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Oxidative degradation of benzene rings

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1. Introduction

Since the late 19th century, benzene ring degradation has been used to help elucidate and identify the structure of unknown compounds, like morphine,[1,2] for example. Although in some early cases the structures of the products were not conclusive, more recent studies have alleviated initial problems, allowing broader application. It is this broader application which the authors wish to bring to the attention of the chemical community.

In particular, this review is concerned with the formation of ring-cleaved products such as carboxylic acids, lactones, muconic acids and their respective derivatives, thereby expanding the utility of benzenoid synthons in organic synthesis.

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2. Carboxylic acids

The carboxylic acid group is one of the most commonly-appearing functional groups in organic chemistry and plays an important role in organic synthesis. Although there are many different ways to synthesise this group, it is not always an easy task to carry this functionality through a long sequence of transformations, especially when organometallic reagents are involved. Even protection and deprotection of this group can cause unwanted difficulties. This section will accordingly focus on the synthetic advantages of benzene ring oxidation for the synthesis of the carboxylic acid function.

2.1. Oxidation with ruthenium tetraoxide

Although a strong oxidant, ruthenium tetraoxide (RuO_4) has found wide use in the synthesis of carboxylic acids from relatively inert benzene rings, such as phenyl. Djerassi[3]

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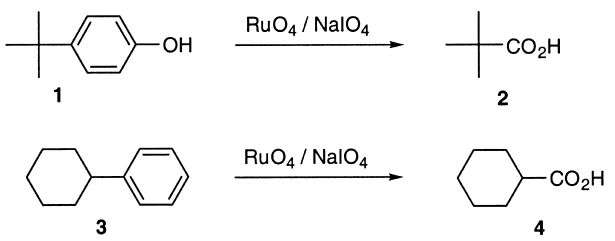


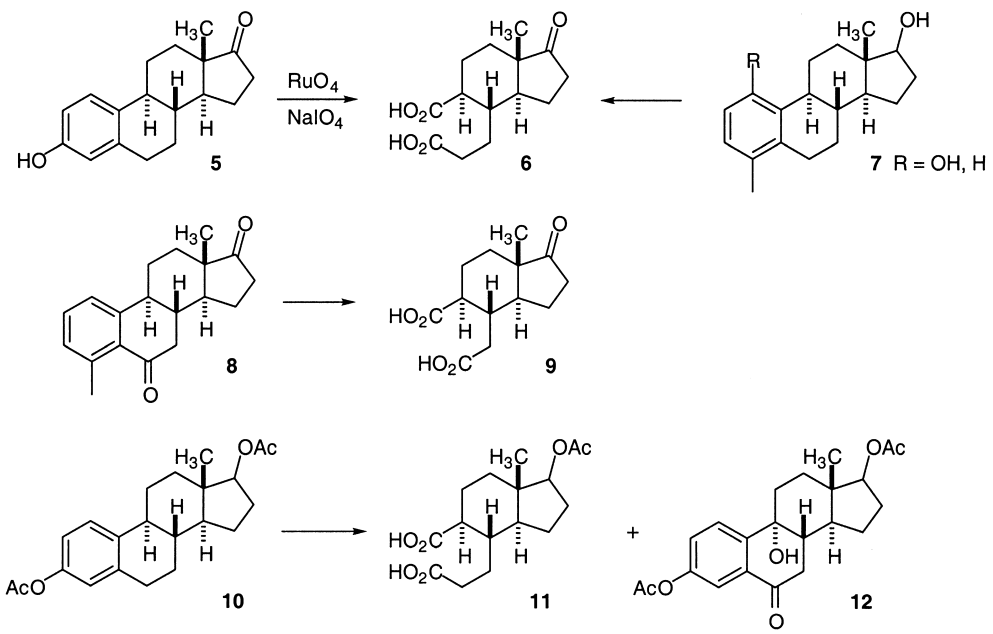
Scheme 1.

found that when RuO_4 was used to oxidise sulfides, solvents such as ether, benzene and pyridine could not be used as they too were oxidised. Berkowitz and Rylander subsequently investigated the oxidation of aromatic rings with RuO_4, but the products were not isolated and identified.[4] Caputo and Fuchs,[5,6] nine years later, decided to investigate the degradation of the benzene moiety of a 3-phenylcyclobutanecarboxylic acid sample for the purpose of determining the stereochemistry (stereochemical determinations using this method have also been utilised by Shingu[7] and Ziffer[8,9]). The utility of this procedure was further demonstrated when *p*-*t*-butylphenol **1** was transformed into pivalic acid **2** and phenylcyclohexane **3** was converted into cyclohexanoic acid **4**, using catalytic amounts of RuO_4 with the co-oxidant sodium periodate (Scheme 1).

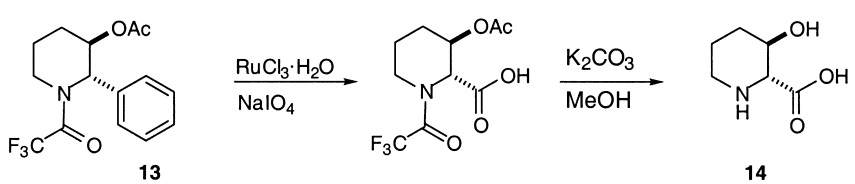
Prior to the work of Caputo and Fuchs, oxidation of sulfides, alcohols, aldehydes, acetylenes and other functional groups had been investigated, but only in a few cases was RuO_4 used as a catalyst in the presence of a co-oxidant. This is essential not only for economical reasons, but because strong adsorption of the substrate to ruthenium lowers the yields. It should be mentioned that Sharpless[10] discovered that the addition of acetonitrile to the existing CCl_4/H_2O system greatly improves the yields; this variant has been profiled by Ranganathan.[11] *N*,*N*-dimethylformamide in place of acetonitrile is equally effective.[12]

Piatak et al.[13] applied this method to estrone **5**, affording the acid **6** in good yield. Placing the hydroxy functionality at other positions [**7** (R=OH)] around the ring had no effect on the outcome and nor did the introduction of a 4-methyl group [**7** (R=OH)]. The authors also discovered that the diacid **6** could be obtained from derivatives that did not contain a hydroxy functionality [**7** (R=H)] (Scheme 2). When a keto functionality was placed at position **6** of the steroidal nucleus (e.g. **8**), a 1,5-diacid system (**9**) was obtained instead of the 1,6-diacid (i.e. **6**) observed previously. When the phenol was protected as an acetate (**10**), however, diacid **11** was obtained as the minor product with the major product obtained (40%) being the ketone **12**, arising from benzylic oxidation (Scheme 2). This outcome has also been demonstrated by Ayres.[14]

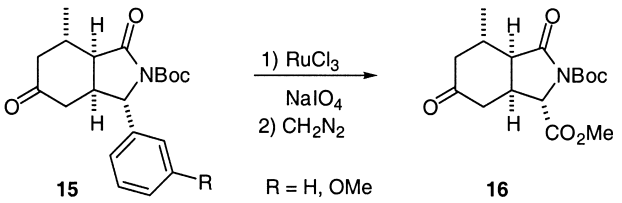
Ruthenium tetraoxide degradation of benzene rings has played a major role in the synthesis of amino acids and peptides. Ayres[15] initiated the original work by treating various phenylalkylamines with ruthenium tetraoxide in the presence of sulfuric acid, thereby affording glycine (66%), α-alanine (50%), β-alanine (86%) and γ-aminobutyric (69%) and aspartic (60%) acids. Conversion of aromatic



Scheme 2.



Scheme 3.



Scheme 4.

amines to trifluoroacetamides was, however, required for selective degradation of biphenyl systems,[16] while trifluoroacetamide protection was utilised by Haddad[17] in the synthesis of *trans*-(2*R*,3*R*)-3-hydroxypipecolic acid **14** derived from phenyl degradation of **13** (Scheme 3).

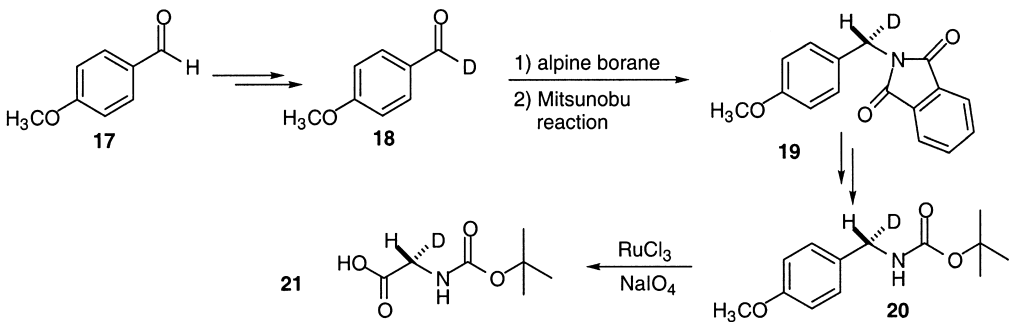
t-Butyloxycarbonyl-(Boc)-protected amides (imides), e.g. **15**, are also well tolerated by this reagent system as demonstrated by Clayden[18] in the synthesis of (−)-kainic acid, dearomatisation unveiling the carboxy functionality α to nitrogen (**16**) (Scheme 4).

The large-scale synthesis of the chiral deutero Boc-protected glycine **21** starting from *p*-methoxybenzaldehyde **17** has been achieved using RuO_4.[19] *p*-Methoxybenzaldehyde **17** was initially converted into the deuteroaldehyde **18** which was enantioselectively reduced to the alcohol **19** using (*S*)-(−)-alpine borane. The alcohol was treated with phthalimide under Mitsunobu conditions and then protected as the Boc derivative **20**. Treatment of the Boc-protected benzylamine with ruthenium chloride and sodium periodate afforded the desired optically pure deutero Boc-protected glycine **21** (see also Welzel[20] for glycerine derivatives, and Townsend[21] and Martin[22] for α-hydroxyacids) (Scheme 5).

Phytosiderophores, mugineic acid **22**, 3-*epi*-hydroxy-mugineic acid **23** and distichonic acid **24** are a series of iron-chelating amino acids isolated from graminaceous plants (Fig. 1).

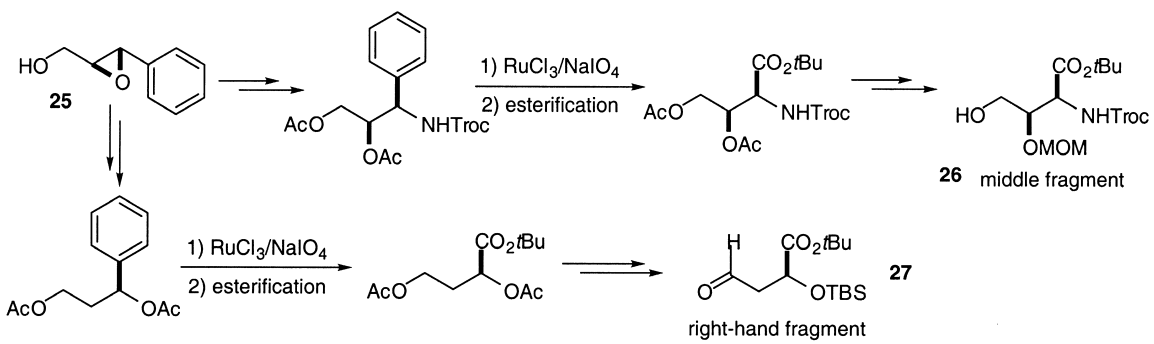
The key process in the synthesis of these naturally occurring compounds is the unveiling of the carboxyl functionality at various points throughout the synthesis or in the construction of the required intermediates. Mugineic acid **22** was the first synthesised analogue by the Shioiri group,[23,24] who utilised ruthenium chloride/sodium periodate benzene degradation in both the construction of the middle (**26**) and right-hand (**27**) halves of the molecule, starting from the same optically pure epoxide **25** (Scheme 6).

The synthesis of 3-*epi*-hydroxymugineic acid **23** and distichonic acid **24**[25] followed similar protocols and used the same intermediates synthesised for the construction of mugineic acid **22**. The degradation protocol was, however, also used to build the functionalised azetidine ring used in

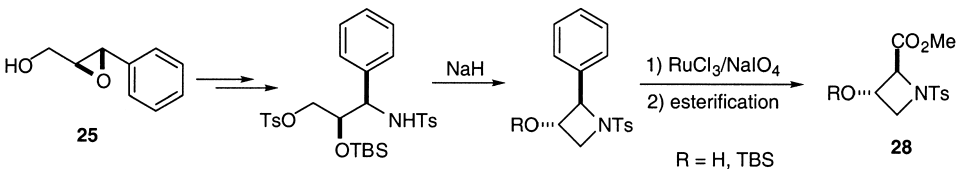


Scheme 5.

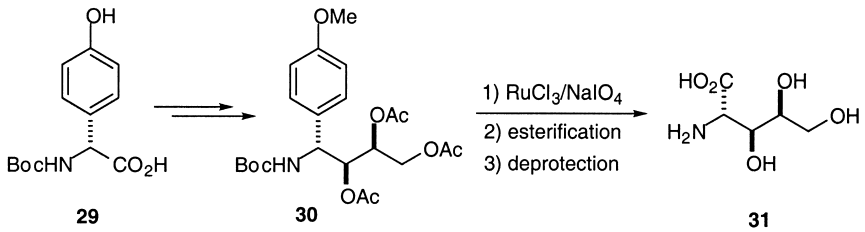
Figure 1.



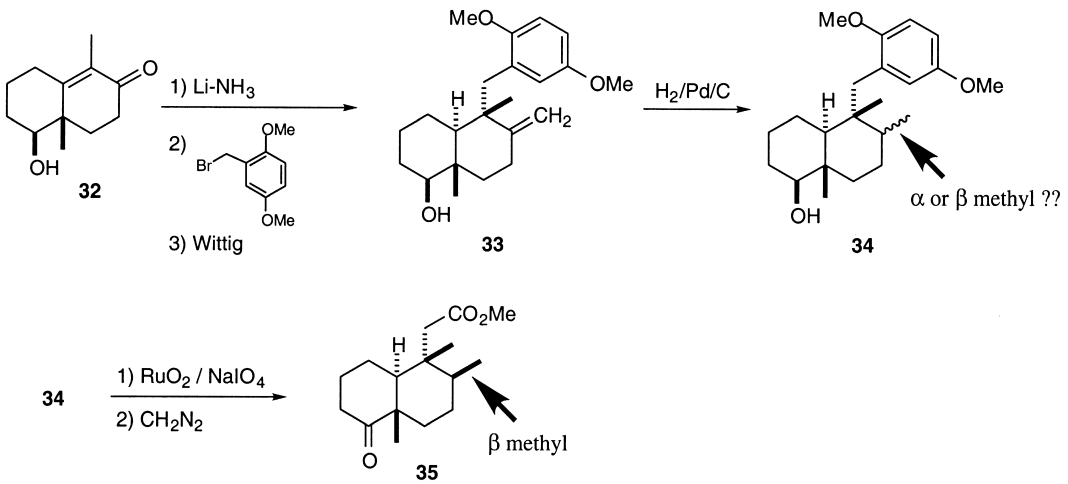
Scheme 6.



Scheme 7.



Scheme 8.



Scheme 9.

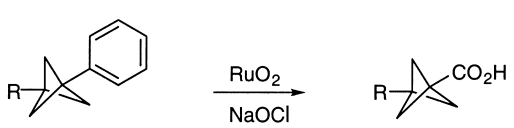
the synthesis of 3-*epi*-hydroxymugineic acid **23** (Scheme 7). Starting from the commonly-used epoxide **25**, the ester **28** could be obtained in five steps. Cyclisation using sodium hydride followed by degradation and esterification gave the desired left-hand fragment.

Shioiri's last involvement in this area was the synthesis of polyoxamic acid **31**, a side-chain hydroxylamino acid moiety of polyoxins, a group of antifungal antibiotics.[26] The synthesis started with the Boc-protected 4-hydroxyphenylglycine **29** which was transformed in eleven steps to the triacetate **30**. Degradation of the benzene ring gave the amino acid which was then esterified and deprotected to afford polyoxamic acid **31** (Scheme 8). The Boc-protected 4-hydroxyphenylglycine **29** was also used to synthesise 2′-deoxymugineic acid and nicotinamide.[27]

During the total synthesis of (±)-avarol, Sarma[28] catalytically hydrogenated the double bond of the intermediate **33** derived from **32** to obtain the major intermediate **34**. The stereochemical outcome was postulated to give a β-methyl group, but this could not be determined with certainty from the spectral data. The intermediate **34** was then subjected to ruthenium dioxide/sodium periodate oxidation, converting the aromatic ring into a carboxy group, and after esterification, this compound **35** was compared with an authentic sample obtained from the degradation of ilimaquinone, thereby confirming the β stereochemistry (Scheme 9).

A number of bicyclo[1.1.1]carboxylic acids **37** were synthesised from the corresponding phenyl-substituted derivatives **36** using ruthenium dioxide and sodium hypochlorite by Applequist[29] (Scheme 10).

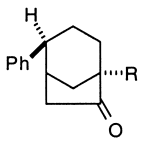
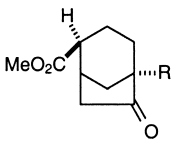
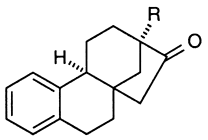
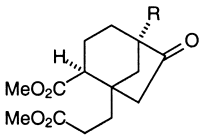
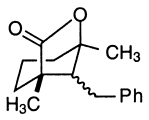
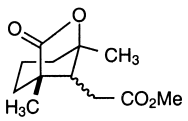
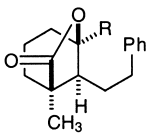
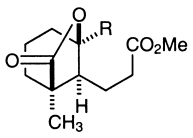
More complicated bicyclic systems were investigated by Ghatak[12] and were found to be oxidised smoothly and in high yields (Table 1). The crude acids were then treated with diazomethane for conversion into methyl esters. Ghatak[30] later improved the yields of degradation with derivatives similar to those shown in Table 1 by using a ruthenium(II)-2,2′-bipyridine chloride complex. Other lactone derivatives have been investigated by Frenette.[31]



R = CN, OAc, CO_2CH_3, NO_2

Scheme 10.

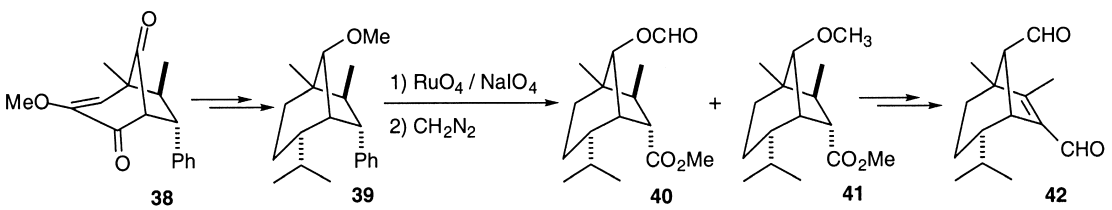
Table 1. Conversion of bicyclic aromatics into bicyclic carboxylic acids

Entry	Substrate	Product	Time (h)	Yield (%)
1			16	88 R=H
			16	92 R=Me
2			24	85 R=H
			24	80 R=Me
3			14	85 (β)
			24	88 (α)
4			24	90 R=H
			24	90 R=Me

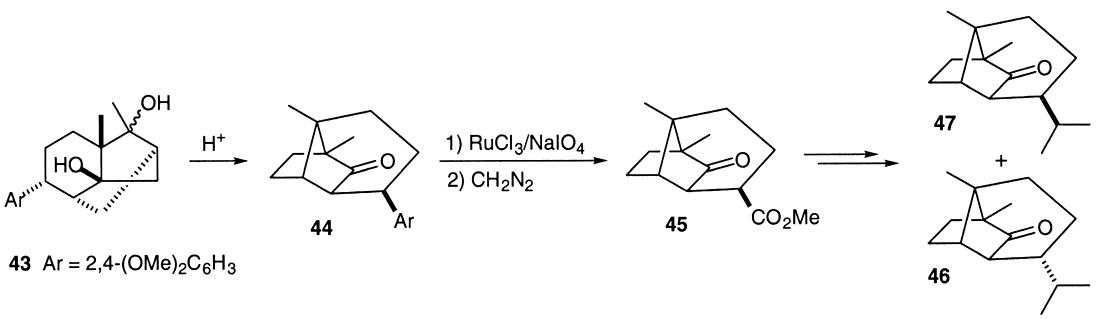
The conversion of a phenyl ring into a carboxyl group allowed access to the aldehyde functionality in the sequence leading to the total synthesis of (±)-helminthosporal **42** by Yamamura.[32] The bicyclic enone **38** was transformed into the bicyclo[3.2.1] ether **39** over a number of steps. The ether **39** was then treated with ruthenium tetraoxide/sodium periodate followed by diazomethane which afforded the two methyl esters **40** and **41**, the former being carried through to the natural product (Scheme 11).

In their synthesis of the naturally occurring products, copacamphor **47** and ylangocamphor **46**, Kasturi and Chandra[33] used the benzene ring as a surrogate for a carboxyl group that was eventually transformed into an isopropyl group. The acid-catalysed rearrangement of the diol **43** afforded the bicycle **44**. Degradation with ruthenium trichloride/sodium periodate afforded the ester **45** after reaction with diazomethane. Reaction of the ester **45** with methyl Grignard followed by dehydration and hydrogenation afforded both (±)-copacamphor **47** and (±)-ylangocamphor **46** (Scheme 12).

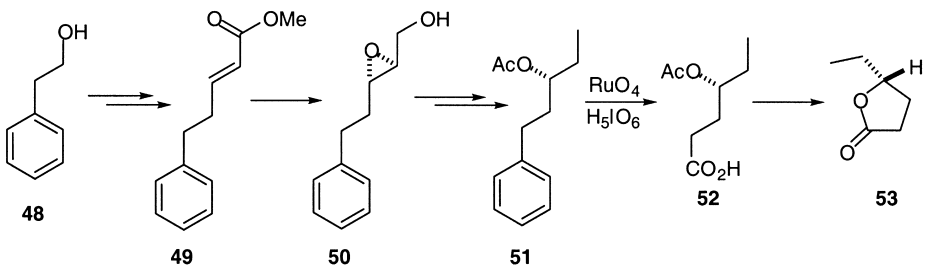
The total synthesis of the insect pheromone (*R*)-γ-caprolactone **53** was accomplished by Martín[22] starting



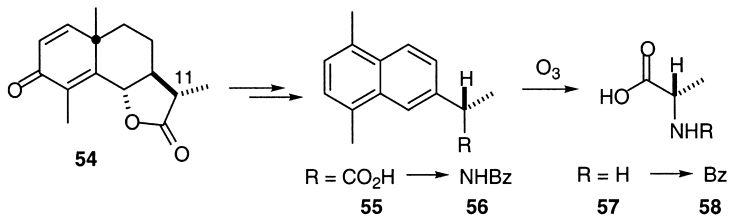
Scheme 11.



Scheme 12.



Scheme 13.



Scheme 14.

from the commercially available 3-phenyl-1-propanol **48**. The alcohol **48** was oxidised to the aldehyde and the crude material treated with the sodium salt of trimethyl phosphonoacetate, giving rise to the unsaturated ester **49** which was reduced and epoxidised to give **50**. The epoxide ring was opened and the terminal hydroxyl group removed via the tosylate, affording **51**. The acetate **51** was oxidised with ruthenium tetraoxide and, after saponification and acid treatment of **52**, (*R*)-γ-caprolactone **53** was obtained (Scheme 13). The superiority of periodic acid over sodium periodate had been previously reported.[34]

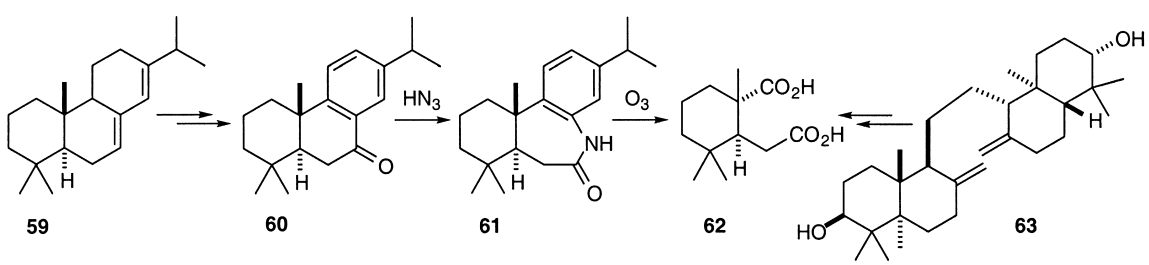
2.2. Oxidation with ozone

Ozone can cleave aromatic rings in an analogous fashion to RuO_4, affording unsaturated carboxylic acids. In some cases, ozone is superior to RuO_4 as Klein[35] has demonstrated. Electron-withdrawing substituents, however, such as a nitro group, prevent cleavage.

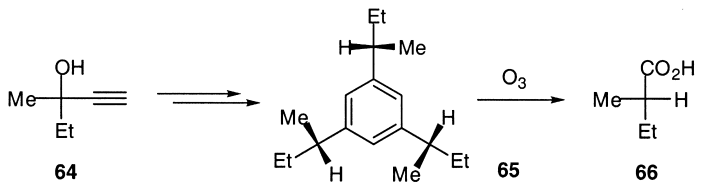
The absolute configuration of the C_{11} stereocentre of santonin **54** was determined with the aid of ozone-mediated aromatic oxidative cleavage.[36] Santonin **54** was converted into santinic acid **55** and the acid functionality converted into the amide **56** via a number of transformations. The amide **56** was then ozonised affording the alanine **57** (the benzoyl group was also removed) which was converted into the *N*-benzoyl derivative **58**. The benzoyl derivative **58**, when compared with authentic samples of both rotations, was found to be (+)-benzoyl-L-alanine implying, contrary to prior belief, that the C_{11} stereocentre of santonin **54** has the *S* configuration (Scheme 14).

In 1956 Schaffner et al.[37] were interested in determining the stereochemistry of α-onocerin **63** by comparing the diacid **62** obtained from both degradation of α-onocerin **63** and **61**. The synthesis of the diacid **62** started with the conversion of abietic acid **59** into the 7-keto-dehydroabietane **60** which was treated with sodium azide and trichloroacetic acid (Schmidt reaction), affording the amide **61**. The amide **61** was ozonised for 3.5 h at room temperature, affording the diacid **62**, which was compared to diacids of known stereochemistry (Scheme 15). Later, it was reported that the diacid **62** was obtained from a totarol derivative[38] via degradation.

Ozone has been used in other syntheses of chiral carboxylic acids. In an attempt to understand the in vivo ring expansion of penicillin N, Townsend[39] synthesised (3*R*,4*S*)- and (3*R*,4*R*)-[4-^{2}H,^{3}H]-valine. Floss[40] produced (*R*)- and (*S*)-[2-^{2}H,2-^{3}H]-acetic acids in high enantiomeric purity starting from 3,5-dimethoxy-[7-^{2}H]-benzaldehyde. A series of benzo-α-tetralone derivatives were reduced by *Sporobolomycetes pararoseus* and the absolute configurations of the alcohols determined as *S* by degradation to dimethyl (−)-α-acetoxyadipate and dimethyl (−)-α-acetoxyglutarate.[41] One of the more interesting approaches to enantiopure carboxylic acids was taken by Snatzke[42] who cyclotrimerised acetylene derivatives such as **64** containing identical asymmetry, affording the 1,3,5-trisubstituted



Scheme 15.

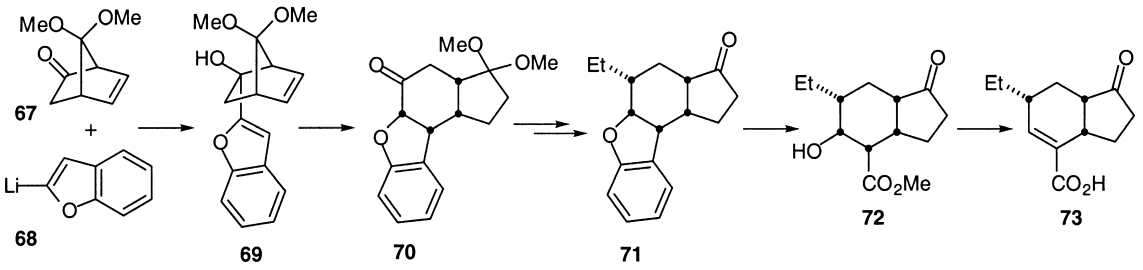


Scheme 16.

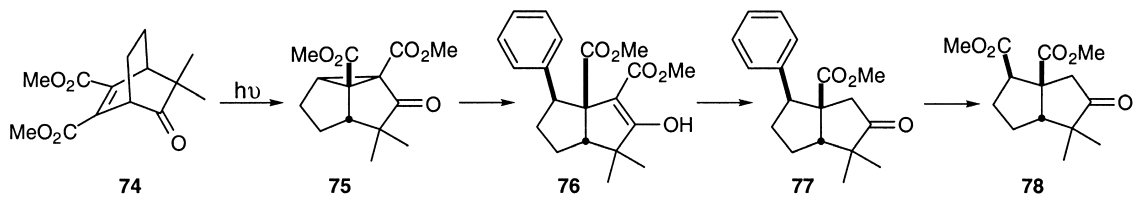
benzenes **65**. Hydrogenolysis removed the alcohol functionalisation and treatment with ozone afforded the enantiopure acid **66** (Scheme 16).

The synthesis of (±)-coronafacic acid **73**[43] involved two key steps, the first of which was an oxy-Cope rearrangement while the second was the introduction of the carboxyl functionality by oxidative dearomatisation. The bicyclo-[2.2.1] ketone **67** was treated with the 2-lithobenzofuran **68**, affording the bicyclo alcohol **69** which underwent the oxy-Cope rearrangement, giving the ketone **70**. The ketone **70** was functionally manipulated, affording the ketone **71**, which was treated with ozone then diazomethane, producing the β-hydroxyester **72**. Two further steps gave the natural product **73** (Scheme 17).

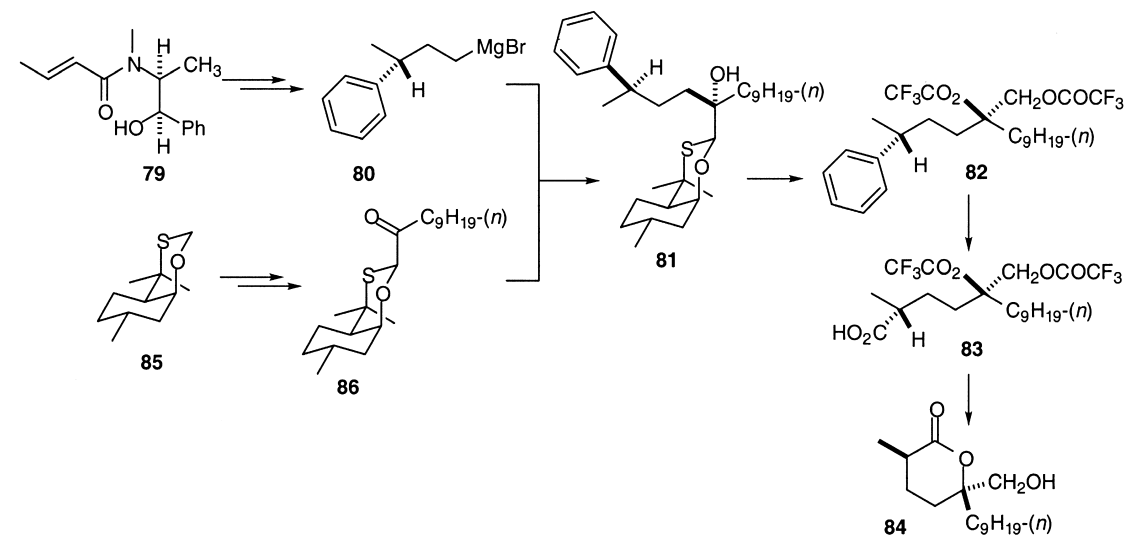
The synthesis of some cedranoid sesquiterpenes has been achieved by Yates.[44,45] Photochemical rearrangement of the bicyclo[2.2.2]octane **74** gave the tricyclo[3.2.1.$0^{2,8}$]-octanone **75** which underwent homoconjugate addition with lithium diphenylcuprate, affording **76**. The β-keto-ester **76** was subjected to selective demethoxycarbonylation with sodium chloride in aqueous dimethyl sulfoxide (DMSO), giving the ketone **77**. The ketone **77** was then ozonised, affording the cedranoid intermediate **78** (Scheme 18).



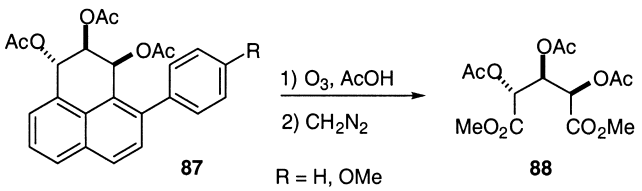
Scheme 17.



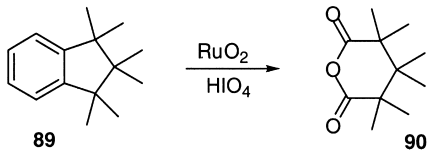
Scheme 18.



Scheme 19.



Scheme 20.



Scheme 21.

(−)-Malyngolide **84**, an antibiotic of algal origin, was synthesised by Eliel[46] in high diastereomeric and enantiomeric purity by means of a convergent asymmetric synthesis. The enantiopure Grignard **80** was synthesised in five steps starting from *N*-crotonyl-(−)-ephedrine **79**, while the ketone **86** was synthesised from the oxathiane **85** in three steps. Reaction of **80** with the ketone **86** afforded the carbinol **81** in 96% yield in 98% diastereomeric excess. Deprotection, reduction and subsequent protection afforded the bistrifluoroacetate **82** which was ozonised, deprotected (**83**) and lactonised, thereby affording (−)-malyngolide **84** (Scheme 19).

Cascading benzenoid degradation was observed by Hirai[47] when he treated derivatives of phenylphenalenones **87** with ozone in acetic acid. Presumably, the peripheral aromatic ring is the first ring to be attacked, resulting in the polarisation of the remaining naphthalene moiety sufficiently to allow further degradation. Treatment of the product with diazomethane gave the diester **88** (Scheme 20).

2.3. Miscellaneous

Deno[48] demonstrated that, after heating toluene, ethylbenzene, propylbenzene or isopropylbenzene with 30% hydrogen peroxide/trifluoroacetic acid under reflux for 1h, only the corresponding aliphatic acid was formed. These oxidations were termed 'inverse oxidations', since the aliphatic component of the structure was preserved, in contrast to oxidising agents such as nitric acid, molecular oxygen, manganate and chromate that oxidised the benzylic position.

Figure 2.

3. Lactones/lactols

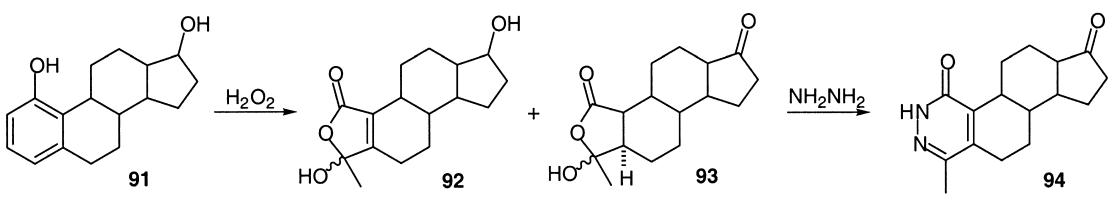
Hexamethylglutaric anhydride **90** was obtained by ruthenium dioxide/periodate oxidation of the hexamethylindane **89**,[49] although, a different solvent system (CCl_4/CH_3CO_2H/H_2O) was required because of the difficult nature of the oxidation (Scheme 21).

Treatment of the aromatic steroid **91** with alkaline hydrogen peroxide was found to give a mixture of products from which the lactols **92** (20%) and **93** (40%) were isolated.[50] These products were then converted into the 2,3-diazasteroid **94** for biological testing[51] (Scheme 22).

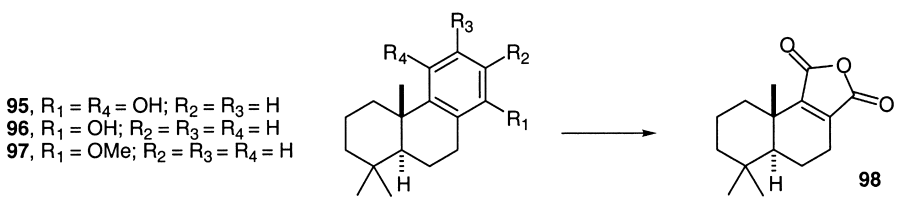
A partial synthesis of (±)-winterin **98** was achieved through oxidative degradation by ozonolysis[52] of the aromatic ring of the (+)-podocarpatriene hydroquinone **95**. Gosh and Ghatak subsequently undertook a thorough investigation of the influence of electron-donating aromatic substituents on the RuO_4-catalysed oxidation of (±)-podocarpa-8,11,13-trienes[53] (Scheme 23). The yields of **98** were increased with this procedure, starting from **95**. The anhydride **98** could also be obtained from the phenol **96** and the corresponding ether **97**.

4. Muconic acids/anhydrides and lactones

The most common product arising from oxidative cleavage (enzymatic or chemical) of catechol is muconic acid **99** from which muconolactone **100** is derived (Fig. 2).



Scheme 22.



Scheme 23.

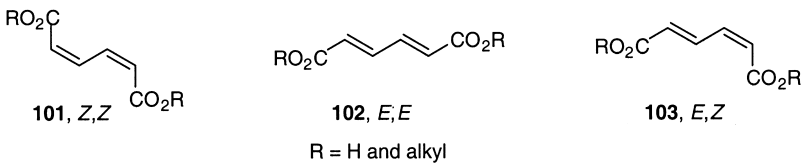


Figure 3.

For a long time, however, the stereochemistry of muconic acids **101**–**103** was under question and in the early 1950s Elvidge et al.[54–57] investigated the three possibilities (**101**–**103**), finally assigning their correct geometries, stereochemistries and conformations (Fig. 3).

The stereochemistry of the asymmetric centre at position 4 of muconolactone **100** has also been investigated using bacterial and fungal metabolism which suggest that the carboxyl group cyclises by *syn* addition.[58,59]

4.1. Periodate/perchlorate

Andersson[60] confirmed Adler and Magnusson's[61] findings that periodate reacted rapidly with 6-substituted phenols to give non-dimerising *o*-quinols, *o*-quinol ethers and *o*-quinone ketals. Further reaction with periodate was much slower and only in the case of *o*-cresol and 2,3,5-trimethylphenol did small amounts of oxidative ring cleavage occur, affording the *Z*,*Z*-β-methylmuconic acid and the dimethylmuconolactone.

Baxendale and Wells[62,63] discovered that oxidation of benzene in an aqueous solution of cobalt(III) perchlorate gave mainly *p*-quinone and muconic acid. They found that the probable intermediates, phenol, catechol, *o*-quinone and hydroquinone, were oxidised much more rapidly than benzene and so it was concluded that the primary oxidation of benzene was the slow step. No biphenyl was detected and the reaction was unaffected by oxygen. It was suggested that a phenyl radical was generated, which then coupled with hydroxide to give phenol which was subsequently oxidised (Scheme 24, Eqs. (1) and (2)), (See Dainton and Bawn for further mechanistic considerations[64]).

$$Co^{3+} + PhH \rightarrow Co^{2+} + Ph\bullet\ H^{+} \quad \text{(Equation 1)}$$

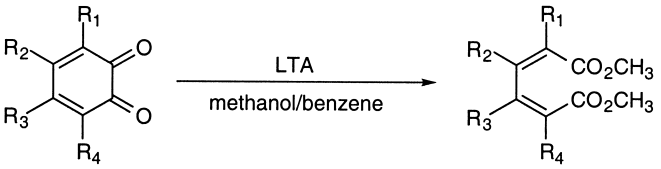
$$HO^{-} + Co^{3+} + Ph\bullet \rightarrow Co^{2+} + PhOH \quad \text{(Equation 2)}$$

Scheme 24.

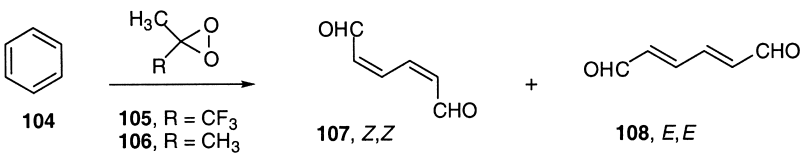
4.2. Dioxirane

Curci et al.[65] found that benzene **104** is not inert towards methyl(trifluoromethyl)dioxirane **105** as was believed from the results obtained with dimethyloxirane **106**. After hours of exposure, these authors were able to isolate *Z*,*Z*-**107** and *E*,*E*-muconic dialdehyde **108** which presumably arises from initial benzene oxide/oxepin formation (Scheme 25). Later, Curci[66] found that when catechol was treated with methyl(trifluoromethyl)dioxirane, **105** *Z*,*Z*-muconic acid was obtained in 88% yield.

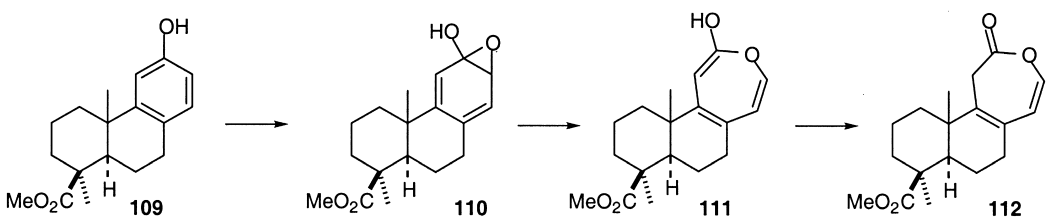
Table 2. Conversion of *o*-quinones into dimethyl *cis*,*cis*-muconates with LTA



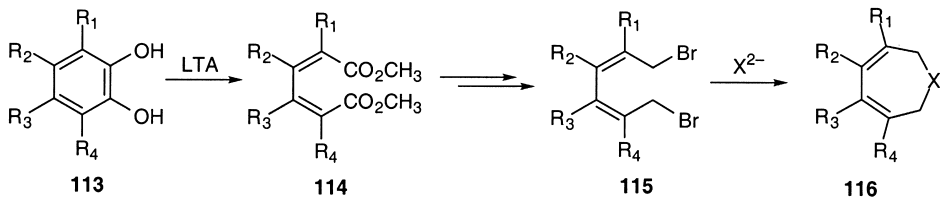
Entry	R_1	R_2	R_3	R_4	Yield (%)	Reference
1	CH_3	H	CH_3	H	75	68
2	H	CH_3	CH_3	H	70	
3	CH_3	H	H	CH_3	60	
4	*t*-Bu	H	*t*-Bu	H	90	
5	*t*-Bu	H	H	*t*-Bu	60	
6	H	$-(CH_2)_3-$		H	60	
7	H	$-(CH_2)_5-$		H	70	
8	H	CH_3	H	H	57	69
9	H	F	H	H	75	70
10	H	Cl	H	H	50	
11	H	Br	H	H	25	



Scheme 25.



Scheme 26.



R_1	R_2	R_3	R_4	X	Yield (%)
H	H	H	H	NBn	55
t-Bu	H	*t*-Bu	H	N-*n*-Bu	41
t-Bu	H	*t*-Bu	H	NBn	71
t-Bu	H	*t*-Bu	H	NTs	49
t-Bu	H	*t*-Bu	H	$NCH_2CH(OMe)_2$	56
H	H	*t*-Bu	H	N-*n*-Bu	66
H	H	*t*-Bu	H	NTs	56
H	H	*t*-Bu	H	$NCH_2CH(OMe)_2$	74
Cl	Cl	Cl	Cl	NTs	48
Cl	Cl	Cl	Cl	N-*n*-Bu	51
Br	Br	Br	Br	N-*n*-Bu	60
Br	Br	Br	Br	NBn	45
Br	Br	Br	Br	$NCH_2CH(OMe)_2$	39
H	H	H	H	S	50
t-Bu	H	*t*-Bu	H	S	82
H	H	*t*-Bu	H	S	81
Cl	Cl	Cl	Cl	S	66
t-Bu	H	*t*-Bu	H	O	83
H	H	*t*-Bu	H	O	87
t-Bu	H	*t*-Bu	H	P(O)Ph	10
H	H	H	H	$C(CO_2Me)_2$	40
t-Bu	H	*t*-Bu	H	$C(CO_2Me)_2$	52
H	H	*t*-Bu	H	$C(CO_2Me)_2$	60

Scheme 27.

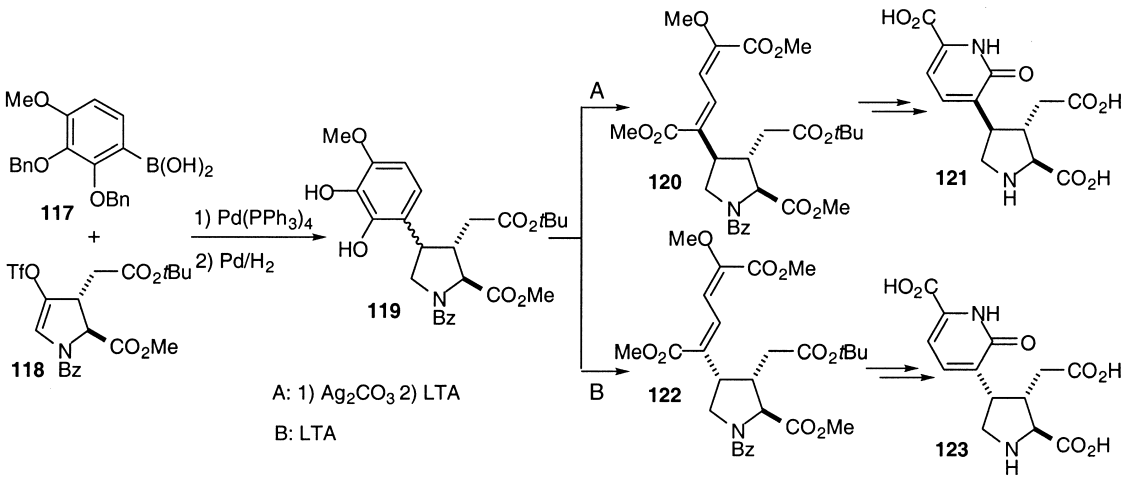
Treatment of methyl 12-hydroxypodocarpa-8,11,13-trien-19-oate **109** with dimethyldioxiran, prepared from Oxone® and acetone in the presence of sodium hydrogencarbonate, resulted in mainly benzylic oxidation, but also afforded a low yield (3%) of the unsaturated ε-lactone **112**.[67] The authors suggested that the lactone **112**, a Baeyer–Villiger type product, arose from conversion of the phenol **109** into an epoxyalcohol **110**, which underwent electrocyclic ring expansion to afford an oxepin enol **111** which tautomerised to the observed product **112** (Scheme 26).

4.3. Lead tetraacetate

Wiessler[68] found that *o*-quinones underwent carbon–carbon cleavage when treated with lead tetraacetate (LTA), affording dimethyl *Z*,*Z*-muconates (Table 2).

This was confirmed by Jaroszewski[69] who isolated dimethyl (2*Z*,4*Z*)-3-methyl-2,4-hexadienedioate when 4-methyl-1,2-benzoquinone was oxidised in methanol/benzene with LTA. Kozarich[70] discovered seven years later that the halogenated derivatives were amenable to this two-step process of ring cleavage.

Although technically *o*-quinones have been dearomatised prior to ring cleavage (see above) with this reagent, it was Gilheany[71,72] who made the discovery that LTA can convert catechols directly to muconic systems. A large range of catechols **113** was subjected to LTA oxidation in methanol/benzene which afforded directly the dimethyl muconates **114** in yields ranging from 10 to 87%. Reduction of the diester and conversion to the dibromides **115** allowed access to unsaturated seven-membered rings **116** via dialkylation (Scheme 27).



Scheme 28.

The synthesis of acromelic acid A **123** and *allo*-acromelic acid A **121** was achieved in a concise manner using both LTA protocols detailed above. The key step in the synthesis of both *allo*-acromelic acid A **121** and acromelic acid A **123** was the respective stepwise or direct degradation of the catechol moiety **119**. A palladium-based cross-coupling of the vinyl triflate **118** and boronic acid **117** gave, after deprotection, the catechol **119**. Fétizon's reagent (silver carbonate on Celite®) afforded the *o*-quinone which was ring cleaved with LTA affording the respective muconic ester **120**, whereas in the case of acromelic acid A **123** direct ring opening could be achieved with LTA (**122**) and was quoted as proceeding much faster than the two-step procedure (Scheme 28).[73]

4.4. Photolytic cleavage

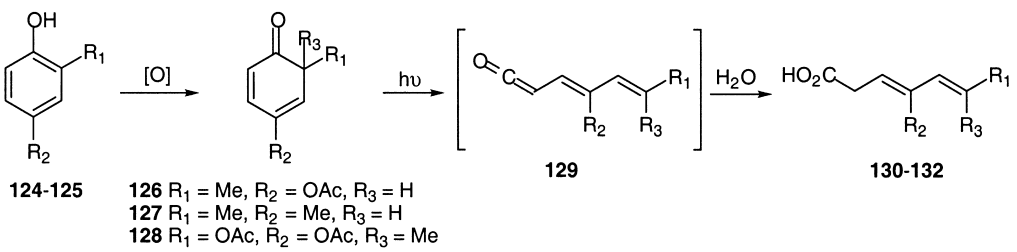
There are two areas of photolytic cleavage, the minor area involving stepwise ring opening and the major area direct ring opening.

Stepwise ring opening was first discovered by Barton and Quinkert[74,75] in the late 1950s. The substituted phenols **124**–**125** were oxidised with LTA (or by other means) to the dienones **126**–**128** which were subjected to photolysis at 300 nm in the absence of oxygen, thereby affording the dienoic acids **130**–**132** (54–79%) via a ketene intermediate **129** (Scheme 29). Other derivatives[75] were found to give conjugated dienoic acids.

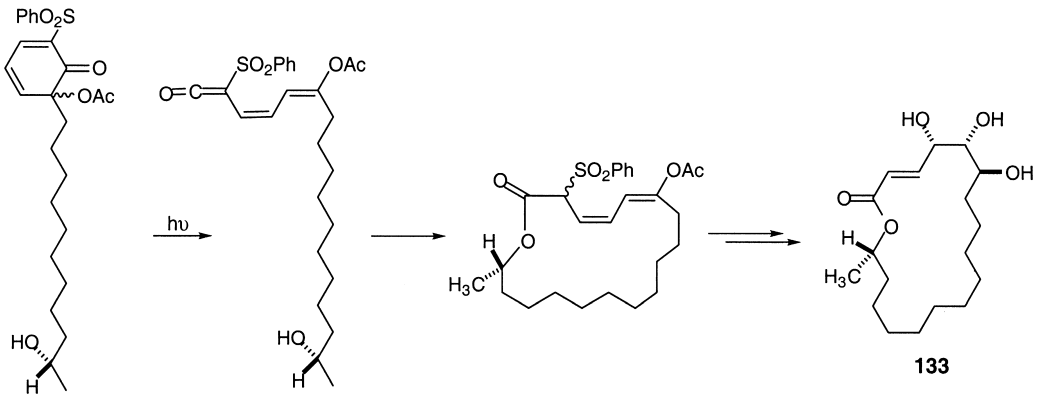
Although this procedure has been briefly used elsewhere, it was not until years later that Quinkert found synthetic applications after reinvestigating the reaction and the products obtained from trapping with cyclohexylamine.[76] Quinkert then used this protocol for the synthesis of macrolides[77] and finally as the key step in the synthesis of the natural product, (+)-aspicilin **133**[78,79] (Scheme 30).

Snider[80] adopted this method for the synthesis of the antitumour cyclic peroxy ketals **136** and **137** which are related to chondrillin and xestins A and B. LTA oxidation of the phenol **134** in acetic acid followed by irradiation in methanol gave the *Z*,*Z*-diene **135** which was irradiated in the presence of oxygen, affording the desired targets **136** and **137** (Scheme 31).

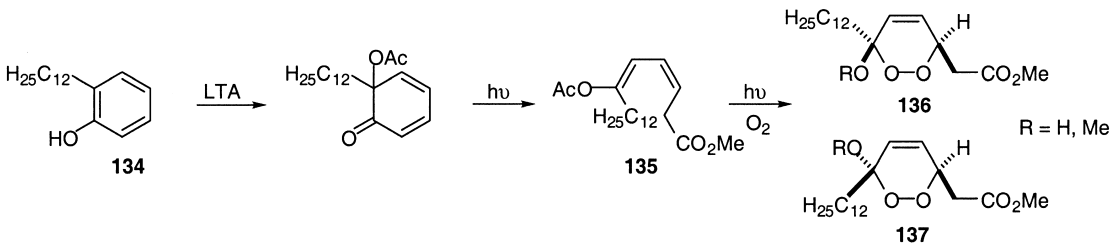
Photolytic cleavage involving direct ring opening was observed by Stein and Weiss[81] when they investigated the action of neutrons and α-radiation on dilute aqueous solutions of benzene. In addition to obtaining phenol and biphenyl by irradiation with X-rays, tetrahydromucondialdehyde was isolated, obviously derived from mucondialdehyde **138**. Later,[82,83] it was discovered that oxygen enhanced the yields of muconic products via the formation of peroxy radicals. Subsequent work by Stein suggested that only mucondialdehyde **138** was formed in conjunction with phenol.[84,85] Additional studies[86] found that even pure liquid benzene upon irradiation gave mucondialdehyde **138**, but was accompanied by the longer carbon-chain analogue **139**. Work finally conducted in this area showed that together with mucondialdehyde **138** an α-formyl-γ-pyran **140** could be isolated as a very unstable crystalline solid from the photolysis of benzene in aqueous solution. Farenhorst[87] suggested that longer irradiation times produced more



Scheme 29.



Scheme 30.



Scheme 31.

mucondialdehyde **138** and therefore the pyran **140** is possibly formed independently, but decomposes into mucondialdehyde **138** (Fig. 4).

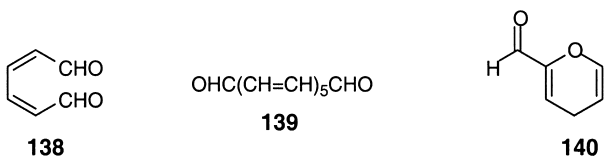
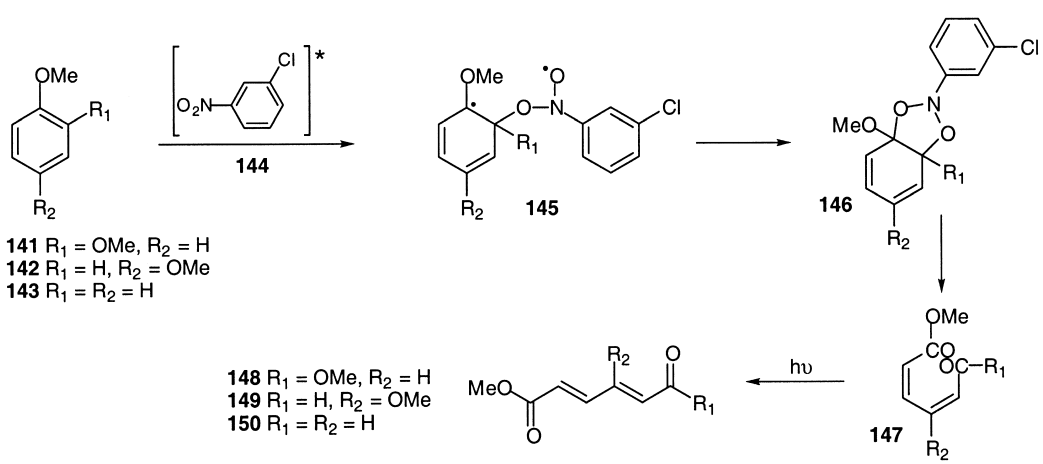
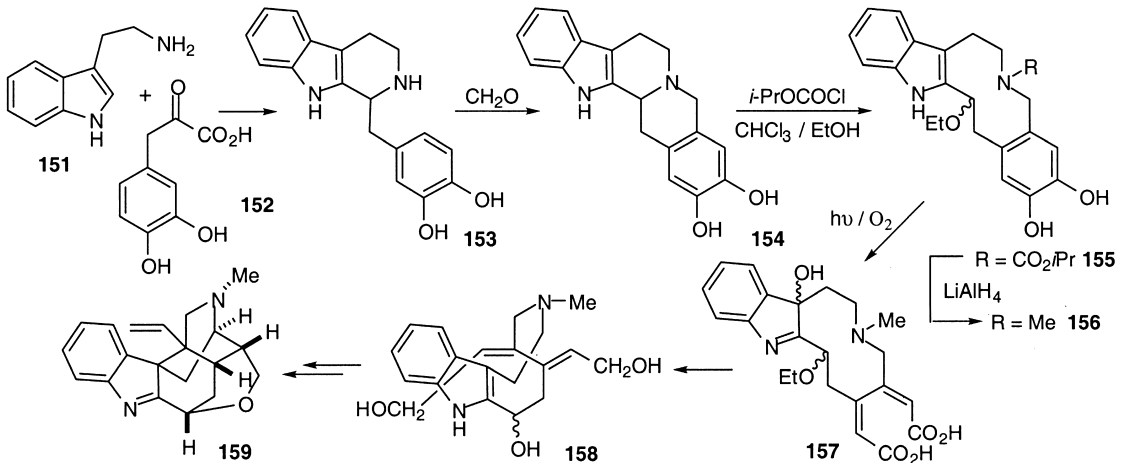


Figure 4.

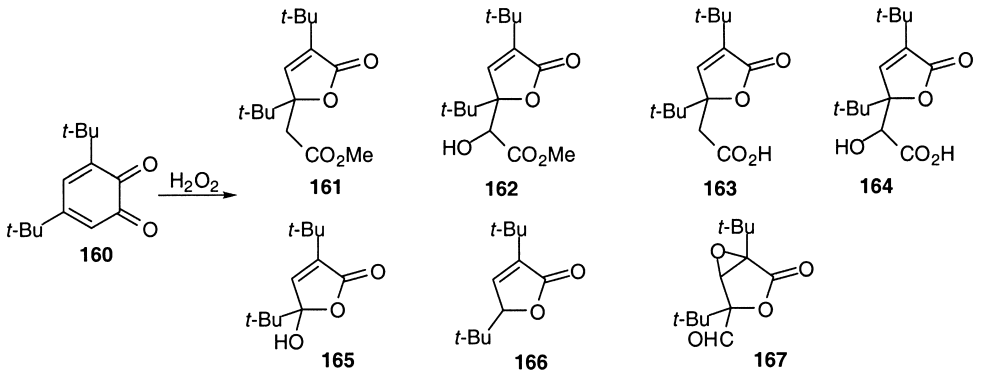
The photooxidative ring cleavage of di-*t*-butylcatechols and their derivatives has been thoroughly investigated jointly by Matsuura and Saito.[88–91] These researchers demonstrated that a number of products are formed which resemble the products obtained from treatment with hydrogen peroxide (cf. Section 4.5). From additional work,[92,93] however, the authors made a breakthrough in confirming some mechanistic aspects of the reaction of oxygen and its implementation in biological benzene degradation pathways. When the anisoles **141**–**143** were photolysed in the presence of *m*-chloronitrobenzene **144**, the nitrobenzene added to the ring, affording the muconic acid derivatives **148**–**150**. Although the yields of the products were low, the results indicated that a 1,2-cleavage of anisoles occurs selectively at the bond substituted with a methoxy group. The formation of the cleaved products may be explained by a mechanism that involves the addition of a triplet excited nitrobenzene to the anisoles, giving a dioxazolidine intermediate **146**, presumably via **145**. The intermediate **146** decomposes, affording the *Z*,*Z*-diene **147**, undergoes photochemical isomerisation, giving the *Z*,*E* products **148**–**150** (Scheme 32).



Scheme 32.



Scheme 33.



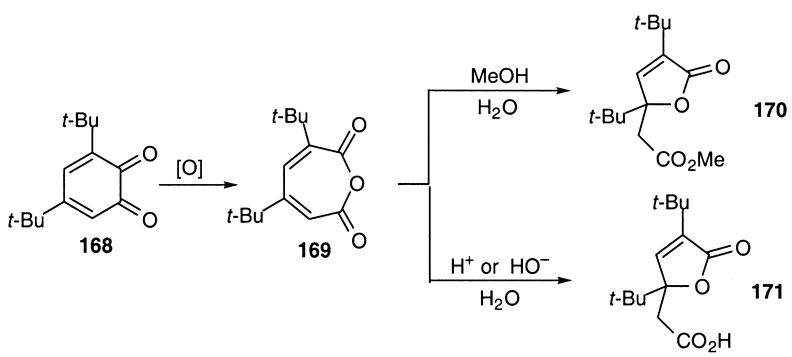
Scheme 34.

Photooxidation was used by Liu[94] in an approach to the synthesis of a probable precursor to koumine **159**. Cyclocondensation of tryptamine **151** with the catechol-substituted pyruvic acid **152** afforded **153**, which was treated with formaldehyde under Mannich conditions, giving the pentacyclic compound **154**. The compound **155** was obtained by C/D ring opening of **154**, achieved with isopropoxychloroformate, and was subsequently converted to the *N*-Me derivative **156** on treatment with lithium aluminium hydride. Photolytic oxidation of **156** (rose bengal/oxygen) afforded the muconic acid **157**. Further reduction of **157** gave **158** which may be regarded as a precursor to koumine **159** (Scheme 33).

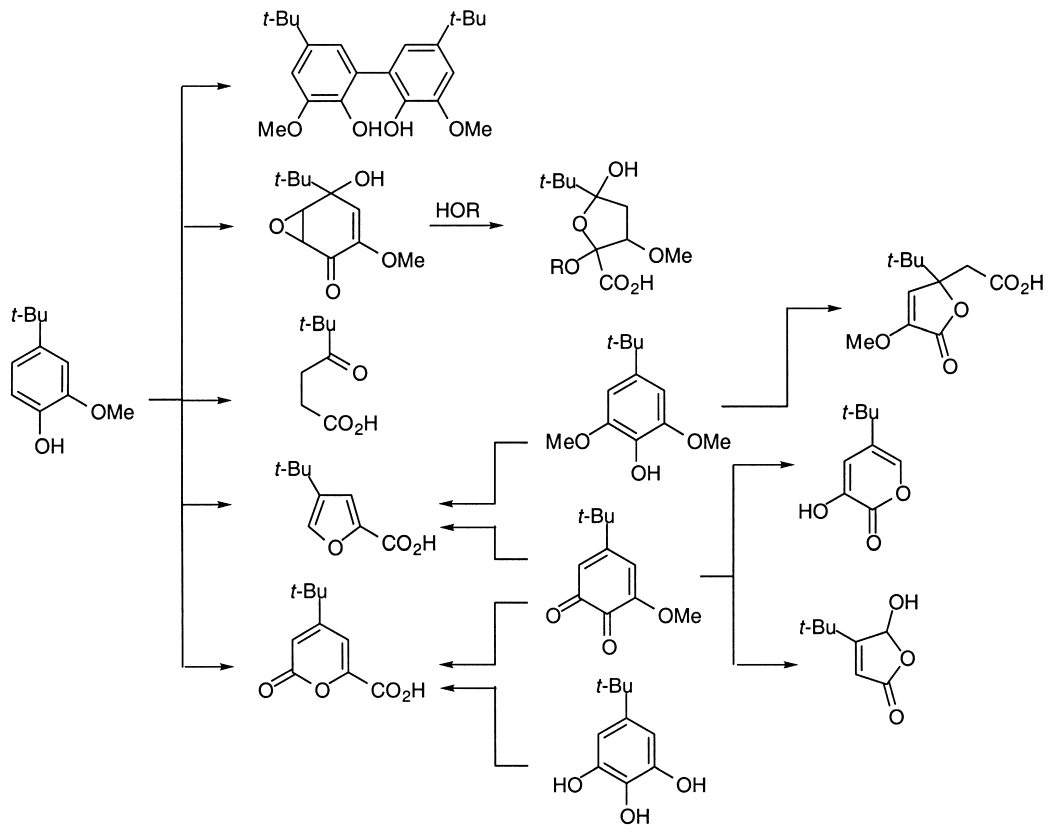
4.5. Hydrogen peroxide

This oxidising agent has been mainly used in conjunction with *o*-quinones, e.g. 3,5-di-*t*-butyl-*o*-quinone **160**, for correlation of mechanistic details and general comparison with pyrocatechases. Foote[95] found that the reaction of 3,5-di-*t*-butyl-*o*-quinone **160** with hydrogen peroxide afforded eight products. The major products **161**–**164** could be isolated as a single or major product, depending on the reaction conditions, whereas the minor products **165**–**167** were isolated in yields ranging from 0 to 5% (Scheme 34).

The products **161**–**164** arise from intradione cleavage,



Scheme 35.



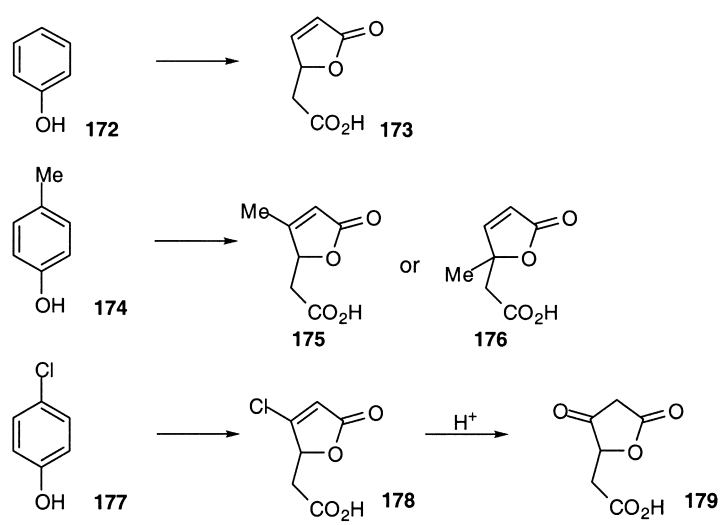
Scheme 36.

whereas the products **165–167** arise from extradione cleavage.[95,96] The products **170** and **171** can be obtained as the sole products if the *o*-quinone **168** is treated with monoperphthalic acid[97,98] (Scheme 35) (see Karrer for the 4-methyl,[99] 4,5-dimethyl[100] and the tetrabromo or tetrachloro derivatives[101,102]). This is a Baeyer–Villiger type reaction, affording the anhydride **169** as the intermediate.

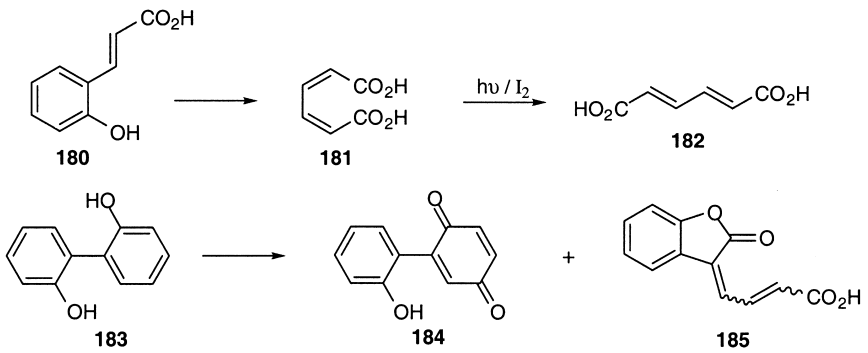
4.6. Oxygen

A significant body of research has been conducted on the role of oxygen, mainly in alkaline solution, in the autooxidation of mono- or di-*t*-butyl-substituted guaiacol and related derivatives.[103–111] Unfortunately, when these compounds react under these conditions, many different compounds are produced in low yield providing little synthetic value. The compounds obtained from this procedure are the same as those obtained from the treatment with hydrogen peroxide (see Scheme 34).

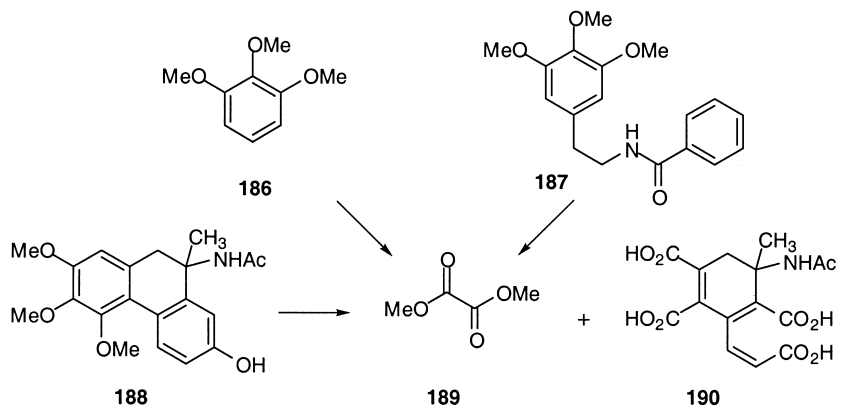
Gierer and Imsgrad[112,113] have summarised the products obtained from both their work and the work of others regarding the autooxidation (oxygen/alkaline solution) of mono- and di-*t*-butyl-substituted guaiacol and related derivatives (only the products obtained from the mono-*t*-butyl derivatives are shown in Scheme 36).



Scheme 37.



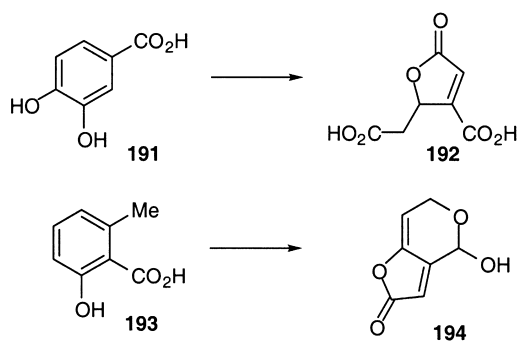
Scheme 38.



Scheme 39.

4.7. Peroxycarboxylic acids

The first use of peroxycarboxylic acids with aromatic systems was reported in 1930 by Böeseken,[114] who treated *o*-quinone with peracetic acid, which afforded *Z*,*Z*-muconic acid. In 1931 the same author reported that phenol was cleaved to give *Z*,*Z*-muconic acid.[115] A full report[116] 5 years later demonstrated that phenol **172**, *p*-methylphenol **174** and *p*-chlorophenol **177** also underwent ring opening, affording the muconolactones **173**, **175**, **176** and **178**, respectively (Scheme 37). In the case of *p*-methylphenol **174**, it was not clear whether the lactone **175** or **176** had formed. When *p*-chlorophenol **177** reacted under the same conditions and was then hydrolysed, however, lactone **179** was obtained, suggesting to the reviewers that **174** had given the lactone **175** and not **176**. Early studies on phenol were also conducted by Wacek and Fiedler.[117]



Scheme 40.

Grundman[118] applied Böeseken's procedure to the degradation of both *o*-coumaric acid **180** and 2,2′-dihydroxybiphenyl **183**. *o*-Coumaric acid **180** afforded *Z*,*Z*-muconic acid **181** which was, within minutes, isomerised to *E*,*E*-muconic acid **182** with light and with the aid of a catalytic amount of iodine, although iodine was later shown not to be necessary.[54] 2,2′-Dihydroxybiphenyl **183** afforded the mono-*p*-quinone **184** and the lactone **185** when treated with peracetic acid (Scheme 38).

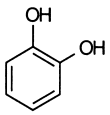
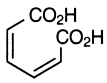
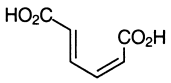
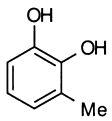
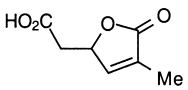
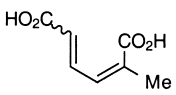
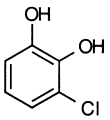
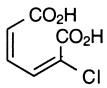
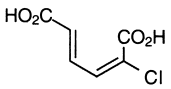
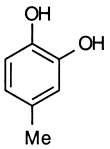
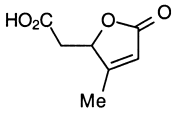
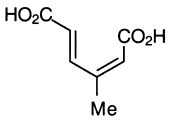
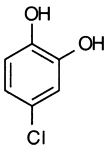
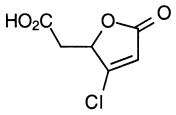
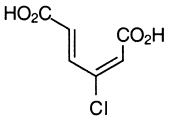
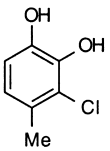
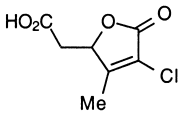
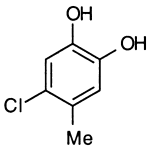
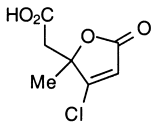
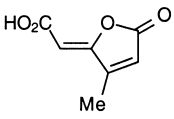
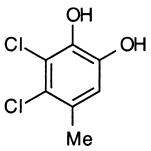
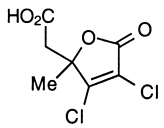
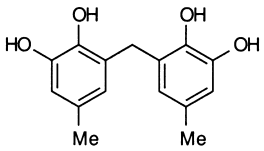
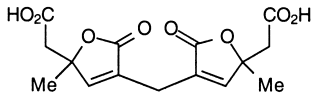
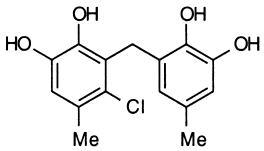
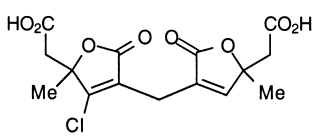
Some years later, Fernholz[119,120] found, under far more vigorous conditions, i.e. a large excess of perbenzoic acid in boiling benzene solution, that *N*-acetylcolchinol **188**, 1,2,3-trimethoxybenzene **186** and *N*-benzoylmescaline **187** gave dimethyl oxalate **189** as the common by-product. In the case of *N*-acetylcolchinol **188**, the other product obtained was thought to be **190** (Scheme 39).

3,4,5-Trimethoxybenzoic acid also affords dimethyl oxalate when treated with perbenzoic acid and acetomesitylene affords pyruvaldehyde.[121] Friess[122] observed similar results and conducted some kinetic studies as well as an investigation of the number of moles of peracid consumed with tri- and di- polymethoxy compounds.

Protocatechuic acid **191** has been found to give the β-carboxy-muconolactone **192**,[123,124] whereas the salicylic acid **193** affords an interesting lactone **194**[124] when treated with peracetic acid (Scheme 40). Other derivatives have been investigated by Johnson.[125]

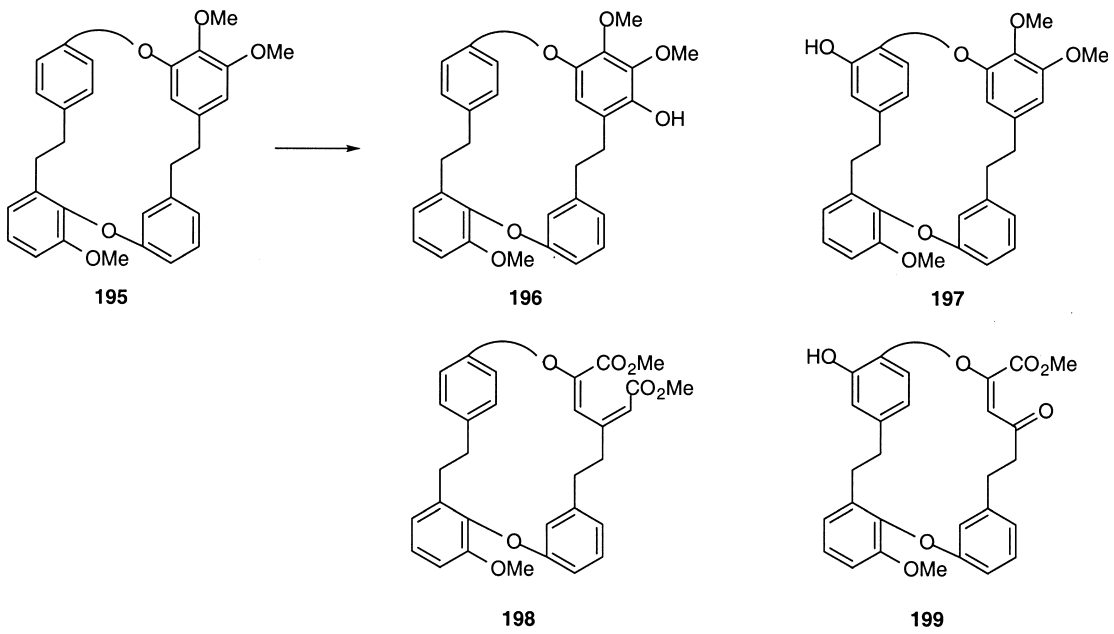
Muconic acids were recently identified in the effluents from

Table 3. Peroxycarboxylic acid oxidation of catechols

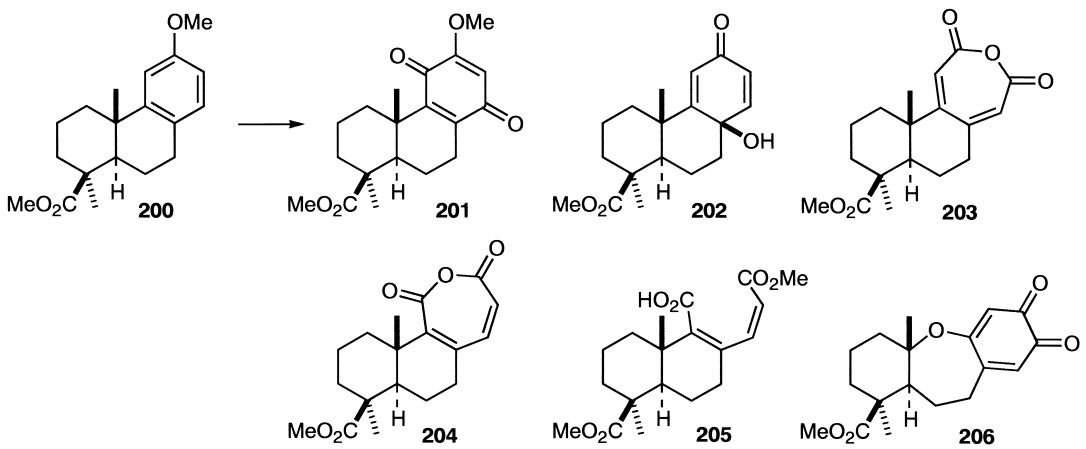
Entry	Catechol	Muconic acids	Ratio	Yield (%)
1		 	5:2	70
2		  2 isomers	2:1	50
3		 	2:1	83
4		 	15:1	45
5		 	2:1	40
6			–	60
7		 	1:1	45
8			–	45
9			–	50
10			–	30

the bleaching of wood pulps. In order to determine their behaviour and facilitate further identification work, a simple general procedure was required for the preparation of muconic acids having a variety of substituents. McKague[126] set about treating a number (Table 3) of methylated and/or chlorinated derivatives with peracetic acid, which afforded the monomeric and dimeric muconic acids in 30-83% yield. The reaction of ozone with lignin and lignin models has been reported.[127]

Marchantin A **195**, isolated from the liverwort *Marchantia polymorpha*, displays a variety of biological activities. Tori and Asakawa[128,129] desired to have similar compounds that contained an additional hydroxy functionality on any aromatic ring in the hope of obtaining more active compounds. Marchantin A **195** was subjected to treatment with *m*-chloroperbenzoic acid which afforded four products. Two products (**196** and **197**) contained the desired extra hydroxylation, whereas the other two products (**198** and



Scheme 41.

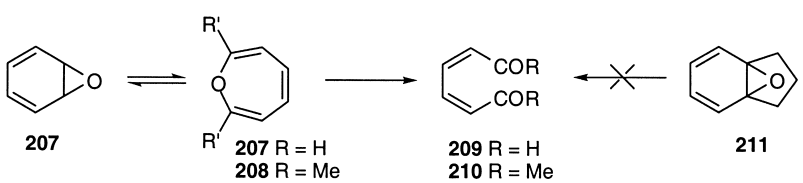


Scheme 42.

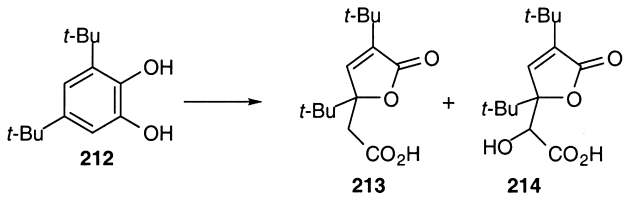
199) had undergone ring opening. Of these later products, the first was the muconic acid derivative **198** derived from intradiol cleavage and the second was the ketone **199** resulting from further oxidation of **198** (Scheme 41).

In an attempt to obtain reasonable yields of the *p*-quinone **201**, oxidation of the ether **200** with peracids was examined.[130] Treatment of **200** with an excess of *m*-chloroperbenzoic acid gave a mixture of six compounds which could be individually isolated, namely the desired quinone **201** (12%), enone **202** (6%), the muconic anhydrides **203** and **204**, the half ester **205** and finally the tetrahydrooxepin **206** (Scheme 42). The reaction with peracetic acid gave similar results and the yields could not be increased with other reagents, although some product yields could be increased (~20%) starting with other substrates. *m*-Chloroperbenzoic acid has been found to react with carnosol affording only the muconic anhydride similar to that observed by Cambie (e.g. **204**).[131]

In a slight variation on the general theme, it was discovered that benzene oxide-oxepin **207** readily reacted with peracids to yield *Z*,*Z*-muconaldehyde **209** which was thermally unstable and isomerised to the *E*,*E*-derivative. The 2,7-dimethyloxepin **208** derivative afforded the corresponding diketone **210**, but the indane derivative **211** failed to give muconic products (Scheme 43).[132]



Scheme 43.



Scheme 44.

The literature indicates that peracetic acid is more active than perbenzoic acid and the authors suggest that peracetic acid be the first choice so as to avoid quinones, the single step oxidation by-products. Trifluoroperacetic acid,[133] on the other hand, seems to be more active than peracetic acid and can completely destroy the aromatic ring and the subsequent muconic derivatives, affording carboxylic acids in a similar manner to ruthenium tetroxide (Section 2.1).

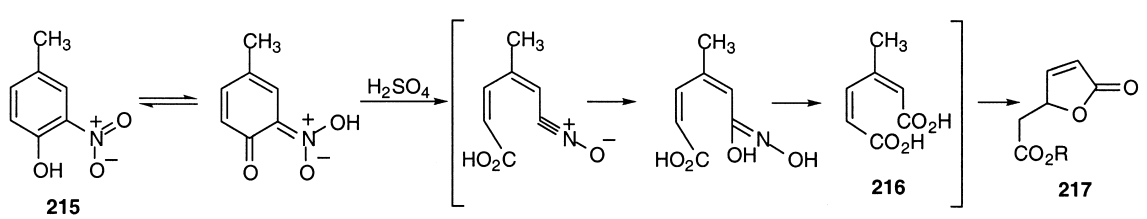
4.8. Free radical initiation

The free radical oxidation of catechols to *Z,Z*-muconic acids is not too well known and the first report by Schenk and Brown[134] showed that treatment of catechol with diphenylpicrylhydrazyl (DPPH) effected this transformation, an outcome that is supported by the work of Hasegawa.[135]

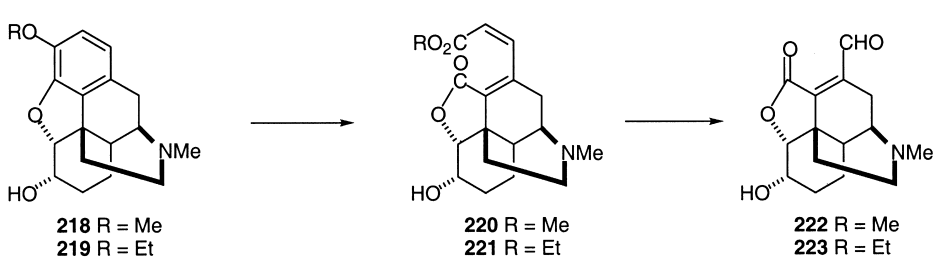
Potassium superoxide, another reagent for inducing free radical oxidation, was first reported in 1976 by Foote[136] for the conversion of 3,5-di-*t*-butylcatechol **212** into the furanones **213** and **214** (muconolactones) (Scheme 44), but in the same year Lee-Ruff et al.[137] reported the conversion of catechol to *Z,Z*-muconic acid.

4.9. Mineral acids

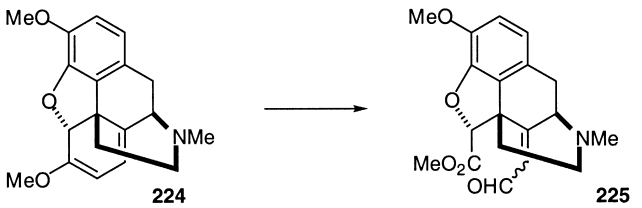
When Wieland and Kappelmeier[1] were investigating morphine in 1911, they found that treatment with nitric acid gave a ring-cleaved muconic acid derivative of undetermined structure. In 1914[138] and, later, in 1918,[139] Pauly et al. reported that sulfuric acid was able to ring open 2-nitro-4-methylphenol **215** without further degradation, affording β-methylmuconic acid **216** which lactonised to give muconolactone **217** (Scheme 45).



Scheme 45.



Scheme 46.



Scheme 47.

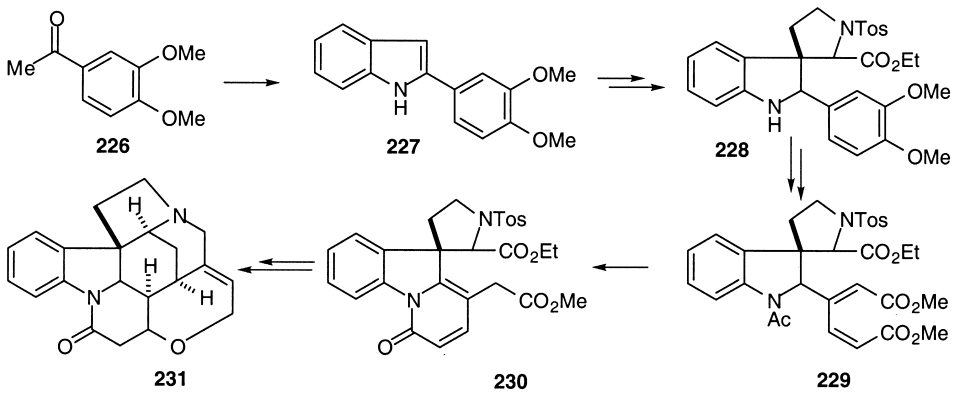
4.10. Ozone

Speyer[140,141] subjected dihydrocodeine **218** and ethyldihydromorphine **219** to ozonolysis that, in contrast to thebaine, attacked the aromatic ring affording the muconic acid derivatives **220** and **221**. Further degradation was observed on longer exposure to ozone affording the aldehydes **222** and **223** (Scheme 46).

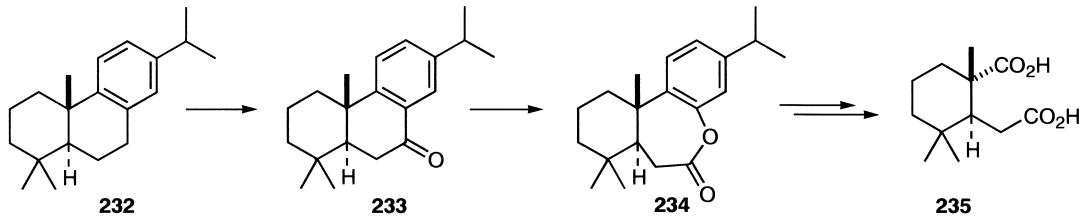
Rapoport and Payne[142] were able to obtain a higher yield of **220** (75%) (Scheme 46) compared to that of Speyer (40%) if the ozonolysis was carefully controlled, i.e. changing the solvent to acetic acid and allowing only 1 mol of ozone to react. Morphine gave the corresponding muconic derivative.

Pschorr[2] had investigated the effect of ozone on thebaine **224**, but did not put forward a possible structure for the isolated product. Later, when the correct structures of the opium alkaloids were known, Wieland[143] suggested that Pschorr's ozonolysis product was **225**, resulting from opening at ring C (Scheme 47).

The most famous use of ozone benzene degradation was made by Woodward in his synthesis of strychnine **231**.[144,145] After he had ascertained that enzymatic ring cleavage was probably involved in the biosynthetic pathway,[146] Woodward constructed his synthesis accordingly. Starting with 2-veratrylindole **227**, derived from acetoveratrone **226**, Woodward attached the spiropyrrolidine, affording **228**. After protection of the indole nitrogen as the acetate derivative, the product was ozonised. Treatment of the muconate **229** with acid afforded in one step the pyridone **230**, which was then transformed into the natural product



Scheme 48.



Scheme 49.

231 following a number of further steps (Scheme 48). Although Woodward[145] makes a comment on benzene degradation by peracids, he makes no mention of previous reports using ozone. It therefore seems likely that this concept was made use of as a consequence of the prior work conducted on the morphine alkaloids (see above).

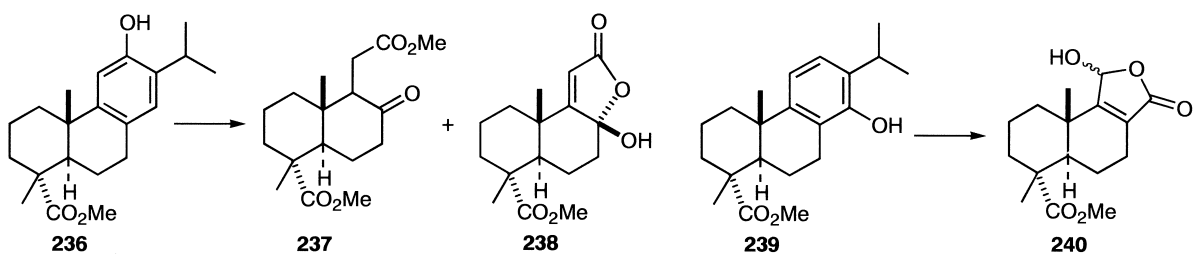
Drimanic sesquiterpenes were synthesised by Wenkert and Strike[147] from the common intermediate, drimic acid **235**, derived from dehydroabietane **232**. Oxidation of **232** with chromic acid afforded the 7-keto derivative **233** which was converted to the lactone **234** using trifluoroperacetic acid. Hydrolysis of **234** followed by ozonolysis gave the key intermediate, drimic acid **235** (Scheme 49). A podocarpic acid derivative was converted into **235** in a similar fashion.

Phenolic dehydroabietic acid derivatives were ozonised with a view to investigating the direction of cleavage and the effect of the hydroxyl group at different positions.[148] The compound **236** gave the ketone **237** and the lactone **238**, after ozonolysis and subsequent hydrogenation and methylation, and the lactone **238** could be converted into **237** by treatment with diazomethane followed by hydrogenation. In contrast, the compound **239** gave the lactol **240** after ozonolysis and subsequent hydrogenation (Scheme 50). The authors concluded that the direction of benzene cleavage by ozonolysis was subtly affected by the substitution pattern of the hydroxy group.

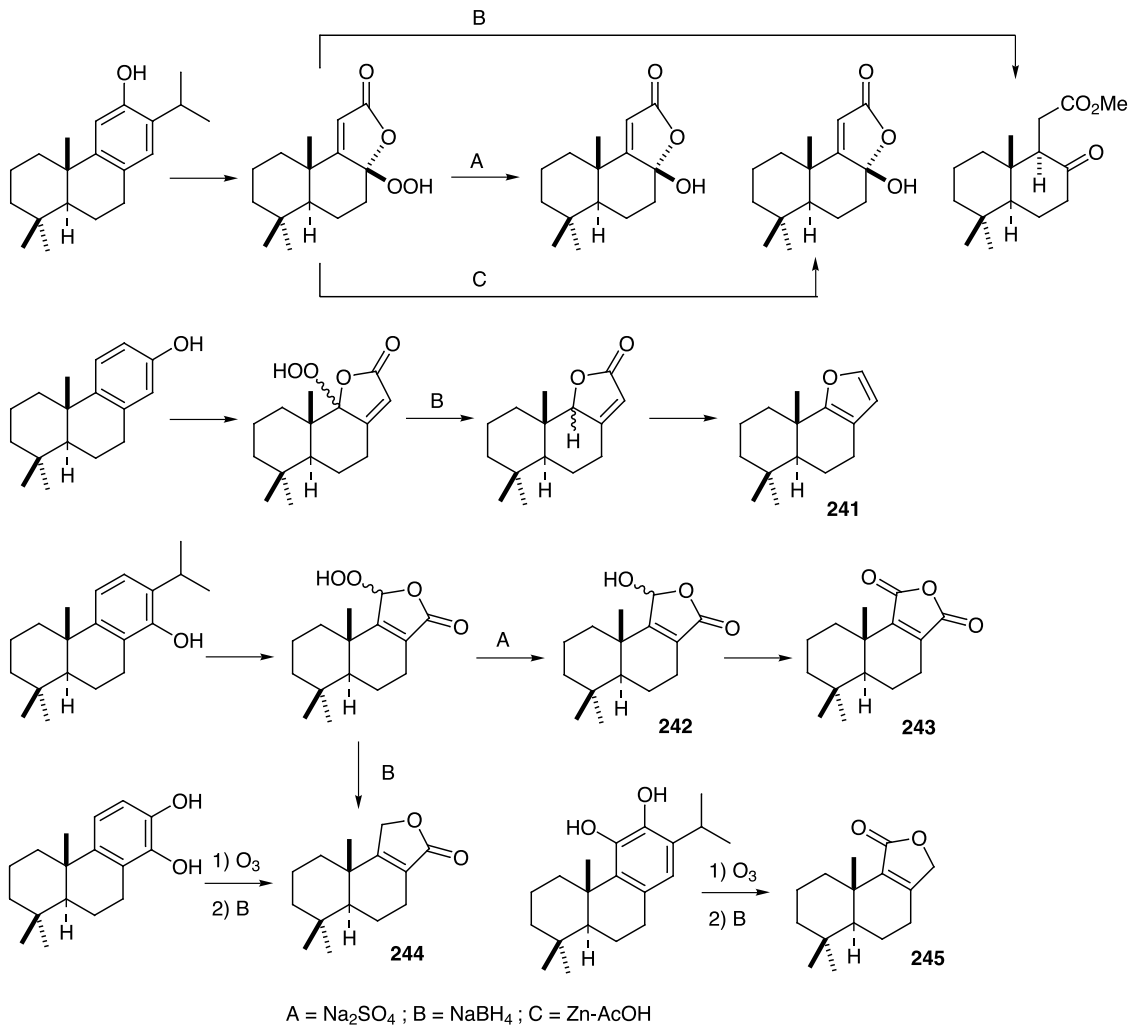
This theme was continued by Akita and Oishi[149,150] who later conducted a more systematic study on the ozonolysis of phenolic dehydroabietic acid derivatives. The ozonolysis products were then treated with either sodium sulfate, sodium borohydride or zinc/acetic acid which led directly to a number of different naturally occurring sesquiterpenoids, such as pallescensin A **241**, valdiviolide **242**, winterin **243**, confertifolin **244** and isodrimenin **245**, as depicted in Scheme 51.

In the same year, the authors reported[151] that the natural products fragrolide **246** and bernadienolide **247** could be obtained using the same strategy. Confertifolin **244**, winterin **243** and isodrimenin **245** can also be obtained from royleanone **248** via an initial two-step oxidation process followed by treatment with periodic acid[152] (Fig. 5).

The ozonolysis of methyl *O*-methylpodocarpate **249** (R^1=R^2=Me) was first conducted by Bell and Gravestock[153] in 1970 (*O*-methylpodocarpane was first ozonised



Scheme 50.



Scheme 51.

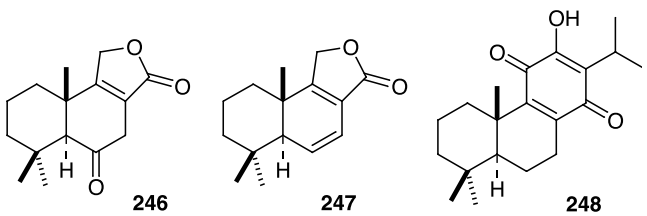
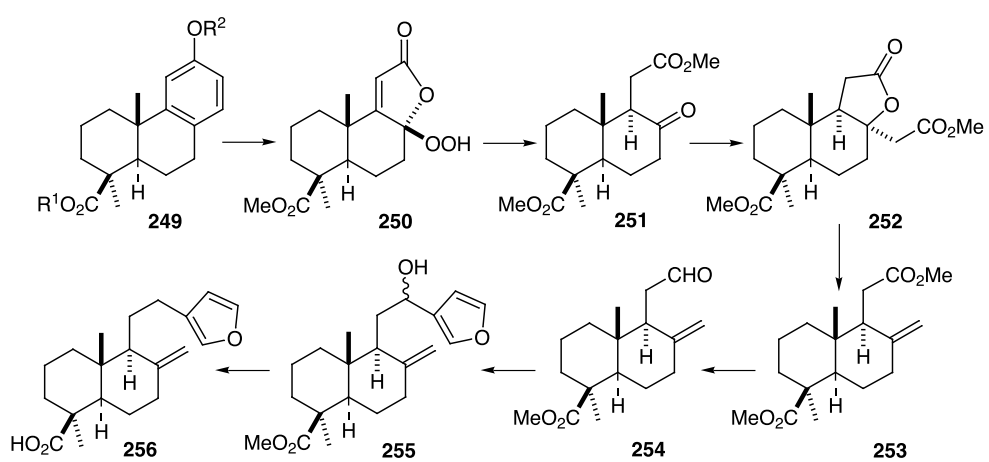


Figure 5.

in 1964[147]). The sole product obtained was the hydroperoxylactone **250** used to synthesise 2-oxonaphtho[2,1-*b*]-furan-6α-carboxylic acid derivatives for an anti-inflammatory investigation.[154] Bell and Gravestock[155] later converted the hydroperoxylactone **250** into lambertianic acid **256**. Hydrogenation of the lactone **250** afforded the ketone **251** which underwent a Reformatsky reaction, affording the lactone **252**. Treatment with sodium hydroxide and



Scheme 52.

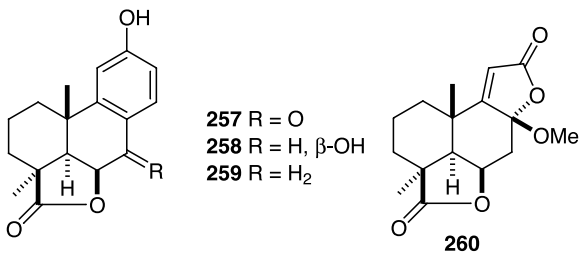


Figure 6.

subsequent decarboxylation gave the monoacid **253**, which was esterified and selectively reduced, and then oxidised to the aldehyde **254**. Reaction with 3-lithiofuran afforded the alcohol **255**. The remaining ester was demethylated (potassium *t*-butoxide/DMSO) and then treated with mesityl chloride. Lambertianic acid **256** was then obtained after reduction of the mesylate with lithium in ammonia (Scheme 52).

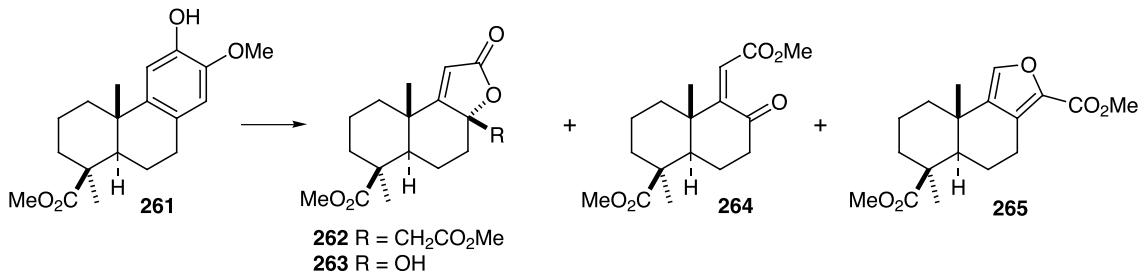
As methyl *O*-methylpodocarpate **249** (R^1=R^2=Me) had been the main focus of attention for a number of reasons including higher yields of the lactone **250**, Cambie[156] decided that the investigation of the unmethylated derivative [methyl podocarpate **249** (R^1=Me, R^2=H)] could be profitable. Initially, this substrate lacked reactivity when in contact with ozone and, subsequently, it was discovered that the absence of reactivity was due to the purity of solvent (methanol). Before methanol had been used in the reaction, it had been dried and purified using the magnesium/iodine procedure which removed all acidic impurities. When a trace of Lewis or mineral acid was added to the mixture, the ozonolysis therefore proceeded smoothly, giving the hydroperoxylactone **250**. More than trace amounts, however, led to later problems when the ozonolysis products were hydrogenated.

Cambie[157] then set about investigating other podocarpate derivatives in the hope of simplifying future synthetic sequences. Only podocarpic acid **249** (R^1=R^2=H) underwent transformation into the lactone **250**. The derivatives **257** and **258** failed to react smoothly, affording gross mixtures (Fig. 6), although the parent phenol **259** gave a product that was tentatively assigned as the lactone **260** in 29% yield.

On the other hand, dioxygenated derivatives undergo ozonolysis, although in the case of the derivative **261** four products **262**–**265** were obtained, resulting from additional oxidation of the lactone **262** (Scheme 53).[67]

From this work, Cambie was able to synthesise in a formal sense a number of naturally occurring products and derivatives, including homologues (**266**–**268**) of ambrox and isoambrox,[158] γ-bicyclohomofarnesals[159] (**269**–**271**), winterin[160] **243** and the congeners of confertifolin, winterin and isodrimenin[130] (Fig. 7). Pelletier[52] has also synthesised winterin from podocarpric acid derivatives.

Cambie[161–163] also investigated the structurally-related totarol derivatives and found that totarol **272** can be transformed, via the catechol **273**, into the muconate derivative **274** (Scheme 54). The lactone **275** offered a potential route to the naturally occurring nagilactones and was obtained by treating the muconate **274** with base followed by thermolysis.[164]



Scheme 53.

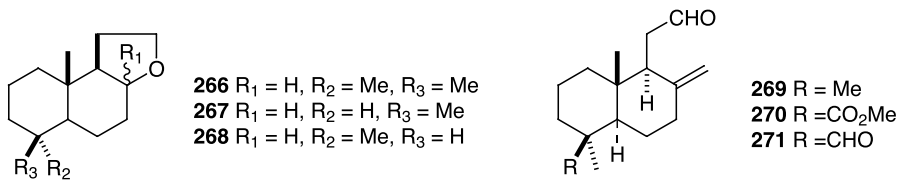
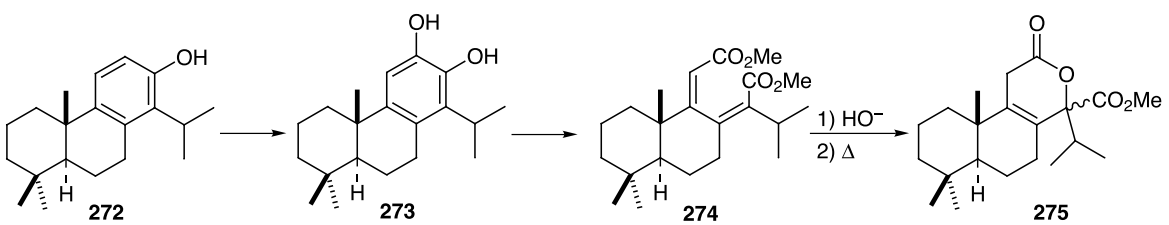
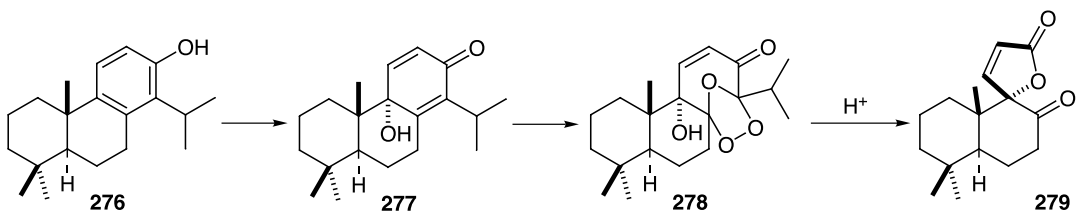


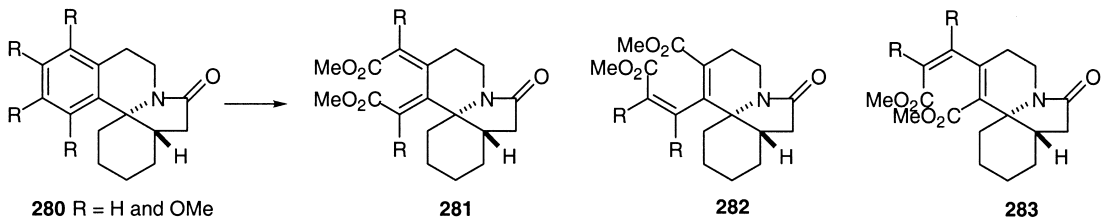
Figure 7.



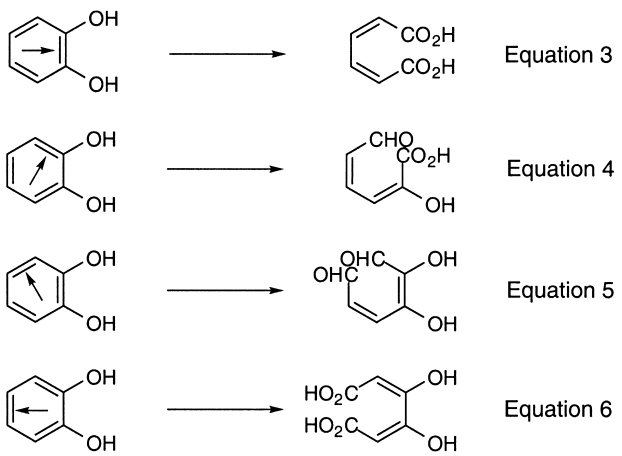
Scheme 54.



Scheme 55.



Scheme 56.

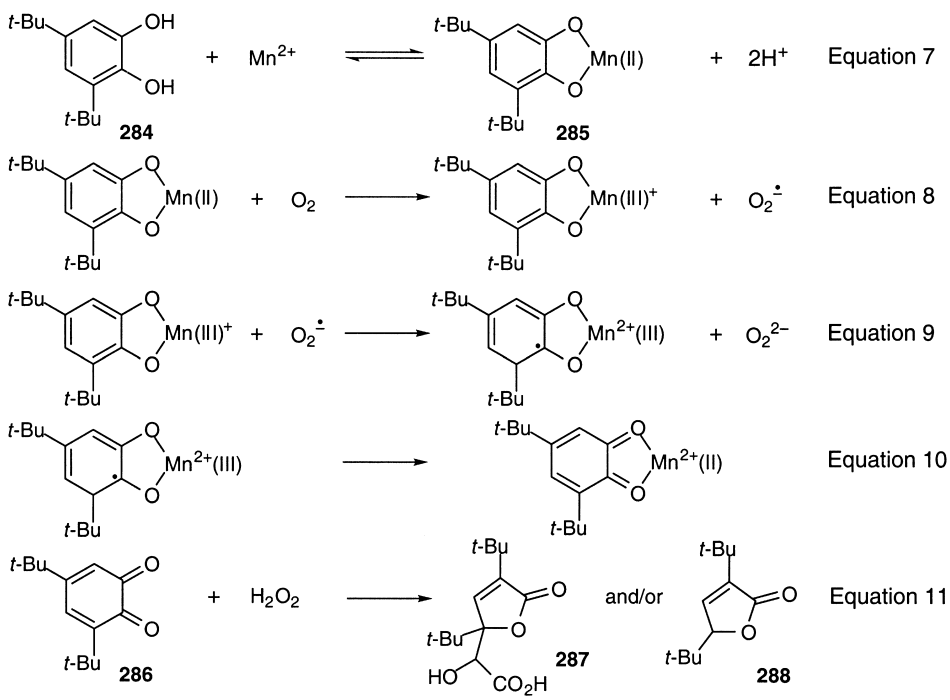


Scheme 57.

If, however, totarol **276** is initially oxidised to the enone **277** with benzeneseleninic anhydride and then ozonised, a completely different lactone **279** was obtained via the isolatable ozonide **278**, on treatment with acid[165] (Scheme 55).

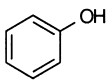
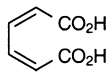
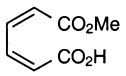
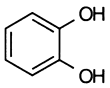
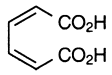
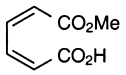
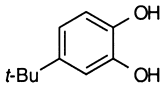
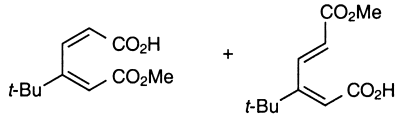
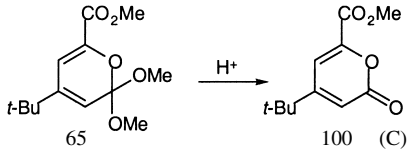
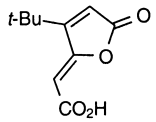
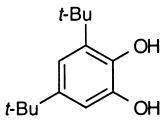
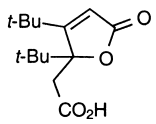
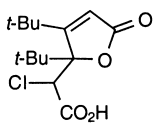
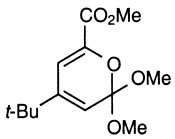
Although Cambie was not the first researcher to investigate the ozonolysis of podocarpanes or podocarpates, his contributions have been the most significant in the last three decades, with his final report published in 1998.[67]

Simple systems, such as eugenol and safrole, have been investigate by Costa[166] and found to give dimethyl muconates, although the author does not mention similar work conducted earlier by Briner.[167] See Mahatam and Gurbakhsh for an investigation of fused 1,2-dimethoxybenzo systems.[168]



Scheme 58.

Table 4. Enzyme dearomatisation mimics using copper salts

Entry	Substrate	Ligand/[O]	Catalyst	Products (%)	Reference
1		AcOH AcOOH	$Cu(OAc)_2$	 24	178
2		Pyridine Oxygen	CuCl	 44	179,180
3		Pyridine Oxygen	pyCuClOMe	60–70	181,182
4		AcOH AcOOH	$Cu(OAc)_2$	 40	178
5		Pyridine Oxygen	CuCl	 71–82 (D)	180,183,184
6		Pyridine Oxygen	CuClOMe	85	181,182
7		Pyridine Oxygen	$Cu(OMe)_2$	20	182
8		Pyridine KOH	$CuCl_2$	82	
9		Pyridine KO_2	$CuCl_2$	85	
10		Pyridine Oxygen	PyCuClOMe	 55 + 40 (A,D)	181
11		Pyridine Water	PyCuClOMe	55 + 40	182
12		Pyridine Water	$Cu(OMe)_2$	35 (B)	
13		Pyridine –	pyCuClOMe	 65 → 100 (C)	182,185
14		Pyridine Water	pyCuClOMe		186
15		Pyridine Oxygen	CuCl	 35	187
16		Pyridine Oxygen	CuCl	 15	72
17		Pyridine –	pyCuClOMe		185

A: lactonisation readily occurred on silica gel; B: combined yield of both isomers; C: acid hydrolysis gave the pyrone in quantitative yield; D: a range of alcohols can be used to generate different esters.

Isobe[169] found that the ozonolysis of these simple systems could be controlled by the use of the Lewis acid, boron trifluoride. This method was then applied to erythrinan derivatives **280** affording *seco*-erythrinans **281**, **282** and **283** in appreciable yields (Scheme 56).

Finally, Karpel Vel Leitner[170] has undertaken a kinetic investigation of benzene degradation by ozone using 1,3,5-trifluorobenzene and α,α,α-trifluorotoluene as model substrates.

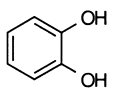
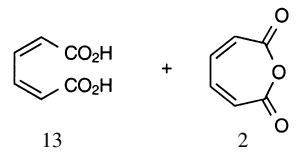
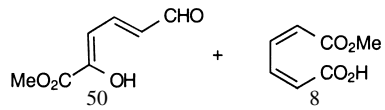
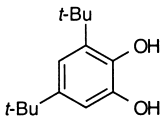
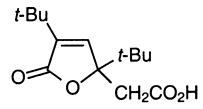
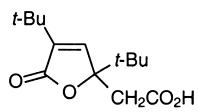
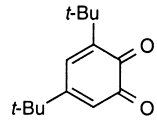
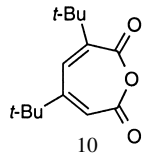
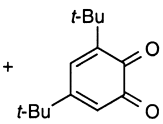
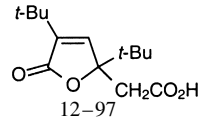
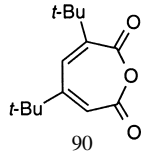
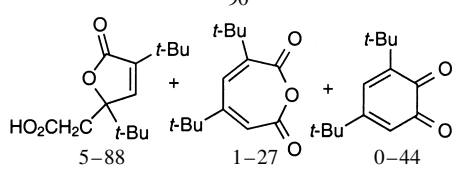
4.11. Transition metals/enzyme mimics

For quite some time, scientists have been trying to mimic enzymatic oxidative aromatic cleavage. Enzymes that cleave aromatic rings are mainly oxygenases and dioxygenases, both of which have been comprehensively reviewed.[171–175] Although enzymatic degradation will not be covered in this review, enzyme mimics are included because they are often a combination of simple chemical reagents and simple ligands e.g., iron(II) chloride with 1,4,9-triazacyclononane.[176]

Theoretically, four types of oxidative ring cleavage of catechol are possible, as indicated in Scheme 57. Equation (3) is commonly called intradiol cleavage, Equation (4) extradiol cleavage, whereas cleavage according to Equations (5) and (6) has yet to be observed.

Grinstead[177] was the first to adopt the idea of an enzyme mimic when he investigated the oxidation of 3,5-di-*t*-butylpyrocatechol **284** with oxygen in the presence of

Table 5. Enzyme dearomatisation mimics using iron salts

Entry	Substrate	[O]	Catalyst	Products (%)	Reference
1		Oxygen	$Fe^{II}(DPAH)_2$	 13 + 2	190
2		AcOOH	$Fe(Oac)_3$	65	178,191
3		Oxygen	$FeCl_2$ or $FeCl_3$	 50 + 8	177
			TACN		
4		AcOOH	$Fe(Oac)_3$	 56	192
5		Oxygen	$[Fe(bipy)_3]Cl_2{\cdot}7H_2O$	 0–14 +  17–51	193
6		Oxygen	Fe(NTA)	41–86 + 2–80	194
7			$Fe(bpnp)Cl_2$	 10 +  40	195
8		Oxygen	$[Fe(L)DBC]^{2-}$	 12–97	196–199
9		Oxygen	$[Fe(bpia)(MeCN)_2]^{3+}$	 90	200
10		Oxygen	$FeX_3{\cdot}nH_2O$	 5–88 + 1–27 + 0–44	201–203

NTA=nitrilotriacetate; bpnp=2-[bis(2-pyridylmethyl)aminomethyl]-4-nitrophenol; DBC=3,5-di-*t*-butylcatechol; bpia=bis[(2-pyridyl)methyl][(1-methyl-imidazol-2-yl)methyl]amine; X=Cl, NO_3, ClO_4; TACN=1,4,7-triazacyclononane.

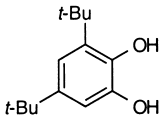
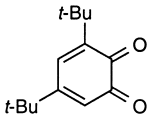
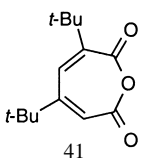
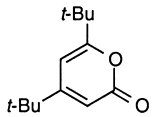
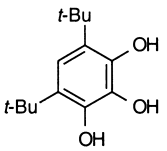
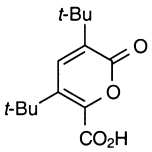
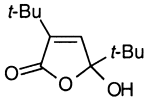
various metals (Mn^{2+}, Co^{2+}, Fe^{2+}, Cu^{2+}, Zn^{2+}, Ni^{2+}) as catalysts in an attempt to rationalise the mechanism of pyrocatechase action. He also investigated the action of hydrogen peroxide on 3,5-di-*t*-butyl-*o*-benzoquinone **286** which allowed a probable mechanism to be suggested. It was inferred that the most likely function of the polyvalent metal-ion catalyst was to scavenge aryl radicals, oxidising them to quinones before side reactions could occur. Using manganese, for example, the catechol **284** forms a metal chelate **285** as indicated in Equation (7). Equations (8) and (9) involve one-electron transfers from the chelate to the oxygen molecule or its reduction products. It is important to note that the dianion is formed as the by-product in Equation (9). Equation (10) represents an internal redox reaction in the form of electron transfer from the organic portion of the chelate to the metal ion. Hydrogen peroxide, produced as a by-product, then effects ring fission, affording the lactones **287** and **288** (Scheme 58, Eq. (11)).

The following subsection is divided into investigations involving the salts of copper (Table 4), iron (Table 5) and vanadium (Table 6), respectively, and then a discussion of a selection of miscellaneous examples.

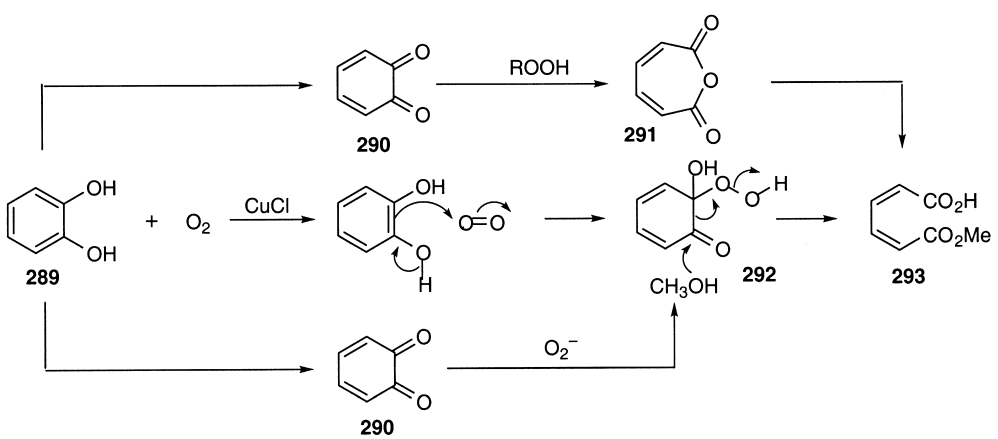
After conducting oxygen-18 labelling studies, Tsuji[188] suggested an alternative mechanism for the formation of the monoacid **293** from catechol (entry 2). It was confirmed by mass spectrometry that one atom of the labelled oxygen had been introduced into the free acid group, but not into the ester group. Catechol **289** is oxidised to the *o*-quinone **290** which is attacked by a peroxide dianion. Alternatively, catechol nucleophilically attacks oxygen to give the common hydroperoxide intermediate **292** which is ring opened by methoxide, affording the monoester **293**. The opposing mechanism is that derived from the anhydride **291**, which is a Baeyer–Villiger type product isolated from the reaction of *o*-quinone **290** and hydrogen peroxide (see above) or peracid[189] (Scheme 59).

Ruthenium [$RuCl_2(PPh_3)_3$; $RuBr_2(PPh_3)_3$; $Ru(H)Cl(PPh_3)_3$;

Table 6. Enzyme dearomatisation mimics using vanadium salts

Entry	Substrate	[O]	Catalyst	Products (%)			Reference
1		Oxygen	$VO(acac)_2$	 27	 41	 15	204
2			VO(salen)	22	39	7	
3			VCl(salen)	28	43	7	
4			VCl(saldpt)	23	41	6	
5			$[VO(acac)OMe]_2$	25	47	10	205
6			$[VO(tmh)OMe]_2$	24	46	7	
7			$(VOaap)_2$	23	48	9	
8			$(VOdmba)_2$	24	47	8	
9			$(VOdba)_2$	22	46	10	
10			VO(acac)(TCCat)	24	45	6	206
11		Oxygen	VO(salen)	 41	 8	Quinone dimmer 24	207

tmh=2,2,6,6-tetramethylheptandione; H_2aap=*o*-hydroxyacetophenone; H_2dmba=1,5-bis(*p*-methoxyphenyl)-1,3,5-pentanedione; H_2dba=1,5-diphenyl-1,3,5-pentanetrione; TCCat=tetrachlorocatecholate.



Scheme 59.

$Ru(H)SiClPh_2(PPh_3)_3$; $Ru(H)OAc(PPh_3)_3$][208] and rhodium[209] catalysts, when allowed to react with 3,5-di-*t*-butylcatechol, have been found to give varying ratios of the corresponding *o*-quinone **294**, anhydride **295** and pyrone **296** (Fig. 8).

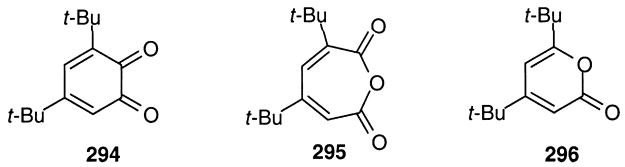
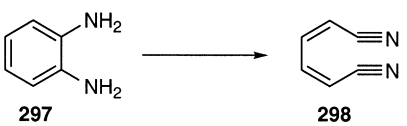


Figure 8.

Catechol units already chelated to metals[210] or bound to porphyrin units[211,212] have been investigated, but have afforded little synthetic value.

4.12. Heteroatom variants

To date, only nitrogen has been integrated into the aromatic degradation protocol. The first derivative synthesised was *Z,Z*-muconononitrile **298** from *o*-phenylenediamine **297**. Nakagawa and Onoue found that stoichiometric amounts of nickel peroxide[213] or LTA[214] effected the transformation, but the yields were low (Scheme 60).



Scheme 60.

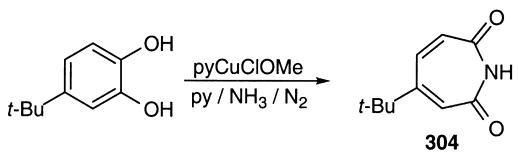
Tsuji[215] was able to significantly improve the yields of *Z,Z*-muconononitrile **298**, on a relatively large scale,[216] with the use of oxygen and cuprous chloride, as well as a number of other derivatives shown in Table 7. Cupric chloride is inactive in the presence of oxygen, but copper(II) salts can be used in the absence of oxygen[180] under special conditions to afford **298**.

Table 7. Oxidation of 2,3-diaminobenzenes

Entry	Substrate	Yield (%)	Reference
1	2,3-Diaminobenzene	95	180,215,216
2	4-Methoxy-2,3-diaminobenzene	75	215,217
3	4,5-Dimethyl-2,3-diaminobenzene	95	
4	4-Nitro-2,3-diaminobenzene	0	
5	4-Aceto-2,3-diaminobenzene	0	217
6	4-Methyl-2,3-diaminobenzene	62	
7	4-Chloro-2,3-diaminobenzene	43	

A nice variant to this reaction is the synthesis of mononitriles of muconic acids from *o*-benzoquinones, catechols and phenols.[186,218] Treatment of the catechol **299** or the phenol **300** with a copper/ammonia species, generated from a copper (II)–oxygen complex which had been allowed to react with ammonia, and oxygen afforded the mononitrile of muconic acid **301** (R_2=*t*-Bu or H) in high yields. Hydrogenation of **301** over Raney nickel provided the ω-aminocaproic acid **302**, which was readily converted to caprolactam **303** (Scheme 61).

The same authors[186] demonstrated, that using a slightly different catalyst, the cyclic imides (e.g. **304**) could be isolated in approximately 50% yield (Scheme 62).



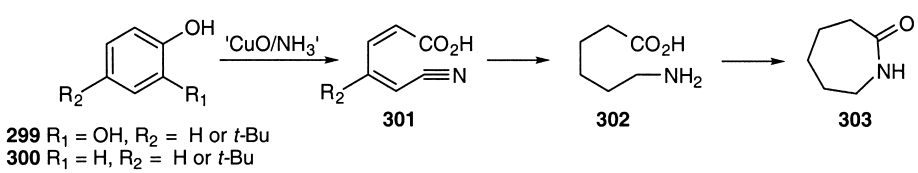
Scheme 62.

Photolysis of benzfurazane **305** in benzene yields the azepine **308** as the main product. When irradiation of **305** is conducted in methanol, the carbamate **309** is isolated which then isomerises to a mixture of the *Z*- and *E*-isomers. The mechanism involves initial ring opening to give the nitrile oxide **306** which undergoes a further rearrangement to an acylnitrene **307**. The acylnitrene **307** inserts into benzene, affording the azepin **308** or undergoes additional rearrangement to an isocyanate **310** which is trapped by methanol, affording the carbamate **309**[219] (Scheme 63).

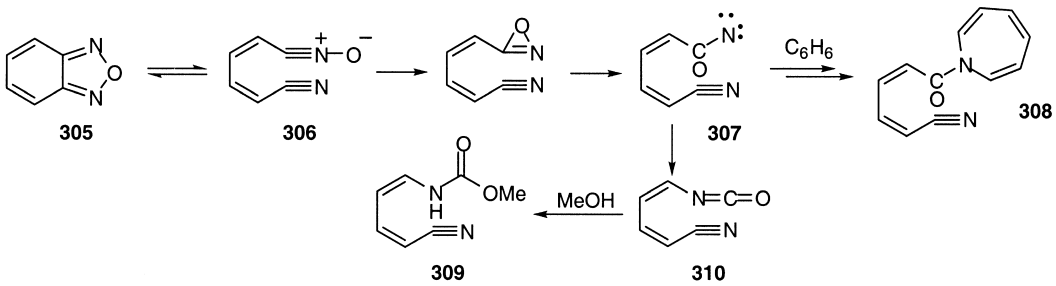
Rose Bengal-sensitised photooxidation of the dimethylaniline **311** in methanol yielded the 1,2-cleavage product, muconoic amide **313**, in 60% yield. The formation of **313** was suggested to indicate a 1,2-cycloaddition of singlet oxygen to give a benzene dioxetane **312** or its equivalent[220] (Scheme 64).

Oxidation of the *o*-quinone **314** with monoperphthalic acid[97,98] affords the anhydride **315** which is then treated with ammonia gas, giving the mucono-amidolactone **316** (Scheme 65). Brassard and Karrer were first to obtain this type of product, but their work was conducted using the 4,5-dimethyl derivative.[100]

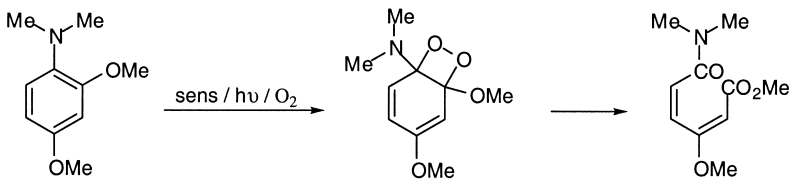
Organic peracids transform 3-aminocatechols **317**–**319** into the corresponding 6-hydroxypicolinic acids **323**–**325** via the anhydride **321** which ring opens **322** and isomerises before closing. Although perbenzoic acid transforms 3-aminobenzo-1,2-quinone **320** to 6-hydroxypicolinic acid **323**, the substitution of peracetic for perbenzoic acid



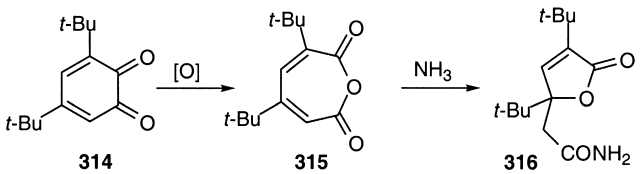
Scheme 61.



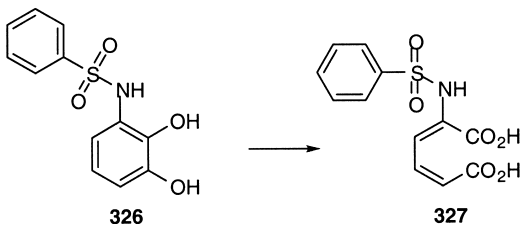
Scheme 63.



Scheme 64.



Scheme 65.



Scheme 67.

followed by hydriodic acid leads to the unexpected formation of pyridine and 2-hydroxypyridine. The latter is produced in similar reactions between the aminoquinone **320** and trifluoroperacetic or paraperiodic acid or more concentrated solutions of peracetic acid[221,222] (Scheme 66).

If the amino function is protected in the form of a tosylate **326**, however, the α-tosyl-*Z*,*Z*-muconic acid **327** can be isolated using peracetic acid, and can be converted into the *E*,*E*-derivative by means of iodine and light[124] (Scheme 67).

5. Conclusion

In conclusion, methods that mediate benzene oxidation supplement other dearomatisation procedures and have proven extremely valuable to the synthetic chemist. It is the expectation of the reviewers that this trend will continue.

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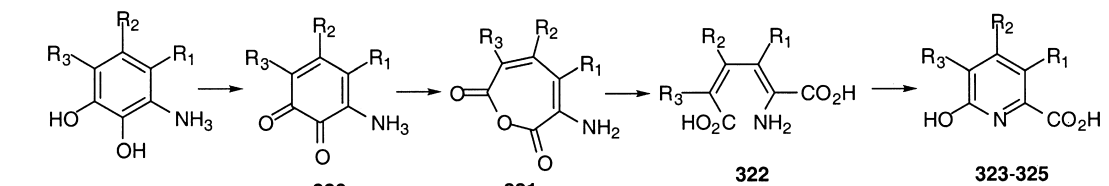

Scheme 66.

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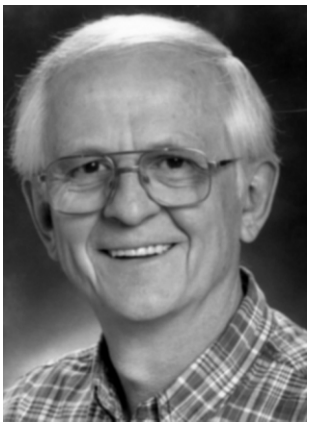

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