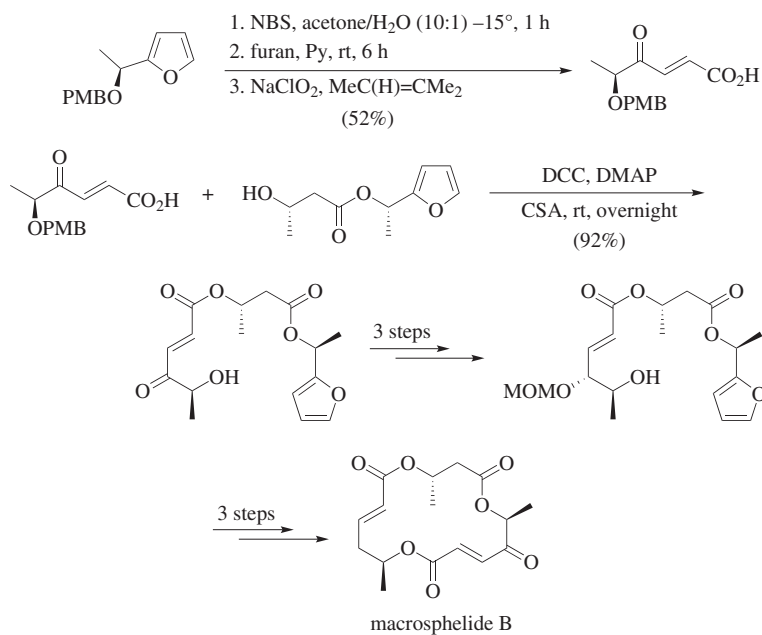
Conversions of 2,5-disubstituted furans into the corresponding dioxoalkenes by the action of *N*-bromosuccinimide in pyridine has been used to prepare precursors of the alkaloid nothapodytine (Scheme 157).¹⁵⁰



Scheme 157

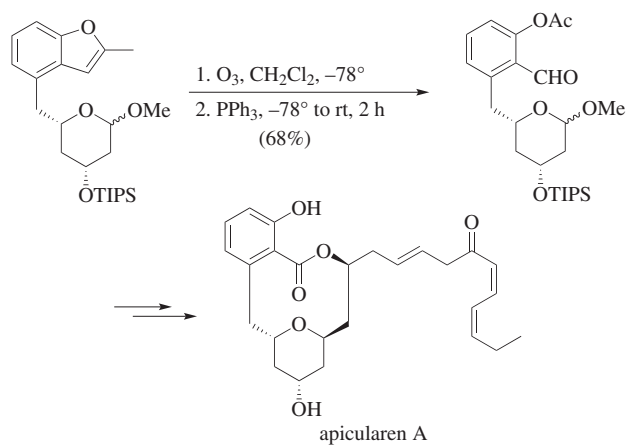
The convenient protocol for converting 2-substituted furans into 4-oxoalkenoic acids, involving oxidation with *N*-bromosuccinimide and further oxidation of the 4-oxoalkenal formed with sodium chlorite, has been applied to the synthesis of a variety of macrolides. The presence of several 4-oxoalkenoic acid moieties in these compounds makes the furan oxidation approach highly attractive. Among the macrolides synthesized by utilizing this method are brefeldin,¹⁸³ (+)-aspicilin,¹⁹⁸ the antibiotic

(-)-A26771B,¹⁸⁶ and macrospinelides A and B (Scheme 158),^{185,569} C and D,⁵⁷⁰ and H and G.⁵⁷¹



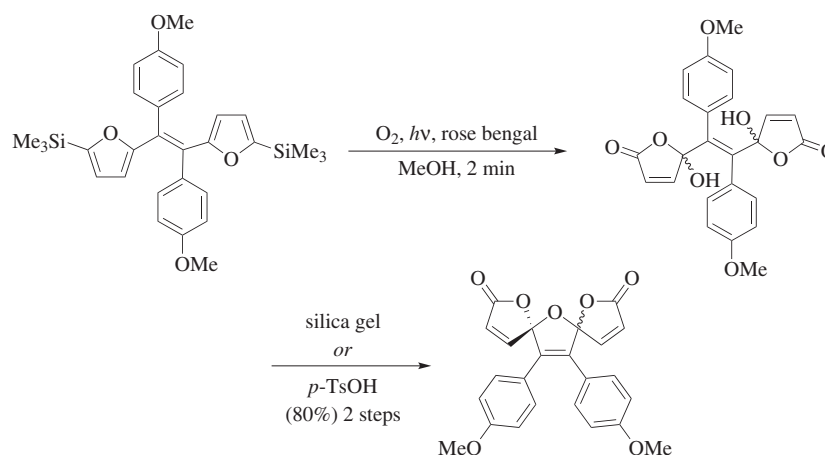
Scheme 158

Conversion of a 2-methyl-4-substituted benzofuran into a 2-substituted 6-acetoxybenzaldehyde using ozonolysis at low temperature followed by treatment with triphenylphosphine has been employed as a key step in the synthesis of the antimicrobial agent apicularen A (Scheme 159).⁵⁷²



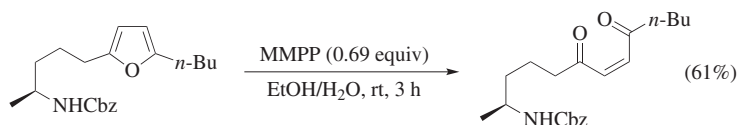
Scheme 159

Biomimetic syntheses of natural products from the litseaverticillol and prunolide families have been designed based on photooxygenations of furan derivatives (Scheme 160).⁹⁵ Similarly, photooxygenations of 2-(trimethylsilyl)furan derivatives have been used in synthetic pathways to prepare (+)-premnalene A and its 8-epimer.³¹⁴



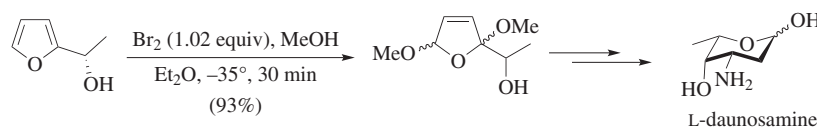
Scheme 160

Transformations of a 2,5-disubstituted furan into the corresponding 1,4-dioxoalkene by employing magnesium monoperoxyphthalate (MMPP) as the oxidant is a key step in the synthesis of the alkaloid monomorine (Scheme 161).¹⁴¹



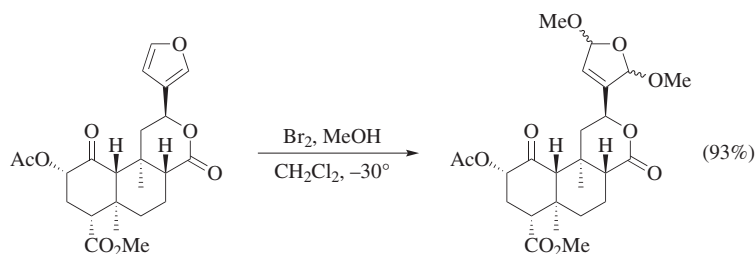
Scheme 161

Bromination of 1-(2-furyl)ethanol in methanol to afford the corresponding 2,5-dimethoxydihydrofurans is used as the first step in the synthesis of racemic daunosamine and related amino sugars.²⁴⁰ The same process using an enantiomerically pure starting material leads to L-daunosamine (Scheme 162).²⁴¹



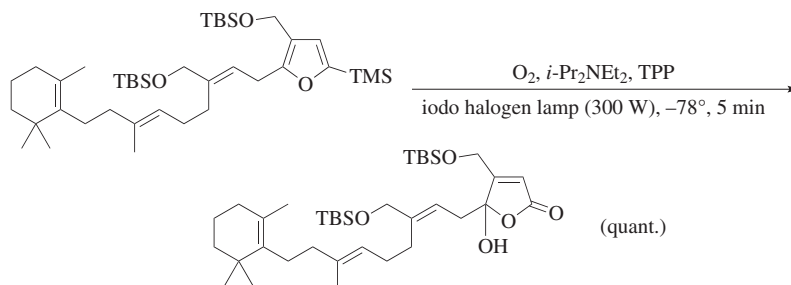
Scheme 162

Routes for the total synthesis of neopatulin²³⁸ and patulin²³⁹ begin with oxidations of furfuryl alcohols utilizing bromine in methanol. The formation of 2,5-dimethoxydihydrofurans in this way has also been employed in the synthesis of phytoalexins²⁶⁴ and several diterpenes^{233–235} from *Salvia divinorum* (Scheme 163).



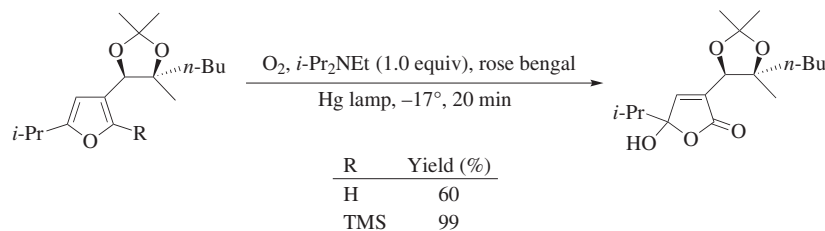
Scheme 163

Conversions of furans into 4-hydroxybutenolides offer direct entry to the synthesis of a broad number of polyoxygenated natural products and related compounds. Among the various methods for carrying out this transformation, photooxygenation is ideal because it serves as a powerful tool to increase the molecular complexity of the system in one step and in high yields.²⁸ A chemoselective photooxygenation reaction of a 2-(trimethylsilyl)furan has been used in the first synthesis of the marine natural product (*E*)-neomanoalide (Scheme 164).³¹⁵ A similar transformation establishes the structure of gloeosporone.³¹⁹



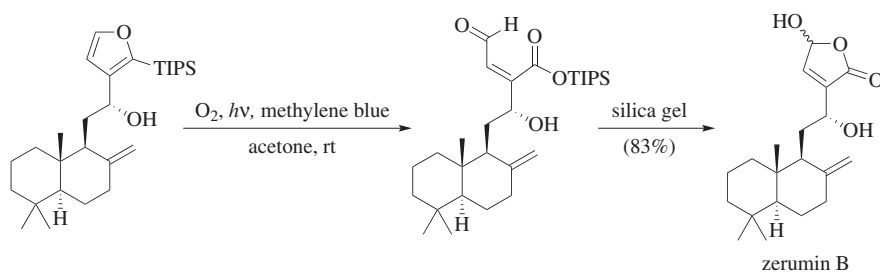
Scheme 164

Photooxygenation of a trisubstituted 2-(trimethylsilyl)furan derivative is a key step in the synthesis of PI-091, a platelet aggregation inhibitor (Scheme 165).^{311,318}



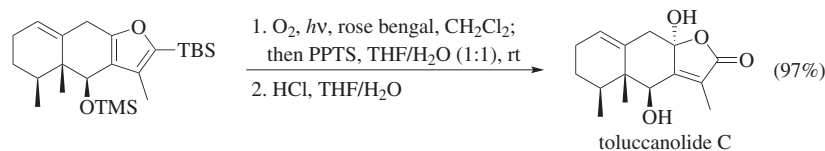
Scheme 165

Similarly, the photooxygenation of a 2-(triisopropyl)furan leads to a late-stage precursor of (+)-zerumin B and (+)-12-epizerumin B (Scheme 166).³²⁰



Scheme 166

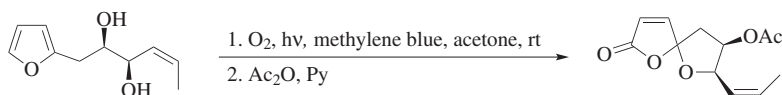
Biomimetic syntheses of bis-sesquiterpene lactones have been developed based on photooxygenations of 2-(trialkylsilyl)furans.³¹² Using this method, dimeric biatractylolide and biepiasterolide^{222,313} as well as furanoeremophilane sesquiterpenoids such as toluccanolide C (Scheme 167)⁵⁷³ are readily prepared.



Scheme 167

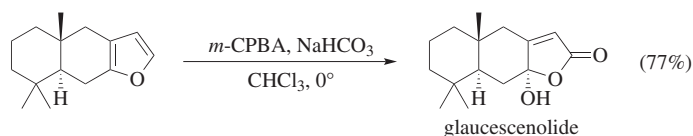
The spirocyclic core of the prunolides, cytotoxic marine products, can be constructed using photooxygenation reactions of bis(2-trimethylsilyl)furans in methanol.⁹⁶ In the same manner, γ -spiroketal lactone precursors for pyrenolide D and the anticancer natural product crassalactone D, are accessible by irradiation

promoted reaction of 2-(2,3-dihydroxyalkyl)furans in the presence of oxygen and methylene blue followed by dehydration (Scheme 168).²²⁴



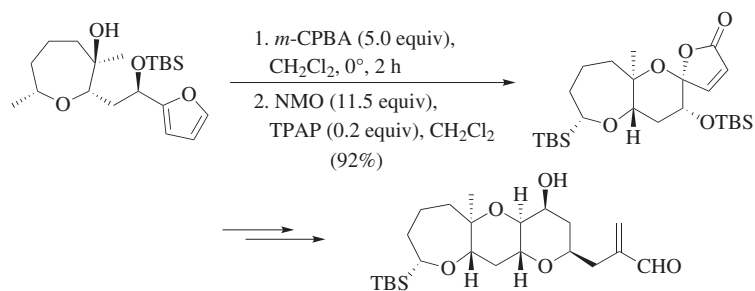
Scheme 168

(+)-Crassalactone D can also be prepared by a sequence using *m*-CPBA to oxidize a furan precursor.⁵⁷⁴ Oxidation with *m*-CPBA is a key step in the synthesis of glaucescenolide, a cytotoxic sesquiterpenoid, and confirms its absolute configuration (Scheme 169).²¹⁸



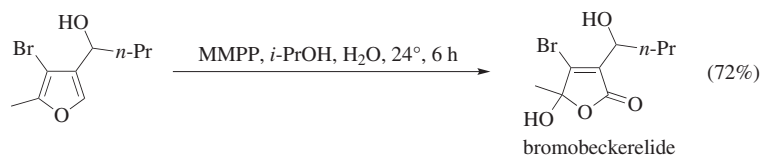
Scheme 169

The ABC ring system of hemibrevetoxin B is synthesized by oxidizing a furan ring with *m*-CPBA with subsequent oxidation of the resulting spirocyclic hemiacetal (Scheme 170).⁵⁷⁵



Scheme 170

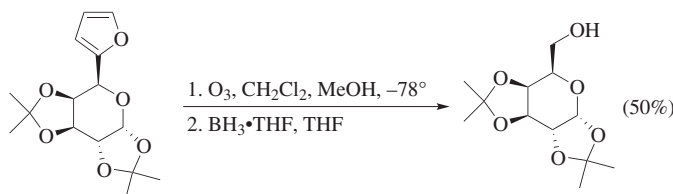
A total synthesis of racemic bromobeckerelide is accomplished in five steps from 5-methylfurfural using a photooxidation promoted by magnesium monoperoxyphthalate (MMPP) as a final step (Scheme 171).²⁰⁹



Scheme 171

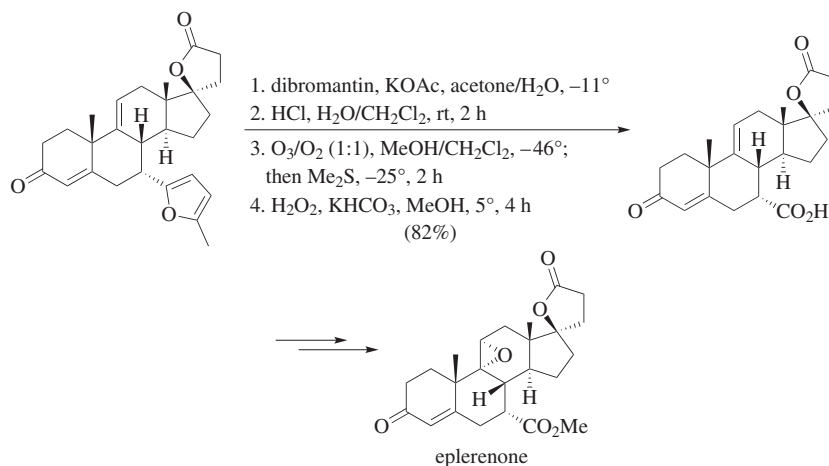
Oxidations to Carboxylic Acids

The synthetic equivalence of a furan ring and a carboxylic acid has been exploited in carbohydrate chemistry and related fields. For example, ozonization of a 2-furyl glycoside and further reduction is used as a key step in the synthesis of hikosamine, the undecose part of hikizimycin, an antibacterial and antihelminthic agent (Scheme 172).³⁹⁷



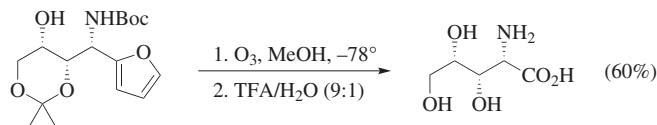
Scheme 172

On the other hand, direct ozonolysis of the furan ring in an attempted synthesis of eplerenone, a new drug for cardiovascular indications, was unsuccessful, necessitating prior treatment with HOBr (generated in situ from dibromantin) followed by ozonolysis of the resulting *trans* enedione to achieve carboxylic acid unmasking (Scheme 173).¹⁰⁷



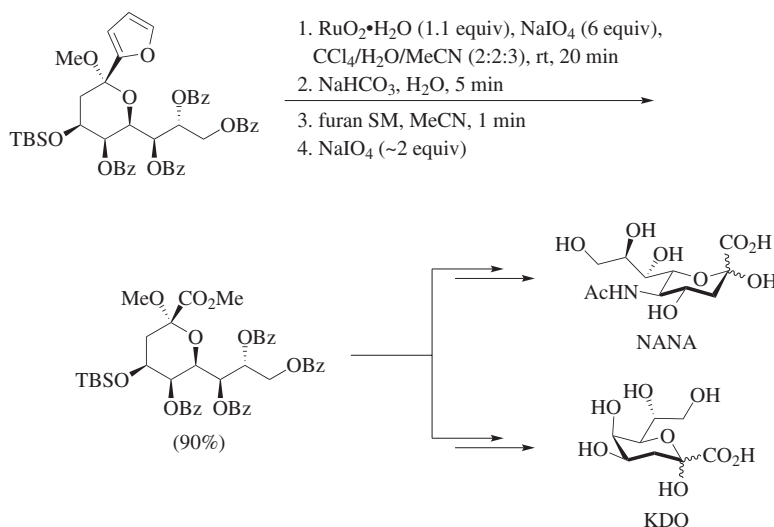
Scheme 173

Ozonization of an *N*-Boc-polyhydroxylated furfurylamine produces an advanced intermediate in the synthesis of polyoxamic acid, a component of the nucleoside antibiotic polyoxins (Scheme 174).^{404,407}



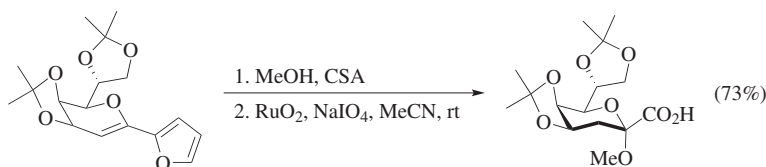
Scheme 174

Several higher ulosonic acids, including the important *N*-acetylneuraminic acid (NANA), are accessible through a strategy based on the use of a furan ring as a carboxylic acid surrogate. 2-Furylsugars are used as key intermediates and transformation of the furan ring into a carboxylic acid group is achieved using ruthenium tetroxide generated from ruthenium(IV) oxide and sodium periodate. To preserve the integrity of several protecting groups, the reaction is carried out in the presence of sodium bicarbonate as a buffer (Scheme 175).³⁶⁸



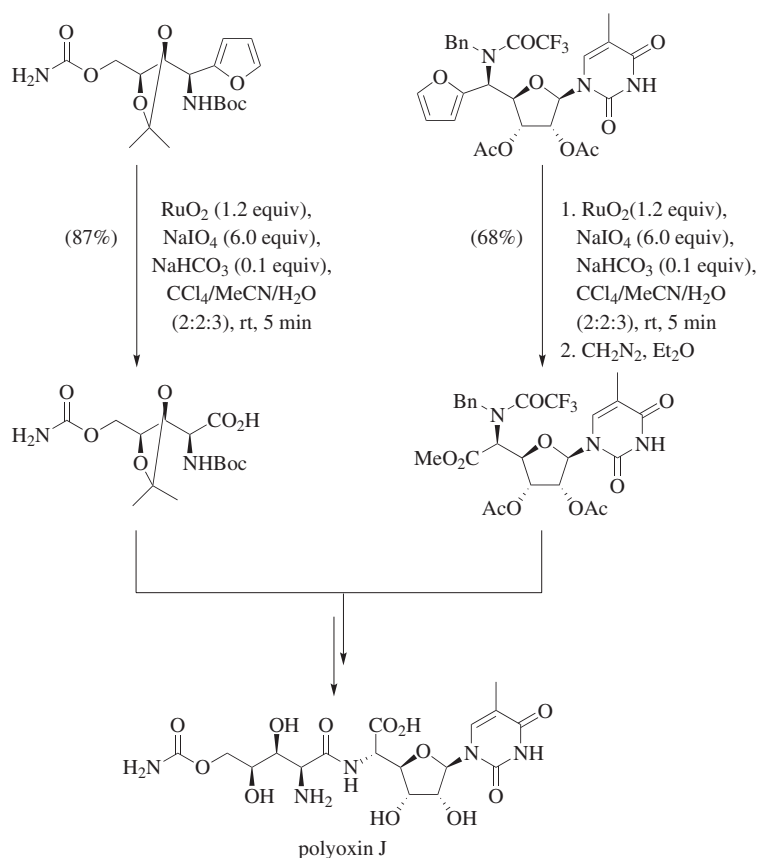
Scheme 175

A similar synthesis of 3-deoxy-D-manno-2-octulosonic acid (KDO) has been achieved using 2-furylglycals as intermediates (Scheme 176).³⁷⁰



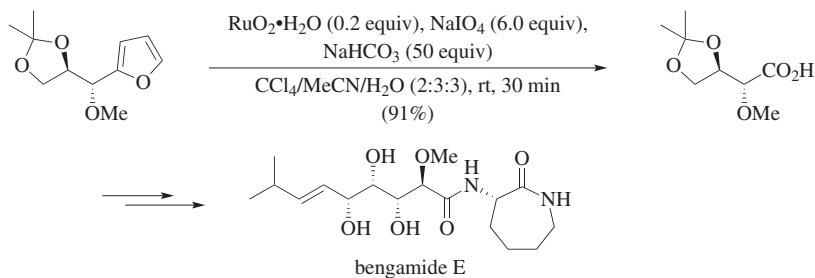
Scheme 176

A strategy based on the use of furan as the synthetic equivalent of a carboxylic acid has been designed for a total synthesis of polyoxin J, a dipeptide nucleoside antibiotic. Both fragments, polyoxamic acid,³⁷⁴ and thymine polyoxin C³⁸¹ are stereoselectively constructed from furan derivatives, which are oxidized with ruthenium tetroxide in a late stage of the synthesis.³⁴⁶ Further coupling of those fragments results in the formation of polyoxin J (Scheme 177).³⁴¹ A similar strategy is applied to the preparation of other polyoxins³⁵⁸ and related nikkomycins.³⁷⁸



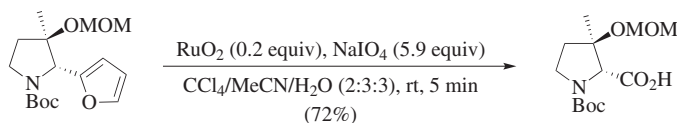
Scheme 177

Other dipeptides, such as bengamide E, a marine natural product, are prepared by oxidation of a furan precursor using ruthenium tetroxide to form a carboxylic acid (Scheme 178).³⁷²



Scheme 178

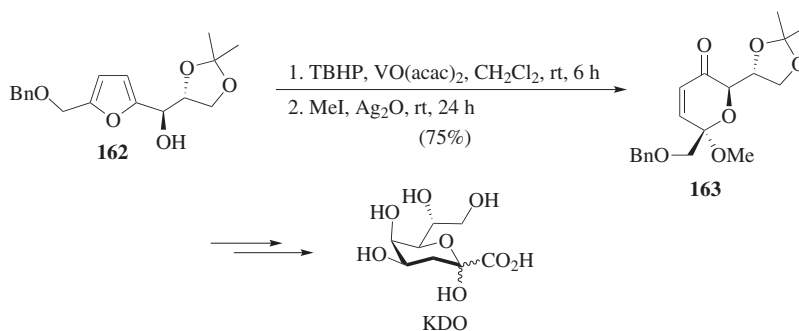
The complete degradation of the furan ring to a carboxylic acid by the action of ruthenium tetroxide has also been employed in the synthesis of members of the cyclothreonamides,³⁴⁸ another family of marine natural products, as well as in the preparation of naturally occurring substituted proline fragments of more complex compounds (Scheme 179).³⁷¹



Scheme 179

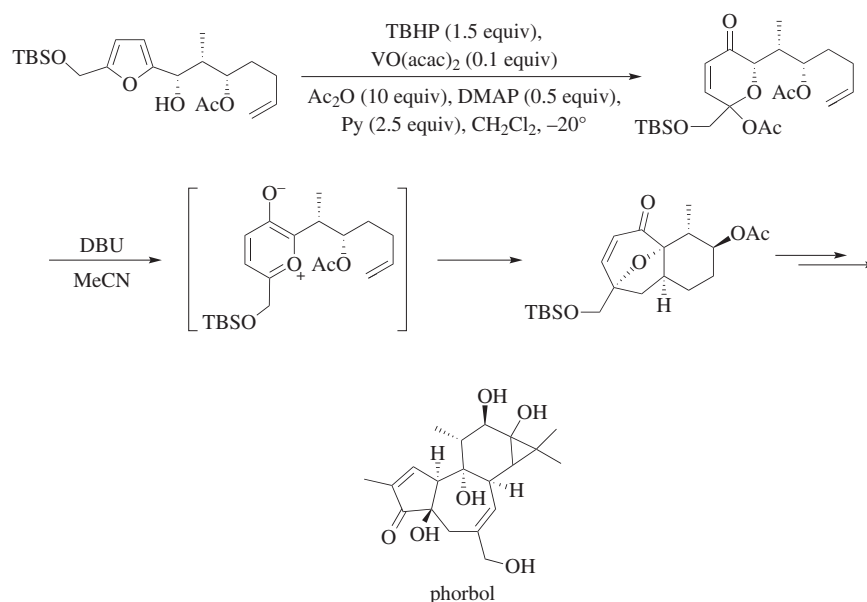
The Achmatowicz Reaction

The Achmatowicz reaction has enjoyed considerable synthetic application because it is atom economic and simultaneously introduces several important functionalities that enable further transformations. Indeed, the reaction was initially described as a de novo entry to higher carbohydrates³¹ because of the excellent possibilities it offered for the synthesis of the so-called hexenuloses.^{576,577} For example, the intermediate **163** in the synthesis of monosaccharide 3-deoxy-D-manno-2-octulosonic acid (KDO) is available from furan precursor **162** through use of the Achmatowicz reaction promoted by TBHP in the presence of a catalytic amount of vanadyl acetylacetonate ($\text{VO}(\text{acac})_2$) (Scheme 180).⁴⁸⁸

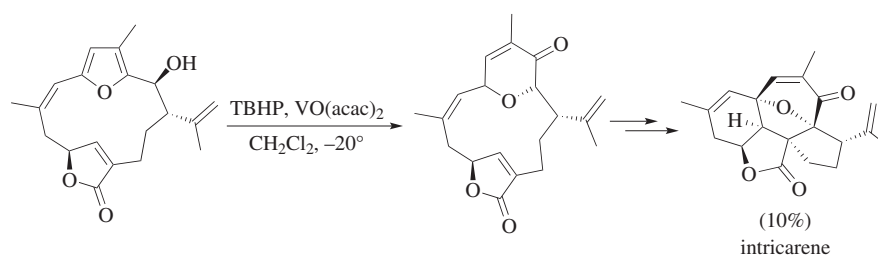


Scheme 180

The Achmatowicz reaction of 5-substituted furfuryl alcohols, promoted by TBHP/VO(acac)₂, has also been used in the formal synthesis of the diterpene phorbol (Scheme 181),⁵⁰⁹ daphnetoxins,⁴⁹⁶ the C₂₇–C₃₈ and C₄₄–C₅₃ subunits of norhalichondrin B,⁵⁰⁵ and a biomimetic synthesis of the polycyclic diterpene (+)-intricarene (Scheme 182).¹⁰

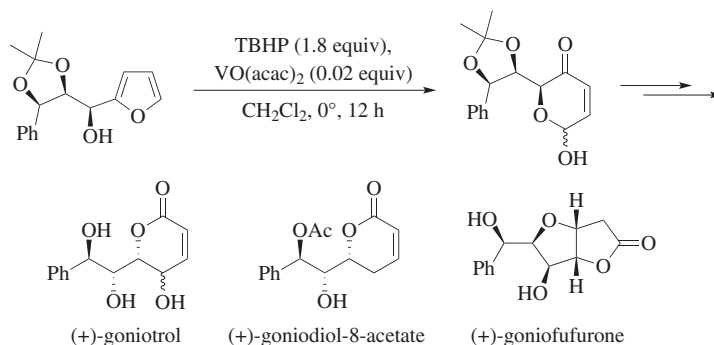


Scheme 181



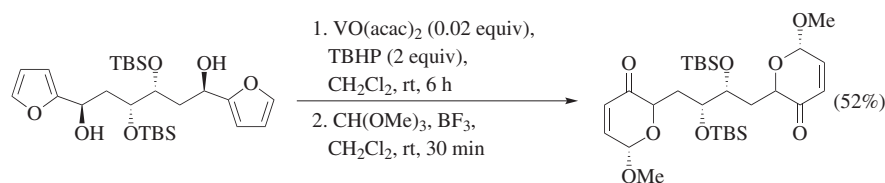
Scheme 182

A total synthesis of the natural antitumor styryl lactones (+)-goniodol-8-acetate,⁴⁸⁷ (+)-goniotrol, and (+)-goniofufurone⁵⁷⁸ are achieved in a stereoselective manner via treatment of a polyhydroxylated furfuryl alcohol with TBHP/VO(acac)₂ at 0° (Scheme 183).



Scheme 183

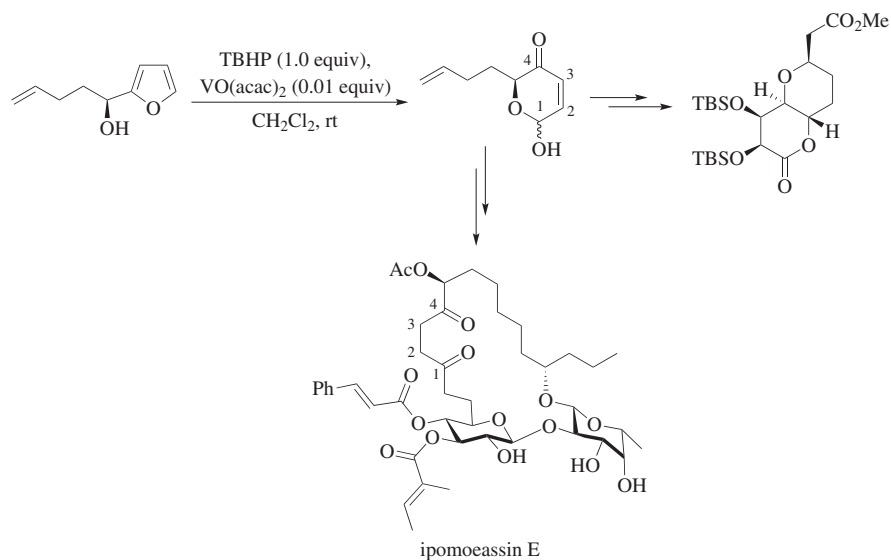
The fungal metabolite mycoepoxydiene is obtained by employing oxidative rearrangement of a furfuryl alcohol using the conditions described above.⁴⁹⁵ The related natural product (–)-1893A is also accessible by the same process.⁵⁰⁷ A two-directional synthesis of the C₅₈–C₇₁ fragment of palytoxin was designed based on a C2-symmetrical dipyranone obtained via a double Achmatowicz reaction of a bis-furan derivative (Scheme 184). Two equivalents of TBHP are necessary for completion of the reaction.⁵¹²



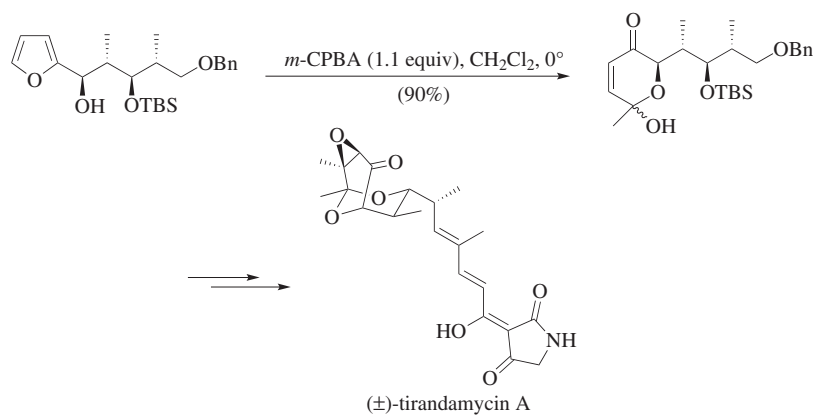
Scheme 184

Ipomoeassin E is prepared using an enantiomerically pure alkenyl furfuryl alcohol as starting material through treatment with TBHP/VO(acac)₃ in dichloromethane (Scheme 185).⁵⁰⁴ The same initial step is employed in a synthesis of the C₁–C₁₅ domain of the marine macrolide halichondrins.⁵⁰⁶

The Achmatowicz transformation carried out using *m*-CPBA as the oxidizing reagent has been used in the synthesis of racemic tirandamycin A (Scheme 186)⁴⁴² and pheromones from the olive fruit fly⁴⁴¹ and hepialid moth.⁴⁵³

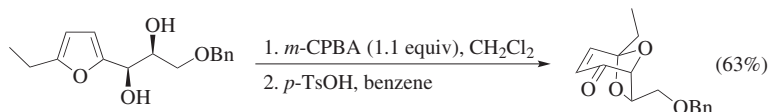


Scheme 185



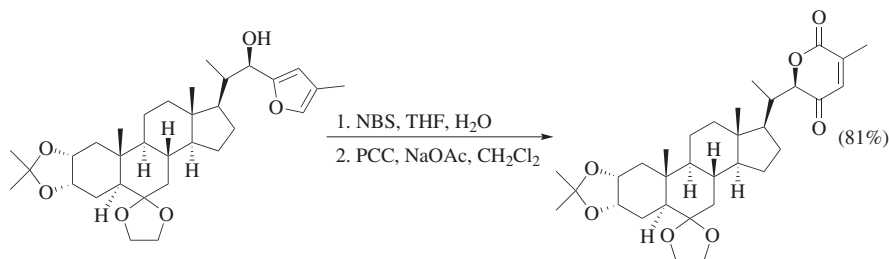
Scheme 186

The reaction of a polyhydroxylated 2,5-disubstituted furan with *m*-CPBA in dichloromethane is a key step in a synthesis of (–)-exo-isobrevicomin (Scheme 187).⁴⁵⁸



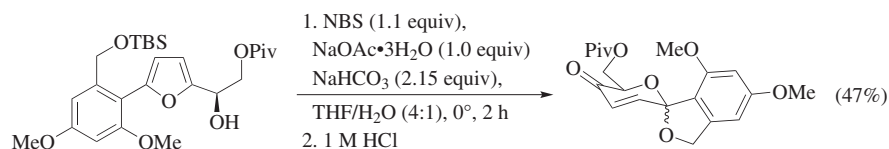
Scheme 187

The steroid castasterone is obtained using a route involving treatment of a furan intermediate with NBS in THF/H₂O (Scheme 188).⁴⁶¹ The same reaction, but in a buffered medium, is used as the first step in syntheses of important α,β -unsaturated lactones such as isoaltholactone,⁵⁷⁹ (*R*)-(-)-argentilactone,⁵⁸⁰ basilolide B,⁵⁸¹ and phomopsolides C,⁵⁸² D,⁴⁶² and E.⁵⁸³



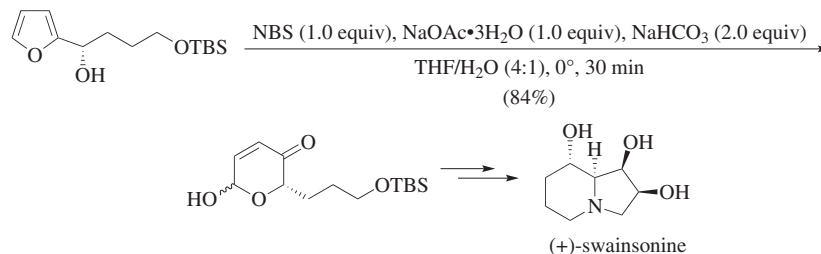
Scheme 188

The starting materials required for the synthesis of the *C*-aryl glycoside tricyclic spiroketal nucleus of the antifungal agents papulacandins are obtained by implementation of the Achmatowicz reaction using NBS/water systems and 5-aryl-2-(1,2-dihydroxyethyl)furans (Scheme 189).⁴⁸³



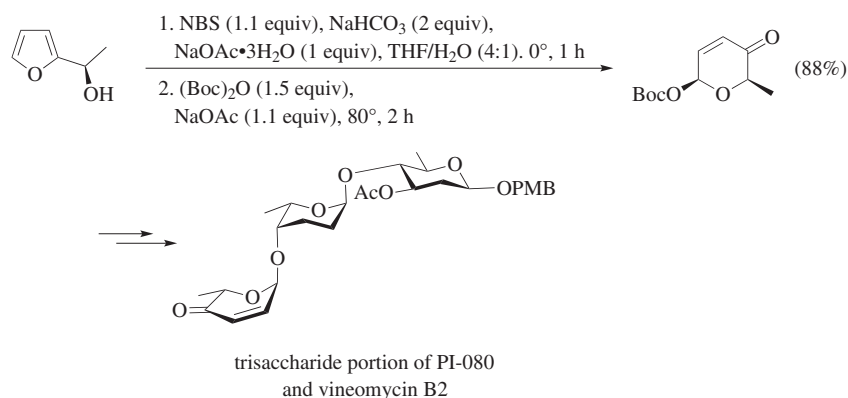
Scheme 189

A *de novo* synthesis of both enantiomers of the alkaloid (+)-swainsonine relies on the use of an Achmatowicz reaction of a furfuryl alcohol as the initial step to construct a C₆-substituted pyranone precursor of the final product (Scheme 190).⁴⁶⁹



Scheme 190

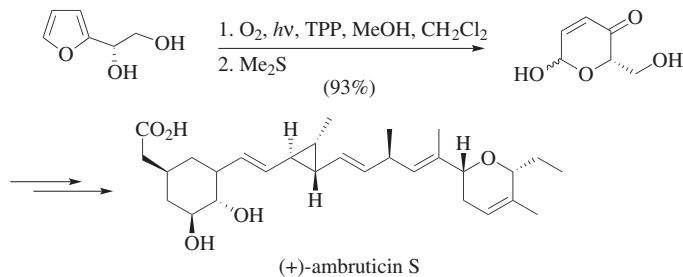
Complex carbohydrate-containing substrates are accessible using NBS-promoted Achmatowicz reactions of enantiomerically pure α -methyl furfuryl alcohol. Following this approach, syntheses of the trisaccharide subunit of landomycins A and E,⁴⁹⁸ and the trisaccharide portion of PI-080 and vineomycin B2 (Scheme 191)⁴⁹⁹ have been accomplished.



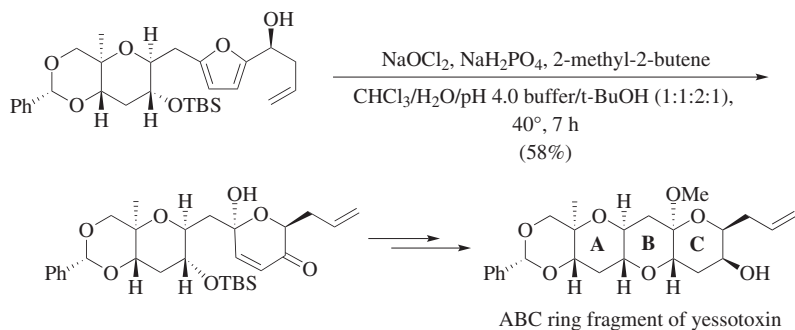
Scheme 191

Other oxidants have also been employed for the Achmatowicz reaction and applied in synthetic pathways. Photooxygenation of $(\alpha$ -hydroxymethyl)furfuryl alcohol, promoted by tetraphenylporphyrin (TPP), is the first step in a total synthesis of (+)-ambruticin S (Scheme 192).⁵²⁷ The antibiotic (+)-macbecin I is accessed in a similar way,⁴³¹ as is the (+)-Prelog–Djerassi lactone.⁴²⁸

The synthesis of the complex structure of the marine polyether toxin yessotoxin is addressed through use of an Achmatowicz approach that employs sodium chlorite as the oxidizing agent. In this approach, the ABC ring fragment is prepared in the manner illustrated in Scheme 193.⁵³⁵

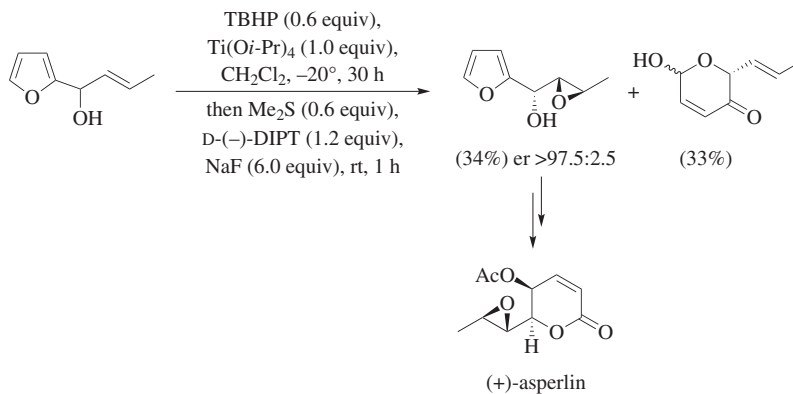


Scheme 192



Scheme 193

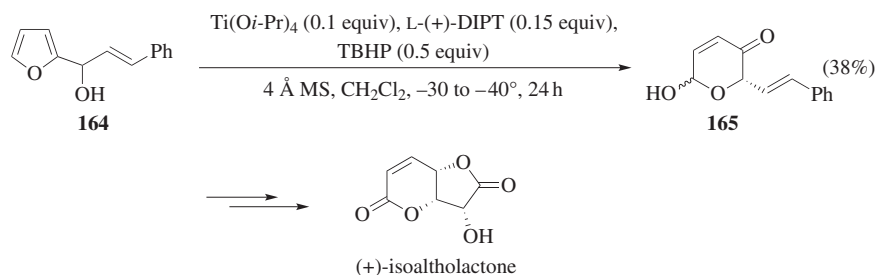
Kinetic resolution of racemic furfuryl alcohols achieved by treatment with TBHP in the presence of L-(+)-diisopropyl tartrate and titanium isopropoxide has been used for the preparation of an enantiomerically enriched starting material required for the synthesis of (+)-asperlin (Scheme 194).⁵¹⁸ In a similar way, an enantiomerically pure



Scheme 194

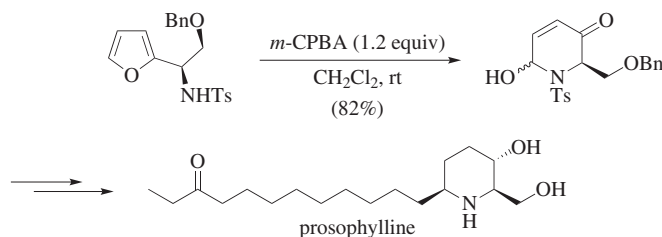
furfuryl alcohol with >95:5 er is obtained using this procedure in a route for preparation of the 14-membered bis-lactone grahamimycin A.¹⁸⁴

Treatment of alkenyl furfuryl alcohol **164** under kinetic resolution conditions results in the formation of pyranone **165**, which is a precursor of (+)-isoalcoholone (Scheme 195).⁵²⁴



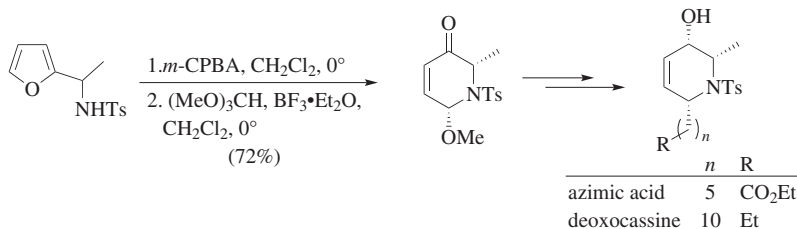
Scheme 195

The aza-Achmatowicz reaction³³ has enormous synthetic potential, including obtaining enantiomerically enriched compounds through kinetic resolution.³⁴ Oxidation of a furfurylamine derivative with *m*-CPBA is used as the starting step in a synthesis of (+)-deoxoprosophylline⁵⁴² and prosophylline (Scheme 196).⁵⁴³ This method is applicable to solid-phase synthesis, although it has been used only to prepare racemic targets.⁵³⁷

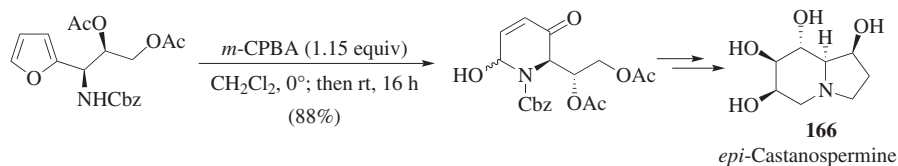


Scheme 196

Hydroxylated piperidine alkaloids, like azimic acid, spicigenine, cassine, and deoxocassine are prepared in racemic form through oxidation of *N*-tosyl furfuryl-amines mediated by *m*-CPBA (Scheme 197).^{551,552} The same type of oxidation can be applied to the generation of several azasugars including mannojirimycin,⁵⁴⁹ *epi*-indolizidine 223A,⁵⁵³ indrizidine 223AB,⁴⁰⁵ 8a-*epi*-swainsonine,⁵⁶¹ and *epi*-castanospermine (**166**) (Scheme 198).⁵⁴⁶

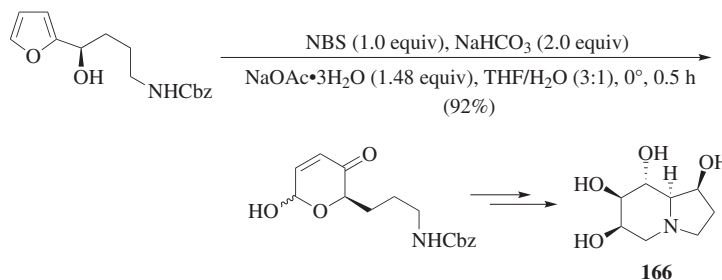


Scheme 197



Scheme 198

Swainsonine⁴² and deoxymannojirimycin⁵⁶⁴ are obtained in enantiomerically pure forms by performing kinetic resolution of a furfuryl tosylamide as a key step. *epi*-Castanospermine (**166**) is also prepared from a furfuryl amine through treatment with aqueous NBS at 0°⁴⁶³ and in the presence of sodium acetate (Scheme 199).⁴⁷³



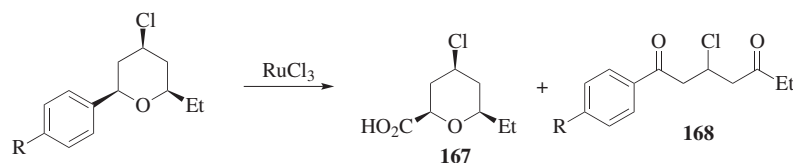
Scheme 199

COMPARISON WITH OTHER METHODS

The utility of furan ring cleavage reactions is heightened by the fact that no alternative C₄ synthons exist that can be used to generate 1,4-dioxo derivatives or functionalized heterocycles like 6-hydroxy-2*H*-pyran-3(6*H*)-ones and 6-hydroxy-1,2-dihydropyridin-3(6*H*)-ones. In addition, although there are several methods for generating carboxylic acids from other functional groups, these procedures cannot be considered to be competitive with oxidations of furans. However, several other functional groups can be oxidatively transformed to carboxylic acids, including

heteroaromatics, phenyl groups,¹¹³ alkynes, and alkenes.¹¹⁴ In all cases, the processes involve complete degradation, giving the carboxylic acids as final products. The same conditions (RuCl_3 or RuO_2 , NaIO_4 in 2:2:3 $\text{CCl}_4/\text{MeCN}/\text{H}_2\text{O}$) are usually employed for all of these reactions,³³⁶ with variations being found in only the reaction times and temperatures, which in some cases are as high as 70° .⁵⁸⁴ Nevertheless, the use of other solvents like acetone⁵⁸⁵ or the environmentally friendly dimethyl carbonate/water system⁵⁸⁶ is also possible. Periodic acid^{587–590} and sodium hypochlorite⁵⁹⁰ can be used as primary oxidants instead of sodium metaperiodate.

The oxidation of benzene rings with ruthenium tetroxide is very sensitive to the nature of the ring substituents and site-selective oxidations can be performed when more than one aromatic ring is present in a molecule.⁵⁸⁸ In general, the procedure is compatible with a variety of functional groups except for those sensitive to ruthenium oxidations and acidic media. In fact, oxidations of benzene rings with ruthenium(III) chloride in the presence of sodium periodate under classical conditions either are unsuccessful or low yielding when methoxymethyl and *tert*-butyldimethylsilyl ethers are present on the ring.⁵⁹¹ In the same study, the authors demonstrate that oxidation of phenyl groups are more efficient when an acetoxy group is present. The same conditions are compatible with nitrogen atoms protected as carbamates, which serve to prepare non-natural amino acids by using the phenyl group as a synthetic equivalent of a carboxylic acid.⁵⁹² The chemoselective oxidation of an aromatic ring in the presence of a tetrahydropyran is possible when the primary oxidant is changed from sodium periodate to periodic acid, and water is absent from the solvent system. When a benzene ring is activated by the presence of a methoxy group, complete chemoselectivity is observed as evidenced by the ratio of product **167** to product **168**. (Scheme 200).⁵⁹³



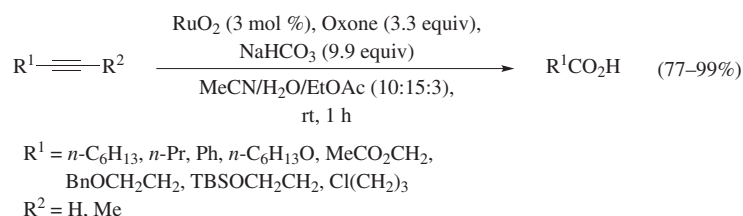
R	Co-Oxidant	Solvents	167 + 168 Yield (%)	167/168
H	NaIO_4	$\text{H}_2\text{O}/\text{MeCN}/\text{CCl}_4$	—	0:100
H	H_5IO_6	MeCN/CCl_4	52	87:13
MeO	H_5IO_6	MeCN/CCl_4	72	100:0

Scheme 200

Oxidations of 2,5-disubstituted oxazoles with ozone, followed by treatment of the crude reaction mixture with sodium borohydride in methanol, afford carboxylic acids. This reaction takes place through an intermediate anhydride, which is transformed into the carboxylic acid by the action of the reducing agent.⁵⁹⁴

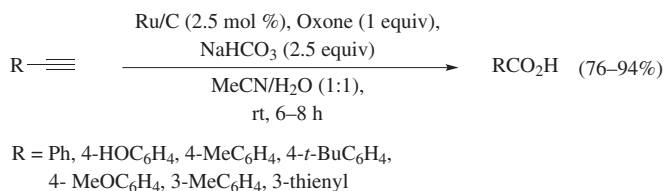
In addition to ruthenium tetroxide,⁴⁸⁹ other oxidants have been used for transforming alkynes into carboxylic acids. These include ozone,^{490–493} potassium

permanganate,^{595,596} polyoxometals derived from molybdenum and tungsten,⁵⁹⁷ [bis(trifluoroacetoxy)iodo]benzene,⁵⁹⁸ and hydrogen peroxide in the presence of methyltrioxorhenium,⁵⁹⁹ peroxotungsten compounds,⁶⁰⁰ or under a basic medium.⁶⁰¹ A synthetically useful method for the oxidative degradation of alkynes to form carboxylic acids consists of a combination of ruthenium(IV) oxide, Oxone[®], and sodium bicarbonate in a 10:15:3 acetonitrile/water/ethyl acetate mixture as the solvent (Scheme 201).⁶⁰² The reaction proceeds to completion at room temperature in 1 hour and high yields are obtained. The reaction conditions are compatible with the presence of phenyl groups and several protecting groups including benzyl and *tert*-butyldiphenylsilyl ethers.



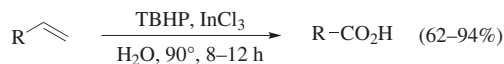
Scheme 201

Aromatic terminal alkynes are cleanly converted into carboxylic acids by the action of recyclable ruthenium supported on charcoal in the presence of Oxone[®] as the oxidant. The procedure, similar to that described above but using lesser amounts of the reoxidant and sodium carbonate, is also fully compatible with the presence of aromatic and heteroaromatic rings like thiophene (Scheme 202).⁶⁰³ The reaction can be carried out on a 100 mmol scale.



Scheme 202

Alkynes also undergo oxidation to form carboxylic acids by the action of cobalt acetate bromide in the presence of air. Although the initial products are diketones, prolonged reaction times afford carboxylic acids.⁶⁰⁴ Typically, alkenes are converted into carboxylic acids by ozonolysis followed by oxidative workup. A safer and more efficient method utilizes *tert*-butyl hydroperoxide and indium(III) chloride as the catalyst with water as the solvent.⁶⁰⁵ Examples of several alkenes undergoing this process are illustrated in Scheme 203. The reaction can be extended to formation of more complex products.



R = Ph, 4-MeOC₆H₄, 4-ClC₆H₄, 1-naphthyl

Scheme 203

Oxidation of alkenes to yield carboxylic acids can also be carried out using ruthenium-based systems. Aqueous reactions can be performed in the presence of an emulsifying agent and under ultrasonic irradiation.⁶⁰⁶ Several cosolvents can be used successfully in the oxidation of alkenes with ruthenium trichloride in the presence of sodium periodate.⁶⁰⁷ However, it is possible to design ruthenium-based oxidation protocols of less than fully substituted alkenes that afford aldehydes rather than carboxylic acids.⁶⁰⁸

EXPERIMENTAL CONDITIONS

All oxidants must be handled with caution, as they can lead to flammable oxidation products. Although oxidants like tert-butyl hydroperoxide, meta-chloroperoxybenzoic acid, dimethyldioxirane, and hydrogen peroxide can be used in water, peroxides are potentially flammable and/or explosive and may ignite fires when they come in contact with other materials, especially flammable solvents. Consequently, in many cases it is strongly recommended that an inert atmosphere be used. In addition these substances can cause skin and eye burns on contact. Bromine must be used with extreme caution because it can cause severe damage to the skin.

In general, metal-based oxidants, such as ruthenium dioxide or trichloride, potassium permanganate, and lead tetraacetate, are toxic as a consequence of the presence of heavy metals. Thus, special care must be taken in their manipulation and disposal (avoid skin contact, inhalation, and, of course, ingestion).

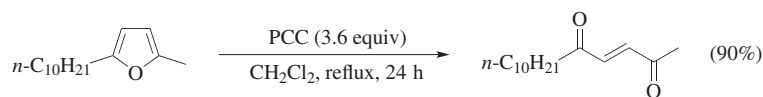
*Ozone is a powerful oxidizing reagent and thus it reacts with unsaturated organic compounds, like furans, to form peroxides, which are unstable and can decompose violently. Ozonization reactions on the micro- and semimicro scale are carried out safely with a glass apparatus consisting of two separated chambers with inlet and outlet tubes.*⁶⁰⁹

Photooxygenation reactions are usually carried out by generating singlet oxygen in situ. A solution of the sensitizer and substrate in an appropriate solvent (usually dichloromethane) is irradiated under an atmosphere of dry oxygen for the desired time at a given temperature ranging from -78° to room temperature. Irradiation is carried out in a Pyrex flask with halogen or tungsten lamps, using powers of 200–650W. Shallow, silvered Dewar flasks can be used for reactions carried at low temperatures. Preparative photooxygenations are best carried out with a low-power (150W) mercury high pressure lamp. An irradiation unit with an automatic oxygen consumption recording system and a cut-off filter ($<380 \text{ nm}$) is also recommended.⁷⁹ A catalytic amount of a sensitizer is needed to promote the formation of singlet oxygen. Rose bengal and methylene blue are the most commonly used sensitizers although other compounds such as tetraphenylporphyrin can also be employed.

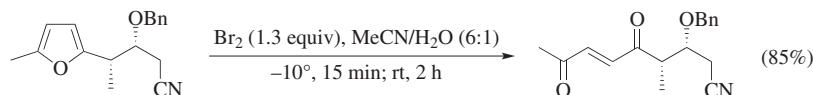
Special attention should be paid to oxidations carried out with NBS in the presence of water to avoid the formation of byproducts. In particular, the reaction temperature should be maintained below 5° and NBS must be added as a solid in order to promote the immediate consumption of the bromine liberated in situ. The oxidation of furan derivatives with *N*-bromosuccinimide is usually carried out in 4:1 tetrahydrofuran/water at 0° but has been conducted in 1:1 tetrahydrofuran/water⁵⁷⁵ and ethyl acetate at reflux.⁶¹⁰ High yields are obtained when the reaction is carried out in the presence of sodium bicarbonate and sodium acetate.^{579,582,583} Optimal conditions consist of employing 1.05 equivalents of NBS, 1.0 equivalent of sodium acetate, and 2.0 equivalents of sodium bicarbonate.⁶¹¹ Under these conditions oxidations are carried out smoothly in less than 1 hour and in excellent yields.^{580,581,612} If the oxidation is carried out in the presence of acetic anhydride, the corresponding acetoxypyranone is obtained directly⁶¹³ although a two-step procedure (oxidation and then acetylation) may afford a better overall yield.⁶¹⁴

Electrochemical oxidations of furan derivatives are typically performed by passing a constant current of 4 A through an alcoholic (e.g. methanolic) solution containing the furan and an electrolyte until 4 F/mol of current is passed. Normally, ammonium bromide, tetraethylammonium perchlorate, sodium acetate, or lithium perchlorate are employed as electrolytes. A platinum anode encased in an ion-exchange membrane containing the electrolyte ions can also be used to avoid the use of added electrolyte.⁶¹⁵ In some instances 7–8 F/mol, twice the theoretical amount of electricity needed, are required to achieve good yields.⁶¹⁶ This amount of electricity is required in reactions involving polymer-supported materials, which typically give low yields. These reactions suffer from the intrinsic difficulty of obtaining direct contact between the polymer-bound substrate and the electrode.⁶¹⁷

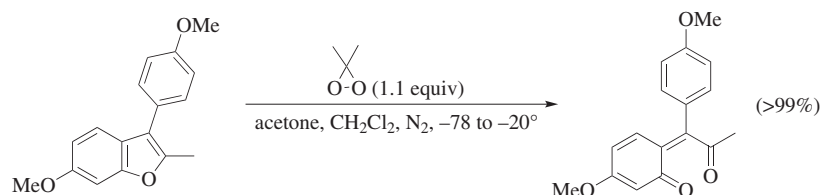
EXPERIMENTAL PROCEDURES



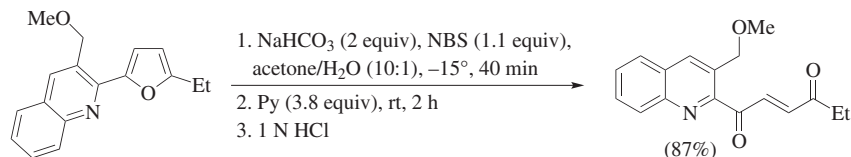
(*E*)-3-Pentadecene-2,5-dione [Oxidation of a Furan to a 1,4-Dicarbonyl Derivative with Pyridinium Chlorochromate].⁶¹⁸ 2-Methyl-5-decylfuran (1.10 g, 0.05 mmol), diluted with anhydrous CH₂Cl₂ (10 mL), was added to a suspension of PCC (4 g) in anhydrous CH₂Cl₂ (50 mL). The mixture was heated to reflux for 24 h and then filtered through a short pad of Florisil. The crude product obtained after removal of the solvent was chromatographed on SiO₂. Elution with hexane yielded (*E*)-3-pentadecene-2,5-dione (1.06 g, 90%): mp 68–69°; IR (CCl₄) 2970, 2872, 1680, 1620, 1360, 980 cm⁻¹; ¹H NMR (CCl₄) δ 6.77 (s, 2H), 2.60 (t, *J* = 8 Hz, 2H), 2.31 (s, 3H), 1.31 (s, 17H), 0.92 (m, 3H); EIMS (70 eV) (*m/z*): M⁺ 238. Anal. Calcd for C₁₅H₂₆O₂: C, 75.58; H, 10.99. Found: C, 75.44; H, 11.09.



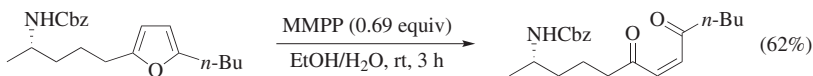
(3R,4S)-3-Benzyloxy-4-methyl-5,8-dioxonon-6-enenitrile [Oxidation of a Furan to a 1,4-Dicarbonyl Derivative with Bromine].¹⁴² To a stirred solution of nitrile (200 mg, 0.74 mmol) in a 6:1 mixture of MeCN/H₂O (6 mL), bromine (154 mg, 0.96 mmol) in MeCN (2 mL) was added dropwise at -10° , and the reaction mixture was stirred at -10° for 15 min. The cooling bath was removed and the reaction mixture was stirred at rt for 2 h to complete *cis/trans* isomerization (TLC, hexane/EtOAc, 6:4). Brine was added, the aqueous layer was extracted with EtOAc, combined organic phases were dried (MgSO₄), evaporated, and purified by column chromatography (hexane/EtOAc, 7:3) to give the pure product as a yellow solid (180 mg, 85%): mp $59-61^{\circ}$ (hexane/ether); $[\alpha]_D^{25}$ 5.15 (c 1.6, CHCl₃); IR (film) 3037, 2967, 2899, 2247, 1674, 1458, 1423, 1359, 1298, 1270, 1103, 1049, 996, 743, 700, 591, 477 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.35 (s, 5H), 6.88 (s, 2H), 4.73 (d, J = 11.4 Hz, 1H), 4.55 (d, J = 11.4 Hz, 1H), 3.97 (ddd, J = 4.8, 5.6, 6.8 Hz, 1H), 3.22 (dq, J = 6.8, 7.1 Hz, 1H), 2.68 (dd, J = 17.1, 4.8 Hz, 1H), 2.55 (dd, J = 17.1, 5.6 Hz, 1H), 2.34 (s, 3H), 1.26 (d, J = 7.1 Hz, 3H); ¹³C NMR (50 MHz, CDCl₃) δ 201.2, 197.7, 137.6, 136.8, 135.5, 128.6, 128.3 (4-Ph), 128.1 (3-Ph), 117.1, 75.0, 72.9, 48.7, 28.5, 20.9, 12.8 (4-Me); EIMS (m/z): $[M + H]^+$ 286; HRMS-EI (m/z): $[M + H]^+$ calcd for C₁₇H₁₉NO₃, 286.14408; found 286.144. Anal. Calcd for C₁₇H₁₉NO₃: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.31; H, 6.73; N, 4.97.



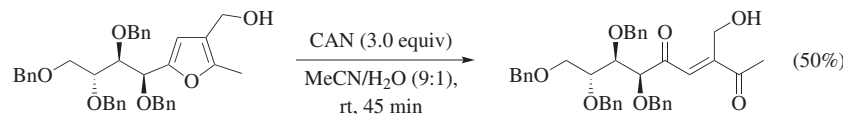
(Z)-3-Methoxy-6-[1-(3-methoxyphenyl)-2-oxopropylidene]-2,4-cyclohexadienone [Oxidation of a Furan to a 1,4-Dicarbonyl Derivative with Dimethyldioxirane].³⁸ A cooled (-78°) solution of dimethyldioxirane^{619,620} in acetone (8 mL of a 0.067 M solution, 0.536 mmol), dried over molecular sieves at -20° , was rapidly added to a cooled (-78°), stirred solution of 6-methoxy-3-(4-methoxyphenyl)-2-methylbenzylfuran (134 mg 0.5 mmol) in anhydrous CH₂Cl₂ (2 mL), under a N₂ atmosphere. The reaction temperature was allowed to increase to -20° while stirring until complete consumption of the benzo[b]furan was indicated by TLC. The solvent was evaporated (-20° at 0.01 mm Hg, 1–2 h) to yield 3-methoxy-6-[1-(3-methoxyphenyl)-2-oxopropylidene]-2,4-cyclohexadienone in quantitative yield: ¹H NMR (CDCl₃, -20°) δ 7.47–7.33 (m, 2H), 6.97–6.87 (m, 3H), 6.21 (dd, J = 2.2, 10.1 Hz, 1H), 5.71 (d, J = 2.3 Hz, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 2.29 (s, 3H); ¹³C NMR (CDCl₃, -20°) δ 204.9, 185.4, 170.7, 161.3, 160.8, 131.8, 131.7, 126.6, 123.6, 122.2, 114.2, 101.5, 56.0, 55.4, 28.4.



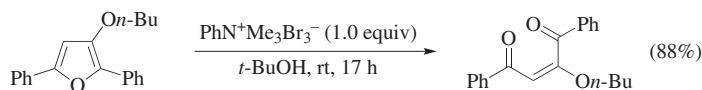
(*E*)-1-[3-(Methoxymethyl)quinolin-2-yl]-hex-2-ene-1,4-dione [Oxidation of a Furan to a 1,4-Dicarbonyl Derivative with *N*-Bromosuccinimide].¹⁵⁰ A solution of NBS (1.57 g, 8.8 mmol) in a 10:1 acetone/water mixture (11 mL) was added dropwise to a solution of the furan derivative (2.14 g, 8 mmol) and NaHCO_3 (1.34 g, 16 mmol) in the same solvent (32 mL) at -15° . After stirring for 40 min at -15° , pyridine (2.4 mL, 30 mmol) was added, and the reaction mixture was allowed to warm to rt. After 2 h at rt, the mixture was quenched with 1 N HCl to neutral pH and extracted with EtOAc (3×15 mL). The combined extracts were dried (Na_2SO_4) and evaporated, and the crude product was purified on silica gel (15% EtOAc/hexane) to yield (*E*)-1-[3 (methoxymethyl)quinolin-2-yl]-hex-2-ene-1,4-dione as a yellowish solid (1.97 g, 87%): mp 87° (EtOH); IR (neat) 2906, 1698, 1668 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.46 (d, $J = 16.17$, 1H), 8.45 (s, 1H), 8.17 (d, $J = 8.46$ Hz, 1H), 7.85 (d, $J = 8.46$ Hz, 1H), 7.74 (t, $J = 7.35$ Hz, 1H), 7.63 (t, $J = 7.35$ Hz, 1H), 7.13 (d, $J = 16.17$ Hz, 1H), 4.97 (s, 2H), 3.55 (s, 3H), 2.80 (q, $J = 7.35$ Hz, 2H), 1.18 (t, $J = 7.35$ Hz, 3H); ^{13}C NMR (CDCl_3) 201.2, 191.7, 150.2, 145.8, 137.6, 135.0, 134.6, 134.2, 132.7, 130.1, 129.9, 129.2, 127.6, 71.3, 59.0, 34.8, 7.8. EIMS (m/z): M^+ 283, 226, 195, 166; HRMS-EI (m/z): M^+ calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_3$, 283.1208; found, 283.1204.



(2*S*)-2-(*N*-Benzyloxycarbonylamino)-6,9-dioxo-7-tridecene [Oxidation of a Furan to a 1,4-Dicarbonyl Derivative with Magnesium Monoperoxyphthalate].¹⁴¹ To a solution of 2-((2*S*)-2-*N*-benzyloxycarbonylamino-5-butyl)-5-butylfuran (0.023 g, 0.067 mmol) in EtOH (0.3 mL) was added magnesium monoperoxyphthalate (0.023 g, 0.046 mmol) in water (0.3 mL) at rt and the mixture was stirred for 3 h. Addition of saturated aq NaHCO_3 solution to the mixture was followed by extraction with CH_2Cl_2 (2×3 mL). The combined organic layers were dried over MgSO_4 , concentrated, and the residue was purified by silica gel column chromatography (hexane/EtOAc, 3:1) to provide (2*S*)-2-(*N*-benzyloxycarbonylamino)-6,9-dioxo-7-tridecene (0.015 g, 62%): $[\alpha]_{\text{D}}^{24} + 0.8$ (c 1.50, CHCl_3); IR (neat) 3342, 2958, 1700, 1699, 1527 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.34–7.26 (m, 5H), 6.25 (s, 2H), 5.06 (s, 2H), 4.52 (br d, $J = 9.3$ Hz, 1H), 3.58 (m, 1H), 2.54 (t, $J = 6.9$ Hz, 2H), 2.49 (t, $J = 7.3$ Hz, 2H), 1.61 (m, 2H), 1.46 (m, 2H), 1.38 (m, 2H), 1.35 (m, 2H), 0.89 (t, $J = 7.3$ Hz, 3H), 0.85 (d, $J = 4.2$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 202.7 (2C), 155.8, 136.6, 136.0, 135.2, 128.5 (3C), 128.0 (2C), 66.5, 46.8, 42.3, 41.8, 36.1, 25.5, 22.2, 21.2, 19.7, 13.8; HRMS (m/z): M^+ calcd for $\text{C}_{21}\text{H}_{29}\text{NO}_4$, 359.4593; found 359.4499.

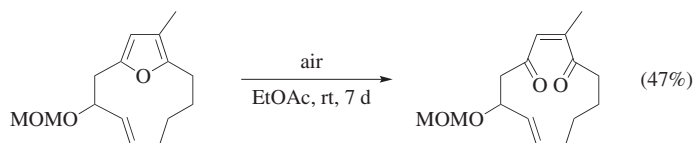


(6*S*,7*R*,8*R*,3*E*)-6,7,8,9-tetrakis(Benzyloxy)-3-(hydroxymethyl)non-3-ene-2,5-dione [Oxidation of a Furan to a 1,4-Dicarbonyl Derivative with Ceric Ammonium Nitrate].¹³² To a stirred solution of (2-methyl-5-((1*S*,2*R*,3*R*)-1,2,3,4-tetrakis(benzyloxy)butyl)furan-3-yl)methanol (64 mg, 0.108 mmol) in MeCN/H₂O (9:1, 5 mL) at rt, was added CAN (180 mg, 0.327 mmol, 3 equiv) over 45 min (adding 64 mg, 0.108 mmol, every 15 min). After the first addition, the initial red–orange color had faded to colorless. Further CAN was added and the mixture was stirred for 15 min. The reaction mixture was diluted with dichloromethane and washed successively with brine and H₂O (3 × 25 mL), dried (Na₂SO₄), and concentrated. The residue was purified by silica gel chromatography (Et₂O/petroleum ether, 1:3–1:1) to afford pure (6*S*,7*R*,8*R*,3*E*)-6,7,8,9-tetrakis(benzyloxy)-3-(hydroxymethyl)non-3-ene-2,5-dione as a colorless oil (50 mg, 50%): [α]_D²⁵ – 34.6 (*c* 1, CH₂Cl₂); IR (neat) 3468, 1696, 1625 cm^{–1}; ¹H NMR (CDCl₃) δ 7.32–7.24 (m, 20H), 6.56 (t, *J* = 1.9 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.52 (s, 2H), 4.40 (d, *J* = 11.1 Hz, 1H), 4.34 (d, *J* = 11.6 Hz, 1H), 4.22 (d, *J* = 3.4 Hz, 1H), 4.12 (br s, 2H), 4.06 (dd, *J* = 8.2 Hz, 1H), 3.84 (m, 1H), 3.80 (dd, *J* = 2.4, 10.7 Hz, 1H), 3.68 (dd, *J* = 3.9, 1H), 2.21 (s, 3H); ¹³C NMR (CDCl₃) δ 205.5, 200.6, 157.9, 138.2, 138.0, 137.7, 137.1, 128.3–127.5 (20C), 120.1, 84.8, 79.8, 77.5, 74.4, 73.4, 71.7, 71.3, 68.1, 63.0, 29.5; MS–FAB (*m/z*): [*M* + Na]⁺ 631 (100%); HRMS–FAB (*m/z*): [*M* + Na]⁺ calcd for C₃₈H₄₀O₇, 631.2671; found, 631.2644. Anal. Calcd for C₃₈H₄₀O₇: C, 75.00; H, 6.62. Found: C, 75.53; H, 6.55.

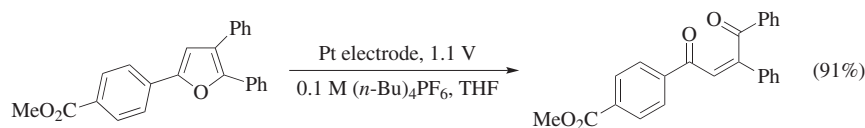


(*E*)-1,4-Diphenyl-2-hydroxy-2-butene-1,4-dione [Oxidation of a Furan to a 1,4-Dicarbonyl Derivative with Phenyltrimethylammonium Tribromide].¹⁷⁶ To a solution of 3-butoxy-2,5-diphenylfuran (292 mg, 1.0 mmol) in *t*-BuOH (10 mL) at rt, was added phenyltrimethylammonium tribromide (376 mg, 1.0 mmol). After being stirred for 17 h at rt the reaction mixture was treated with 0.5 M aq Na₂S₂O₃ and saturated aq NaCl, and subsequently extracted with EtOAc. The organic layer was washed with 0.5 M aq Na₂S₂O₃ and brine, and then was dried with MgSO₄. Removal of the solvent in vacuo afforded 1,4-diphenyl-2-hydroxy-2-butene-1,4-dione, which was purified by column chromatography on silica gel (CCl₄/CHCl₃, 3:2) to afford the pure title product (222 mg, 88%): IR (neat) 3381, 3065, 2926, 1681, 1600, 1566, 1490, 1449, 1358, 1320, 1267, 1181, 1144, 1100, 1076, 1053, 1026, 1001, 970, 899, 872, 832, 809, 774, 735 cm^{–1}; ¹H NMR (CDCl₃) δ 8.14–7.25 (m, 10H), 6.85 (s, 1H). ¹³C NMR (CDCl₃) δ 190.4, 187.0, 182.3, 134.2, 133.7, 133.4, 130.4, 128.8, 128.8, 128.6, 127.6, 96.2; HRMS (*m/z*): [*M* + Na]⁺ calcd for C₁₆H₁₂O₃,

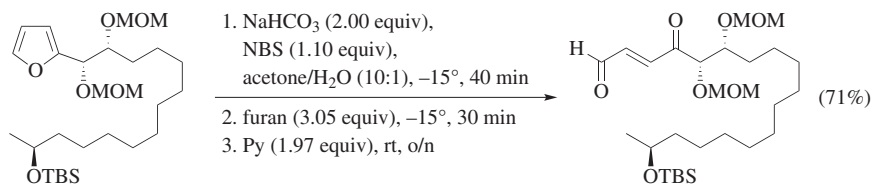
275.0679; found, 275.0678. Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80. Found: C, 76.31; H, 4.92.



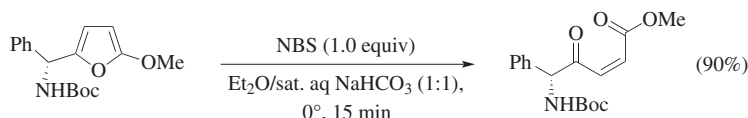
(2Z,7E)-6-(Methoxymethoxy)-2-methylcyclododeca-2,7-diene-1,4-dione [Oxidation of a Furan to a 1,4-Dicarbonyl Derivative with Air].¹⁷³ A stream of air was passed over a stirred solution of (*E*)-3-(methoxymethoxy)-11-methyl-13-oxabicyclo[8.2.1]trideca-1(12),4,10-triene (153.0 mg, 0.611 mmol) in EtOAc (6.1 mL) at rt for 7 d. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (hexanes/ether, 6:1–1:1–1:2) to afford the starting furan (31.2 mg) and (2*Z*,7*E*)-6-(methoxymethoxy)-2-methylcyclododeca-2,7-diene-1,4-dione (76.6 mg, 47%) as an oil: IR (film) 1694, 1612 cm^{-1} ; ^1H NMR (CDCl_3) δ 6.23 (d, $J = 1.5$ Hz, 1H), 5.69–5.61 (m, 1H), 5.59–5.24 (m, 1H), 4.71 (ABq, $J = 6.8$ Hz, 1H), 4.52 (ABq, $J = 6.8$ Hz, 1H), 4.49–4.41 (m, 1H), 3.35 (s, 3H), 2.86–2.73 (m, 2H), 2.38–2.31 (m, 3H), 2.01–1.96 (m, 1H), 1.92 (d, $J = 12.1$ Hz, 3H), 1.62–1.35 (m, 2H).



(Z)-Methyl 4-(4-Oxo-3,4-diphenylbut-2-enoyl)benzoate [Electrochemical Oxidation of a Furan to a 1,4-Dicarbonyl Derivative].⁶⁹ A bulk electrolysis was carried out using a tube-shaped Pt-web (52 mesh, diameter 1.5 cm, height 1.5 cm) working electrode, a Pt foil counter electrode, and an Ag/Ag^+ (10 mM AgNO_3) reference electrode. A THF solution (50 mL) containing 0.1 M Bu_4NPF_6 and methyl 4-(4,5-diphenylfuran-2-yl)benzoate (150 mg, 0.42 mmol) was electrolyzed at 1100 mV. The electrolytic solution was stirred continuously throughout the electrolysis process. The charge consumption (102.1 Coulombs) was calculated by integrating the current–time curve. The electrolyte was evaporated in vacuo, and the pure product was obtained after workup and chromatographic separation on silica gel (CH_2Cl_2 /hexane, 2:1). (*Z*)-methyl 4-(4-oxo-3,4-diphenylbut-2-enoyl)benzoate was obtained (143 mg, 91%) as a white powder: mp 114–115°; IR (KBr) 1722, 1674, 1651 cm^{-1} ; ^1H NMR (CDCl_3) δ 8.09 (d, $J = 8.4$ Hz, 2H), 8.03 (d, $J = 8.4$ Hz, 2H), 7.99 (d, $J = 7.8$ Hz, 2H), 7.67 (s, 1H), 7.61–7.57 (m, 3H), 7.50–7.41 (m, 5H), 3.92 (s, 3 H); ^{13}C NMR (CDCl_3) δ 196.6, 187.9, 166.0, 155.8, 139.1, 136.9, 134.2, 133.7, 133.4, 130.8, 129.9, 129.2, 128.6, 128.5, 128.3, 127.1, 121.1, 52.5; HRMS–FAB (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{18}\text{O}_4$, 371.1283; found 371.1292.

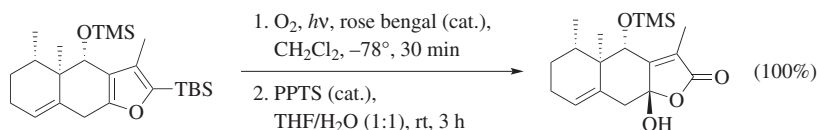


(2*E*,5*S*,6*R*,17*S*)-17-[(*tert*-Butyldimethylsilyl)oxy]-5,6-bis(methoxymethoxy)-4-oxo-2-octadecenal [Oxidation of a Furan to a 4-Oxoalkenal with *N*-Bromosuccinimide].¹⁸² To a mixture of (1*S*,2*R*,13*S*)-2-(13-[(*tert*-butyldimethylsilyl)oxy]-1,2-bis(methoxymethoxy)-1-tetradecanyl)furan (793 mg, 1.54 mmol) and NaHCO₃ (258 mg, 3.08 mmol) in acetone/H₂O (10:1, 3 mL) was added NBS (304 mg, 1.69 mmol) dissolved in acetone/H₂O (10:1, 1.5 mL) at -15°. The mixture was stirred for 40 min, and furan (0.34 mL, 4.7 mmol) was added to quench excess NBS. After 30 min at -15°, pyridine (0.24 mL, 3.03 mmol) was added. The mixture was stirred at rt overnight and then was poured into phosphate buffer (pH 3.6) and EtOAc. The phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over MgSO₄ and concentrated to give a residue that was purified by chromatography (hexane/EtOAc) to furnish (2*E*,5*S*,6*R*,17*S*)-17-[(*tert*-butyldimethylsilyl)oxy]-5,6-bis(methoxymethoxy)-4-oxo-2-octadecenal (584 mg, 71%): IR (neat) 1697, 1032, 835, 775 cm⁻¹; ¹H NMR (CDCl₃) δ 9.77 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 16.0 Hz, 1H), 6.88 (dd, *J* = 16.0, 8.0 Hz, 1H), 4.72 (d, *J* = 7.0 Hz, 1H), 4.70 (d, *J* = 7.0 Hz, 1H), 4.64 (d, *J* = 7 Hz, 1H), 4.57 (d, *J* = 7 Hz, 1H), 4.27 (d, *J* = 3 Hz, 1H), 3.95–3.87 (m, 1H), 3.81–3.69 (m, 1H), 3.37 (s, 3H), 3.26 (s, 3H), 1.76–1.12 (m, 20H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); HRMS–CI (*m/z*): [*M* + *H*]⁺ calcd for C₂₄H₅₄O₇Si, 531.3717; found, 531.3718.

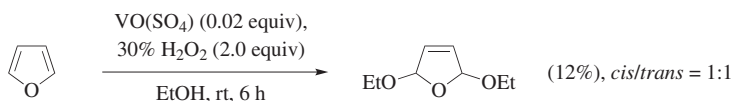


***tert*-Butyl (Z)-4-(Methoxycarbonyl)-2-oxo-1-phenylbut-3-enyl carbamate [Oxidation of a Furan to a 4-Oxoalkenoic Ester with *N*-Bromosuccinimide].**²⁰² To a stirred solution of the furan derivative (151.7 mg, 0.5 mmol) in diethyl ether (5 mL) was added saturated aq NaHCO₃ (5 mL). To the resulting biphasic solution was added NBS (89.0 mg, 0.5 mmol) over 15 min as a solid at 0°. When the addition was complete, the resulting clear solution was diluted with water and extracted with CH₂Cl₂. The organic extract was dried over Na₂SO₄ and filtered. After concentration, the residue was purified by column chromatography (EtOAc/hexane, 1:10–1:4). The 4-oxoalkenoic ester was obtained as a liquid (144 mg, 90%): IR (KBr) 3389, 2976, 2943, 1738, 1724, 1693, 1624, 1501, 1439, 1354, 1290, 1244, 1167, 1051, 891, 700 cm⁻¹; ¹H NMR (CDCl₃, 270 MHz) δ 7.39–7.29 (m, 5H), 6.32 (d, *J* = 12.2 Hz, 1H), 6.05 (d, *J* = 12.2 Hz, 1H), 6.03 (br s, 1H), 5.55 (br d, *J* = 6.2 Hz, 1H), 3.78 (s, 3H), 1.41 (br s, 9H); ¹³C NMR (CDCl₃, 67.8 MHz)

δ 197.4, 165.6, 154.7, 137.8, 136.2, 129.1, 128.6, 128.0, 127.2, 79.9, 64.2, 52.3, 28.3; HRMS–ESI (m/z): $[M + Na]^+$ calcd for $C_{18}H_{23}NO_4$, 342.1312; found, 342.1312.

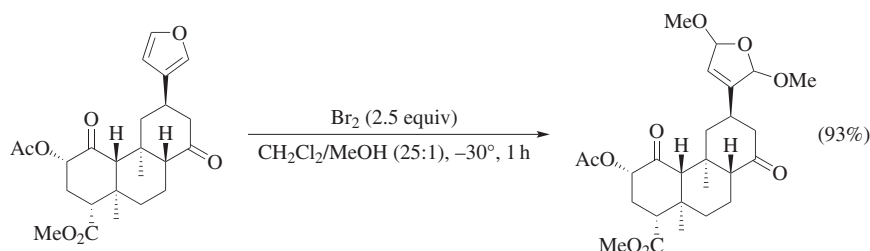


9a-Hydroxy-3,4a,5-trimethyl-4-trimethylsilyloxy-4a,5,6,7,9a-hexahydro-4H-naphtho[2,3-b]furan-2-one [Oxidation of a Furan to a γ -Butenolide with Singlet Oxygen].⁵⁷³ A solution of 2-(*tert*-butyldimethyl)silyl-3,4a,5-trimethyl-4-trimethylsilyloxy-4a,5,6,7,9a-hexahydronaphtho[2,3-*b*]furan (7.9 mg, 0.019 mmol) in CH_2Cl_2 (1.3 mL) containing a crystal of rose bengal was flushed with O_2 , then was cooled to -78° and irradiated with a 300W tungsten lamp. After 30 min, a crystal of pyridinium *p*-toluenesulfonate in THF (1 mL) and water (1 mL) was added, and the mixture was stirred at rt for 3 h. The mixture was extracted with Et_2O (3×5 mL) and the combined extracts were concentrated to dryness. The residue was purified by silica gel column chromatography (hexane/ $EtOAc$, 90:10) to yield 9a-hydroxy-3,4a,5-trimethyl-4-trimethylsilyloxy-4a,5,6,7,9a-hexahydro-4H-naphtho[2,3-*b*]furan-2-one (7.2 mg, 100%) as a colorless solid: mp $192\text{--}196^\circ$; IR (neat) 3347, 2957, 2922, 2852, 1740, 1694, 1435, 1306, 1253, 1232, 1204, 1121, 1086, 1062, 1013, 954, 909, 882, 840, 753 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 5.75 (br s, 1H), 4.47 (d, $J = 2.0$ Hz, 1H), 2.76 (s, 1H), 2.65 (d, $J = 14.0$ Hz, 1H), 2.54 (dd, $J = 14.0, 2.0$ Hz, 1H), 2.07–2.00 (m, 2H), 2.02 (d, $J = 2.0$ Hz, 3H), 1.82 (dtd, $J = 16.0, 7.0, 3.0$ Hz, 1H), 1.59–1.51 (m, 1H), 1.36 (dddd, $J = 14.0, 10.0, 7.0, 7.0$ Hz, 1H), 1.10 (d, $J = 7$ Hz, 3H), 0.88 (s, 3H), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.0, 159.7, 134.8, 129.8, 124.4, 102.5, 78.4, 47.5, 46.2, 36.7, 28.6, 24.7, 18.5, 12.8, 9.2, -0.2 ; CIMS (m/z): $[M + H]^+$ 337, 319, 247, 229; HRMS–CI (m/z): $[M + H]^+$ calcd for $C_{18}H_{28}O_4Si$, 337.1835; found, 337.1820.

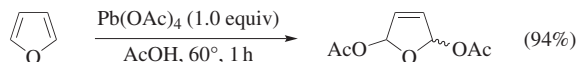


2,5-Diethoxy-2,5-dihydrofuran [Oxidation of a Furan to a 2,5-Dihydrofuran with Hydrogen Peroxide].⁶²¹ A mixture of furan (23.8 g, 0.35 mol), 30% H_2O_2 (75 mL, 0.70 mol), and vanadyl sulfate (2.1 g, 0.007 mol) in ethanol (100 mL) was stirred at rt for 6 h. The reaction mixture was extracted with Et_2O , and the extract was dried over sodium sulfate. The mixture was filtered, and the solvent was removed by distillation. Vacuum distillation of the residue gave 2,5-diethoxy-2,5-dihydrofuran (6.6 g, 12%) as a 1:1 mixture of *cis/trans* isomers: bp $70\text{--}75^\circ$ (10 mm Hg), n_D^{20} 1.4340, d_4^{20} 1.0031; IR (neat) 1115, 1130, 1350, 1370, 1635, 2895, 2940, 2990 cm^{-1} ; ^1H NMR ($CDCl_3$) δ (*cis* isomer) 6.07 (m, 2H), 5.68 (m, 2H), 3.68 (m, 4H), 1.24 (m, 6H); (*trans* isomer) 6.07 (m, 2H), 5.68 (m, 2H), 3.68 (m, 4H), 1.24

(m, 6H); ^{13}C NMR (CDCl_3) δ (*cis* isomer) 131.0 (2C), 105.9 (2C), 62.3, 14.9; (*trans* isomer) 131.4 (2C), 107.4 (2C), 62.7, 15.0; Anal. Calcd for $\text{C}_8\text{H}_{14}\text{O}_3$: C 60.74; H 8.92. Found: C 60.54; H 8.86.



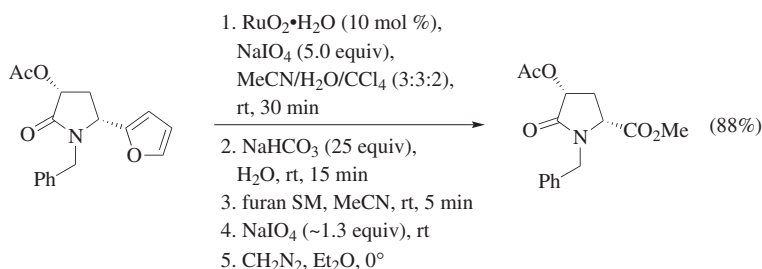
(2*S*,4*aR*,6*aR*,7*R*,9*S*,10*aS*,10*bR*)-9-(Acetyloxy)-2-(2,5-dimethoxy-2,5-dihydrofuran-3-yl)-dodecahydro-6*a*,10*b*-dimethyl-4,10-dioxo-2*H*-naphtho-[2,1-*c*]pyran-7-carboxylic Acid, Methyl Ester [Oxidation of a Furan to a 2,5-Dihydrofuran with Bromine].²³³ A solution of bromine (0.075 mL, 1.46 mmol) in MeOH (1 mL) was added dropwise to a solution of methyl (1*R*,3*S*,4*aR*,4*bS*,6*R*,8*aR*,10*aR*)-3-acetoxy-6-(furan-3-yl)-4*b*,10*a*-dimethyl-4,8-dioxo-tetradecahydrophenanthrene-1-carboxylate (0.25 g, 0.59 mmol) in a mixture of CH_2Cl_2 (50 mL) and MeOH (2 mL) at -30° . The mixture was stirred at -30° for 1 h and was quenched by the addition of saturated aq NaHCO_3 solution (100 mL). The layers were separated, and the organic layers washed with saturated aq NaHCO_3 (50 mL) and H_2O (70 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a white foam. The foam was purified by flash column chromatography (hexane/EtOAc, 3:2) to afford the title compound (0.27 g, 93%) as a colorless oil: ^1H NMR (CDCl_3) δ 5.85 (m, 2H), 5.59 (m, 1H), 5.14 (m, 2H), 3.73 (s, 3H), 3.44 (m, 3H), 3.39 (dd, $J = 1.4, 2.0$ Hz, 3H), 2.75 (dd, $J = 5.6, 10.9$ Hz, 1H), 2.47 (m, 1H), 2.30 (m, 2H), 2.17 (s, 3H), 2.17 (s, 1H), 2.13 (m, 1H), 2.03 (dd, $J = 2.7, 11.4$ Hz, 1H), 1.78 (dd, $J = 2.7, 9.9$ Hz, 1H), 1.68 (dd, $J = 2.7, 12.6$ Hz, 1H), 1.56 (m, 2H), 1.40 (s, 3H), 1.10 (s, 3H); HRMS (m/z): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{34}\text{O}_{12}$, 551.2104; found, 551.2080.



2,5-Diacetoxy-2,5-dihydrofuran [Oxidation of a Furan to a 2,5-Dihydrofuran with Lead Tetraacetate].⁶²² To a solution of $\text{Pb}(\text{OAc})_4$, (5.0 g, 11.3 mmol) in acetic acid (10 mL) at 60° was added furan (0.85 mL, 11.4 mmol). After 1 h the mixture was allowed to cool to rt. The acetic acid was removed under vacuum until a thick paste remained. To this material was added ether (30 mL), and the vessel was vigorously shaken until the lead salts formed a precipitate. Filtration through Celite, followed by evaporation of the solvent, afforded the crude product. Bulb to bulb vacuum distillation (90° , 0.1 mm Hg) provided 2,5-diacetoxy-2,5-dihydrofuran (1.98 g, 10.6 mmol, 94%) as a 2:1 (by NMR) mixture of isomers: IR

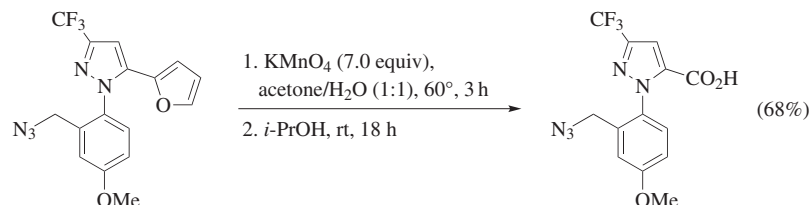
(neat) 1757 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 6.96 (s, 1H), 6.73 (s, 1H), 6.21 (s, 1H), 6.19 (s, 1H), 2.08 (s, 3H), 2.06 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3) δ 169.9, 169.7, 131.3, 130.9, 101.5, 100.0, 21.1, 20.9; MS (m/z): 127 (3), 84 (5), 68 (3), 43 (100).

Selective crystallization of the major isomer was effected by taking up the mixture of isomers in an equal volume of ether and cooling the solution to its freezing point followed by warming to rt, and recooling. This procedure was repeated four times, at which stage the crystals no longer dissolved at rt. The mother liquors were removed from the solid material, which was then washed with cold diethyl ether. Removal of the residual solvent under vacuum afforded 637 mg of the crystalline, major isomer (mp $50\text{--}51^\circ$). Vacuum removal of the solvent from the mother liquors afforded 1.34 g of a 1:1 isomeric mixture of 2,5-diacetoxy-2,5-dihydrofurans.

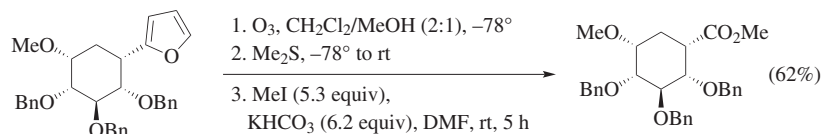


(3*R*,5*R*)-3-Acetoxy-1-benzyl-5-(methoxycarbonyl)pyrrolidin-2-one [Oxidation of a Furan to a Carboxylic Ester with Ruthenium Tetroxide].³⁸² To a well-stirred mixture of MeCN, (9.5 mL), CCl_4 (6.3 mL), and H_2O (9.5 mL) were added sequentially NaIO_4 (0.98 g, 4.6 mmol) and $\text{RuO}_2 \cdot \text{H}_2\text{O}$ (12.2 mg, 0.092 mmol). After 30 min at rt, NaHCO_3 (1.9 g, 23 mmol) was added in one portion followed by H_2O (4.6 mL). After 15 min, the resulting mixture was treated with a solution of (3*R*,5*R*)-3-acetoxy-1-benzyl-5-(2-furyl)pyrrolidin-2-one (0.275 g, 0.92 mmol) in MeCN (0.7 mL). The solution turned black, and after 5 min enough NaIO_4 (~0.250 g, 1.2 mmol) was added in small portions to turn the color light green. The mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The aqueous layer was acidified with 1 N HCl to pH 2–3 and reextracted with EtOAc (3 x 20 mL). The combined organic extracts were washed sequentially with 20% aq NaHSO_3 until colorless and then with brine and dried (MgSO_4). The solvent was evaporated under reduced pressure. The crude acid was dissolved in Et_2O (20 mL), and the solution was cooled to 0° and treated with an ethereal solution of diazomethane until a slight yellow color persisted. The excess diazomethane was destroyed with acetic acid. The resulting solution was concentrated under reduced pressure, and the crude ester was purified by column chromatography on silica gel (hexane/ Et_2O , 50:50) to afford (3*R*,5*R*)-3-acetoxy-1-benzyl-5-(methoxycarbonyl)pyrrolidin-2-one (0.236 g, 88%) as an oil: $[\alpha]_D -16.2$ (c 0.55, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ 7.10–7.30 (m, 5H), 5.29 (dd, $J = 6.4, 8.5$ Hz, 1H), 5.13 (d, $J = 14.9$ Hz, 1H), 4.13 (d, $J = 14.9$ Hz,

1H), 3.92 (dd, $J = 6.4, 8.5$ Hz, 1H), 3.65 (s, 3H), 2.77 (dt, $J = 8.5, 13.9$ Hz, 1H), 2.07 (s, 3H), 2.00 (dt, $J = 6.4, 13.9$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 170.8, 170.1, 170.0, 134.8, 128.7, 128.4, 128.0, 69.5, 55.4, 52.5, 45.8, 29.9, 20.6. Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.93; H, 6.01; N, 4.72.

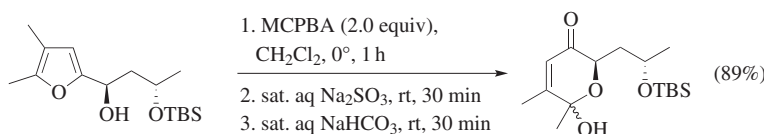


1-(2-Azidomethyl-4-methoxyphenyl)-3-trifluoromethyl-1H-pyrazole-5-carboxylic Acid [Oxidation of a Furan to a Carboxylic Acid with Potassium Permanganate].³⁹¹ To 1-(2-azidomethyl-4-methoxyphenyl)-3-trifluoromethyl-5-(furan-2-yl)-1H-pyrazole (1.43 g, 3.9 mmol) in acetone (60 mL) was added a solution of KMnO_4 (5.0 g, 27.5 mmol) in water (60 mL). The reaction mixture was heated at 60° for 3 h, then was cooled to ambient temperature, and isopropyl alcohol (60 mL) was added. This mixture was stirred for 18 h and then filtered through a Celite pad and washed with copious amounts of isopropyl alcohol. The combined filtrates were evaporated, the residue was dissolved in 1 N NaOH (50 mL) and the solution was washed with Et_2O (2×50 mL). The basic layer was acidified with 1 N HCl (75 mL) and solid NaCl was added. The suspension was extracted with EtOAc (3×100 mL), and the extracts were dried and evaporated to give 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid (0.91 g, 68%): ^1H NMR (CDCl_3) δ 7.3 (s, 1H), 7.25 (d, $J = 8.0$ Hz, 1H), 7.1–7.0 (br s, 1H), 7.05 (d, $J = 1.0$ Hz, 1H), 6.95 (dd, $J = 8.0, 1.0$ Hz, 1H), 4.05 (br s, 2H), 3.9 (s, 3H); EIMS (70 eV) (m/z): 340.

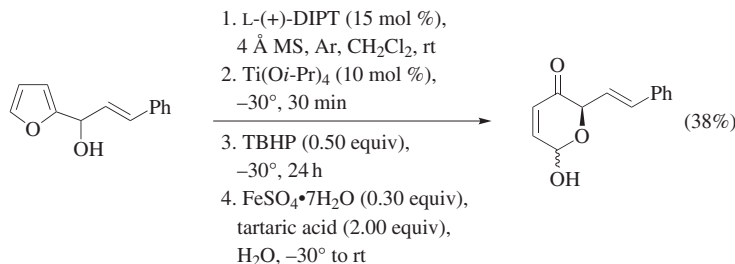


(1S,2S,3R,4R,5R)-Methyl 2,3,4-tris(Benzyloxy)-5-methoxycyclohexane-carboxylate [Oxidation of a Furan to a Carboxylic Ester with Ozone].³⁹⁶ Ozone gas was bubbled through a solution of 2-((1S,2S,3R,4R,5R)-2,3,4-tris(benzyloxy)-5-methoxycyclohexyl)furan (92 mg, 0.18 mmol) in MeOH (3 mL) and CH_2Cl_2 (6 mL) at -78° until the solution remained blue in color. Oxygen was then bubbled through the solution for 1 min and then dimethyl sulfide (50 μL) was added. The solution was allowed to warm to rt, and the solvent was removed under vacuum. The residue

was dissolved in DMF (3 mL), and MeI (59 μ L, 0.95 mmol) and KHCO_3 (111 mg, 1.11 mmol) were added. After stirring for 5 h at rt, TLC (cyclohexane/EtOAc, 7:3) indicated completion of the reaction. The solvent was removed under vacuum and the residue was partitioned between CH_2Cl_2 (5 mL) and water (5 mL). The organic layer was dried (MgSO_4), and the solvent was removed under vacuum. The residue was purified by silica gel chromatography (cyclohexane/EtOAc, 85:15), to afford (1*S*,2*S*,3*R*,4*R*,5*R*)-methyl 2,3,4-tris(benzyloxy)-5-methoxycyclohexanecarboxylate (56 mg, 62%), as a colorless oil: $[\alpha]_{\text{D}}^{20} - 14$ (c 0.5, CHCl_3); ^1H NMR (CDCl_3) δ 7.40–7.26 (m, 15H), 4.73 (d, $J = 12.3$ Hz, 1H), 4.63 (d, $J = 12.3$ Hz, 1H), 4.62 (d, $J = 12.0$ Hz, 1H), 4.58 (d, $J = 11.7$ Hz, 1H), 4.55 (d, $J = 11.7$ Hz, 1H), 4.48 (d, $J = 12.0$ Hz, 1H), 3.99 (br s, 1H), 3.88 (br s, 1H), 3.74 (br s, 1H), 3.69 (s, 3H), 3.50 (dt, 1H, $J = 10.3, 3.3$ Hz, 1H), 3.37 (s, 3H), 2.84 (dt, $J = 10.8, 3.8$ Hz, 1H), 2.49 (td, $J = 12.3$ Hz, 1H), 1.94–1.86 (m, 1H); ^{13}C NMR (CDCl_3) δ 173.0, 138.8, 138.4, 138.0 (3C), 128.4–127.3 (15C), 77.6, 76.3, 73.1, 72.8, 72.3 (3C), 56.6, 51.6 (2C), 42.5, 26.9; EIMS (70 eV) (m/z): $[\text{M} + \text{H}]^+$ 491. Anal. Calcd for $\text{C}_{30}\text{H}_{34}\text{O}_6$: C, 77.08; H, 6.87. Found: C, 77.03; H, 6.92.

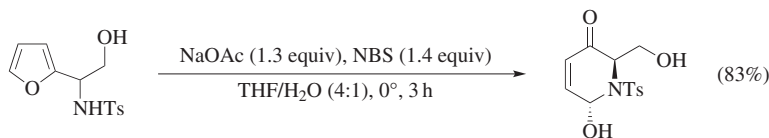


(2*R*,6*RS*,2'*S*)-2-(2'-*tert*-butyldimethylsilyloxypropyl)-6-hydroxy-5,6-dimethyl-2*H*-pyran-3-one [Achmatowicz Reaction Using *m*-Chloroperoxybenzoic Acid].⁴⁵³ *m*-CPBA (70%, 8.60 g, 34.9 mmol) was added to a stirred solution of (1*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-1-(4,5-dimethylfuran-2-yl)butan-1-ol (5.20 g, 17.4 mmol) in dry CH_2Cl_2 (100 mL) at 0°. The mixture was stirred for 1 h, poured into a saturated aq Na_2SO_3 solution, stirred for 30 min, then poured into saturated aq NaHCO_3 solution and stirred for an additional 30 min. The mixture was then extracted with Et_2O . The organic layers were washed with saturated aq Na_2SO_3 solution and brine, dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by chromatography over silica gel (100 g, *n*-hexane/EtOAc, 5:1) yielding (2*R*,6*RS*,2'*S*)-2-(2'-*tert*-butyldimethylsilyloxypropyl)-6-hydroxy-5,6-dimethyl-2*H*-pyran-3-one (4.59 g, 89%) as a colorless solid (4:1 diastereomeric mixture). This material was further purified by crystallization from *n*-pentane to give the pure product mixture as colorless needles: mp 68–74°; $[\alpha]_{\text{D}}^{24} + 19.9$ (c 1.08, CHCl_3); IR (nujol): 3430, 1660, 1255, 1140, 1025, 835, 780 cm^{-1} ; ^1H NMR (CDCl_3) δ 5.85 (br s, 1H), 4.13–4.00 (m, 1H), 2.59 (br s, 1H), 2.16 (ddd, $J = 14.3, 9.8, 2.7$ Hz, 0.8H), 2.08 (ddd, $J = 14.3, 9.8, 2.7$ Hz, 0.2H), 2.02 (br s, 3H), 1.68 (ddd, $J = 14.3, 10.5, 2.9$ Hz, 0.2H), 1.60 (s, 2.4H), 1.59 (s, 0.6H), 1.50 (ddd, $J = 14.3, 10.5, 2.9$ Hz, 0.8H), 1.15 (d, $J = 6.1$ Hz, 3H), 0.87 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (CDCl_3) δ 197.4, 158.7, 124.3, 94.9, 71.3, 64.2, 39.7, 27.1, 25.8, 24.4, 19.4, 18.0, –4.1, –4.6. Anal. Calcd for $\text{C}_{16}\text{H}_{30}\text{O}_4\text{Si}$: C 61.11, H 9.61. Found C 60.60, H 9.91.



(2S)-6-Hydroxy-2-[(E)-styryl]-6H-pyran-3(2H)-one [Achmatowicz

Reaction Using *tert*-Butyl Hydroperoxide].⁵²⁴ To a stirred solution of (*E*)-1-(furan-2-yl)-3-phenylprop-2-en-1-ol (11.0 g, 0.055 mol) and L-(+)-DIPT (1.93 g, 8.25 mmol) in anhydrous CH₂Cl₂ (120 mL) was added activated 4 Å molecular sieves (1.84 g) at rt under argon. The stirred mixture was cooled to -30°, treated with Ti(Oi-Pr)₄ (1.57 g, 5.5 mmol), and stirring was continued for 30 min at -30°. The reaction mixture was treated with TBHP (5.0–6.0 M, nonane solution, 5.5 mL, 27.5 mmol) and was then stirred for 24 h at the same temperature. A freshly prepared solution of FeSO₄·7H₂O (4.62 g, 16.6 mmol) and tartaric acid (16.6 g, 110 mmol) in deionized water (30 mL) was added to the reaction mixture at -30°. The resulting mixture was stirred at rt until the mixture was clear. The phases were separated and the aqueous layer was extracted with CH₂Cl₂ (5 × 40 mL). The organic layer was combined and washed with brine and dried over anhydrous Na₂SO₄. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel (petroleum ether/EtOAc, 4:1 v/v) to afford (2*S*)-6-hydroxy-2-[(*E*)-styryl]-6H-pyran-3(2*H*)-one (4.51 g, 38%) as a brown oil: [α]_D²⁰ +126.3 (c 0.5, CHCl₃); IR (KBr) 3350, 1720, 1680, 1640 cm⁻¹; ¹H (CDCl₃) δ 7.45–7.25 (m, 5H), 6.98 (dd, *J* = 10.3, 1.9 Hz, 0.2H), 6.95 (dd, *J* = 10.3, 3.3 Hz, 0.8H), 6.75 (dd, *J* = 15.8, 1.9 Hz, 1H), 6.48 (dd, *J* = 15.8, 6.3 Hz, 0.2H), 6.39 (dd, *J* = 15.8, 5.7 Hz, 0.8H), 6.18 (dd, *J* = 10.3, 1.5 Hz, 1H), 5.77 (br s, 1H), 5.26 (dd, *J* = 5.7, 1.5 Hz, 0.8H), 4.80 (d, *J* = 5.9 Hz, 0.2H), 4.2–3.8 (br s, 1H); ¹³C (CDCl₃) δ 190.2, 133.6, 131.2, 129.5, 128.5 (2C), 127.4, 126.9, 126.5, 125.8 (2C), 91.8, 86.3. EIMS (*m/z*): M⁺ 216 (6), 198 (8), 131 (16), 115 (29), 84 (84), 77 (19). Anal Calcd for C₁₃H₁₂O₃: C, 72.2; H, 5.56. Found: C, 72.4; H, 5.57.



6-Hydroxy-2-(hydroxymethyl)-1-[(4-methylphenyl)sulfonyl]-1,6-dihydropyridin-3(2H)-one [Aza-Achmatowicz Reaction Using *N*-Bromosuccinimide].⁵⁵⁸ The furan derivative (5.00 g, 17.8 mmol) and sodium acetate (1.86 g,

22.7 mmol) were dissolved in THF/H₂O (80 mL, 4:1), cooled to -5° , and then treated portionwise with *N*-bromosuccinimide (4.37 g, 24.6 mmol) such that the reaction temperature did not exceed 0° . The deep-orange solution was then stirred at 0° for 3 h. After the addition of EtOAc (200 mL), the mixture was treated sequentially with saturated aq KI (100 mL), saturated aq Na₂S₂O₃ (100 mL) and saturated aq NaHCO₃ (100 mL). The organic layer was separated, washed with saturated aq NaCl (80 mL), and dried over MgSO₄. Removal of the solvent and silica gel chromatography (cyclohexane/EtOAc) afforded the title compound (4.38 g, 83%): mp $132-136^{\circ}$ (dec.); $[\alpha]_{\text{D}}^{20} + 40$ (*c* 1.0, acetone); IR (neat) 3193, 3113, 3068, 2980, 2887, 1691, 1597, 1453, 1388, 1340, 1310, 1230, 1153, 1060, 970, 917, 850, 811, 730 cm⁻¹; ¹H NMR (400 MHz, [*d*⁶]acetone) δ 7.42 (m, 4H), 7.05 (dd, *J* = 4.7, 10.2 Hz, 1H), 6.06 (dd, *J* = 4.7, 8.6 Hz, 1H), 6.01 (d, *J* = 10.2 Hz, 1H), 5.92 (d, *J* = 9.4 Hz, 1H), 5.03 (s, 1H), 4.39 (m, 1H), 3.93 (m, 1H), 3.65 (d, *J* = 11.1 Hz, 1H), 2.41 (s, 3H); ¹³C NMR (100 MHz, [*d*⁶]acetone) δ 194.3, 147.7, 145.5, 139.4, 131.4, 128.9, 128.7, 73.7, 64.9, 64.3, 22.1.

TABULAR SURVEY

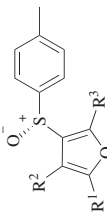
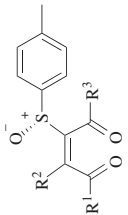
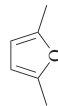
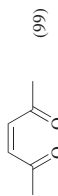
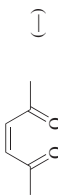
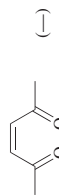
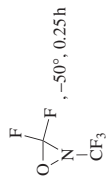
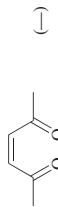
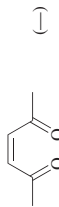
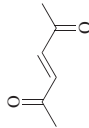
The furan oxidation to give 1,4-diketoalkenes, 4-oxoalkenals, 4-oxoalkenoic acids and esters, and 4-hydroxybutenolides are grouped in Tables 1–4. Reactions yielding the complete oxidation of furan derivatives to give carboxylic acids and esters are collected in Table 5 and transformations of furans into 2,5-dialkoxy-2,5-dihydrofurans are compiled in Table 6. The Achmatowicz reaction and the aza version of the process are grouped in Tables 7 and 8. Within each table entries are listed by increasing numbers of carbon atoms, using the *Chemical Abstracts* convention, and excluding chiral auxiliaries, protecting groups, and simple alkyl groups on heteroatoms. Yields, in parentheses, are based on isolated products. Em-dashes (—) indicate that no yield was reported. Numbers not in parentheses are product ratios. The literature has been reviewed to mid-2014.

The following abbreviations (not included in “*The Journal of Organic Chemistry* Standard Abbreviations and Acronyms”) are used in the Tabular Survey:

Ad	adamantyl
BOM	benzyloxymethyl
DET	diethyltartrate
DIPT	diisopropyltartrate
DMP	Dess–Martin periodinane
HMIM	1-hexyl-3-methylimidazolium
MCPBA	meta-chloroperoxybenzoic acid
MMPP	magnesium monoperoxyphthalate
PMP	<i>p</i> -methoxyphenyl
PTSA	<i>p</i> -toluenesulfonic acid

TBDPS	<i>tert</i> -butyldiphenylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxy
TPP	<i>meso</i> -tetraphenylporphyrin
Tr	trace

TABLE 1. SYNTHESIS OF 1,4-DIKETOALKENES

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₄₋₆		O ₂ , methylene blue, hv, solvent, -40°, 20 min; then Me ₂ S, -40° to rt, 3 h		297
C ₆		MMPP (0.5 eq), EtOH/H ₂ O (2:1), rt, 10 min		139, 623
		H ₂ O ₂ (35 wt %, 1.25 eq), titanium silicalite (10 g/mol), MeCN, rt, 3 h		48
		O ₂ , methylene blue, hv, -78°, CFCl ₃ ; then Me ₂ S, -78° to rt		624
				39
C ₆		<i>m</i> -CPBA (0.9 eq), CH ₂ Cl ₂ , -10° to rt, 2 h		35, 625
		1. O ₂ , methylene blue, hv, CFCl ₃ 2. PPh ₃ (1.5 eq), benzene, 0°, 1 h		624, 79

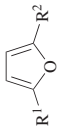
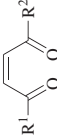
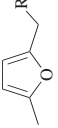
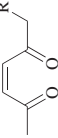
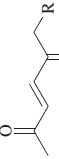
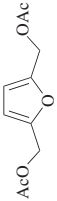
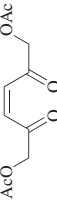
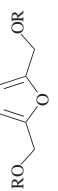
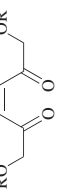
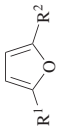
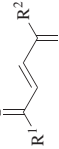
C ₆₋₁₈		NaClO ₂ (3 eq), NaH ₂ PO ₄ (1.5 eq), <i>t</i> -BuOH/H ₂ O (5:1), rt, 1 h		R ¹ Me Me CHO(CH ₂) ₇	R ² Me (<i>E</i>)- <i>n</i> -C ₄ H ₉ CH=CH (<i>E</i>)- <i>n</i> -C ₄ H ₉ CH=CH	(93) (78) (76)	211
C ₆₋₁₅		cumyl hydroperoxide (1.0 eq), Mo(CO) ₆ (0.1 eq), Na ₂ CO ₃ (1.0 eq), CHCl ₃ , 50°		R	Time (h) 24 20 16 20	(93) (65) (67) (63)	41
		cumyl hydroperoxide (1.0 eq), Mo(CO) ₆ (0.1 eq), CHCl ₃ , 50°		R	Time (h) 12 20 20 24	(53) (64) (61) (63)	41
C ₆		O ₂ , methylene blue, hv, CH ₂ Cl ₂ , -40°, 5 h; then Me ₂ S (1.2 eq), -40° to rt		AcO	(88)		161
C ₆₋₇		<i>m</i> -CPBA (1.9 eq), CH ₂ Cl ₂ , rt, 18 h		RO	OR	R Ac (90) Bn (70)	161
		O ₂ , rose bengal, hv, MeOH, -40°, 2 h; then Me ₂ S, -40° to rt		R ¹	R ² (EtO) ₂ PO(CH ₂) ₂ (EtO) ₂ PO(CH ₂) ₃ (EtO) ₂ PO(CH ₂) ₂ (EtO) ₂ POCH=CH	(92) (94) (96) (76)	249

TABLE 1. SYNTHESIS OF 1,4-DIKETOALKENES (Continued)

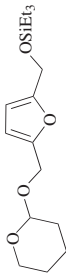
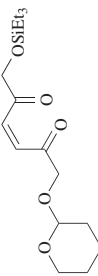
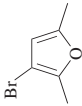
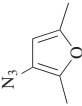
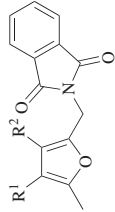
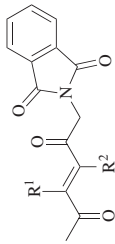
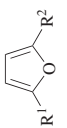
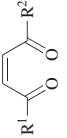
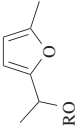
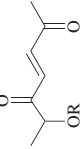
	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₆		<i>m</i> -CPBA (1.5 eq), CH ₂ Cl ₂ , rt, 3 h	 (51)	625a
		<i>m</i> -CPBA (1.5 eq), CH ₂ Cl ₂ , −10°, 2 h	(—)	626
		Br ₂ (1.05 eq), py, acetone, H ₂ O, rt to −20°, 0.5 h	(—)	627
C ₆₋₈		1. Br ₂ (1.05 eq), CH ₂ Cl ₂ , MeOH, −40 to −50°, 35 min 2. 2 N HCl, CH ₂ Cl ₂ , rt, 4 h		226
C ₇₋₁₀		350 U laccase (<i>T. versicolor</i>), 4-OH-TEMPO (10 mol %), pH 4.5, <i>n</i> -octane, rt		174
C ₇		Py (4.0 eq), acetone/H ₂ O (85:15), Br ₂ (1.0 eq)		97, 118 97, 118 118 118 118

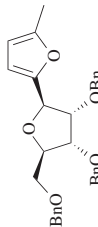
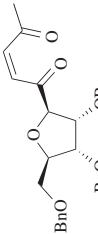
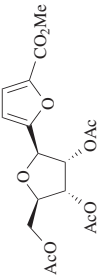
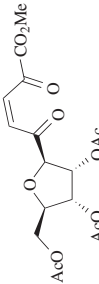
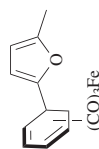
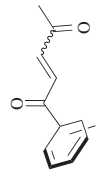
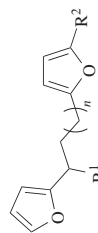
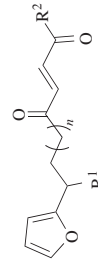
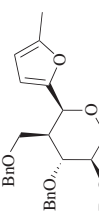
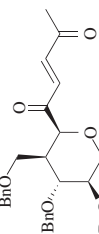


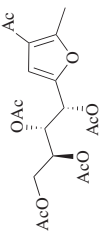
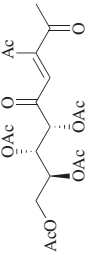
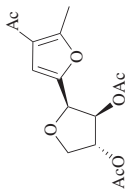
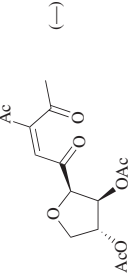
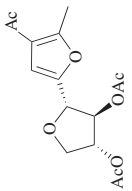
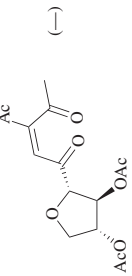
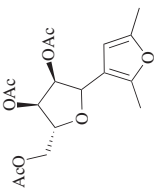
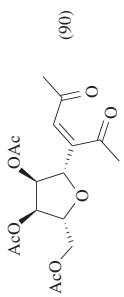
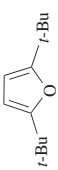
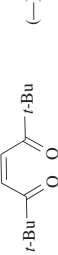
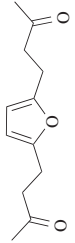
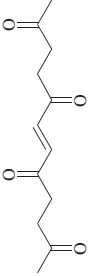
TABLE 1. SYNTHESIS OF 1,4-DIKETOALKENES (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₉₋₁₃		1. O ₂ , rose bengal (cat.), hv, MeOH, 0°, 2 min 2. Me ₂ S (10 eq), CH ₂ Cl ₂ , rt, 18 h; then 4-TsOH, rt, 0.5-6 h	 R ¹ R ² Me TBSOCH ₂ 1.0 (85) H <i>n</i> -Bu 0.5 (83) Me <i>n</i> -Bu 0.5 (90) H Ph 3.5 (86)	309
C ₉		NBS; then py		152
		<i>m</i> -CPBA (1.1 eq), CH ₂ Cl ₂ , -10°, 36 h		162
		PCC (5.0 eq), CH ₂ Cl ₂ , rt, 24 h; then reflux, 9 h		162
		Py (4.0 eq), acetone, H ₂ O, Br ₂		162
C ₉₋₁₀		CAN (5.0 eq), MeCN/H ₂ O (9:1), rt, 75 min		161 161 161, 131

C ₁₀		DDQ, CH ₂ Cl ₂ , rt, 15–28 h		(57)	628
C ₁₀₋₁₂		<i>m</i> -CPBA (0.9 eq), CH ₂ Cl ₂ , –10° to rt, 2 h		R <i>i</i> -Pr (–) <i>i</i> -Bu (–)	625
C ₁₀₋₁₄		MMPP (1.0 eq), EtOH, H ₂ O, rt, 2 h		R <i>n</i> -Bu (95) Ph (88) CH ₂ =CH(CH ₂) ₂ CH(Me)(CH ₂) ₂ (64)	138 (95) (88) (64)
C ₁₀		NBS, NaOAc, THF, H ₂ O		(95)	154
C ₁₀₋₁₂		Br ₂ (1.3 eq), MeCN/H ₂ O (6:1), –10°, 15 min; then –10° to rt, 2 h		(85)	142
C ₁₀₋₁₅		<i>m</i> -CPBA (0.9 eq), CHCl ₃ , 50°, 12 h		R H (71) Me (52)	629
C ₁₀₋₁₅		Dimethyldioxirane (2.5 eq), acetone, CH ₂ Cl ₂ , –78 to 20°		R Me (66) Ph (100)	46 38, 630

TABLE 1. SYNTHESIS OF 1,4-DIKETOALKENES (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.																		
C ₁₀		O ₂ , methylene blue, hv, CH ₂ Cl ₂ , -20°, 30 min; then Et ₂ S (1.2 eq), -20° to rt, 1 h	 (—)	293																		
		O ₂ , methylene blue, hv, CH ₂ Cl ₂ , -20°; then Et ₂ S (1.2 eq), Et ₂ O, -20° to rt, overnight	 (68)	86																		
C ₁₁		O ₂ , hv, MeOH, 0°, 2 h; then PPh ₃ , Et ₂ O, 20°	 (65)	631																		
C ₁₁₋₁₃		O ₂ , rose bengal, hv, MeOH, 0°, 2 h; then PPh ₃ , Et ₂ O, 20°		97																		
			<table><tr><th>n</th><th>R¹</th><th>R²</th></tr><tr><td>0</td><td>MeO</td><td>Me</td></tr><tr><td>1</td><td>H</td><td>TMS</td></tr><tr><td>1</td><td>H</td><td>Me</td></tr><tr><td>1</td><td>MeO</td><td>Me</td></tr><tr><td>2</td><td>MeO</td><td>Me</td></tr></table>	n	R ¹	R ²	0	MeO	Me	1	H	TMS	1	H	Me	1	MeO	Me	2	MeO	Me	(75) (58) (75) (80) (75)
n	R ¹	R ²																				
0	MeO	Me																				
1	H	TMS																				
1	H	Me																				
1	MeO	Me																				
2	MeO	Me																				
C ₁₁		1. O ₂ , methylene blue, hv, CH ₂ Cl ₂ , -20° 2. Et ₂ S, CCl ₄ , -20° to rt, 1 h 3. SiO ₂	 (70)	94																		

		O₂, methylene blue, hv, acetone, rt, 45 min; then Me₂S (10 eq)	(—)	289
		O₂, hv, acetone, rt, 40 min; then Me₂S (10 eq)	(—)	292
		O₂, hv, acetone, rt, 40 min; then Me₂S (10 eq)	(—)	292
		1. O₂, methylene blue, hv, CH₂Cl₂, −20°, 1.5 h 2. Et₂S (1.2 eq), Et₂O, −20° to rt, 2 h	(90)	93, 293
		Ca(OCi)₂, HCl	(—)	632
		<i>m</i>-CPBA, CHCl₃	(51)	629

C₁₂

TABLE 1. SYNTHESIS OF 1,4-DIKETOALKENES (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.																			
C ₁₂ -13		<i>m</i> -CPBA (0.9 eq), CH ₂ Cl ₂ , rt, 15 h		<table><tr><th>R¹</th><th>R²</th><th></th></tr><tr><td>H</td><td>Ph</td><td>(88)</td></tr><tr><td>H</td><td>3-ClC₆H₄</td><td>(83)</td></tr><tr><td>H</td><td>3-MeOC₆H₄</td><td>(91)</td></tr><tr><td>Me</td><td>Ph</td><td>(79)</td></tr><tr><td>Me</td><td>4-FC₆H₄</td><td>(85)</td></tr></table>	R ¹	R ²		H	Ph	(88)	H	3-ClC ₆ H ₄	(83)	H	3-MeOC ₆ H ₄	(91)	Me	Ph	(79)	Me	4-FC ₆ H ₄	(85)	156
R ¹	R ²																						
H	Ph	(88)																					
H	3-ClC ₆ H ₄	(83)																					
H	3-MeOC ₆ H ₄	(91)																					
Me	Ph	(79)																					
Me	4-FC ₆ H ₄	(85)																					
C ₁₂		MMPP (0.68 eq), EtOH/H ₂ O (1:1), rt, 3 h		141																			
C ₁₂ -17		O ₂ , SiO ₂		<table><tr><th>R¹</th><th>R²</th><th></th></tr><tr><td>Me</td><td>Me</td><td>(—)</td></tr><tr><td>Me</td><td>Ph</td><td>(—)</td></tr><tr><td>Ph</td><td>Me</td><td>(—)</td></tr></table>	R ¹	R ²		Me	Me	(—)	Me	Ph	(—)	Ph	Me	(—)	633						
R ¹	R ²																						
Me	Me	(—)																					
Me	Ph	(—)																					
Ph	Me	(—)																					
C ₁₂		<i>m</i> -CPBA (1.5 eq), CH ₂ Cl ₂ , rt, 5 min		163																			
		<i>m</i> -CPBA (1.9 eq), CH ₂ Cl ₂ , rt, 18 h		<table><tr><th>R</th><th></th></tr><tr><td>Ac</td><td>(93)</td></tr><tr><td>Bn</td><td>(90)</td></tr></table>	R		Ac	(93)	Bn	(90)	161												
R																							
Ac	(93)																						
Bn	(90)																						

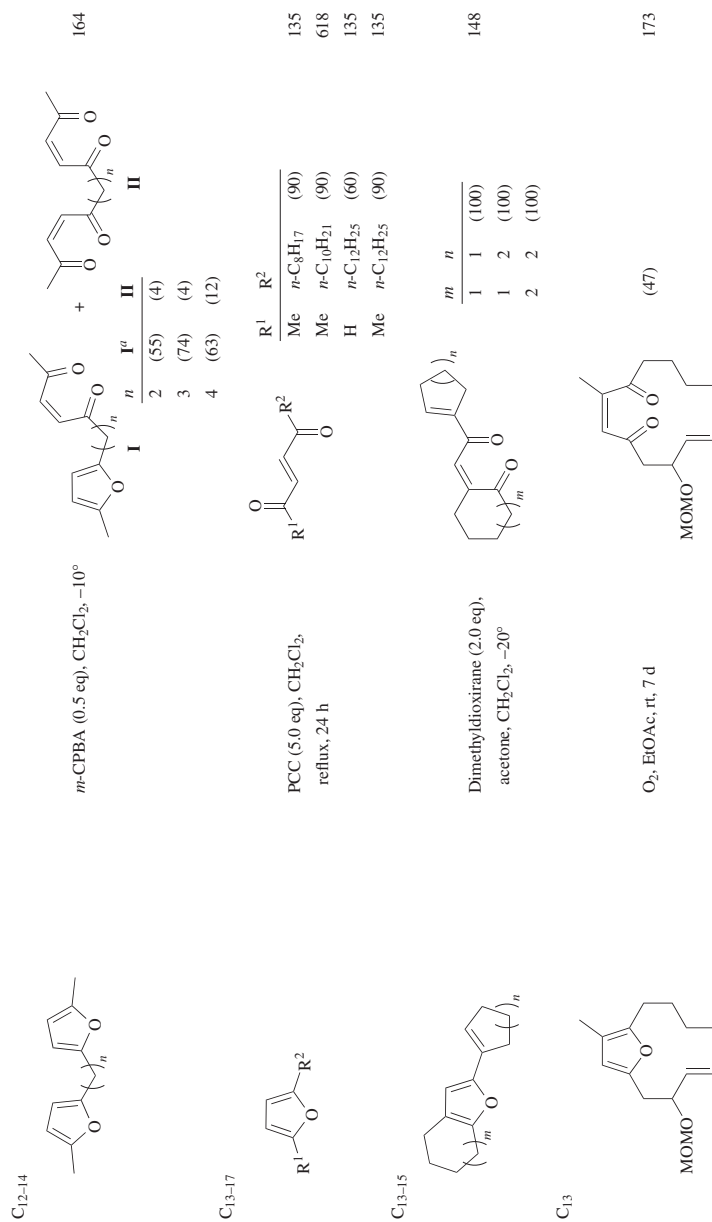


TABLE 1. SYNTHESIS OF 1,4-DIKETOALKENES (Continued)

C ₁₃₋₁₄	Furan	Conditions	Product(s) and Yield(s) (%)		Refs.
			I	II	
C ₁₃₋₁₄		O ₂ , rose bengal, hv, MeCN, 0°, 5 min; then rt, 12 h			300, 298
				R	
				H (68)	
				F (62)	
				Cl (68)	
C ₁₃₋₂₀		NBS, PPTS, CH ₂ Cl ₂ , 40-45°, 20 h			175, 153
				R	
				H (81)	
C ₁₄		H ₂ SO ₄ , KOAc			634
				(-)	
C ₁₅		Dimethyldioxirane (1.5 eq), acetone, CH ₂ Cl ₂ , -45°, 2 h			147

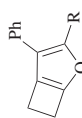
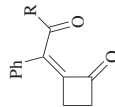
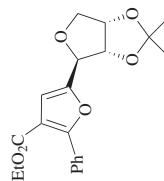
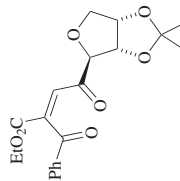
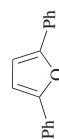
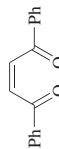
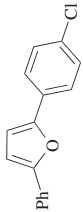
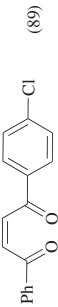
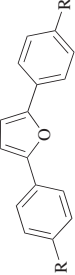
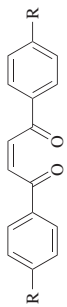
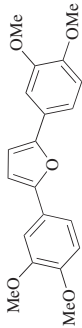
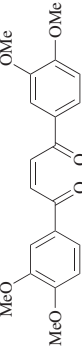
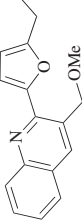
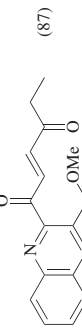
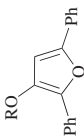
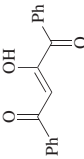
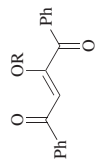
C ₁₅₋₁₉			DMP (2.5 eq), CH ₂ Cl ₂ , rt, 5 h	R	635	
				<i>n</i> -Pr (62)		
				<i>i</i> -Pr (53)		
				<i>n</i> -Bu (66)		
				Bn (64)		
C ₁₅			O ₂ , hv, acetone, rt, 20 min; then Me ₂ S (10 eq), rt, 30 min	(67)	292	
C ₁₆			CAN, MeCN, H ₂ O	(77)	636	
			Pb(OAc) ₄ (2 eq), CHCl ₃ , 20–30°, 5 h	(59)	129	
			<i>m</i> -CPBA (1.5 eq), CH ₂ Cl ₂ , rt, 5 min	(92)	163	
			K ₂ S ₂ O ₈ (1 eq), MeCN, H ₂ O, rt, 15 min		308	
				Atm	Temp	Time (h)
				O ₂	rt	48 (57)
				O ₂	rt	72 (62)
				O ₂	rt	192 (74)
				O ₂	70°	0.5 (97)
				O ₂	70°	1 (97)
				Ar	70°	0.5 (97)
				Ar	70°	1 (87)

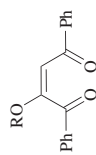
TABLE 1. SYNTHESIS OF 1,4-DIKETOALKENES (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
	<i>m</i> -CPBA (1.5 eq), CH ₂ Cl ₂ , rt, 5 min	 (89)	163
	Selectfluor (2 eq), THF, H ₂ O, 60–70°, 3 h	 R H (100) Br (69)	177
	K ₂ Cr ₂ O ₇ , AcOH, H ₂ O	 (17)	637
	1. NBS (1.1 eq), NaHCO ₃ (2 eq), py (3.75 eq), H ₂ O 2. HCl (1 N)	 (87)	150
	PhNMMe ₃ •Br ₃ (1 eq), <i>i</i> -BuOH, rt, 15 h	 R Me (80) Et (83) <i>n</i>-Pr (92) <i>i</i>-Pr (80) <i>n</i>-Bu (90) <i>i</i>-Bu (83)	176

R	Solvent	Time (h)	
Me	THF/DMSO (2:1)	22	(80) 175
Et	DMSO	24	(88)
Et	THF/DMSO (2:1)	24	(89)
<i>n</i> -Pr	THF/DMSO (2:1)	21	(82)
<i>i</i> -Pr	THF/DMSO (2:1)	22	(95)
<i>n</i> -Bu	DMSO	21	(96)
<i>n</i> -Bu	THF/DMSO (2:1)	17	(95)
<i>i</i> -Bu	DMSO	22	(96)
<i>i</i> -Bu	THF/DMSO (2:1)	31	(96)



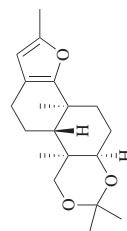
PhNM₃•Br₃ (1 eq), rt, 20 h



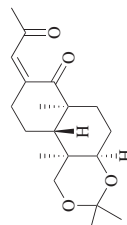
DDQ (1 eq), CH₂Cl₂, rt,
15–28 h

R	
Me	(98)
Et	(98)
<i>n</i> -Pr	(98)
<i>i</i> -Pr	(80)
<i>n</i> -Bu	(87)
<i>i</i> -Bu	(90)

628



m-CPBA (1 eq), CH₂Cl₂, 0°, 1 h;
then rt, 7 h



(97)

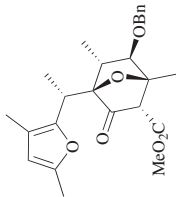
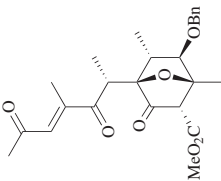
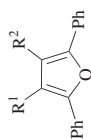
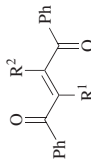
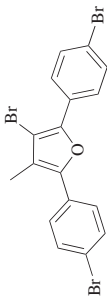
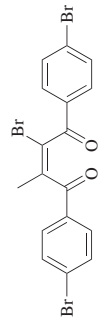
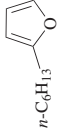
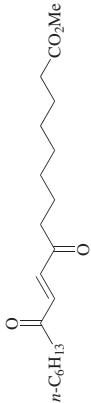
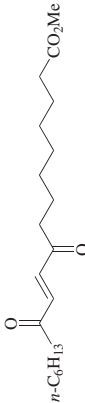
159, 158

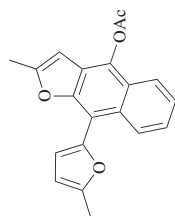
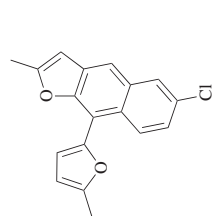
TABLE 1. SYNTHESIS OF 1,4-DIKETOALKENES (Continued)

C ₁₆₋₂₂	Furan	Conditions	Product(s) and Yield(s) (%)		Refs.
			R ¹	R ²	
C ₁₆₋₂₂		DDQ (1 eq), <i>t</i> -BuOH, rt, 21 h			176
			Me	H	
			Et	H	
			<i>n</i> -Pr	H	
			<i>i</i> -Pr	H	
			<i>n</i> -Bu	H	
			<i>i</i> -Bu	H	
			Et	Ph	
			<i>n</i> -Pr	Ph	
			<i>i</i> -Pr	Ph	
			<i>n</i> -Bu	Ph	
			<i>i</i> -Bu	Ph	
C ₁₆₋₂₈		NH ₄ NO ₃ (1.25 eq), AcOH, H ₂ O, reflux, 1.5 h			126 126 126 126, 127 126 126 126 126 126 126
			H	H	
			Ph	H	
			Ph	Cl	
			Ph	Br	
			Ph	Br	
			Ph	Br	
			Ph	Cl	
			Ph	Br	
			Ph	Me	
			Ph	Br	
			Ph	Br	

C ₁₆		Br ₂ , AcOH		R H (—) Cl (—)	638
C ₁₇		CAN (2.3 eq), MeCN, H ₂ O, -20°		(45)	134
		CAN (2.3 eq), MeCN, H ₂ O, -20°, 0.5 h		(45)	134
		<i>m</i> -CPBA (1.1 eq), CF ₃ CO ₂ H, CH ₂ Cl ₂ , rt		(70)	639
		<i>m</i> -CPBA (1.0 eq), CH ₂ Cl ₂		(46)	640

TABLE 1. SYNTHESIS OF 1,4-DIKETOALKENES (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.															
C ₁₇		MMPP (0.5 eq), DMF	 (61)	641															
C ₁₇₋₂₁		EtCO ₂ H, HNO ₃ , -5°, 15 min	 <table><tr><th>R¹</th><th>R²</th><th>Yield (%)</th></tr><tr><td>H</td><td>HOCH₂</td><td>(70)</td></tr><tr><td>H</td><td>ClCH₂</td><td>(—)</td></tr><tr><td>H</td><td>Et</td><td>(74)</td></tr><tr><td>Me</td><td>1-morpholinyl</td><td>(95)</td></tr></table>	R ¹	R ²	Yield (%)	H	HOCH ₂	(70)	H	ClCH ₂	(—)	H	Et	(74)	Me	1-morpholinyl	(95)	125 125 122 642
R ¹	R ²	Yield (%)																	
H	HOCH ₂	(70)																	
H	ClCH ₂	(—)																	
H	Et	(74)																	
Me	1-morpholinyl	(95)																	
C ₁₇		HNO ₃ , AcOH, 50°, 1 h	 (91)	123															
C ₁₈		PCC, CH ₂ Cl ₂	 (95)	643															
		MMPP, EtOH, H ₂ O	 (93)	643															

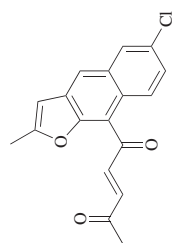


PCC (2.0 eq), CH_2Cl_2 , rt, 60 h

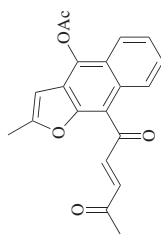
KNO_3 (1.5 eq), AcOH, 50° , 1 h

PCC (2.0 eq), CH_2Cl_2 , rt, 60 h

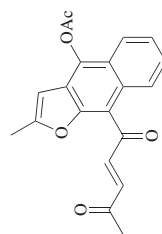
MMPP (10 eq), benzene,
reflux, 5 h



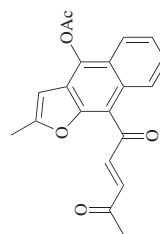
(35)



(50)



(50)



(34)

136

136

136

136

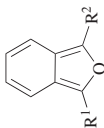
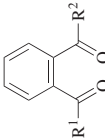
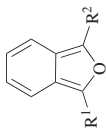
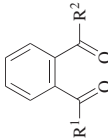
TABLE 1. SYNTHESIS OF 1,4-DIKETOALKENES (Continued)

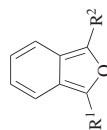
	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₈		Dimethyldioxirane, acetone, CHCl ₃ , rt	 (100)	644
		1. O ₂ , rose bengal, hv, CH ₂ Cl ₂ , 0°, 12 h 2. TBAF (1.5 eq), MeI (2.0 eq), THF, rt, 1 h	 (97)	322
		Pb(OAc) ₄ (2.0 eq), Et ₂ O	 (89)	645
		H ₂ SO ₄ , K ₂ Cr ₂ O ₇ , Et ₂ O	 (71)	645
C ₁₈₋₃₄		<i>m</i> -CPBA (1.5 eq), CH ₂ Cl ₂ , rt, 5 min	 R	(88)
			 4-MeOC ₆ H ₄	(93)
			 4-Ph ₂ NC ₆ H ₄	(81)
			 9- <i>n</i> -hexyl-9 <i>H</i> -carbazole-3-yl	(80)
			 9-(2-ethylhexyl)-9 <i>H</i> -carbazole-3-yl	(83)

C ₁₈ –39					
			R		
		Pb(OAc) ₄ (1.0 eq), THF, 50°, 0.5 h	2-thienyl 4-MeOC ₆ H ₄ 4-MeC ₆ H ₄ 3,4-Me ₂ -C ₆ H ₃ 3-benzothienyl 1-naphthyl 2-MeO-1-naphthyl 4-Me-1-naphthyl 4-PhC ₆ H ₄ dibenzol[<i>b,d</i>]thiophene-2-yl 9-(2-ethylhexyl)-9 <i>H</i> -carbazole-3-yl 9,9-dihexyl-9 <i>H</i> -fluorene-2-yl	(84) (87) (87) (90) (85) (85) (88) (87) (85) (81) (83) (71)	646 646, 163 646 646 646 646 646 646 646 646 646 646

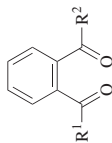
C ₁₈ -43			<i>m</i> -CPBA (1.5 eq), CH ₂ Cl ₂ , rt, 5 min	2-thienyl 2-thienyl 4-MeOC ₆ H ₄ 4-MeOC ₆ H ₄ 4-BnC ₆ H ₄ 4-MeC ₆ H ₄ 2,2'-bithiophene-5-yl 4-Ph ₂ NC ₆ H ₄ 4-MeC ₆ H ₄ 2,2'-bithiophene-5-yl 5-hexyl-2-thienyl 1-naphthyl 9-hexyl-9 <i>H</i> -carbazole-5-yl	(77) (86) (94) (83) (91) (88) (79) (91) (85) (87) (90) (78)	163
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TABLE 1. SYNTHESIS OF 1,4-DIKETOALKENES (*Continued*)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.																																	
C₁₈₋₄₃ 	 <i>m</i>-CPBA (1.5 eq), CH₂Cl₂, rt, 5 min	<table><thead><tr><th>R¹</th><th>R²</th><th></th></tr></thead><tbody><tr><td>5-hexyl-2-thienyl</td><td>dibenzo[<i>b,d</i>]furan-2-yl</td><td>(80)</td></tr><tr><td>1-naphthyl</td><td>dibenzo[<i>b,d</i>]furan-2-yl</td><td>(83)</td></tr><tr><td>4-MeC₆H₄</td><td>pyrene-1-yl</td><td>(94)</td></tr><tr><td>4-MeOC₆H₄</td><td>9-hexyl-9<i>H</i>-carbazole-3-yl</td><td>(82)</td></tr><tr><td>4-MeC₆H₄</td><td>9-hexyl-9<i>H</i>-carbazole-3-yl</td><td>(82)</td></tr><tr><td>1-naphthyl</td><td>9-hexyl-9<i>H</i>-carbazole-3-yl</td><td>(81)</td></tr><tr><td>2-thienyl</td><td>9,9-dihexyl-9<i>H</i>-fluorene-2-yl</td><td>(78)</td></tr><tr><td>4-MeOC₆H₄</td><td>9,9-dihexyl-9<i>H</i>-fluorene-2-yl</td><td>(81)</td></tr><tr><td>4-MeC₆H₄</td><td>9,9-dihexyl-9<i>H</i>-fluorene-2-yl</td><td>(83)</td></tr><tr><td>1-naphthyl</td><td>9,9-dihexyl-9<i>H</i>-fluorene-2-yl</td><td>(80)</td></tr></tbody></table>	R ¹	R ²		5-hexyl-2-thienyl	dibenzo[<i>b,d</i>]furan-2-yl	(80)	1-naphthyl	dibenzo[<i>b,d</i>]furan-2-yl	(83)	4-MeC ₆ H ₄	pyrene-1-yl	(94)	4-MeOC ₆ H ₄	9-hexyl-9 <i>H</i> -carbazole-3-yl	(82)	4-MeC ₆ H ₄	9-hexyl-9 <i>H</i> -carbazole-3-yl	(82)	1-naphthyl	9-hexyl-9 <i>H</i> -carbazole-3-yl	(81)	2-thienyl	9,9-dihexyl-9 <i>H</i> -fluorene-2-yl	(78)	4-MeOC ₆ H ₄	9,9-dihexyl-9 <i>H</i> -fluorene-2-yl	(81)	4-MeC ₆ H ₄	9,9-dihexyl-9 <i>H</i> -fluorene-2-yl	(83)	1-naphthyl	9,9-dihexyl-9 <i>H</i> -fluorene-2-yl	(80)	163
R ¹	R ²																																			
5-hexyl-2-thienyl	dibenzo[<i>b,d</i>]furan-2-yl	(80)																																		
1-naphthyl	dibenzo[<i>b,d</i>]furan-2-yl	(83)																																		
4-MeC ₆ H ₄	pyrene-1-yl	(94)																																		
4-MeOC ₆ H ₄	9-hexyl-9 <i>H</i> -carbazole-3-yl	(82)																																		
4-MeC ₆ H ₄	9-hexyl-9 <i>H</i> -carbazole-3-yl	(82)																																		
1-naphthyl	9-hexyl-9 <i>H</i> -carbazole-3-yl	(81)																																		
2-thienyl	9,9-dihexyl-9 <i>H</i> -fluorene-2-yl	(78)																																		
4-MeOC ₆ H ₄	9,9-dihexyl-9 <i>H</i> -fluorene-2-yl	(81)																																		
4-MeC ₆ H ₄	9,9-dihexyl-9 <i>H</i> -fluorene-2-yl	(83)																																		
1-naphthyl	9,9-dihexyl-9 <i>H</i> -fluorene-2-yl	(80)																																		
C₁₈₋₃₀ 	 Pb(OAc)₄ (1.0 eq), THF, 50°, 0.5 h	<table><thead><tr><th>R¹</th><th>R²</th><th></th></tr></thead><tbody><tr><td>2-thienyl</td><td>4-ClC₆H₄</td><td>(72)</td></tr><tr><td>2-thienyl</td><td>4-MeOC₆H₄</td><td>(91)</td></tr><tr><td>2-thienyl</td><td>3,4-(MeO)₂C₆H₃</td><td>(89)</td></tr><tr><td>2-thienyl</td><td>2,4-Me₂C₆H₃</td><td>(91)</td></tr><tr><td>2-thienyl</td><td>3,4-Me₂C₆H₃</td><td>(85)</td></tr><tr><td>2-thienyl</td><td>3-benzothieryl</td><td>(88)</td></tr><tr><td>2-thienyl</td><td>2-Me-3-benzothieryl</td><td>(92)</td></tr><tr><td>2-thienyl</td><td>1-naphthyl</td><td>(—)</td></tr></tbody></table>	R ¹	R ²		2-thienyl	4-ClC ₆ H ₄	(72)	2-thienyl	4-MeOC ₆ H ₄	(91)	2-thienyl	3,4-(MeO) ₂ C ₆ H ₃	(89)	2-thienyl	2,4-Me ₂ C ₆ H ₃	(91)	2-thienyl	3,4-Me ₂ C ₆ H ₃	(85)	2-thienyl	3-benzothieryl	(88)	2-thienyl	2-Me-3-benzothieryl	(92)	2-thienyl	1-naphthyl	(—)	646						
R ¹	R ²																																			
2-thienyl	4-ClC ₆ H ₄	(72)																																		
2-thienyl	4-MeOC ₆ H ₄	(91)																																		
2-thienyl	3,4-(MeO) ₂ C ₆ H ₃	(89)																																		
2-thienyl	2,4-Me ₂ C ₆ H ₃	(91)																																		
2-thienyl	3,4-Me ₂ C ₆ H ₃	(85)																																		
2-thienyl	3-benzothieryl	(88)																																		
2-thienyl	2-Me-3-benzothieryl	(92)																																		
2-thienyl	1-naphthyl	(—)																																		

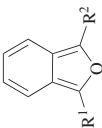
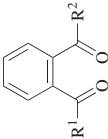
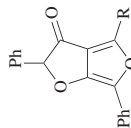
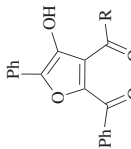
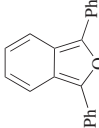
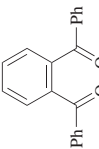


Pb(OAc)₄ (1.0 eq), THF,
50°, 0.5 h



			R ¹	R ²	
2-thienyl	2-MeO-1-naphthyl	(93)	2-MeC ₆ H ₄	2-thienyl	(88) 646
2-thienyl	4-Me-1-naphthyl	(83)	4-MeC ₆ H ₄	2-thienyl	(89) 646
1-naphthyl	3,4-(MeO) ₂ C ₆ H ₃	(87)	4-MeOC ₆ H ₄	4-Ph ₂ NC ₆ H ₄	(24) 163
2-thienyl	4-PhC ₆ H ₄	(85)	4-MeC ₆ H ₄	3,4-(MeO) ₂ C ₆ H ₃	(90) 646
2-thienyl	dibenzo[<i>b,d</i>]thiophene-2-yl	(92)	4-MeC ₆ H ₄	4-MeC ₆ H ₄	(86) 646
5-hexyl-2-thienyl	dibenzo[<i>b,d</i>]furan-2-yl	(89)	4-MeOC ₆ H ₄	3,4-Me ₂ C ₆ H ₃	(96) 646
1-naphthyl	2-MeO-1-naphthyl	(89)	4-MeOC ₆ H ₄	3-benzothieryl	(92) 646
1-naphthyl	4-Me-1-naphthyl	(85)	4-MeC ₆ H ₄	3-benzothieryl	(85) 646
1-naphthyl	dibenzo[<i>b,d</i>]thiophene-2-yl	(87)	4-MeC ₆ H ₄	2,2'-bithiophene-5-yl	(88) 646
			4-MeC ₆ H ₄	2-Me-3-benzothieryl	(91) 646
			4-MeOC ₆ H ₄	4-Me-1-naphthyl	(88) 646
			2-MeC ₆ H ₄	2-MeO-1-naphthyl	(89) 646
			4-MeC ₆ H ₄	1-naphthyl	(85) 163, 646
			4-MeC ₆ H ₄	2-MeO-1-naphthyl	(96) 646
			4-MeOC ₆ H ₄	dibenzo[<i>b,d</i>]thiophene-2-yl	(89) 646

TABLE 1. SYNTHESIS OF 1,4-DIKETOALKENES (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.																								
C ₁₉₋₄₀ 	 Pb(OAc) ₄ (1.0 eq), THF, 50°, 0.5 h	<table><thead><tr><th>R¹</th><th>R²</th><th></th></tr></thead><tbody><tr><td>4-MeC₆H₄</td><td>4-Me-1-naphthyl</td><td>(82)</td></tr><tr><td>2,4-Me₂-C₆H₃</td><td>1-naphthyl</td><td>(89)</td></tr><tr><td>2-MeC₆H₄</td><td>dibenzo[<i>b,d</i>]thiophene-2-yl</td><td>(82)</td></tr><tr><td>4-MeC₆H₄</td><td>4-PhC₆H₄</td><td>(96)</td></tr><tr><td>4-MeC₆H₄</td><td>dibenzo[<i>b,d</i>]thiophene-2-yl</td><td>(90)</td></tr><tr><td>4-MeC₆H₄</td><td>4-Ph₂NC₆H₄</td><td>(25)</td></tr><tr><td>4-MeC₆H₄</td><td>9,9-dihexyl-9<i>H</i>-fluorene-2-yl</td><td>(88)</td></tr></tbody></table>	R ¹	R ²		4-MeC ₆ H ₄	4-Me-1-naphthyl	(82)	2,4-Me ₂ -C ₆ H ₃	1-naphthyl	(89)	2-MeC ₆ H ₄	dibenzo[<i>b,d</i>]thiophene-2-yl	(82)	4-MeC ₆ H ₄	4-PhC ₆ H ₄	(96)	4-MeC ₆ H ₄	dibenzo[<i>b,d</i>]thiophene-2-yl	(90)	4-MeC ₆ H ₄	4-Ph ₂ NC ₆ H ₄	(25)	4-MeC ₆ H ₄	9,9-dihexyl-9 <i>H</i> -fluorene-2-yl	(88)	646 646 646 646 646 163 646
R ¹	R ²																										
4-MeC ₆ H ₄	4-Me-1-naphthyl	(82)																									
2,4-Me ₂ -C ₆ H ₃	1-naphthyl	(89)																									
2-MeC ₆ H ₄	dibenzo[<i>b,d</i>]thiophene-2-yl	(82)																									
4-MeC ₆ H ₄	4-PhC ₆ H ₄	(96)																									
4-MeC ₆ H ₄	dibenzo[<i>b,d</i>]thiophene-2-yl	(90)																									
4-MeC ₆ H ₄	4-Ph ₂ NC ₆ H ₄	(25)																									
4-MeC ₆ H ₄	9,9-dihexyl-9 <i>H</i> -fluorene-2-yl	(88)																									
C ₁₉₋₂₄ 	 <i>m</i> -CPBA, dichloroethane, rt, 2 h	<table><thead><tr><th>R</th><th></th></tr></thead><tbody><tr><td>Me</td><td>(86)</td></tr><tr><td>Ph</td><td>(83)</td></tr></tbody></table>	R		Me	(86)	Ph	(83)	647																		
R																											
Me	(86)																										
Ph	(83)																										
C ₂₀ 	 H ₂ O ₂ , Na ₂ MoO ₄ •2H ₂ O, NaOH, THF, 30°, 280 min	(96) ^c	77																								
	H ₂ O ₂ , Na ₂ MoO ₄ •2H ₂ O, sodium dodecyl sulfate, BuOH, H ₂ O, rt	(91) ^c	50																								

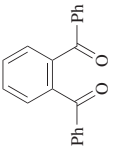
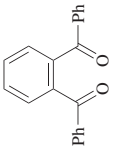
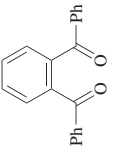
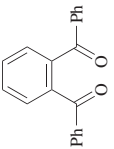
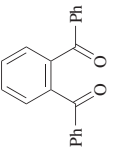
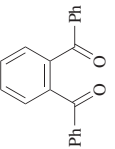
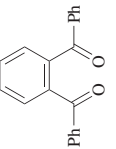
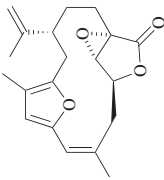
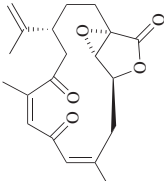
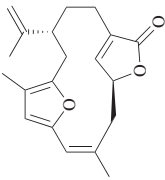
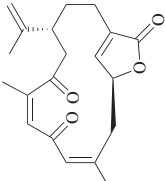
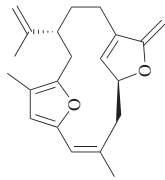
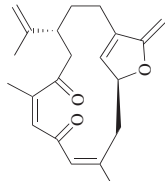
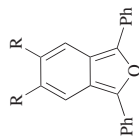
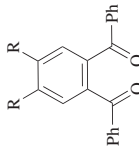
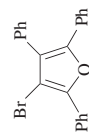
 $\text{PhI}(\text{O}_2\text{CCF}_3)_2$ (2.5 eq), H_2O_2 (6.0 eq), CH_2Cl_2 , 10° , 2–3 h	(80)	76
 $\text{CaO}_2 \cdot 2\text{H}_2\text{O}_2$ (8.0 eq), MeOH , 50° , 3 h	(88)	648
 O_3 , $\text{P}(\text{OPh})_3$, CH_2Cl_2	(88)	649
 O_2 , hv, CH_2Cl_2 , -78° , 4 h	(40)	171
 O_2 , benzene, reflux, 34 h	(86)	168
 <i>m</i> -CPBA (1.5 eq), CH_2Cl_2 , rt , 5 min	(92)	163
 $^1\text{O}_2$, <i>t</i> -BuOK, Ac_2O , MeCN , rt , 5 min	(31)	78

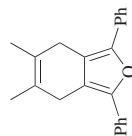
TABLE 1. SYNTHESIS OF 1,4-DIKETOALKENES (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₂₀		<i>m</i> -CPBA (1.0 eq), CH ₂ Cl ₂ , 0°	 (73)	650
		<i>m</i> -CPBA (1.0 eq), CH ₂ Cl ₂ , 0°	 (73)	180
		<i>m</i> -CPBA (1.0 eq), CH ₂ Cl ₂ , 0°	 (88)	310
C ₂₁		hv, CH ₂ Cl ₂ , air, rt, 48 h	 R NC- (99) EtO ₂ C (99)	301

C₂₂

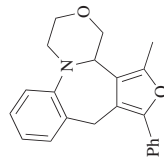
KNO₃ (1.25 eq), AcOH, H₂O,
reflux, 10 min

(80)



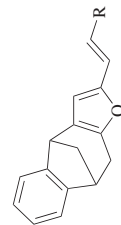
Br₂, NaOAc, AcOH, H₂O,
reflux, 5 min

(90)



m-CPBA (0.9 eq), CH₂Cl₂, 0°

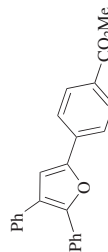
(81)

C₂₂₋₂₄

m-CPBA (1.0 eq), CH₂Cl₂, -10°;
then rt, 2.5 h

R	
Ph	(88)
2-MeC ₆ H ₄	(83)
2-(CH ₂ =CH)C ₆ H ₄	(71)

652

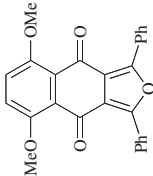
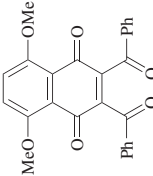
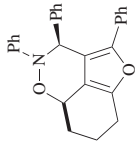
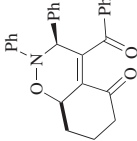
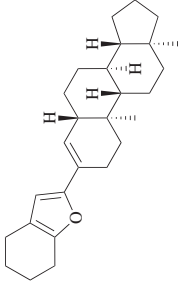
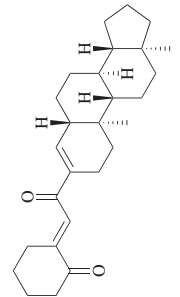
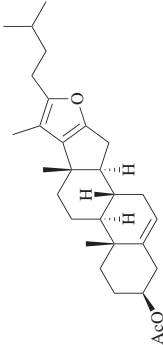
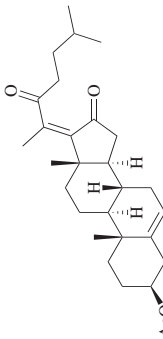
C₂₃

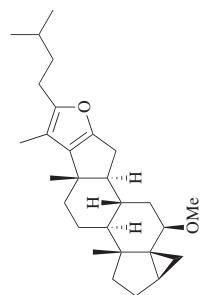
e⁻ (Ag/Ag⁺), Bu₄NPF₆, THF

(91)

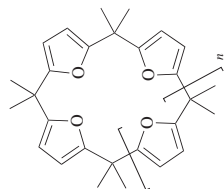
69

TABLE 1. SYNTHESIS OF 1,4-DIKETOALKENES (Continued)

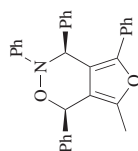
	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₂₄		CAN (2.2 eq), MeCN, H ₂ O	 (64)	653
C ₂₇		CAN (2.2 eq), MeCN/H ₂ O (10:1), rt, 30 min	 (62)	133
		Dimethyldioxirane (1.0 eq), acetone, CH ₂ Cl ₂ , -20°	 (100)	148
		<i>m</i> -CPBA (1.0 eq), CH ₂ Cl ₂ , rt, 1 h	 (84)	654



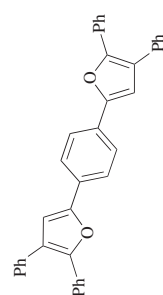
C₂₈₋₄₂



C₃₁



C₃₈

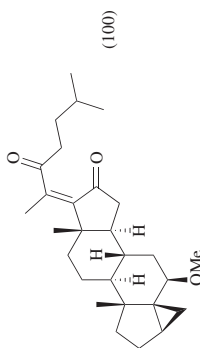


air

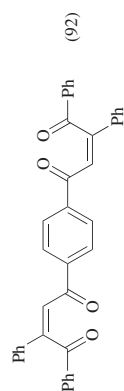
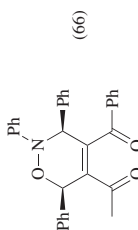
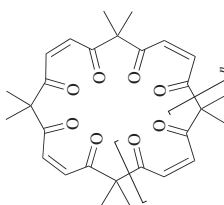
m-CPBA (1.1 eq), CHCl₃, rt

CAN (2.2 eq),
MeCN/H₂O (1:1), rt

e⁻ (Ag/Ag⁺), Bu₄NPF₆, THF



<i>n</i>	
1	(78)
2	(56)
3	(85)



172

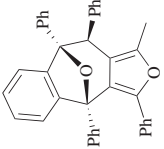
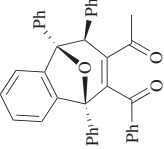
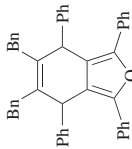
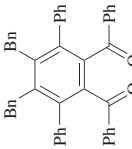
144
165
144, 166

133

69



TABLE 1. SYNTHESIS OF 1,4-DIKETOALKENES (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₃₈		<i>m</i> -CPBA (1.1 eq), CH ₂ Cl ₂ , 0°, 3 h	 (91)	655
C ₄₆		Br ₂ , MeOH	 (70)	656

^aThe yield is based on recovered starting material.

^bThe yield was determined by LCMS.

^cThe yield was determined by GC.

TABLE 2. SYNTHESIS OF 4-OXOALKENALS

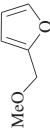
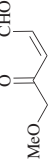
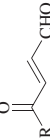
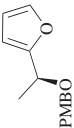
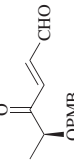
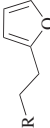
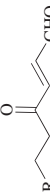
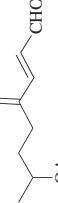
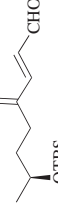
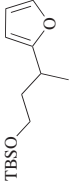
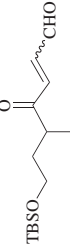
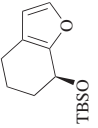
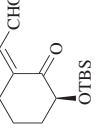
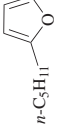
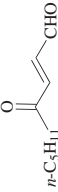
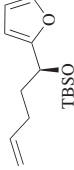
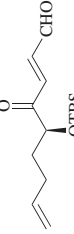
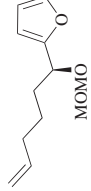
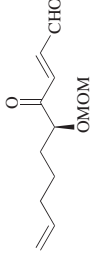
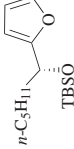
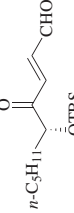
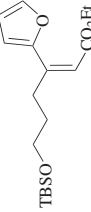
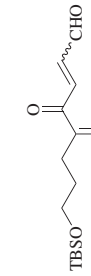
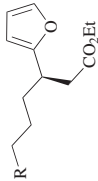
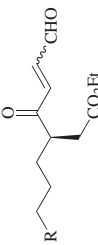
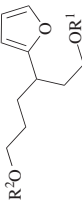
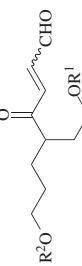
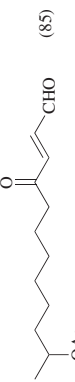
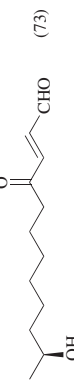
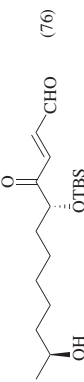
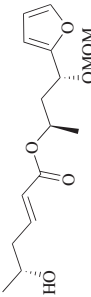
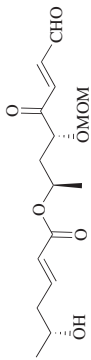
Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
	O ₂ , rose bengal, 18-crown-6 (0.01 eq), CH ₂ Cl ₂ , -60°; then CHCl ₃ , -10°	 (96)	304
	NBS, py, acetone/H ₂ O, rt, 2 h	(—)	657
	NBS (1.1 eq), NaHCO ₃ (2.0 eq), acetone/H ₂ O (10:1), -15°, 0.5 h	 R	188
		R	Et (44) n-Pr (64) n-Bu (46) n-C ₃ H ₁₁ (44)
	NBS (1.1 eq), NaHCO ₃ (2.0 eq), acetone/H ₂ O (10:1), -15°, 0.5 h; then py (2.1 eq), rt, 6 h	 (74)	185, 569
	NBS (1.5 eq), py (1.33 eq), THF/acetone/H ₂ O (5:4:1), -20°, 1 h; then rt, 3 h	 R	658, 659
		R	Time (h) EtO ₂ C 3 (60) n-Pr 6 (44)
	PCC (5.3 eq), CH ₂ Cl ₂ , rt, 12 h; then reflux, 36 h	 (60)	179
	NBS (1.3 eq), py (4.0 eq), THF/acetone/H ₂ O (5:4:1), -20°, 1 h; then rt, 5 h	 (64)	182

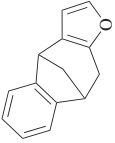
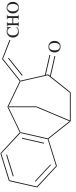
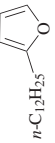
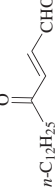
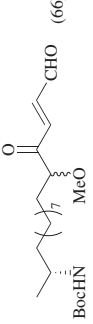
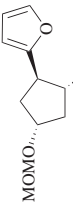
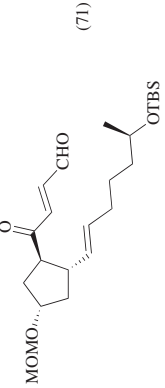
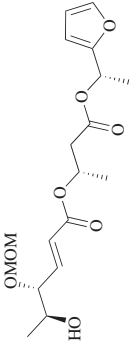
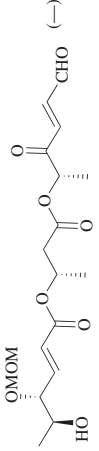
TABLE 2. SYNTHESIS OF 4-OXOALKENALS (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₈		NBS (1.1 eq), NaHCO ₃ (2.0 eq), acetone/H ₂ O (10:1), -15°, 1 h; then py (1.5 eq), rt, 1 h	 (72)	187
C ₉		<i>m</i> -CPBA, CH ₂ Cl ₂	 (50)	660
		PCC (5.2 eq), CH ₂ Cl ₂ , rt, 12 h	 (70)	178
		NBS (1.2 eq), acetone/H ₂ O (10:1), NaHCO ₃ (2.0 eq), -15°, 2 h; then py (1.0 eq), rt, 4 h	 (55)	661
C ₁₀		NBS (1.3 eq), NaHCO ₃ (2.0 eq), py (4.0 eq), THF/acetone/H ₂ O (5:4:1), -20°, 1 h	 (55)	186
		NBS (1.1 eq), NaHCO ₃ (2.0 eq), acetone/H ₂ O (10:1), -15°, 1 h; then py (1.5 eq), rt, 1 h	 (—)	662
		NBS (1.1 eq), NaHCO ₃ (2.0 eq), acetone/H ₂ O (10:1), -15°, 1 h; then py (1.5 eq), rt, 1 h	 (62)	187

	NBS (1.1 eq), NaHCO ₃ (2.0 eq), acetone/H ₂ O (10:1), -15°, 1 h; then py (1.5 eq), rt, 1 h		R BocHN (56) TBSO (67)	187
	NBS (1.1 eq), NaHCO ₃ (2.0 eq), acetone/H ₂ O (10:1), -15°, 1 h; then py (1.5 eq), rt, 1 h		R ¹ R ² Ac TBS (89) TBS MOM (81)	187
	Br ₂ (0.1 eq), py (5.0 eq), acetone/H ₂ O (4:1), -20°; then rt, 12 h		(85)	181
	NBS (1.3 eq), py (4.0 eq), THF/acetone/H ₂ O (5:4:2), -20°, 1 h; then rt, 4 h		(73)	182
	NBS, H ₂ O, NaHCO ₃ , acetone, -15°, 30 min; then py, rt, 5 h		(76)	663
	NBS (1.2 eq), NaHCO ₃ (2.0 eq), acetone/H ₂ O (10:1), -15°, 2.5 h; then py (1.0 eq), rt, 21 h		(—)	184

C₁₂C₁₄

TABLE 2. SYNTHESIS OF 4-OXOALKENALS (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₄ 	<i>m</i> -CPBA (1.0 eq), CH ₂ Cl ₂ , -10°, 2.5 h	 (77)	652
C₁₆ 	NBS (1.2 eq), NaHCO ₃ (2.0 eq), acetone/H ₂ O (10:1), -15°, 1 h; then py (2.0 eq), rt, 2 h	 (60)	199
	NBS, H ₂ O, NaHCO ₃ , acetone, -15°, 30 min; then py, rt	 (66)	664
	NBS, THF/acetone/H ₂ O, -20°, 0.5 h; then rt, 4 h	 (71)	183
	NBS (1.1 eq), NaHCO ₃ (2.0 eq), acetone/H ₂ O (10:1), -15°, 0.5 h; then py (2.1 eq), rt, 6 h	 (—)	185, 569

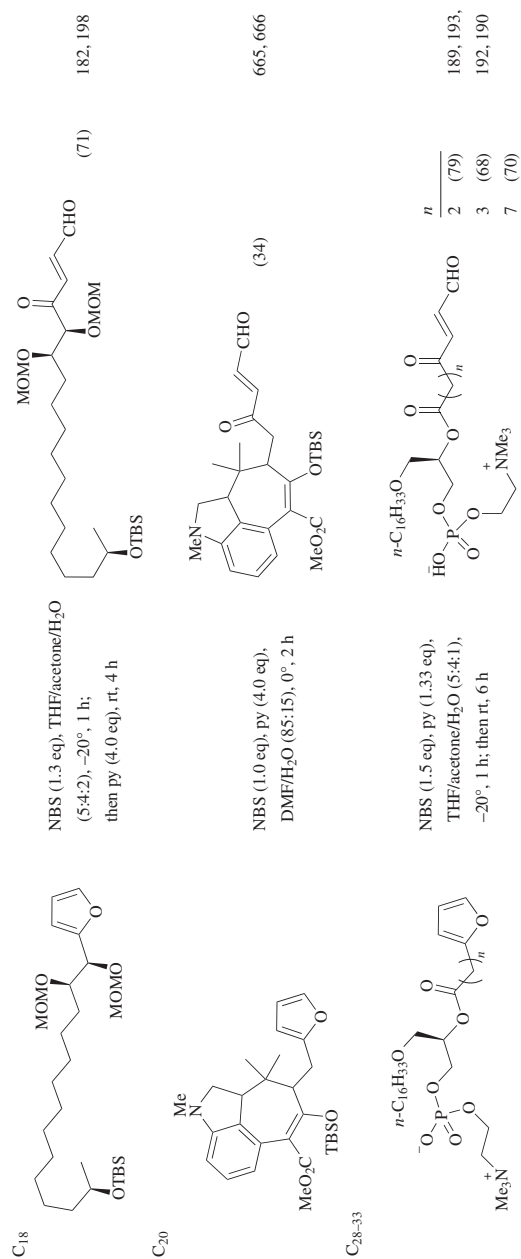
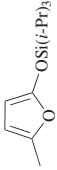
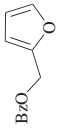
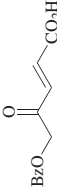
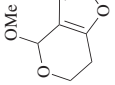
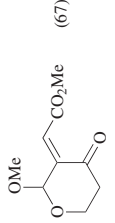
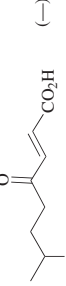
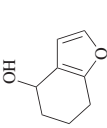
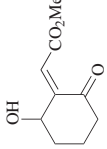
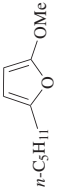
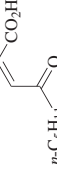
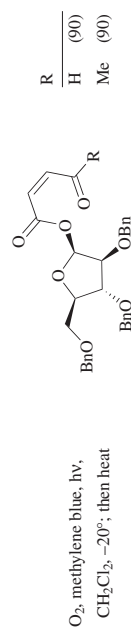
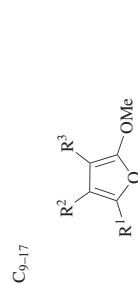
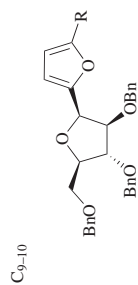


TABLE 3. SYNTHESIS OF 4-OXALKENOIC ACIDS AND ESTERS

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
	Dimethyldioxirane (1.1 eq), acetone, -78°, 1 h	 (100)	203
	O ₂ , methylene blue, hv, solvent, 10°, 2 d	 (14)	92
	1. <i>m</i> -CPBA (2.0 eq), CH ₂ Cl ₂ , darkness, rt, 2 h 2. CH ₂ N ₂ , Et ₂ O	 (67)	197
	1. PCC (1.43 eq), acetone, rt, 2.5 h 2. 2-Mercaptobenzimidazole (0.03 eq), rt, 6 h	 (16)	195
	1. <i>m</i> -CPBA (2.0 eq), CH ₂ Cl ₂ , darkness, rt, 2 h 2. CH ₂ N ₂ , Et ₂ O	 (87)	197
	MeCO ₃ H, NaOAc, CH ₂ Cl ₂ , rt, 6.5 h TPP, Me ₂ S, CCl ₄ , -20°; then O ₂ , hv, -20° to rt, 40 min	 (99)	667 668



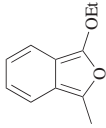
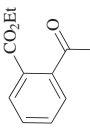
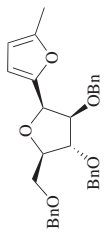
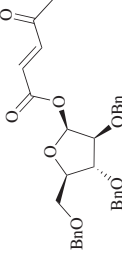
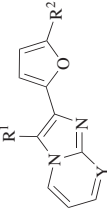
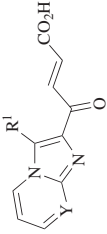
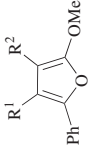
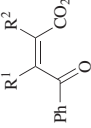
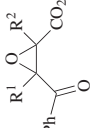
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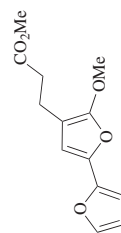
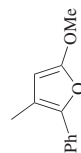
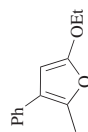
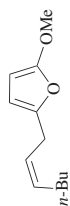
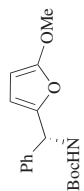
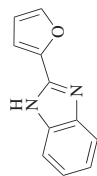


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R ¹	R ²	R ³	Time (h)
MeO ₂ C	Et	Et	180 (77)
H	MeO ₂ C	Ph	15 (98)
H	MeO ₂ C	4-BrC ₆ H ₄	15 (98)
H	MeO ₂ C	3-MeOC ₆ H ₄	15 (92)
MeO ₂ C	H	Ph	30 (85)
MeO ₂ C	H	4-BrC ₆ H ₄	30 (80)
MeO ₂ C	H	3-MeOC ₆ H ₄	30 (94)
MeO ₂ C	H	4-MeOC ₆ H ₄	30 (88)
H	Ac	Ph	15 (76)
H	MeO ₂ C	4-MeC ₆ H ₄	15 (92)
Ac	H	Ph	10 (90)
MeO ₂ C	H	4-MeC ₆ H ₄	15 (89)
MeO ₂ C	Me	Ph	60 (75)
MeO ₂ C	MeO ₂ C	Ph	15 (92)
MeO ₂ C	Me	Bn	30 (83)
MeO ₂ C	MeO ₂ C	Bn	720 (90)
EtO ₂ C	Ph	Ph	30 (84)

TABLE 3. SYNTHESIS OF 4-OXOALKENOIC ACIDS AND ESTERS (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₉		air	 (—)	669
C ₁₀		O ₂ , methylene blue, hv, CH ₂ Cl ₂ , -20°, 1–1.5 h; then 40°, SiO ₂	 (70)	94
C ₁₀₋₁₁		93% HNO ₃ , H ₂ SO ₄ , 15 min		670 670 196 196 196
C ₁₀₋₁₂		O ₂ , methylene blue, hv, nitromethane, -25°, 2 h	 I +  II	88

C₁₁

O₂, methylene blue, hv,
MeOH, 18 h; then SiO₂

NBS (1.0 eq), NaHCO₃,
Et₂O/H₂O, 0°, 15 min

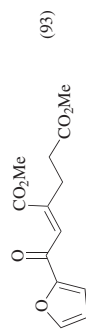
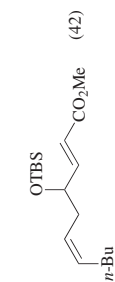
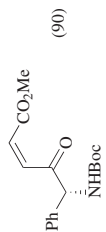
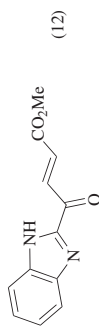
1. PCC (5.0 eq), CH₂Cl₂, rt, 2.5 h
2. I₂ (0.15 eq), Et₂O, rt, 4 h
3. NaBH₄ (1.0 eq), MeOH,
0°, 0.25 h
4. TBSCl (1.1 eq), imidazole
(2.2 eq), DMF, 50°, 2.5 h

Pb(OAc)₄, benzene, 60°

O₂, hexane, 15–20°

O₂, rt, 10 d

10% HCl, MeOH, H₂O, rt, 4 h



307

202

200

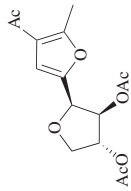
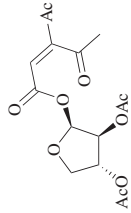
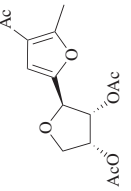
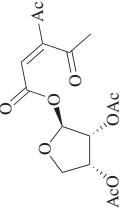
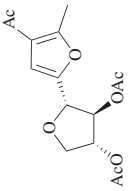
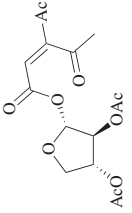
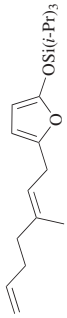
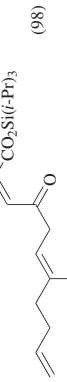
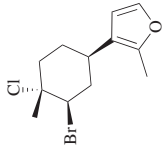
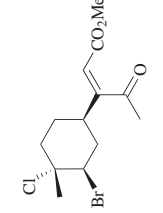
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TABLE 3. SYNTHESIS OF 4-OXOALKENOIC ACIDS AND ESTERS (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₁		1. O ₂ , methylene blue, hv, acetone, -20°, 30 min 2. Petroleum ether, -20°, 48 h 3. Acetone, rt, 50 h	 (—)	292
		O ₂ , methylene blue (0.01 mol %), hv, acetone, -20°, 40 min; then rt, 24 h	 (47)	292
		1. O ₂ , methylene blue, hv, acetone, -20°, 25 min 2. Acetone, rt, 10 h	 (78)	292
C ₁₂		Dimethyldioxirane (1.1 eq), acetone, -78°, 1 h	 (98)	203
		1. <i>m</i> -CPBA, CH ₂ Cl ₂ 2. CH ₃ N ₂ , Et ₂ O	 (—)	216

C₁₂₋₁₃

1. O₂, methylene blue, hv, MeOH
2. HCl (2 N), acetone, rt, 0.5 h

674

R ¹	R ²	R ³	Temp (°)	Time (h)
Ph	Ac	H	-40	3
Ph	MeO ₂ C	MeO ₂ C	-20	5
Bn	MeO ₂ C	MeO ₂ C	-20	2

C₁₄

H₂SO₄, MeOH, H₂O, 0°, 1 h

675

1. *m*-CPBA (1.0 eq), CH₂Cl₂, rt, 43 h
2. CH₂N₂, Et₂O

191, 676

C₁₈

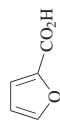
1. O₂, rose bengal, CH₂Cl₂, 0°, 12 h
2. MeI, Bu₄NF, THF, rt, 1 h

(97)

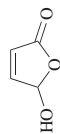
677, 305

TABLE 4. SYNTHESIS OF 4-HYDROXYBUTENOLIDES

	Furan	Conditions	Product(s) and Yield(s) (%)				Refs.
			R ¹	R ²	TBSCH ₂ O	(94) (91)	
C ₄		O ₂ , TPP, hv, CH ₂ Cl ₂ , -78°, 5 min	H		TBSCH ₂ O	(94) (91)	316
C ₅₋₉		NaClO ₂ (3.0 eq), NaH ₂ PO ₄ (1.5 eq), <i>t</i> -BuOH/H ₂ O (5:1), rt, 1 h	R				
			Me			0.5 (96)	211
			TsO(CH ₂) ₄			4 (90)	
			THPO(CH ₂) ₄			2 (78)	
			TBSO(CH ₂) ₄			2 (77)	
			Me(TBSO)CH(CH ₂) ₂			2 (75)	
			<i>n</i> -C ₅ H ₁₁			1.5 (95)	
C ₅		Br ₂ , H ₂ O		Br		(73)	678
		O ₂ , methylene blue, hv, MeOH, rt, 23 h				(96)	679
		O ₂ , rose bengal, hv, 2-BuOH, rt, 1 h				(95)	680
		O ₂ , rose bengal wool, hv, CHCl ₃ , rt, 8 h				(72)	82

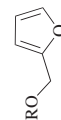


O₂, sensitizer, hv, solvent,
rt, 6 h

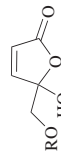


679

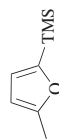
Sensitizer	Solvent
rose bengal disodium salt	MeOH (79)
rose bengal-polystyrene 1% cross-linking	MeOH (70)
rose bengal-resin 20% cross-linking	MeOH (68)
rose bengal-resin 80% cross-linking	MeOH (71)
rose bengal disodium salt	CH ₂ Cl ₂ (100)
rose bengal-polystyrene 1% cross-linking	CH ₂ Cl ₂ (65)
rose bengal-resin 20% cross-linking	CH ₂ Cl ₂ (67)
rose bengal-resin 80% cross-linking	CH ₂ Cl ₂ (100)



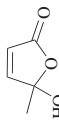
O₂, methylene blue, hv,
EtOH, 10–15°, 2 d



92

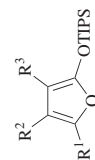


O₂, TPP, hv, CCl₄, 0°



91

C₅₋₁₄

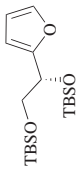
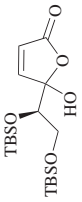
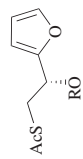
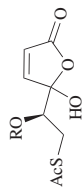
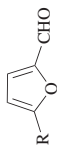
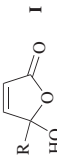
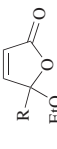
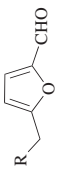
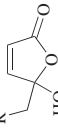
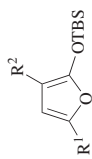
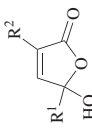


1. Dimethyldioxirane (1.1 eq),
acetone, –78°, 0.5–1 h
2. Amberlyst-15, H₂O,
rt, 1–12 h

R ¹	R ²	R ³
H	H	Me (87)
H	Me	H (81)
H	ClCH ₂	H (94)
H	BnOCH ₂	H (89)
Me	H	H (77)
H	<i>i</i> -Pr	Bn (87)

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TABLE 4. SYNTHESIS OF 4-HYDROXYBUTENOLIDES (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C₆ 	O ₂ , rose bengal, hv, EtN(<i>i</i> -Pr) ₂ , MeOH	 (88)	327
	O ₂ , rose bengal, hv, EtN(<i>i</i> -Pr) ₂ , MeOH, CH ₂ Cl ₂ , -78°	 R TBS (71) TBDPS (69)	225
	O ₂ , rose bengal, hv, Sephadex A-25, EtOH, 20°	 I +  II R (20) (80) Me (73) (11) HOCH₂ (77) (0) MeOCH₂ (72) (0) HO(CH₂)₂OCH₂ (72) (0)	681
	O ₂ , rose bengal, hv, EtOH, 20°, 4 h; then rt, 12 h	 R AcO (90) BnO (80) AcHN (58) BzHN (61) phthalimide (71)	324
C₆₋₈ 	<i>m</i> -CPBA (1.0 eq), CH ₂ Cl ₂ , rt, 0.5 h	 R¹ R² Et H (50) Me <i>i</i>-Pr (53)	221

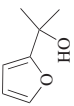
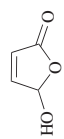
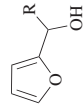
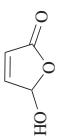
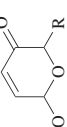
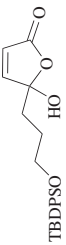
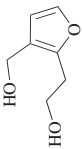
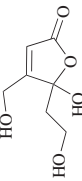
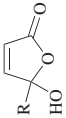
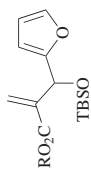
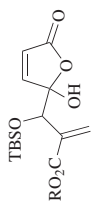
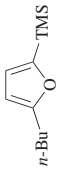
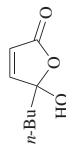
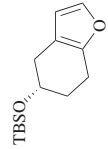
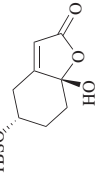
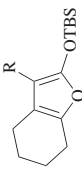
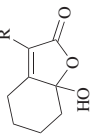
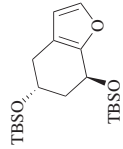
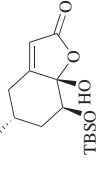
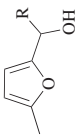
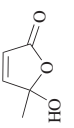
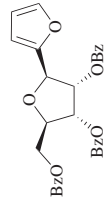
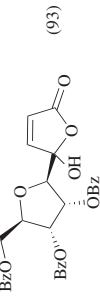
C ₇		O ₂ , rose bengal, MeOH, 5°, 4 min; then Me ₂ S (3.0 eq), CH ₂ Cl ₂ , rt, 15 h		(—)	682																		
C ₇₋₉		O ₂ , rose bengal, MeOH, 5°, 4 min; then Me ₂ S (3.0 eq), CH ₂ Cl ₂ , rt, 15 h	 + 	I I + II (—) II	<table><tr><th>I/II</th><th>R</th></tr><tr><td>98:2</td><td>EtO₂CCH₂</td></tr><tr><td>100:0</td><td>Me₂C=CHCH₂</td></tr><tr><td>98:2</td><td><i>n</i>-Bu</td></tr></table>	I/II	R	98:2	EtO ₂ CCH ₂	100:0	Me ₂ C=CHCH ₂	98:2	<i>n</i> -Bu	682									
I/II	R																						
98:2	EtO ₂ CCH ₂																						
100:0	Me ₂ C=CHCH ₂																						
98:2	<i>n</i> -Bu																						
C ₇		O ₂ , rose bengal (0.02 eq), hv, [HMIM]Cl, rt, 2 h		(76)	90																		
C ₈₋₁₂		NaOCl ₂ (3.0 eq), <i>t</i> -BuOH/H ₂ O, 20°, 3 h		(86)	212																		
C ₈		NaOCl (3.2 eq), NaH ₂ PO ₄ •H ₂ O (1.6 eq), <i>t</i> -BuOH, rt, 1.5 h		<table><tr><th>R</th><th>R</th></tr><tr><td>TBSO(CH₂)₄</td><td>(98)</td></tr><tr><td>HO₂C(CH₂)₇</td><td>(80)</td></tr></table>	R	R	TBSO(CH ₂) ₄	(98)	HO ₂ C(CH ₂) ₇	(80)	683												
R	R																						
TBSO(CH ₂) ₄	(98)																						
HO ₂ C(CH ₂) ₇	(80)																						
C ₈		O ₂ , rose bengal (0.001 eq), hv, EtN(<i>i</i> -Pr) ₂ (1.2 eq), CH ₂ Cl ₂ , −78°		<table><tr><th>R</th><th>R</th></tr><tr><td>Me</td><td>(88)</td></tr><tr><td>ClCH₂</td><td>(78)</td></tr><tr><td>Et</td><td>(91)</td></tr><tr><td>allyl</td><td>(82)</td></tr><tr><td><i>n</i>-Bu</td><td>(90)</td></tr><tr><td>Bn</td><td>(80)</td></tr><tr><td>(<i>E</i>)-PhCH=CHCH₂</td><td>(87)</td></tr><tr><td><i>n</i>-C₁₂H₂₅</td><td>(78)</td></tr></table>	R	R	Me	(88)	ClCH ₂	(78)	Et	(91)	allyl	(82)	<i>n</i> -Bu	(90)	Bn	(80)	(<i>E</i>)-PhCH=CHCH ₂	(87)	<i>n</i> -C ₁₂ H ₂₅	(78)	89
R	R																						
Me	(88)																						
ClCH ₂	(78)																						
Et	(91)																						
allyl	(82)																						
<i>n</i> -Bu	(90)																						
Bn	(80)																						
(<i>E</i>)-PhCH=CHCH ₂	(87)																						
<i>n</i> -C ₁₂ H ₂₅	(78)																						

TABLE 4. SYNTHESIS OF 4-HYDROXYBUTENOLIDES (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
 C ₈	O ₂ , rose bengal, hv, MeOH, 20°, 5 min	 (90)	306
 C ₈₋₉	<i>m</i> -CPBA (2.4 eq), NaOAc (2.9 eq), CH ₂ Cl ₂ , 22°, 1.25 h	 (86)	660
 C ₈	<i>m</i> -CPBA (1.0 eq), CH ₂ Cl ₂ , rt, 0.5 h	 R H (45) Me (45)	221
 C ₈	<i>m</i> -CPBA (2.4 eq), NaOAc (2.9 eq), CH ₂ Cl ₂ , rt, 1.25 h	 (81)	660
 C ₉₋₁₂	O ₂ , rose bengal, MeOH, 5°, 4 min; then Me ₂ S (3.0 eq), CH ₂ Cl ₂ , rt, 15 h	 R Me ₂ C=CHCH ₂ (—) Ph (—)	682
 C ₉	CrO ₃ (2.0 eq), H ₂ SO ₄ (concd), acetone, 0°; then rt, 4 h	 (93)	208



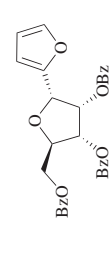
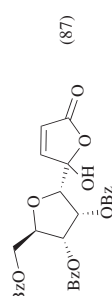
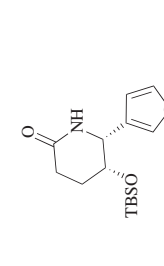
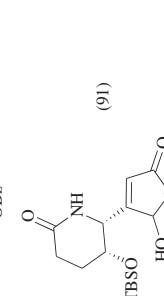
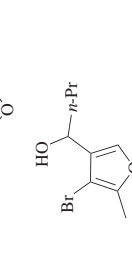
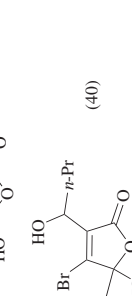
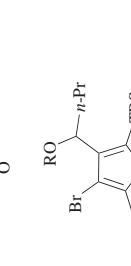
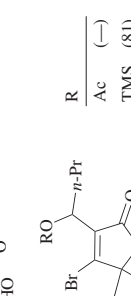
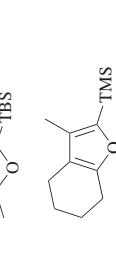
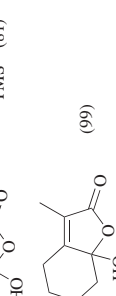
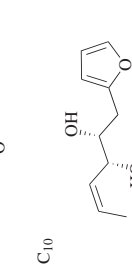
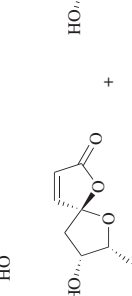
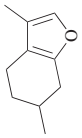
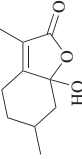
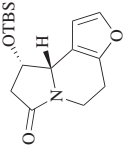
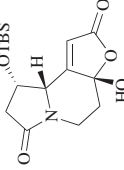
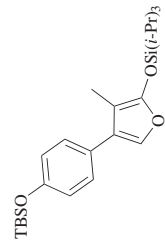
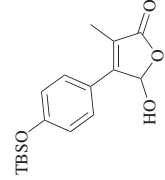
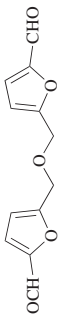
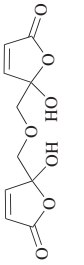
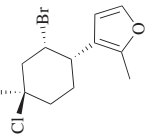
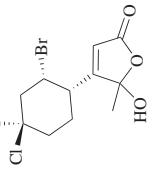
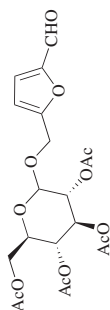
		208
	CrO_3 (2.0 eq), H_2SO_4 (concd), acetone, 0° ; then rt, 4 h	(87)
		684
	O_2 , rose bengal, hv, $\text{EtN}(i\text{-Pr})_2$ (1.0 eq), CH_2Cl_2 , -78° , 1 h	(91)
		209
	MMPP (1.6 eq), $\text{H}_2\text{O}/i\text{-PrOH}$ (7:3), rt, 6 h	(40)
		317
	O_2 , TPP, hv, -78°	R Ac (—) TMS (81)
		313, 312
	O_2 , rose bengal, hv, MeOH, -78° , 3 h	(99)
		224
	O_2 , methylene blue, hv, CH_2Cl_2 , 2.5 min; then Ac_2O , py	 I (—) $\text{I/II} = 2.7:1$  II (56)

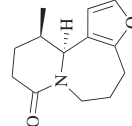
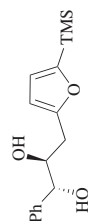
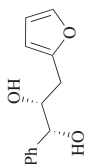
TABLE 4. SYNTHESIS OF 4-HYDROXYBUTENOLIDES (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₀		O ₂ , neat, 100°, 1 h	 (3)	313
		<i>m</i> -CPBA (3.0 eq), CH ₂ Cl ₂ , rt, 2 h	 (68)	684
C ₁₁		Dimethyldioxirane (2.0 eq), acetone, CH ₂ Cl ₂ , -78° to rt, 1 h; then 10% HCl/THF (2:1), H ₂ O, rt, 18 h	 (92)	685
C ₁₂		O ₂ , rose bengal, hv, EtOH, 20°, 4 h	 (68)	324
		<i>m</i> -CPBA, CH ₂ Cl ₂	 (—)	684

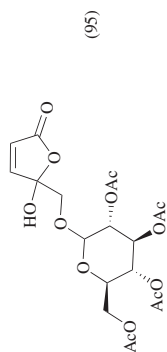
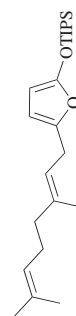


C₁₃

151

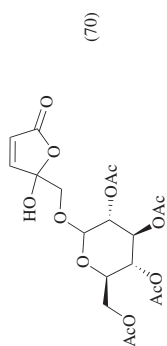


C₁₄



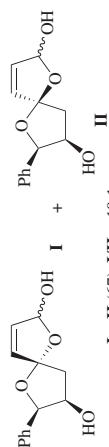
O₂, methylene blue, hv, -40°,
5 h; then Me₂S (1.25 eq), rt

161



m-CPBA (1.15 eq), CH₂Cl₂,
0°, 18 h

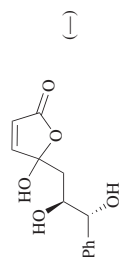
161



m-CPBA (1.3 eq), CH₂Cl₂,
0°, 3 h

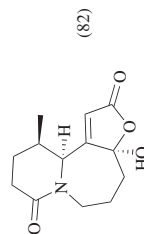
574

I + II (67), I/II = 10:1



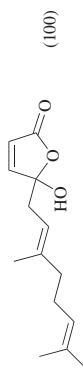
O₂, methylene blue, hv,
CH₂Cl₂, 1.5 min

224



m-CPBA (3.0 eq), CH₂Cl₂, rt, 3 h

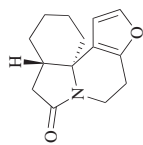
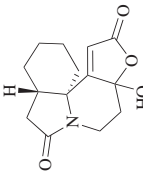
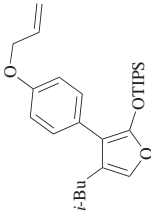
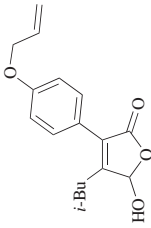
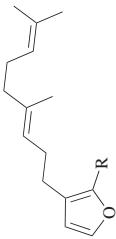
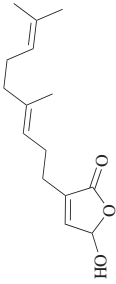
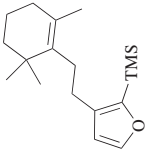
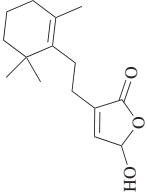
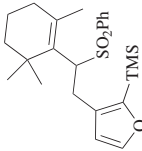
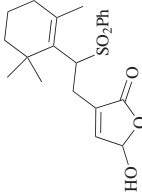
684



1. Dimethyldioxirane (1.1 eq),
acetone, -78°, 0.5–1 h
2. Amberlyst-15, H₂O,
rt, 1–12 h

203

TABLE 4. SYNTHESIS OF 4-HYDROXYBUTENOLIDES (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.	
	NBS (3.0 eq), dioxane, H ₂ O, rt, 1.5 h	 (72)	214, 213	
	1. Dimethyldioxirane (2.0 eq), CH ₂ Cl ₂ , -78°, 0.5 h 2. Amberlyst-15, acetone, rt, 0.5 h	 (98)	686	
	O ₂ , rose bengal, NaNO ₂ , hv, CH ₂ Cl ₂ , -78°, 5 min		R H(48) TMS(93)	316
	O ₂ , rose bengal, NaNO ₂ , hv, CH ₂ Cl ₂ , -78°, 5 min	 (93)	316	
	O ₂ , TPP, hv, CH ₂ Cl ₂ , -78°, 5 min	 (93)	316	

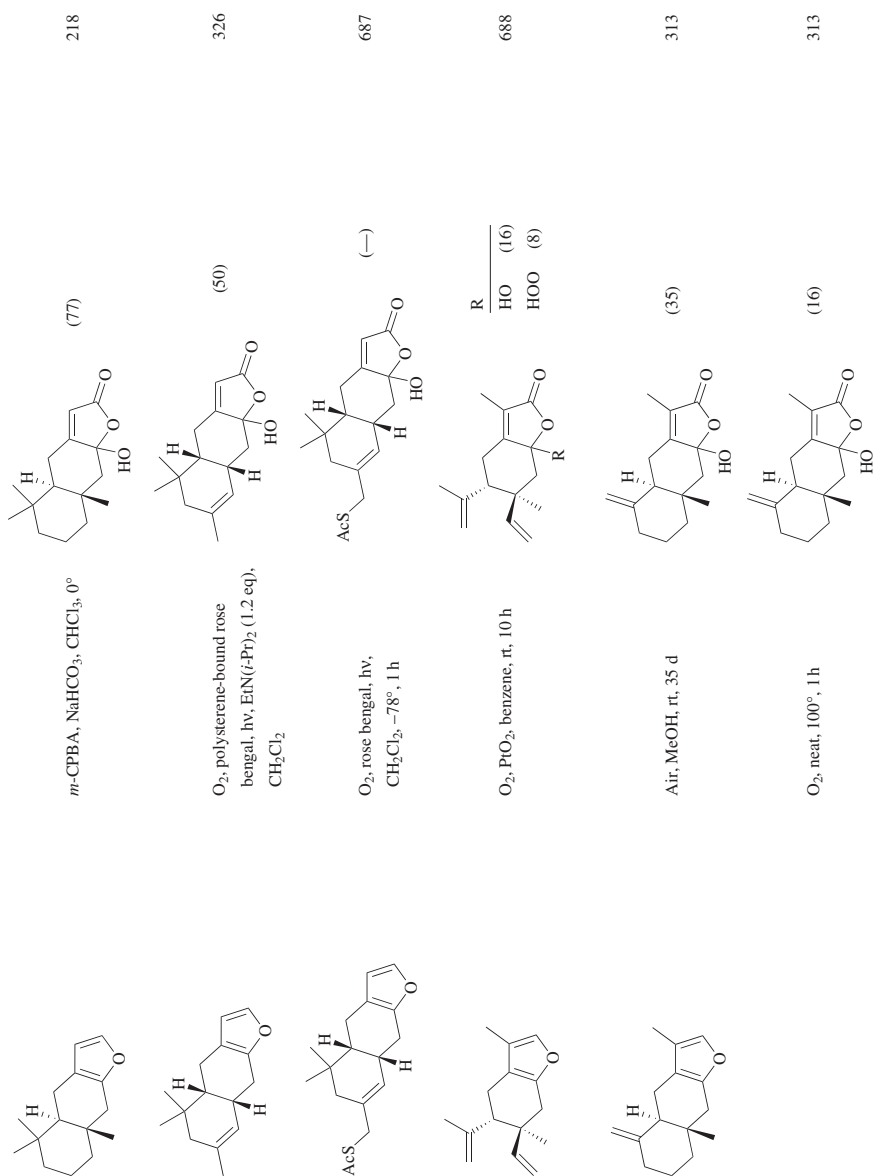
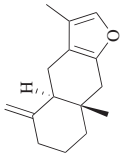
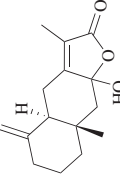
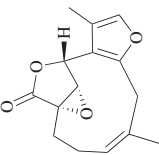
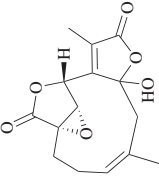
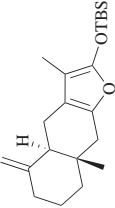
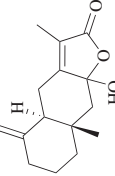
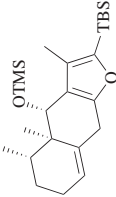
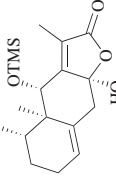
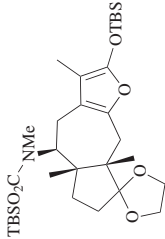
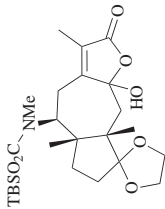


TABLE 4. SYNTHESIS OF 4-HYDROXYBUTENOLIDES (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
	<i>Aspergillus niger</i> , H ₂ O	 (8)	689
	Air, AcOH, CHCl ₃ , rt, 15 d	 (—)	690
	<i>m</i> -CPBA (1.0 eq), CH ₂ Cl ₂ , rt, 0.5 h	 (55)	221, 313, 222
	1. O ₂ , rose bengal, hv, CH ₂ Cl ₂ , –78°, 30 min 2. PPTS, THF/H ₂ O (1:1), rt, 3 h	 (100)	573
	Dimethyldioxirane (2.0 eq), THF/acetone, –15°, 0.5 h	 (—)	691

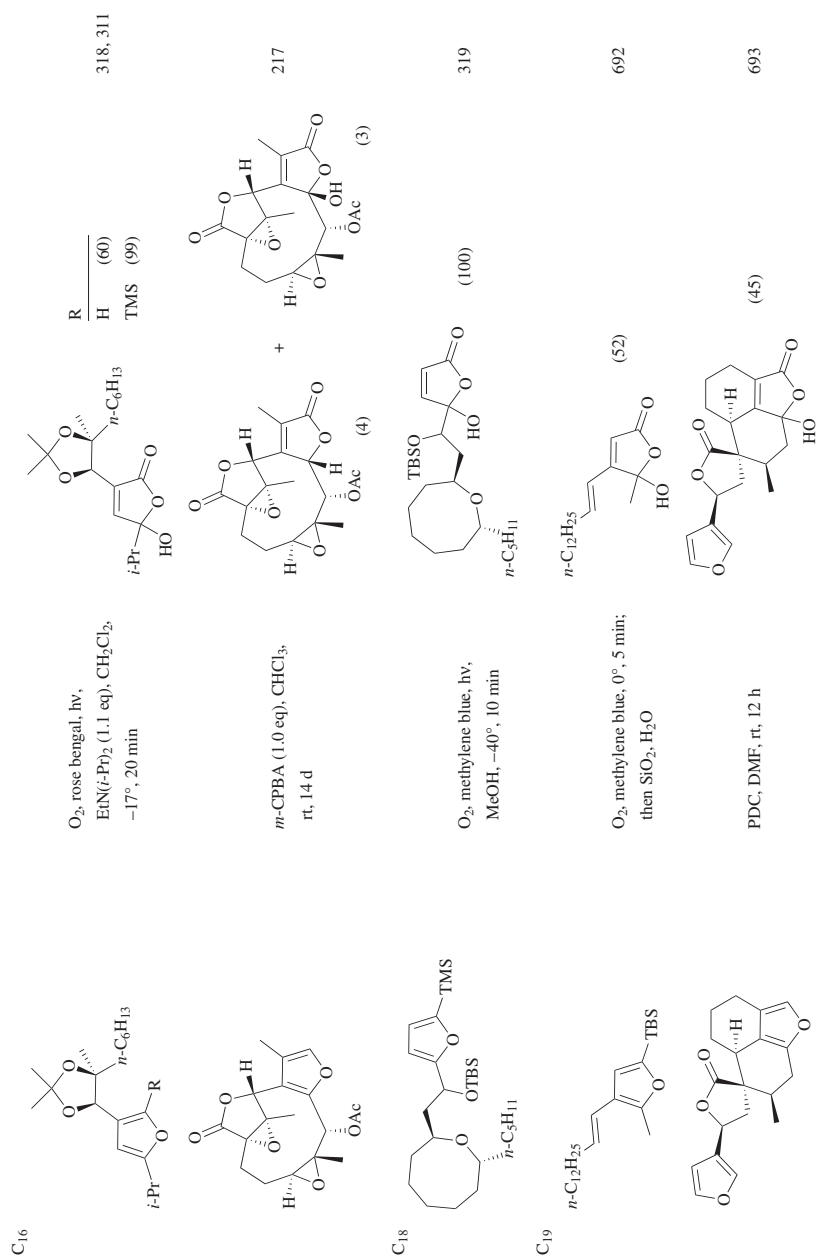
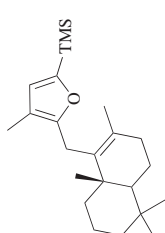
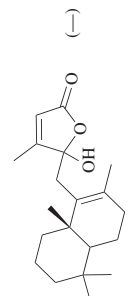
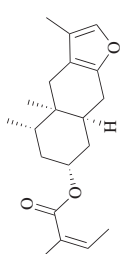
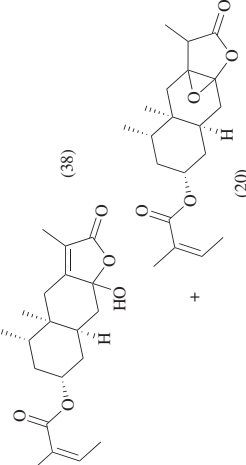
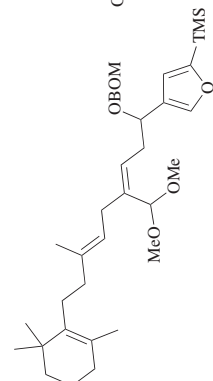
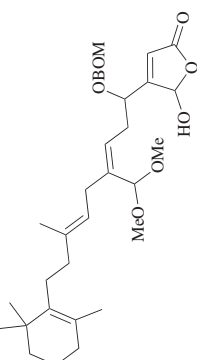


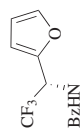
TABLE 4. SYNTHESIS OF 4-HYDROXYBUTENOLIDES (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₂₀		O ₂ , methylene blue, hv, CDCl ₃ , 8°, 30 s	 (—)	314
		Air, hv, benzene	 (38) (20)	80
C ₂₄		O ₂ , rose bengal, NaNO ₂ , hv, CH ₂ Cl ₂ , -78°, 5 min	 (93)	316

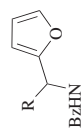
C ₂₅		O ₂ , rose bengal, NaNO ₂ , hv, CH ₂ Cl ₂ , -78°, 5 min		(100)	315
C ₂₇		1. O ₂ , rose bengal, hv, EtN(<i>i</i> -Pr) ₂ , CH ₂ Cl ₂ , -78°, 1 h 2. (CO ₂ H) ₂ , H ₂ O, rt, 0.5 h		(55)	694
C ₂₉₋₃₃		NaClO ₂ (3.0 eq), NaH ₂ PO ₄ (1.5 eq), phosphate buffer (pH 3.5)/CHCl ₃ /H ₂ O (2:1:1), 1 h		$\frac{n}{3 \quad 7}$ (66) (64)	211

TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS

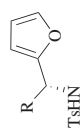
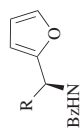
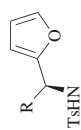
	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₅		1. O ₃ , MeOH, CH ₂ Cl ₂ , 1 h, -78° 2. TMSCHN ₂ , Et ₂ O, 0°, 1 h		408
C ₆		1. RuO ₄ (0.012 eq), NaIO ₄ (15 eq), CCl ₄ /MeCN/H ₂ O (2:2:3), rt, 44 h 2. CH ₂ N ₂ , EtOAc		113
C ₆₋₁₁		O ₃ , MeOH, -78°, 2 h		520
C ₆		O ₃ , MeOH		695, 379
		RuY (0.035 eq), NaIO ₄ (16 eq), CCl ₄ /MeCN/H ₂ O (1:1.5:1), rt, 2 h		380 379
		RuCl ₃ (0.035 eq), NaIO ₄ (16 eq), CCl ₄ /MeCN/H ₂ O (1:1.5:1), rt, 0.5 h		379
		O ₃ , MeOH		415



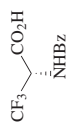
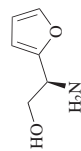
C₆₋₉



C₆₋₁₁

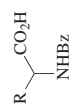


C₆



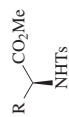
O₃, MeOH, -78°, 30 min

(91)



KMnO₄, trichloroacetone, H₂O,
15°, overnight

R
Me (50)
n-Pr (60)
n-Bu (70)



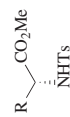
O₃, CH₂Cl₂/MeOH (20:1), -70°, 5 min;
then Me₂S (2.0 eq)

R
Me (80)
n-Pr (88)
n-Bu (88)
i-Bu (82)
Ph (85)



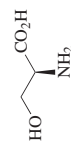
RuO₂ (0.035 eq), NaO₄ (16 eq),
CCl₄/MeCN/H₂O (1.5:1), rt, 2.5 h

R
Me (88)
Ph (75)



O₃, CH₂Cl₂/MeOH (20:1), -70°, 5 min;
then Me₂S (2.0 eq)

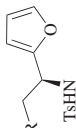
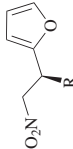
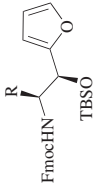
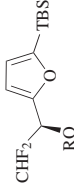
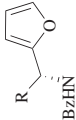
R
Me (82)
n-Pr (85)
n-Bu (89)
i-Bu (86)
Ph (88)



O₃, CH₂Cl₂, -78°, 30 min

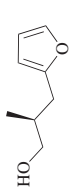
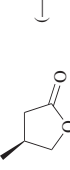
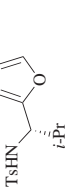
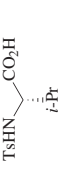
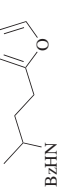
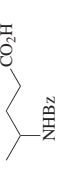
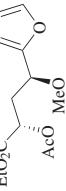
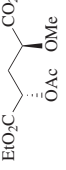
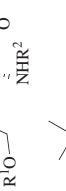
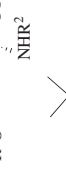
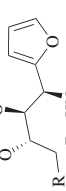
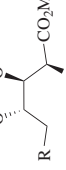
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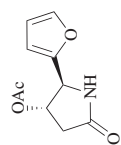
TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.														
C ₆₋₁₃		RuO ₂ (0.05 eq), NaIO ₄ (14.67 eq), MeCN/CCl ₄ /H ₂ O (3:2:2), rt, 1 h	<table><tr><td>R</td><td></td></tr><tr><td>BnO</td><td>(61)</td></tr><tr><td>Et</td><td>(71)</td></tr><tr><td><i>n</i>-Pr</td><td>(66)</td></tr><tr><td><i>i</i>-Bu</td><td>(68)</td></tr><tr><td>Bn</td><td>(68)</td></tr></table>	R		BnO	(61)	Et	(71)	<i>n</i> -Pr	(66)	<i>i</i> -Bu	(68)	Bn	(68)	377		
R																		
BnO	(61)																	
Et	(71)																	
<i>n</i> -Pr	(66)																	
<i>i</i> -Bu	(68)																	
Bn	(68)																	
C ₆		RuCl ₃ (0.02 eq), NaIO ₄ (5.0 eq), NaHCO ₃ (3.0 eq), MeCN/CCl ₄ /H ₂ O (3:2:2), 0°, 0.25 h	<table><tr><td>R</td><td></td></tr><tr><td>BocHN</td><td>(72)</td></tr><tr><td>CbzHN</td><td>(65)</td></tr></table>	R		BocHN	(72)	CbzHN	(65)	697								
R																		
BocHN	(72)																	
CbzHN	(65)																	
C ₆₋₁₃		1. O ₃ , MeOH, CH ₂ Cl ₂ , -70°; then -70° to rt 2. THF/MeCN/H ₂ O (3:1:1), 40°, 2 h	<table><tr><td>R</td><td></td></tr><tr><td>H</td><td>(80)</td></tr><tr><td>Me</td><td>(61)</td></tr><tr><td><i>i</i>-Pr</td><td>(52)</td></tr><tr><td><i>i</i>-Bu</td><td>(61)</td></tr><tr><td>Ph</td><td>(69)</td></tr><tr><td>Bn</td><td>(52)</td></tr></table>	R		H	(80)	Me	(61)	<i>i</i> -Pr	(52)	<i>i</i> -Bu	(61)	Ph	(69)	Bn	(52)	412, 411
R																		
H	(80)																	
Me	(61)																	
<i>i</i> -Pr	(52)																	
<i>i</i> -Bu	(61)																	
Ph	(69)																	
Bn	(52)																	
C ₆		O ₃ , MeOH; then CH ₂ N ₂ , Et ₂ O	<table><tr><td>R</td><td></td></tr><tr><td>Ac</td><td>(100)</td></tr><tr><td>Bn</td><td>(100)</td></tr></table>	R		Ac	(100)	Bn	(100)	420								
R																		
Ac	(100)																	
Bn	(100)																	
C ₇₋₁₂		RuCl ₃ (0.05 eq), NaIO ₄ (6.0 eq), MeCN/H ₂ O/CCl ₄ (3:3:2), 20°, 1 h	<table><tr><td>R</td><td></td></tr><tr><td>Et</td><td>(75)</td></tr><tr><td><i>i</i>-Pr</td><td>(88)</td></tr><tr><td><i>i</i>-Bu</td><td>(98)</td></tr><tr><td><i>n</i>-C₃H₁₁</td><td>(77)</td></tr><tr><td>Bn</td><td>(90)</td></tr></table>	R		Et	(75)	<i>i</i> -Pr	(88)	<i>i</i> -Bu	(98)	<i>n</i> -C ₃ H ₁₁	(77)	Bn	(90)	698		
R																		
Et	(75)																	
<i>i</i> -Pr	(88)																	
<i>i</i> -Bu	(98)																	
<i>n</i> -C ₃ H ₁₁	(77)																	
Bn	(90)																	

C ₇		O ₃ , MeOH, -78°		(30)	405
		1. O ₃ , MeOH, -78°, 10 min; then -78° to rt 2. Me ₂ S, rt, 12 h		(62)	699
		RuO ₂ (0.2 eq), NaIO ₄ (6 eq), NaHCO ₃ (50 eq), MeCN/H ₂ O/CCl ₄ (3:3:2), rt		(91)	372
		1. RuCl ₃ (1.2 eq), NaIO ₄ (6.0 eq), NaHCO ₃ (0.1 eq), MeCN/CH ₂ Cl ₂ /H ₂ O (3:2:2), rt, 2 min 2. CH ₂ N ₂ , Et ₂ O		(78)	374
		1. RuCl ₃ (1.2 eq), NaIO ₄ (6.0 eq), NaHCO ₃ (0.1 eq), MeCN/CH ₂ Cl ₂ /H ₂ O (3:2:2), rt, 2 min 2. CH ₂ N ₂ , Et ₂ O		(72)	374
		RuCl ₃ (0.03 eq), NaIO ₄ (4.0 eq), H ₂ O/MeCN/CH ₂ Cl ₂ (3:2:2), rt, 2.5 h		(60)	343
		1. O ₃ , CH ₂ Cl ₂ , MeOH, 0°, 15 min 2. Me ₂ S (1.0 eq), rt, 1 h		(74)	548

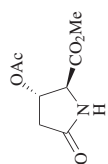
TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₈			
	O ₃ , CH ₂ Cl ₂ , -60°; then HCO ₂ H, -10°, 1 h; then H ₂ O ₂ (0.5 eq), H ₂ O, 90°	 (—)	395
	RuCl ₃ (cat.), NaIO ₄ (15.0 eq), H ₂ O/MeCN/CCl ₄ , rt, 1 h	 (82)	700
	RuCl ₃ (0.012 eq), NaIO ₄ (15 eq), H ₂ O/MeCN/CCl ₄ (3:2:2), rt, 44 h	 (—)	515
	KMnO ₄ , H ₂ O	 (50)	696
	RuCl ₃ (cat.), NaIO ₄ (15 eq), H ₂ O/MeCN/CCl ₄ (3:2:2), rt, 40 min	 (90)	337
	1. RuCl ₃ (1.2 eq), NaIO ₄ (6 eq), NaHCO ₃ (0.1 eq), MeCN/CH ₂ Cl ₂ /H ₂ O (3:2:2), rt, 2 min 2. CH ₂ N ₂ , Et ₂ O	 R ¹ R ² TBS Ac (72) Bn Boc (40)	374
	1. RuCl ₃ (1.2 eq), NaIO ₄ (6 eq), NaHCO ₃ (0.1 eq), MeCN/CH ₂ Cl ₂ /H ₂ O (3:2:2), rt, 2 min 2. CH ₂ N ₂ , Et ₂ O	 R H ₃ NCO ₂ (87) BnO (56)	373, 346 374
	KMnO ₄ , HCl, acetone	 (62)	701



O₃, MeOH, -78°, 2 hr;
Then rt, 30 min;
then CH₂N₂, 0°

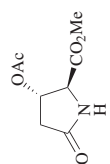
(83)



362

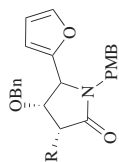
1. O₃, MeOH, -78°
2. CH₂N₂

(—)



414

C₈₋₉

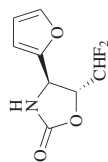


1. RuCl₃ (0.05 eq), NaIO₄ (9 eq),
MeCN/H₂O/CCl₄ (3:3:2), 0°, 20 min
2. CH₂N₂, Et₂O, rt

R
H (78)
Me (75)

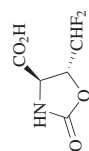
338
338, 702

C₈

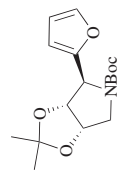


O₃, MeOH, -78°

(72)



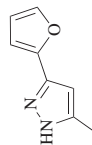
413



1. RuCl₃·H₂O (0.1 eq), NaIO₄ (5 eq),
MeCN/H₂O/CCl₄ (3:3:2), rt, 5 min
2. CH₂N₂, AcOH

(82)

383

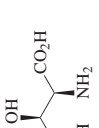
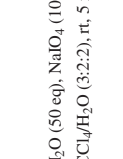
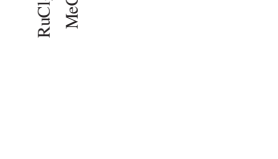


KMnO₄, H₂O, acetone

(69)

703

TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₈	1. RuCl ₃ (1.7 eq), NaIO ₄ (15 eq), MeCN/CH ₂ Cl ₂ (1:1), rt, 2 h 2. SOCl ₂ , MeOH, reflux, 20 min	 (33)	352
	1. O ₃ , MeOH, -78°, 5 min 2. Me ₂ S (1.0 eq), -78° to rt, overnight 3. TFA/H ₂ O (9:1), thiophenol (6 eq), 0° to rt, overnight	 (60)	407
	KMnO ₄	 (76)	704
C ₈₋₉	RuCl ₃ •3H ₂ O (50 eq), NaIO ₄ (10 eq), MeCN/CCl ₄ /H ₂ O (3:2:2), rt, 5 min	 R	350
	RuCl ₃ •3H ₂ O (50 eq), NaIO ₄ (10 eq), MeCN/CCl ₄ /H ₂ O (3:2:2), rt, 5 min	 R	350
		CF ₃ (90) CF ₃ CF ₂ (88) CH ₃ CF ₂ (76)	351
C ₈₋₉	RuCl ₃ •3H ₂ O (50 eq), NaIO ₄ (10 eq), MeCN/CCl ₄ /H ₂ O (3:2:2), rt, 5 min	 R	350
		CF ₃ (85) EtO ₂ C (90) CH ₃ CHF (77) CF ₃ CHF (93) CF ₃ CH ₂ (60) CHF ₂ CH ₂ (65) CH ₂ FCH ₂ (75) CF ₃ CF ₂ (75) CH ₃ CF ₂ (85)	351
			350

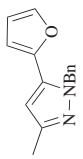
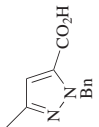
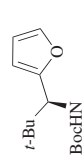
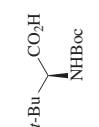
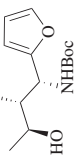
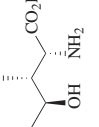
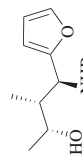
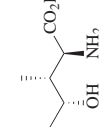
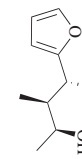
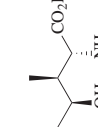
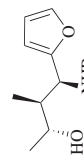
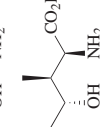
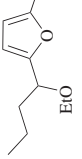
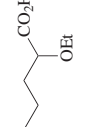
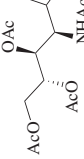
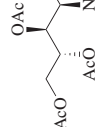
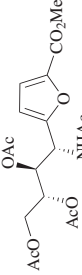
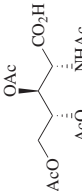
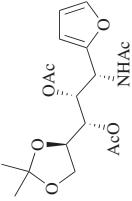
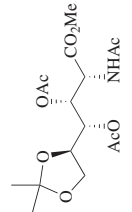
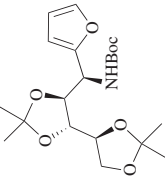
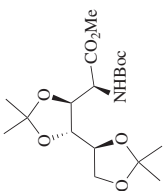
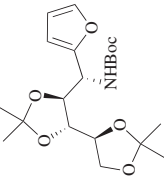
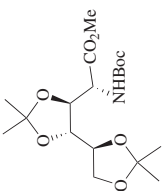
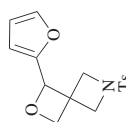
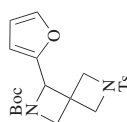
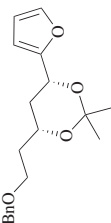
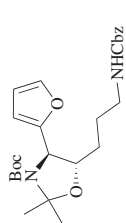
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		705
		402
		402
		402
		402
		706
		707

TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₉		RuCl ₃ (0.022 eq), NaIO ₄ (1.0 eq), H ₂ O/CH ₂ Cl ₂ /MeCN (3:2:2)	 (86)	707
		1. RuO ₂ , NaIO ₄ , CCl ₄ /MeCN/H ₂ O 2. CH ₂ N ₂	 (—)	708
		1. RuCl ₃ (1.2 eq), NaIO ₄ (6 eq), NaHCO ₃ (0.1 eq), CCl ₄ /MeCN/H ₂ O (3:2:2), rt, 2 min 2. CH ₂ N ₂ , Et ₂ O	 (82)	374
		1. RuCl ₃ (1.2 eq), NaIO ₄ (6 eq), NaHCO ₃ (0.1 eq), CCl ₄ /MeCN/H ₂ O (3:2:2), rt, 2 min 2. CH ₂ N ₂ , Et ₂ O	 (74)	374



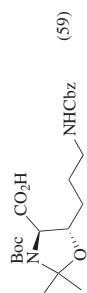
167

RuCl₃ (cat.), NaIO₄,
H₂O/CH₂Cl₂/MeCN (3:2:2)

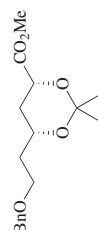
1. O₃, CH₂Cl₂/MeOH (1:1)
2. Ph₃P (1.5 eq)
3. CH₂N₂, Et₂O

RuCl₃ (0.05 eq), NaIO₄ (1.0 eq),
H₂O/MeCN/CCl₄ (3:2:2), rt, 40 min

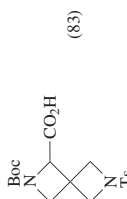
RuCl₃ (0.05 eq), NaIO₄ (1.0 eq),
H₂O/MeCN/CCl₄ (3:2:2), rt, 40 min



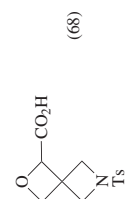
348



400

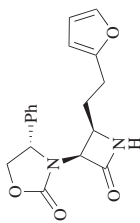
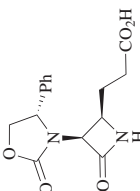
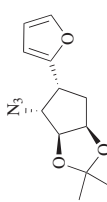
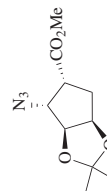
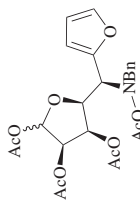
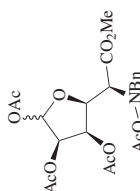
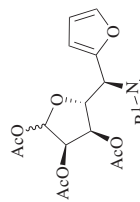
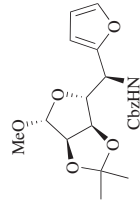
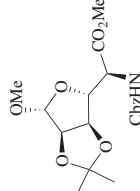


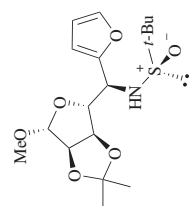
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TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

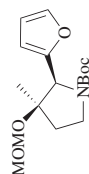
Furan	Conditions	Product(s) and Yield(s) (%)	Refs.								
	O ₃ , CH ₂ Cl ₂ , MeOH; then H ₂ O ₂	 (77)	417								
	1. RuCl ₃ ·3H ₂ O (cat.), NaIO ₄ (10 eq), H ₂ O/CCl ₄ /MeCN (3:2:2), 0°, 1 h 2. CH ₂ N ₂ , Et ₂ O, 0°, 75 h	 (80)	340								
	RuO ₂ (cat.), NaIO ₄ (4 eq), CCl ₄ /MeCN/H ₂ O (2:3:2); then CH ₂ N ₂ , Et ₂ O, 0°, 5 min	 (46)	381								
	1. RuCl ₃ (0.05 eq), NaIO ₄ (6 eq), NaHCO ₃ , MeCN/CCl ₄ /H ₂ O (3:2:3) 2. CH ₂ N ₂ , Et ₂ O, rt, 5 min	<table><tr><th>R¹</th><th>R²</th></tr><tr><td>H</td><td>Cbz</td></tr><tr><td>Bn</td><td>AcO</td></tr><tr><td>Bn</td><td>CF₃CO</td></tr></table> (65) (46) (60)	R ¹	R ²	H	Cbz	Bn	AcO	Bn	CF ₃ CO	346 346 341, 346
R ¹	R ²										
H	Cbz										
Bn	AcO										
Bn	CF ₃ CO										
	1. RuCl ₃ (0.05 eq), NaIO ₄ (6 eq), NaHCO ₃ , MeCN/CCl ₄ /H ₂ O (3:2:3) 2. CH ₂ N ₂ , Et ₂ O, rt, 5 min	 (72)	346								



RuCl₃, NaIO₄,
MeCN/CH₂Cl₂/H₂O (17.5:1:25), rt, 1 h;
then CH₂N₂, Et₂O, 0°, 1 h

(72)

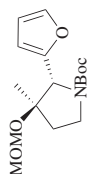
358



RuO₂ (0.2 eq), NaIO₄ (5.9 eq),
CCl₄/MeCN/H₂O (2:3:3), rt, 5 min

(72)

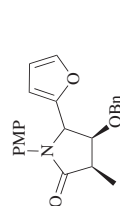
371



RuO₂ (0.2 eq), NaIO₄ (5.9 eq),
CCl₄/MeOH/H₂O (2:3:3),
rt, 5 min

(72)

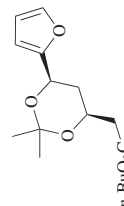
371



RuCl₃, NaIO₄, CCl₄/MeCN/H₂O;
then CH₂N₂, Et₂O

(56)

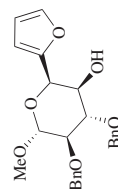
702



1. O₃
2. TMSCHN₂

(86)

406

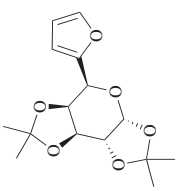
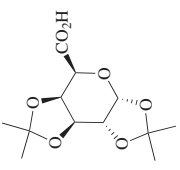
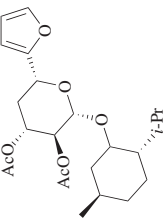
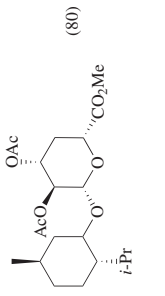
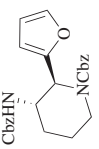
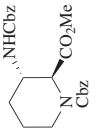
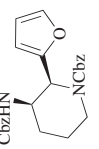
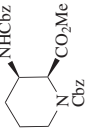
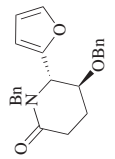
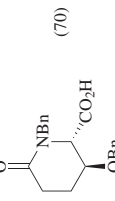


1. O₃, MeOH, CH₂Cl₂, -78°, 40 min
2. Me₂S, -78° to rt, 2 h

(73)

111

TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
	O ₃ , CH ₂ Cl ₂ , MeOH, -78°	 (50)	397
	1. O ₃ , CH ₂ Cl ₂ , MeOH, -78°, 2 min 2. CH ₂ N ₂ , Et ₂ O, rt, 10 min	 (80)	399
	1. RuCl ₃ (0.02 eq), NaIO ₄ (6.9 eq), MeCN/EtOAc/H ₂ O (3:2:2), 0°, 15 min 2. TMSCH ₂ N ₂ , benzene, 0°, 3 h	 (62)	710
	1. RuCl ₃ (0.02 eq), NaIO ₄ (6.9 eq), MeCN/EtOAc/H ₂ O (3:2:2), 0°, 15 min 2. TMSCH ₂ N ₂ , benzene, 0°, 3 h	 (—)	710
	RuCl ₃ (0.05 eq), NaIO ₄ (10 eq), MeCN/EtOAc/H ₂ O (3:2:2), rt, 10 min	 (70)	359

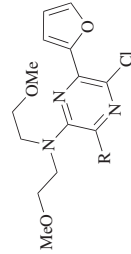
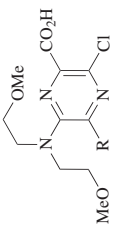
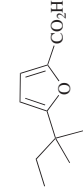
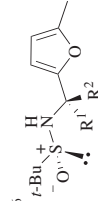
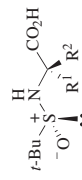
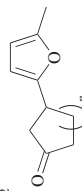
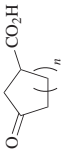
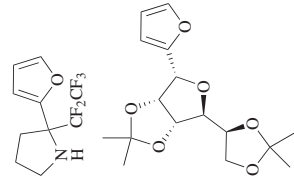
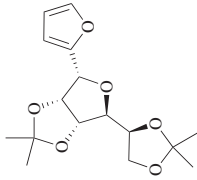
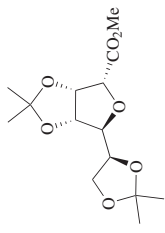
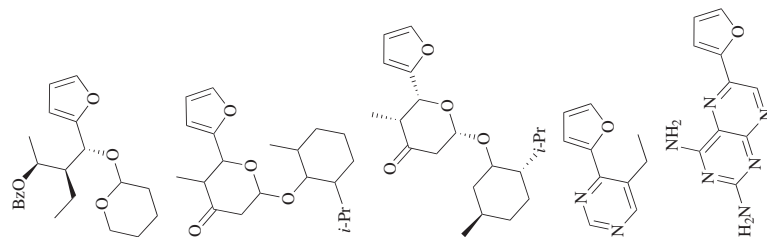
C ₉₋₁₅		RuO ₂ , NaIO ₄ , CCl ₄ /MeCN/H ₂ O, rt, 0.5 h		R	711
C ₁₀		KMnO ₄ , KOH (aq), rt		NC- 4-CbzNHC ₆ H ₄ (—)	712
C ₁₀₋₁₆		RuCl ₃ , NaIO ₄ , CH ₂ Cl ₂ /MeCN/H ₂ O		R ¹ R ² Me <i>i</i> -Pr (63) Me <i>i</i> -Bu (69) <i>i</i> -Pr <i>n</i> -Bu (69) Ph Me (62) Ph <i>n</i> -Bu (67)	342
C ₁₀₋₁₂		O ₃ , MeOH, -78°, 0.5 h; then -78° to rt, 10 min		<i>n</i> 1 (85) 2 (87) 3 (83)	713
C ₁₀		O ₃ , MeOH, -78°		(84)	714
		1. O ₃ , CH ₂ Cl ₂ , MeOH 2. CH ₂ N ₂ , Et ₂ O		(60)	398

TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. RuCl_3 , NaIO_4 , $\text{CCl}_4/\text{MeCN}/\text{H}_2\text{O}$, rt, 40 min 2. BnBr , Bu_4NBr , K_2CO_3 , 50°	 (59)	715
	1. O_3 , CH_2Cl_2 , MeOH , -78° , 1 h; then Me_2S (4.5 eq) 2. KHCO_3 (6.2 eq), MeI (5.3 eq), DMF , rt, 5 h	 (62)	396
	1. RuO_2 (0.012 eq), NaIO_4 (15 eq), $\text{CCl}_4/\text{MeCN}/\text{H}_2\text{O}$ (2:2:3) 2. CH_2N_2 , Et_2O 3. DBU , CH_2Cl_2 , 20°	 (88)	716
	RuCl_3 (cat.), NaIO_4 , $\text{CH}_2\text{Cl}_2/\text{MeCN}/\text{H}_2\text{O}$	 (80)	355
	RuO_2 (cat.), NaIO_4 (14.7 eq), $\text{CH}_2\text{Cl}_2/\text{MeCN}/\text{H}_2\text{O}$ (2:2:3), rt, 2 d	 (77)	369
	1. O_3 , CH_2Cl_2 , MeOH , -78° 2. CH_2N_2 , Et_2O	 (40)	398



RuCl₃ (0.45 eq), NaIO₄ (200 eq),
MeCN/CCl₄/H₂O (2:2:3), rt

O₃, CH₂Cl₂, MeOH

1. O₃, CH₂Cl₂, MeOH, -78°, 2 min
2. CH₂N₂, Et₂O, rt, 10 min

KMnO₄, H₂O, acetone, 50°, 0.25 h;
then reflux, 1 h

KMnO₄, NaOH, H₂O

717

718

399

719, 720

721

(82)

(-)

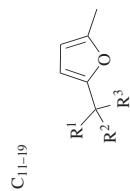
(77)

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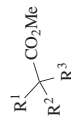
(67)

TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

C ₁₁	Furan	Conditions	Product(s) and Yield(s) (%)		Refs.
			Y	Time (h)	
		RuCl ₃ , NaIO ₄ , EtOAc/MeCN/H ₂ O, rt, 1.5 h		(92)	722
				(70)	
		1. RuCl ₃ (0.06 eq), NaIO ₄ (6 eq), CH ₂ Cl ₂ /MeCN/H ₂ O (2:2:3) 2. CH ₂ N ₂ , Et ₂ O		(84)	360
				(82)	
		RuCl ₃ (0.02 eq), NaIO ₄ (8 eq), CCl ₄ /MeCN/H ₂ O (2:2:3), rt, 1 h		(83)	520
				(75)	
		RuY (0.035 eq), NaIO ₄ (16 eq), CCl ₄ /MeCN/H ₂ O (2:3:2), rt, 30 min		(78)	379, 380
				(75)	
		RuY (0.035 eq), NaIO ₄ (16 eq), CCl ₄ /MeCN/H ₂ O (2:3:2), rt, 30 min		(89)	379, 695
				(92)	

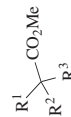


1. RuCl₃ (0.05 eq), NaIO₄ (7 eq), CCl₄/MeCN/H₂O (2:2:3), 20°, 24 h
2. TMSCHN₂, benzene/MeOH



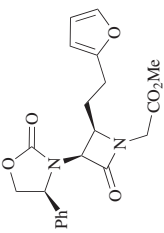
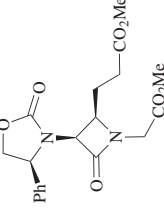
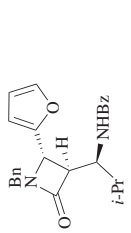
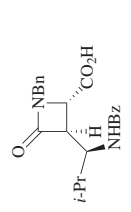
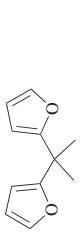
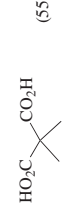
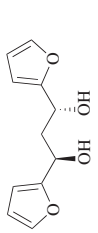
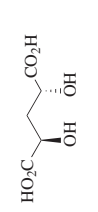
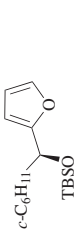
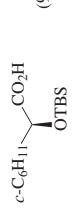
R ¹	R ²	R ³	
Me	H	2-thienyl	(11)
Me	H	4-ClC ₆ H ₄	(71)
Me	H	4-MeOC ₆ H ₄	(87)
Me	H	4-BnOC ₆ H ₄	(86)
Me	H	4-CbzHNC ₆ H ₄	(85)
Me	Me	Ph	(65)
Me	H	4-MeC ₆ H ₄	(68)
Me	H	1-naphthyl	(70)
Me	H	2-MeO-1-naphthyl	(8)
Me	H	2-naphthyl	(51)
Me	H	6-MeO-2-naphthyl	(21)
H	Ph	Ph	(80)
Me	H	4-PhC ₆ H ₄	(78)

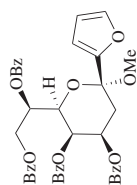
1. RuCl₃ (0.05 eq), NaIO₄ (7 eq), hexane/EtOAc/H₂O (*xy/z*), 20°, 24 h
2. TMSCHN₂, benzene/MeOH



R ¹	R ²	R ³	<i>xy/z</i>
Me	H	2-thienyl	0:4:4 (51)
Me	H	4-ClC ₆ H ₄	2:2:4 (77)
Me	H	4-MeOC ₆ H ₄	1:3:4 (92)
Me	H	4-BnOC ₆ H ₄	1:3:4 (96)
Me	H	4-CbzHNC ₆ H ₄	1:3:4 (86)
Me	Me	Ph	2:2:4 (88)
Me	H	4-MeC ₆ H ₄	1:3:4 (74)
Me	H	1-naphthyl	2:2:4 (88)
Me	H	2-MeO-1-naphthyl	2:2:4 (27)
Me	H	2-naphthyl	2:2:4 (80)
Me	H	6-MeO-2-naphthyl	1:3:4 (65)
H	Ph	Ph	1:3:4 (87)
Me	H	4-PhC ₆ H ₄	1:3:4 (89)

TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

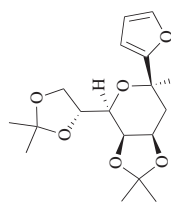
Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
 C ₁₁	H ₂ O ₂ , CH ₂ Cl ₂ , MeOH	 (84)	723
 	RuCl ₃ (0.02 eq), H ₂ O ₆ (15 eq), CCl ₄ /MeCN/H ₂ O (2:2:3), rt, 10 min	 (90)	365
 	KMnO ₄ (10 eq), H ₂ O, rt, 23 h	 (55)	724
 	1. O ₃ , HCO ₂ H, CH ₂ Cl ₂ , MeOH 2. H ₂ O ₂ , HCO ₂ H 3. Ba(OH) ₂	 (42)	419
 	O ₃ , MeOH, -78°, 1 h	 (96)	725, 726



1. RuCl₃ (1.0 eq), NaIO₄ (10 eq),
NaHCO₃ (83 eq),
MeCN/CH₂Cl₂/H₂O (3:2:2)
2. CH₂N₂, Et₂O

368

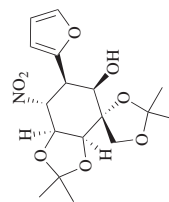
(94)



1. RuO₂ (0.03 eq), NaIO₄ (14.7 eq),
MeCN/CCl₄/H₂O (3:2:2)
2. CH₂N₂, Et₂O

370

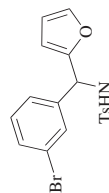
R	(60)	(73)
H		
MeO		



RuCl₃ (10 mol %), NaIO₄ (8 eq),
MeCN/CCl₄/H₂O (1:1:1.25), rt, 20 min

727

(52)

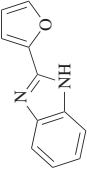
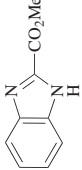
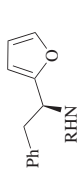
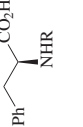
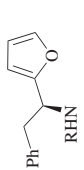
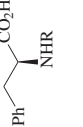
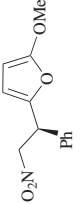
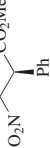
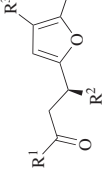
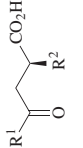
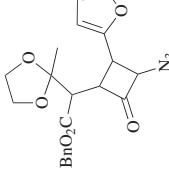
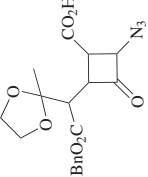
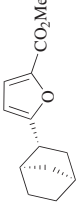
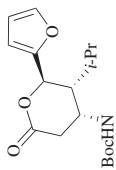
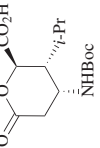


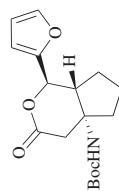
O₃, MeOH, -78°, 0.5 h

728

(82)

TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

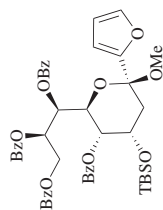
Furan	Conditions	Product(s) and Yield(s) (%)				Refs.
		R	Temp (°)	Time (h)		
	O ₂ , methylene blue, hv, MeOH, rt, 18 h				(13)	307
	O ₃ , MeOH		Bz	—	(88)	695
	O ₃ , MeOH		Chz	—78	(79)	729
	RuCl ₃ (0.06 eq), NaIO ₄ (1.52 eq), MeCN/CCl ₄ /H ₂ O (2:2:3), rt, 2 h				(77)	364
	O ₃ , MeOH, -78°, 0.5 h; then -78° to rt, 10 min		R ¹		H	(96)
			R ²		H	(89)
			R ³		Me	(85)
	O ₃ , AcOH, rt, 2 h		n-Pr		H	(85)
			n-Bu		H	(85)
			Me		H	(85)
			n-C ₅ H ₁₁		H	(85)
	1. O ₃ , CH ₂ Cl ₂ , -78°, 20 min 2. PPh ₃ , CH ₂ Cl ₂ , -78° to rt					731
	RuCl ₃ (0.03 eq), NaIO ₄ (15 eq), CCl ₄ /MeCN/H ₂ O (1:1:2.5), rt					344



RuCl₃ (0.03 eq), NaIO₄ (15 eq),
CCl₄/MeCN/H₂O (1:1:2.5), rt

(92)

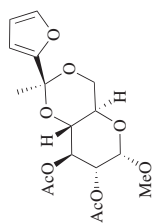
344



1. RuCl₃ (1.0 eq), NaIO₄ (10 eq),
NaHCO₃ (83 eq),
MeCN/CCl₄/H₂O (3:2:2)
2. CH₂N₂, Et₂O

(90)

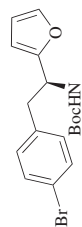
368, 732



RuO₂, NaIO₄, CCl₄

(74)

733



RuCl₃•3H₂O (0.02 eq), H₂IO₆ (5.0 eq),
CCl₄/MeCN/H₂O (3:3:4), rt, 20 min

(33)

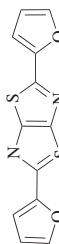
587



O₃, MeOH, -78°, 30 min

(91)

418

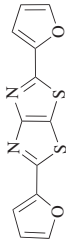
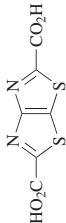
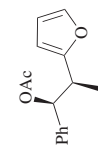
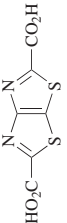
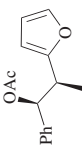
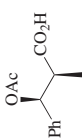
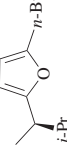
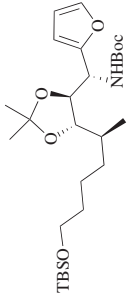
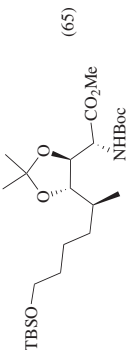
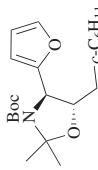
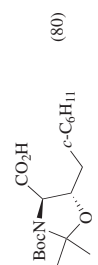
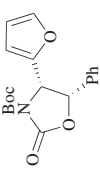
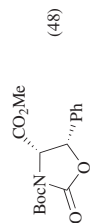


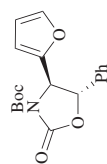
KMnO₄ (10.7 eq), py/H₂O (6.3:1),
15–40°, 12 h

(65)

734

TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

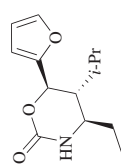
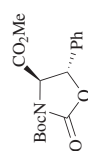
	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₂		KMnO ₄ , H ₂ O, rt to 40°, 12 h	 (56)	735
C ₁₃		KMnO ₄ , <i>t</i> -BuOH, 70°, 18 h	 (85)	736
		RuCl ₃ ·6H ₂ O, NaIO ₄ , H ₂ O, EtOAc, rt	 (68)	360
		RuCl ₃ (0.09 eq), NaIO ₄ (4.0 eq), CCl ₄ /MeCN/H ₂ O (1:1:1.4), rt, 15 h	 (48) + <i>n</i> -BuCO ₂ H (71)	361
		1. RuO ₂ , NaIO ₄ , MeCN/CCl ₄ /H ₂ O, rt, 0.25 h 2. MeI, KHCO ₃ , rt, 12 h	 (65)	375
		RuCl ₃ , NaIO ₄ , CCl ₄ /MeCN/H ₂ O	 (80)	347
		RuCl ₃ , NaIO ₄ , CCl ₄ /MeOH/H ₂ O, rt, 1 h	 (48)	737



RuCl₃, NaIO₄, CCl₄/MeOH/H₂O,
rt, 1 h

737

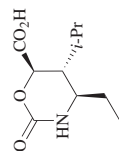
(92)



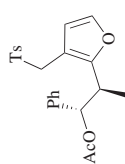
RuCl₃ (0.03 eq), NaIO₄ (15 eq),
CCl₄/MeCN/H₂O (1:1:1.25), rt

344

(71)



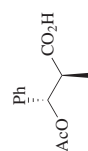
C₁₄



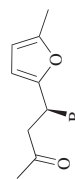
181

360

(68)



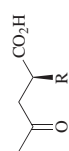
C₁₄₋₁₅



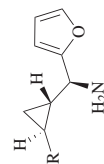
O₃, MeOH, -78°, 0.5 h;
then -78° to rt, 10 min

713

R
n-C₃H₁₁ (85)
Ph (91)



C₁₄₋₁₈

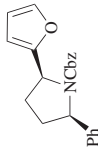
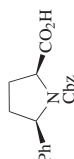
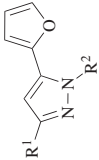
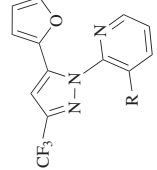
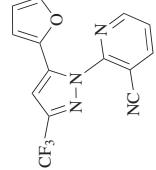
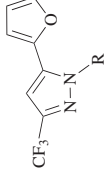


RuO₂·H₂O (0.04 eq), NaIO₄ (16.6 eq),
CCl₄/MeCN/H₂O (1:1.5:1), rt, 2 h

385

R
Ph (—)
2-ClC₆H₄ (—)
4-MeOC₆H₄ (—)
3-MeC₆H₄ (—)
2-naphthyl (—)

TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

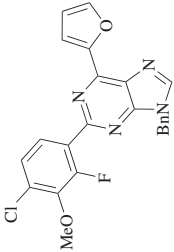
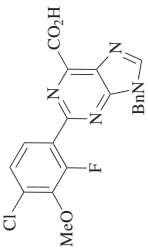
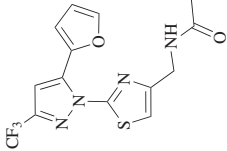
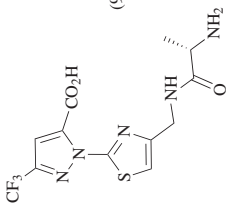
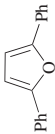
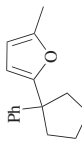
Furan	Conditions	Product(s) and Yield(s) (%)	Refs.												
C₁₄ 	KMnO ₄ (8.0 eq), KOH (20% aq), acetone/H ₂ O, rt, 1 h	 (80)	389												
C₁₄₋₁₅ 	KMnO ₄ (7 eq), acetone/H ₂ O (1:1), 60°, 3 h	<table><tr><th>R¹</th><th>R²</th><th></th></tr><tr><td>NC-</td><td>4-MeOC₆H₄</td><td>(71)</td></tr><tr><td>CF₃</td><td>2-BocHNCH₂C₆H₄</td><td>(71)</td></tr><tr><td><i>t</i>-BuO₂C</td><td>3-NC-4-FC₆H₃</td><td>(68)</td></tr></table>	R ¹	R ²		NC-	4-MeOC ₆ H ₄	(71)	CF ₃	2-BocHNCH ₂ C ₆ H ₄	(71)	<i>t</i> -BuO ₂ C	3-NC-4-FC ₆ H ₃	(68)	738, 739 392 391
R ¹	R ²														
NC-	4-MeOC ₆ H ₄	(71)													
CF ₃	2-BocHNCH ₂ C ₆ H ₄	(71)													
<i>t</i> -BuO ₂ C	3-NC-4-FC ₆ H ₃	(68)													
C₁₄ 	KMnO ₄ (5 eq), acetone/H ₂ O (1:1), reflux, 0.5 h	<table><tr><th>R</th><th></th></tr><tr><td>NC-</td><td>(51)</td></tr><tr><td>EtO₂C</td><td>(50)</td></tr></table>	R		NC-	(51)	EtO ₂ C	(50)	740 741						
R															
NC-	(51)														
EtO ₂ C	(50)														
C₁₄₋₁₈ 	KMnO ₄ (5 eq), KH ₂ PO ₄ , acetone/H ₂ O, reflux, 1 h	(56)	742												
C₁₄₋₁₈ 	KMnO ₄ (7 eq), acetone/H ₂ O (1:1), 60°, 3 h	<table><tr><th>R</th><th></th></tr><tr><td>Ph</td><td>(—)</td></tr><tr><td>3-O₂NC₆H₄</td><td>(30)</td></tr><tr><td>2-MeO₂CC₆H₄</td><td>(35)</td></tr><tr><td>2-N₃CH₂-4-MeOC₆H₃</td><td>(68)</td></tr><tr><td>3-F-2-naphthyl</td><td>(—)</td></tr></table>	R		Ph	(—)	3-O ₂ NC ₆ H ₄	(30)	2-MeO ₂ CC ₆ H ₄	(35)	2-N ₃ CH ₂ -4-MeOC ₆ H ₃	(68)	3-F-2-naphthyl	(—)	743 738 393, 391 391 390
R															
Ph	(—)														
3-O ₂ NC ₆ H ₄	(30)														
2-MeO ₂ CC ₆ H ₄	(35)														
2-N ₃ CH ₂ -4-MeOC ₆ H ₃	(68)														
3-F-2-naphthyl	(—)														

C ₁₄		RuCl ₃ (0.15 eq), NaIO ₄ (4.5 eq), MeCN/CCl ₄ (1:1), rt, 12 h	(64)	349
C ₁₄₋₁₇		RuCl ₃ , NaIO ₄ , MeCN/CH ₂ Cl ₂ /H ₂ O	R 3-BrC ₆ H ₄	744 (75)
				425 (—)
				425 (100)
C ₁₄₋₂₀		NaClO ₂ , NaH ₂ PO ₄ , MeCN/H ₂ O	R Ph 2-ClC ₆ H ₄ 3-ClC ₆ H ₄ 4-ClC ₆ H ₄ 3-F-4-BrC ₆ H ₃ 2-NCCH ₂ C ₆ H ₄ 2-N ₃ CH ₂ C ₆ H ₄ 3-BocHN(CH ₂) ₂ C ₆ H ₄	745 (90) 745 (90) 745 (90) 745 (75) 746 (90) 391 (60) 424 (—)

TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

C ₁₄₋₁₉			RuCl_3 , NaIO ₄ , CH ₂ Cl ₂ /MeCN/H ₂ O	$\frac{\text{R}}{\text{Me}} \quad \frac{(90)}{n\text{-C}_6\text{H}_{13}} \quad (94)$	357, 356
C ₁₄			RuCl_3 , NaIO ₄ , MeCN/CCl ₄ /H ₂ O, rt, 2 h	(60)	756
C ₁₅₋₁₆			1. RuCl ₃ (0.05 eq), NaIO ₄ (7.0 eq), CCl ₄ /MeCN/H ₂ O (2:2:3), 20°, 24 h 2. TMSCHN ₂ , benzene/MeOH	$\frac{\text{R}}{\text{H}} \quad \frac{a}{\text{Me}} \quad \frac{(73)}{(59)}$	363
C ₁₅			1. RuCl ₃ (0.05 equiv), NaIO ₄ (7 eq), hexane/EtOAc/H ₂ O (v/v/z), 20°, 24 h 2. TMSCHN ₂ (1.5 eq), benzene/MeOH (2:7), rt, 5 min	$\frac{\text{R}}{\text{H}} \quad \frac{a}{\text{Me}} \quad \frac{x/y/z}{1:3:4} \quad \frac{a}{(85)} \quad \frac{(90)}$	363
			$\text{RuCl}_3 \cdot \text{H}_2\text{O}$ (0.03 eq), NaIO ₄ (15 eq), CCl ₄ /MeCN/H ₂ O (1:1:1.25), rt	(70)	344

TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.															
C ₁₅		1. O ₃ , CH ₂ Cl ₂ , -78° 2. Me ₂ S, -78° to rt 3. rt, 4 h	 (100)	757															
		NaClO ₂ , NaH ₂ PO ₄ , MeCN/H ₂ O	 (90)	425															
C ₁₆		1. O ₃ , CH ₂ Cl ₂ 2. NaOH, CH ₂ Cl ₂ , EtOH (aq)	PhCO ₂ H (59) + PhCO ₂ Et (39)	758															
		1. O ₃ , CH ₂ Cl ₂ 2. NaBH ₄ , EtOH	PhCO ₂ H (66)	759															
		RuCl ₃ (0.05 eq), NaIO ₄ (7.0 eq), solvents (2:2:x)	<table><tr><td>Ph</td><td></td><td>CO₂H</td><td>Solvents</td><td>x</td></tr><tr><td></td><td></td><td></td><td>hexane/EtOAc/H₂O</td><td>4 (81)</td></tr><tr><td></td><td></td><td></td><td>CCl₄/MeCN/H₂O</td><td>3 (60)</td></tr></table>	Ph		CO ₂ H	Solvents	x				hexane/EtOAc/H ₂ O	4 (81)				CCl ₄ /MeCN/H ₂ O	3 (60)	363
Ph		CO ₂ H	Solvents	x															
			hexane/EtOAc/H ₂ O	4 (81)															
			CCl ₄ /MeCN/H ₂ O	3 (60)															

		760
		761
		384
		416
		423

RuCl₃, NaIO₄, NaHCO₃,
MeCN/CCl₄/H₂O, rt, 0.5 h

O₃, MeOH

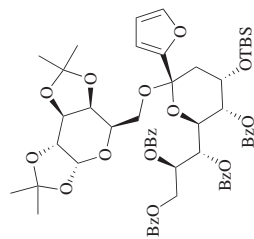
RuO₂, NaIO₄,
CCl₄/MeCN/EtOAc/H₂O

1. O₃, MeOH, CH₂Cl₂, -78°
2. CH₂N₂, MeOH, Et₂O, 0°

1. HNO₃, NH₄VO₃ (0.014 eq),
H₂O, reflux, 4 h
2. H₂SO₄, H₂O, EtOH,
reflux, overnight

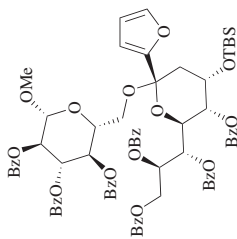
TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₆		1. HNO ₃ , NH ₄ VO ₃ (0.014 eq), H ₂ O, reflux, 4 h 2. H ₂ SO ₄ , H ₂ O, EtOH, reflux, overnight		423
			(56)	
C ₁₇		1. RuCl ₃ (0.05 eq), NaIO ₄ (7.0 eq), solvents (2:2:x), 20°, 24 h 2. TMSCHN ₂ , benzene/MeOH		363
			Ph-CO ₂ Me hexane/EtOAc/H ₂ O 4 (81) CCl ₄ /MeCN/H ₂ O 3 (60)	
		1. RuCl ₃ (1.0 eq), NaIO ₄ (10 eq), NaHCO ₃ (83 eq), MeCN/CH ₂ Cl ₂ /H ₂ O (3:2:2) 2. CH ₂ N ₂ , Et ₂ O		368
			(75)	
		O ₃ , CH ₂ Cl ₂ , MeOH; then H ₂ O ₂		417
			(77)	



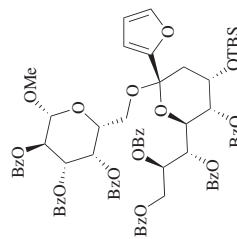
1. RuCl₃ (1.0 eq), NaIO₄ (10 eq),
NaHCO₃ (83 eq),
MeCN/CCl₄/H₂O (3:2:2)
2. CH₂N₂, Et₂O

368



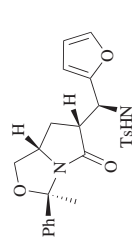
1. RuCl₃ (1.0 eq), NaIO₄ (10 eq),
NaHCO₃ (83 eq),
MeCN/CCl₄/H₂O (3:2:2)
2. CH₂N₂, Et₂O

368



1. RuCl₃ (1.0 eq), NaIO₄ (10 eq),
NaHCO₃ (83 eq),
MeCN/CCl₄/H₂O (3:2:2)
2. CH₂N₂, Et₂O

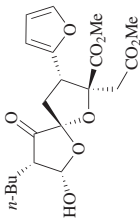
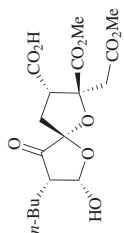
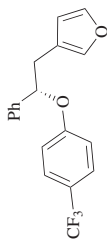
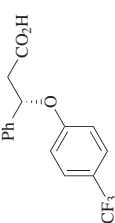
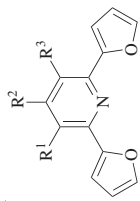
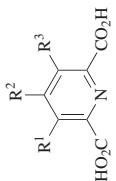
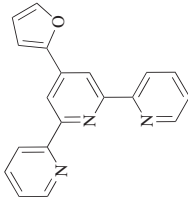
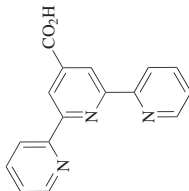
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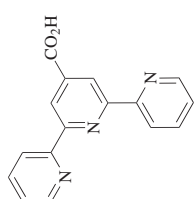


1. RuCl₃ (0.01 eq), NaIO₄ (10.5 eq),
CCl₄/MeCN/H₂O (3:3:5), rt, 4 h
2. CH₂N₂, THF/Et₂O, rt, 10 min

376

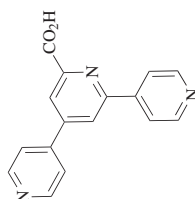
TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₈		RuCl ₃ •3H ₂ O (0.05 eq), NaIO ₄ (7.0 eq), EtOAc/H ₂ O (1:1), rt, 5.5 h	 (68)	762
C ₁₉		RuCl ₃ •4H ₂ O (0.02 eq), NaIO ₄ (7.25 eq), EtOAc/H ₂ O (1:1), rt, 1.75 h	 (85)	763
C ₁₉₋₂₁		KMnO ₄ (3.0 eq), acetone, rt, 4 dt, then H ₂ O, rt, 1 h		764 764 765 764 764 765 764 764 764 764
C ₁₉		KMnO ₄ (4.0 eq), KOH, H ₂ O, pH 10, reflux, 2 h	 (68)	766



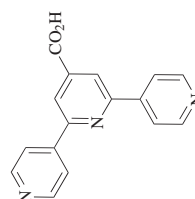
(78)

KMnO₄ (4.7 eq), py/H₂O (2:1),
rt, 24 h



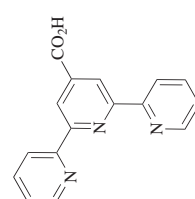
(89)

KMnO₄, *t*-BuOH, H₂O



(82)

KMnO₄, py/H₂O (2:1), 100^o, 7 d



(75)

KMnO₄ (6.4 eq), py/H₂O (2:1),
rt, 48 h

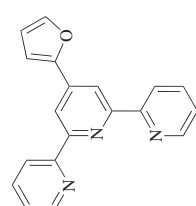
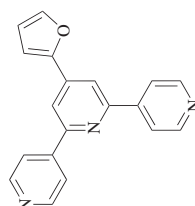
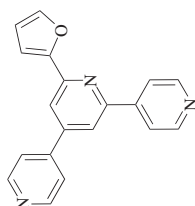
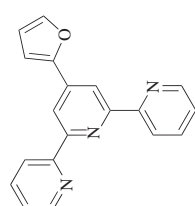
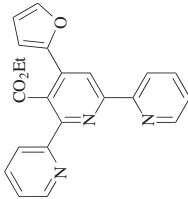
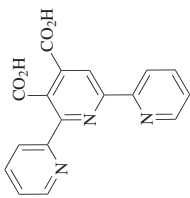
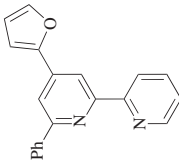
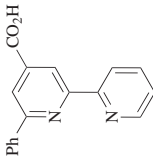
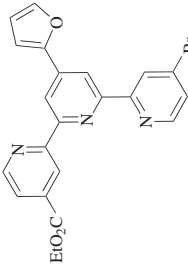
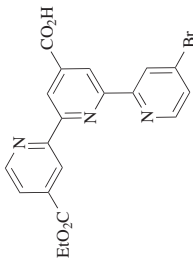
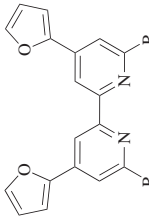
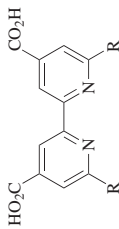
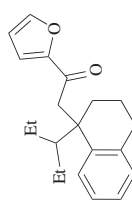


TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

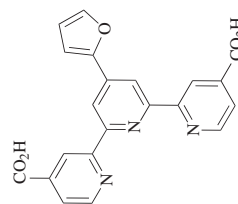
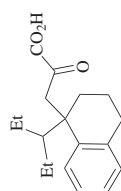
Furan	Conditions	Product(s) and Yield(s) (%)	Refs.				
	KMnO ₄ (4.7 eq), py/H ₂ O (2:1), rt, 24 h	 (68)	771				
	KMnO ₄ (1.2 eq), NaOH (aq), reflux, 2 h	 (40)	772				
	1. KMnO ₄ (5.5 eq), py/H ₂ O (2:1), rt 2. EtOH, rt	 (49)	773				
	KMnO ₄ (13 eq), <i>t</i> -BuOH/H ₂ O (4:8:1), reflux, overnight	 R <table><tr><td>Me</td><td>(—)</td></tr><tr><td>Ph</td><td>(64)</td></tr></table>	Me	(—)	Ph	(64)	774
Me	(—)						
Ph	(64)						

C₂₁

1. O₃, MeOH, -78°, 1 h
2. Me₂S (29 eq), rt, 1 h

421

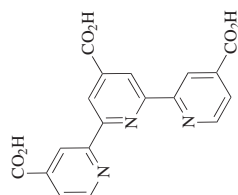
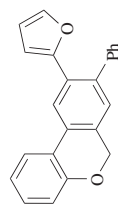
(99)



KMnO₄, NaOH (aq), rt, 24 h

775

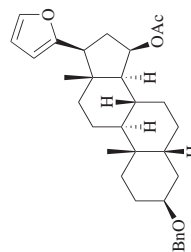
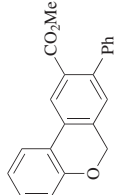
(93)

C₂₃

1. RuCl₃ (0.022 eq), NaIO₄ (4.1 eq),
MeCN/CCl₄/H₂O (2:2:3), rt, 1 h
2. CH₂N₂, Et₂O

776

(80)



1. NBS, NaOAc, H₂O, dioxane
2. KMnO₄, NaIO₄, K₂CO₃,
18-crown-6

387

(—)

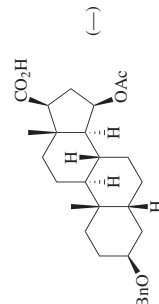
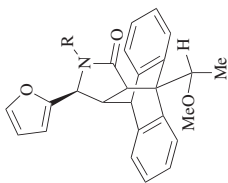
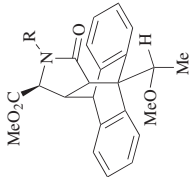
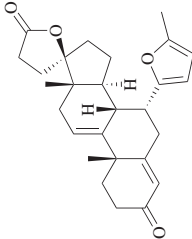
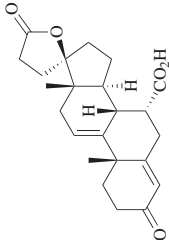


TABLE 5. SYNTHESIS OF CARBOXYLIC ACIDS AND ESTERS (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.								
C ₂₄		1. RuCl ₃ , NaIO ₄ , hexane, H ₂ O, rt, 10 min 2. TMSCH ₂ N ₂ , toluene, rt, 1 h	 <table><tr><th>R</th><th></th></tr><tr><td>Me</td><td>(80)</td></tr><tr><td>4-MeOC₆H₄</td><td>(78)</td></tr><tr><td>PMB</td><td>(71)</td></tr></table>	R		Me	(80)	4-MeOC ₆ H ₄	(78)	PMB	(71)	777
R												
Me	(80)											
4-MeOC ₆ H ₄	(78)											
PMB	(71)											
C ₂₇		O ₃ , CH ₂ Cl ₂ , MeOH, -46°; then Me ₂ S (3.74 eq)	 (82)	107								

^aThe yield was determined by GC.

TABLE 6. SYNTHESIS OF 2,5-DIALKOXY-2,5-DIHYDROFURANS

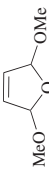
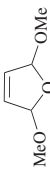
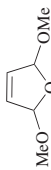
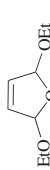
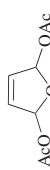
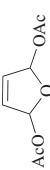
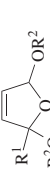
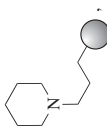
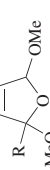
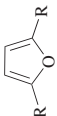
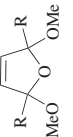
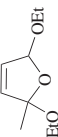
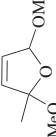
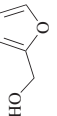
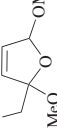
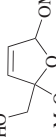
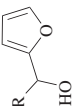
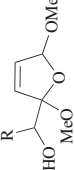
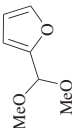
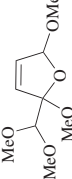
Furan	Conditions	Product(s) and Yield(s) (%)	Refs.																					
C ₄ 	Pt/Ni electrolyzer, 2 F/mol, NH ₄ Br (4.6 eq), MeOH, -22°, 7.5 h	 (85)	121																					
	-2e ⁻ , NH ₄ Br, MeOH, -22°, 16 h	 (73)	231																					
	Br ₂ (1.0 eq), MeOH, -25°	 (77)	778																					
	H ₂ O ₂ (2.0 eq), VOSO ₄ (0.01 eq), H ₂ O, EtOH, rt, 6 h	 (12)	621																					
	Br ₂ , Ac ₂ O, KOAc, AcOH	 (83)	779																					
	Pt/C electrolyzer, -2e ⁻ , 2.5 F/mol, AcOH, NaOAc, MeCN, 7°	 (57)	279																					
C ₄₋₅ 	Br ₂ (1.0 eq), CaCO ₃ , R ² OH, -40°, 2 min	<table><tr><th>R¹</th><th>R²</th><th></th></tr><tr><td>H</td><td>Et</td><td>(79)</td></tr><tr><td>H</td><td><i>n</i>-Pr</td><td>(42)</td></tr><tr><td>H</td><td><i>n</i>-Pr</td><td>(65)</td></tr><tr><td>Me</td><td>Et</td><td>(66)</td></tr><tr><td>HOCH₂</td><td>Et</td><td>(49)</td></tr><tr><td>(EtO)₂CH</td><td>Et</td><td>(70)</td></tr></table> 	R ¹	R ²		H	Et	(79)	H	<i>n</i> -Pr	(42)	H	<i>n</i> -Pr	(65)	Me	Et	(66)	HOCH ₂	Et	(49)	(EtO) ₂ CH	Et	(70)	237
R ¹	R ²																							
H	Et	(79)																						
H	<i>n</i> -Pr	(42)																						
H	<i>n</i> -Pr	(65)																						
Me	Et	(66)																						
HOCH ₂	Et	(49)																						
(EtO) ₂ CH	Et	(70)																						
C ₄₋₆ 	 , Pt-Pt, -2e ⁻ , 7 F/mol, MeOH	<table><tr><th>R</th><th></th></tr><tr><td>H</td><td>(78)</td></tr><tr><td>Me(OH)CH</td><td>(96)</td></tr></table>  <i>cis/trans</i> 1:1	R		H	(78)	Me(OH)CH	(96)	616															
R																								
H	(78)																							
Me(OH)CH	(96)																							

TABLE 6. SYNTHESIS OF 2,5-DIALKOXY-2,5-DIHYDROFURANS (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₄₋₆ 	PhI(OAc) ₂ (1.0 eq), Mg(ClO ₄) ₂ (2.0 eq), MeOH, rt, 2 h	 R H (—) Me (—)	70
C ₅ 	Br ₂ , Na ₂ CO ₃ , EtOH	 (90)	780
	Anodic oxidation, 1.6 amp/h, –2e [–] , NH ₄ Br (0.06 eq), MeOH	 (49)	263
	Br ₂ (1.09 eq), MeOH, Et ₂ O, –61 [°] , 3 h	 (60)	781
	Br ₂ (1.2 eq), MeOH/Et ₂ O (3.6:1), –45 [°] ; then rt, 2 h	 (91)	244, 238, 236
C ₅₋₇ 	2.02 F/mol, Et ₄ NClO ₄ (cat.), MeOH, rt, 10 min	 R H (91) Me (95) Et (94)	782
C ₅ 	NBS (1.4 eq), NaOAc (2.4 eq), MeOH, 5 [°] , 0.5 h	 (27)	256

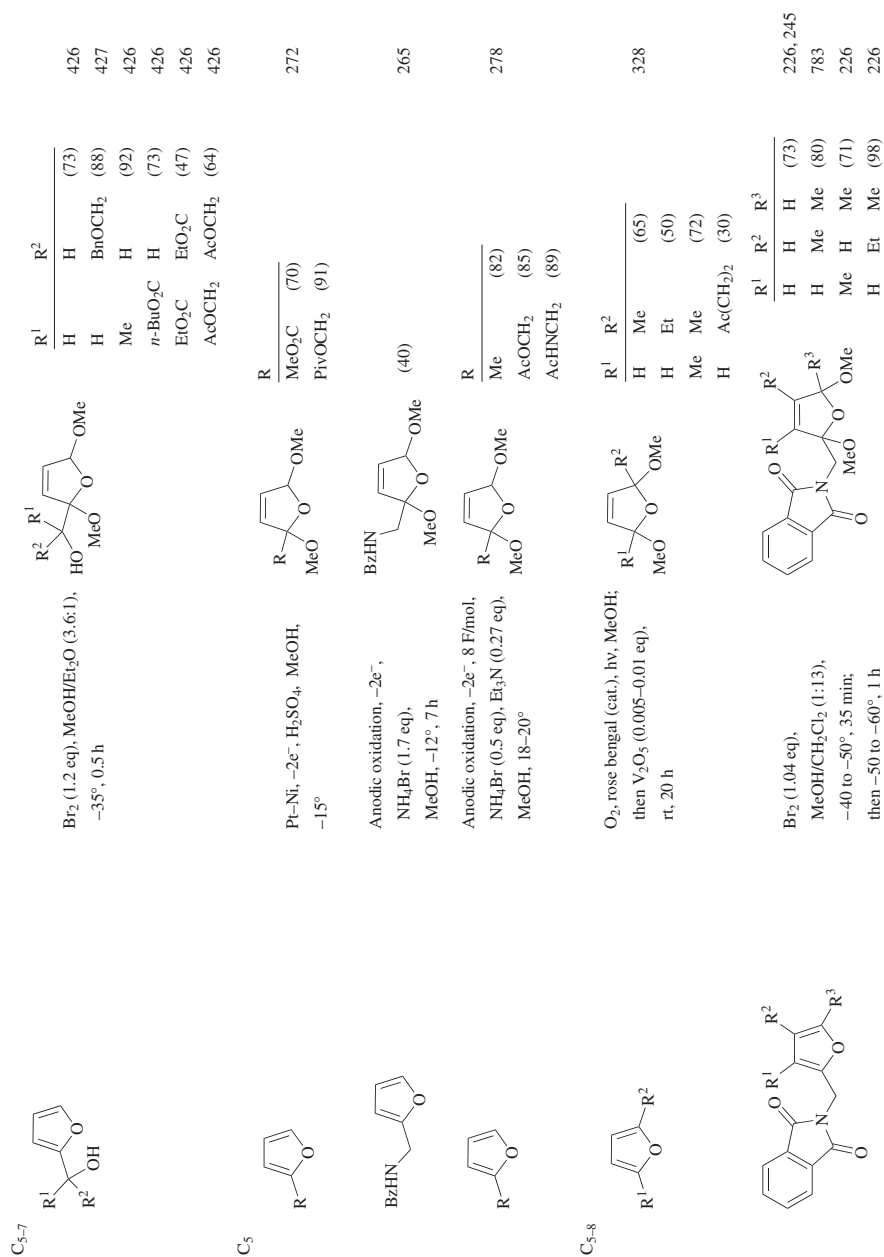
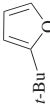
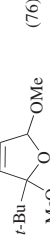
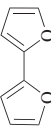
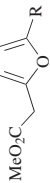
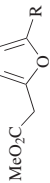
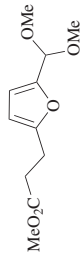
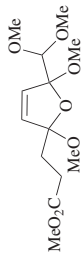
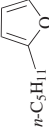
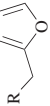


TABLE 6. SYNTHESIS OF 2,5-DIALKOXY-2,5-DIHYDROFURANS (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
	Br ₂ (1.03 eq), MeOH/Et ₂ O (2.8:1), -40°, 20 min	 Temp (°) -40 (89) -35 (93)	242, 243 241
	Br ₂ , MeOH	 (60)	140, 784
	MMPP (2.0 eq), MeOH, rt, 15 h	 R Me (95) <i>n</i> -C ₆ H ₁₃ (91) <i>n</i> -C ₇ H ₁₅ (93) <i>n</i> -C ₈ H ₁₇ (83) <i>n</i> -C ₉ H ₁₉ (95)	37
	Br ₂ (1.1 eq), NaHCO ₃ (2.2 eq), MeOH, -30°; then rt, 2 h	 (75)	430
	Br ₂ (1.0 eq), MeOH/Et ₂ O (2.8:1), -25°, 0.5 h; then -15°, 2 h; then rt, 20 h	 (59)	253
	-2e ⁻ , 50 F/mol, NH ₄ Br (0.12 eq), 1,4-dioxane, MeOH, 0°	 n R 1 H (57) 1 Me (19) 2 H (100) 3 H (63)	617 617 785 617

C ₆₋₇		Ni, 3.74 amp/h, -2e ⁻ , H ₂ SO ₄ , MeOH, -30°		R H (38) MeO ₂ C (72)	266
C ₇		Br ₂ (1.0 eq), NaCO ₃ (2.0 eq), MeOH		(—)	248
C ₇₋₈		Anodic oxidation, -2e ⁻ , NH ₄ Br (0.7 eq), MeOH		n 1 (95) 2 (83)	271
C ₇		Br ₂ , MeOH, Et ₂ O, -40°		(91)	567
C ₇₋₉		Pt-Ni, -2e ⁻ , H ₂ SO ₄ , -15°		(85-95) Y = O, CH ₂ , (CH ₂) ₂	272
C ₇		Br ₂ (1.2 eq), MeOH/Et ₂ O (1:1.33), -45°, 0.5 h		(94)	32

TABLE 6. SYNTHESIS OF 2,5-DIALKOXY-2,5-DIHYDROFURANS (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.								
C ₈ 	Anodic oxidation, -2e ⁻ , 4 F/mol, NH ₄ Br (0.4 eq), MeOH, -25°	 (76)	268								
C ₈₋₁₀ 	Anodic oxidation, -2e ⁻ , 4 F/mol, NH ₄ Br (0.4 eq), MeOH, -25°	 (42)	268								
C ₈₋₂₂ 	Anodic oxidation, -2e ⁻ , NH ₄ Br, MeOH	<table><tr><th>Y</th><th>R</th></tr><tr><td>O</td><td>H</td></tr><tr><td>CH</td><td>H</td></tr><tr><td>CH</td><td>Me</td></tr></table>	Y	R	O	H	CH	H	CH	Me	271
Y	R										
O	H										
CH	H										
CH	Me										
C ₈₋₂₂ 	Br ₂ (1.15 eq), Na ₂ CO ₃ (4.2 eq), MeOH, rt, 1 h	<table><tr><th>R</th></tr><tr><td>Et</td></tr><tr><td><i>n</i>-Bu</td></tr><tr><td><i>n</i>-C₆H₁₃</td></tr><tr><td><i>n</i>-C₁₀H₂₁</td></tr></table>	R	Et	<i>n</i> -Bu	<i>n</i> -C ₆ H ₁₃	<i>n</i> -C ₁₀ H ₂₁	252 252 252 230, 229, 252, 251			
R											
Et											
<i>n</i> -Bu											
<i>n</i> -C ₆ H ₁₃											
<i>n</i> -C ₁₀ H ₂₁											
C ₈ 	Br ₂ , NaHCO ₃ , MeOH	 (—)	250								
C ₉ 	Br ₂ (1.0 eq), Na ₂ CO ₃ (4.0 eq), MeOH, -15°, 10 min	 (86)	228								
C ₉₋₁₁ 	Anodic oxidation, -2e ⁻ , 4 F/mol, NH ₄ Br (0.27 eq), MeOH, -30°	<table><tr><th>R</th></tr><tr><td>2-thienyl</td></tr><tr><td>Ph</td></tr></table>	R	2-thienyl	Ph	270					
R											
2-thienyl											
Ph											

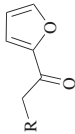
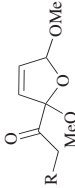
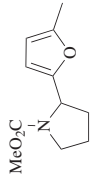
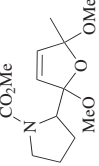
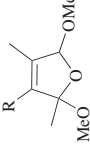
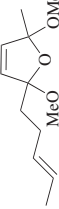
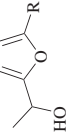
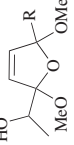
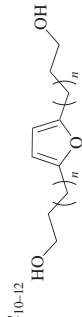
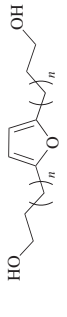
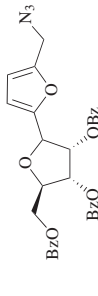
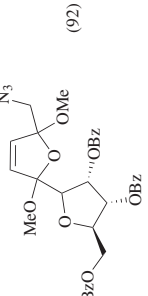
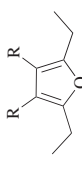
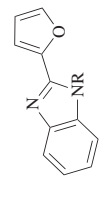
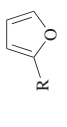
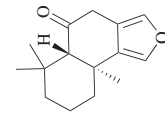
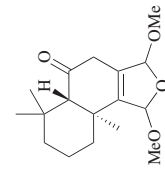
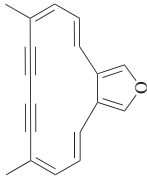
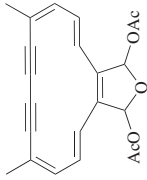
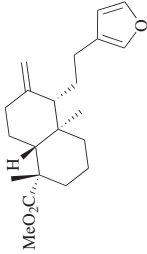
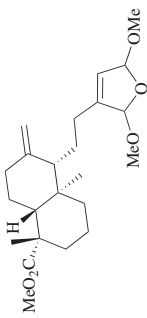
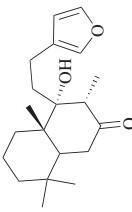
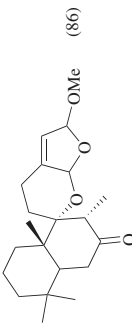
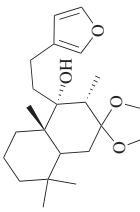
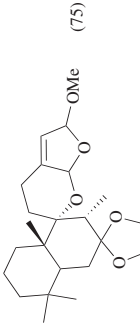
C ₉₋₂₃		Pt, -2e ⁻ , 3 F/mol, LiClO ₄ (0.3 eq), MeOH, 45°, 0.5 h		R	274
				<i>n</i> -C ₃ H ₇ (81)	
				<i>n</i> -C ₅ H ₁₁ (75)	
				<i>n</i> -C ₇ H ₁₅ (73)	
				<i>n</i> -C ₉ H ₁₉ (71)	
				<i>n</i> -C ₁₁ H ₂₃ (81)	
				<i>n</i> -C ₁₃ H ₂₇ (83)	
				<i>n</i> -C ₁₅ H ₃₁ (80)	
				<i>n</i> -C ₁₇ H ₃₅ (77)	
C ₉		Anodic oxidation, -2e ⁻ , NH ₄ Br, MeOH		(96)	271
C ₉₋₁₃		Pt, 2.78 F/mol, Et ₃ NClO ₄ (0.25 eq), MeOH, rt, 4 h		R	273
				allyl (93)	
				Bn (85)	
				PMB (90)	
C ₁₀		Anodic oxidation, -2e ⁻ , NH ₄ Br, MeOH		(71)	786
C ₁₀₋₁₁		-2e ⁻ , NaBr, MeOH		R	264
				<i>n</i> -C ₄ H ₉ (—)	
				<i>n</i> -C ₅ H ₁₁ (—)	

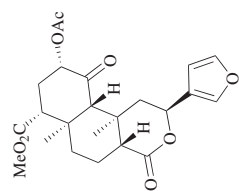
TABLE 6. SYNTHESIS OF 2,5-DIALKOXY-2,5-DIHYDROFURANS (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10-12} 	O_2 , methylene blue, hv, CH_2Cl_2 , 0° , 2 min; then Me_2S (10 eq)	n 1 (80) 2 (77)	330
	NBS (1.2 eq), THF/ H_2O (3:1), 0° , 20 min	n 1 (46) 2 (65)	120
C_{10} 	Br_2 , $NaHCO_3$, MeOH	 (92)	787
C_{10-20} 	Br_2 , Na_2CO_3 , EtOH	R Me (94) Ph (73)	329
C_{11} 	Pt/Ni electrolyzer, $-2e^-$, 3–4 F/mol, NH_4Br (1.0 eq), MeOH, -15°	R H (70) Me (91)	269
C_{12-16} 	Br_2 (0.04 eq), Na_2CO_3 (1.8 eq), MeOH, -25° , 2 h	R $n-C_8H_{17}$ (70) $n-C_{10}H_{21}$ (71) $n-C_{12}H_{25}$ (70)	232

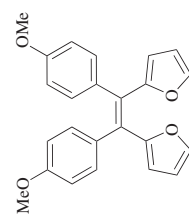
C ₁₂		Br ₂ , Na ₂ CO ₃ , MeOH		R H (15) Me (73)	146
C ₁₃		Br ₂ , MeOH		(—)	227
C ₁₄		Pt, 2.78 F/mol, Et ₄ NClO ₄ (0.25 eq), MeOH, rt, 4 h		R Bn (74) PMB (77)	273
C ₁₅		Br ₂ , MeOH, Et ₂ O, -35°, 1 h		(80)	254
		AcNHBr, MeOH, 0° to rt, 5 min		(79)	214
		O ₂ , methylene blue, hv, MeOH, 1 min		(—)	95

TABLE 6. SYNTHESIS OF 2,5-DIALKOXY-2,5-DIHYDROFURANS (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
 C ₁₅	Br ₂ (1.93 eq), Na ₂ CO ₃ (0.67 eq), MeOH, -25 to 0°, 1 h	 (94)	276
 C ₁₈	Ph(OAc) ₄ , AcOH, 20°, 0.5 h	 (-)	275
 C ₂₀	NBS, MeOH, 0°, 10 min	 (85)	788
	(+)-Pt-Ni(-), 2 F/mol, NH ₄ Br (4.6 eq), MeOH, -45°, 7 min	 (86)	121
	(+)-Pt-Ni(-), 2 F/mol, NH ₄ Br (4.6 eq), MeOH, -22°, 7 min	 (75)	121

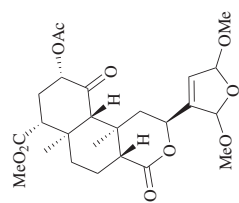


C₂₂



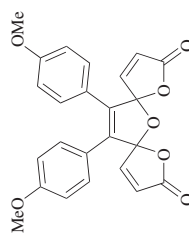
205

Br₂, MeOH, CH₂Cl₂, -30°



(84)

234, 235,
233

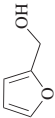
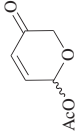
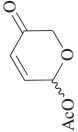
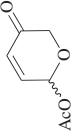
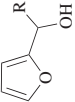
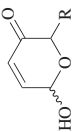
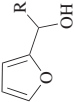
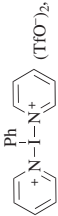
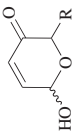
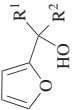
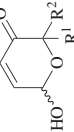
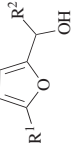
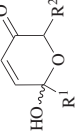


(80)

O₂, rose bengal, hv, MeOH,
2 min, then silica gel

96

TABLE 7. SYNTHESIS OF 6-HYDROXY-2H-PYRAN-3(6H)-ONES

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₅		NBS (1.05 eq), NaHCO ₃ (2.0 eq), NaOAc (1.0 eq), THF/H ₂ O (4:1), 0°, 10 min; then Ac ₂ O (3.0 eq), 0° to rt, overnight	 (64)	614
		NBS, THF/H ₂ O (4:1), 0°, 0.5 h; then Ac ₂ O, py, DMAP, CH ₂ Cl ₂	 (59)	460
		NBS, NaHCO ₃ , Ac ₂ O, MeOH, H ₂ O, 0° to rt, 18 h	 (55)	613
C ₅₋₈		2-HO ₂ CC ₆ H ₄ CO ₂ H, CHCl ₃	 R H (77) <i>i</i> -Pr (80)	789
C ₅₋₉		 (1.0 eq), MeCN, H ₂ O, pH 7, 10 min	 R H (85) Me (85) <i>n</i> -Bu (80)	533
C ₅₋₇		Br ₂ (1.0 eq), NaHCO ₃ (2.0 eq), MeCN, H ₂ O, 0°, 10 min	 R ¹ R ² H H (86) H Me (82) H (76) Me Me (78)	429
C ₅₋₆		H ₂ O ₂ (1.25 eq), titanium silicalite, MeCN, 40°	 R ¹ R ² Time (h) H H 3.5 (99) H Me 6.5 (93) Me H 9.5 (79)	48

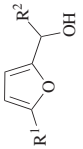
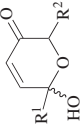
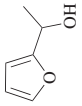
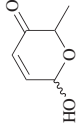
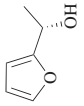
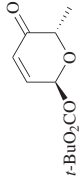
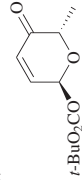
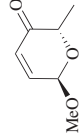
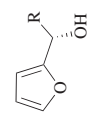
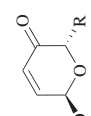
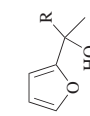
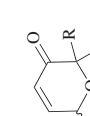
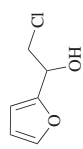
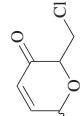
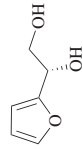
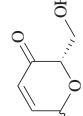
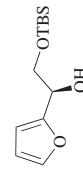
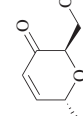
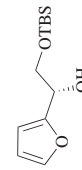
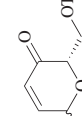
C_{5-16}		O_2 , TPP (cat.), hv, CH_2Cl_2 , -70° , 2 h; then Ph_3P (1.0 eq), 10 min		R^1	R^2	dr	
				H	H	(95)	526
				H	Me	(90)	2:1
				Me	H	(93)	—
				$HOCH_2$	H	(85)	—
				$AcOCH_2$	H	(90)	—
				$BzOCH_2$	H	(90)	—
				H	Et	(90)	2:1
				Me	Me	(89)	3:2
				Et	H	(80)	—
				Et	Me	(70)	3:2
				H	Ph	(65)	2:1
				H	$n-C_{11}H_{23}$	(80)	3:2
C_6		Br_2 , THF/ H_2O , 5°		(17)			526
		1. NBS, NaOAc, $NaHCO_3$, THF/ H_2O , 0° 2. (<i>t</i> -BuCO) $_2$ O, DMAP, CH_2Cl_2		(54)			790
		1. NBS (1.05 eq), $NaHCO_3$ (2.0 eq), $NaOAc$ + $3H_2O$ (1.0 eq), THF/ H_2O (4:1), 0° , 1 h 2. (<i>t</i> -BuCO) $_2$ O (1.5 eq), $NaOAc$ (1.1 eq), 80° , 2 h		(82)			499, 498
		Br_2 , MeOH, Et_2O , -78° , 35 min		(67)			791

TABLE 7. SYNTHESIS OF 6-HYDROXY-2*H*-PYRAN-3-(6*H*)-ONES (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C₆ 	1. NBS (1.05 eq), NaHCO ₃ (2.0 eq), NaOAc•3H ₂ O (1.0 eq), THF/H ₂ O (4:1), 0°, 1 h 2. (<i>t</i> -BuCO ₂ O) (1.2 eq), DMAP (1.01 eq), -78°, 1 h	 R Me (90) TBSOCH₂ (88) BnOCH₂ (48)	467, 792 467, 793 794
C₆₋₁₈ 	NBS (1.18 eq), THF/H ₂ O (4:1), 0°	 R H (65) 4-PhSC₆H₄ (78) 4-PhSOC₆H₄ (67) 4-PhSO₂C₆H₄ (69)	435, 434
	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0°, 3 h	 (70)	795
	O ₂ , TPP, MeOH, CH ₂ Cl ₂ ; then Me ₂ S	 (93)	527
	1. NBS 2. PivCl, DMAP	 (57)	497
	NBS (1.0 eq), NaOAc•3H ₂ O (1.0 eq), NaHCO ₃ (2.0 eq), THF/H ₂ O (4:1), 0°, 1 h	 (95)	481, 580, 579, 793

C₆

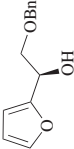
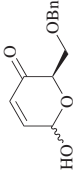
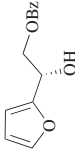
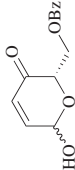
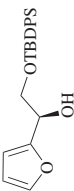
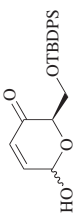
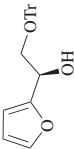
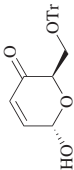
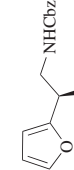
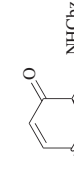
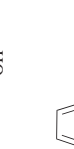
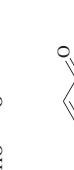
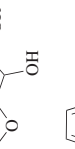
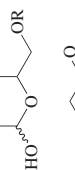
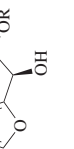
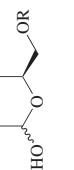
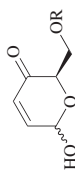
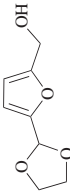
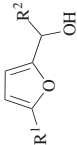
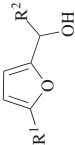
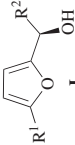
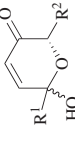
	Br ₂ , MeCN/H ₂ O		(89)	497
	Br ₂ , MeCN/H ₂ O		(80)	796
	NBS, NaOAc, THF/MeOH		(97)	797
	NBS (1.2 eq), NaOAc (1.0 eq), THF/H ₂ O (4:1)		(80)	440
	NBS (1.0 eq), NaOAc•3H ₂ O (1.0 eq), NaHCO ₃ (2.0 eq), THF/H ₂ O (4:1)		(82)	464, 611
	<i>m</i> -CPBA, CH ₂ Cl ₂		R H (70) Tr (80)	440
	NBS (1.0 eq), NaOAc•3H ₂ O (1.0 eq), NaHCO ₃ (2.0 eq), THF/H ₂ O (4:1), 0°, 1 h		R TBS (95) Piv (95)	466
	NBS (1.0 eq), NaOAc•3H ₂ O (1.0 eq), NaHCO ₃ (2.0 eq), THF/H ₂ O (4:1), 0°, 1 h		R TBS (92)	583, 468, 798, 471,
			Bn (—)	465, 799 794

TABLE 7. SYNTHESIS OF 6-HYDROXY-2*H*-PYRAN-3-(6*H*)-ONES (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.																																																	
C₆ 	<i>m</i> -CPBA, CH ₂ Cl ₂	(—)	800																																																	
C₆₋₁₆ 	PhI(OAc) ₂ (1.0 eq), MeCN/H ₂ O (1:1), pH 7, 24 h	<table><tr><th>R¹</th><th>R²</th><th>Temp</th></tr><tr><td>H</td><td>Me</td><td>50° (30)</td></tr><tr><td>Me</td><td>Me</td><td>rt (50)</td></tr><tr><td>Me</td><td>Et</td><td>rt (50)</td></tr><tr><td>H</td><td><i>n</i>-Bu</td><td>50° (30)</td></tr><tr><td>Me</td><td><i>n</i>-Bu</td><td>rt (50)</td></tr><tr><td>Me</td><td><i>n</i>-C₁₀H₂₁</td><td>rt (70)</td></tr></table>	R ¹	R ²	Temp	H	Me	50° (30)	Me	Me	rt (50)	Me	Et	rt (50)	H	<i>n</i> -Bu	50° (30)	Me	<i>n</i> -Bu	rt (50)	Me	<i>n</i> -C ₁₀ H ₂₁	rt (70)	533																												
R ¹	R ²	Temp																																																		
H	Me	50° (30)																																																		
Me	Me	rt (50)																																																		
Me	Et	rt (50)																																																		
H	<i>n</i> -Bu	50° (30)																																																		
Me	<i>n</i> -Bu	rt (50)																																																		
Me	<i>n</i> -C ₁₀ H ₂₁	rt (70)																																																		
C₆₋₁₁ 	<i>t</i> -BuOOH (0.6 eq), Ti(O- <i>i</i> -Pr) ₄ (1.2 eq), L-(+)-DIPT (1.25 eq), -21°	 I +  II	<table><tr><th>R¹</th><th>R²</th><th>Time (h)</th><th>I</th><th>I er</th><th>II</th></tr><tr><td>H</td><td>Me</td><td>24</td><td>(32)</td><td>>97.5;2.5</td><td>(53)</td></tr><tr><td>H</td><td>EtO₂CCH₂</td><td>24</td><td>(45)</td><td>>97.5;2.5</td><td>(42)</td></tr><tr><td>H</td><td><i>i</i>-Pr</td><td>25</td><td>(39)</td><td>>97.5;2.5</td><td>(55)</td></tr><tr><td>H</td><td><i>t</i>-Bu</td><td>40</td><td>(41)</td><td>53.0;47.0</td><td>(58)</td></tr><tr><td>H</td><td><i>n</i>-C₃H₁₁</td><td>25</td><td>(42)</td><td>>97.5;2.5</td><td>(53)</td></tr><tr><td>H</td><td>Ph</td><td>40</td><td>(42)</td><td>>99.5;0.5</td><td>(44)</td></tr><tr><td>Me</td><td><i>n</i>-C₃H₁₁</td><td>6</td><td>(40)</td><td>>97.5;2.5</td><td>(55)</td></tr></table>	R ¹	R ²	Time (h)	I	I er	II	H	Me	24	(32)	>97.5;2.5	(53)	H	EtO ₂ CCH ₂	24	(45)	>97.5;2.5	(42)	H	<i>i</i> -Pr	25	(39)	>97.5;2.5	(55)	H	<i>t</i> -Bu	40	(41)	53.0;47.0	(58)	H	<i>n</i> -C ₃ H ₁₁	25	(42)	>97.5;2.5	(53)	H	Ph	40	(42)	>99.5;0.5	(44)	Me	<i>n</i> -C ₃ H ₁₁	6	(40)	>97.5;2.5	(55)	514 801 514 514 514 514 514
R ¹	R ²	Time (h)	I	I er	II																																															
H	Me	24	(32)	>97.5;2.5	(53)																																															
H	EtO ₂ CCH ₂	24	(45)	>97.5;2.5	(42)																																															
H	<i>i</i> -Pr	25	(39)	>97.5;2.5	(55)																																															
H	<i>t</i> -Bu	40	(41)	53.0;47.0	(58)																																															
H	<i>n</i> -C ₃ H ₁₁	25	(42)	>97.5;2.5	(53)																																															
H	Ph	40	(42)	>99.5;0.5	(44)																																															
Me	<i>n</i> -C ₃ H ₁₁	6	(40)	>97.5;2.5	(55)																																															

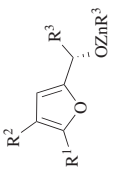
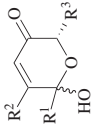
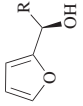
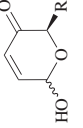
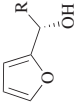
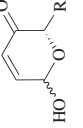
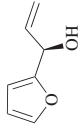
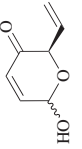
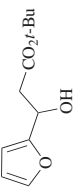
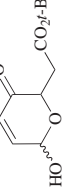
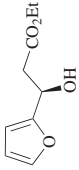
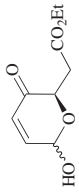
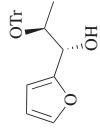
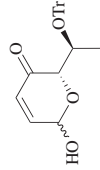
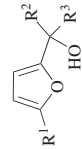
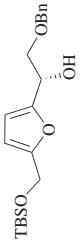
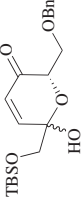
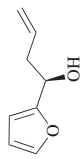
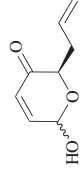
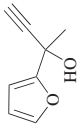
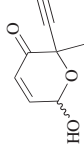
C ₆₋₉			NBS, (1.1 eq), THF/H ₂ O (4:1) rt, 4 h	R ¹	R ²	R ³	
				H	H	Me	(70)
				H	H	Et	(73)
				Me	H	Et	(71)
				Me	Me	Me	(46)
				Et	H	Me	(76)
				TBSOCH ₂	H	Et	(72)
				H	H	TBSO(CH ₂) ₄	(61)
				Me	Me	Et	(63)
				Et	H	Et	(77)
C ₇₋₁₁			NBS, NaHCO ₃ , THF, H ₂ O	R			
				Et	(42)		513
				allyl	(52)		
				<i>n</i> -Bu	(46)		
				<i>c</i> -C ₆ H ₁₁	(52)		
C ₇₋₉			NBS, NaOAc, NaHCO ₃ , THF, H ₂ O, 0°, 1 h	R			
				Et	(88)		802
				<i>n</i> -Pr	(84)		
				<i>i</i> -Pr	(87)		
				<i>t</i> -Bu	(79)		
C ₇			NBS, THF/H ₂ O (4:1), 0°, 0.5 h	(97)			476
			NBS (1.05 eq), NaHCO ₃ (2.0 eq), NaOAc•3H ₂ O (1.0 eq), THF/H ₂ O (4:1), 0°, 10 min	(97)			581, 612, 803

TABLE 7. SYNTHESIS OF 6-HYDROXY-2*H*-PYRAN-3-(6*H*)-ONES (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.																																				
C₇ 	NBS (1.0 eq), NaOAc•3H ₂ O (1.0 eq), NaHCO ₃ (2.0 eq), THF/H ₂ O (4:1), 0°, 1 h	 (96)	804, 801																																				
	Br ₂ , Na ₂ CO ₃ , MeOH	 (93)	805																																				
C₇₋₁₇ 	PhI(OAc) ₂ (1.0 eq), Mg(ClO ₄) ₂ , MeCN/H ₂ O (1:1), 24 h	<table border="1"> <thead> <tr> <th>R¹</th><th>R²</th><th>R³</th><th></th></tr> </thead> <tbody> <tr> <td>Me</td><td>H</td><td>Me</td><td>(72)</td></tr> <tr> <td>Me</td><td>H</td><td>Et</td><td>(80)</td></tr> <tr> <td>H</td><td>H</td><td><i>n</i>-Bu</td><td>(55)</td></tr> <tr> <td>H</td><td>-(CH₂)₅-</td><td></td><td>(75)</td></tr> <tr> <td>Me</td><td>H</td><td><i>n</i>-Bu</td><td>(90)</td></tr> <tr> <td>Me</td><td>-(CH₂)₅-</td><td></td><td>(95)</td></tr> <tr> <td>Me</td><td>H</td><td><i>n</i>-C₁₀H₂₁</td><td>(85)</td></tr> <tr> <td>H</td><td>Ph</td><td>Ph</td><td>(80)</td></tr> </tbody> </table>	R ¹	R ²	R ³		Me	H	Me	(72)	Me	H	Et	(80)	H	H	<i>n</i> -Bu	(55)	H	-(CH ₂) ₅ -		(75)	Me	H	<i>n</i> -Bu	(90)	Me	-(CH ₂) ₅ -		(95)	Me	H	<i>n</i> -C ₁₀ H ₂₁	(85)	H	Ph	Ph	(80)	70, 533
R ¹	R ²	R ³																																					
Me	H	Me	(72)																																				
Me	H	Et	(80)																																				
H	H	<i>n</i> -Bu	(55)																																				
H	-(CH ₂) ₅ -		(75)																																				
Me	H	<i>n</i> -Bu	(90)																																				
Me	-(CH ₂) ₅ -		(95)																																				
Me	H	<i>n</i> -C ₁₀ H ₂₁	(85)																																				
H	Ph	Ph	(80)																																				
C₇ 	NBS, THF/H ₂ O, 0°	 (—)	806																																				
C₈ 	<i>t</i> -BuOOH, VO(acac) ₃ , CH ₂ Cl ₂ , rt, 3 h	 (91)	476																																				
	<i>m</i> -CPBA, CH ₂ Cl ₂	 (43)	807																																				

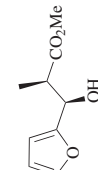
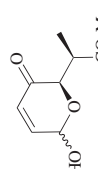
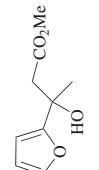
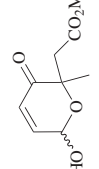
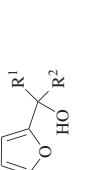
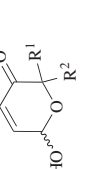
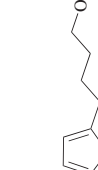
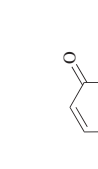
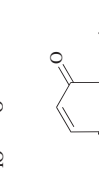
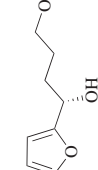
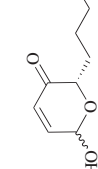
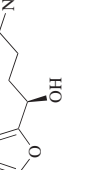
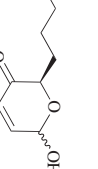
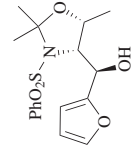
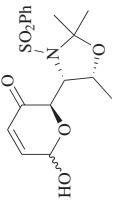
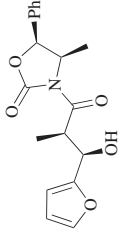
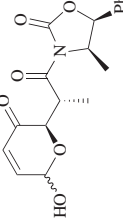
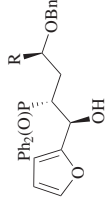
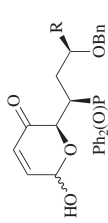
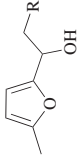
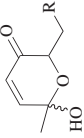
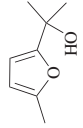
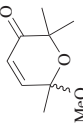
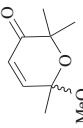
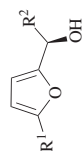
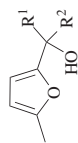
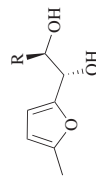
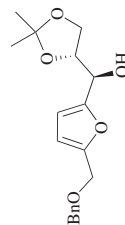
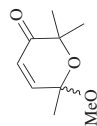
		428
	Br ₂ (2.1 eq), MeOH, CHCl ₃ , -78°, 1 h	
		808
	<i>m</i> -CPBA, CH ₂ Cl ₂ , 6 h, 0°	
		479
	NBS, THF/H ₂ O (4:1), 0°	
		463, 469
	NBS (1.0 eq), NaOAc·3H ₂ O (1.0 eq), NaHCO ₃ (2.0 eq), THF/H ₂ O (4:1), 0°, 30 min	
		809
	<i>m</i> -CPBA, CH ₂ Cl ₂	
		810
	NBS, NaOAc, NaHCO ₃ , THF/H ₂ O, 0°, 1 h; then Me ₂ S, 0°, 5 min	
		473 473, 474, 475
	NBS (1.1 eq), THF/H ₂ O (1:1), rt, 4 h	

TABLE 7. SYNTHESIS OF 6-HYDROXY-2H-PYRAN-3(6H)-ONES (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
 C ₈	<i>m</i> -CPBA, CH ₂ Cl ₂	 (98)	811
 C ₈₋₁₂	Br ₂ (1.2 eq), MeCN/H ₂ O (11:1), -20°, 1 h	 (95)	431
 C ₈₋₁₂	<i>m</i> -CPBA (1.0 eq), CH ₂ Cl ₂ , 0°, 2 d	 R H R (95) (65)	812
 C ₈₋₁₄	O ₂ , rose bengal, hv, MeOH, 5°, 4 min; then Me ₂ S (3.0 eq), CH ₂ Cl ₂ , rt, 15 h	 R R EtO ₂ C (91) Bz (92)	682
 C ₈	<i>t</i> -BuOOH (2.5 eq), VO(acac) ₃ (0.015 eq), CH ₂ Cl ₂ ; then CH(OMe) ₃ (1.2 eq), BF ₃ •Et ₂ O (0.05 eq)	 (90)	521
 C ₈	O ₂ , hv, H ₂ O, 5°, 0.5 h	 (71)	813

C₈₋₁₁C₈₋₁₅C₈₋₁₃C₈

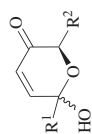
O₂, rose bengal, hv,
MeOH, 5°, 4 min; then
Me₂S (3.0 eq), CH₂Cl₂, rt, 15 h



(80)

682

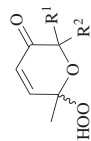
i-BuOOH (1.5 eq),
VO(acac)₂ (0.1 eq),
CH₂Cl₂, 0°, 14 h; then
Me₂S (1.5 eq), 0°, 30 min

R¹ R²

R ¹	R ²	
H	<i>i</i> -Pr	(85)
H	<i>n</i> -C ₅ H ₁₁	(90)
H	Ph	(88)
Me	<i>n</i> -C ₃ H ₇	(93)

520

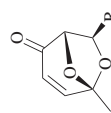
30% H₂O₂ (1.0 eq),
PTSA (0.43 eq), DME, rt

R¹ R² Time (h)

R ¹	R ²	Time (h)
Me	Me	7 (77)
H	<i>i</i> -Pr	16 (64)
H	<i>n</i> -C ₆ H ₁₃	18 (75)
H	<i>c</i> -C ₆ H ₁₁	23 (77)
Et	<i>n</i> -C ₆ H ₁₃	5 (65)
H	<i>n</i> -C ₈ H ₁₇	20 (65)

531

O₂, rose bengal, hv,
MeOH, 5°, 4 min; then
Me₂S (3.0 eq), CH₂Cl₂, rt, 15 h



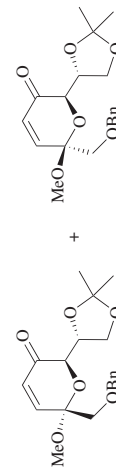
R

R	
MeO ₂ C	(74)
Ph	(60)

813, 682

682

1. *t*-BuOOH, VO(acac)₂,
CH₂Cl₂, rt, 6 h
2. Ag₂O, MeI, rt, 2 h



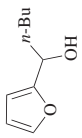
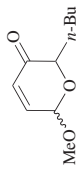
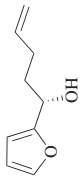
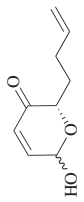
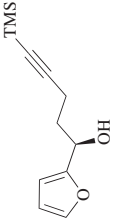
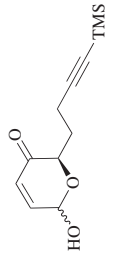
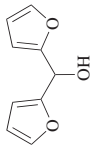
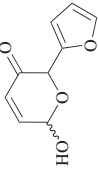
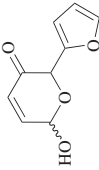
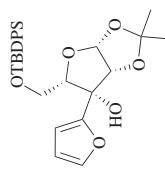
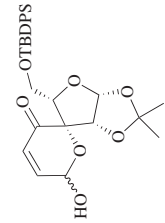
I

II

I + II (75), *I/II* = 4.5:1

488

TABLE 7. SYNTHESIS OF 6-HYDROXY-2*H*-PYRAN-3-(6*H*)-ONES (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. <i>t</i> -BuOOH (2.5 eq), VO(acac) ₂ (0.015 eq) 2. CH(OMe) ₃ (1.2 eq), BF ₃ •Et ₂ O (0.05 eq)	 (89)	521
	<i>t</i> -BuOOH (1 eq), VO(acac) ₂ (0.01 eq), CH ₂ Cl ₂ , rt, 1 h	 (83)	506, 519, 474, 504
	NBS, NaOAc, THF/H ₂ O	 (98)	814, 815
	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0°	 (48)	40
	NBS (1.0 eq), NaOAc•3H ₂ O (1.0 eq), NaHCO ₃ (2.0 eq), THF/H ₂ O (4:1), 0°, 3 h	 (44)	40
	NBS (1.0 eq), THF/H ₂ O (4:1), 0°, 5 min	 (85)	482

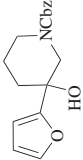
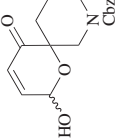
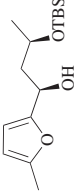
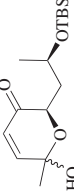
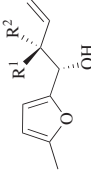
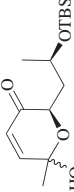
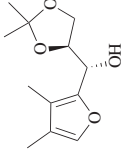
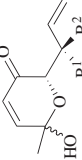
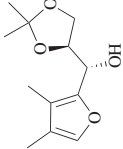
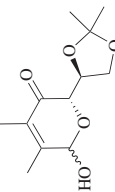
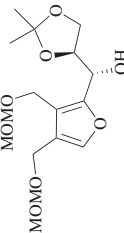
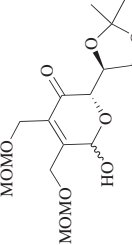
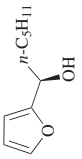
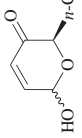
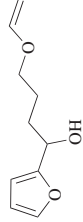
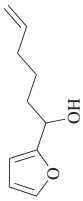
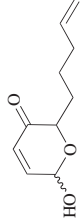
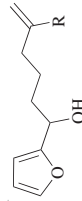
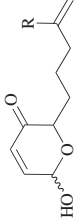
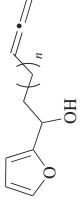
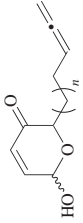
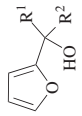
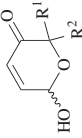
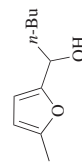
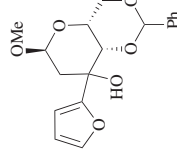
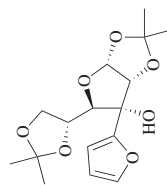
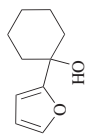
		<i>m</i> -CPBA, CH ₂ Cl ₂ , 0°	316
		HCl	445
		<i>m</i> -CPBA, CH ₂ Cl ₂	445
		NBS (1.0 eq), THF/H ₂ O (4:1), 0°	817
		NBS (1.0 eq), THF/H ₂ O (4:1), rt, 4 h	818
		NBS, NaOAc, THF/H ₂ O, 0°, 0.5 h	819

TABLE 7. SYNTHESIS OF 6-HYDROXY-2*H*-PYRAN-3-(6*H*)-ONES (Continued)

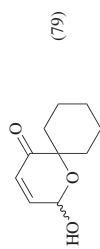
Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₀			
	<i>t</i> -BuOOH, VO(acac) ₃	 (78)	497
	O ₂ , rose bengal, hv, MeOH, CH ₂ Cl ₂ , -78°, 2 h; then Me ₂ S, CH ₂ Cl ₂ , 0°, 0.5 h	(—)	820
	<i>m</i> -CPBA (1.0 eq), CH ₂ Cl ₂ , 5–10°, 30 min; then rt, 2 h	(80)	821
	<i>t</i> -BuOOH (1.5 eq), VO(acac) ₃ (0.1 eq), CH ₂ Cl ₂ , 0°, 3 h	(—)	822
C ₁₀₋₁₁			
	O ₂ , rose bengal, hv, MeOH/CH ₂ Cl ₂ (1:2), -60°, 8 h; then Me ₂ S (2.0 eq), -60° to rt	 R H (95) Me (83)	525
	<i>t</i> -BuOOH (1.5 eq), VO(acac) ₃ (0.1 eq), CH ₂ Cl ₂ , 0°, 1 h	 n 1 (75) 2 (80)	823
C ₁₀₋₁₃			
	<i>m</i> -CPBA (1.1 eq), CH ₂ Cl ₂ , -10° to rt, 3 h	 R ¹ R ² -(CH ₂) ₅ - (79) Me Ph (81) Me PMP (85) MeO ₂ CCH ₂ Ph (—)	437 437 437 824

C₁₀

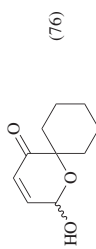


219

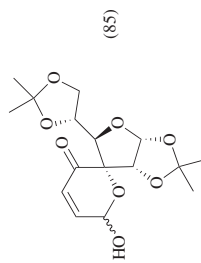
m-CPBA (1.45 eq), CH₂Cl₂,
7–15°, then rt, 3 h



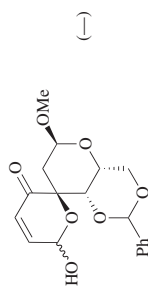
NBS (1.0 eq), THF/H₂O (4:1), 0°



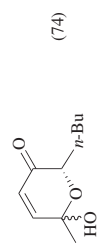
NBS (1.0 eq), THF/H₂O (4:1),
–5°, 5 min



m-CPBA, CH₂Cl₂, 0°



O₂, H₂O, 5°, 0.5 h



239

435

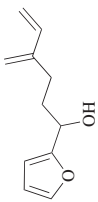
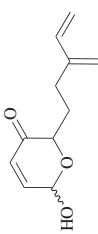
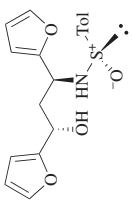
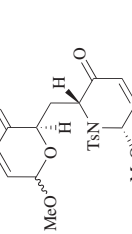
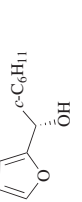
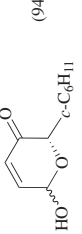
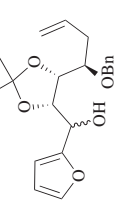
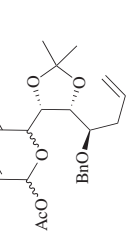
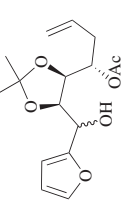
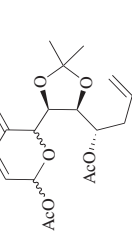
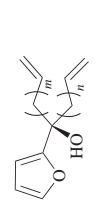
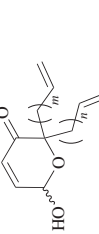
482

454

813

TABLE 7. SYNTHESIS OF 6-HYDROXY-2*H*-PYRAN-3(6*H*)-ONES (Continued)

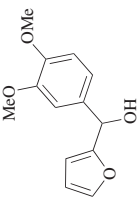
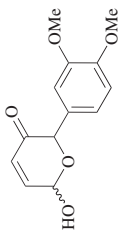
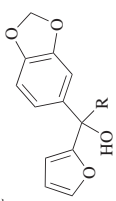
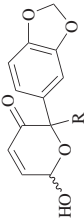
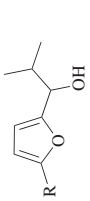
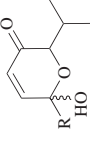
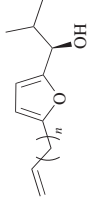
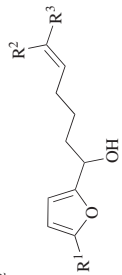
	Furan	Conditions	Product(s) and Yield(s) (%)			Refs.
			R	Temp		
C ₁₀₋₁₁		PhI(OAc) ₂ (1.0 eq), MeCN/H ₂ O (1:1), pH 7, 24 h		H 50° Me rt	(40) (76)	533
		<i>m</i> -CPBA (2.0 eq), CH ₂ Cl ₂ , 0°, 1 h			(96)	453, 445
		<i>m</i> -CPBA (2.0 eq), CH ₂ Cl ₂ , 0°, 1 h			(89)	453
		<i>m</i> -CPBA, CH ₂ Cl ₂			(90)	445
C ₁₁		1. O ₂ , rose bengal, hv, CH ₂ Cl ₂ /MeOH (3:1), -78°, 2 h; then Me ₂ S, 0°, 5 h 2. Ac ₂ O, DMAP, py, CH ₂ Cl ₂ , 0°, 3 h			(66)	820
		NBS (1.0 eq), NaOAc/3H ₂ O (1.0 eq), NaHCO ₃ (2.0 eq), THF/H ₂ O (4:1), 0° to rt			(90)	825

		O₂, rose bengal, hv, MeOH, CH₂Cl₂; then Me₂S	(82)	826, 447														
		NBS (1.2 eq), NaOAc•3H₂O (1.4 eq), THF/H₂O (1:1), 0°, 1 h; then CH(OMe)₃ (2.0 eq), BF₃•Et₂O (0.05 eq)	(29) dr 66:34	562, 563														
		NBS (1.0 eq), THF/H₂O (4:1), rt, 4 h	(94)	725, 726														
		<i>t</i>-BuOOH (1.2 eq), VO(acac)₃ (0.6 eq), CH₂Cl₂, -20°, 5 h; then Ac₂O, DMAP (cat.), py, CH₂Cl₂, 0°, 1 h	(88)	501, 500														
		1. <i>t</i>-BuOOH, VO(acac)₃, CH₂Cl₂, -20°, 5 h 2. Ac₂O, py, DMAP, CH₂Cl₂, 0°, 1 h	(—)	501														
		<i>m</i>-CPBA, CH₂Cl₂, 0°, 1.5 h	<table><tr><th><i>m</i></th><th><i>n</i></th></tr><tr><td>1</td><td>1 (62)</td></tr><tr><td>2</td><td>1 (58)</td></tr><tr><td>1</td><td>3 (55)</td></tr><tr><td>2</td><td>2 (58)</td></tr><tr><td>2</td><td>3 (56)</td></tr><tr><td>3</td><td>3 (59)</td></tr></table>	<i>m</i>	<i>n</i>	1	1 (62)	2	1 (58)	1	3 (55)	2	2 (58)	2	3 (56)	3	3 (59)	448
<i>m</i>	<i>n</i>																	
1	1 (62)																	
2	1 (58)																	
1	3 (55)																	
2	2 (58)																	
2	3 (56)																	
3	3 (59)																	

C₁₁₋₁₅

C₁₁₋₁₅

TABLE 7. SYNTHESIS OF 6-HYDROXY-2*H*-PYRAN-3-(6*H*)-ONES (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₁ 	<i>m</i> -CPBA, CH ₂ Cl ₂	(79) 	827
C₁₁₋₁₂ 	<i>m</i> -CPBA, CH ₂ Cl ₂	R  H (72) Me (73)	828
C₁₁₋₁₄ 	<i>m</i> -CPBA (1.1 eq), CH ₂ Cl ₂ , 0°, 1 h	R  TBSO(CH₂)₃ (88) TBSO(CH₂)₄ (90)	441
C₁₁₋₂₂ 	<i>m</i> -CPBA (1.1 eq), CH ₂ Cl ₂ , 0° to rt	n 1 (81) 2 (77) 3 (96) 4 (75)	486
C₁₁₋₂₂ 	<i>t</i> -BuOOH (1.5 eq), VO(acac) ₂ (0.1 eq), CH ₂ Cl ₂ , 0°, 1 h	R¹ R² R³ H H Me (69) TBSOCH₂ H Me (80) Ph Me H (63) Ph Me MeO₂C (83) Ph Ph H (70)	823, 822 823 823 823 823

C ₁₁₋₁₄		1. NBS (1.0 eq), NaOAc·3H ₂ O (1.0 eq), NaHCO ₃ (2.0 eq), THF/H ₂ O (4:1), 0°, 0.5 h 2. Amberlyst 15, CH ₂ Cl ₂ , rt, 0.5 h		<i>n</i>	<i>R</i>	
				1	<i>i</i> -Pr	(87)
				1	allyl	(93)
				1	(<i>E</i>)-MeCH=CH	(54)
				1	TBDPSO(CH ₂) ₃	(70)
				1	Ph	(56)
				2	<i>i</i> -Pr	(84)
C ₁₁		<i>t</i> -BuOOH (1.7 eq), VO(acac) ₂ (0.1 eq), CH ₂ Cl ₂ , 0° to rt; then Et ₃ SiH (5.0 eq), TFA, CH ₂ Cl ₂ , -40°, 15 h				(86) dr >20:1
		<i>t</i> -BuOOH (1.7 eq), VO(acac) ₂ (0.1 eq), CH ₂ Cl ₂ , 0° to rt; then Et ₃ SiH (5.0 eq), TFA, CH ₂ Cl ₂ , -40°, 15 h				(90)
		<i>m</i> -CPBA (1.0 eq), CH ₂ Cl ₂ , 0°, 1 h; then Ac ₂ O, (<i>i</i> -Pr) ₂ EtN, DMAP (cat.)				(72)
		<i>m</i> -CPBA (1.0 eq), CH ₂ Cl ₂ , 0°, 1 h				(89)
		<i>m</i> -CPBA (1.0 eq), CH ₂ Cl ₂ , 0°, 1 h				(90)

TABLE 7. SYNTHESIS OF 6-HYDROXY-2*H*-PYRAN-3-(6*H*)-ONES (Continued)

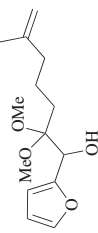
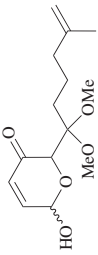
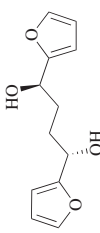
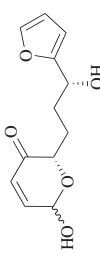
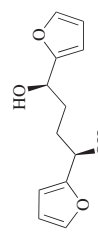
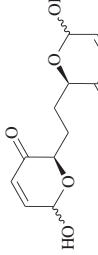
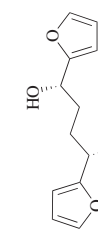
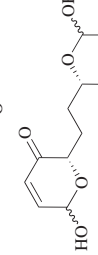
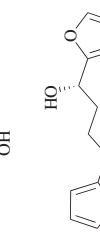
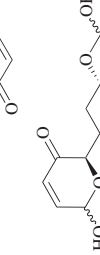
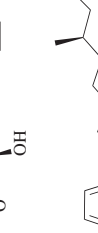
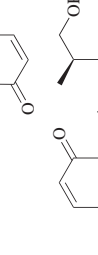
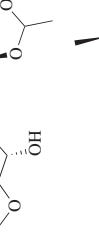
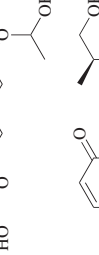
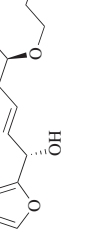
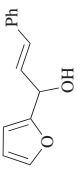
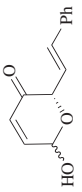
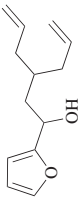
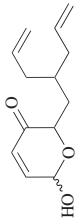
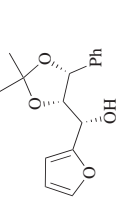
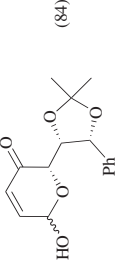
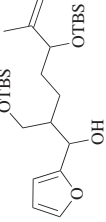
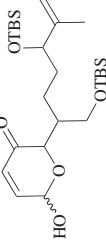
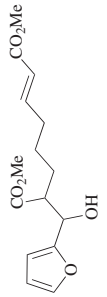
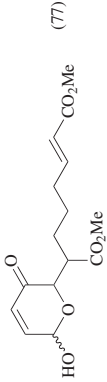
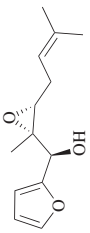
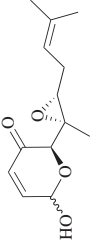
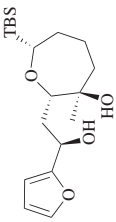
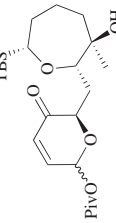
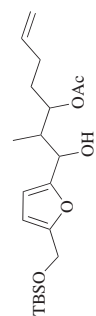
	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₂		O ₂ , rose bengal, hv, MeOH, CH ₂ Cl ₂ ; then Me ₂ S	 (90)	832
		<i>t</i> -BuOOH (1.2 eq), (+)-L-DET (1.2 eq), Ti(O <i>i</i> -Pr) ₄ (1.0 eq), -40°, 2 h	 (79)	523
		<i>t</i> -BuOOH (2.5 eq), VO(acac) ₃ (0.05 eq), CH ₂ Cl ₂ , rt, 6 h	 (95)	511, 510
		<i>t</i> -BuOOH (2.5 eq), VO(acac) ₃ (0.015 eq), CH ₂ Cl ₂ , rt, 7 h	 (82)	40
		<i>t</i> -BuOOH (2.5 eq), VO(acac) ₃ (0.015 eq), CH ₂ Cl ₂ , rt, 7 h	 (89)	40
		NBS, NaHCO ₃ , H ₂ O	 (—)	833
		NBS (1.2 eq), NaHCO ₃ (1.9 eq), NaOAc (0.9 eq), THF/H ₂ O (4:1), 0°, 1 h	 (—)	834
				

TABLE 7. SYNTHESIS OF 6-HYDROXY-2*H*-PYRAN-3(6*H*)-ONES (Continued)

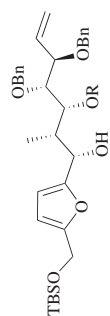
Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
	<i>t</i> -BuOOH (0.6 eq), (+)-L-DIPT (0.3 eq), Ti(O <i>i</i> -Pr) ₄ (0.2 eq), 4 MS, CH ₂ Cl ₂ , -30°, 24 h	 (35)	836, 524
	<i>t</i> -BuOOH (1.78 eq), VO(acac) ₂ (0.02 eq), CH ₂ Cl ₂ , 0°, 1 h	 (85)	823
	<i>t</i> -BuOOH, VO(acac) ₂ , CH ₂ Cl ₂ , 0°	 (84)	487, 578
	O ₂ , rose bengal, hv, MeOH, CH ₂ Cl ₂ ; then Me ₂ S	 (—)	528
	NBS (1.1 eq), NaHCO ₃ (2.0 eq), NaOAc (1.0 eq), THF/H ₂ O (4:1), 0°, 10 min	 (77)	581
	<i>m</i> -CPBA (1.1 eq), CH ₂ Cl ₂ , 0°, 22 h	 (51)	449
	NBS (1.17 eq), NaOAc (1.33 eq), THF/H ₂ O (1:1); then PivCl (1.5 eq), DMAP (0.17 eq), Et ₃ N (4.0 eq), CH ₂ Cl ₂	 (57) dr 70:30	575



m-CPBA, CH₂Cl₂

(—)

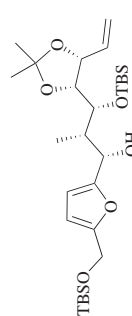
837



1. *t*-BuOOH (1.5 eq),
VO(acac)₂ (0.01 eq),
CH₂Cl₂, 0° to rt, 1 h
2. Ac₂O (1.0 eq), DMAP (0.5 eq),
py (2.5 eq), rt, 4 h

R
Ac (56)
TBS (93)

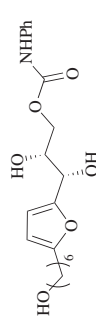
496



1. *t*-BuOOH (1.5 eq),
VO(acac)₂ (0.01 eq),
CH₂Cl₂, 0° to rt, 1 h
2. Ac₂O (1.0 eq), DMAP (0.5 eq),
py (2.5 eq), rt, 4 h

(71)

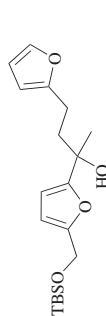
496



NBS (34.6 eq), NaHCO₃ (104 eq),
NaOAc (52 eq),
THF/H₂O (4:1), rt, 1 h; then
PPTS, CH₂Cl₂, 40–45°, 20 h

(33)

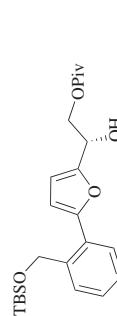
151, 153



t-BuOOH, VO(acac)₂,
CH₂Cl₂, rt, 3 h

(80)

838

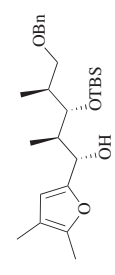
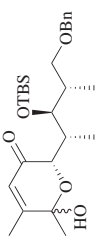
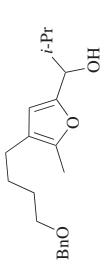
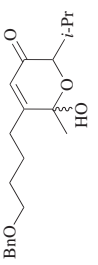
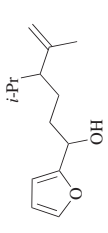
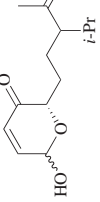
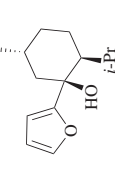
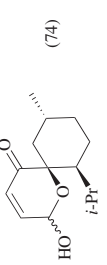
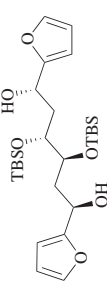
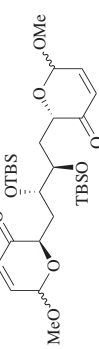
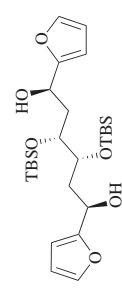
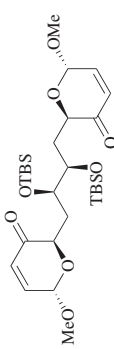


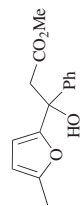
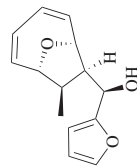
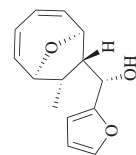
NBS (1.08 eq), NaHCO₃ (20 eq),
NaOAc*3H₂O (1.0 eq),
THF/H₂O (4:1), 0°, 2 h

(72)

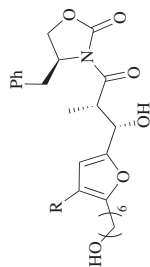
472

TABLE 7. SYNTHESIS OF 6-HYDROXY-2*H*-PYRAN-3-(6*H*)-ONES (Continued)

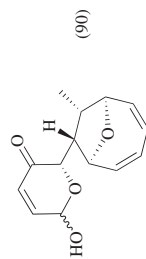
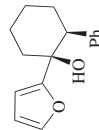
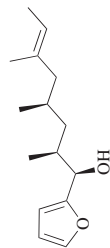
Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₃ 	<i>m</i> -CPBA (1.0 eq), CH ₂ Cl ₂ , 0°, 30 min	 (90)	442
	<i>m</i> -CPBA (1.0 eq), CH ₂ Cl ₂ , 0° to rt, 0.5 h	 (84)	444
C₁₄ 	<i>t</i> -BuOOH, VO(acac) ₂ , CH ₂ Cl ₂	 (71)	503
	<i>m</i> -CPBA (1.0 eq), CH ₂ Cl ₂ , 0°	 (74)	452
	1. <i>t</i> -BuOOH (3.25 eq), VO(acac) ₂ (0.02 eq), CH ₂ Cl ₂ 2. CH(OMe) ₃ , (74 eq), BF ₃ •Et ₂ O (0.1 eq)	 (93)	523
	1. <i>t</i> -BuOOH (3.25 eq), VO(acac) ₂ (0.02 eq), CH ₂ Cl ₂ 2. CH(OMe) ₃ , (74 eq), BF ₃ •Et ₂ O (0.1 eq)	 (52)	512



C₁₄₋₂₁

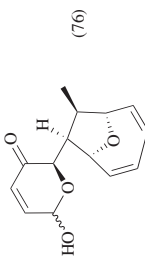


C₁₅



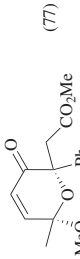
507

t-BuOOH (6.0 eq),
VO(acac)₂ (0.015 eq),
CH₂Cl₂, 0°, 3 h



495

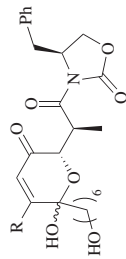
t-BuOOH (3.0 eq),
VO(acac)₂ (0.02 eq),
CH₂Cl₂, 0°, 3.5 h



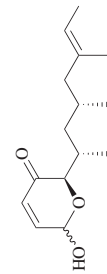
808

1. *m*-CPBA (1.6 eq),
CH₂Cl₂, 0°, 6 h
2. Ag₂O (1.0 eq), MeI (15 eq)

R	
H	(100)
Br	(100)
4-MeC ₆ H ₄	(100)

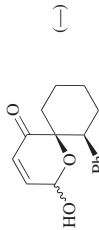


NBS (34.6 eq), NaHCO₃ (104 eq),
NaOAc (52 eq),
THF/H₂O (4:1), rt, 1 h; then
PPTS, CH₂Cl₂, 40–45°, 2 h



839

t-BuOOH, VO(acac)₂ (0.05 eq),
CH₂Cl₂, 0°; then 0° to rt, 0.67 h

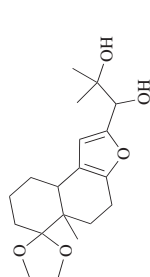


455

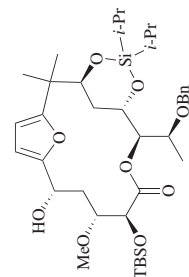
m-CPBA, CH₂Cl₂, 10°, 4 h

TABLE 7. SYNTHESIS OF 6-HYDROXY-2*H*-PYRAN-3-(6*H*)-ONES (Continued)

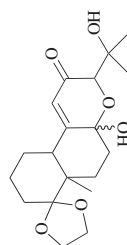
Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₅			
	NBS (2.86 eq), EtOAc, reflux, 4 h		610
C ₁₆			
	<i>m</i> -CPBA (2.0 eq), CH ₂ Cl ₂ , 0°; then rt, 1 h		840
	NaClO ₂ , NaH ₂ PO ₄ , 2-methyl-2-butene, CHCl ₃ /H ₂ O/pH 4.0 buffer/ <i>t</i> -BuOH (1:1:2:1), 40°, 7 h		535
	<i>m</i> -CPBA (1.1 eq), CH ₂ Cl ₂ , 0°, 2 h		841
C ₁₇			
	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0° to rt, 12 h		446



C₁₈



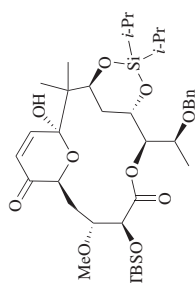
C₂₀



(93)

m-CPBA (1.1 eq), CH₂Cl₂, 0°;
then rt, 5 h

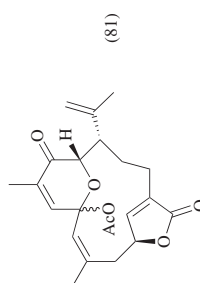
842



(64)

m-CPBA (1.3 eq),
CH₂Cl₂, rt, 1 h

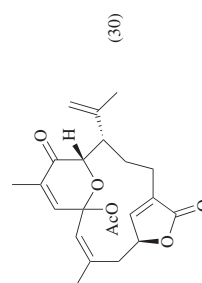
843



(81)

m-CPBA (1.0 eq), CH₂Cl₂, 0°;
then Ac₂O (2.5 eq),
DMAP (0.1 eq), py (5.0 eq), rt, 2 h

310, 10



(30)

1. *t*-BuOOH (2.5 eq),
VO(acac)₃ (0.16 mol %),
CH₂Cl₂, -20°, 4 h
2. Ac₂O (4 eq), DMAP (0.4 eq),
Et₃N (10 eq), CH₂Cl₂,
0° to rt, 2.5 h

844

TABLE 7. SYNTHESIS OF 6-HYDROXY-2*H*-PYRAN-3-(6*H*)-ONES (Continued)

	Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₂₂		CH ₃ CO ₃ H, AcOH	 (65)	432
C ₂₇		NBS (1.18 eq), THF/H ₂ O (4:1), 0°, 30 min	 (92)	845, 461
C ₂₈		<i>m</i> -CPBA (2.2 eq), NaOAc (2.0 eq), CHCl ₃ , 0°, 1.5 h	 (91)	439
		NBS (1.1 eq), NaOAc (1.1 eq), THF/H ₂ O (4:1)	 (84)	846, 847, 848

TABLE 8. SYNTHESIS OF 6-HYDROXY-1,2-DIHYDROPYRIDIN-3(6*H*)-ONES

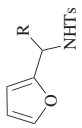
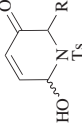
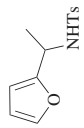
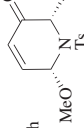
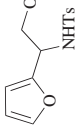
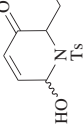
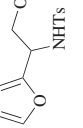
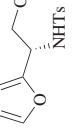
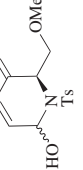
Furan	Conditions	Product(s) and Yield(s) (%)	Refs.																																																												
	 <i>m</i> -CPBA (2.1 eq), CH ₂ Cl ₂ , rt, 2 h	<table border="1"> <thead> <tr> <th>R</th><th>Temp</th><th>Time (h)</th><th>Yield (%)</th></tr> </thead> <tbody> <tr><td>H</td><td>0°</td><td>2</td><td>(90)</td></tr> <tr><td>H</td><td>rt</td><td>2</td><td>(—)</td></tr> <tr><td>Me</td><td>0°</td><td>2</td><td>(97)</td></tr> <tr><td>Me</td><td>rt</td><td>2</td><td>(85)</td></tr> <tr><td>AcOCH₂</td><td>30°</td><td>4.5</td><td>(70)</td></tr> <tr><td><i>t</i>-BuPh₂SiOCH₂</td><td>rt</td><td>2</td><td>(80)</td></tr> <tr><td>Et</td><td>0°</td><td>2</td><td>(51)</td></tr> <tr><td><i>n</i>-Pr</td><td>0°</td><td>2</td><td>(78)</td></tr> <tr><td><i>i</i>-Pr</td><td>0°</td><td>2</td><td>(36)</td></tr> <tr><td><i>t</i>-BuPh₂SiO(CH₂)₃</td><td>rt</td><td>2</td><td>(80)</td></tr> <tr><td><i>n</i>-Bu</td><td>0°</td><td>2</td><td>(49)</td></tr> <tr><td><i>n</i>-Bu</td><td>rt</td><td>2</td><td>(—)</td></tr> <tr><td><i>i</i>-Bu</td><td>0°</td><td>2</td><td>(69)</td></tr> <tr><td>Ph</td><td>rt</td><td>2</td><td>(80)</td></tr> </tbody> </table>	R	Temp	Time (h)	Yield (%)	H	0°	2	(90)	H	rt	2	(—)	Me	0°	2	(97)	Me	rt	2	(85)	AcOCH ₂	30°	4.5	(70)	<i>t</i> -BuPh ₂ SiOCH ₂	rt	2	(80)	Et	0°	2	(51)	<i>n</i> -Pr	0°	2	(78)	<i>i</i> -Pr	0°	2	(36)	<i>t</i> -BuPh ₂ SiO(CH ₂) ₃	rt	2	(80)	<i>n</i> -Bu	0°	2	(49)	<i>n</i> -Bu	rt	2	(—)	<i>i</i> -Bu	0°	2	(69)	Ph	rt	2	(80)	540 538 540 554, 553, 538 539 437 540 540 540 540 553, 849 540 538 540 437
R	Temp	Time (h)	Yield (%)																																																												
H	0°	2	(90)																																																												
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<i>n</i> -Bu	rt	2	(—)																																																												
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Ph	rt	2	(80)																																																												
	1. <i>m</i> -CPBA (2.1 eq), CH ₂ Cl ₂ , rt, 2 h 2. CH(OMe) ₃ (2.0 eq), BF ₃ ·Et ₂ O (0.1 eq), CH ₂ Cl ₂ , 0°, 3 h	 (85)	551, 554, 553																																																												
	NBS, 4°, 4 h	 (83)	539																																																												
	Ti(O <i>i</i> -Pr) ₄ , L-(+)-DIPT, <i>t</i> -BuOOH, silica gel, CaH ₂ , CH ₂ Cl ₂ , rt, 3 d	 I (—) +  II (—)	564																																																												

TABLE 8. SYNTHESIS OF 6-HYDROXY-1,2-DIHYDROPYRIDIN-3(6H)-ONES (Continued)

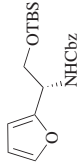
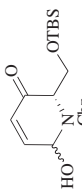
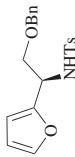
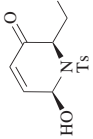
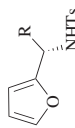
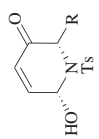
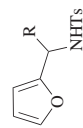
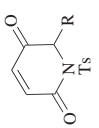
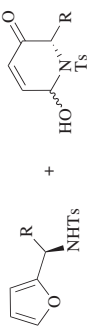
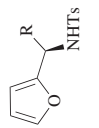
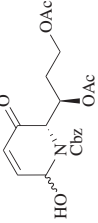
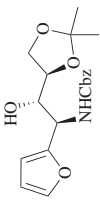
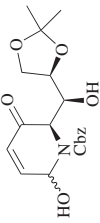
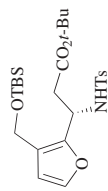
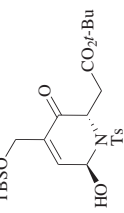
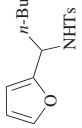
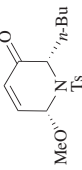
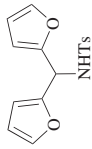
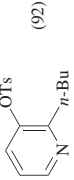
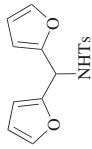
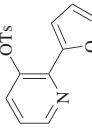
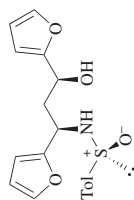
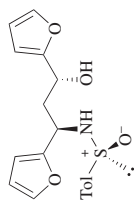
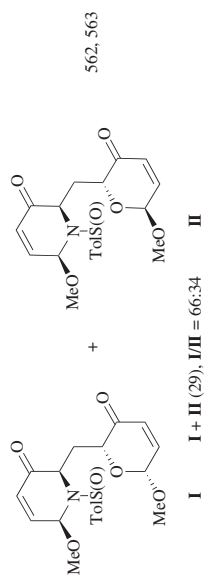
Furan	Conditions	Product(s) and Yield(s) (%)	Refs.																		
 C ₆	<i>m</i> -CPBA (2.0 eq), CH ₂ Cl ₂ , 0°, 3 h	 (87)	549																		
 C ₆₋₈	<i>m</i> -CPBA (1.2 eq), CH ₂ Cl ₂ , rt, 16 h	 (82)	543, 542																		
 C ₆₋₈	<i>m</i> -CPBA (1.5 eq), CH ₂ Cl ₂ , rt, 4 h		552, 550 545, 556 541, 544 405 537																		
		<table><tr><th>R</th><th>Time (h)</th><th></th></tr><tr><td>Me</td><td>2</td><td>(85)</td></tr><tr><td><i>t</i>-BuMe₂SiOCH₂</td><td>4</td><td>(92)</td></tr><tr><td><i>t</i>-BuPh₂SiOCH₂</td><td>4</td><td>(94)</td></tr><tr><td><i>n</i>-Pr</td><td>3</td><td>(74)</td></tr><tr><td>Merrifield resin-O</td><td>4</td><td>(—)</td></tr></table>	R	Time (h)		Me	2	(85)	<i>t</i> -BuMe ₂ SiOCH ₂	4	(92)	<i>t</i> -BuPh ₂ SiOCH ₂	4	(94)	<i>n</i> -Pr	3	(74)	Merrifield resin-O	4	(—)	
R	Time (h)																				
Me	2	(85)																			
<i>t</i> -BuMe ₂ SiOCH ₂	4	(92)																			
<i>t</i> -BuPh ₂ SiOCH ₂	4	(94)																			
<i>n</i> -Pr	3	(74)																			
Merrifield resin-O	4	(—)																			
 C ₆₋₁₁	1. <i>m</i> -CPBA (1.1 eq), CH ₂ Cl ₂ , rt, 3 h 2. Jones reagent, acetone, rt, 0.25 h	 <table><tr><th>R</th><th></th></tr><tr><td><i>t</i>-BuPh₂SiOCH₂</td><td>(93)</td></tr><tr><td>Ph</td><td>(96)</td></tr></table>	R		<i>t</i> -BuPh ₂ SiOCH ₂	(93)	Ph	(96)	437												
R																					
<i>t</i> -BuPh ₂ SiOCH ₂	(93)																				
Ph	(96)																				
	Ti(O <i>i</i> -Pr) ₄ , D-(−)-DIPT, <i>t</i> -BuOOH, silica gel, CaH ₂ , CH ₂ Cl ₂ , rt, 3 d	 +  <table><tr><th>R</th><th></th></tr><tr><td>Me</td><td>(—)</td></tr><tr><td><i>n</i>-Pr</td><td>(—)</td></tr><tr><td><i>n</i>-Bu</td><td>(—)</td></tr><tr><td><i>i</i>-Bu</td><td>(—)</td></tr><tr><td>Ph</td><td>(—)</td></tr></table>	R		Me	(—)	<i>n</i> -Pr	(—)	<i>n</i> -Bu	(—)	<i>i</i> -Bu	(—)	Ph	(—)	566						
R																					
Me	(—)																				
<i>n</i> -Pr	(—)																				
<i>n</i> -Bu	(—)																				
<i>i</i> -Bu	(—)																				
Ph	(—)																				

TABLE 8. SYNTHESIS OF 6-HYDROXY-1,2-DIHYDROPYRIDIN-3(6H)-ONES (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C₈ 	<i>m</i> -CPBA (1.15 eq), CH ₂ Cl ₂ , rt, 16 h	 (88)	546, 852
	<i>m</i> -CPBA, CH ₂ Cl ₂ , rt, 20 h	 (72)	561
	NBS (0.67 eq), NaOAc•3H ₂ O (0.86 eq), THF/H ₂ O (4:1), -5 to 0°, 3 h	 (83)	850
C₉ 	NBS (1.2 eq), NaOAc•3H ₂ O (1.4 eq), THF/H ₂ O (1:1); then CH(OMe) ₃ (2.0 eq), BF ₃ •Et ₂ O (0.05 eq), CH ₂ Cl ₂	 (85)	562
	1. NBS, NaOAc, THF/H ₂ O, 0° 2. AlCl ₃ (1.2 eq), CH ₂ Cl ₂ , -78°, 0.5 h 3. Et ₃ N	 (92)	154
	NBS, NaOAc, THF/H ₂ O, 0°	 (50)	154

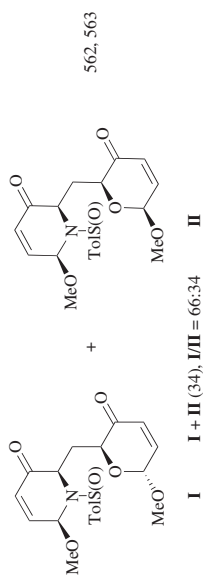
C₁₁

NBS (1.2 eq),
NaOAc•3H₂O (1.4 eq),
THF/H₂O (1:1); then
CH(OMe)₃ (2.0 eq),
BF₃•Et₂O (0.05 eq), CH₂Cl₂



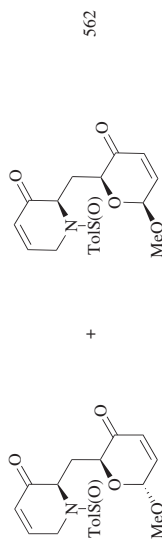
562, 563

NBS (1.2 eq),
NaOAc•3H₂O (1.4 eq),
THF/H₂O (1:1); then
CH(OMe)₃ (2.0 eq),
BF₃•Et₂O (0.05 eq), CH₂Cl₂



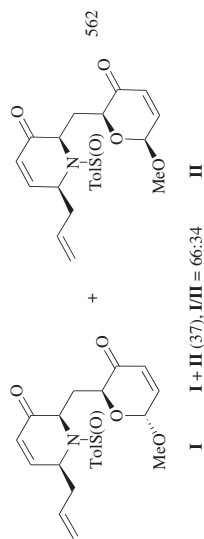
562, 563

NBS (1.2 eq),
NaOAc•3H₂O (1.4 eq),
THF/H₂O (1:1); then
CH(OMe)₃ (2.0 eq),
BF₃•Et₂O (0.05 eq), CH₂Cl₂



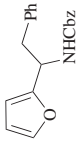
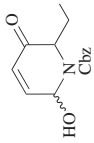
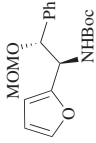
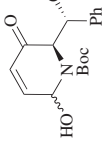
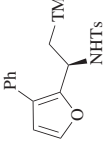
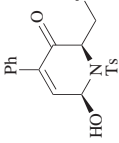
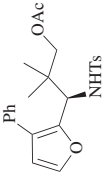
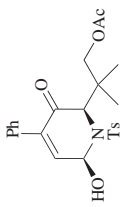
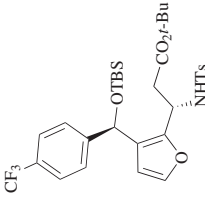
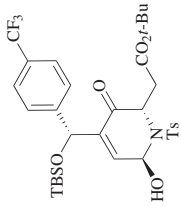
562

NBS (1.2 eq),
NaOAc•3H₂O (1.4 eq),
THF/H₂O (1:1); then
CH(OMe)₃ (2.0 eq),
BF₃•Et₂O (0.05 eq), CH₂Cl₂,
then, allylSiMe₃, BF₃, CH₂Cl₂



562

TABLE 8. SYNTHESIS OF 6-HYDROXY-1,2-DIHYDROPYRIDIN-3(6H)-ONES (Continued)

Furan	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₂ 	<i>m</i> -CPBA, CH ₂ Cl ₂	 (69)	560
	<i>m</i> -CPBA, CH ₂ Cl ₂	 (80)	547
	<i>m</i> -CPBA (2.0 eq), CH ₂ Cl ₂ , rt, 1 h	 (94)	557
C₁₅ 	<i>m</i> -CPBA (2.0 eq), CH ₂ Cl ₂ , rt, 1 h	 (83)	557
	NBS (0.67 eq), NaOAc•3H ₂ O (0.86 eq) THF/H ₂ O (4:1), -5 to 0°, 3 h	 (64)	850

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