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# Recent synthetic developments in the nitro to carbonyl conversion (Nef reaction)

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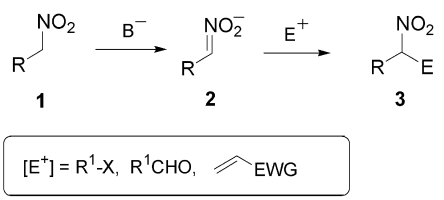
## 1. Introduction

Interconversion of functional groups represents an important aspect in every process leading to the synthesis of structurally-defined compounds. Indeed, many activating groups that promote the formation of carbon–carbon bonds often need to be replaced by other functional entities once they have assisted the main synthetic process. The availability of a consistent number of such transformations for a particular functional group largely contributes to the success and development of the related chemistry. The importance of nitroalkanes **1** in synthesis is mainly due to their easy conversion into the corresponding nitronate anions **2** because of the high electron-withdrawing power of the nitro group that provides an outstanding enhancement of the hydrogen acidity at the α-position (cf. $pk_a$ $MeNO_2$=10).[1–5] Nitronate salts can therefore act as carbon nucleophiles with a range of electrophiles including haloalkanes,[6] aldehydes[7,8] and Michael acceptors,[9] leading to carbon–carbon bond formation (Scheme 1).




**Scheme 1.** Nitroalkanes as nucleophiles.

*Keywords*: Nitro compounds; Carbonyl group; Nef reaction.

*Abbreviations:* BINAP, 2,2′-bis(diphenyphoshino)-1,1′-binaphthyl; BINOL, 1,1′-binaphthalene-2,2′-diol; Bn, benzyl; Boc, *t*-butoxycarbonyl; BY, Baker's yeast; CAN, ceric ammonium nitrate; Cbz, benzyloxycarbonyl; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, dicyclohexylcarbodiimide; DHP, dihydropyran; DIBALH, diisobutylaluminium hydride; DMD, dimethyldioxirane; DMAP, 4-*N*,*N*-dimethylaminopyridine; DMF, dimethylformamide; DMI, 1,3-dimethyl-2-imidazolidinone; DMSO, dimethylsulphoxide; DPPA, diphenylphosphoryl azide; IBX, 1-hydroxy-1,2-benzodioxol-3(1*H*)-one-1-oxide; LiHMDS, lithium 1,1,1,3,3,3-hexamethyldisilazide; MCPBA, *m*-chloroperoxybenzoic acid; MOM, methoxymethyl; Ms, methanesulphonyl; $Ni(acac)_2$, nickel bis(acetylacetonate); NMO, *N*-methylmorpholine-*N*-oxide; $Pd_2(dba)_3$, tris(dibenzylideneacetone)-dipalladium; Phth, phthalimidoyl; PMB, *p*-methoxybenzyl; PPTS, pyridinium *p*-toluenesulphonate; Py, pyridyl; SET, single electron transfer; TBDPS, *t*-butyldiphenylsilyl; TBS, *t*-butyldimethylsilyl; Tf, trifluoromethanesulphonyl; TFAA, trifluoroacetic anhydride; THF, tetrahydrofuran; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; THP, tetrahydropyranyl; TMS, trimethylsilyl; TPAP, tetrapropylammonium perruthenate; Ts, *p*-toluenesulphonyl; *p*TSA, *p*-toluenesulphonic acid; TMG, tetramethylguanidine; Tol, *p*-methylphenyl; Tx, 2,3-dimethyl-2-butyl (thexyl).

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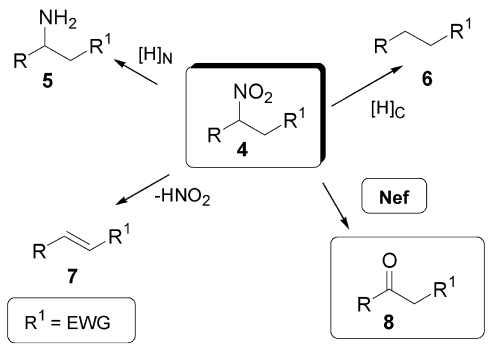



**Scheme 2.** General transformations of the nitro group.

Once these adducts have been formed, the nitro group can be retained in the molecular framework if this is useful for a further nucleophilic addition or it can be transformed into other functionalities following a defined synthetic strategy (Scheme 2). Reduction of the nitro group in compound **4** allows the preparation of a primary amine **5**, in which a simple modification of the oxidation state of the nitrogen atom is carried out. Alternatively, the nitro group can be removed from the molecule by replacing it with hydrogen giving the corresponding denitrated product **6**[10,11] or by elimination as nitrous acid, introducing a double bond in the molecular structure **7**.[12] A further option consists of the conversion of the nitro group into a carbonyl group **8**.[13] This process is probably the most exploited transformation of the nitro group, since it definitively reverses the polarity of the neighbouring carbon atom from nucleophilic to electrophilic.

The synthetic opportunity offered by this conversion has been focusing the attention on the chemistry of aliphatic nitro compounds since its discovery by Nef in 1894.[14] As a matter of fact, the transformation of sugar nitromethyl groups into aldehydes represents an alternative procedure for the chain elongation of carbohydrates, known for at least half a century as the Sowden protocol.[15] The aim of this review is to collect the new procedures which have appeared in the last decade after the comprehensive report by Pinnick in 1990.[16] In addition, several significant applications of this transformation to the synthesis of pivotal building blocks and important biologically active compounds will be discussed.

## 2. General aspects of the Nef reaction

The original procedure for the nitro to carbonyl transformation, as described by Nef, was essentially the hydrolysis in strongly acidic conditions of a nitronate salt **9** produced by basic treatment of a nitroalkane (Scheme 3).

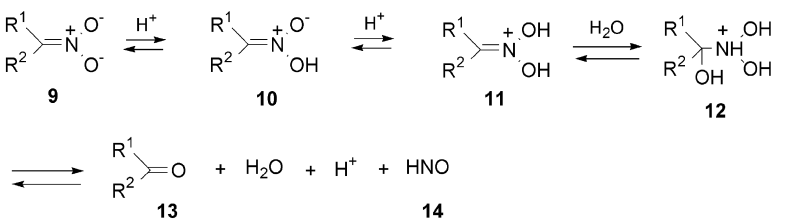
Hydrolysis occurs on a protonated form **11** of the corresponding nitronic acid **10**, giving as intermediate **12** that, by loss of water and hyponitrous acid **14**, gives the carbonyl derivative **13**. The product distribution in this reaction is strongly affected by the acidity level of the system. At pH>1, oximes as well as other hydroxynitroso compounds can be formed in appreciable amounts. For this reason, a rapid acidification of the nitronate salt is required and it is very often operationally desirable to add the nitronate salt to the acid solution. The harsh conditions in which this conversion is usually carried out (pH<1) have spurred the development of alternative methods that can be performed in oxidative, reductive, as well as almost neutral, conditions. It is interesting to note that a common factor in all of the oxidative procedures is the formation of the corresponding nitronate anion as the reactive species; the subsequent cleavage occurs on the carbon–nitrogen double bond to give the carbonyl derivative. Conversely, reductive methods can be carried out both on the nitronate anion or directly on the nitroalkane, even in acidic conditions. An important aspect of this transformation concerns the nature of the nitroalkane used as the substrate. Indeed, secondary nitro compounds are conveniently transformed into ketones, but primary nitro derivatives can be converted into aldehydes or carboxylic acids, depending on the reaction conditions. Particular care must therefore be taken in this reaction, especially when oxidative procedures are chosen to transform primary nitroalkanes into aldehydes. Nitroalkenes that are powerful Michael acceptors can also be used as substrates for the Nef reaction.[17–22] In addition, the conjugate addition of nucleophilic reagents to nitroolefins provides the formation of a nitronate anion as an intermediate that can usually be transformed by a tandem process into the corresponding carbonyl derivative.

## 3. Recent modifications of the Nef reaction

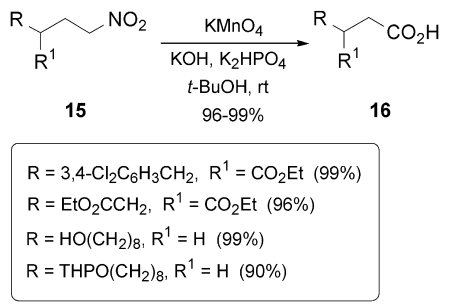
### 3.1. Oxidative methods

As previously stated, cleavage of the carbon–nitrogen double bond is the key step in almost all of the oxidative methods that are currently used for the Nef reaction. $KMnO_4$ is certainly the most widely used oxidant for this purpose and, in controlled conditions, it is able to convert primary nitro compounds into aldehydes.[23] Buffered permanganate solutions (pH=11) can oxidise primary nitroalkanes such as **15** into alkanoic acids **16** without affecting other functions such as esters, amides, primary alcohols and acetals (Scheme 4).[24]

Dimethyldioxirane (DMD) is a strong oxidising agent readily prepared by the reaction of Oxone® with acetone

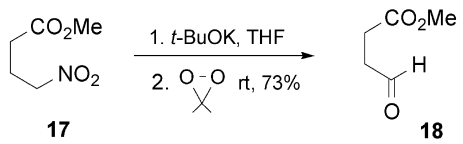



**Scheme 3.** Mechanism for the original Nef reaction.



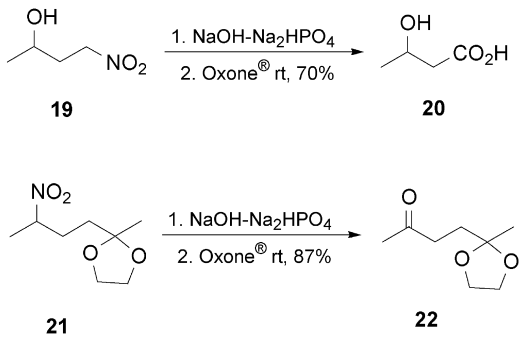

**Scheme 4.** Permanganate oxidation of primary nitroalkanes to carboxylic acids.

and, among various applications it has been used for the regeneration of the carbonyl group from acetals, hydrazones and other derivatives. DMD attacks nitronate anions obtained from nitro compounds such as **17**, giving the corresponding carbonyl derivative **18** in good yields (Scheme 5).[25]




**Scheme 5.** Nef reaction using dimethyldioxirane.

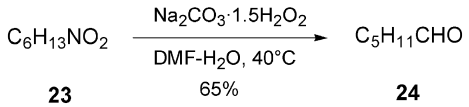
Oxone®, from which DMD derives, is also able to convert nitroalkanes into carbonyl derivatives, but shows less selectivity since primary nitro compounds such as **19** are converted into carboxylic acids **20**. Common protecting groups such as acetals, TBS and acetates are, however, not affected by these conditions as demonstrated for the conversion of nitro compound **21** into ketone **22** (Scheme 6).[26]




**Scheme 6.** Oxidations with Oxone®.

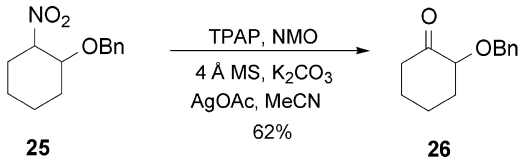
Another peroxide-based system, bis(trimethylsilyl)-peroxide, has also been used for this transformation, but it is applicable only to secondary and benzylic nitro compounds.[27]

Sodium percarbonate ($Na_2CO_3{\cdot}1.5H_2O_2$) can be considered as a stable source of hydrogen peroxide and can be used for the cleavage of carbon–nitrogen double bonds of hydrazones and nitronate salts. This reagent displays a better selectivity than Oxone®, since it converts 1-nitrohexane **23** to hexanal **24** without any overoxidation (Scheme 7).[28]



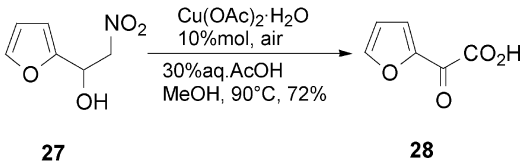

**Scheme 7.** Reaction of 1-nitrohexane with sodium percarbonate.

Secondary α-alkoxy nitro derivatives such as **25** can be efficiently converted into α-alkoxy ketones **26** using catalytic amounts of tetrapropylammonium perruthenate (TPAP) with *N*-methylmorpholine-*N*-oxide (NMO). The presence of 4 Å molecular sieves and silver salts is mandatory for the efficiency of the procedure (Scheme 8).[29]




**Scheme 8.** Nef reaction on nitrocycloalkanones with TPAP.

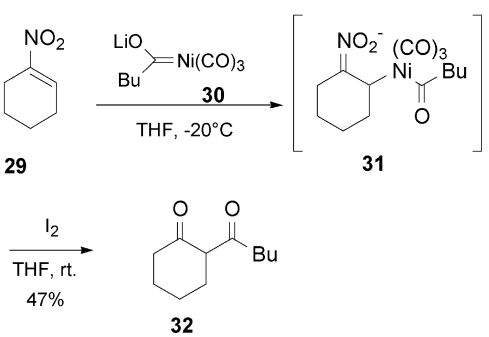
Molecular oxygen is an appealing system to perform oxidations, since it is a cheap, readily available and environmental friendly reagent. Some nitro compounds such as **27** can be transformed into the corresponding carbonyl derivatives **28** when exposed to air in the presence of copper salts (Scheme 9).[30]




**Scheme 9.** Reaction with $O_2$ catalyzed by Cu(II) salts.

Metallic copper can also be used for this purpose, but with considerably less efficiency.[31]

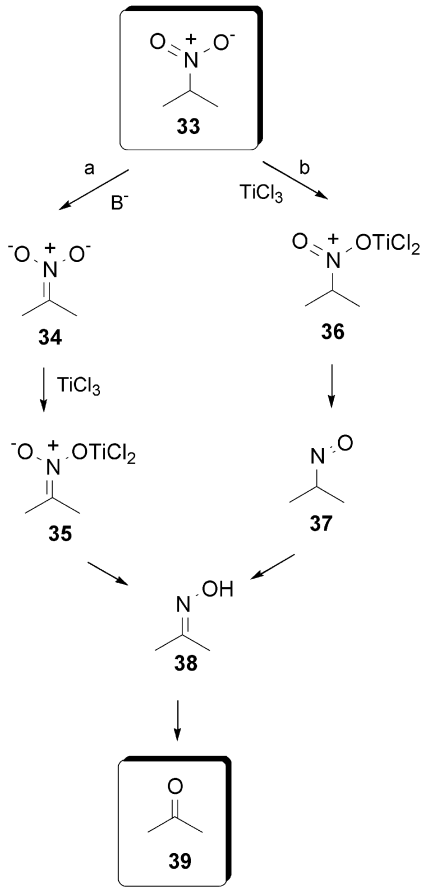
The reaction of nickel acylate complex **30** with nitroalkenes such as **29** gives the corresponding addition products **31** that, by treatment with iodine, affords the 1,3-dicarbonyl derivatives **32**. Iodine provides cleavage of the nickel adduct and of the nitronate anion in a tandem process (Scheme 10).[32]




**Scheme 10.** Tandem cleavage of the Ni-complex and nitronate salt **31** by iodine.

### 3.2. Reductive methods

A limited number of reducing agents are currently available for the nitro to carbonyl transformation The most important procedure, known as the McMurry method, employs $TiCl_3$ to reduce nitronate salts **34** (path a) or nitro compounds **33** (path b) into aldehydes or ketones (Scheme 11).[33] A likely intermediate in this process is the oxime **38** that can be obtained by reduction of the titanium nitronate **35** (path a) or the iminium ion **36** that produces the nitroso derivative **37** which tautomerise to the oxime **38** (path b). The oxime **38** is further reduced to the imino derivative and then cleaved to the parent carbonyl compound **39**.

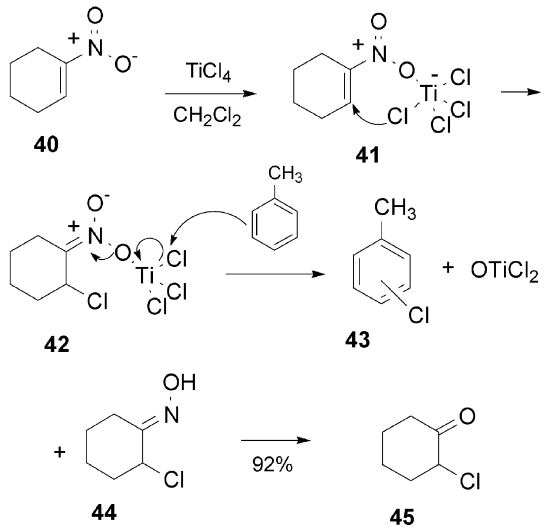



**Scheme 11.** Mechanism of the Nef reaction using $TiCl_3$.

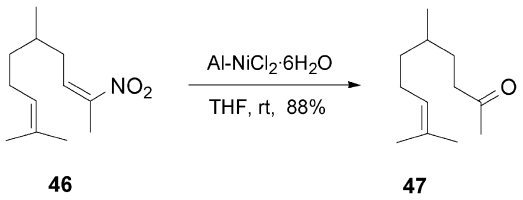
Nitroalkenes such as **40**, can be converted into α-chloroketone **45** using $TiCl_3$ or $TiCl_4$ in the presence of toluene.[34] Titanium tetrachloride attacks the oxygen atom of the nitro group and acts as a chlorinating agent. The intermediate **42** formed by the adduct **41**, is able to chlorinate toluene with a concomitant reduction of the nitro group to the parent oxime **44** that is further reduced to the carbonyl compound **45** (Scheme 12).[35]

Aluminium powder in the presence of $NiCl_2{\cdot}6H_2O$ transforms nitroolefins into carbonyl compounds.[36] Reduction of the nitroalkene **46** to the nitronate probably proceeds through a SET mechanism and is followed by the usual hydrolysis to the carbonyl derivative **47** (Scheme 13).

A similar procedure involves the utilisation of zinc dust–



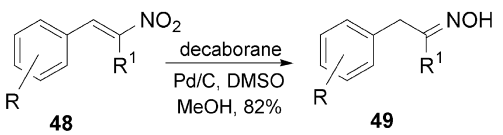

**Scheme 12.** 2-Chloroketones from nitroalkenes and $TiCl_4$ in the presence of toluene.




**Scheme 13.** Selective conversion of nitroalkenes into carbonyls by metals.

trifluoroacetic acid[37] or magnesium powder–$CdCl_2$–water in THF.[38] The latter method can be used to transform 6-nitro-$\Delta^5$-steroids into 6-ketosteroids in good yield.

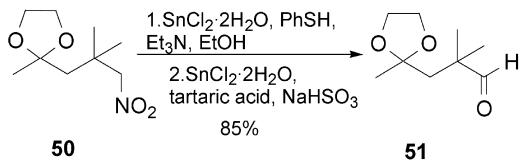
A chemoselective conversion of nitroalkenes **48** to oximes **49** in the presence of aromatic nitro groups can be carried out using decaborane–Pd/C–DMSO in methanol.[39] The role of the DMSO, which is added in an excess of 5 equiv., is not clear, but without this co-reagent only a sluggish conversion occurs (Scheme 14).




R = 3-$NO_2$, $R^1$ = H, (82%)
R = 4-Br, $R^1$ = H, (73%)
R = 4-MeO, $R^1$ = H, (72%)
R = 3,4-$OCH_2O$, $R^1$ = H, (77%)
R = 4-Cl, $R^1$ = Me, (93%)

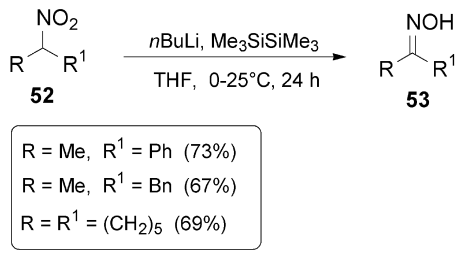
**Scheme 14.** Synthesis of oximes from nitroalkenes.

The reduction of primary nitroalkanes such as **50** to oximes can be carried out by $SnCl_2{\cdot}2H_2O$ in the presence of thiophenol and triethylamine. Adding a further equivalent of $SnCl_2{\cdot}2H_2O$ and tartaric acid–$NaHSO_3$ to the reaction mixture ensures the reduction of the oxime into the imine, which is rapidly hydrolysed to the aldehyde **51** in good yield (Scheme 15).[40,41]



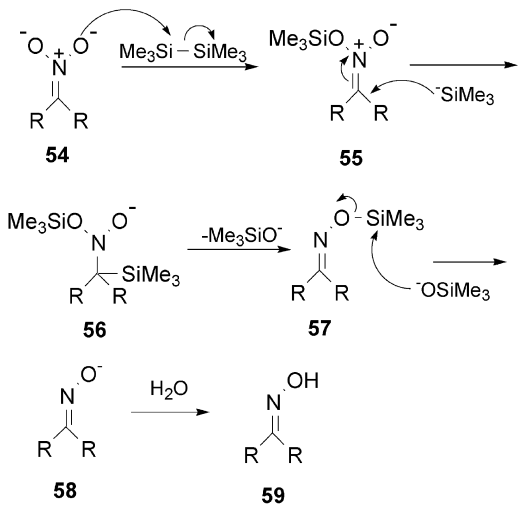

**Scheme 15.** Nef reaction using tin(II) chloride.

Various metal nitronates of secondary nitroalkanes **52** can be converted into the corresponding oximes **53** by treatment with hexamethyldisilane (Scheme 16).[42]




**Scheme 16.** Reaction with hexamethyldisilane.

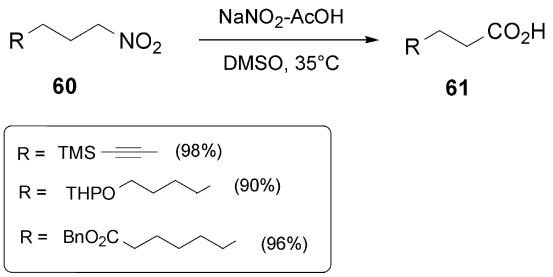
According to the proposed mechanism, hexamethyldisilane acts as a 'counterattack reagent', towards nitronate anion **54** giving a silyl nitronate **55** as the first intermediate. The trimethylsilyl anion attacks the silyl nitronate **55** giving the adduct **56**, that eliminates $Me_3SiO^-$ providing the *O*-silylated oxime **57**. The trimethylsilyloxy anion cleaves derivative **57** to the oxime anion **58**, which upon hydrolysis leads to the formation of the final oxime **59** in a process that closely resembles the Peterson olefination (Scheme 17).




**Scheme 17.** Mechanism of the Nef reaction using hexamethyldisilane as a counterattack reagent.

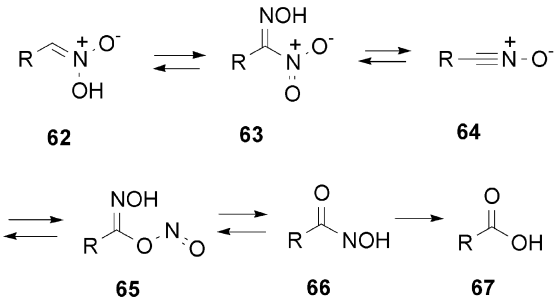
### 3.3. Other methods

During the course of a multistep synthesis, the number of functional groups present in the molecular framework grows quite rapidly and this dictates the utilisation of ever more selective and mild reagents to carry out chemical transformations. A combination of $NaNO_2$ and acetic acid in DMSO at 35 °C converts primary nitroalkanes **60** into carboxylic acids **61**.[43] The mildness of the reaction conditions makes it possible for some acid- and base-sensitive functions to survive (Scheme 18).



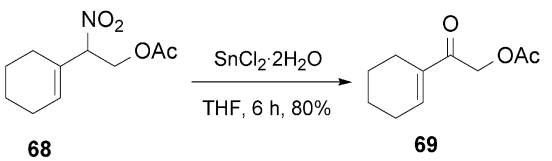

**Scheme 18.** Reaction of primary nitroalkanes with $NaNO_2$.

In nitrosating conditions the nitronic acid **62** is converted into a nitrolic acid **63** that is in equilibrium with a nitrile oxide **64** (Scheme 19). This reactive intermediate is further nitrosated to derivative **65** and leads to hydroxamic acid **66** that is hydrolysed to the carboxylic acid **67**. It is worth noting that the existence of some of these intermediates has been proved by their isolation (nitrolic acid) or trapping as the cycloadducts (nitrile oxide).




**Scheme 19.** Mechanism for the Nef reaction using $NaNO_2$.

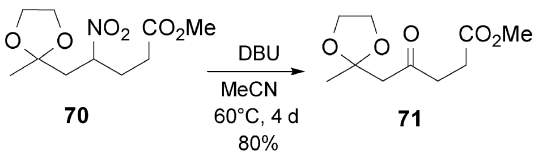
The same reagent can be used to prepare 1-oximino-1-arylacetones starting from 2-nitro-1-arylpropanes.[44] Although α,β-unsaturated nitro compounds are the most popular form of such reactive substrates, β,γ-nitroalkenes can be also prepared, especially when the double bond is inserted into a cyclic structure. These derivatives such as **68** can be transformed into α,β-unsaturated ketones using hydrolytic conditions by activation with $SnCl_2{\cdot}2H_2O$. A stannylnitronate is believed to be the 'activated' intermediate that promotes a subsequent hydrolysis to the final product **69** (Scheme 20).[45]




**Scheme 20.** $SnCl_2{\cdot}2H_2O$-promoted hydrolysis of β,γ-unsaturated nitroalkenes.

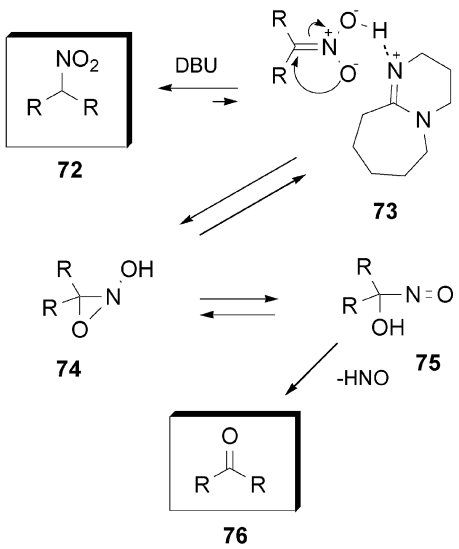
Direct cleavage of the nitronate anion under basic conditions has been only observed on dry activated silica gel and in reactions that involve neighbouring group participation.[46] Some amidine bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) are, however, able

to convert secondary nitroalkanes such as **70** into the corresponding ketones **71** when heated at 60 °C in acetonitrile for few days. The procedure shows a consistent degree of chemoselectivity, since primary nitroalkanes are unaffected by these reaction conditions (Scheme 21).[47]




**Scheme 21.** Nef reaction in basic conditions with DBU.

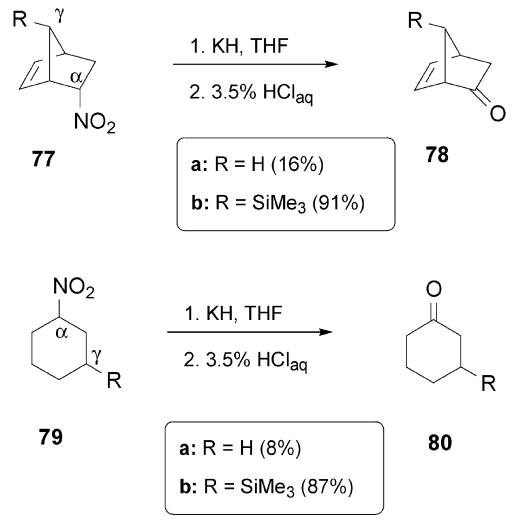
A possible mechanism for this transformation would involve a complex **73**, obtained by reaction of secondary nitroalkane **72** with DBU, that in the absence of water, gives the oxaziridine **74**, and then the hydroxynitroso derivative **75**. The latter intermediate affords the final ketone **76** by elimination of hyponitrous acid (Scheme 22).




**Scheme 22.** Mechanism for the Nef conversion of a secondary nitroalkane with DBU/MeCN.

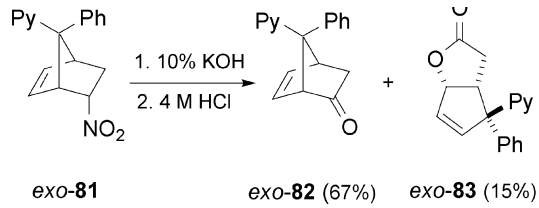
Some nitroalkanes, in spite of a large number of synthetic methods attempting to carry out the Nef reaction, seem to be quite inert towards the nitro to carbonyl conversion. Among the other electronic properties displayed by silicon, the γ-effect has been revealed to be of fundamental importance in order to promote the conversion of some cyclic nitro derivatives into the corresponding ketones (Scheme 23).[48] Under the usual hydrolytic conditions, a negligible amount of the carbonyl derivative **78** is formed when silicon is not present at the γ-position in nitro compound **77**. This behaviour exerted by silicon has been shown to be of general utilisation in the chemistry of nitro compounds as demonstrated for the conversion of **79** into cyclohexanone **80**.[49]

It has recently been observed, however, that the 7-diaryl-5-nitronorbornene *exo*-**81** actually does give as the main product the ketone *exo*-**82** arising from a Nef reaction, along




**Scheme 23.** Nef reaction promoted by the silicon γ-effect.

with the lactone *exo*-**83** and some unreacted nitro derivative (13%) (Scheme 24).[50]



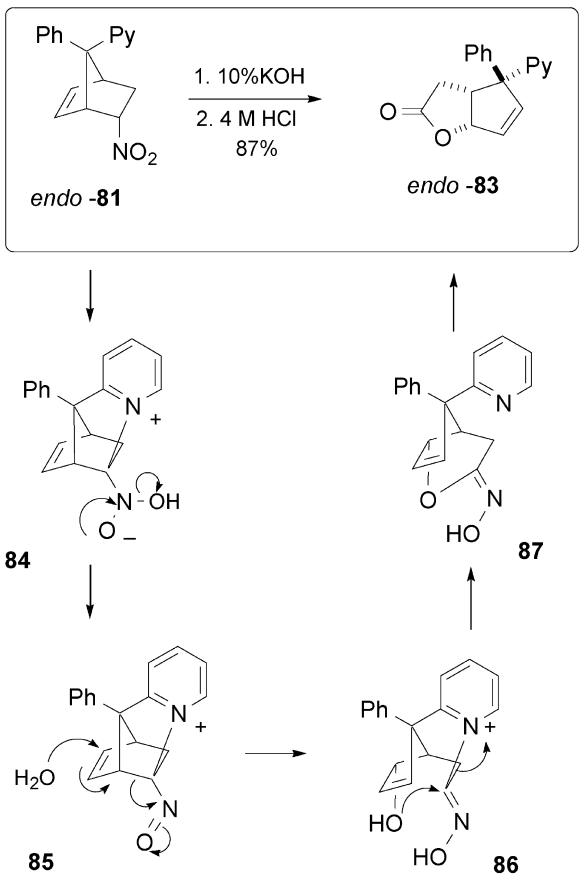

**Scheme 24.** Nef reaction on a 7-diaryl-5-nitronorbornene.

Interestingly, the reaction of *endo*-**81** under the same conditions affords exclusively *endo*-**83** in 87% yield (Scheme 25). It is conceivable that the presence of the pyridine nitrogen completely suppresses the Nef reaction through coordination with the nitronic acid carbon in the intermediate **84**, leading to the nitroso derivative **85**. Addition of water to the double bond causes a ring cleavage to the oxime **86** that suffers an intramolecular attack by the hydroxy group to give the bicyclic derivative **87**. Further hydrolysis of the oximino group leads to the final bicyclic product *endo*-**83**. This mechanistic hypothesis is also supported by the observation that, with the corresponding norbornanes, lacking the double bond in the bicyclic structure, both the *exo* and *endo* stereoisomers give the norbornanone derivatives in 78 and 53% yields, respectively.

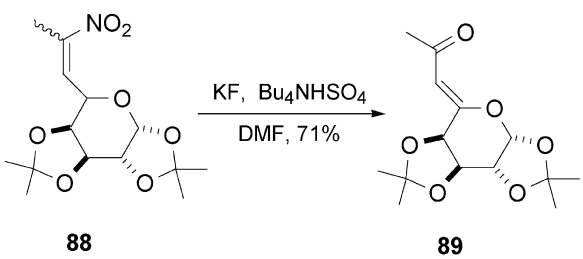
Some sugar nitroolefins such as **88** are converted into the corresponding enol ethers **89** by treatment with a mixture of KF and $Bu_4NHSO_4$ in DMF at room temperature.[51] A vinylogous Nef-type reaction would probably operate, because of the acidity of the allylic proton in γ-alkoxy-nitroalkenes (Scheme 26). The role played by $Bu_4NHSO_4$ could have some similarity with a related method that makes use of anhydrous silica gel.[52]

## 4. Applications of the Nef reaction

The utilisation of nitro compounds for the synthesis of




**Scheme 25.** Mechanism for the rearrangement of *endo*-**81**.

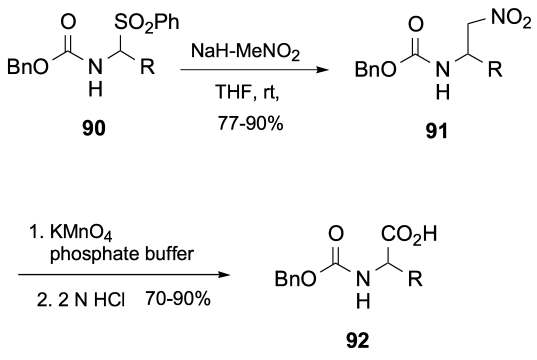



**Scheme 26.** Nef reaction on sugar nitroolefins.

useful building blocks or in multistep procedures devoted to the preparation of complex molecules is a field that is experiencing a rapid growth. In many of these synthetic pathways, the nitro to carbonyl conversion plays a central role, so that the array procedures to carry out the Nef reaction represents a formidable tool for every organic chemist. In this part of the report, the application of the Nef reaction to the preparation of carbonyl derivatives or in multistep syntheses is presented.

### 4.1. Oxidative methods

Since primary nitroalkanes are readily converted into carboxylic acids using the Nef reaction, this procedure has often been involved in the synthesis of α-amino acids. The α-amidoalkyl phenyl sulphones **90** can be considered as precursors of reactive *N*-acylimines and therefore react with the anion of nitromethane to give the corresponding adduct **91** (Scheme 27).[53]

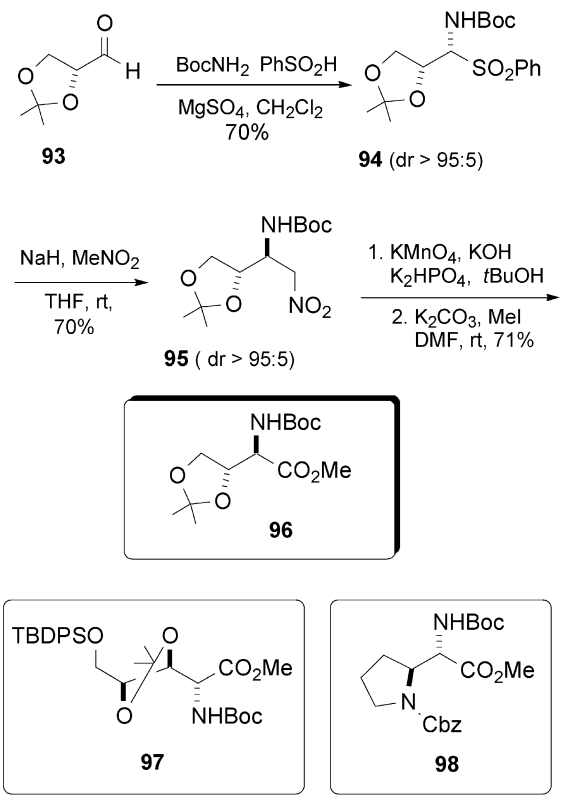



| R | **91** (yield %) | **92** (yield %) |
|---|---|---|
| $PhCH_2CH_2$ | 87 | 90 |
| *c*-$C_6H_{11}$ | 90 | 88 |
| $Cl(CH_2)_4$ | 77 | 85 |
| $C_7H_{14}CH{=}CH(CH_2)_2$ | 85 | 72 |

**Scheme 27.** Synthesis of α-amino acids.

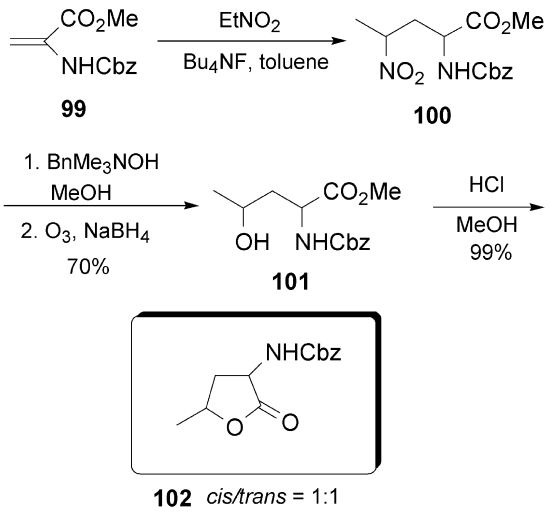
Conversion of the nitro group into carboxylic acids is better realised using $KMnO_4$ in phosphate buffer and leads directly to the *N*-carbobenzoxy α-amino acids **92**. This procedure can be applied to the synthesis of the optically active α-amino acid ester **96** using chiral aldehyde **93**, that can be converted into the α-amidoalkyl phenyl sulphone **94** and then nitro derivative **95** (Scheme 28).[54] The utilisation of other chiral aldehydes allows the preparation of different α-amino acid esters as **97** and **98**.

Michael addition of nitroalkanes to dehydroalanine **99** affords the γ-nitro-α-amino acids such as **100** in racemic




**Scheme 28.** Synthesis of optically active α-amino acids.

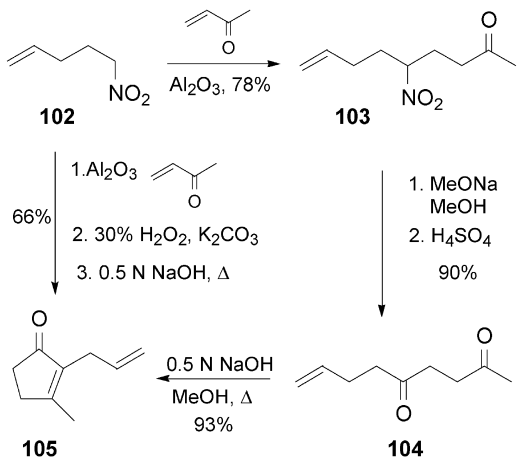
form. These adducts are further elaborated by converting the nitro group into a carbonyl moiety that can be reduced in situ to a diastereomeric pair of γ-hydroxy-α-amino acids **101** in a 1:1 ratio (Scheme 29).[55] The acid-catalysed cyclisation of these hydroxy derivatives gives the 2-amino-lactones **102**.




**Scheme 29.** Synthesis of 2-aminolactones.

A similar strategy can be used for the preparation of paramagnetic pyrrolidine dienes.[56]

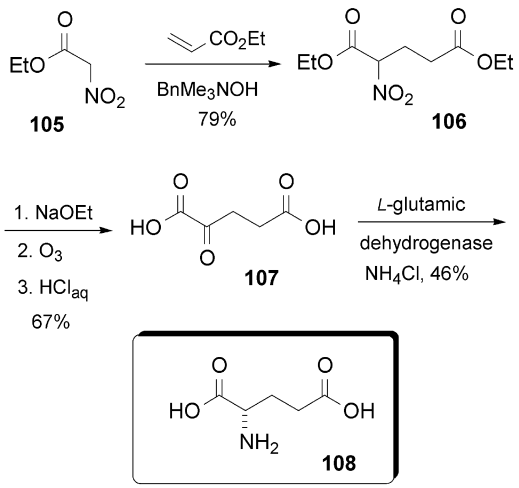
For obvious reasons, it is often advantageous to carry out a synthetic process in a 'one-pot' system, adding the appropriate reagents sequentially to the reaction mixture. Allylrethrone **105** is an important component of an insecticidal pyrethroid and its preparation can be realised in three distinct steps, starting from the nitroalkene **102** and methyl vinyl ketone (Scheme 30).




**Scheme 30.** Synthesis of allylrethrone.

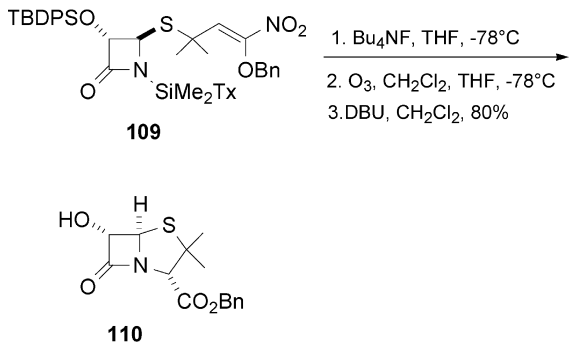
The obtained Michael adduct **103** is converted into the diketone **104** by a hydrolytic Nef reaction and is then cyclised to allylrethrone **105** under basic conditions.[57] Alternatively, the same process can be realised in a one-pot reaction, using hydrogen peroxide to carry out the nitro-to-carbonyl conversion.

Stable-isotope labelled *L*-glutamic acid can be prepared from $^{13}$C-enriched compounds, following a strategy involving the conjugate addition of ethyl nitroacetate **105** to ethyl acrylate.[58] Oxidative Nef conversion of the 2-nitroglutarate **106** to diethyl 2-oxoglutarate and ester hydrolysis gives 2-oxoglutaric acid **107**. This diacid is transformed into L-glutamic acid **108** using the commercially available enzyme glutamic dehydrogenase, in the presence of ammonium ions (Scheme 31).



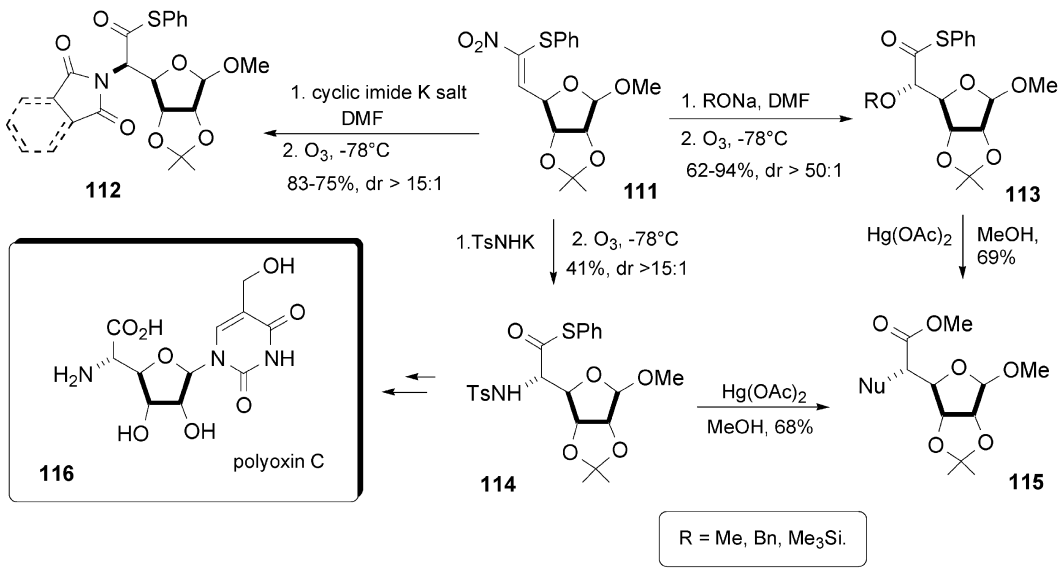

**Scheme 31.** Synthesis of isotope-labelled L-glutamic acid.

A key step in the stereocontrolled synthesis of a penicillanic acid derivative consists of the intramolecular conjugate addition of a 2-azetidinone nitrogen to a nitroalkene framework in compound **109**.[59] The intermediate nitronate anion obtained is oxidised with ozone to afford a mixture of the *endo* and *exo* epimers that can be completely converted into the more stable *exo* isomer **110** using DBU (Scheme 32).

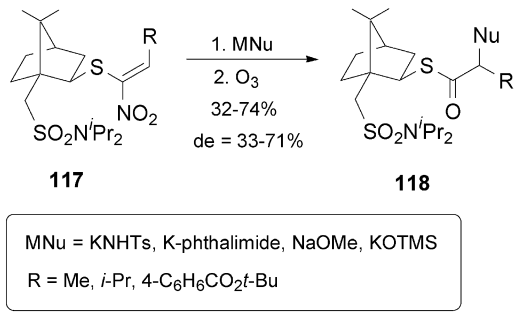



**Scheme 32.** Synthesis of a penicillanic acid derivative.

The nitroalkene **111** obtained from D-ribose reacts with different nucleophiles with appreciable stereoselectivity.[60] The potassium salts of cyclic imides give a stereochemical outcome which is opposite with respect to sodium alkoxides and TsNHK.[61] Cleavage of the obtained nitronate salts with ozone gives the thiol esters **112**–**114** that can be finally converted into a methyl esters such as **115** using mercuric acetate in methanol (Scheme 33). This strategy can be successfully used for the total synthesis of the nucleoside antibiotic polyoxin C **116**.[62]




**Scheme 33.** Synthesis of optically active α-substituted methyl esters.



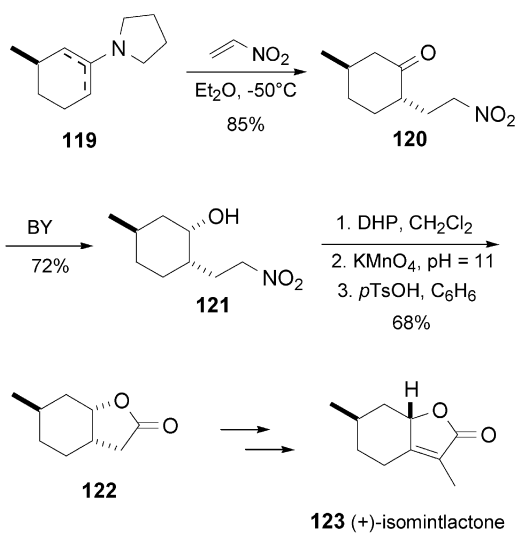

**Scheme 34.** Synthesis of α-substituted thiol acids.

Optically active nitroalkenes **117** bearing a chiral auxiliary on sulphur react in a similar fashion, but adducts **118** are only obtained with a modest level of diastereoselectivity (Scheme 34).[63]

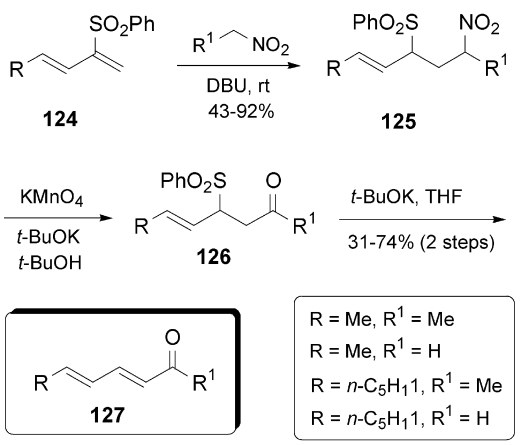
In a related procedure, the addition of diethyl phosphite in the presence of DBU and TMSCl gives trimethylsilyl-α-phosphoryl nitronates that undergo to a Nef reaction using *m*-chloroperoxybenzoic acid. The resulting 1-aryl-2-oxo-alkylphosphonates are useful reagents in the Wadsworth–Horner–Emmons condensations.[64]

Michael addition of the chiral cyclic enamine **119** to nitroethylene is involved in the initial step of the synthesis of optically active (+)-isomintlactone **123**, a constituent of the American peppermint oil.[65] Since the two regioisomers of the enamine **119** are in equilibrium, a single nitro ketone **120** is obtained by the reaction of the more reactive isomer. The compound **120** is reduced to the nitro alcohol **121** using Baker's yeast (BY) and the hydroxy group is protected before the oxidative Nef conversion. Upon removal of the protective group, a spontaneous lactonisation occurs, giving the γ-lactone **122** that can be converted into (+)-isomintlactone **123** in few steps (Scheme 35).

Among the various Michael acceptors, the 2-phenylsulphonyl-1,3-dienes **124** react with nitroalkanes in the presence of DBU to give the nitrosulphones **125**.[66] The



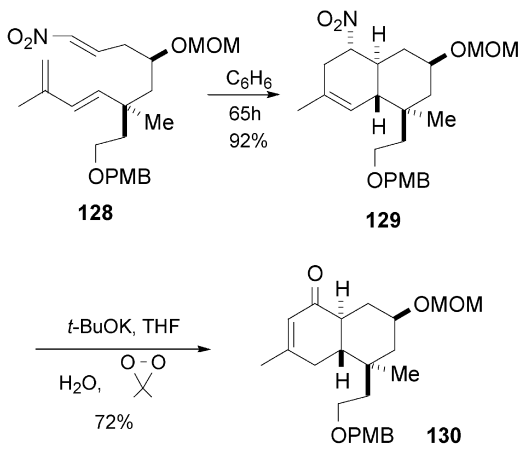

**Scheme 35.** Synthesis of (+)-isomintlactone.




**Scheme 36.** Synthesis of conjugated dienones.

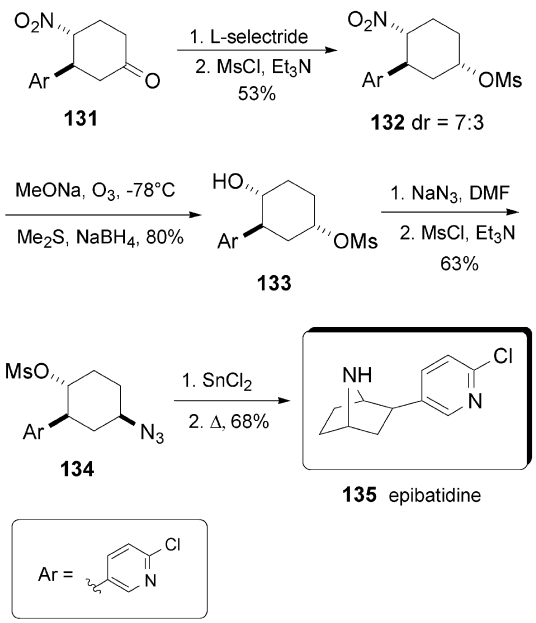
nitro-to-carbonyl conversion on these compounds leads to the keto sulphones **126** that, in basic conditions, eliminate benzenesulphinic acid to afford the conjugated dienones **127** (Scheme 36).

Nitroalkenes are powerful dienophiles in Diels–Alder reactions and react both inter- and intramolecularly to give cycloadducts. For the construction of the AB ring system of the marine alkaloid, norzoanthamine, the nitroalkene **128** is cyclised with outstanding diastereoselectivity.[67] Nef reaction of the obtained cycloadduct **129** with dimethyldioxirane occurs with concomitant double bond migration to give the α,β-unsaturated ketone **130** (Scheme 37).



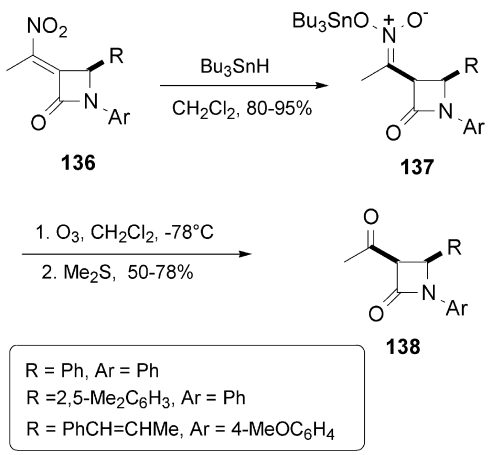

**Scheme 37.** Synthesis of the AB ring system of norzoanthamine.

The nitrocycloalkanone **131**, obtained from a Diels–Alder reaction, represents an important intermediate towards the total synthesis of racemic alkaloid, epibatidine **135**.[68] A noteworthy feature of the Nef reaction is that the ozonisation of the nitro derivative **132**, followed by treatment with $NaBH_4$, occurs with complete retention of configuration, giving the alcohol **133** in good yield. Further manipulation of this intermediate via **134**, ensures an efficient synthesis of epibatidine **135** (Scheme 38).



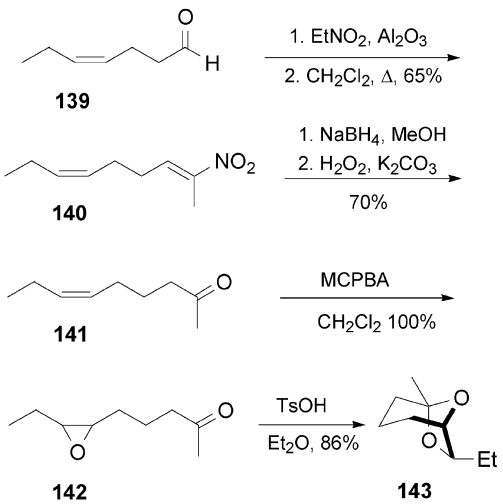

**Scheme 38.** Synthesis of epibaditine.

The reduction of nitroalkenes such as **136** with $Bu_3SnH$ occurs in neutral conditions, giving the corresponding stannylnitronates **137**.[69] These nitronates can be oxidised to the parent carbonyl derivatives using ozone at low temperatures. This procedure is particularly effective in the synthesis of β-lactam building blocks **138** (Scheme 39).




**Scheme 39.** Synthesis of β-lactam building blocks.

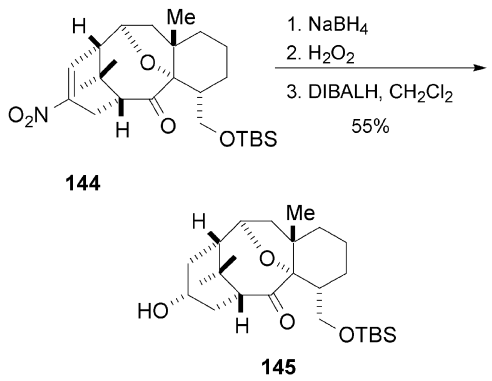
Sodium borohydride reduces a nitroalkene to the corresponding nitronate anion that can be oxidised by hydrogen peroxide to the corresponding carbonyl derivative. This procedure is particularly effective when other unsaturations are present in the molecule and is illustrated for the synthesis of *exo*-brevicomin **143**, the principal pheromone of *Dentroctonus brevicomin*.[70] (*Z*)-4-Heptenal **139** reacts with nitroethane in the presence of $Al_2O_3$ to give a nitro alcohol that is dehydrated to the corresponding nitroalkene **140** simply by adding dichloromethane and heating at reflux. The nitroalkene **140** is transformed into the unsaturated ketone **141** that, after epoxidation to **142** is converted into *exo*-brevicomin **143** (Scheme 40).




**Scheme 40.** Synthesis of *exo*-brevicomin.

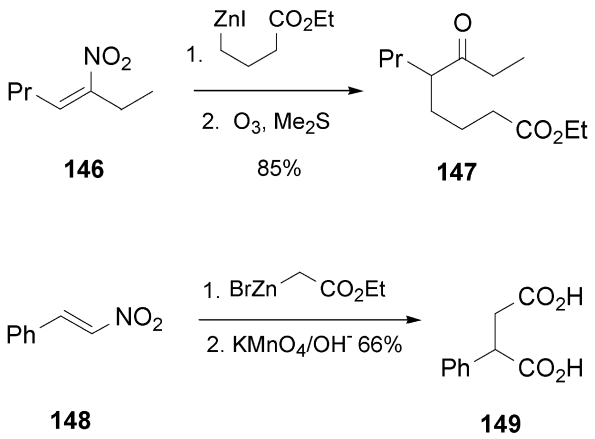
This strategy has also been used for the synthesis of the A-ring of taxane diterpene **145** starting from nitroalkene **144** (Scheme 41).[71,72]

Organometallic addition to nitroalkenes allows the




**Scheme 41.** Synthesis of the A-ring of taxane diterpenes.

formation of new carbon–carbon bonds and, at the same time, leads to the synthesis of nitronate anions that can be directly converted into carbonyl groups in one-pot reactions. Organozinc reagents add efficiently to nitroolefins **146**, **148** and the obtained nitronates are then oxidised to the parent carbonyl derivatives **147**, **149** (Scheme 42).[73,74]

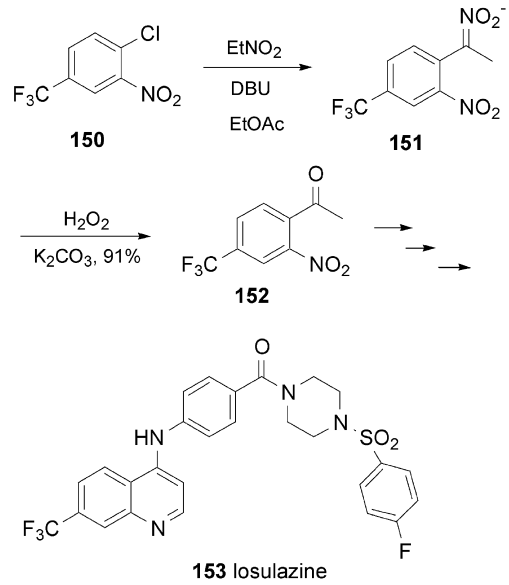



**Scheme 42.** Coupling of nitroalkenes with organozinc reagents and tandem Nef reaction.

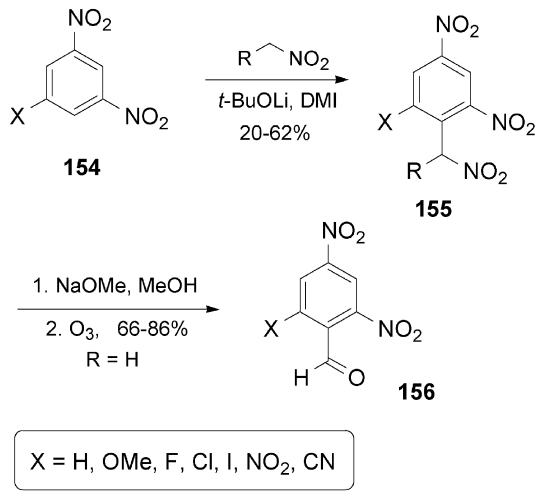
Strongly electron-withdrawing substituents on aromatic derivatives such as **150** greatly facilitate nucleophilic substitutions, so that nitro compounds can add to the ring in the presence of a base such as DBU. The obtained substitution product **151** can undergo a Nef reaction, giving a keto derivative **152**, a key intermediate for the synthesis of the antihypertensive agent, losulazine **153**.[75] The overall procedure can be considered as 'nucleophilic acylation', a synthetic transformation particularly effective on substrates that are not prone to the usual Friedel–Crafts reaction (Scheme 43).

Similarly, primary nitroalkanes react in basic conditions [*t*-BuOLi/1,3-dimethyl-2-imidazolidinone (DMI)] with 1,3-dinitrobenzene and its derivatives **154** to give the corresponding adducts **155**.[76] Various nitromethyl derivatives obtained by this method can be transformed into formyl derivatives **156** by oxidation with ozone (Scheme 44).

The reaction of stabilised carbanions with nitroarenes **157** give rise to the corresponding nitronate anions **158** that, by oxidation, afford the substituted nitroaromatic derivatives.



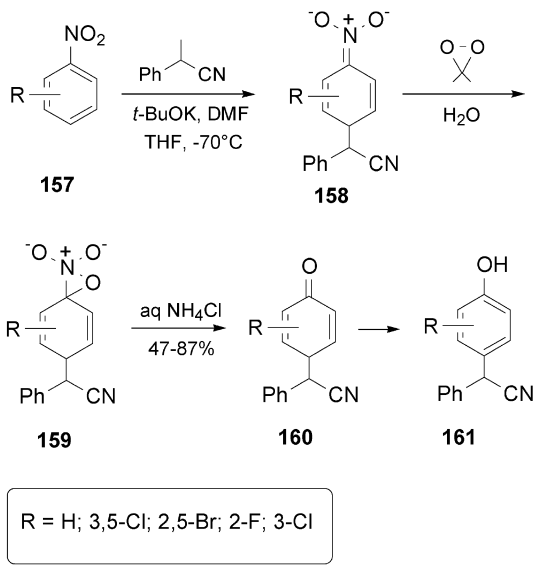

**Scheme 43.** Nuclephilic acylation on electro-poor aromatics.



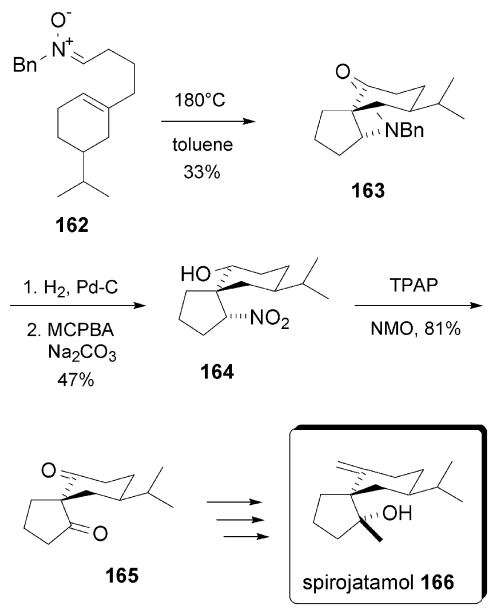

**Scheme 44.** Synthesis of nitrobenzaldehydes.

When dimethyldioxirane is used as an oxidant for this purpose, however, the intermediate anion is transformed into the corresponding phenol **161**.[77,78] The oxidation is likely to proceed through an oxaziridine **159** that is hydrolysed to the cyclohexadienone **160** that readily tautomerise to the more stable phenol **161** (Scheme 45).[79]

The nitro group is usually introduced in complex molecular frameworks by the reaction of simple or functionalised nitroalkanes with aldehydes or α,β-unsaturated derivatives. Occasionally, the nitro group is generated by the oxidation of amino derivatives and is then converted into a carbonyl group. In a synthetic approach to the spirobicyclic sesquiterpene spirojatamol **166**, the nitrone **162** undergoes an intramolecular cycloaddition to give the tricyclic derivative **163**.[80] This intermediate is first reduced to give an amino alcohol and is then oxidised to the nitro alcohol **164**. A Nef reaction on this nitro alcohol using TPAP–NMO affords the diketone **165** that is then converted into spirojatamol **166** in a few steps (Scheme 46).



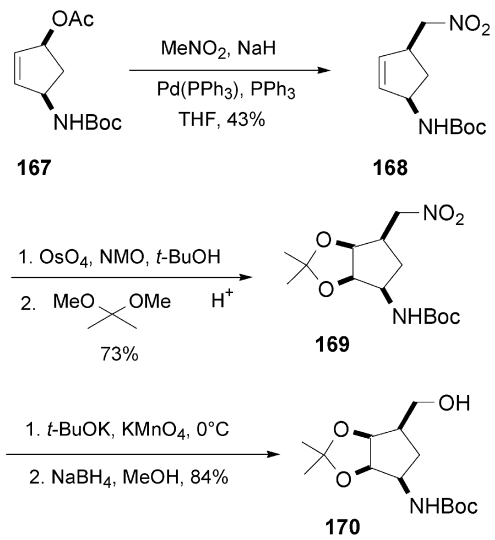

**Scheme 45.** Synthesis of phenols from nitroarenes.




**Scheme 46.** Synthetic route to spirojatamol.

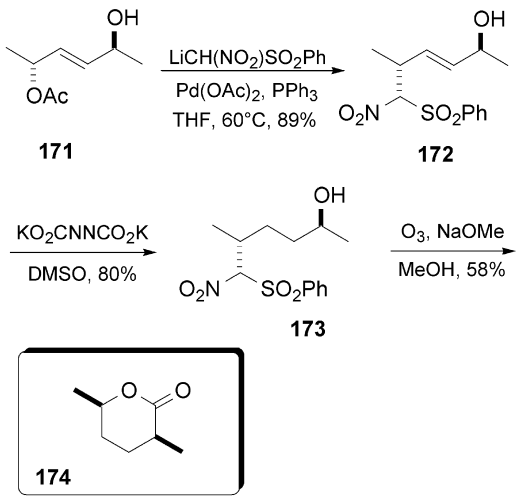
Palladium(0) chemistry represents an alternative method for the introduction of a nitromethyl moiety into a molecule.[81] Allyl acetate **167** reacts with nitromethane in the presence of $Pd(PPh_3)$ to give the corresponding substitution product **168** with retention of the configuration of the acetoxy stereocentre.[82] The nitromethyl group which is introduced acts as a hydroxymethyl synthon, since, after double bond *cis*-dihydroxylation and protection as acetonide **169**, it can be oxidised to the parent aldehyde and then reduced to the alcohol **170** (Scheme 47). The obtained cyclopentyl derivative is a precursor of important carbacyclic nucleosides.[83]

A related procedure can be used for the synthesis of



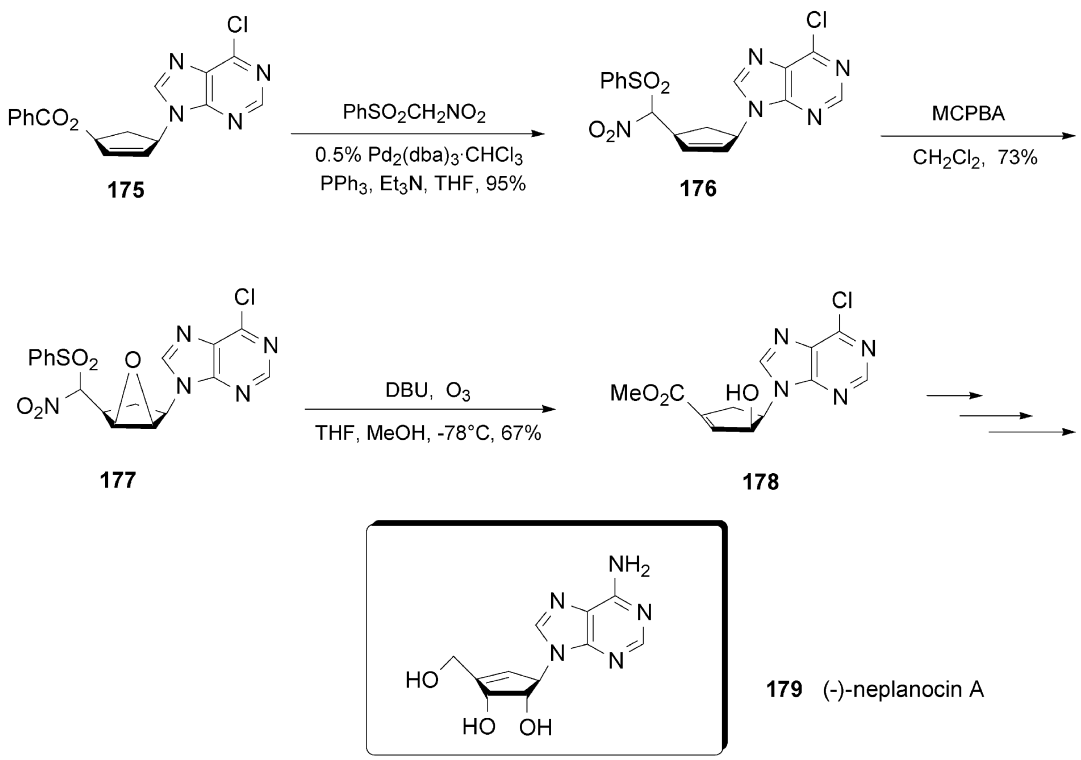

**Scheme 47.** Synthesis of carbacyclic nucleoside precursors.

enantiomerically enriched lactones, starting from optically active monoacetates such as **171**. These compounds react with the lithium anion of (phenylsulphonyl)nitromethane in the presence of $Pd(OAc)_2$ giving the substitution product **172** with high diastereoselectivity.[84] Reduction of the double bond, to give **173**, and Nef reaction affords the *cis*-lactone **174** that is the major component of the pheromone of the Carpenter bee *Xylocopa hirutissima* (Scheme 48).




**Scheme 48.** Synthesis of the enantiomerically pure lactone **174**.

The conversion of a (phenylsulphonyl)nitromethyl group into a carboxylic acid is a key step in many processes directed toward the asymmetric synthesis of important biologically active molecules. (−)-Neplanocin A **179** is a carbanucleoside of natural origin that shows some inhibitory properties towards enzymes and is therefore a potentially useful antitumour and antiviral agent.[85,86] A one-carbon unit is introduced into purine **175** by means of $PhSO_2CH_2NO_2$ in the presence of $Pd_2(dba)_3$ and the resulting adduct **176** is converted into the oxirane **177**. The compound **177** undergoes a Nef reaction using ozone in basic conditions to afford the ester **178** that is a key intermediate for the synthesis of (−)-neplanocin A **179** (Scheme 49).

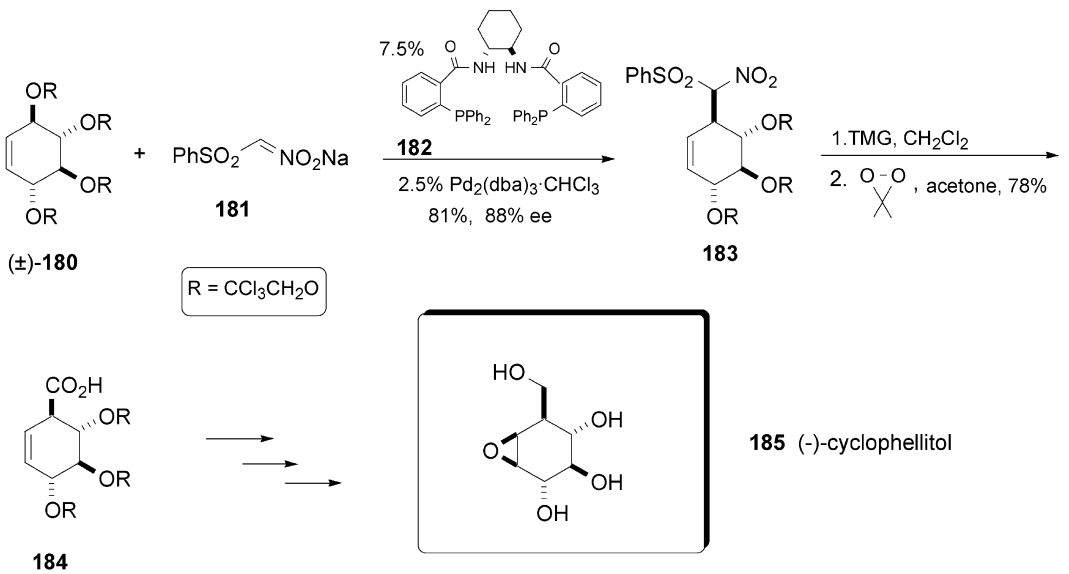



**Scheme 49.** Synthesis of (−)-neplanocin A.

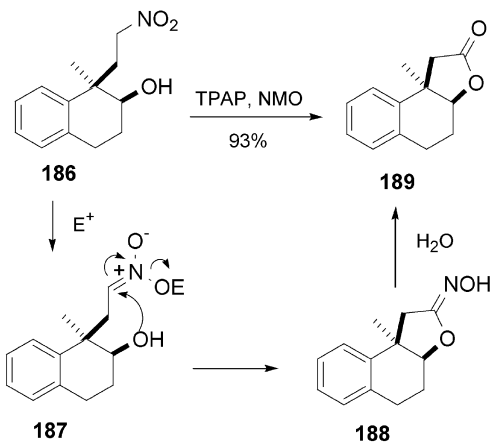
A related strategy can be used for the enantioselective synthesis of other carbanucleosides as (−)-carbovir. The Nef reaction is carried out on a derivative similar to **176** using tetrabutylammonium-oxone buffered with sodium carbonate.[87]

Both enantiomers of the glycosidase inhibitor, cyclophellitol, can be prepared starting from racemic conduriol B **180** using a dynamic kinetic asymmetric transformation.[88] The reaction of **180** with the sodium salt of (phenylsulphonyl)nitromethane **181** in the presence of $Pd_2(dba)_3$ and a chiral ligand **182** affords the corresponding substitution product **183** in satisfactory yield and enantiomeric excess (Scheme 50). The Nef conversion of this derivative is carried out using dimethyldioxirane in basic conditions, leading to the acid **184**, that is transformed into the final product (−)-cyclophellitol **185**, by further synthetic manipulations.

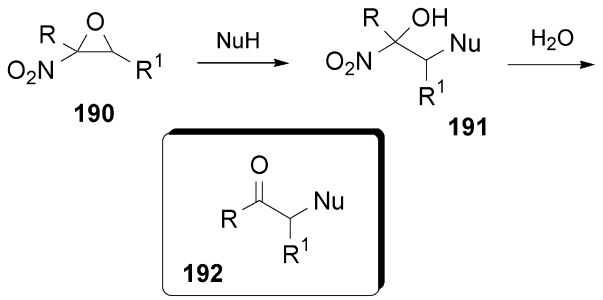
In rigid bicyclic structures, the presence of hydroxy groups in the proximity of the nitro function can lead to unexpected results during oxidation procedures. Oxidation of the nitro alcohol **186** with TPAP–NMO, as well as with other common oxidants, gives the tricyclic lactone **189** in high yield (Scheme 51).[89] This unusual transformation is probably caused by the electrophilic centre of the oxidising




**Scheme 50.** Synthesis of (−)-cyclophellitol.




**Scheme 51.** Unusual Nef reaction on bicyclic derivatives.




**Scheme 52.** Nucleophilic ring opening of α-nitroepoxides.

agent that favours the *aci*-nitro form **187** which allows the attack of the hydroxy group to form the *N*-hydroxyimidate **188**. Hydrolysis of this intermediate affords the final lactone **189**.

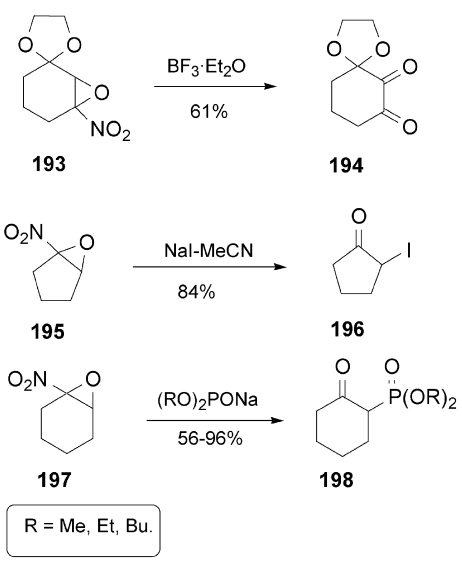
α-Nitroepoxides **190** can be obtained from conjugated nitroalkenes using hydrogen peroxide in basic conditions.[90] Nucleophilic ring opening of these epoxides usually leads to the α-hydroxy nitro intermediates **191** that are prone to a fast hydrolysis to the parent carbonyl compound **192** (Scheme 52).

Some interesting transformations involving these intermediates are depicted in Scheme 53.[91–93]

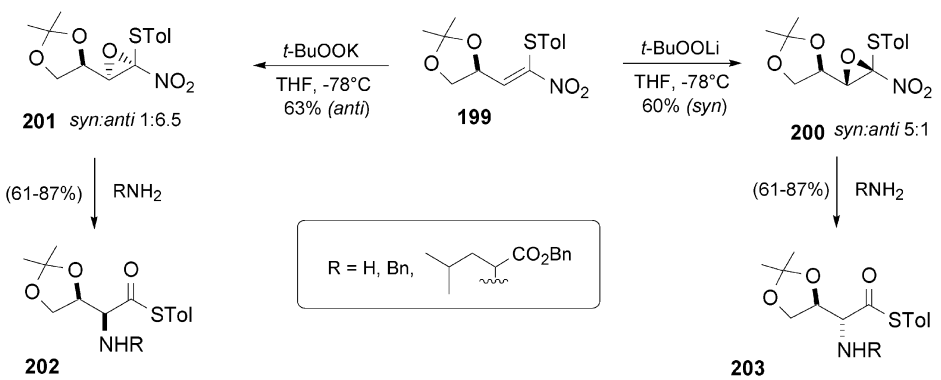
Condensation of (*p*-tolylthio)nitromethane with (*R*)-2,3-*O*-isopropylideneglyceraldehyde affords the corresponding nitroalkene **199** as a single *Z* stereoisomer (Scheme 54). Epoxidation with *t*-BuOOLi leads to the α-nitroepoxide **200**, with a strong preference for the *syn* diastereomer. Conversely, the utilisation of *t*-BuOOK provides a reversal in the diastereoselectivity, with preferential formation of the *anti* diastereomer **201**. Stereospecific opening of the oxirane ring using amino derivatives gives the α-amino *S*-tolyl thioesters **202** and **203** that are amenable to further synthetic transformations.[94–96] This procedure can be successfully extended to other chiral α-hydroxyaldehydes for the preparation of various β-hydroxy-α-amino acid derivatives.[97–100]

Cyclic 2-nitroketones are easily cleaved in different conditions to afford α,ω-difunctionalised systems.[101] When the cleavage is carried out in oxidative conditions, terminal dicarbonyl derivatives are usually obtained in good yield. Potassium persulphate in methanol in the presence of sulphuric acid is able to cleave the 2-nitrocycloalkanones, **204** giving the corresponding α,ω-dicarboxylic acid methyl esters **205** (Scheme 55).[102]

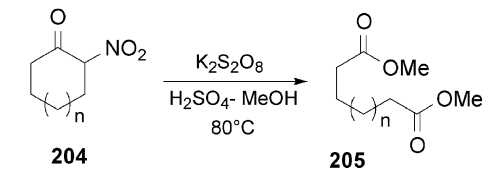
α,ω-Dicarboxylic acids or their methyl monoesters such as **207** can be obtained regioselectively starting from 2-nitrocycloalkanones **206** using Oxone® in buffered




**Scheme 53.** Synthetic applications of α-nitroepoxides.

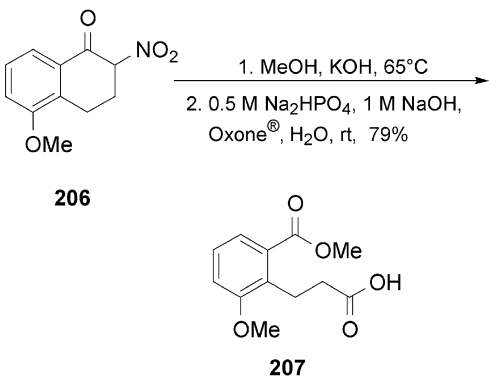



**Scheme 54.** Nucleophilic ring opening of α-nitroepoxides.



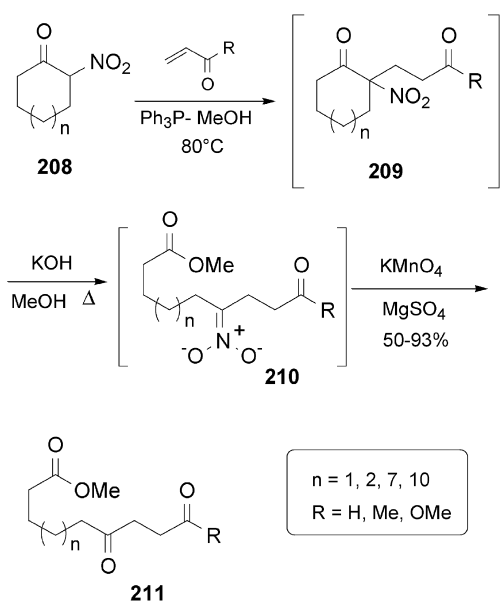

**Scheme 55.** Oxidative ring cleavage of 2-nitrocycloalkanones using potassium persulphate.

conditions.[103] The carbon atom bearing the nitro group is always converted into a free acid function (Scheme 56).




**Scheme 56.** Oxidative ring cleavage of 2-nitrocycloalkanones using Oxone®.

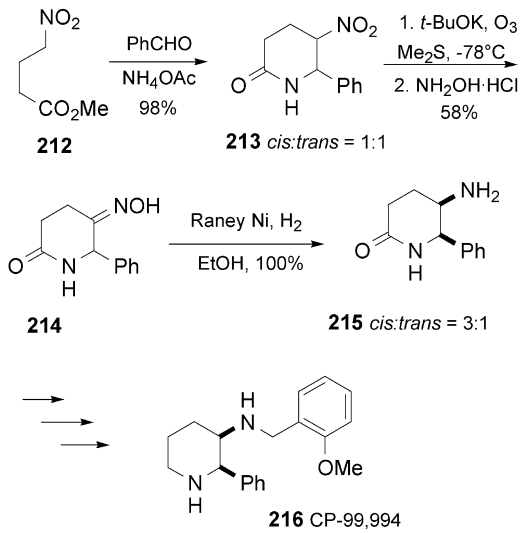
2-Nitroketones form the corresponding nitronate anion in weakly basic conditions, because of the additional activating effect of the carbonyl group.[104] The 2-nitrocycloalkanones **208** therefore, react with enones in the presence of triphenylphosphine to give the Michael adducts **209** that, by the simple addition of a methanolic solution of KOH, are cleaved to the corresponding open-chain nitronate anions **210**.[105,106]




**Scheme 57.** Synthesis of triketo derivatives.

These intermediates undergo a Nef reaction using $KMnO_4$ to afford the triketo derivatives **211** (Scheme 57). This overall transformation is realised in a one-pot procedure and avoids the isolation of any intermediates.

The utilisation of a Nef protocol can be used to overcome some stereoselectivity troubles occurring during the reduction of a nitro group into the corresponding amine. This procedure is illustrated for the total synthesis of racemic CP-99,994 **216**, a potent substance P antagonist.[107] Condensation of methyl γ-nitrobutyrate **212** with benzaldehyde in the presence of ammonium acetate affords the lactam **213** in good yield, but with no stereoselectivity. Reduction of the nitro group at this stage would provide an equimolar amount of the stereoisomeric amines, which would lower the efficiency of the synthetic process. Oxidative conversion of the nitro group into a carbonyl moiety, however, followed by reaction with hydroxylamine, affords the oxime **214** that, upon reduction with Raney Ni, gives the amine **215** quantitatively and with a better stereoselectivity in favour of the desired *cis* isomer **216** (Scheme 58).



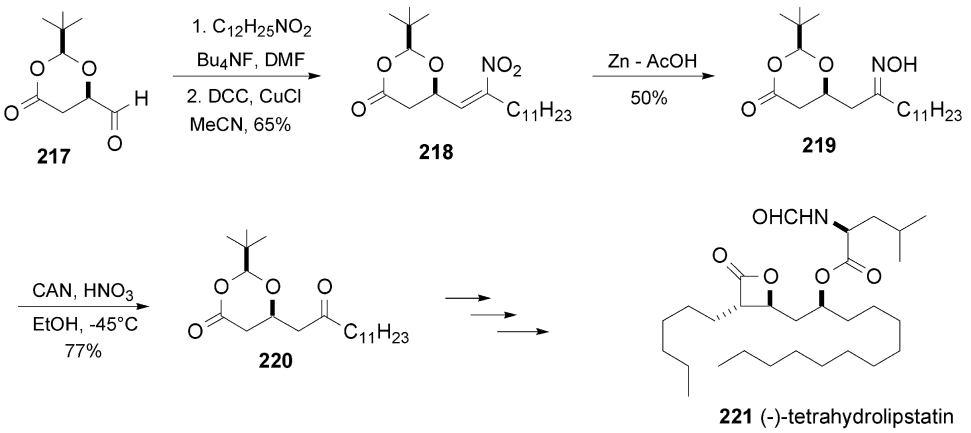

**Scheme 58.** Synthesis of the substance P antagonist, CP-99,994.

## 4.2. Reductive methods

Since oximes are known intermediates in the reductive conversion of a nitro group to a carbonyl function, it is sometimes preferable to realise this Nef reaction in two distinct steps, namely nitro-to-oxime conversion, followed by oxime hydrolysis. A recent strategy for the asymmetric synthesis of (−)-tetrahydrolipstatin **221**, a pancreatic lipase inhibitor, utilises the aldehyde **217** as the substrate for a nitroaldol condensation.[108] The obtained nitroalcohol is transformed into the corresponding nitroalkene **218** and then reduced to the oxime **219** using Zn powder in AcOH.

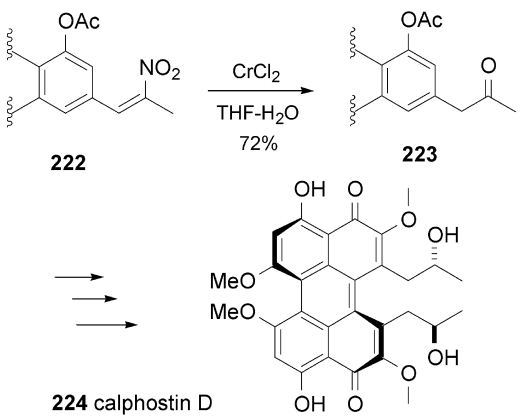
The oxime is cleaved to the parent ketone **220** in oxidative conditions using CAN in the presence of nitric acid (Scheme 59).

A related procedure can be applied en route to the total synthesis of calphostin D **224**, a potent inhibitor of protein




**Scheme 59.** Nef reaction for the synthesis of (−)-tetrahydrolipstatin.

kinase C.[109] The nitroalkene **222** is directly transformed into the ketone **223** using $CrCl_2$, which avoids the formation of the intermediate oxime (Scheme 60).[110]



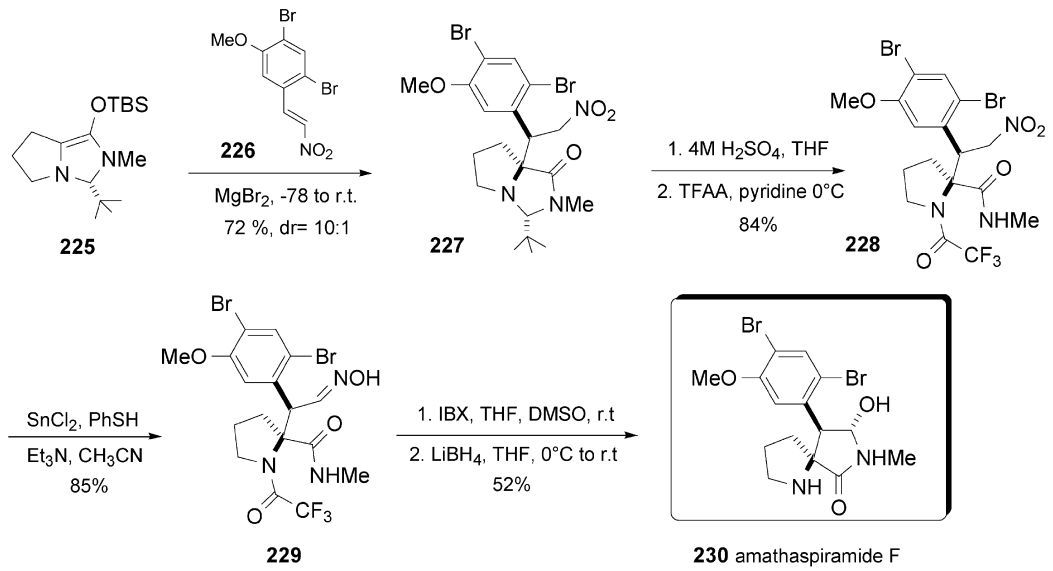

**Scheme 60.** A key step in the synthesis of calphostin D.

The presence of free amine bases in the molecular structure often makes the Nef conversion a rather troublesome process. It is therefore advisable to protect the amino group as an amide, as demonstrated in the total synthesis of the marine alkaloid, (−)-amathaspiramide F **230** (Scheme 61).[111]

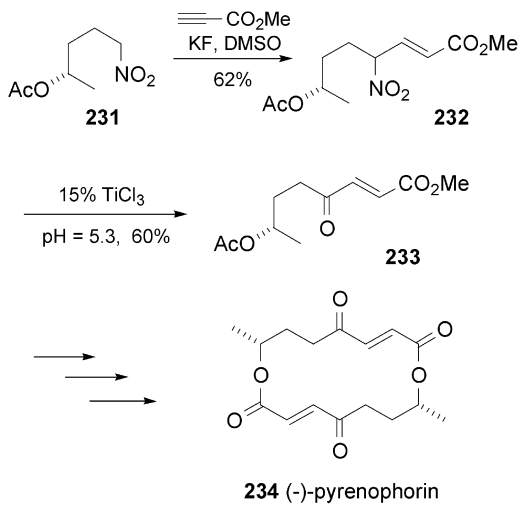
Conjugate addition of the enolate **225** to the nitroalkene **226** affords the product **227** with a high diastereoselectivity, but every attempt to convert the primary nitro group into a carbonyl moiety at this stage does not give any satisfactory results. Hydrolysis of the imidazolidinone ring and protection of the nitrogen as trifluoroacetic amide, however, allows the conversion of **228** into the oxime **229** that, by further functional group manipulations is transformed into amathaspiramide F **230**.

The enedione system is present in a large number of natural products endowed with interesting biological activity. Conjugate addition of the chiral nitroacetate **231** to methyl propiolate gives the corresponding adduct **232** that is converted into the enedione **233** by a classical McMurry reaction.[112] This derivative can be converted into optically active (*R*,*R*)-(−)-pyrenophorin **234**, an antifungal macrolide dilactone (Scheme 62).

A related strategy can be applied to the synthesis of other macrolides featuring enone systems.[113]



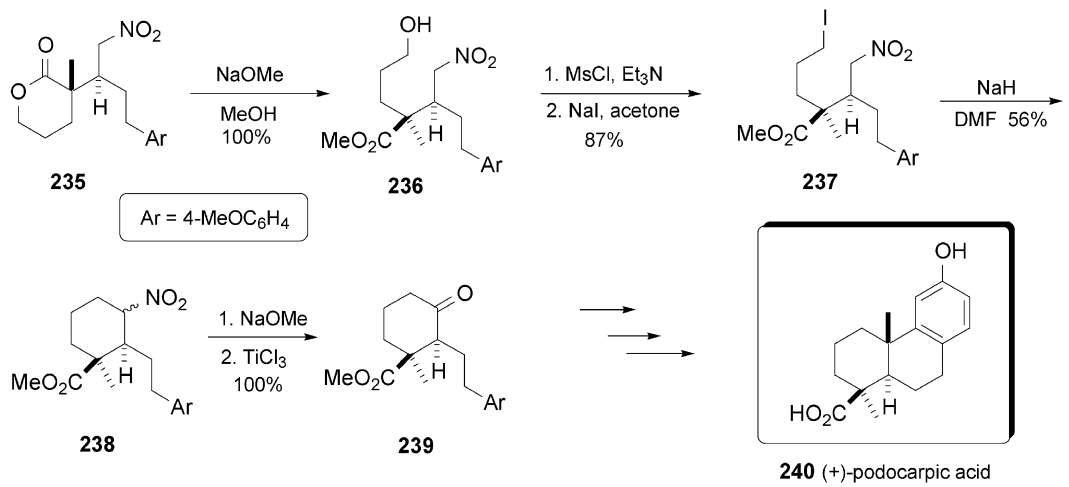

**Scheme 61.** Nef reaction for the synthesis of amathaspiramide F.




**Scheme 62.** Synthesis of (−)-pyrenophorin.

conditons to give the nitroalcohol **236**, which is transformed into the corresponding iodide **237** in a two-step process (Scheme 63).[114,115] Intramolecular ring closure, using NaH to generate the nitronate anion, affords the nitrocyclohexane **238** that is converted into the cyclohexanone **239** using the McMurry method. This intermediate can be transformed into (+)-podocarpic acid **240** in a few steps.

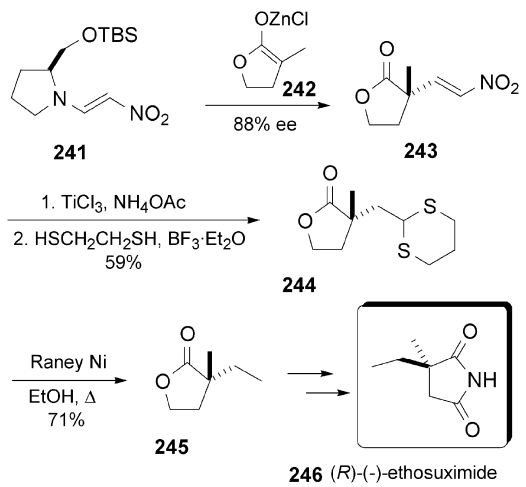
Nitroolefins can be converted directly into carbonyl derivatives using reductive methods. The chiral nitroenamine **241**, obtained from L-proline, reacts with the zinc ester enolate **242**, giving the corresponding lactone **243** in 88% ee (Scheme 64).[116] A reductive Nef reaction using $TiCl_3$ affords an aldehyde that is readily converted into the corresponding thioacetal **244**. Desulphurisation of the thioacetal **244** with Raney Ni leads to the chiral lactone **245** that is transformed in a few steps into the anticonvulsant agent, (*R*)-(−)-ethosuximide **246**.



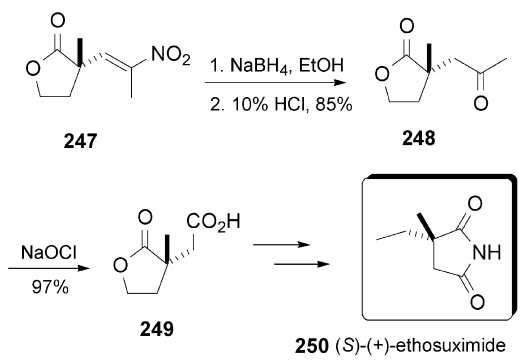

**Scheme 63.** Synthesis of (+)-podocarpic acid.

Although C-alkylation of nitronate anions is a less common process which respect to nitroaldol condensation, it can be particularly effective in intramolecular reactions. The nitrolactone **235**, obtained by the reaction of a chiral nitroalkene with a Grignard reagent, is opened in basic

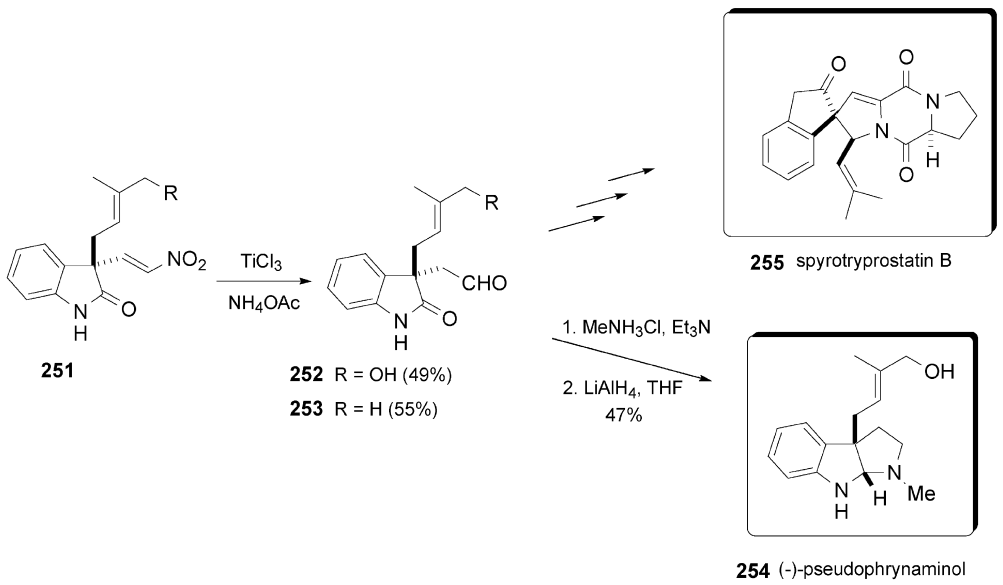
The chiral nitroolefin lactone **247** obtained by a similar procedure can be transformed into the ketone **248** by a tandem nitroolefin reduction-nitronate hydrolysis (Scheme 65). The keto group is cleaved to the parent carboxylic acid **249** by a haloform reaction and ultimately leads to the *S* enantiomer of ethosuximide **250**. The whole process represents a divergent asymmetric synthesis of both enantiomers of ethosuximide, starting from the inexpensive




**Scheme 64.** Synthesis of (*R*)-(−)-ethosuximide.




**Scheme 65.** Synthesis of (*S*)-(+)-ethosuximide.

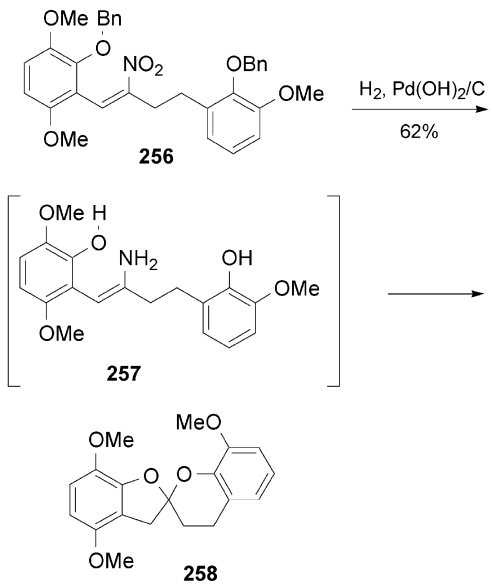



**Scheme 66.** Syntheses of (−)-pseudophrynaminol and spyrotryprostatin B.

L-proline. This approach follows a related synthesis using both enantiomers of proline as the starting materials.[117]

The final steps towards the total synthesis of the neurotoxin (−)-pseudophrynaminol **254** involve the reductive transformation of the nitroalkene **251** (R=OH) into the aldehyde **252** using $TiCl_3$.[118] Imine formation with methylamine and reductive cyclisation complete the synthesis of (−)-pseudophrynaminol **254** (Scheme 66). The same Nef conversion on the nitroalkene **251** (R=H) gives an aldehyde **253** that, after several steps, can be converted into spirotryprostatin B **255**, a potent antimitotic agent isolated from the fermentation broth of *Aspergillus fumigatus*.[119]

The reduction of nitroalkenes with Pearlman's catalyst [$Pd(OH)_2$/C] initially produces an enamine **257** that is readily hydrolysed to the parent carbonyl compound (Scheme 67).[120,121] In the presence of free hydroxy groups in a suitable position, the spiroketal **258**, which constitutes the core of γ-rubromycin, is directly isolated from nitroalkene **256**.

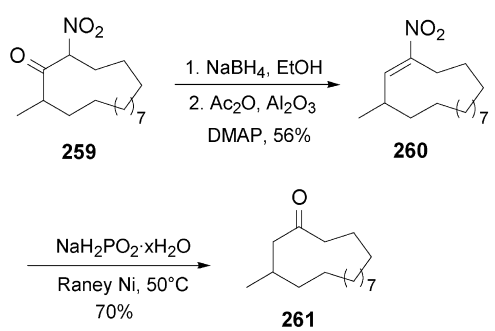



**Scheme 67.** Synthesis of spiroketal derivatives.

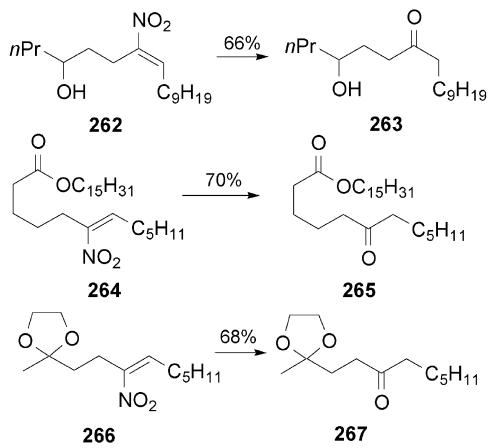
It is highly probable that a similar mechanism occurs in the nitro-to-carbonyl conversion of nitroalkenes using Raney nickel and sodium hypophosphite.[122] This procedure is the key step in the synthesis of several natural products and important synthetic building blocks. The reduction of 2-nitrocyclopentadecanone **259** affords the corresponding nitroalcohol, which is converted into the nitroolefin **260**.[123] This unsaturated compound is converted into muscone **261** using the above-cited procedure (Scheme 68).

Other useful transformations of nitroalkenes **262**, **264** and **266** into ketones **263**, **265** and **267** using Raney-nickel/$NaH_2PO_2$ are collected in Scheme 69.[124–127]

The cyclopentenone unit is a common motif in a wide array of biologically active substances. Nitromethane reacts with the cyclopentenone **268**, giving a *trans*-substituted nitro derivative that is protected at the carbonyl group as the ketal **269**. A Nef reaction on **269** using $TiCl_3$ gives the aldehyde **270** which is converted via **271** into the compound **272** that shows algicidal properties (Scheme 70).[128]

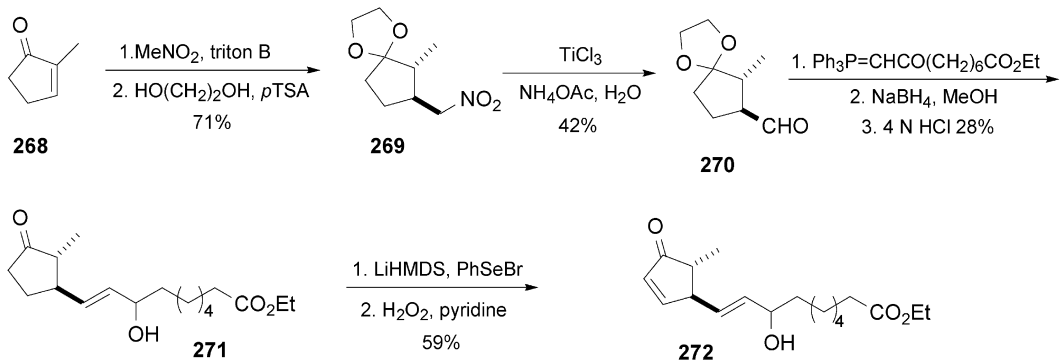



**Scheme 68.** Synthesis of muscone.

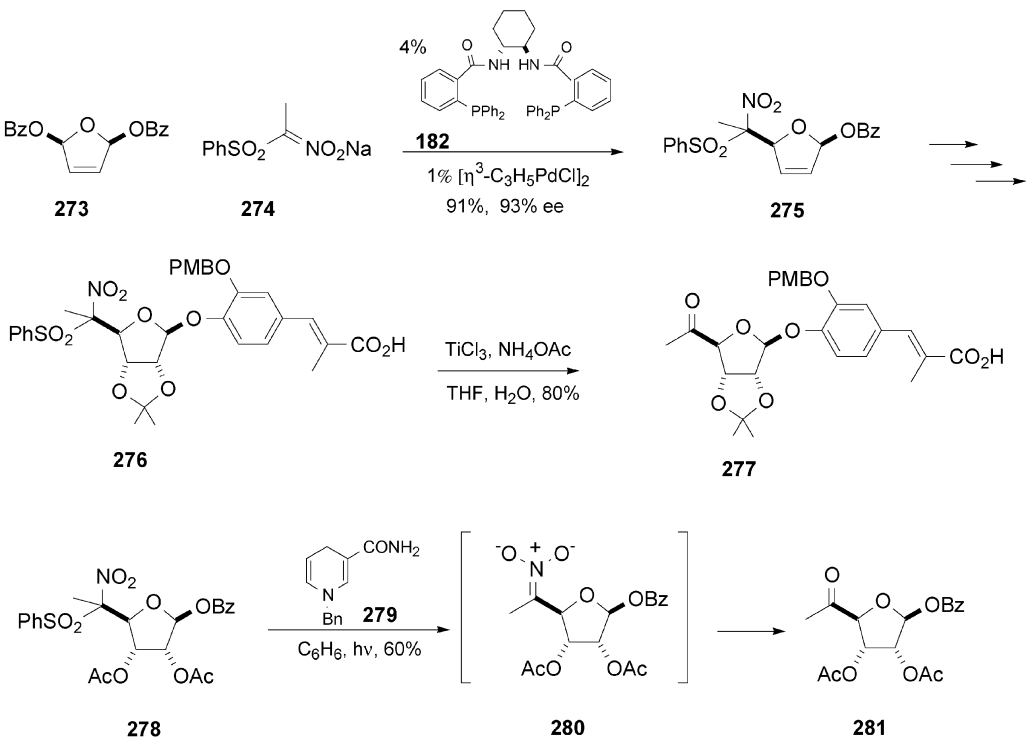



**Scheme 69.** Nef conversions using $NaH_2PO_2{\cdot}xH_2O$ and Raney nickel.

Reaction of the cyclopentene derivative **273** with the sodium salt of 1-phenylsulphonyl-1-nitroethane **274** in the presence of a chiral catalyst **182** and a Pd species gives the corresponding adduct **275** (Scheme 71). This product, after several steps, is converted into compound **276** that needs to be transformed into the corresponding acyl derivative **277**, an advanced intermediate for the total synthesis of *C*-2 *epi*-hygromycin A.[129,130] Since the nitro compound **276** cannot be converted into its nitronate anion, all oxidative methods are ineffective for the Nef reaction. $TiCl_3$ in buffered solution is, however, able to realise this transformation quite efficiently. In this context, it worth noting that this procedure has been revealed to be rather capricious when applied to other structurally-related cyclopentene derivatives since, the compound **278** fails to give the Nef conversion using $TiCl_3$. The acyl derivative **281** can, however, be obtained in fair yield using



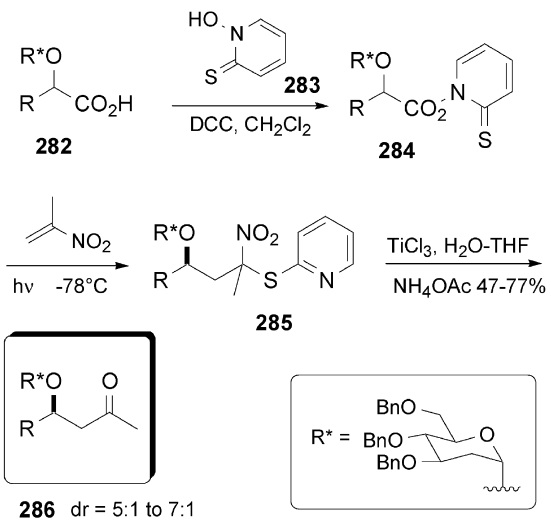

**Scheme 70.** Synthesis of the algicidal cyclopentenone **272**.




**Scheme 71.** Use of 1-phenylsulphonyl-1-nitroethane as an acyl anion equivalent.

*N*-benzylnicotinamide **279** in photochemical conditions. This procedure presumably involves a preliminary desulphonylation that leaves a nitronate anion **280**, which is further reduced by the excess of the nicotinamide to the ketone **281**.[131]

Radical additions to a nitroalkene using Barton's thiohydroxamic protocol provide a rapid entry to thiopyridylnitro derivatives.[132] The α-alkoxy acids **282** bearing a glucal appendage can be transformed with **283** into the corresponding thiohydroxamic anhydrides **284** that react with 2-nitropropene in the usual radical conditions to afford the adducts **285**.[133] A Nef reaction converts these intermediates into the optically active 3-alkoxyketones **286** in good overall yields and diastereomeric ratios (Scheme 72).



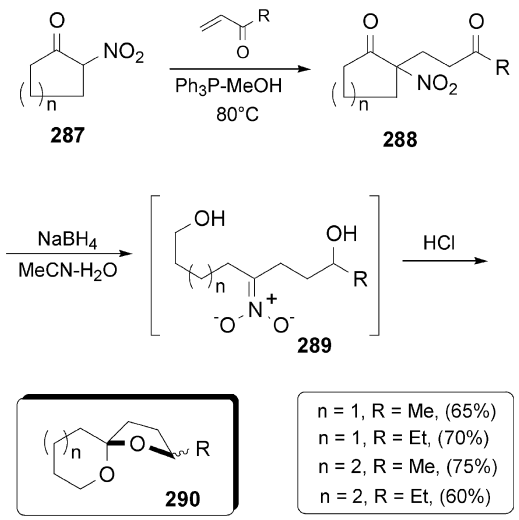

**Scheme 72.** Nef reaction on thiopyridylnitro derivatives.

## 4.3. Other methods

Hydrolytic methods, despite the strongly acidic conditions required, are still applied with success in a considerable number of reactions involving the nitro-to-carbonyl conversion. The application of the classical Nef reaction to the synthesis of spiroketal systems represents an interesting example of a cascade reaction.[134] The adducts **288** obtained from 2-nitrocycloalkanones **287** are made to react with $NaBH_4$, leading to the diols **289** by a first tandem retro-Claisen cleavage-reduction of the carbonyl functions. Meanwhile, in basic conditions, the nitro group is converted into the corresponding nitronate anion. Upon quick acidification with HCl, a Nef reaction occurs, followed by a spontaneous spiroketalisation of the intermediate ketodiol, to give the compound **290** as a mixture of *E*/*Z* isomers (Scheme 73).

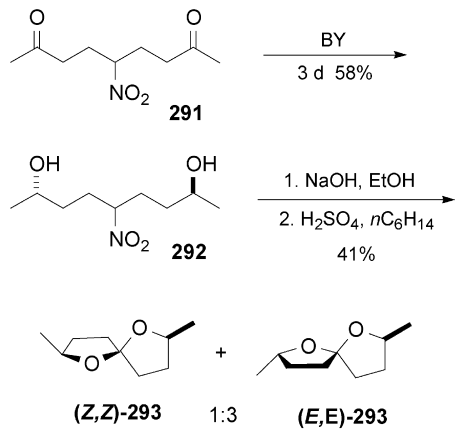
A similar process can be realised stepwise to produce other spiroketal systems.[135]

This procedure can be suitably adapted to the synthesis of spiroketals **293** in an enantiomerically-enriched form, provided that an enantioselective reduction of the carbonyl groups as in the nitroketone **291**, is carried out to give the

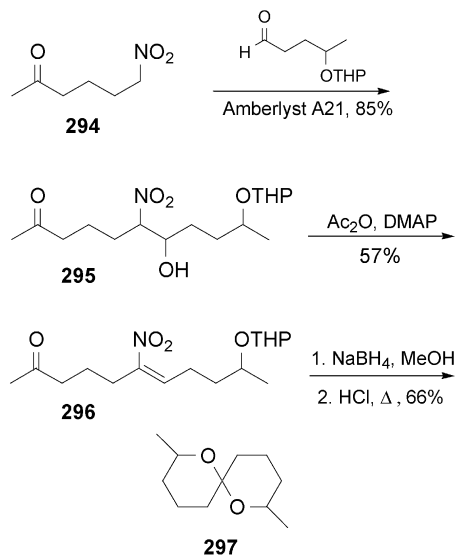



**Scheme 73.** Synthesis of spiroketals.

optically active alcohols **292**, before the Nef reaction-cyclisation step (Scheme 74).[136,137]



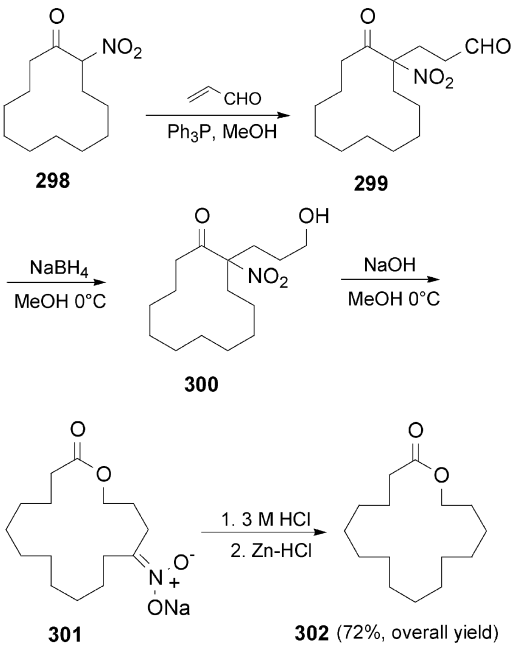

**Scheme 74.** Enantioselective synthesis of spiroketals.




**Scheme 75.** Synthesis of spiroketals.

The nitroalkenes such as **296**, obtained from the nitro compound **294** via the nitroalcohol **295**, react with $NaBH_4$ and lead to the formation of nitronate anions that are converted to carbonyl groups and subsequently cyclised to spiroketals **297** (Scheme 75).[138,139]

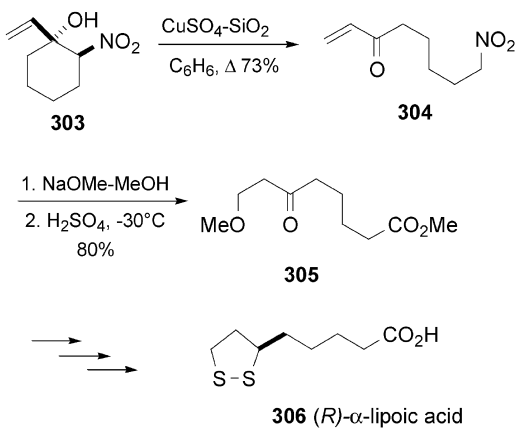
One of the most commonly employed methods for the synthesis of macrocycles involves a ring enlargement reaction of smaller cyclic systems. 15-Pentadecanolide **302**, a component of vegetable musk oils which is of industrial interest, can be prepared starting from 2-nitrocyclododecanone **298** that, upon reaction with acrylaldehyde, gives the adduct **299**.[140,141] Reduction of the aldehyde to **300**, followed by a retro-Claisen process, leads to the 15-membered-ring lactone **301**. Cleavage of the nitronate anion affords a keto derivative that is converted into the macrolide **302** by a Clemmensen reaction (Scheme 76). This process is realised in a one-pot procedure with an overall yield of 72%. A related procedure allows ready access to other macrocycles such as phoracantholide and [10]heterophanes.[142,143]



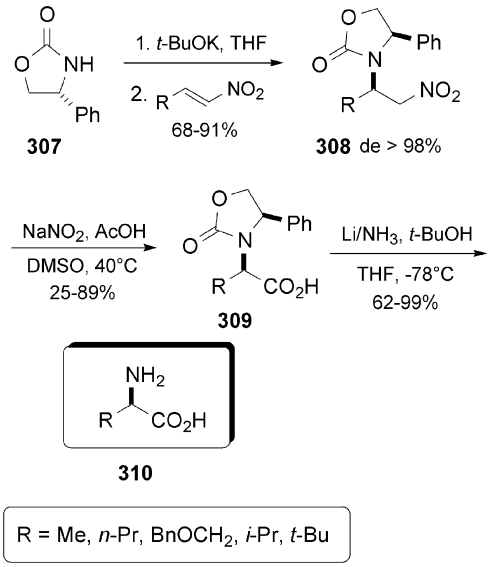

**Scheme 76.** Synthesis of 15-pentadecanolide.

A retro-Henry reaction on the nitrocyclohexanol **303** affords the open-chain nitroketone **304** that undergoes a tandem Michael addition-Nef reaction upon reaction with NaOMe, followed by acidification with $H_2SO_4$ to give the ketoester **305**.[144] This derivative is a key intermediate in the synthesis of optically active (*R*)-α-lipoic acid **306** (Scheme 77).

Nucleophilic addition of the potassium salt of optically active 4-phenyl-2-oxazolidinone **307** to nitroalkenes occurs with a high diastereoselectivity giving the nitro derivatives **308** that are amenable to further synthetic transformations.[145,146] The primary nitro group is converted into the carboxylic acids **309** using $NaNO_2$/AcOH in DMSO, followed by reductive cleavage of the oxazolidin-2-one, that leads to the α-amino acids **310** of high enantiomeric purity (Scheme 78).



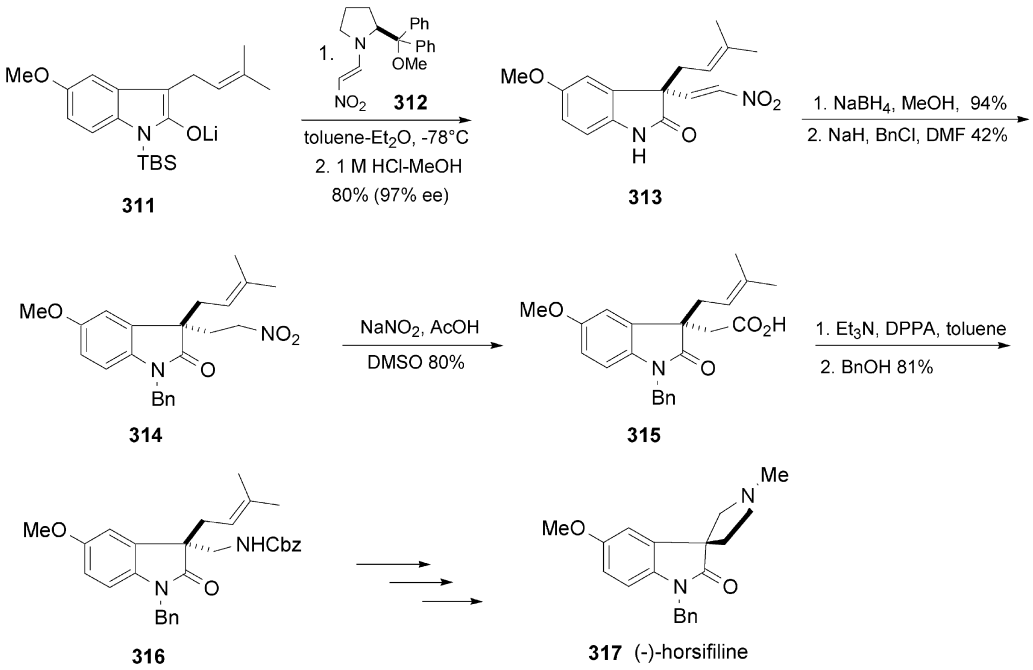

**Scheme 77.** Synthesis of the ketoester **305**.



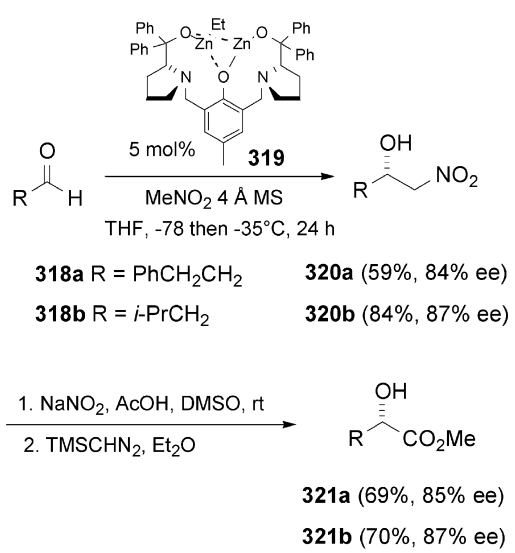

**Scheme 78.** Synthesis of enantiomerically pure α-amino acids.

The same reagent is used in the total synthesis of (−)-horsfiline **317** an oxindole alkaloid isolated from the Malaysian plant *Horsfildea superba*.[147] The lithium enolate of the oxindole **311** is made to react with the chiral nitroenamine **312** in a 4:1 mixture of toluene/ether giving the nitroalkene **313** in 97% ee. Protection of the indole nitrogen and reduction of the nitroolefin affords the nitroalkane **314** that is converted into the carboxylic acid **315** with $NaNO_2$. A thermal Curtius rearrangement of the acid **315** gives the amine **316** protected as the benzyl carbamate and further synthetic transformations lead to the preparation of (−)-horsfiline **317** (Scheme 79).

Optically active β-nitroalcohols can be obtained by an asymmetric nitroaldol reaction using various chiral catalysts.[148,149] A variety of aldehydes **318** react with nitromethane in the presence of small amounts of a dinuclear zinc catalyst **319**.[150] The obtained β-nitroalcohols **320**, can be transformed into the α-hydroxy acids **321**, by a reaction with the system without any epimerization of the stereogenic centre (Scheme 80). A crucial step in the synthesis of the neuraminidase inhibitor BCX-1812 (RWJ-270201) **324**, is the transformation of the primary



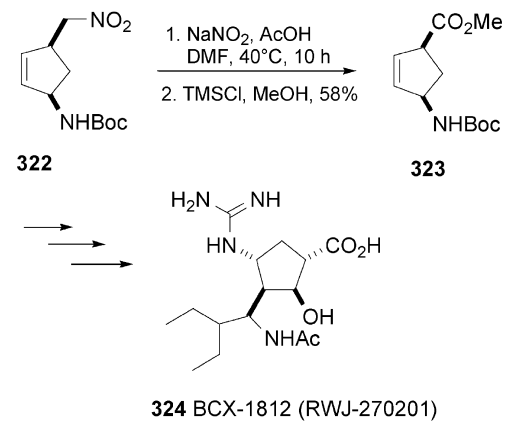

**Scheme 79.** Synthesis of (−)-horsifiline.



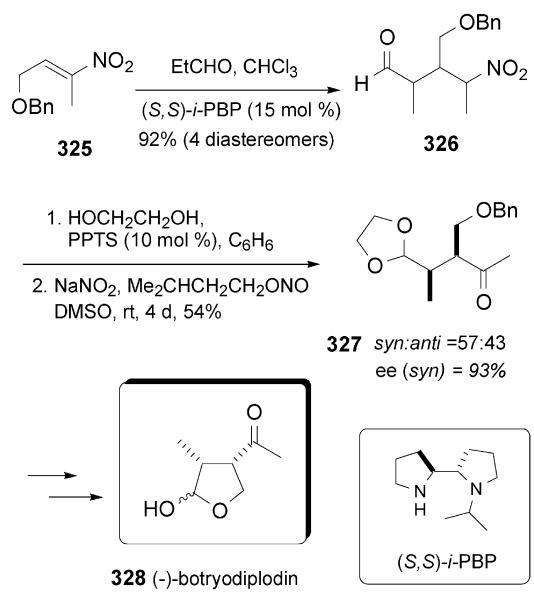

**Scheme 80.** Synthesis of optically active α-hydroxyacids.

nitroalkane **322** into the ester **323** (Scheme 81).[151] The utilisation of $NaNO_2$/AcOH/DMSO causes, however, a substantial epimerization in the formation of the ester **323**, that can be avoided using DMF as the solvent.

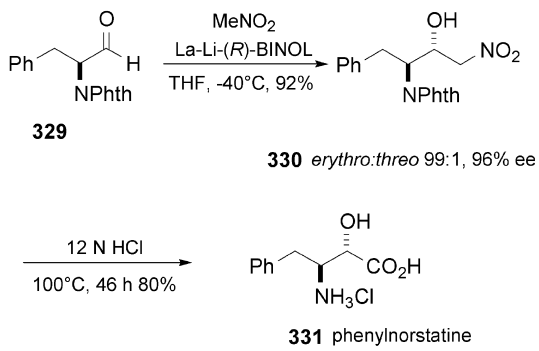
The conjugate addition of propanal to nitroalkene **325**, in the presence of a chiral amine, leads to the formation of the corresponding adduct **326** as a mixture of four diastereomers (Scheme 82).[152] After protection of the carbonyl function as the cyclic acetal, the secondary nitro group can be transformed into the ketone **327** using $NaNO_2$ and isoamyl nitrite in DMSO.[153] The ketone **327** is obtained as a separable mixture of the *syn* (93% ee) and *anti* (74% ee) diastereomers. The *syn* diastereomer is transformed into (−)-botryodiplodin **328**, a compound that exhibits antibiotic and antileukemic activity.



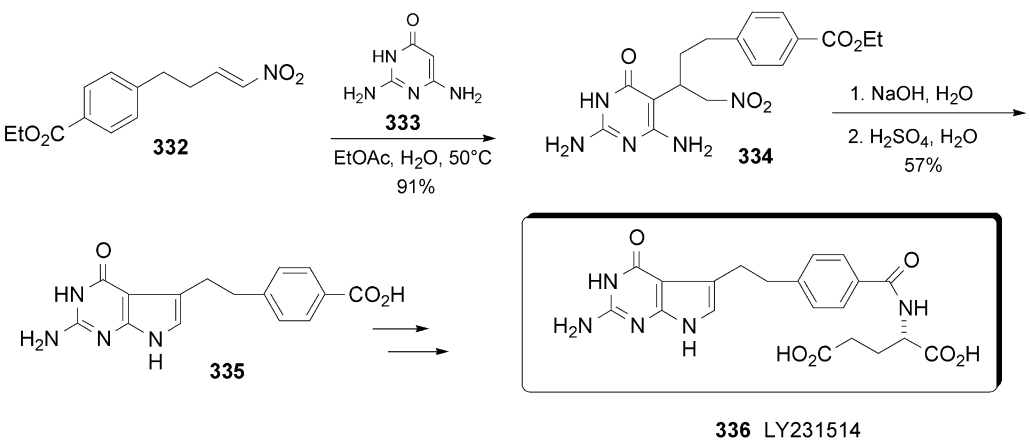

**Scheme 81.** Synthesis of the neuraminidase inhibitor BCX-1812 (RWJ-270201).




**Scheme 82.** Synthesis of (−)-botryodiplodin.



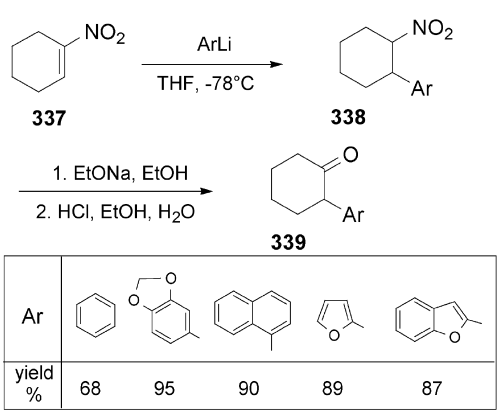

**Scheme 83.** Synthesis of *erythro*-phenylnorstatine.




**Scheme 84.** Synthesis of the anticancer agent, LY231514.

The reaction of nitromethane anion with chiral α-amino-aldehydes usually occurs with poor diastereoselectivity. The presence of small amounts of chiral rare earth–Li–BINOL complexes, however, exerts a powerful effect on the diastereoselection (Scheme 83).[154] The α-aminoaldehyde **329** reacts with nitromethane in the presence of La–Li–(*R*)-BINOL as the catalyst (3.3 mol%) to give the nitroalcohol **330** practically as the sole *erythro* diastereomer in 96% ee.

The nitro moiety can be converted into a carboxyl group by prolonged heating at reflux in concentrated HCl that also ensures the removal of the *N*-phthaloyl protecting group (Phth), leading to phenylnorstatine **331**. Rather surprisingly, these harsh conditions do not affect the integrity of the stereocentres present in the molecule.

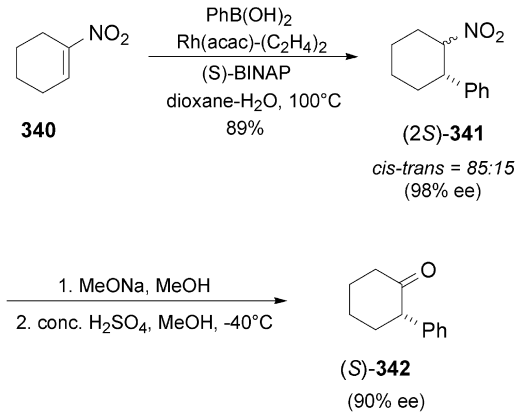



**Scheme 85.** Synthesis of 2-arylcyclohexanones.

The Nef reaction can be coupled with a ring closure to afford fused pyrroles.[155,156] Pyrimidone **333** adds to the nitro-alkene **332** in a very efficient manner to give the compound **334**. This derivative in hydrolytic conditions is transformed into the corresponding aldehyde that undergoes a fast ring closure to the fused pyrrole **335**. This compound is easily converted into the pyrrolo[2,3-*d*]pyrimidine, LY231514 **336**, a potential inhibitor of folate-dependent enzymes (Scheme 84).

The addition of organometallic reagents to nitroalkenes provides an efficient entry to 2-substituted cycloalkanones and similar derivatives.[157] Aryllithium reagents add to 1-nitro-1-cyclohexene **337**, giving the 2-aryl-1-nitro-cyclohexane derivatives **338**.[158] The nitro group is subsequently transformed into a carbonyl function using common hydrolytic conditions, giving the 2-arylcyclo-hexanones **339** in good yields (Scheme 85). A similar procedure can be applied using Grignard reagents to 3-nitro-5,6-dihydro-4*H*-pyran that directly affords the 2-alkyltetra-hydropyran-3-ones in a one-pot reaction.[159] In this context, it is worth noting that alkyl Grignard reagents can be efficiently added to nitroalkenes in the presence of cerium(III) chloride, which considerably suppresses proton abstraction and redox reactions that usually occur in similar processes.[160]

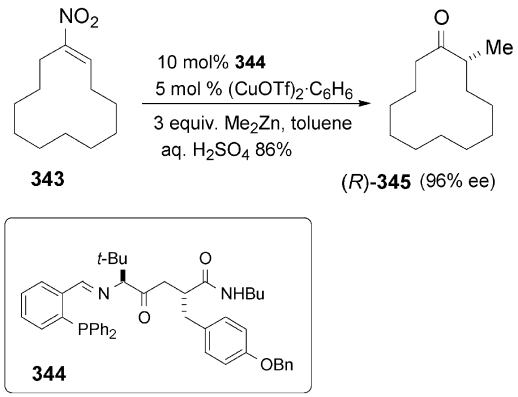
In the presence of chiral catalysts, the organometallic




**Scheme 86.** Synthesis of optically active 2-phenylcyclohexanone.

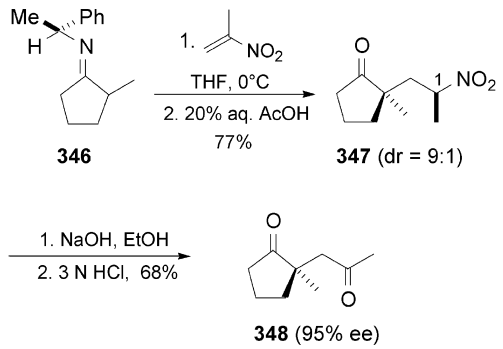
addition to cyclic nitroalkenes produces the corresponding nitro derivatives with variable *cis*/*trans* ratios. Organoboronic acids add to conjugated nitrocycloalkenes such as **340** in the presence of Rh(acac)–$(C_2H_4)_2$/(*S*)-BINAP to give the 2-substituted nitrocycloalkanes **341** that after the Nef conversion, afford the corresponding cycloalkanones **342** in good enantiomeric excesses (Scheme 86).[161]

Similarly, alkylzinc reagents give a conjugate addition to the cyclic nitroalkene **343** in the presence of $(CuOTf)_2{\cdot}C_6H_6$ and a chiral phosphine ligand **344** to afford the corresponding 2-alkyl derivative that undergoes a Nef conversion in hydrolytic conditions.[162] This procedure seems particularly suitable for the enantioselective synthesis of macrocyclic ketones such as (*R*)-2-methylcyclododecanone (*R*)-**345** (Scheme 87).




**Scheme 87.** Enantioselective synthesis of (*R*)-2-methylcyclododecanone.

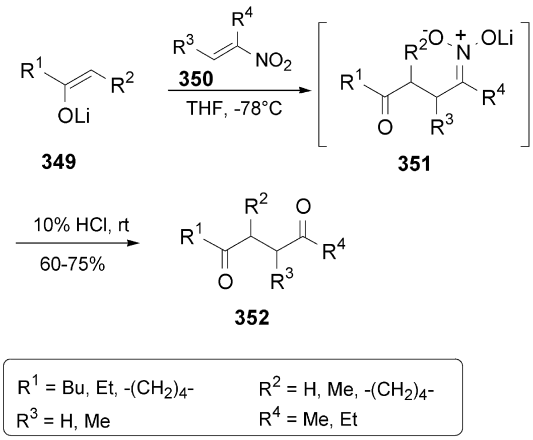
The chiral imine **346** obtained from 2-methylcyclopentanone reacts with 2-nitropropene in a highly regioselective fashion giving a diastereomeric mixture of the C-1 epimeric adducts **347**.[163] Interestingly, the subsequent Nef reaction using $TiCl_3$ gives exclusively the corresponding oxime, while acidic hydrolysis of the nitronate anion affords the diketone **348** in 95% ee (Scheme 88).




**Scheme 88.** Synthesis of the chiral 1,4-diketone **348**.

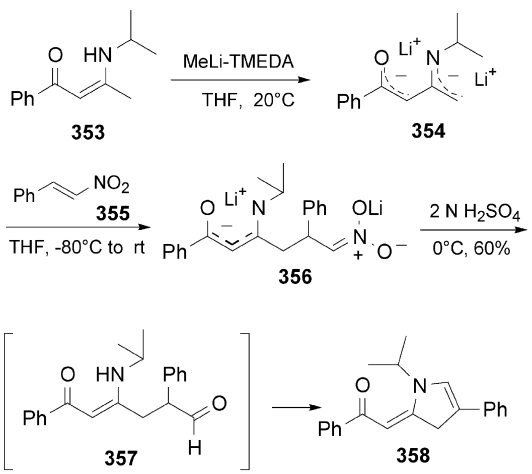
Conjugate addition of lithium ketone enolates **349** to nitroalkenes **350** represents a general method for the direct preparation of 1,4-diketones **352** since the intermediate nitronate anion **351** can be converted directly into a carbonyl group by acid hydrolysis (Scheme 89).[164,165]

The dianion of the β-enaminoketone **354**, prepared from **353**, reacts with nitrostyrene **355** at −80 °C giving the




**Scheme 89.** Synthesis of 1,4-diketones.

corresponding nitronate adduct **356**.[166] Upon quenching of this intermediate at 0 °C with 2 N $H_2SO_4$, the aldehyde **357** is formed, followed by a rapid cyclisation to the dihydropyrrole **358** in 60% overall yield (Scheme 90).

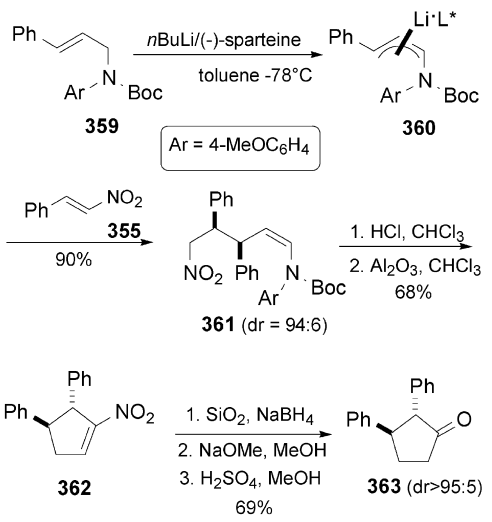



**Scheme 90.** Synthesis of the dihydropyrrole **358**.

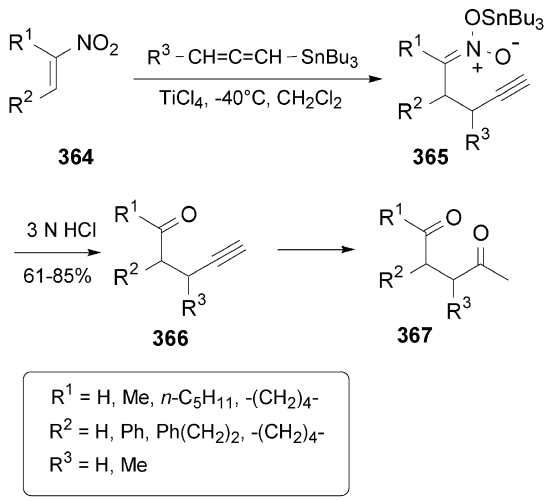
The configurationally-stable organolithium derivative **360** obtained by treatment of the allylic amine **359** with *n*BuLi and (−)-sparteine, adds to the nitroalkene **355** with high diastereomeric and enantiomeric ratios.[167] Hydrolysis of the adduct **361** affords the nitrocycloalkene **362** by an intramolecular nitroaldol-elimination reaction. Conversion of the compound **362** to cyclopentanone **363** is carried out by reduction of the double bond, followed by a Nef reaction in hydrolytic conditions (Scheme 91).

Propargylation of the nitroalkenes **364** can be realised using (tributylstannyl)allenes in the presence of $TiCl_4$.[168] The stannylnitronates **365** that are formed as intermediates can be hydrolysed to the corresponding ketones **366** using 3 N HCl. The obtained α-propargylic ketones **366** are precursors of useful building blocks such as the 1,4-diketones **367** (Scheme 92).

An interesting rearrangement involving a Nef process can be observed in the nitrocyclopropane **368** under strongly



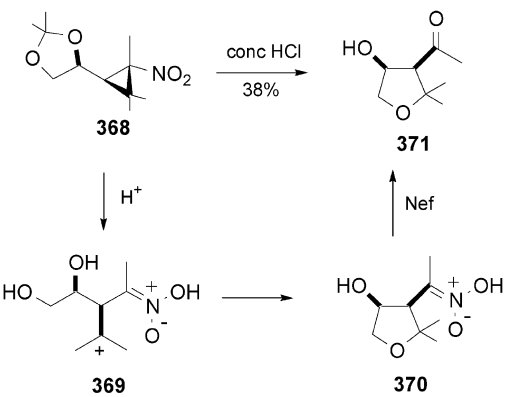

**Scheme 91.** Synthesis of the optically active cyclopentanone **363**.



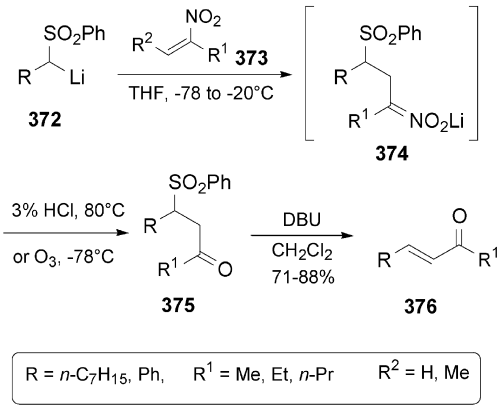

**Scheme 92.** Nef reaction on α-propargyl stannylnitronates.

acidic conditions (conc. HCl).[169] Cyclopropane ring opening affords the carbenium ion **369** that forms the tetrahydrofuran derivative **370** by intramolecular etherification. Finally, the nitronic acid **370** undergoes a Nef reaction, leading to the keto derivative **371** (Scheme 93).

The α-sulphonyl carbanions **372** add to the nitroalkenes **373** giving, after acid hydrolysis of the intermediate nitronates **374**, the 3-phenylsulfonyl ketones **375**.[170] These derivatives can be transformed into the enones **376** by treatment with DBU that causes elimination of benzenesulphinic acid (Scheme 94).

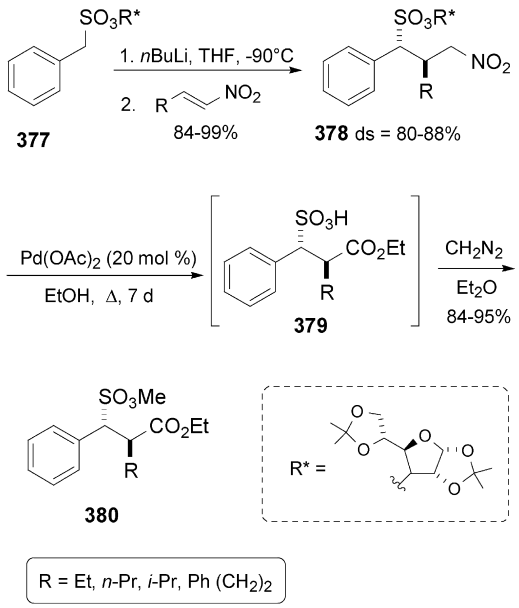



**Scheme 93.** Rearrangement of the chiral nitrocyclopropane **368**.




**Scheme 94.** Synthesis of α,β-unsaturated derivatives.

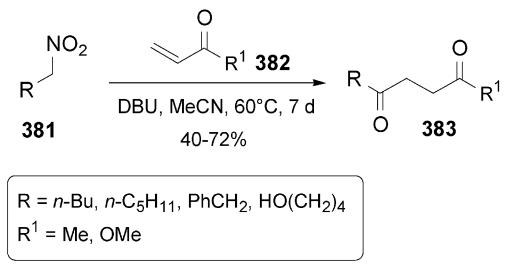
Enantiopure sulphonates **377** bearing a carbohydrate-derived chiral auxiliary can be lithiated at low temperature and then added to nitroalkenes to give the corresponding nitro derivatives **378**.[171] The chiral auxiliary can be subsequently removed in the presence of 20 mol% $Pd(OAc)_2$ in EtOH to afford an intermediate sulphonic acid that also causes the Nef transformation of the primary nitro group into an ethyl carboxylate **379**. The sulphonic acids can be finally methylated using diazomethane to give the diesters **380** (Scheme 95).




**Scheme 95.** Synthesis of optically active methanesulphonates.

The ability of DBU to promote a conjugate addition of nitroalkanes **381** to enones **382**, as well as a Nef reaction on secondary nitroalkanes, can be effectively used in a tandem process that allows the direct synthesis of γ-diketones and γ-keto esters **383** (Scheme 96).[172]

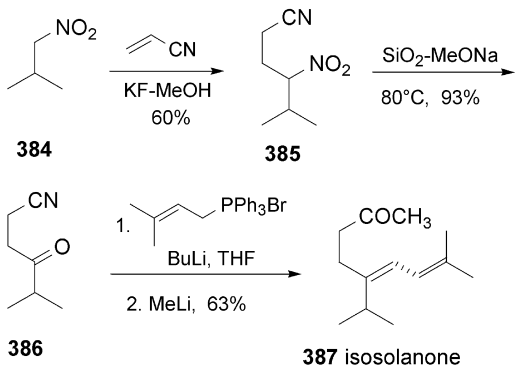
The same transformation can be of course realised in a




**Scheme 96.** DBU-promoted conjugate addition-Nef reaction.

two-step procedure after isolation of the intermediate γ-nitroketone.[173]

A conjugate addition of the nitroalkane **384** to acrylonitrile represents the first step in the synthesis of terpene isosolanone **387**.[174] The obtained nitrile **385** is converted into the ketonitrile **386** in very good yield using MeONa in dry silica. Wittig olefination and conversion of the cyano group to a methyl ketone using MeLi gives isosolanone **387** as an inseparable diastereomeric mixture (*E*/*Z*, 3:1) (Scheme 97).

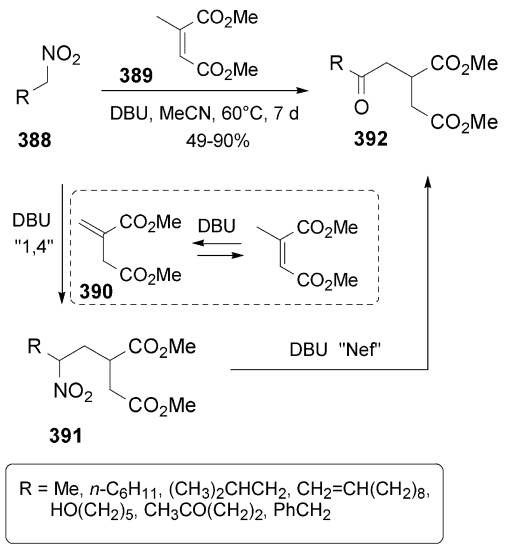



**Scheme 97.** Synthesis of isosolanone.

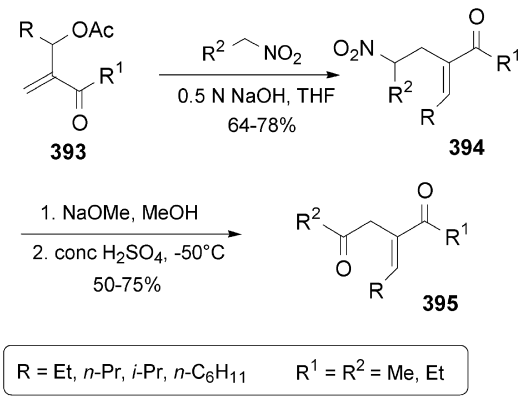
A unusual behaviour can be observed upon reaction of the nitroalkanes **388** with dimethyl citraconate **389** in the presence of DBU.[175] As observed by $^1$H NMR analysis, in the presence of DBU there is an equilibrium between **389** and its regioisomer **390** that is probably more reactive towards Michael addition with nitroalkanes. The adducts **391** formed by the usual conjugate addition are therefore subsequently transformed into the keto diesters **392** by a Nef reaction (Scheme 98).

Allyl Baylis–Hillman acetates **393** react with nitroalkanes through a conjugate addition–elimination process that leads to the formation of the unsaturated esters **394**.[176] A Nef reaction carried out under hydrolytic conditions on these compounds efficiently affords the (*E*)-alkylidene-1,4-diketones **395** (Scheme 99).

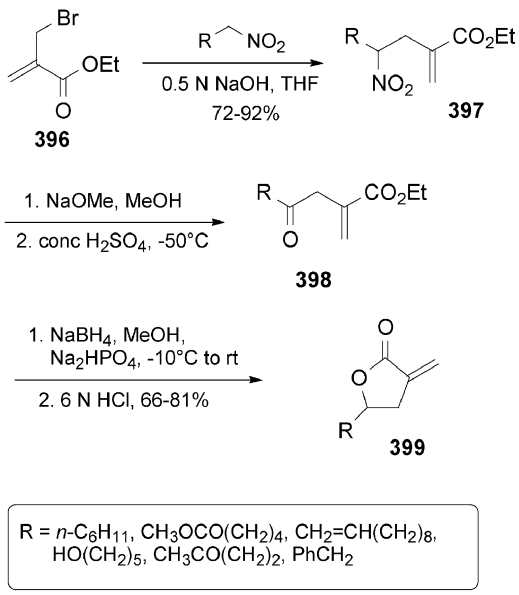
A related procedure involves ethyl (2-bromomethyl)acrylate **396** as a Michael acceptor that behaves similarly to the acetates **393** in the reaction with nitroalkanes, giving the nitro derivatives **397**.[177] The nitro group is best transformed into an hydroxy group by a two-step procedure involving hydrolytic cleavage to **398** and reduction with $NaBH_4$ in the presence of $Na_2HPO_4$. This transformation is followed by a spontaneous lactonisation to the *exo*-methylene butyrolactones **399** in good overall yields (Scheme 100).



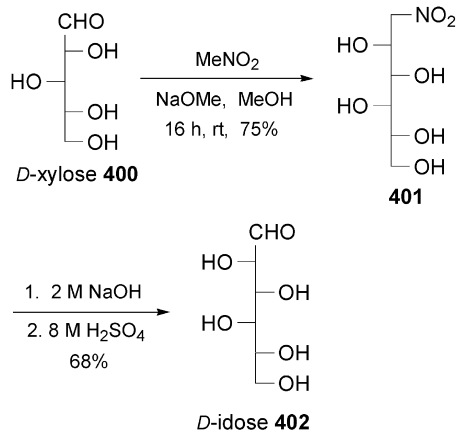

**Scheme 98.** Synthesis of keto diesters.



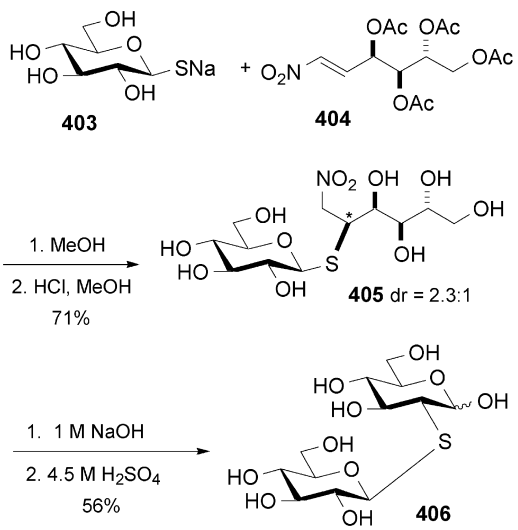

**Scheme 99.** Synthesis of alkylidene-1,4-diketones.




**Scheme 100.** Synthesis of *exo*-methylene butyrolactones.




**Scheme 101.** Synthesis of *D*-idose by chain elongation.



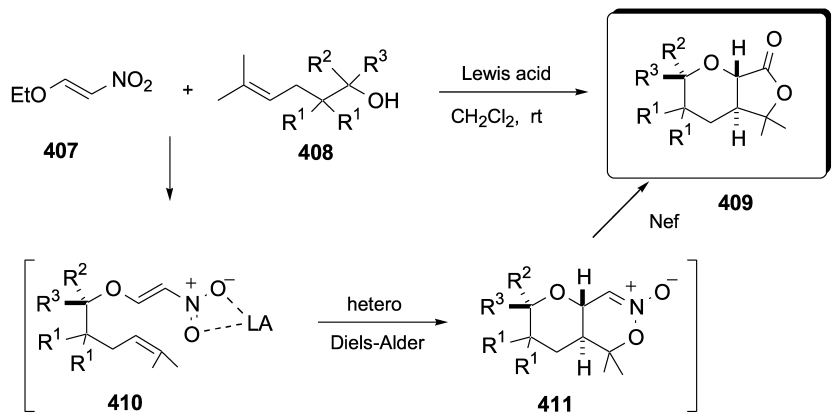

**Scheme 102.** Synthesis of *S*-glycosylthioglycose **406**.

As previously stated, several structural manipulations in the field of carbohydrate chemistry make use of the Nef reaction as a key step to introduce a carbonyl group in the molecular framework.[15] Reaction of nitromethane with D-xylose **400** produces an epimeric pair of nitrosugars from which 1-deoxy-1-nitro-D-iditol **401** can be recovered in 75% yield after multiple fractional crystallisations.[178] This compound can be transformed into D-idose **402** under classical Nef conditions in 68% yield (Scheme 101).

Conjugate additions to sugar α-nitroalkenes provide a viable method for the synthesis of various disaccharides such as *S*-glycosylthioglycose **406** that shows some enzyme inhibitory properties.[179] The sodium salt of 1-thio-*D*-glucose **403** reacts with the nitroalkene **404**, giving, after deacetylation, the corresponding adduct **405** as a mixture of epimers (Scheme 102).

Hydrolytic Nef reaction on **405** followed by equilibration of the resulting epimeric mixture, allows the isolation by fractional crystallisation of the pure thiodisaccharide **406** in fairy good yield.

The conjugate addition of (*E*)-1-ethoxy-2-nitroethylene **407**, with δ,ε-unsaturated alcohols **408**, leads to the synthesis of *trans*-fused bicyclic γ-lactones **409** in the presence of a catalytic amount of different Lewis acids (Scheme 103).[180] The Michael adduct **410** initially formed, undergoes to a hetero Diels–Alder reaction that produces bicyclic nitronates **411**. The intermediate nitronates **411** can be isolated adding 4 Å molecular sieves to the reaction mixture using $Yb(OTf)_3$ as a catalyst. In the presence of the water of crystallisation, however, a Nef reaction occurs with formation of the bicyclic γ-lactone **409** in a one-pot process.




| Lewis acid | $R^1$ | $R^2$ | $R^3$ | **409** yield % |
|---|---|---|---|---|
| $Ni(ClO_4)_2 \cdot 6H_2O$ | H | H | H | 72 |
| $Yb(OTf)_3$ | Me | H | H | 55 |
| $Ni(ClO_4)_2 \cdot 6H_2O$ | H | Me | H | 68 |
| $Ni(ClO_4)_2 \cdot 6H_2O$ | H | Me | Me | 51 |

**Scheme 103.** Synthesis of bicyclic γ-lactones.

## 5. Conclusions

The nitro to carbonyl conversion has been firmly established, since its discovery by Nef more than a century ago, as one of the most important functional group transformations. The success of this procedure has been established by the large body of different synthetic protocols that have been set up over the years in order to accomplish this transformation with an increasingly higher level of chemoselectivity. A literature survey shows that a consistent number of syntheses directed towards the preparation of biologically active and industrially important compounds have inserted the Nef reaction into some crucial step of the overall synthetic plan. The originally designed hydrolytic system for this conversion is still largely practised in many synthetic routes in which acid- or base-sensitive groups are not present in the substrate. Hydrolysis of the nitronate anions can be replaced by an oxidative cleavage of the carbon nitrogen double bond using common oxidising agents. On the other hand, by means of a suitable choice of reaction conditions, it is possible to use reducing agents to transform nitroalkenes or their nitronate salts into carbonyl derivatives. In the conjugate additions of nitroalkenes with nucleophiles, a nitronate derivative is often formed as an intermediate. This represents a formidable opportunity to include the Nef conversion in a tandem sequence, with considerable advantages in the efficiency of the whole synthetic process. All these synthetic opportunities to carry out this transformation help in keeping the chemistry of nitro compounds at the very core of organic chemistry.

## Acknowledgements

The authors are greatly indebted to their co-workers whose names are cited in the references, for their enthusiasm and dedication. Financial support has been granted by M.I.U.R. and the University of Camerino.

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