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Desulfonylation Reactions: Recent Developments

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Contents

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1. INTRODUCTION

The use of sulfones, acting as an auxiliary group, is still an important synthetic strategy, especially for making carbon-carbon double bonds.[1,2] This functional group can modify the polarity of the molecule by acting as an electron-withdrawing group to stabilise carbanions or as a leaving group. Due to this dual chemical behaviour, sulfones have been called chemical chameleons.

Nowadays there are several synthetic methodologies in which sulfones are involved as activating groups. In the last 25 years the use of sulfones as intermediates in the total synthesis of many natural products has become a classic. After the required synthetic operation, the sulfone moiety can be exchanged by hydrogen (reductive desulfonylation), an alkyl group (alkylative desulfonylation), a carbonyl functionality (oxidative desulfonylation) or a nucleophile (nucleophilic displacement) as well as undergo a β-elimination or a sulfur dioxide extrusion process.

The present review deals with all these desulfonylation reactions between 1991 and 1999.

2. REDUCTIVE DESULFONYLATION

2.1. Replacement of the sulfone group by hydrogen

One of the most used transformations in sulfone-mediated synthetic methodologies is the substitution of the sulfone group by hydrogen. For this purpose several reducing agents such as dissolving metals and amalgams, samarium diiodide, hydrides in the presence of a transition metal as catalyst, sodium dithionite, and tin hydrides under free radical conditions, have been most commonly used. In this section, the different reductive desulfonylation methods have been classified depending on the type of sulfone as well as on the functionality present in the molecule.

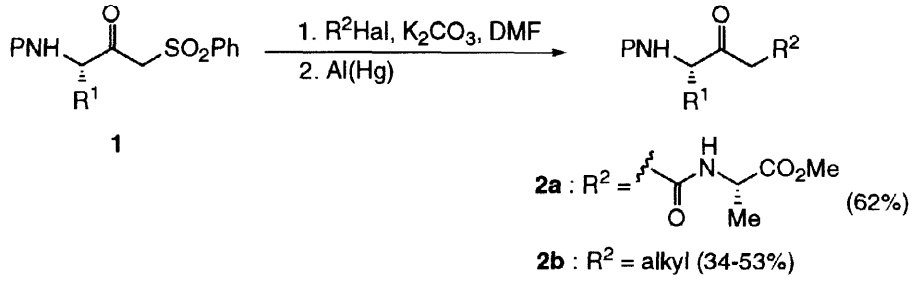
2.1.1. Alkyl sulfones

The most general methods for reducing simple alkyl sulfones can be used in the cases where other functional groups are present. Sodium amalgam (6%) in methanol in the presence of four equivalents of disodium hydrogen phosphate,[3] is still the most popular and general procedure for the reduction of all types of sulfones.

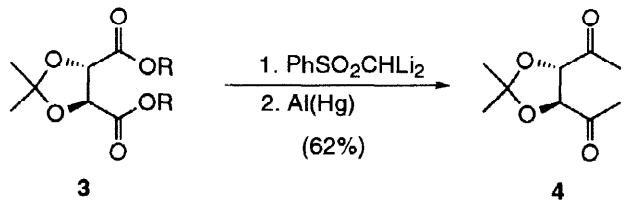
2.1.1.a. α-Functionalised alkyl sulfones

β-Ketosulfones are a very important family of sulfones, which are used as cationic[2b] and as carbanionic[2c] reagents in many syntheses. Corey and Chaykovsky initially used aluminium amalgam for the desulfonylation of this type of compound,[4] and this procedure was used in the total syntheses of okadaic acid,[5] the macrolide, aplasmomycin[6] and the A-ring precursor of 1α,25-dihydroxyvitamin D.[7] The recent applications of this reductive process are based on the alkylation of β-ketosulfones derived from α-amino acids **1** under mild reaction conditions and final desulfonylation, affording peptide isosteres such as **2a**[8] or enantiopure α-amino ketones **2b**.[9]

C_2-Symmetric 1,4-diketone **4** has been prepared from the tartaric acid derivative **3**, after final reduction with aluminium amalgam[10] (Scheme 2).

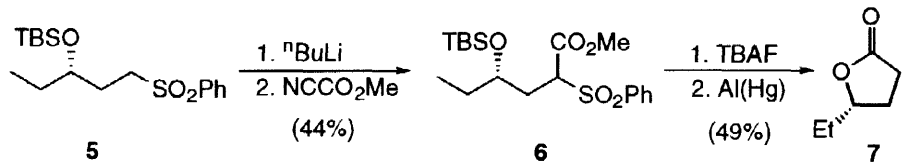


Scheme 1



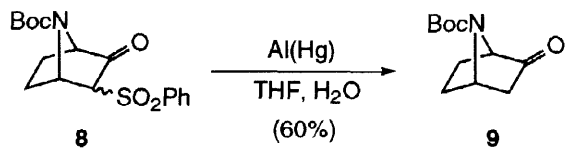
Scheme 2

Chiral γ-hydroxy sulfone **5**, obtained by microbiological reduction of the corresponding γ-keto sulfone, has been used in the synthesis of γ-butyrolactone **7**[11] (Scheme 3).



Scheme 3

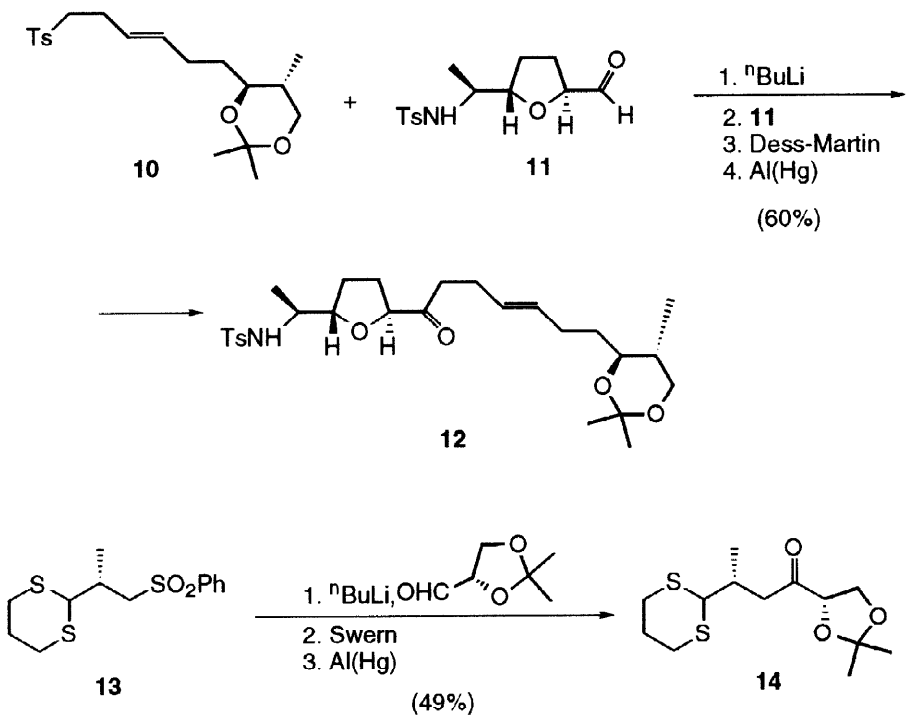
The last step in the preparation of the 7-azabicyclo[2.2.1]heptan-2-one **9**, a key intermediate for the preparation of the alkaloid epibatidine, is also the desulfonylation of the β-ketosulfone **8**[12] (Scheme 4).



Scheme 4

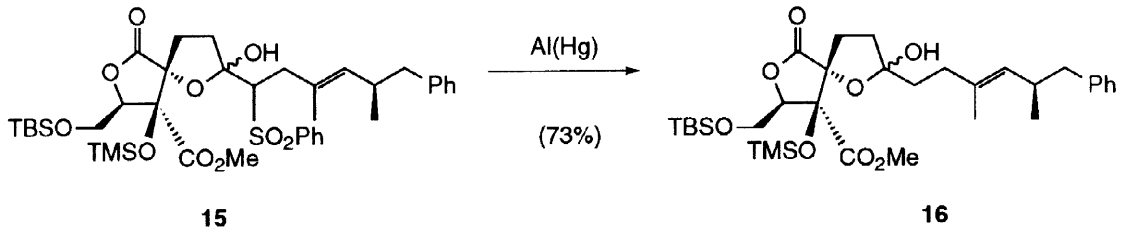
The coupling of the sulfone **10** with the aldehyde **11** is followed by oxidation to give a β-ketosulfone, which is finally reduced to the intermediate **12**[13a] for the synthesis of oligo-THF peptides (Scheme 5). In a similar fashion, the organolithium derivative of sulfone **13** reacts with protected L-glyceraldehyde to give ketone

14, a precursor of fragment B in the total synthesis of the immuno-modulators (-)-rapamycin and (-)-27-demethoxyrapamycin, after Swern oxidation and desulfonylation[13b] (Scheme 5).



Scheme 5

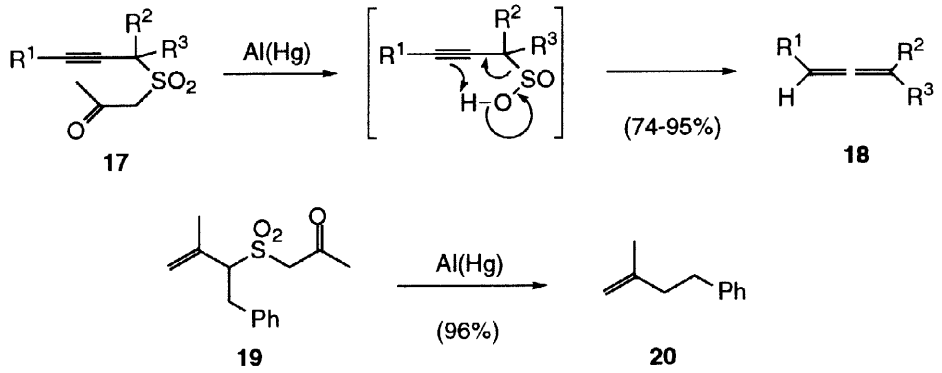
In a recent synthesis of the 6,7-dideoxysqualestatin H5, the β-ketosulfone **15** containing a hemiacetal structure is reduced to the corresponding product **16** using aluminium amalgam[14] (Scheme 6).



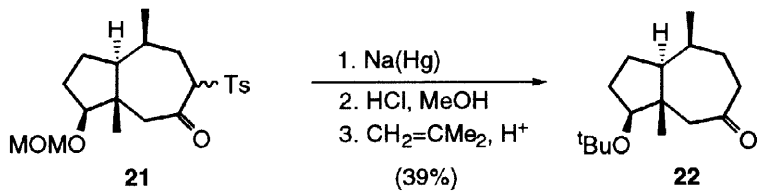
Scheme 6

Alkynyl sulfinic acids, generated by aluminium amalgam reduction of alkynyl sulfones **17**, undergo retro-ene reactions with expulsion of sulfur dioxide to give allenes **18**.[15] When this rearrangement is used with the allyl sulfone **19** alkene **20** is obtained[16] (Scheme 7).

Sodium amalgam is also a useful reagent for the reduction of keto sulfones and α-sulfonyllactones. Bicyclic ketosulfone **21**, obtained by intramolecular addition of the corresponding sulfonyl carbanion to the ester moiety, has been reduced to the ketone **22**, a key intermediate of damsinic acid[17] (Scheme 8).

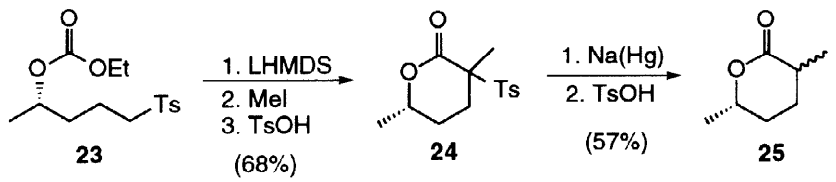


Scheme 7



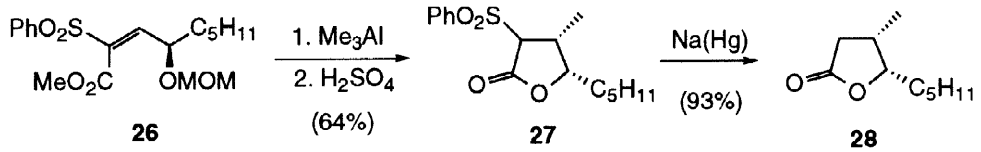
Scheme 8

Chiral α-sulfonyl lactones (for instance, **24**), obtained by intramolecular reaction of sulfonyl carbanions with carbonates, give after reduction the corresponding lactones **25**,[18] the *cis*-derivative being the sex pheromone of the carpenter bee (Scheme 9). If the cyclisation takes place with an ester group, the corresponding lactols are obtained, which after protection and desulfonylation, give the expected ketones.[19]



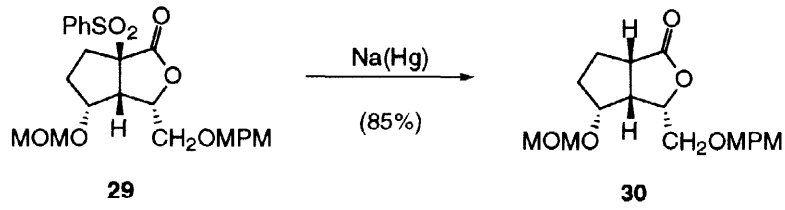
Scheme 9

γ-Butyrolactones have been prepared from chiral γ-hydroxy-α,β-unsaturated phenyl sulfones in a stereoselective manner.[20] This strategy has been applied to the synthesis of (-)-*cis* cognac lactone **28** (Scheme 10).



Scheme 10

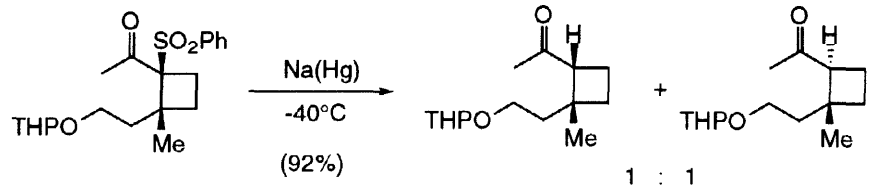
In the recent synthesis of the marine eicosanoid bacillariolide II from (*R*)-malic acid, the intermediate sulfonyl lactone **29** is reduced stereoselectively by sodium amalgam to lactone **30** in 85% yield [21] (Scheme 11).



29 **30**

Scheme 11

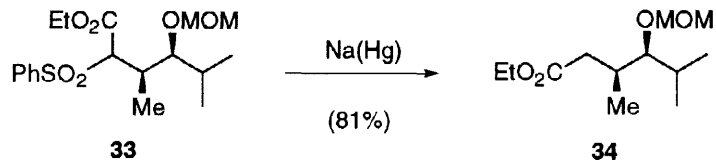
Cyclobutyl sulfone **31** has been transformed into cyclobutanes **32**[31] by removing the sulfone group with sodium amalgam. This process has been applied to the synthesis of grandisol and fragenol, after separation of both epimeric ketones **32**[22] (Scheme 12).



31 **32**

Scheme 12

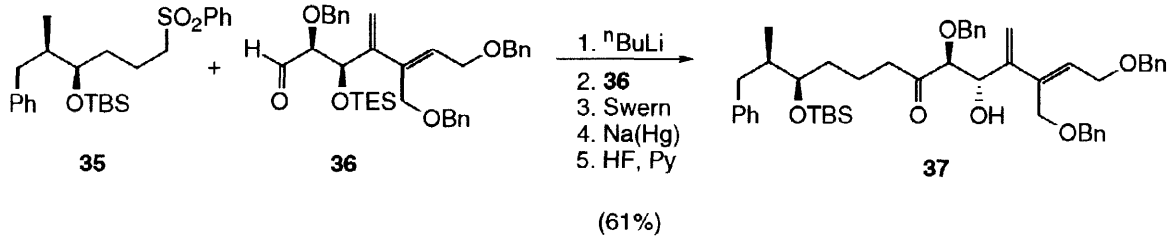
The α-sulfonyl ester **33** prepared by Carretero *et al.* from chiral γ-hydroxy-α,β-unsaturated sulfones, is reduced at room temperature to the ester **34**, a useful intermediate for the iterative construction of enantiomerically pure polypropionate chains[23] (Scheme 13).



33 **34**

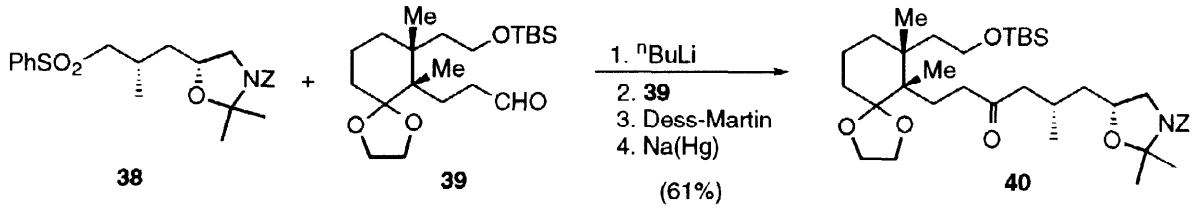
Scheme 13

The reaction of a sulfonyl carbanion with an aldehyde followed by oxidation of the alcohol formed and final desulfonylation with aluminium[13,14] or sodium[24-26] amalgam is a common strategy in many syntheses of natural products. Some recent examples are the studies towards the synthesis of the bicyclic acetal core of zaragozic acid C and the heterocyclic aminal core of zoanthamine and norzoanthamine alkaloids.[25] Thus, the ketone **37**, prepared in 61% yield by reaction of aldehyde **36** with the organolithium derived of the sulfone **35**, is an intermediate for the acetal of zaragozic acid C[24] (Scheme 14).



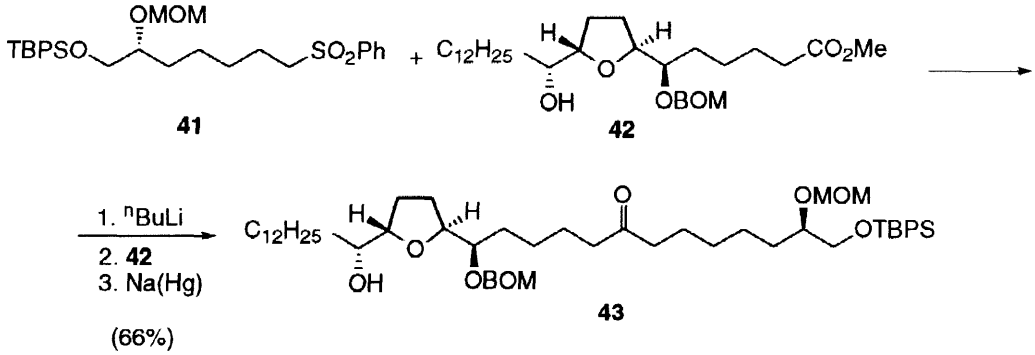
Scheme 14

In Scheme 15 is the enantioselective preparation of ketone **40**, which is an intermediate for the generation of the heterocyclic fragment of some marine alkaloids, such as zoanthamine and norzoanthamine.[25]



Scheme 15

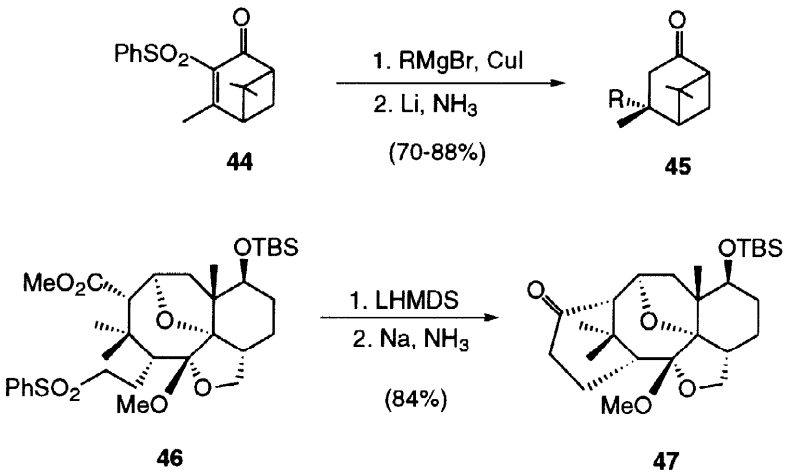
The last example is illustrated in Scheme 16, where the sulfone **41**, prepared from D-glutamic acid is lithiated and reacts with the ester **42**, prepared from L-glutamic acid, to give directly the ketone **43** after desulfonylation. This compound is an intermediate in the synthesis of a diastereoisomer of the monotetrahydrofuran type acetogenin annonacin A.[26]



Scheme 16

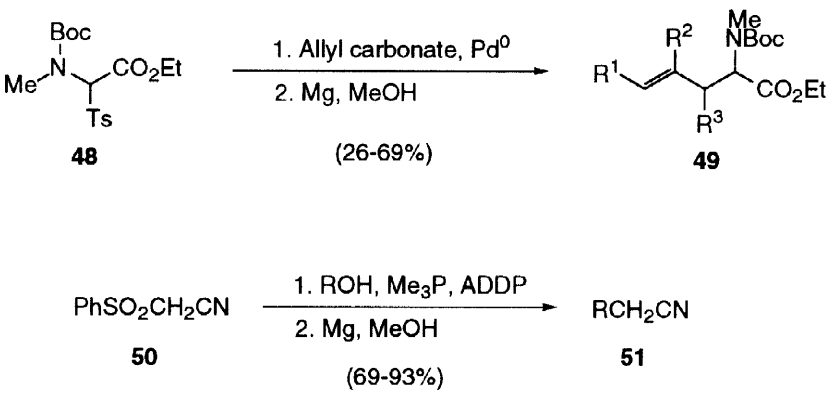
Lithium or sodium in liquid ammonia have been used in the reductive desulfonylation of β-ketosulfones. Thus, 3,3-disubstituted nopinones **45**, useful reagents for the asymmetric synthesis of elemanoid sesquiterpenes, have been prepared by stereoselective Michael addition of cuprates to α,β-unsaturated α-sulfonylketones **44** followed by treatment with lithium in liquid ammonia[27a] (Scheme 17). In addition, the A-ring of the taxane skeleton has been attached to the B/C ring system by cyclisation of the sulfone-ester **46** and

final reduction with sodium in liquid ammonia to yield ketone **47**[27b] (Scheme 17). Moreover, lithium naphthalenide has also been used in the reduction of β-ketosulfones in the synthetic studies of amphidinolides[28a] and galbonolide B.[28b]



Scheme 17

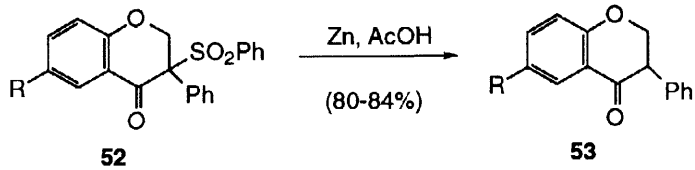
Magnesium in the presence of a catalytic amount of mercury(II) chloride (1 mol %) in methanol[29] or ethanol[30] is an useful reagent for the desulfonylation of simple alkyl sulfones,[30] α-sulfonyl esters,[30] α-sulfonyl lactones,[31] α-tosyl-α-amino esters,[32] and α-sulfonyl phosphonates,[33] but fails with β-ketosulfones.[30] The reduction of α-tosyl-α-amino esters by palladium-catalysed allylation of *N*-Boc-α-tosylsarcosine ethyl ester **48** affords γ,δ-unsaturated *N*-methyl-α-amino esters **49**[32a] (Scheme 18). A two carbon elongation of alcohols to nitriles is based on the Mitsunobu reaction of α-(phenylsulfonyl)acetonitrile **50** with alcohols, followed by desulfonylation with magnesium in methanol[32b] (Scheme 18).



Scheme 18

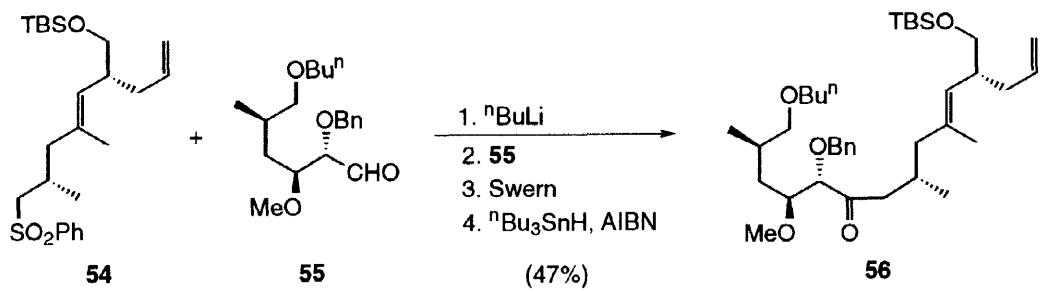
The reductive desulfonylation of β-ketosulfones with zinc and ammonium chloride in THF gives ketones in good yields.[34a] This method has been used in the synthesis of the CDE fragments of the model insect antifeedants, azadiradione and epoxyazadiradione.[34b]

For the desulfonylation of 3-(phenylsulfonyl)chroman-4-ones **52** to isoflavonones **53** only zinc-acetic acid can be used as the reducing agent[35] (Scheme 19). Recently, zinc and titanium tetrachloride in THF have been used in the reductive desulfonylation of β-ketosulfones.[36]

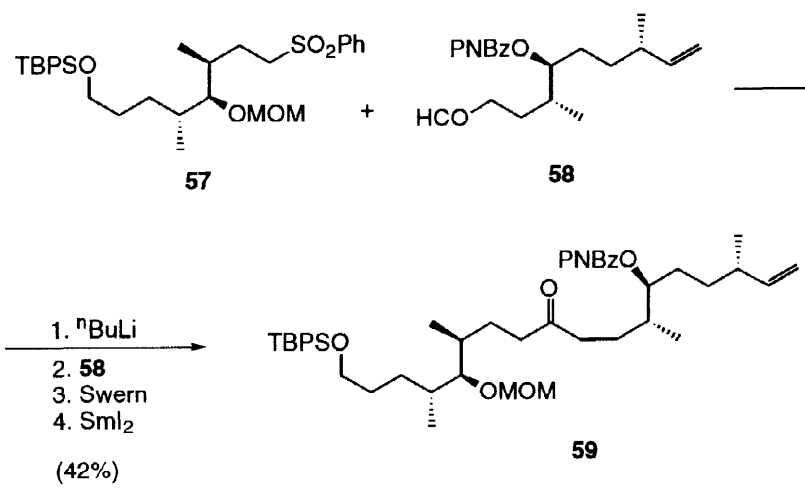


Scheme 19

Other reducing agents such as sodium dithionite in DMF,[37] samarium diiodide[38] and tributylstannane[39] have seldom been used in the case of β-ketosulfones. The synthesis of the C10-C22 fragment of the inmunosuppressant FK506 has been carried out *via* the coupling of sulfone **54** and aldehyde **55** followed by oxidation and finally by desulfonylation with Bu_3SnH to provide the ketone **56**[40c] (Scheme 20).



Scheme 20

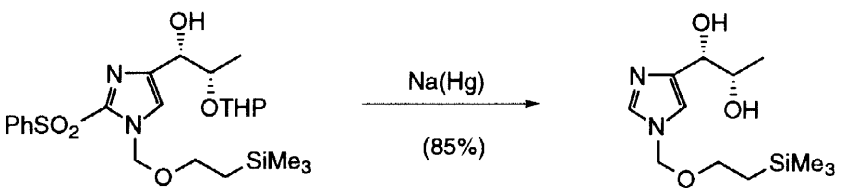


Scheme 21

In the total synthesis carried out by Ichihara's group, of the antifungal antibiotic, tautomycin, a potent protein phosphatase inhibitor, the corresponding β-ketosulfone prepared from aldehyde **58** and sulfone **57** is transformed into the ketone intermediate **59** by means of samarium diiodide[41] (Scheme 21).

Other α-substituted sulfones, *e.g.* α-nitrosulfones, have been desulfonylated by sodium dithionite to nitrocompounds, using octylviologen as an electron transfer catalyst in organic solvent-water, two-phase systems .[42] α-Bromosulfones can be reduced by PhSeNa, prepared *in situ* with diphenyl diselenide and $NaBH_4$.[43]

The phenylsulfonyl moiety has been used as the protecting group at the 2-position of imidazole, in order to carry out metallation at the 4-position, and can finally be removed with sodium amalgam[44] (Scheme 22).



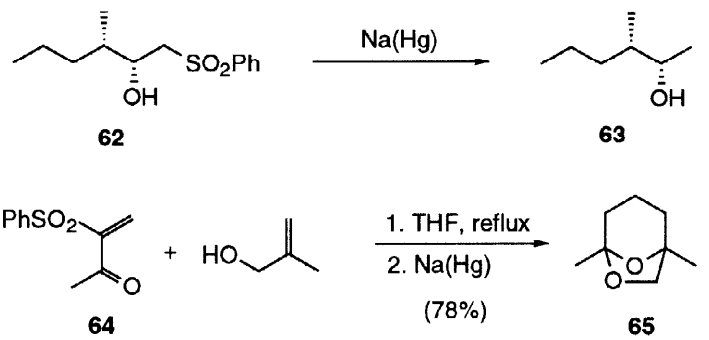
60 **61**

Scheme 22

In the case of aminosulfones with the structure of 3-(phenylsulfonyl)-2-alkyl-2,3-dihydroisoindol-1-ones, the desulfonylation is effected in quantitative yield using Raney nickel promoted by ultrasound.[45]

2.1.1.b. Other functionalised alkyl sufones

β-Hydroxy or β-alkoxy sulfones are prone to undergo β-elimination under reductive conditions, especially with sodium amalgam, affording olefins instead of the corresponding alcohols, ethers or esters (see Section 2.2.1). Some exceptions have been included in Scheme 23: the chiral β-hydroxy sulfone **62**, obtained by yeast reduction of the corresponding β-keto sulfone, has been desulfonylated with sodium amalgam to give the alcohol **63**, for chemical correlation purposes[46] (Scheme 23). The one-pot synthesis of the pheromone, frontalin (**65**) from 3-(phenylsulfonyl)-3-buten-2-one (**64**), is based on a hetero-Diels-Alder reaction with methallyl alcohol, followed by reduction[47] (Scheme 23).

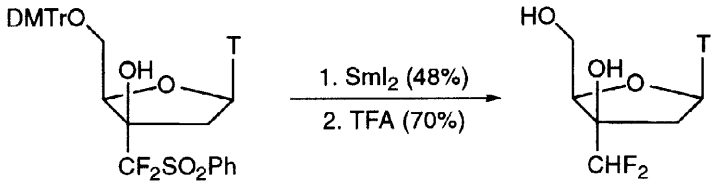


62 **63**

64 **65**

Scheme 23

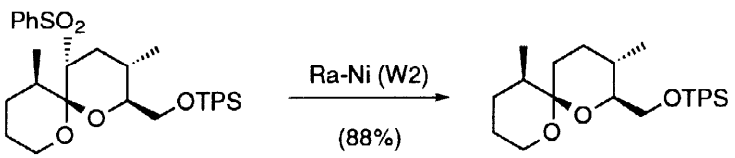
β-Acetoxy sulfones can be reduced with samarium diiodide[38a] as can be β-hydroxy difluoromethyl phenyl sulfone **66**,[48] which has been used for the synthesis of 3'-difluoromethyl-3'-deoxythymidine (**67**) (Scheme 24).



66 **67**

Scheme 24

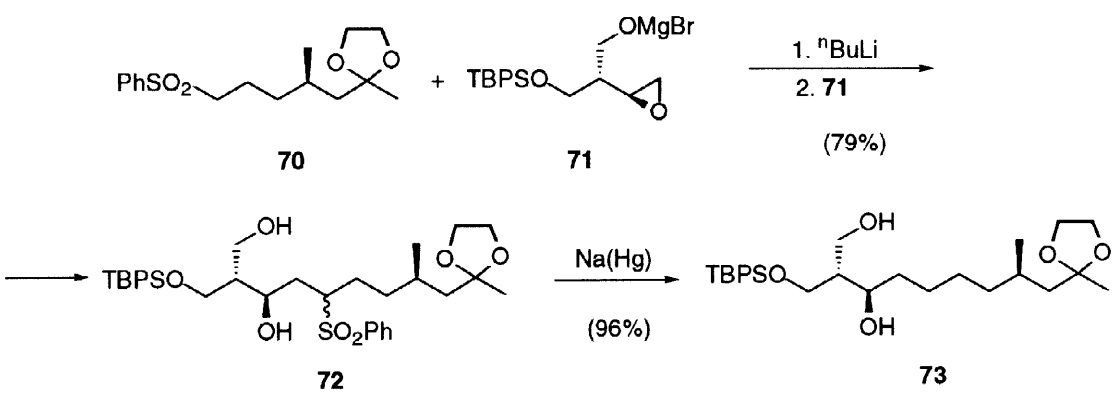
In the case of sulfone **68** the reduction has been carried out with Raney nickel W-2 to give the spiroketal **69**[49a,b] (Scheme 25). Cyclic β-hydroxy sulfones with *cis* configuration have been reduced to the corresponding alcohols with Raney nickel.[49c]



68 **69**

Scheme 25

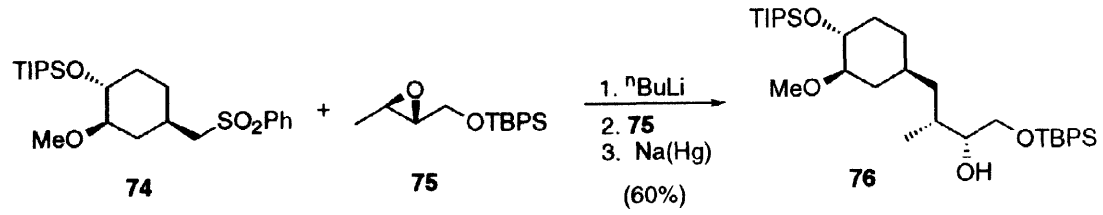
There are many interesting examples of the reductive desulfonylation of γ-hydroxy or γ-alkoxy sulfones with sodium amalgam. One of the most useful strategies for making carbon-carbon bonds, in several convergent syntheses of natural products, is the coupling of a sulfonyl carbanion with an epoxide to give the corresponding γ-hydroxy sulfone and concomitant removal of the sulfone moiety with sodium amalgam. Mori and Takahashi have prepared the antibiotic 1233A, an inhibitor of cholesterol biosynthesis in animal cells, using intermediate **73**, which has been obtained by coupling sulfone **70** with epoxide **71**, to give the γ-hydroxy sulfone **72**, followed by desulfonylation[50] (Scheme 26).



70 **71** **72** **73**

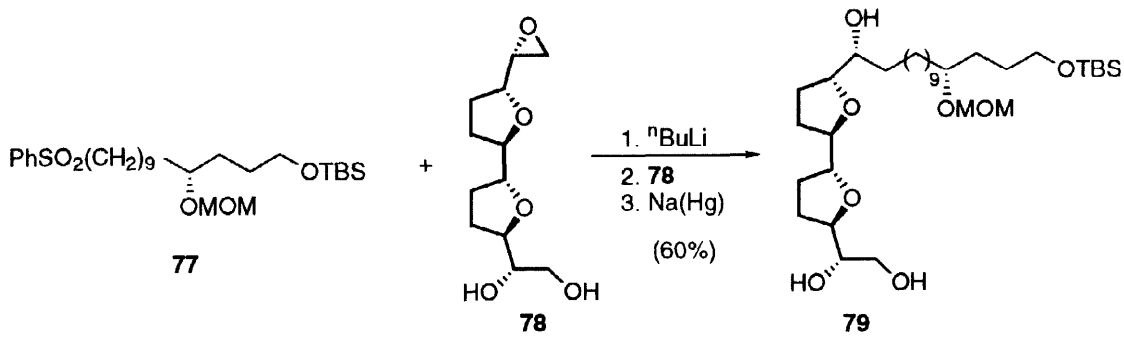
Scheme 26

In the total synthesis of the antibiotic rapamycin,[51] by Smith III *et al.*,[52] the fragment A is prepared by coupling sulfone **74** with epoxide **75**, followed by desulfonylation, to give alcohol **76**[53] (Scheme 27).

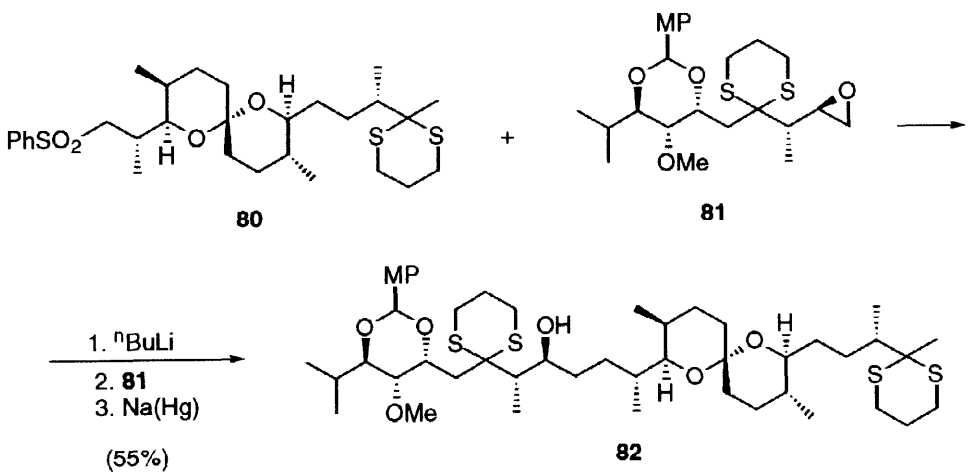


Scheme 27

In the first total synthesis of the potent antitumor *Annonaceous* acetogenin, (+)-bullatacin, isolated from the genera of *Annonoceae* plants, the epoxide **78** containing the bistetrahydrofuran skeleton is condensed with the lithiated sulfone **77** then reduced to the fragment **79**[54] (Scheme 28). A similar procedure has also been carried out for the synthesis of the stereoisomer (+)-(15,24)-*bisepi*-bullatacin.



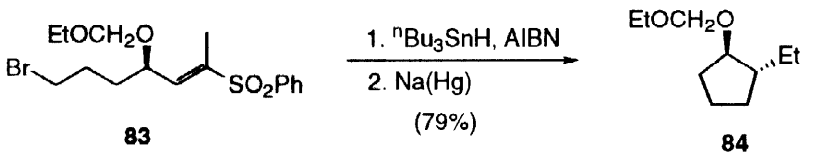
Scheme 28



Scheme 29

The total synthesis of the antibiotic polyether, (+)-tautomycin, by Isobe *et al.*, twice used the reation of a sulfonyl carbanion with an epoxide.[55] In Scheme 29, the coupling of sulfone **80** (segment C) and epoxide **81** (segment B) gives compound **82**. The same group has prepared the okadaic acid-tautomycin hybrid by the same strategy.[56]

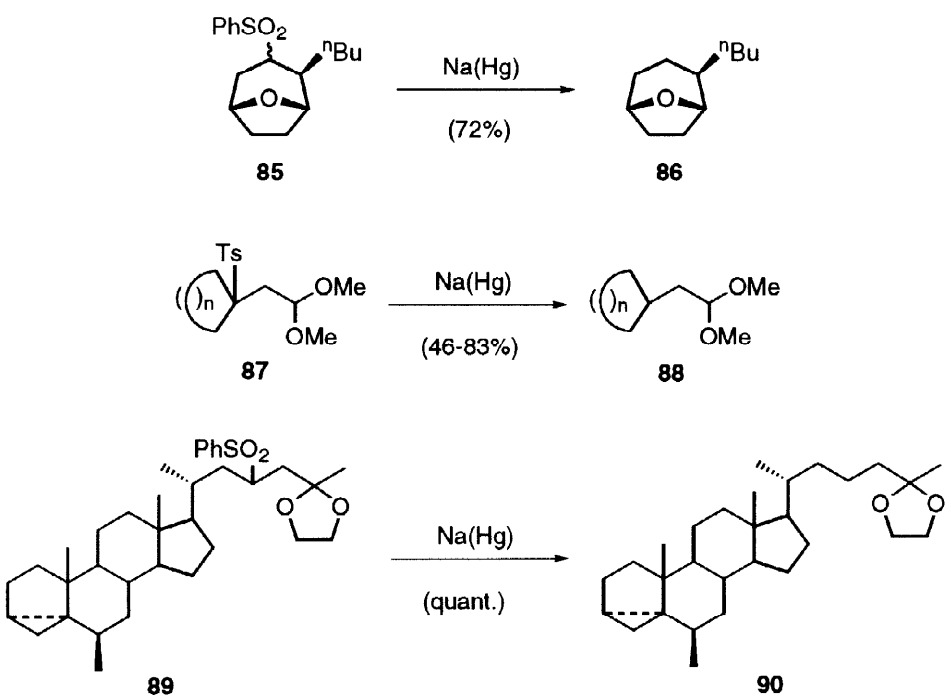
The configurational assignment of γ-hydroxyvinyl sulfones, obtained by lipase-catalysed kinetic resolution, has been carried out by their transformation into the corresponding γ-hydroxy sulfones and final desulfonylation to the expected alcohols.[57] The same authors reduced cyclic sulfones, obtained by radical cyclisation of γ-alkoxyvinyl sulfones **83**, in order to establish the configuration of the cyclic products.[58] (Scheme 30).



83 **84**

Scheme 30

The γ-alkoxy sulfone **85**, obtained from 2-(phenylsulfonyl)-1,3-dienes,[2d] has been desulfonylated by treatment with sodium amalgam to afford the corresponding oxabicyclooctane **86**[59] (Scheme 31). Ketals **87**, which have been prepared by *gem*-dialkylation of the dianion, 3,3-dilithio-1,1-dimethoxy-3-tosylpropane, give β,β-disubstituted propanal acetals **88** after reductive desulfonylation.[60] A quantitative yied has been obtained in the case of the steroidal sulfone **89**[61] (Scheme 31).



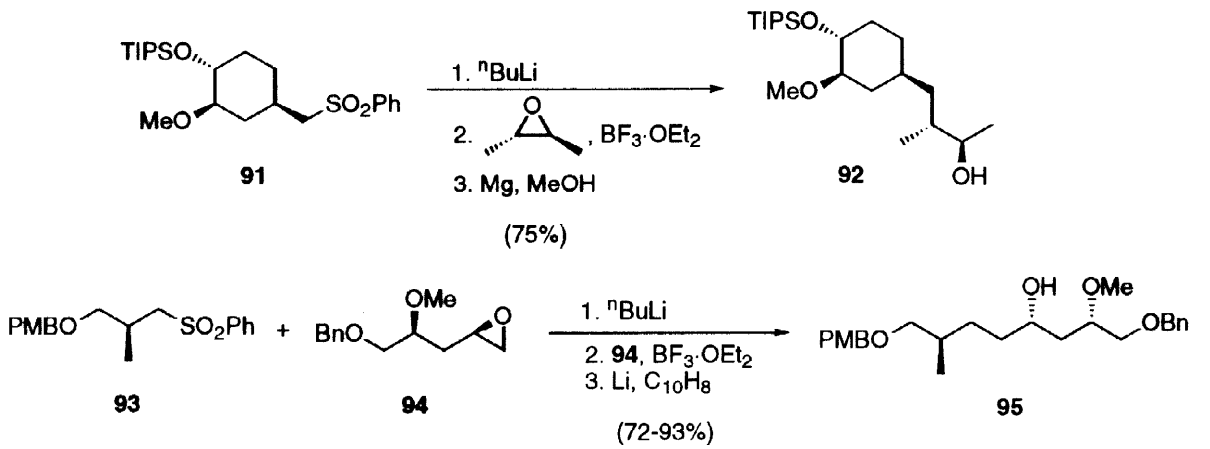
85 **86**

87 **88**

89 **90**

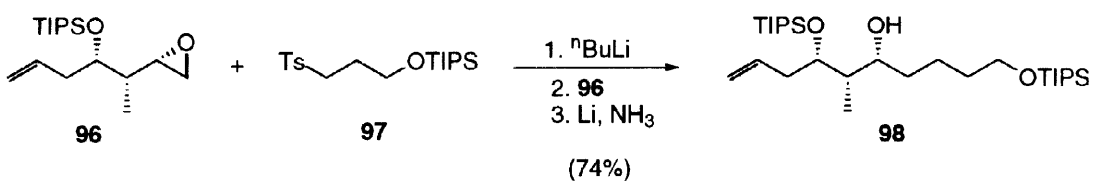
Scheme 31

γ-Alkoxy sulfones have also been reduced with magnesium in ethanol[62] and with samarium diiodide.[39a] The reduction of γ-hydroxy sulfones, prepared by the reaction of sulfonyl carbanions with epoxides, has also been carried out with magnesium in methanol[63] and lithium naphthalenide.[64] These methods have been used in the synthesis of a precursor **92** of the C33-C42 fragment [63] of rapamycin[51] by Kocienski *et al.*, and in the preparation of a precursor **95** of its C10-C17 carbon unit by Ley *et al.*.[64] (Scheme 32).

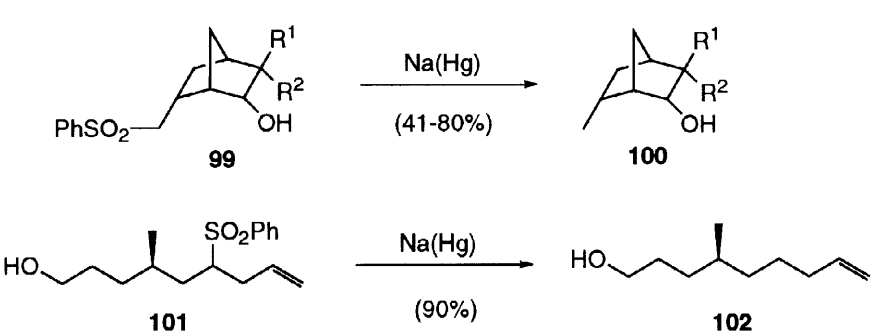


Scheme 32

In the total synthesis of altohyrtin A or spongistatin 1, by Kishi *et al.*, the coupling of an epoxide **96** with a lithiated γ-alkoxy sulfone **97** is followed by reduction with lithium in liquid ammonia at -78°C to provide compound **98**, a precursor of the EF unit[65] (Scheme 33). Mori *et al.* have also used lithium in ethylamine in the preparation of the stereoisomers of 6,10,14-trimethyl-2-pentadecanol, the female-produced sex pheromone of the rice moth.[66]



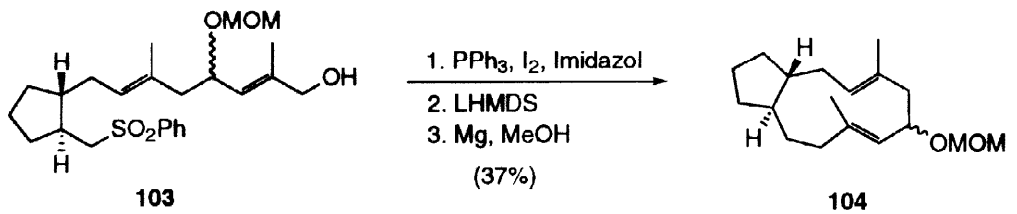
Scheme 33



Scheme 34

Other functionalised sulfones such as bicyclic derivatives **99**[67a] or **101**[67b] have been reduced with sodium amalgam to give the corresponding desulfonylated compounds **100** and **102**, respectively, the latter being the precursor of the female sex pheromone, (*R,R*)-6,12-dimethylpentadecan-2-one, of the banded cucumber beetle[67a] (Scheme 34). The same reductive method has been used in the final step of the solid phase synthesis of 3,5-pyrazolidinedione, for the cleavage from the corresponding PEG-bound sulfones,[68a] and for the desulfonylation of cycloadducts resulting from the reaction of methylenecyclopropanes with vinyl sulfones under Pd(0) catalysis.[68b]

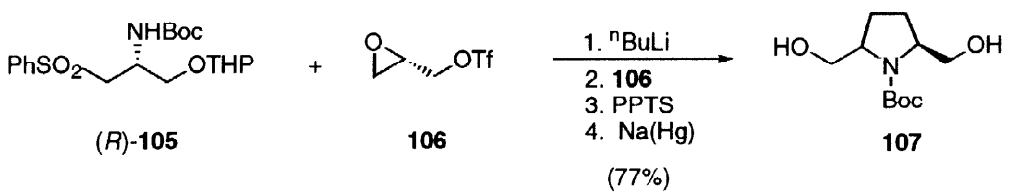
The construction of the bicyclo[9.3.0]tetradecane dolabellane skeleton has been performed by intramolecular alkylation of the α-carbanion of the sulfone **103**, followed by desulfonylation with magnesium in methanol[69] (Scheme 35).



103 **104**

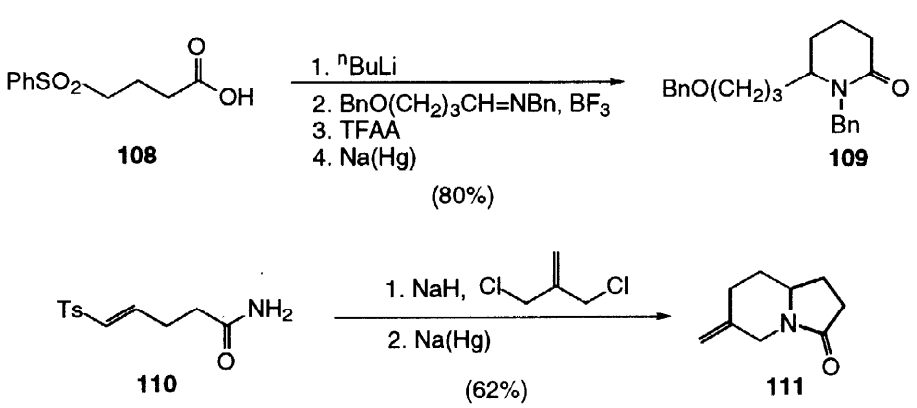
Scheme 35

β-Aminoalkyl sulfones are mainly used as carbanionic reagents for the preparation of nitrogen-containing heterocycles, after final desulfonylation with sodium amalgam. Anions derived from Sasaki's reagents (*R*)- and (*S*)-**105**, prepared from *N*-Boc-L-serine methyl ester, react with dielectrophiles to give *N*-heterocyclic and cyclic α-amino acids.[70] For example, in the case of glycidyl triflate **106**, 2,5-disubstituted pyrrolidines **107** can be prepared[70d] (Scheme 36).



(*R*)-**105** **106** **107**

Scheme 36

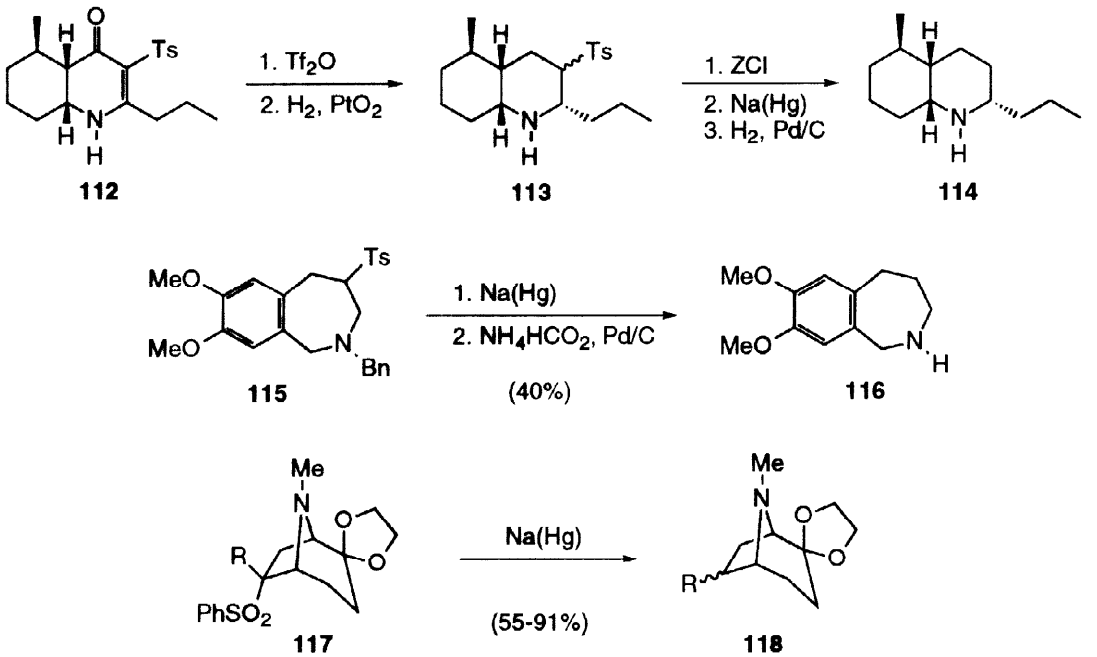


108 **109**

110 **111**

Scheme 37

Indolizidine derivatives have been prepared from lactams **109**, which are obtained by reaction of the 4-(phenylsulfonyl)butanoic acid **108** dianion with imines then reductive desulfonylation[71] (Scheme 37). In the case of the dianion of δ-tosyl amide **110**, the reaction with dielectrophiles, for example 2-(chloromethyl)-3-chloropropene, followed by reduction gives the indolizidone **111** in a two-step procedure[72] (Scheme 37).

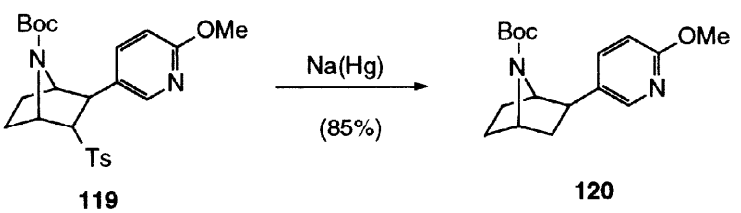


112 **113** **114** **115** **116** **117** **118**

Scheme 38

The alkaloid pumiliotoxin C **114** has been prepared in racemic form *via* the β-aminosulfone **113** from the intermediate enaminone **112** in 46% overall yield[73] (Scheme 38). The precursor **116**[74] of capsazepine, an antagonist of the sensory neuron excitants, capsaicin and resiniferanotoxin,[75] has been obtained by sodium amalgam reduction of sulfone **115** (Scheme 38). In addition, 6-alkyltropan-2-ones **118** have been prepared by the same reduction of sulfones **117**[76] (Scheme 38).

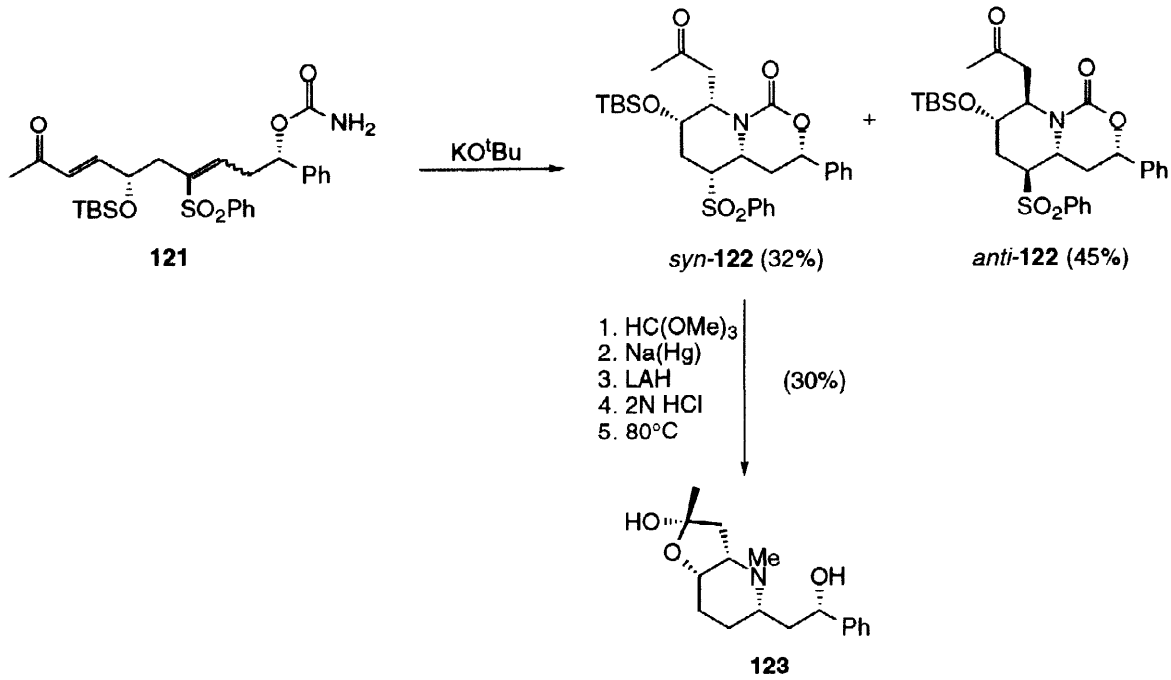
A concise stereoselective synthesis of the alkaloid, epibatidine, is based on a cycloaddition of ethinyl *p*-tolyl sulfone with *N*-Boc-pyrrol. Further hydrogenation and Michael addition of 2-methoxy-5-lithiopyridine provides the β-amino sulfone **119** which, after reduction with sodium amalgam, affords the intermediate azabicyclo[2.2.1]heptane **120**, a precursor of epibatidine[77] (Scheme 39).



119 **120**

Scheme 39

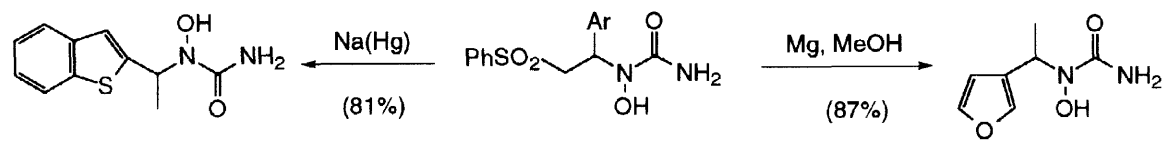
Intramolecular conjugate addition of a carbamate group to the vinyl sulfone **121** takes place with low diastereoselectivity, but both diastereoisomers **122** can be separated and transformed into the piperidine alkaloid (-)-sedacryptine **123**.[78] Scheme 40 shows the case of the 6,7-*anti* isomer, in which the ketone group is protected in order to carry out the desulfonylation process with sodium amalgam.



121 *syn*-**122** (32%) *anti*-**122** (45%) **123**

Scheme 40

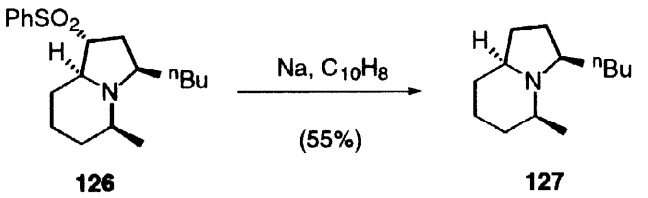
The 5-lipoxygenase inhibitors zileuton **125a** and A-69412 **125b** have been prepared by conjugate addition of hydroxylamine to the corresponding vinyl sulfones followed by transformation into *N*-hydroxy ureas **124a,b**, which are finally desulfonylated either with magnesium or with sodium amalgam[79] (Scheme 41).



125a **124a,b** **125b**

Scheme 41

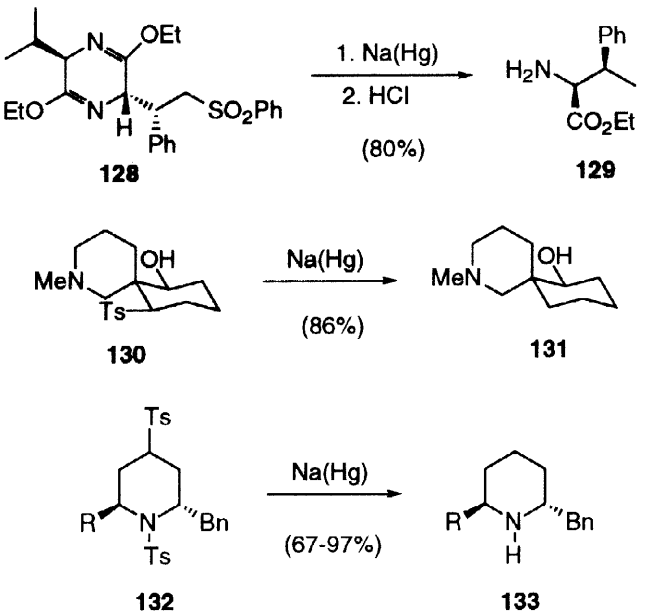
Sodium naphthalenide has been used in the reduction of β-amino sulfone **126**, obtained by intramolecular amination of vinyl sulfones, in the final step of the synthesis of the indolizidine alkaloid monomorine I **127**,[80] the trail pheromone of the Pharaon worker ant *Monomorium pharaonis* (Scheme 42). 2,5-Disubstituted pyrrolidines have also been prepared by intramolecular amination of γ-amino substituted vinyl sulfones and final desulfonylation with samarium diiodide.[81]



126 127

Scheme 42

γ-Amino substituted alkyl sulfones **128** and **130** have been reduced with sodium amalgam for the preparation of β-substituted α-amino acids **129**[82] and the *Nitraria* alkaloids, (+)-isonitramine and (-)-sibirine (**131**),[83] respectively (Scheme 43). The last step in the synthesis of 2,6-disubstituted piperidines **133** from 4-tosyl-2-butanone dimethyl ketal is also the reduction of the ditosylated piperidine **132** with sodium amalgam[84] (Scheme 43).



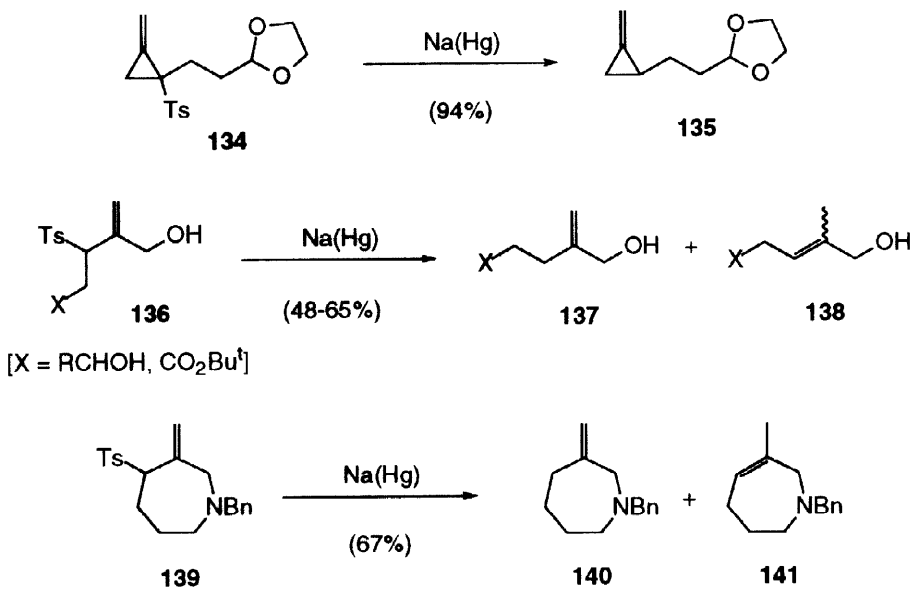
128 129 130 131 132 133

Scheme 43

2.1.2. Allylic sulfones

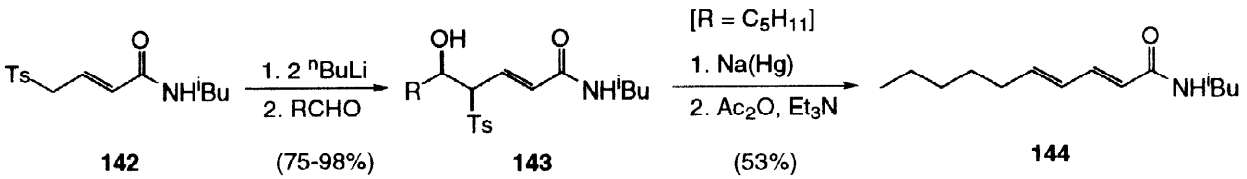
Reductive desulfonylation of allylic sulfones can be carried out with dissolving metals and amalgams or tributyltin hydride under radical conditions. The reduction with hydrides as nucleophiles will be considered in Section 5 as a nucleophilic displacement methodology. The main problem of this reaction is, in general, the control of the regio and stereochemistry of the olefinic product.

The tosylated methylenecyclopropane **134**, obtained from dilithiated 2-(chloromethyl)-3-tosylpropene, is regioselectively reduced with sodium amalgam to give compound **135**.[85] However, γ-hydroxy allylic sulfones **136** gave a mixture of regio and steroisomeric olefins **137** and **138**,[86a] the same problem being observed for cyclic derivatives, for instance the perhydroazepine **139**, which affords the unsaturated heterocycles **140** and **141**[87] (Scheme 44).



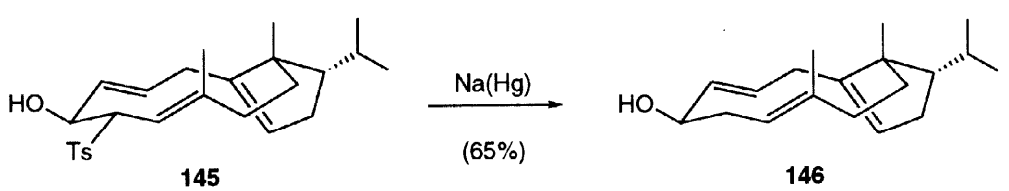
Scheme 44

The reduction of allyl sulfones **143**, prepared by γ-functionalisation of the corresponding γ-tosyl substituted crotonamide **142** dianion, occurs regio and stereoselectively to provide (*E*)-β,γ-unsaturated amides.[88] This methodology has been applied to the synthesis of the naturally occurring dienamide,[89] pellitorine **144** (Scheme 45).



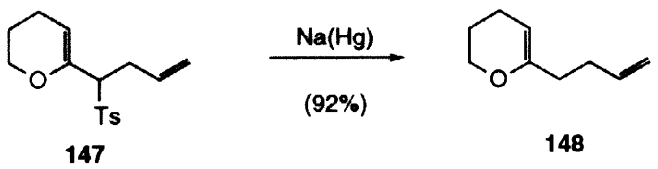
Scheme 45

Allylic sulfone **145** with a hydroxy group at the β-position has been reduced to the diterpene (±)-β-neodolabellenol **146** with sodium amalgam without olefination problems, probably because the hydroxy group is at the equatorial position[90a] (Scheme 46). The final step of the total synthesis of the dolabellane diterpenoid claenone from D-mannitol is the reduction of an allylic sulfone with sodium amalgam.[90b]



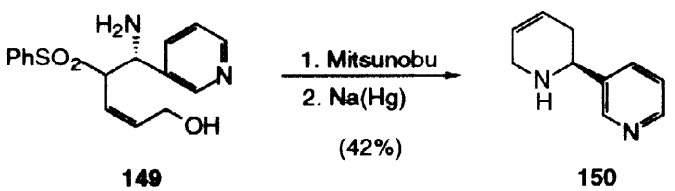
Scheme 46

α-Tosylalkyl substituted dihidro 2*H*-pyran **147** can be desulfonylated with sodium amalgam, whereas the reduction with aluminium amalgam failed[91] (Scheme 47). However, an excess of sodium naphthalenide has been shown to be an adequate reducing agent for this type of sulfone.[92]



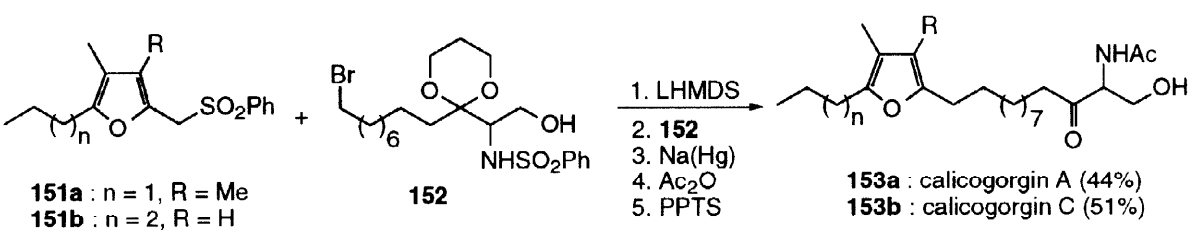
Scheme 47

In the synthesis of the piperidine alkaloid (*S*)-anatabine **150**, allylic sulfone **149** is cyclised under Mitsunobu conditions to provide, after final reduction with sodium amalgam, the expected compound **150**[93] (Scheme 48).



Scheme 48

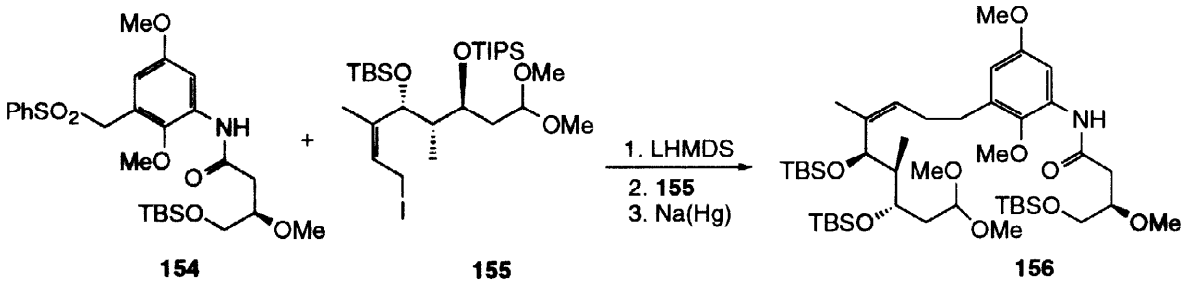
Benzylic sulfones can also be reduced with sodium amalgam in good yields. In the synthesis of calicogorgins, 3-ketosphinganine derivatives isolated from marine invertebrates, the alkylation of sulfones **151** with the bromide **152** is followed by desulfonylation of both sulfonyl moieties to afford, after two more steps, calicogorgin A and C **153**[94] (Scheme 49).



Scheme 49

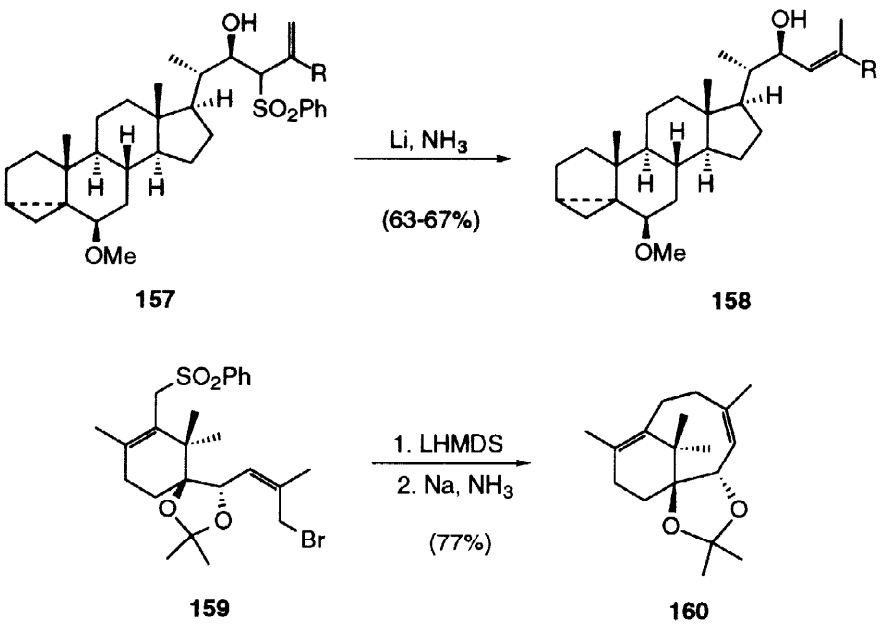
The preparation of compound **156**, a common key intermediate in the total synthesis of the ansamycin antibiotics, (+)-mycotrienin and mycotrienol, is based on the coupling of the benzylic sulfone **154** with the allylic iodide **155** and final reductive desulfonylation[95] (Scheme 50).

Heathcock *et al.* described recently the preparation of substituted pyridines by alkylation of pyridylmethyl phenyl sulfones followed by treatment with sodium amalgam. These compounds are useful fragments for the synthesis of the marine alkaloids, petrosin C and D.[96]



Scheme 50

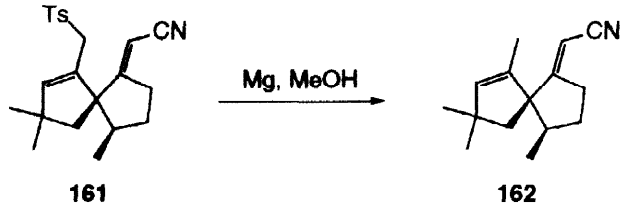
α-Silylated allylic sulfones, prepared by silylation of α-sulfonyl allylic carbanions, have been reduced with sodium dimethylaminonaphthalenide to the corresponding allylsilanes, in a regioselective manner.[97] Sodium or lithium in liquid ammonia usually promotes migration of the double bond. In the construction of brassanolide, side chain allylic alcohols **158** are mainly obtained from the starting material **157**[98] (Scheme 51). However, in the synthesis of the taxol AB-system, no migration of the carbon-carbon double bond is observed for the transformation of compound **159** into **160**[99] (Scheme 51).



Scheme 51

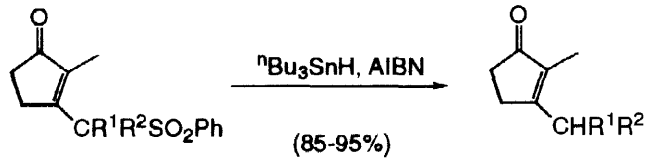
Similar to sulfone **159**, the allylic derivative **161** has been reduced regioselectively to compound **162**, an intermediate in the asymmetric synthesis of triquinanic compounds,[100] by means of magnesium in methanol[30] (Scheme 52).

3-(Phenylsulfonyl)methyl substituted cyclopentenones **163**, prepared by reaction of 2,3-dibromo-1-(phenylsulfonyl)-1-propene with 1,3-dicarbonyl compounds, have been readily desulfonylated to cyclopentenones **164** with tributyltin hydride and AIBN in toluene at 110°C[101] (Scheme 53).



161 162

Scheme 52



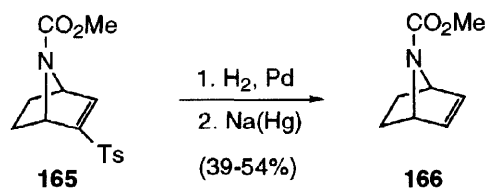
163 164

Scheme 53

Palladium-catalysed reduction of allylic sulfones with borohydrides will be considered later in the nucleophilic substitution reactions (Section 5.3).

2.1.3. Vinyl sulfones

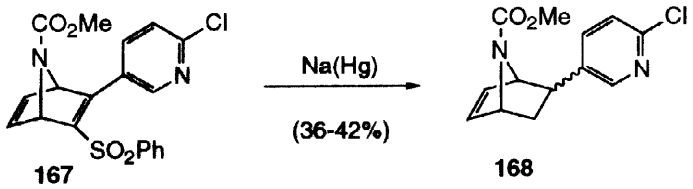
The reduction of vinyl sulfones with dissolving metals or metal amalgams to give the corresponding olefins is synthetically useful in many cases, especially if the vinyl sulfone takes part in a bicyclic system resulting from a Diels-Alder reaction of an alkynyl sulfone. This strategy has been used in several synthesis of epibatidine and its analogous.[102] The cycloaddition between *N*-methoxycarbonyl pyrrole and ethynyl *p*-tolyl sulfone gives the cycloadduct **165**, which is partially hydrogenated then desulfonylated with sodium amalgam to yield the 7-azabicyclo[2.2.1]heptene **166** (Scheme 54), precursor of epibatidine, by palladium-catalysed coupling with 2-chloro-5-iodopyridine.[104] This desulfonylation can also be carried out by using 2.5% sodium amalgam in a 1:1 *tert*-butanol:ethyl acetate mixture, for the *N*-Boc derivative.[105]



165 166

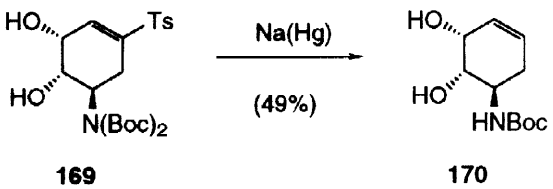
Scheme 54

An alternative strategy for epibatidine is the cycloaddition of *N*-carbomethoxy pyrrole with 1-(phenylsulfonyl)-6-chloro-3-pyridylacetylene to give compound **167**, which during desulfonylation with sodium amalgam undergoes concomitant reduction of the conjugated double bond, providing product **168** as a 1:2 mixture of the corresponding *exo* and *endo* diastereoisomers[106] (Scheme 55).



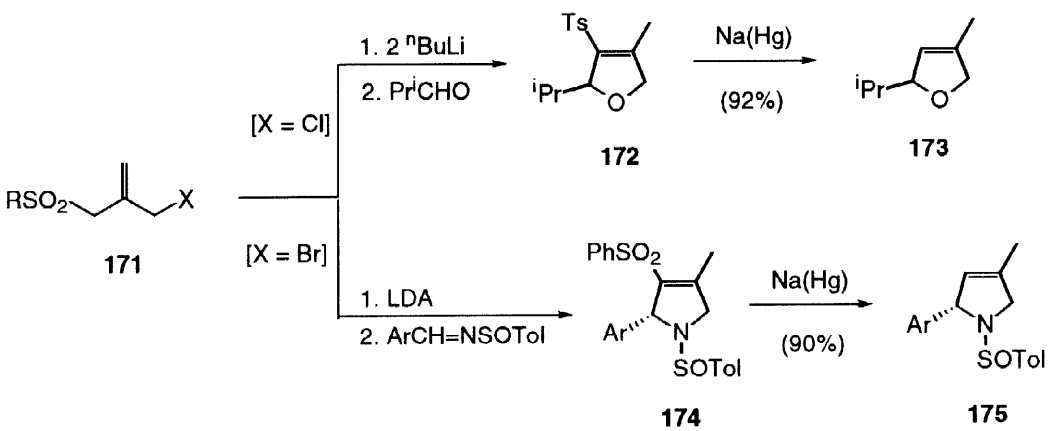
Scheme 55

The synthesis of conduramines is also based on the cycloaddition of Boc-pyrrole and *p*-toluenesulfonyl acetylene followed by opening of the 7-azabicyclo[2.2.1]heptane derivative, hydroxylation to compound **169** and reduction with sodium amalgam to give product **170** (Scheme 56). The acetonide related to compound **169** has to be reduced with samarium diiodide to afford the corresponding cyclohexene derivative in 28-52% yield.[107]



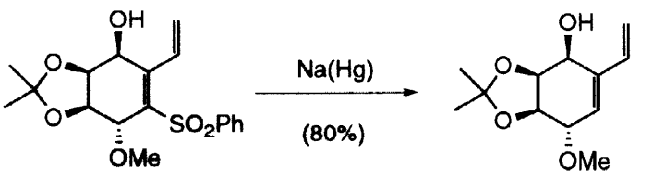
Scheme 56

Other cyclic vinyl sulfones, such as **172**[85] and **174**,[108] obtained by the reaction of the dianion of **171** (X = Cl) with isobutanal[85] and of the monoanion of **171** (X = Br) with sulfinimines,[108] respectively, are reduced, in good yields, with sodium amalgam to afford the corresponding dihydrofuran **173**[85] and chiral pyrrolines **175**,[108] respectively (Scheme 57).



Scheme 57

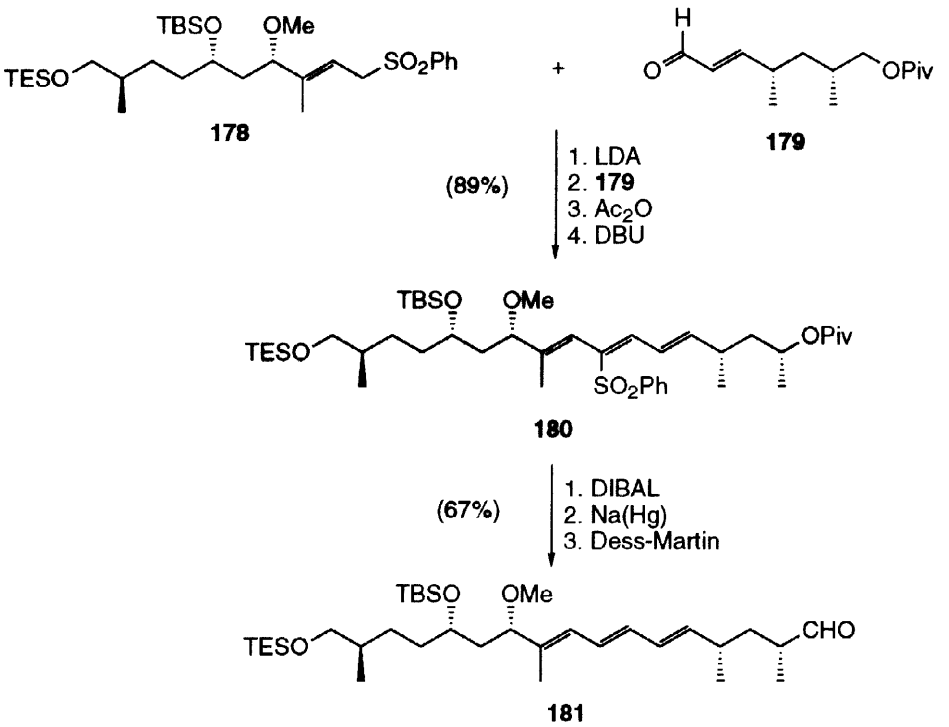
1-Sulfonyl-2,3-diene **176** has also been reduced with sodium amalgam to the diene **177**, a precursor of a carbasugar related to rancinamycin III[109] (Scheme 58).



176 177

Scheme 58

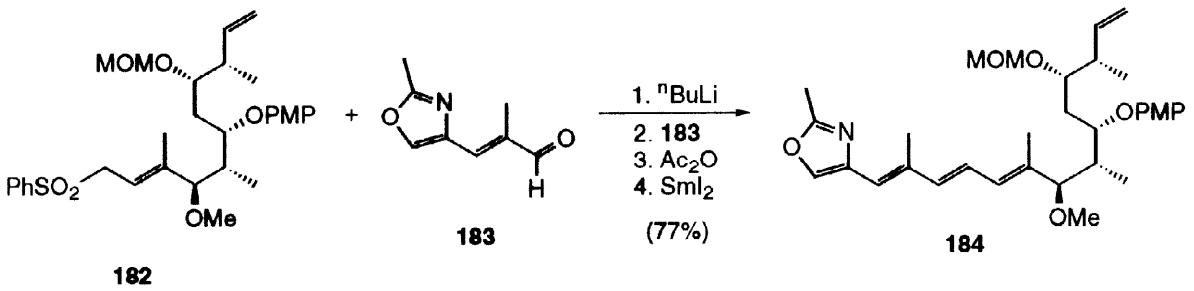
In the synthesis of the C10-C27 segment of rapamycin[51] by Danishefsky *et al.*, the coupling of the carbanion, derived from an allylic sulfone **178**, with an α,β-unsaturated aldehyde **179** gives a sulfonyl triene **180**, which has been reduced stereoselectively with sodium amalgam and then oxidised to the triene **181**[110] (Scheme 59).



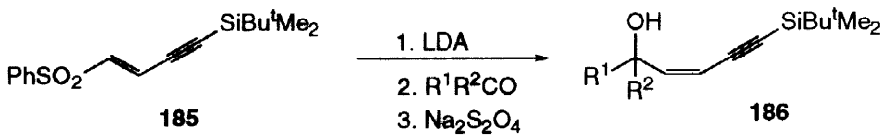
Scheme 59

The synthesis of the C10-C26 fragment of the 16-membered antitumor macrolide rhizoxin uses samarium diiodide for the reduction step[111] (Scheme 60). This synthetic strategy to generate trienes can be also considered as a modified Julia coupling[112] (see below, Section 2.2.1). On the other hand, samarium diiodide has been used successfully in the stereoselective reduction of vinyl sulfones.[38a,113,114]

Julia *et al.* introduced the stereospecific reduction of vinyl sulfones by treatment with sodium dithionite, which takes place after a *syn*-conjugate addition of the HSO_2^- anion followed by loss of sulfur dioxide and final *anti*-elimination of sulfinate.[115] This reduction has been used in the preparation of intermediates of some oligoolefins, which constitute acetogenin pheromonal components for more than 65 species of lepidopteran insects.[116] A stereoselective synthesis of the *cis*-enyne **186** is based on the reaction of the vinyl anion, derived from the starting material **185**, with carbonyl compounds followed by sodium dithionite reduction[117] (Scheme 61).

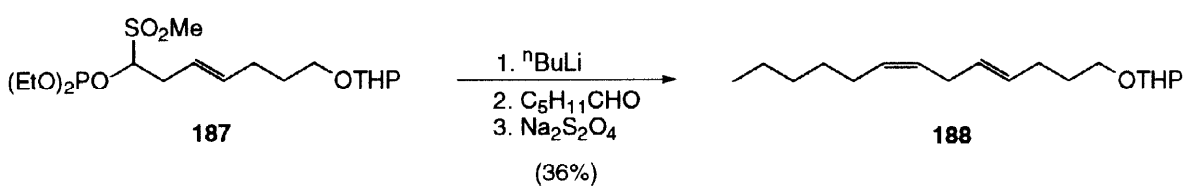


Scheme 60



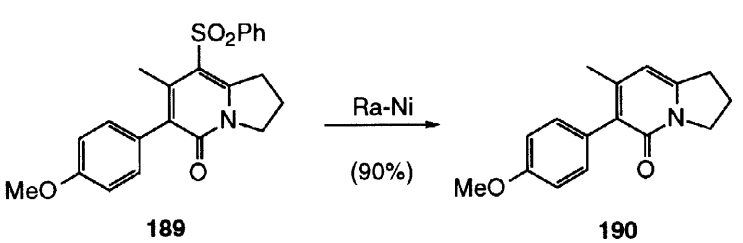
Scheme 61

The (4*E*,7*Z*)-4,7-tridecadienyl acetate derived from compound **188**, a component of the sex pheromone of the potato tuberworm moth, is prepared by the Horner-Wadsworth-Emmons reaction of the phosphonate **187** with hexanal in a 70:30 *E*:*Z* ratio, after chromatographic separation. The corresponding *E*-sulfone was stereoselectively desulfonylated with sodium dithionite[118] (Scheme 62).



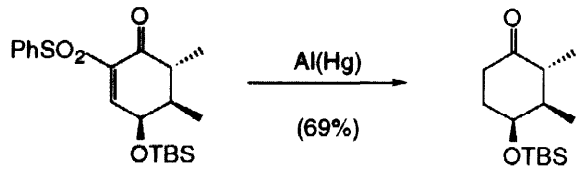
Scheme 62

Raney nickel has been used in the desulfonylation of the dienic sulfone **189** to give the corresponding 2-pyridone **190**, an immediate precursor of the indolizidine alkaloid, (±)-ipalbidine[119] (Scheme 63).



Scheme 63

In the case of the α-phenylsulfonyl cyclohexenone **191**, the reduction with aluminium amalgam gives the saturated cyclohexanone **192**, an intermediate in the total synthesis of progesterone receptor ligands (-)-PF1092A, B and C[120] (Scheme 64).



191 **192**

Scheme 64

As in the case of samarium diiodide,[113] vinylic 1,2-disulfones can be monodesulfonylated to vinyl sulfones by means of tributyltin hydride. (*Z*)-1,2-Bis(phenylsulfonyl)ethylene has been quantitatively transformed into (phenylsulfonyl)ethylene with tributyltin hydride.[121]

2.2. Reductive elimination of the sulfone group

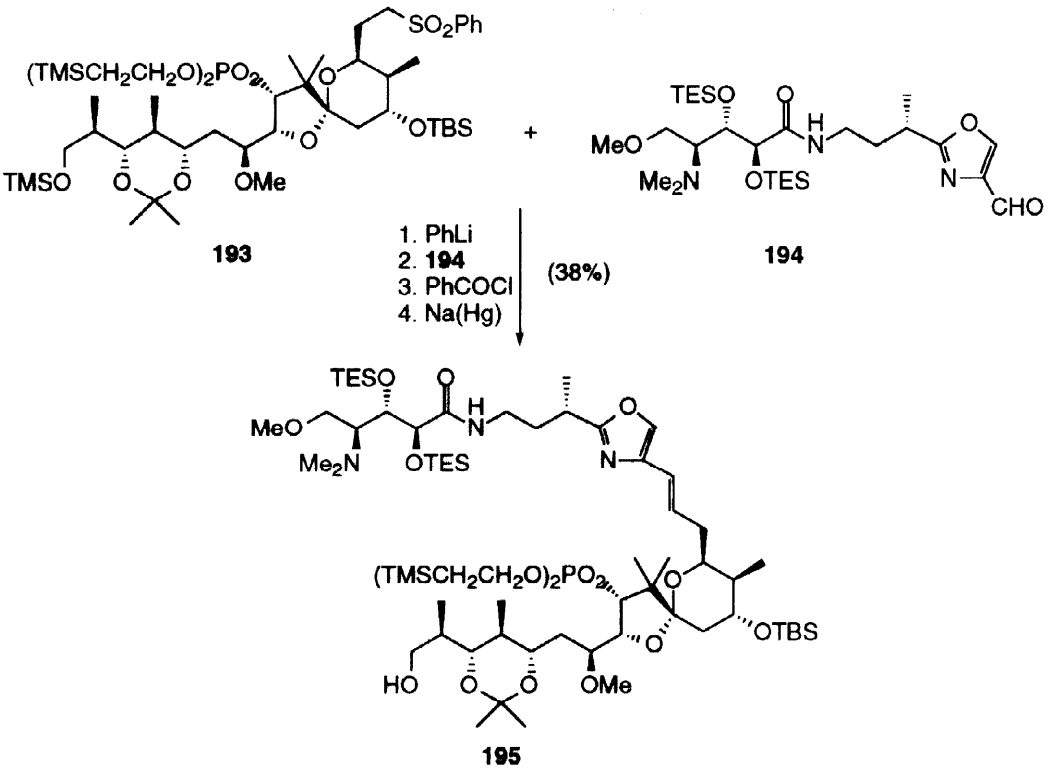
In this section the formation of carbon-carbon multiple bonds by reductive desulfonylation of β-functionalised -mainly β-hydroxy or β-alkoxy sulfones- well known as Julia-Lythgoe or Julia-Paris-Kocienski (JPK) olefination will be considered.[122]

2.2.1. β–Hydroxy or β-alkoxy sulfones

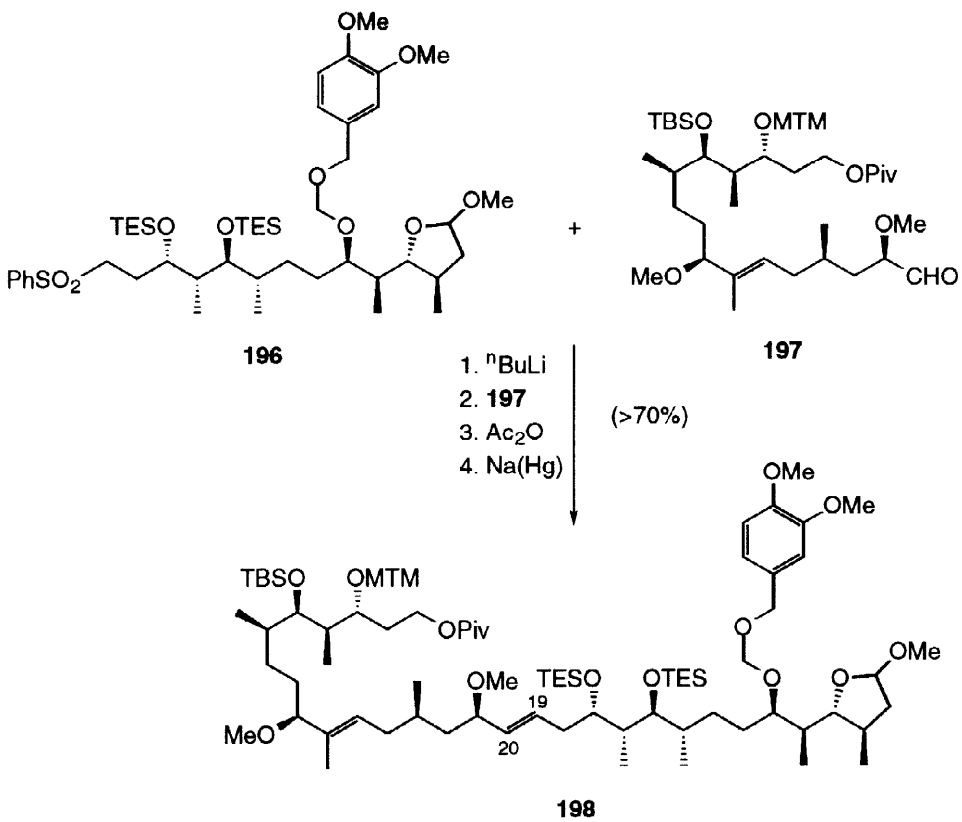
The JPK coupling is one of the most widely used reactions involving sulfones and it represents a reasonable alternative to the Wittig approach. It is a two-step procedure in which the β-hydroxy or β-alkoxy sulfone is formed by reaction of a α-sulfonyl carbanion with a carbonyl compound followed by reduction, mainly with sodium amalgam, to produce the corresponding alkene. The reduction involves an electron transfer to the sulfone group with loss of the arenesulfinate anion to give a β-hydroxy or β-alkoxy carbanion, which undergoes *anti*-elimination to give the olefinic product having mainly *E*-configuration. In other cases, the β-hydroxy sulfone is prepared following different methodologies, the elimination being just called Julia olefination.

In many total syntheses of natural products, the JPK coupling has been widely used. Bryostatin 7, a representative member of potent antileukemic agents, has been prepared by Masamune *et al.*, using the JPK methodology, to form the C16-C17 *E*-double bond.[123a] In the synthesis of the antineoplasic macrolide antibiotic, cytovaricin, the key step is also the formation of the *E*-C15-C16 double bond by JPK coupling of the spiroketal subunit, which bears the aldehyde, and the polyol glycoside subunit, which bears the sulfone group.[123b] More recently, the total synthesis of (-)-calyculin A it has been described,[124] in which the coupling of the B and C fragments is carried out by reaction of the lithiated sulfone **193** with the aldehyde **194** to afford the C25-C26 double bond[124] (Scheme 65).

A recent synthesis of the C12-C29 fragment of laulimalide, a 20-membered macrolide possessing potent cytotoxic activity against the KB cell line, is based on the JPK coupling.[125]



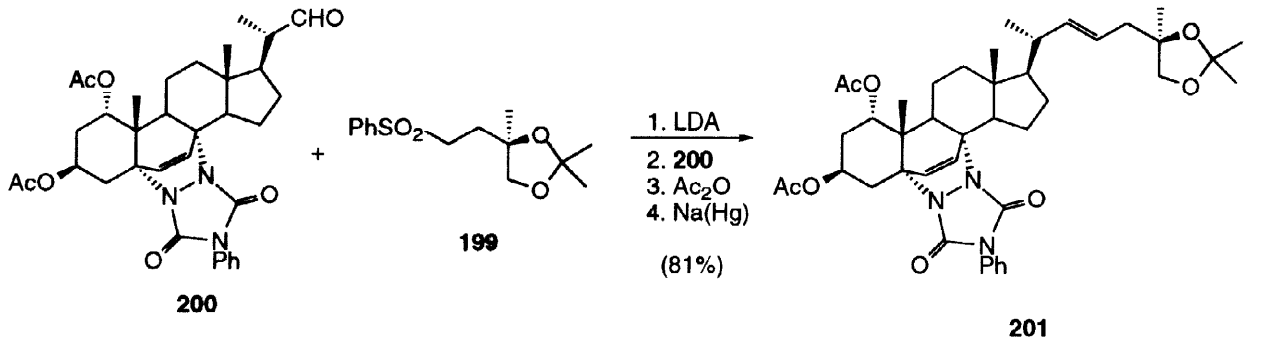
Scheme 65



Scheme 66

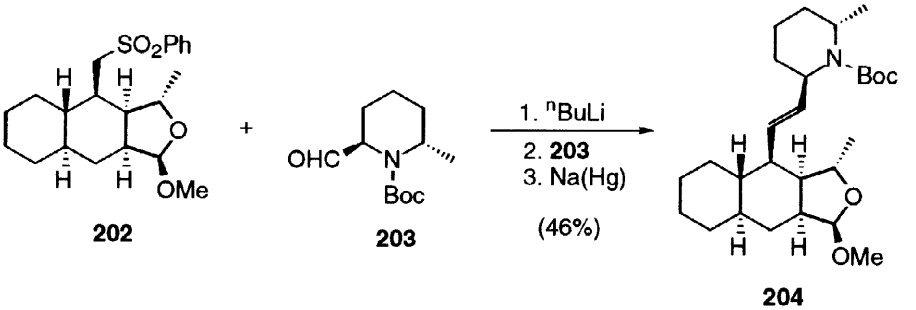
Aplyronine A, a potent antitumor compound of marine origin, has been prepared by Yamada *et al.* by coupling the sulfone **196** with the aldehyde **197**, providing the compound **198** with the C20-C21 double bond in a *ca.* 10:1 *E:Z* ratio[126] (Scheme 66).

In the synthesis of (23*S*,25*R*)-1α,25-dihydroxyvitamin D_3 23,26-lactone, a major metabolite of 1α,25-dihydoxyvitamin D_3, the combination of the side chain chiral C_5 sulfone **199** with the steroidic aldehyde **200** gives the *E*-olefin **201**[127] (Scheme 67). The polyol segment of the antibiotic roxaticin has also been prepared by JPK coupling in 51% yield with the generation of the C26-C27*E*-carbon-carbon double bond.[128]



Scheme 67

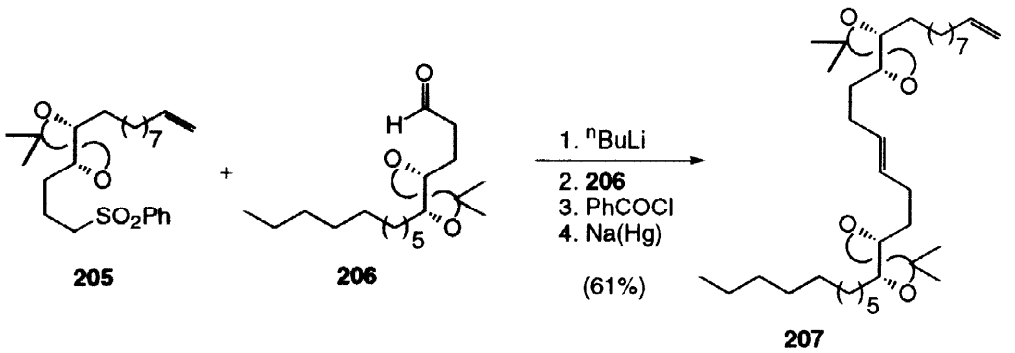
(+)-Himbacine, a potent muscarinic antagonist piperidine alkaloid, has been prepared by a convergent synthesis in which the JPK methodology is successfully used. The sulfone **202** is coupled with the aldehyde **203** derived from (*R*)-pipecolic acid, and the resulting β-hydroxy sulfone stereoselectively reduced to the expected product **204**[129] (Scheme 68).



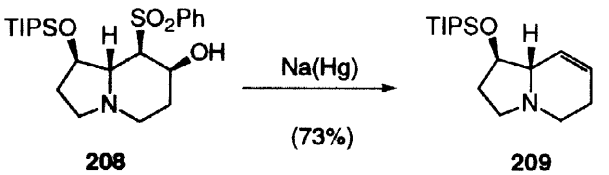
Scheme 68

The alkene **207** is the pivotal intermediate in the preparation of a variety of diastereomeric acetogenins such as (+)-parviflorin, (+)-squamocin K and (+)-(5*S*)-hydroxypaviflorin. The addition of the lithiated sulfone **205** to the aldehyde **206** followed by *in situ* benzoylation and final desulfonylation provides the expected compound **207** as a 3:1 *E/Z* mixture, the separation being unnecessary because the *E*-diastereomer is submitted to dihydroxylation[130] (Scheme 69).

The synthesis of the indolizidine (-)-slaframine has been carried out by the reaction of a serine sulfone derivative, similar to compound **105**, and an aldehyde derived from prolinol, followed by subsequent sodium amalgam desulfonylation.[131] In the synthesis of polyhydroxylated indolizidines, the Julia olefination is performed with β-hydroxy sulfones of the type **208**, obtained by sodium borohydride reduction of a β-ketosulfone, giving after reduction with sodium amalgam the expected indolizidine **209** in 73% yield. The same process using the corresponding mesylated material gives 82% yield[132] (Scheme 70).

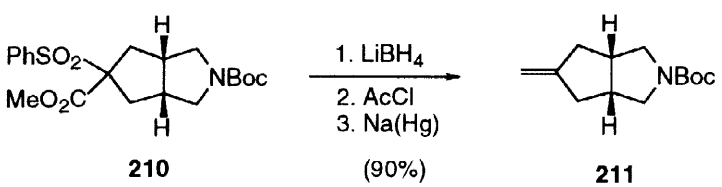


Scheme 69



Scheme 70

In the total synthesis of the HMG-CoA reductase inhibitor, dihydromevinolin, an olefinic intermediate has been prepared in a 1:6 *Z/E* molar ratio by reduction of a β-ketosulfone with sodium borohydride followed by Julia olefination.[133] The α-sulfonyl ester **210** has been transformed into the *exo*-methylene derivative **211** in high yield, following a similar strategy[134] (Scheme 71).

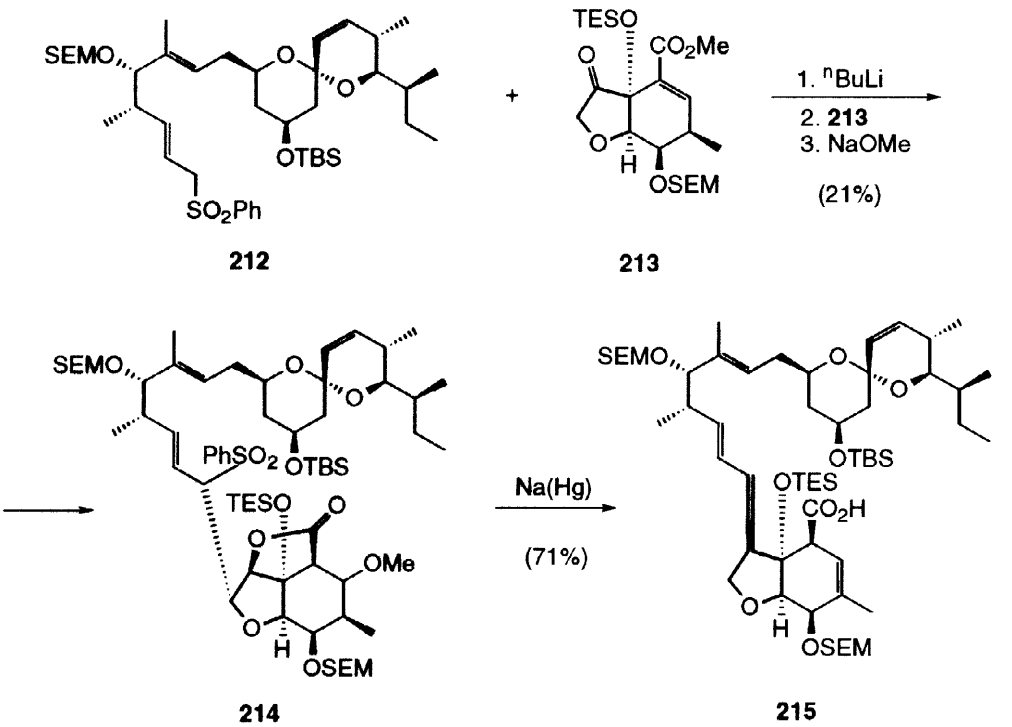


Scheme 71

Another widely used application of the JPK methodology is the condensation of an allyl sulfone carbanion with a carbonyl compound or an alkyl sulfone with a α,β-unsaturated carbonyl compound to give dienes. If the components are an allyl sulfone and a α,β-unsaturated carbonyl compound, a triene can be obtained. These strategies have been used in the syntheses of several natural products. In some cases the dienyl or trienyl sulfone is isolated after treatment with a base, and after final desulfonylation gives the corresponding diene or triene[110-112] (see Schemes 59 and 60).

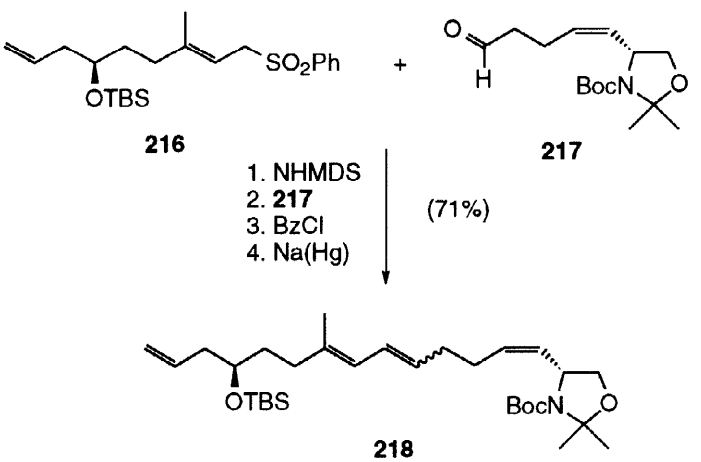
The dienic moiety of calciferol and its relatives has been prepared by JPK methodology.[135]In the synthesis of the antiparasitic agent, avermectin B_{1a}, the key step of the convergent synthesis of the aglycon portion is the reaction of a lithiated allylic sulfone, derived from compound **212**, with the ketone **213**. The reduction with

sodium amalgam of the β-hydroxy sulfone intermediate fails, but the related lactone **214** gives the corresponding product **215** by ring-opening the lactone giving the C8-C9 olefin exclusively with *E*-configuration[136] (Scheme 72). In the case of β,γ-epoxy sulfones the reduction with sodium amalgam also induces ring-opening to afford allylic alcohols.[17]



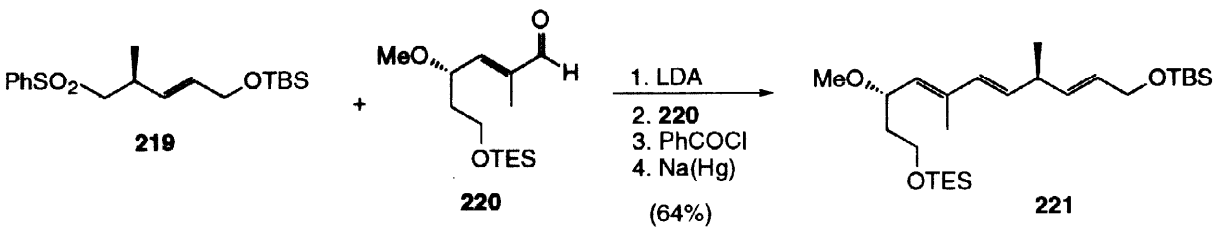
Scheme 72

For the total synthesis of (+)-curacin A, a marine cytotoxic agent, intermediate **218** has been prepared using JPK coupling.[137] Allylic sulfone **216** is deprotonated and allowed to react with aldehyde **217** to yield, after quenching with benzoyl chloride and final reduction with sodium amalgam, the expected product **218** as a 3:1 diastereomeric mixture (Scheme 73). This ratio could not be improved using samarium diiodide.



Scheme 73

The diene **221**, precursor of the C1-C11 subunit of the marine macrolides iejimalides, has been prepared by JPK coupling of the alkyl sulfone carbanion **219** and the α,β-unsaturated aldehyde **220**[138] (Scheme 74).

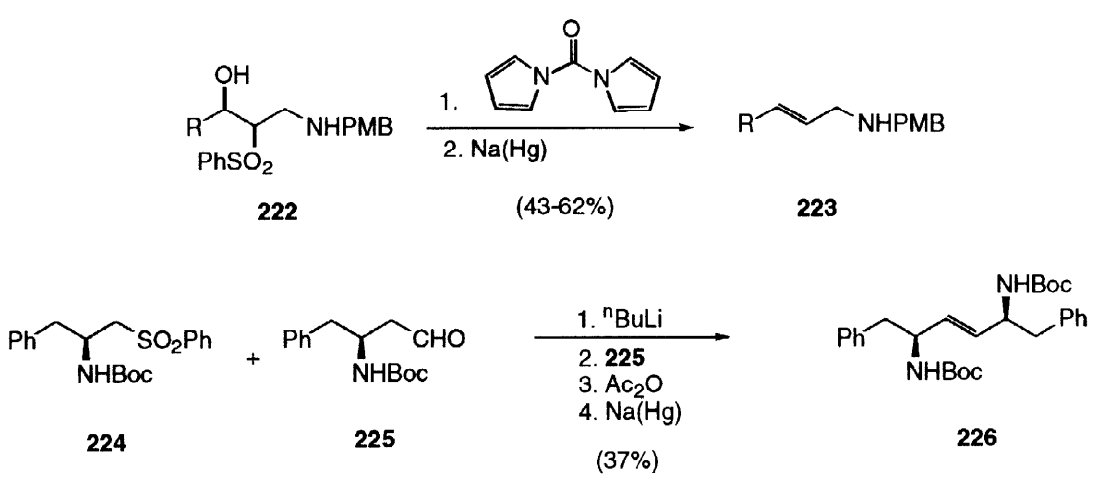


Scheme 74

In the construction of the (*E,E*)-diene fragment in (+)-herboxidiene A,[139a] a diastereomer of the natural herbicide herboxidiene and the triene segment of rapamycin,[139b] Kocienski *et al.* use the new one-pot olefination reaction recently reported by Julia *et al.*[140] This method substitutes the common arylsulfonyl group with the benzothiazolylsulfonyl one, so the coupling of its corresponding organolithium derivative with a α,β-unsaturated carbonyl compound gives rise to the expected diene without using a reducing agent. The intermediate β-oxido sulfone undergoes SO_2 extrusion (see Section 7).

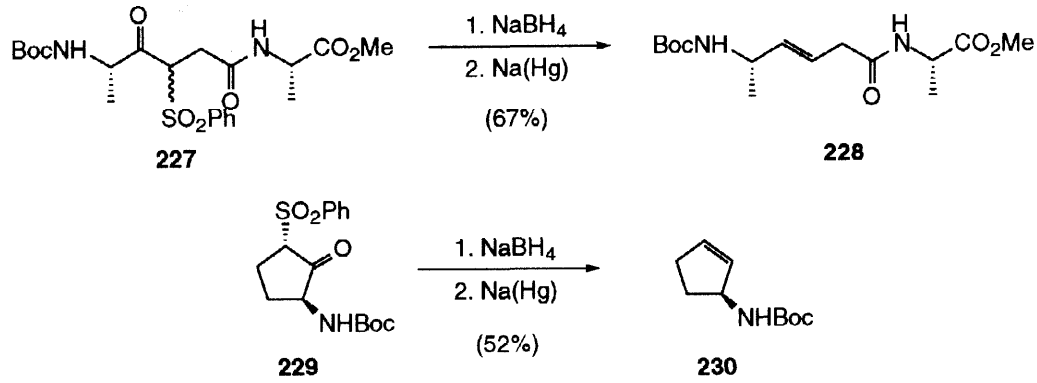
Alkyl sulfones bearing a β-alkoxy group at the β-position give olefins by reduction with sodium amalgam.[141] This strategy has been used in the final step of the synthesis of a protected derivative of 1-(hydroxymethyl)conduritol C[141a] and in the preparation of an intermediate for the neurotrophic illicinones.[141b]

The preparation of allylic amines with the carbon-carbon double bond formed by JPK coupling, has been carried out by reaction of lithiated β-aminosulfones, derived from compounds **222**, with aldehydes, followed by cyclisation to give the corresponding oxazinones and finally, after desulfonylation, the *E*-isomeric products **223**[142a] (Scheme 75). Without protection of the hydroxy group, variable stereoselectivity has been observed depending on the aldehyde employed.[73] In addition, compound **226**, which is a potential protease inhibitor has been stereoselectively prepared by JPK coupling of β-aminosulfone **224** and the aldehyde **225**[142b] (Scheme 75).



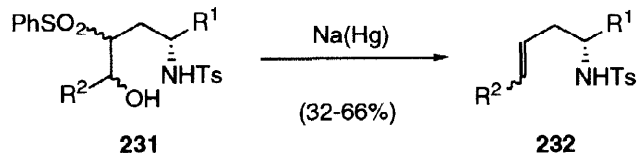
Scheme 75

Other methods for the preparation of allylic amines, such as **228** or **230** are based on the reduction of the β-ketosulfones **227**[8] or **229** to β-hydroxy sulfones,[49c] respectively, and final desulfonylation with sodium amalgam (Scheme 76).



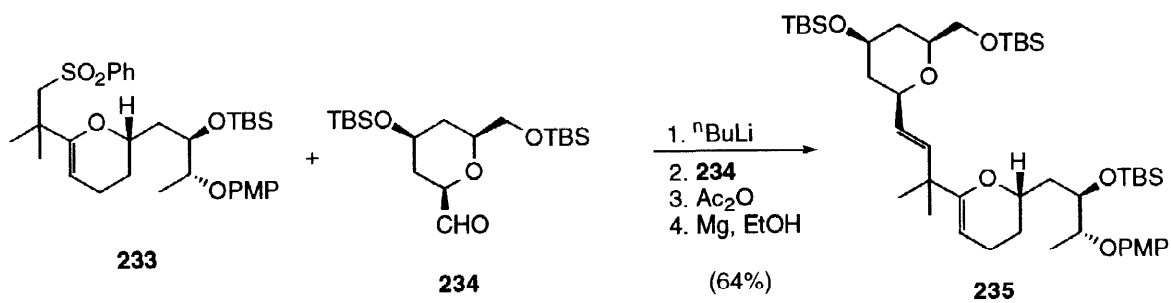
Scheme 76

A two-step procedure for the synthesis of enantiomerically pure *N*-tosyl homoallylic amines **232** is based on the reduction of β-hydroxy sulfones **231**, obtained by a three-component coupling of lithiated methyl phenyl sulfone with chiral aziridines and aldehydes, giving the product with the *E/Z* ratios of between 3:1 and 10:1[143] (Scheme 77).



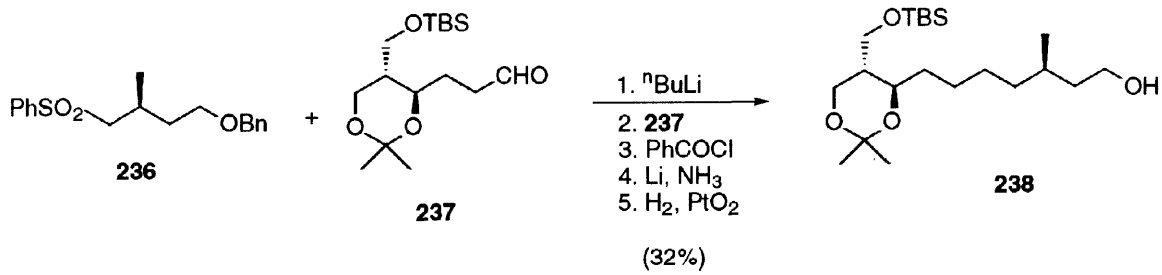
Scheme 77

Other reducing agents can be used in JPK coupling such as magnesium in methanol, lithium in ammonia, sodium naphthalenide and samarium diiodide. Different β-substituted acetoxy or benzoxy sulfones have been reduced in high yields to the corresponding *E*-alkenes, using magnesium powder in the presence of a catalytic amount of mercury(II) chloride in absolute ethanol.[144] This modified JPK coupling has been used by Evans *et al.* in the first asymmetric synthesis of briostatin 2, a biologically active marine macrolide: the sulfone **233** and the aldehyde **234** were coupled to give the olefin **235** with *E/Z* ratio of 95:5 [145] (Scheme 78).



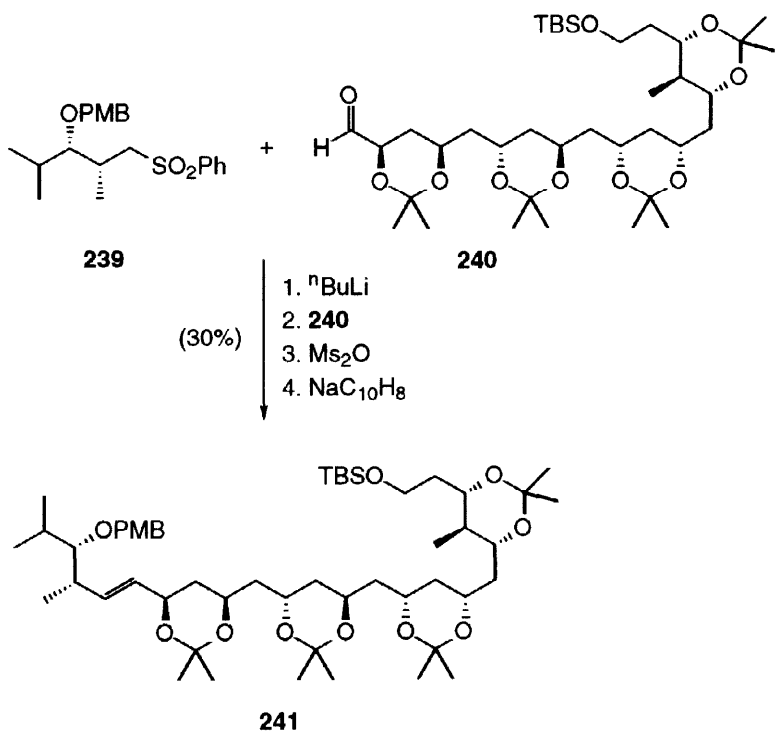
Scheme 78

In the preparation of compound **238**, a key intermediate in the synthesis of the hypocholesterolemic agent 1233A, sulfone **236** is coupled with aldehyde **237** to give the corresponding β-hydroxy sulfone. Reductive elimination of the benzoyl derivative with sodium amalgam affords the product in very low yields. However, lithium in ammonia[146] gives a *ca.* 9:1 *E/Z* mixture of olefins, which was finally hydrogenated to yield product **238**[147] (Scheme 79).



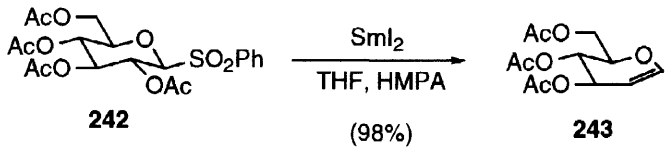
Scheme 79

The use of sodium naphthalenide was first reported in the preparation of a pentaene ester intermediate in the synthesis of myxalamide.[148] Schreiber *et al.* have used the same reaction conditions for the coupling of sulfone **239** with aldehyde **240**, to provide compound **241** with *E* configuration, an intermediate for the polyhydroxylated chain of the oxopolyene antibiotic, (+)-mycoticin A[39] (Scheme 80).



Scheme 80

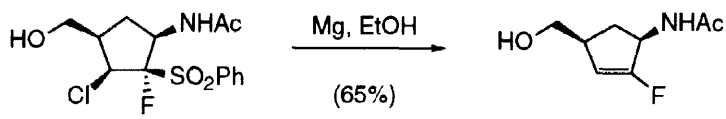
Samarium diiodide in the presence of HMPA readily reductively eliminates β-hydroxy or β-acetoxy sulfones to provide olefins and polyenes,[112,149] giving in many cases better results than sodium amalgam. Sinay *et al.* introduced this methodology in the synthesis of substituted pyranoid glycals such as **243** from compound **242**, where the formation of the anomeric radical by one-electron reduction of the sulfone moiety is proposed[150] (Scheme 81). The anomeric sulfone derived from α-D-isosacharino-lactone has also been converted into a 2'-C-acetoxymethylfuranoid glycal with samarium diiodide in HMPA.[151]



242 **243**

Scheme 81

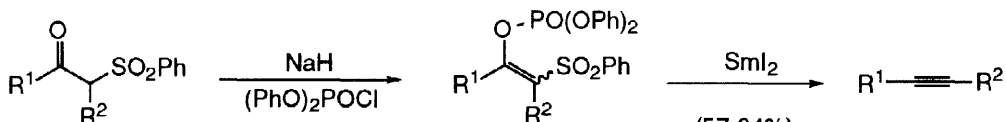
Magnesium in ethanol has been used in the reductive desulfonylation of compound **244** to give the corresponding fluoroalkene **245**, a precursor of 2'-fluoro substituted carbovir[152] (Scheme 82).



244 **245**

Scheme 82

Another type of reductive elimination forming alkynes is the transformation of β-ketosulfones into enol phosphates and subsequent reductive elimination with sodium amalgam or sodium in ammonia.[153] This strategy has been used in the synthesis of 1α-hydroxyprecalciferol 3.[153d] Recently, the same procedure has been carried out with samarium diiodide to give mono and disubstituted acetylenes **248**, from compounds **246**, through the intermediates **247**[154] (Scheme 83). This method requires milder reaction conditions and no formation of β-ketosulfones was observed.



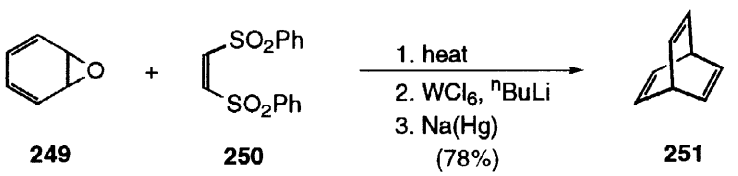
246 **247** **248**

Scheme 83

2.2.2. Vicinal disulfones

The reductive elimination of 1,2-disulfones to give alkenes has usually been carried out with sodium amalgam. Barrelene has recently been prepared by cycloaddition of oxepin **249** with (*Z*)-1,2-

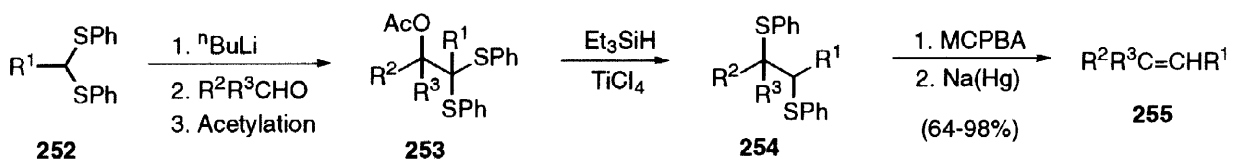
bis(phenylsulfonyl)ethylene **250** followed by de-epoxidation and reductive desulfonylation[155a] (Scheme 84). Cycloadducts resulting from 2-chloro-1,4-benzodithiin 1,1,4,4-tetraoxide and dienes give, upon reductive desulfonylation with sodium amalgam, tetrasubstituted olefins.[155b] Cycloadducts from 2,3-bis(phenylsulfonyl)-1,3-butadiene and enamines are bis-desulfonylated to the corresponding tetrahydroquinoleines by means of sodium amalgam.[155c]



249 **250** **251**

Scheme 84

A new method fot the synthesis of olefins is based on the coupling of aldehydes with dithioacetals **252** to give acetates **253** followed by reductive phenylthio migration to vicinal disulfides **254**. After oxidation of these compounds to disulfones and sodium amalgam reduction, olefins **255** are obtained[156] (Scheme 85). Magnesium in methanol[29] and samarium diiodide[38a] can also be used for this desulfonylation process.

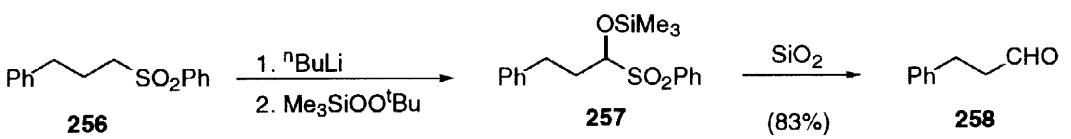


252 **253** **254** **255**

Scheme 85

3. OXIDATIVE DESULFONYLATION

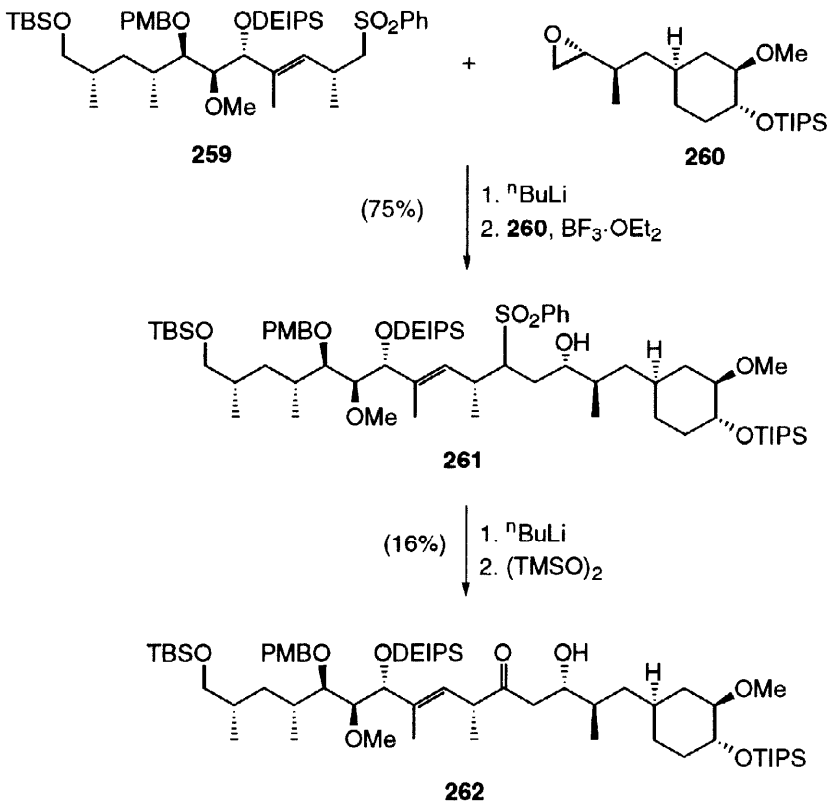
The removal of the sulfone group by oxidation processes provides carbonyl compounds. α-Carbanions of alkyl sulfones are oxidised by electrophilic reagents such as molybdenum peroxide (MoO_5·Py·HMPA) to ketones,[157] bis(trimethylsilyl) peroxide [$(Me_3SiO)_2$][158] and chlorodimethoxyborane [$ClB(OMe)_2$][159] to aldehydes and ketones. More recently, the use of the mixed peroxide *tert*-butyl trimethylsilyl peroxide ($Me_3SiOOBu^t$) for the synthesis of aldehydes *via* α-silyloxy sulfones has been described.[160a] Scheme 86 shows such a transformation of sulfone **256** to the corresponding aldehyde **258** *via* the intermediate **257**, illustrating the easy α-elimination of the sulfonyl group in α-alkoxy sulfones.[160b]



256 **257** **258**

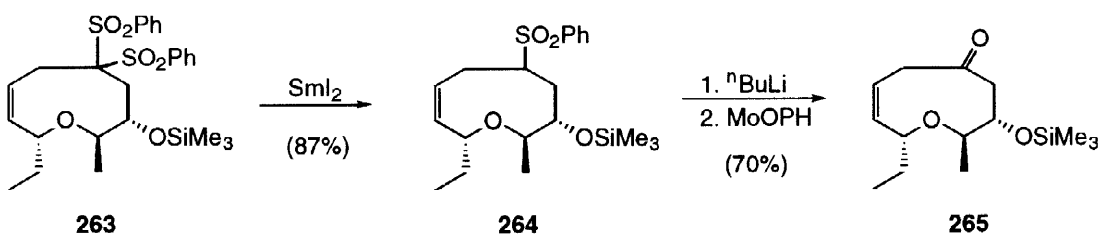
Scheme 86

The C22-C42 fragment **262** of rapamycin[51] has been prepared by Schreiber *et al.* by coupling the carbanion derived from sulfone **259** with the epoxide **260** followed by oxidation of the corresponding sulfone **261**[161a] (Scheme 87). This last step gives poor yields and thus the use of the olefination method of Julia was necessary[161b] (see Section 6, Scheme 154).



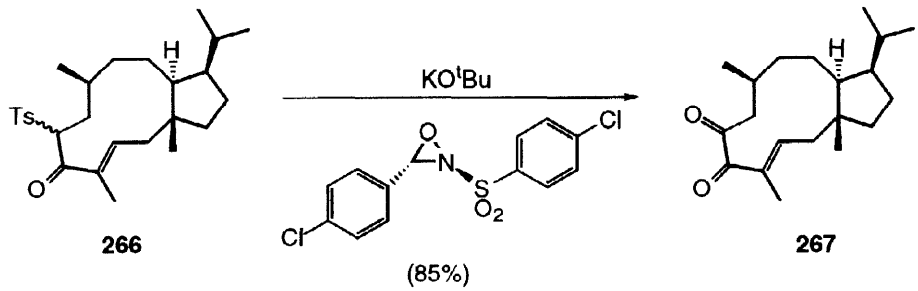
Scheme 87

The ketone functionality in the nine-membered ring ether **265** has been prepared from the disulfone **263**, which was first partially reduced with samarium diiodide to the monosulfone **264** and then submitted to a tandem lithiation-oxidation process[162] (Scheme 88).



Scheme 88

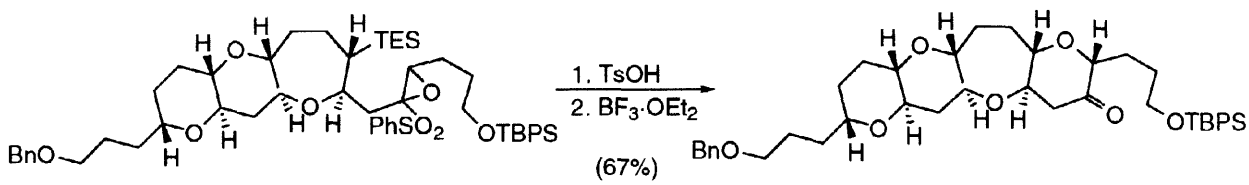
An efficient preparation of unsymmetrical α-diketones is based on the oxidative desulfonylation of β-keto-sulfones. Potassium *tert*-butoxide as the base and 2-[(*p*-chlorophenyl)sulfonyl]-3-)*p*-chlorophenyloxaziridine as the oxidant are used in this procedure, with yields ranging from 67 to 89%. Scheme 89 illustrates the case of transforming compound **266** into the 11-membered diterpene enedione **267**.[163]



266 **267**

Scheme 89

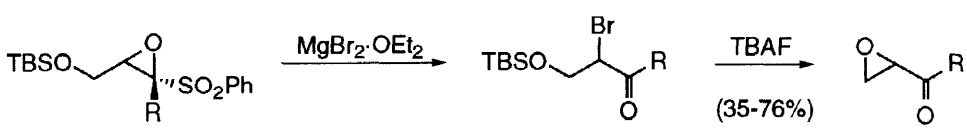
α,β-Epoxy sulfones, generally prepared by nucleophilic epoxidation of vinyl sulfones, can be transformed into ketones by ring opening promoted by a hydroxy group[164] (Scheme 90). This strategy has been widely used by Mori *et al.* for the construction of *trans*-fused tetrahydropyran ring systems with a ketone functionality, ready to be homologated with (trimethylsilyl)diazomethane to the corresponding oxepanes.[165] Hemibrevetoxin B has been prepared using this methodology, which is illustrated in Scheme 90 for the key transformation of compound **268** into **269**.[166]



268 **269**

Scheme 90

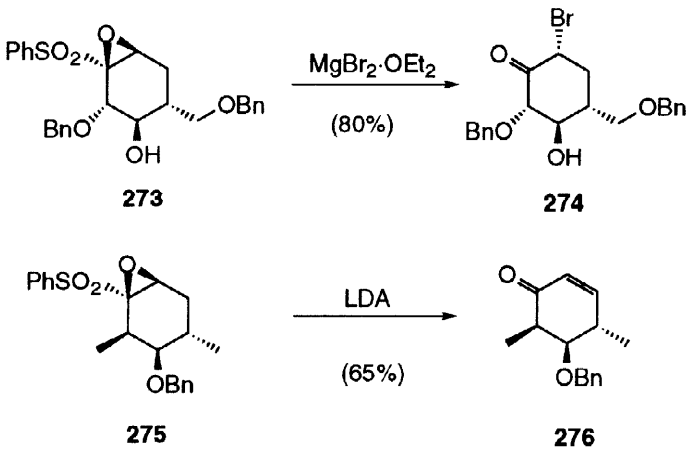
α,β-Epoxy sulfones, prepared by epoxydation of vinyl sulfones, can also be transformed into α-bromo ketones by treatment with magnesium bromide etherate.[167,168] Jackson *et al.* have used this transformation for the preparation of terminal epoxy ketones.[169a] Oxiranes **270** give bromo ketones **271** by reaction with magnesium bromide etherate, and, after desilylation with tetra-*n*-butylammonium fluoride (TBAF), afford the epoxy ketones **272** in a two-step or one-pot process (Scheme 91). When the sulfonyloxirane has a thiophenyl group at the α-position, the reaction with magnesium bromide affords the corresponding α-bromothioester.[169b]



270 **271** **272**

Scheme 91

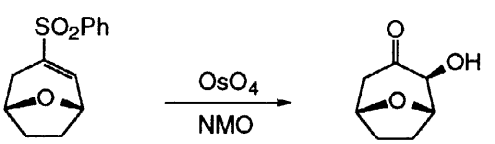
Cyclic α,β-epoxy sulfones have also been transformed into α-bromocycloalkanones with magnesium dibromide etherate in order to prove their configuration.[170] This ring opening has been applied to the synthesis of the 1-aminocarbasugar antibiotic, validamine,[171a] and the glycosidase inhibitor, cyclophellitol,[171b] from the common α-bromocyclohexanone **274** (Scheme 92). Direct transformation of α,β-epoxy sulfones into α,β-unsaturated ketones has been achieved with LDA, as shown in Scheme 92 for the preparation of the enone **276**, a precursor of polypropionate segments, from the cyclic sulfone **275**.[172]



273 **274** **275** **276**

Scheme 92

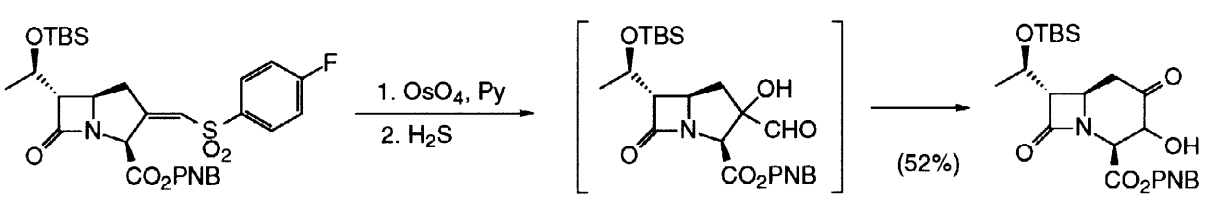
When the vinyl sulfone **277** is subjected to catalytic dihydroxylation with osmium tetraoxide and *N*-methylmorpholine *N*-oxide (NMO), the sulfone group is eliminated to give stereoselectively the α-ketol **278**[173] (Scheme 93).



277 **278**

Scheme 93

In a similar manner, dihydroxylation of carbapenem **279** bearing an exocyclic vinyl sulfone gives the intermediate α-hydroxy aldehyde **280**, which rearranges by ring expansion to yield 2-oxo-3-hydroxy carbacepham **281**[174] (Scheme 94).



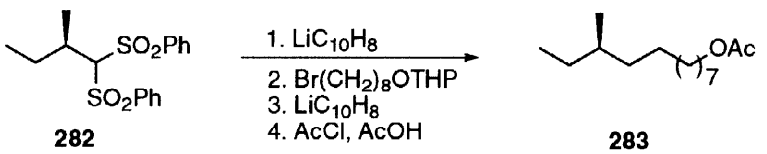
279 **280** **281**

Scheme 94

4. REDUCTIVE ALKYLATION

In this section, reactions where the desulfonative reduction of sulfones takes place with formation of carbon-carbon bonds by reaction with electrophiles or by dimerisation, will be studied. Lithium naphthalenide and samarium diiodide are generally used as reducing agents.

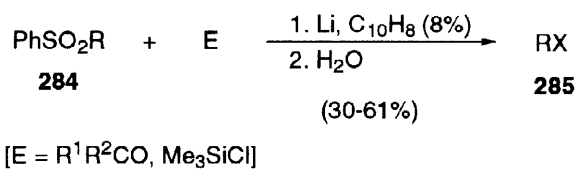
The first examples of the preparation and further reaction with electrophiles of organolithium reagents use α-alkoxy sulfones and lithium naphthalenide. These were described by Beau and Sinay[175] in the case of sulfones derived from 2-deoxy-D-glucose, and by Kruse and Brückner[176] for an alkoxymethyl sulfone to give a [2,3] Wittig rearrangement. Geminal bis-sulfones have been mono lithiated with lithium naphthalenide and reacted with water, alkyl halides and aldehydes giving good yields.[177] In the case of the bis-sulfone **282** derived from (*S*)-2-butanol, successive lithiations afford the pheromone of the lesser tea tortrix **283**[178] (Scheme 95).



282 **283**

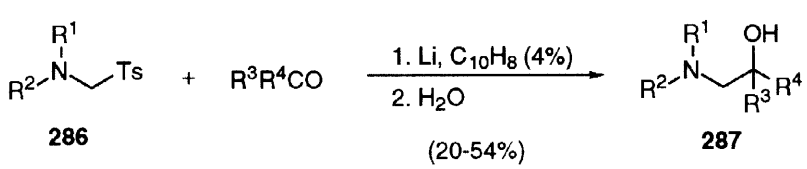
Scheme 95

Alkyl phenyl sulfones **284** react with lithium powder and a catalytic amount of naphthalene (8 mol %) in the presence of electrophiles such as carbonyl compounds or trimethylchlorosilane (Barbier-type conditions) to give the expected products **285**. The reaction is not applicable to vinyl sulfones but works with allylic and benzylic derivatives.[179]



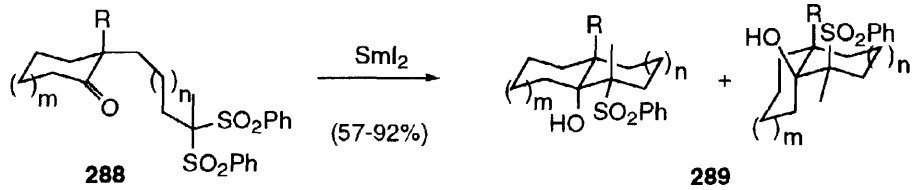
Scheme 96

The same naphthalene-catalysed lithiation in the presence of different electrophiles has been studied with α-amino and α-amido sulfones **286** in order to generate *in situ* the corresponding α-amino and α-amido organolithium compounds.[180] Carbonyl compounds as electrophiles give the best results affording β-aminoalcohols **287** (Scheme 97). This type of coupling has been carried out with tosylmethyl anilines using samarium diiodide.[181]



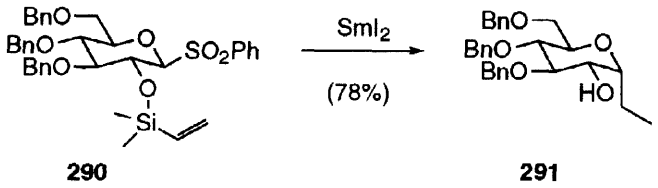
Scheme 97

When samarium diiodide is used as the reducing agent, the alkylation reaction between disulfones and ketones occurs under Barbier conditions.[182] The intramolecular coupling of a disulfone with a carbonyl group in compounds **288** forms bicyclic *cis*- and *trans*-fused β-hydroxy sulfones **289** (Scheme 98). In all cases the hydroxy and the sulfone groups are in a *cis* position, the process being explained by coordination of the carbonyl and sulfone oxygen atoms with samarium in the transition state.[183]



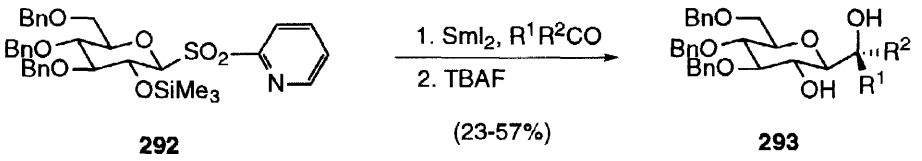
Scheme 98

Beau *et al.* have studied intramolecular *C*-glycosidation *via* glycosyl samarium(III) compounds generated from the corresponding reductive desulfonylation. For instance, from compound **290** with samarium diiodide and HMPA, the expected product **291** is isolated[184] (Scheme 99).



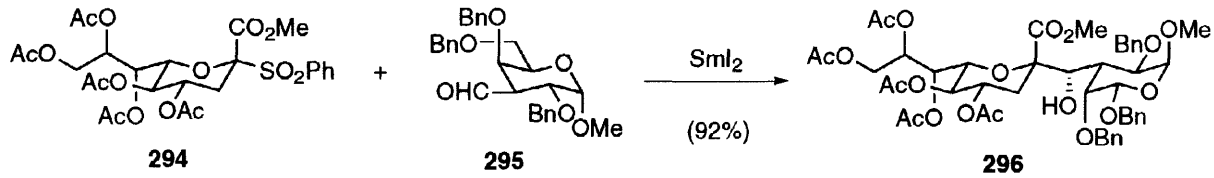
Scheme 99

Intramolecular *C*-glycosidation has been carried out with carbonyl compounds and mannosyl, glucosyl and galactosyl 2-pyridyl sulfones under Barbier conditions, samarium diiodide being the reducing agent. The reaction takes place under mild conditions affording 1,2-*trans*-*C*-glycosides. Scheme 100 illustrates this process for the transformation of compound **292** into the expected product **293**.[185] This methodology has been applied to the stereocontrolled synthesis of α-*C*-galactosamine derivatives *via* chelation of the α-oriented anomeric glycosyl samarium(III) compound with the C2-acetamido group.[186a,b] The pyridyl sulfone derived from *N*-acetylglucosamine also couples directly with carbonyl compounds in the presence of samarium diiodide to give α-*C*-glucosamines.[186c]



Scheme 100

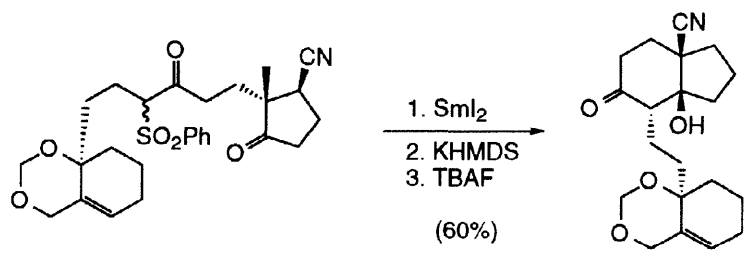
The sulfone **294** couples with aldehyde **295** under samarium diiodide-mediated Barbier conditions to provide diastereoselectively the *C*-disaccharide **296**[187] (Scheme 101).



294 295 296

Scheme 101

The β-ketosulfone **297** has been coupled intramolecularly with a ketone using samarium diiodide as the promoter to give a mixture of hyndranone epimers, which were epimerised through the corresponding silyl enol ether to aldol **298**, an intermediate for the synthesis of the core of cardenolides[188] (Scheme 102).

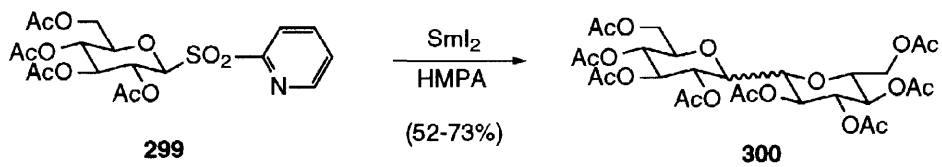


297 298

Scheme 102

The reductive coupling of sulfonyl carbanions, which takes place with dimerisation, was initially observed by Julia and Verpeaux for alkyl or allylic sulfones in the presence of nickel(II) acetylacetonate to afford olefins or polyenes.[189] Iron(III) acetylacetonate has been used recently for the inter or intramolecular homocoupling of lithiated alkyl sulfones to symmetrical acyclic or cyclic alkenes, respectively.[190] Palladium(II) acetylacetonate also catalyses the formation of olefins from lithiated *tert*-butyl alkyl sulfones.[191]

Samarium diiodide promotes the dimerisation of glycosyl 2-pyridyl sulfones, such as compound **299**, in the presence of HMPA to provide a mixture of αα, αβ and ββ glycosyl dimers **300** by a radical mechanism, instead of forming an organosamarium intermediate[192] (Scheme 103).



299 300

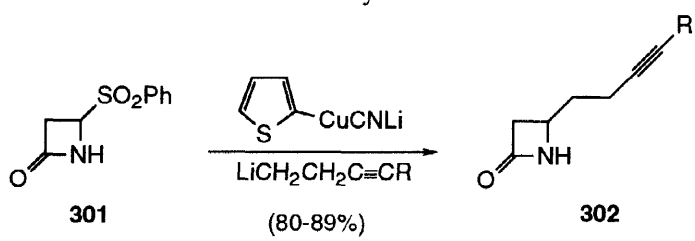
Scheme 103

5. NUCLEOPHILIC DISPLACEMENTS

In this section, the displacement of the sulfone group by carbon- and hetero-nucleophiles, directly or by means of a Lewis acid or catalysed by a transition metal, will be considered. In this type of reaction α-functionalised, allyl, vinyl and acetylenic sulfones act as cationic reagents,[2c] carbon-carbon and carbon-heteroatom bonds being formed respectively. The displacement of the sulfone group by carbon or tin radicals with formation of carbon-carbon or carbon-tin bonds, respectively, will also be studied.

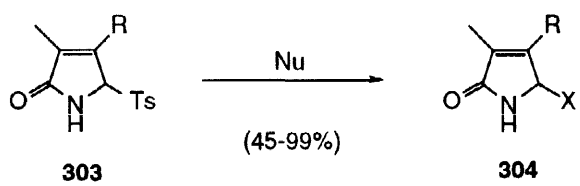
5.1. Direct nucleophilic displacements

α-Substituted sulfones bearing alkoxy, thioalkoxy or seleno groups undergo substitution usually under Lewis acid catalysis. *N*-Acyl-pyrrolidines and piperidines substituted at the α-position of the ring with a phenylsulfonyl group undergo similar reactions (see Section 5.2). However, β-lactams substituted with an arylsulfonyl group at the β-position, undergo easy substitution at this position, especially by carbon nucleophiles, mainly cuprates and Grignard reagents.[193] This strategy has been used in the synthesis of carbapenem antibiotics, such as (+)-thienamycin,[193d-f] and the carbacephem antibiotic loracarbef.[194a,b] 4-(Phenylsulfonyl)-azetidine-2-one (**301**) is coupled with thienyl cyano cuprates ($R_2CuLi{\cdot}LiCN$) derived from homopropargyl iodides to give alkynyl azetidones **302** in high yields[194a] (Scheme 105). 2-(Trimethylsilyl)-ethynylmagnesium bromide reacts directly with 4-phenylsulfonyl substituted azetidinones to afford the corresponding alkynyl azetidinones, which have also been used in the synthesis of carbapenems[194c] and enediynyl monocyclic β-lactams with antibacterial activity.[194d]



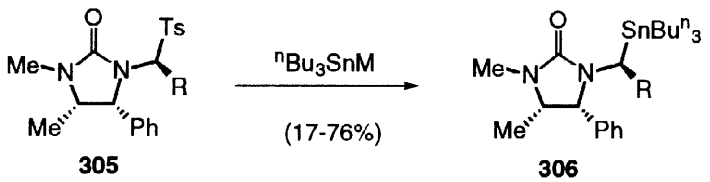
Scheme 104

2-Tosyl substituted pyrroles are transformed into 5-tosyl-Δ^3-pyrrolin-2-ones **303**, which are useful intermediates in the preparation of a variety of Δ^3-pyrrolin-2-one derivatives **304** by reaction with nucleophiles such as amines, alcohols, thiols, malonate and cuprates[195a] (Scheme 105). This type of amidosulfone has been used in a Wittig-type reaction for the preparation of pyrromethenone derivatives by condensation with aldehydes in the presence of tributylphosphine and DBU.[195b] This last strategy has been used in the total synthesis of phycocyanobilin and its photoactivable derivative.[195c]



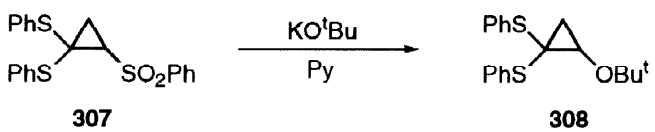
Scheme 105

α-Amidoalkylstannanes are adequate precursors of chiral α-nitrogenated organolithium compounds generated by tin-lithium exchange.[196] They have been prepared stereoselectively from α-amidosulfones, such as **305**, by reaction with tributyltin anions. The observed retention of the configuration in compounds **306** has been explained through a SET mechanism with participation of a nitrogen-substituted radical, a S_N pathway being ruled out (Scheme 106).



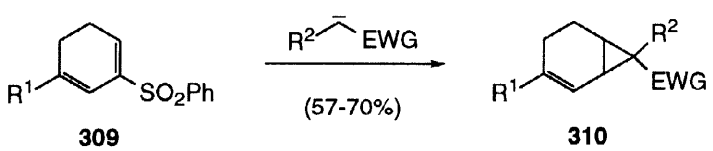
Scheme 106

The reaction of cyclopropyl sulfones **307** with potassium *tert*-butoxide gives the substituted ethers **308**. However, the possible cyclopropene intermediate could not be isolated nor detected[197] (Scheme 107).



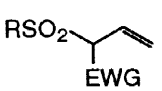
Scheme 107

The γ-elimination reaction of alkyl sulfones which bear an electron-withdrawing group (EWG) at the γ-position is a good strategy for the preparation of cyclopropanes.[198] In general, this protocol involves the Michael addition of an α-sulfonyl carbanion to an electrophilic olefin[199] or the opposite route: addition of an enolate to a vinyl sulfone,[200] followed by intramolecular displacement of the sulfone group. This last procedure has been applied to the synthesis of vinylcyclopropanes **310** by addition of ketone or nitrile enolates to 2-phenylsulfonyl-1,3-cyclohexadienes **309**[201] (Scheme 108).

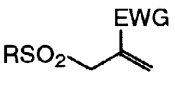


Scheme 108

The direct displacement of the sulfonyl group in simple allylic sulfones is usually carried out with organocopper reagents, other nucleophiles requiring the presence of Lewis acids or transition metals. In the case of functionalised allylic sulfones with electron-withdrawing groups at the α- or β-positions (**311** and **312**, respectively), the direct substitution can be carried out easily. In the first case, only for sulfones **311** with EWG = $PhSO_2$ the substitution of one of the sulfonyl groups takes place with heteronucleophiles (PhSNa, $PhSO_2Na$, H_2O, R_2NH) through a S_N2 mechanism to give *E*-γ-functionalised vinyl sulfones.[202]

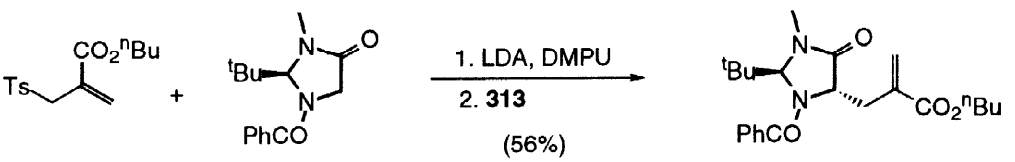


311



312

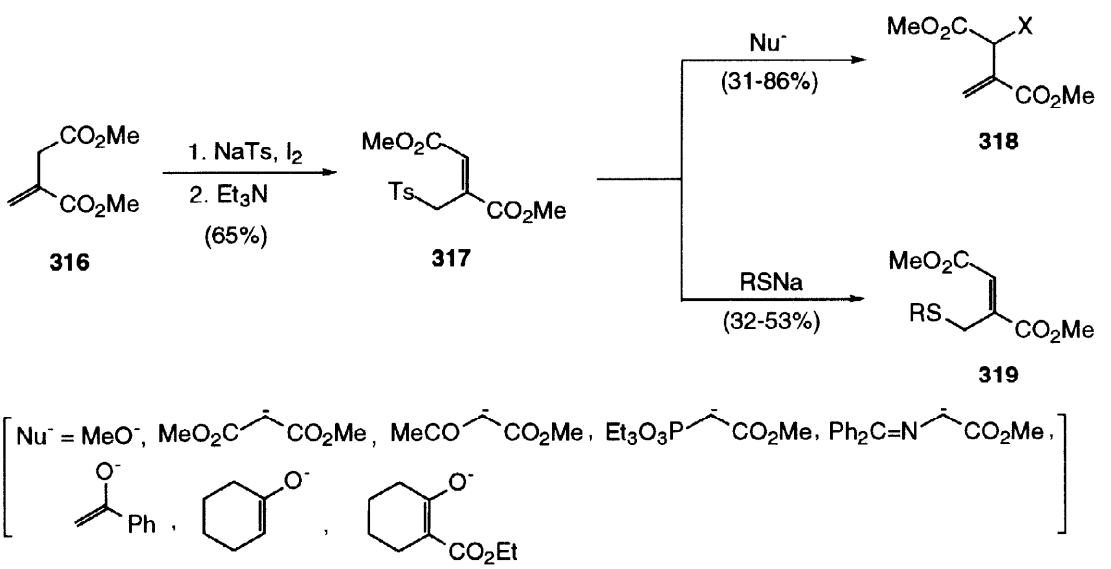
Different sulfones of the type **312** easily undergo nucleophilic displacement by carbon- and hetero-nucleophiles. Thus, α-(phenylsulfonyl)methylacrylates[203] such as **313**, prepared by the one-pot iodosulfonylation-dehydro-iodination of butyl methacrylate followed by isomerisation,[204] reacts with Seebach's glycine enolate of compound **314** to yield product **315** in 98% d.e.[205] (Scheme 109). After cyclopropanation and hydrolysis of compound **315**, the cyclopropyl derivative from 4-methylene-L-glutamic acid is obtained, which is twice as effective as L-glutamic acid as a depolarising agent on spinal cord of the newborn rat .[207]



313 314 315

Scheme 109

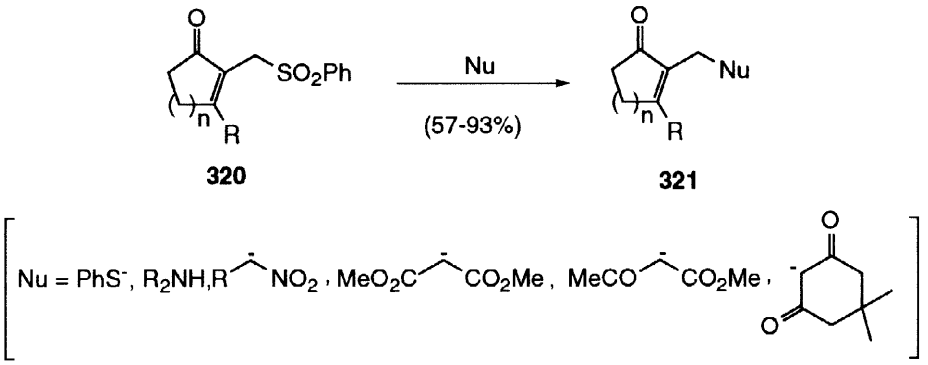
Dimethyl 2-(tosylmethyl)fumarate **317**, prepared by iodosulfonylation-dehydroiodination of methyl itaconate **316**, gives mainly 3-substituted itaconates **318** by reaction with carbon-nucleophiles (enolates) or sodium methoxide *via* a S_N2' pathway. When sodium thiolates are used as nucleophiles 2-substituted fumarates **319** are obtained, resulting from a double S_N2' process[208] (Scheme 110).



316 317 318 319

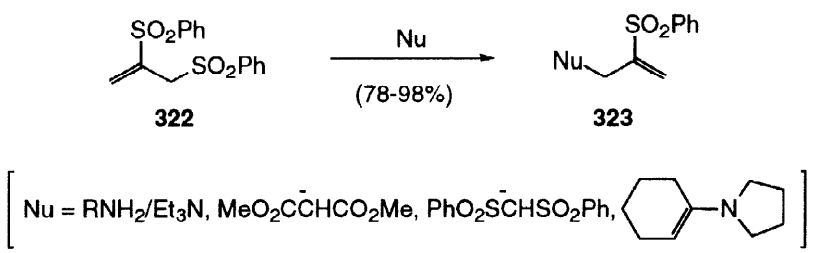
Scheme 110

In the case of cyclic α-(phenylsulfonyl)alkyl enones **320**, it has been demonstrated that the sulfone displacement with α-nitro carbanions and malonates proceeds by a radical chain mechanism involving SET processes.[209] The corresponding sulfones derived from 1,3-cyclopentadiene have been used in the synthesis of PGB_1 analogues **321** (n = 1)[210] (Scheme 111).



Scheme 111

2,3-Bis(phenylsulfonyl)-1-propene (**322**) has been widely used by Padwa *et al.* as a multicoupling reagent. Its behaviour as an allylic sulfone of the type **312** in nucleophilic displacements of type S_N2' has been studied with primary amines in the presence of triethylamine, stabilised carbanions and enamines[211] (Scheme 112).

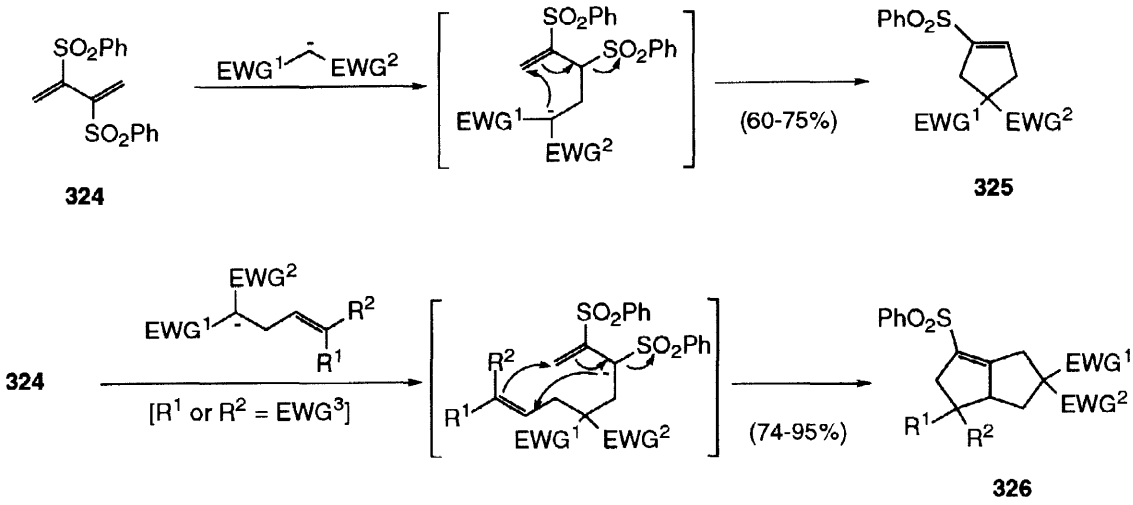


Scheme 112

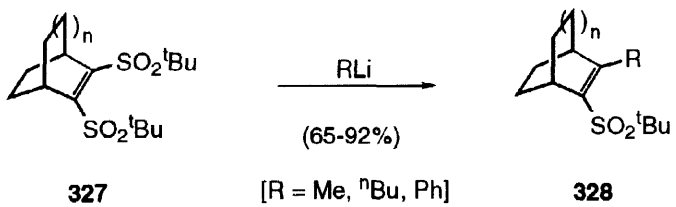
From 2,3-bis(phenylsulfonyl)-1,3-butadiene (**324**) α-substituted allylic sulfone anions related to **322** can be generated by the Michael addition of nucleophiles.[212] This methodology has been applied to the preparation of cyclopentenes **325** by a [4+1] anionic annulation approach, in a tandem process involving a 5-*endo-trig* closure, illustrated in Scheme 113. When the soft carbon-nucleophile bears an allyl substituent, bicyclo[3.3.0]octenes **326** are formed by a tandem Michael addition to compound **324** followed by [3+2]-anionic cyclisation.[213] When indolylmagnesium halides react with the diene **324**, followed by elimination of benzenesulfinate, 3-[(2-phenylsulfonyl)-2,3-butadienyl]indol is obtained.[214]

Generally, the direct substitution on simple vinyl or aryl sulfones by organometallic compounds needs a transition metal as a catalyst (see Section 5.3). When there is an electron-withdrawing group at the β-position, nucleophilic displacement of the sulfonyl group can be carried out with different nucleophiles following an addition-elimination mechanism. 1,2-Bis(sulfonyl)alkenes can be substituted by alkoxides, thioalkoxides, amines, azide anion, trimethyl phosphite and pentylmagnesium bromide.[215]

Diels-Alder adducts **327**, prepared from bis(*tert*-butylsulfonyl)acetylene, can be alkylatively mono-desulfonylated by organolithium compounds to give vinyl sulfones **328**[216] (Scheme 114).

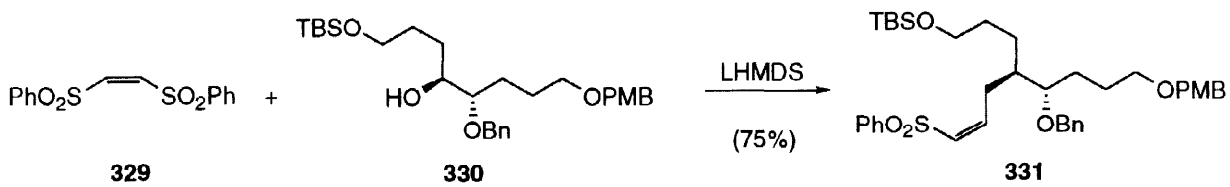


Scheme 113



Scheme 114

The treatment of *Z*-bis-1,2-(phenylsulfonyl)ethylene (**329**) with the lithium alcoholate derived from alcohol **330** takes place with >95% diastereoselectivity, furnishing product **331**, which is a precursor of the tetrahydropyran fragment of the antitumor agent, mucocin[217] (Scheme 115).

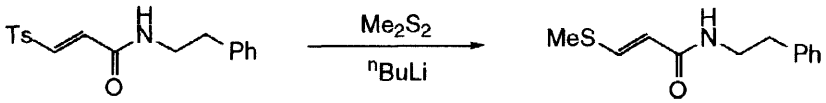


Scheme 115

β-(Phenylsulfonyl)nitroalkenes, which are also powerful electron-deficient olefins, react stereoselectively with copper-zinc organometallics to give *E*-nitroolefins following an addition-elimination mechanism.[218] Organolithium and organomagnesium compounds also give good yields for nitroolefins but only in the presence of copper(I) cyanide.[219]

β-Sulfonyl α,β-unsaturated carbonyl compounds have been used as cationic β-acylvinyl equivalents[2b] in the reaction with carbo- and hetero-nucleophiles.[220] A recent synthesis of the natural antifungal, sinharine **333**,

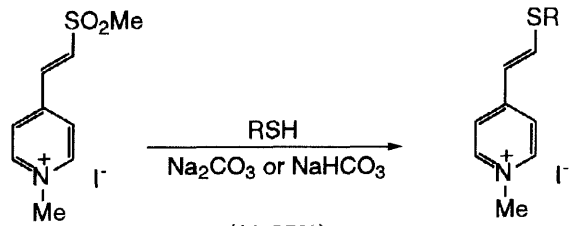
is based on the substitution of the tosyl group in compound **332**, prepared by iodosulfonylation-dehydroiodination of the corresponding acrylamide, by the methylthio group using lithium methanethiolate[221a] (Scheme 116). For the case of trifluoromethyl vinyl ketone substituted at the β-position by a phenylsulfonyl group, the product exists as the corresponding hydrate and reacts with heterocycles providing heteroaryl substituted butenones.[221b]



332 (77%) **333**

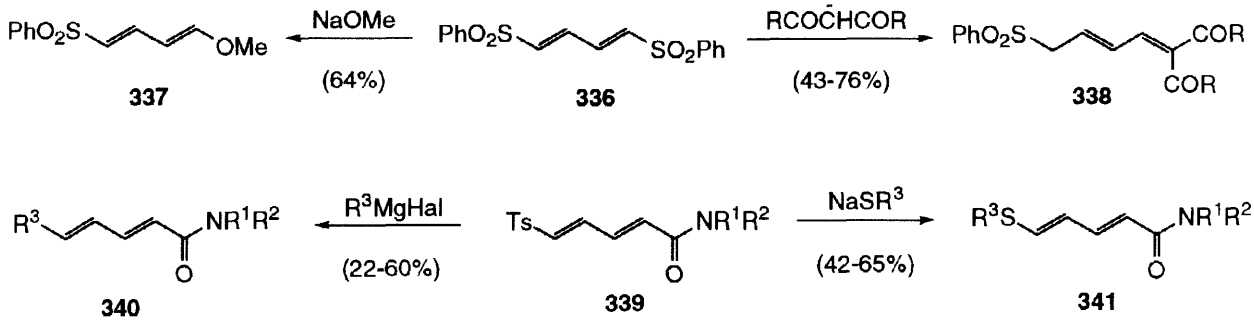
Scheme 116

In the case of the vinyl sulfone conjugated with a pyridinium cation **334**, the reaction with thiols and thioacetic acid with sodium phenyl selenide, in the presence of sodium carbonate or hydrogencarbonate, gives the corresponding pyridinium salts **335**[222] (Scheme 117).



334 (20-85%) **335**

Scheme 117



337 (64%) **336** (43-76%) **338**

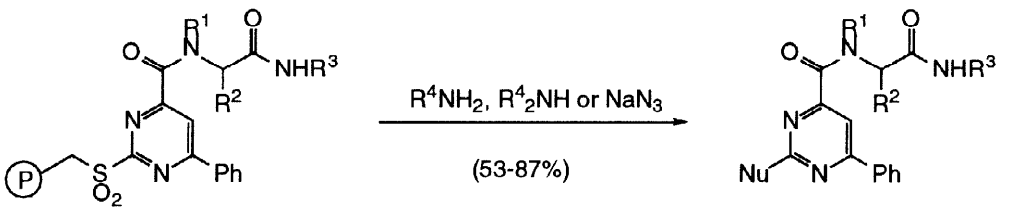
340 (22-60%) **339** (42-65%) **341**

Scheme 118

The dienic sulfone **336** undergoes benzenesulfinate displacement by sodium methoxide or enolates derived from dimethyl malonate or 2,4-pentanedione, through an addition-elimination mechanism providing the dienyl ether **337** or the isomerised products **338**, respectively[223] (Scheme 118). In the case of dienic sulfones **339**,

obtained by simple iodosulfonylation of pentanedienamides, the substitution of the tosyl group by sodium thiolates or Grignard reagents gives dienamides **340**[224] (Scheme 118). These reagents can be considered as δ-acyldienyl cation equivalents and have been used in the synthesis of naturally occurring dienamides,[89] such as sarmentine [**340**, R^1-R^2 = $(CH_2)_4$, R^3 = C_5H_{11}] and Achillea amide [**340**, R^1-R^2 = $(CH_2)_5$, R^3 = C_5H_{11}] when Grignard reagents are used as nucleophiles. Thiolates also give the corresponding δ-alkylthio dienamides **341** (Scheme 118).

Recently, the ability of the sulfonyl substituent to act as a leaving group has been used in the reactions on solid supports for the combinatorial synthesis of diverse pyrimidines. Thus, polymer-bound sulfones **342** are cleaved with different nucleophiles to give products **343**[225] (Scheme 119).



342 **343**

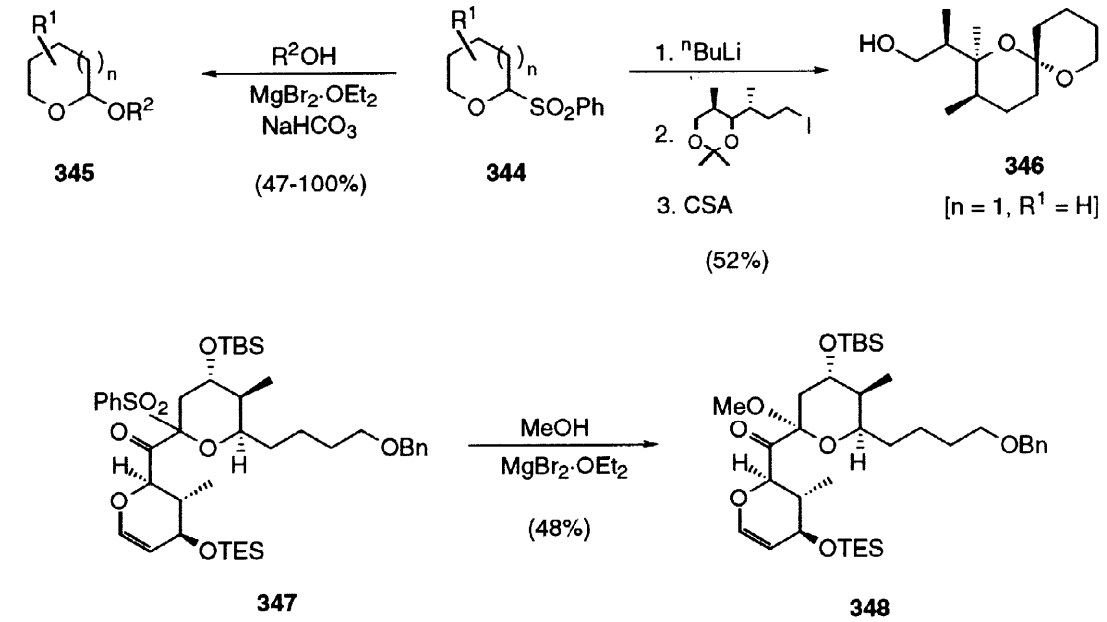
Scheme 119

5.2. Lewis acid-mediated nucleophilic displacements

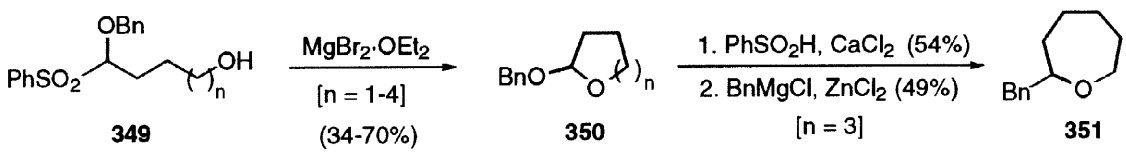
The inter and intramolecular nucleophilic substitution of the sulfonyl group by alcohols, Grignard reagents, allyl silanes or silyl enol ethers by means of a Lewis acid can be easily carried out with α-alkoxy sulfones, which under these conditions behave as oxonium ion precursors. Ley *et al.* have used this procedure for the preparation of cyclic acetals **345**, from α-phenylsulfonyl cyclic ethers **344** and alcohols in the presence of magnesium bromide etherate and sodium bicarbonate at room temperature. These mild reaction conditions tolerate furans, ketones, esters, silyl ethers, acetals, alkenes and alkynes as functional groups[226a] (Scheme 120). This strategy has been used in the synthesis of spiroketals, for instance compound **346**, an intermediate in the synthesis of the ionophore antibiotic CP-61,405 (routienocin),[226b] by reaction of the same precursor **344** with the required iodinated material followed by treatment with CSA (Scheme 120).

The same strategy has been used by Evans *et al.* in the transformation of the sulfone **347** into the ketal **348**[227b] (Scheme 120), an intermediate in the synthesis of the EF-bispyran subunit of altohyrtin C, a spongipyran macrolide of marine origin which exhibits subnanomolar antitumor activity against a number of human cancer cell lines. From its total synthesis[227,228] it can be deduced that altohyrtin C and spongistatin 2 are the same compound.

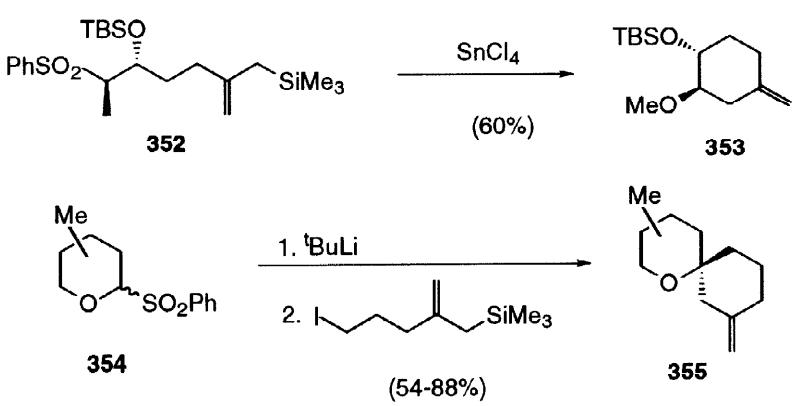
The reaction with Grignard reagents in the presence of zinc bromide has been carried out with cyclic ethers substituted at the α-position by a phenylsulfonyl group.[229] Sequential intramolecular attack on a sulfonyl ether by a hydroxy group (see compound **349**) to give acetal **350**, followed by introduction of the sulfone group again and final benzylation gives the corresponding 2-benzyl substituted ether **351**[230] (Scheme 121).



Scheme 120



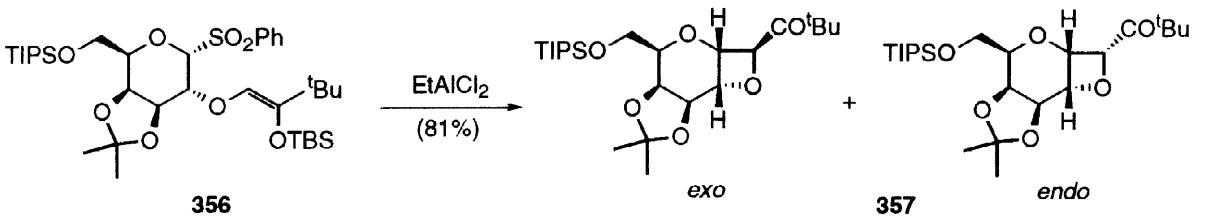
Scheme 121



Scheme 122

The intramolecular reaction of α-methoxy sulfones with an allyl silane, in the presence of a Lewis acid, has been used for the synthesis of methylene cyclohexanes.[231] The cyclohexyl C33-42 fragment of rapamycin[51] has been prepared by Ley *et al.*, by cyclisation of compound **352** in the presence of tin tetrachloride to afford product **353** as a 5/1 *trans/cis* diastereomeric mixture[232] (Scheme 122). In the case of alkyl substituted 2-(phenylsulfonyl)pyrans **354**, the cyclisation to give spiroethers **355** takes place directly, after alkylation with an iodide bearing the allylsilane moiety[233] (Scheme 122).

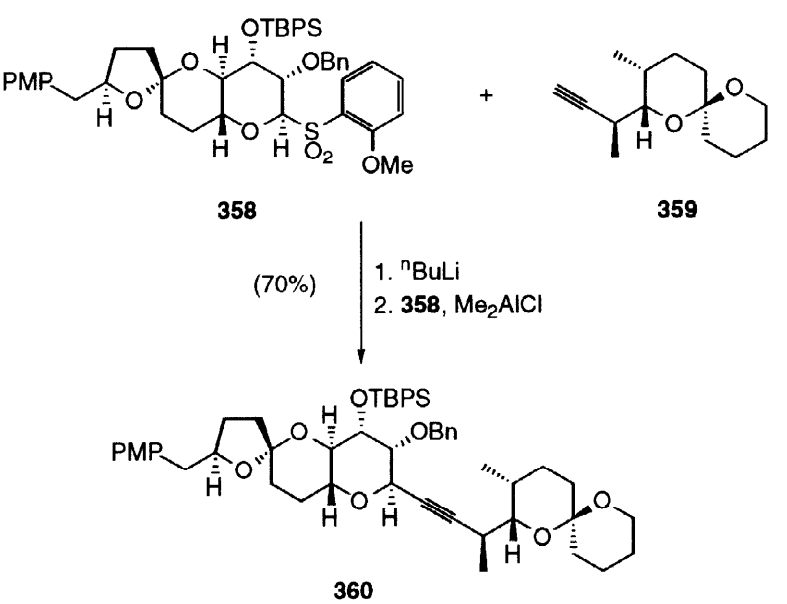
The reaction of the sugar-derived anomeric sulfone **356** with silyl enol ethers occurs in an intramolecular fashion in the presence of diethylaluminium chloride, as the Lewis acid, to afford *C*-glycosidation products as a 1/4 mixture of the corresponding *exo/endo* ketooxetanes **357**[234a] (Scheme 123). In the case of α-benzyloxysulfones, the corresponding ethylaluminium dichloride-promoted intramolecular cyclisation yields mainly tetrahydropyrans[234b].



356 357

Scheme 123

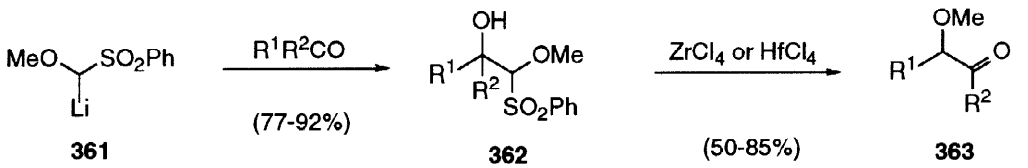
In a recently described total synthesis of the polyether marine natural product, okadaic acid, by Ley *et al.*, the coupling of fragments **358** and **359** takes place easily and in good yield by lithiation of the acetylene **359** followed by transmetallation with dimethylaluminium chloride, affording the product **360**[235] (Scheme 124).



358 359 360

Scheme 124

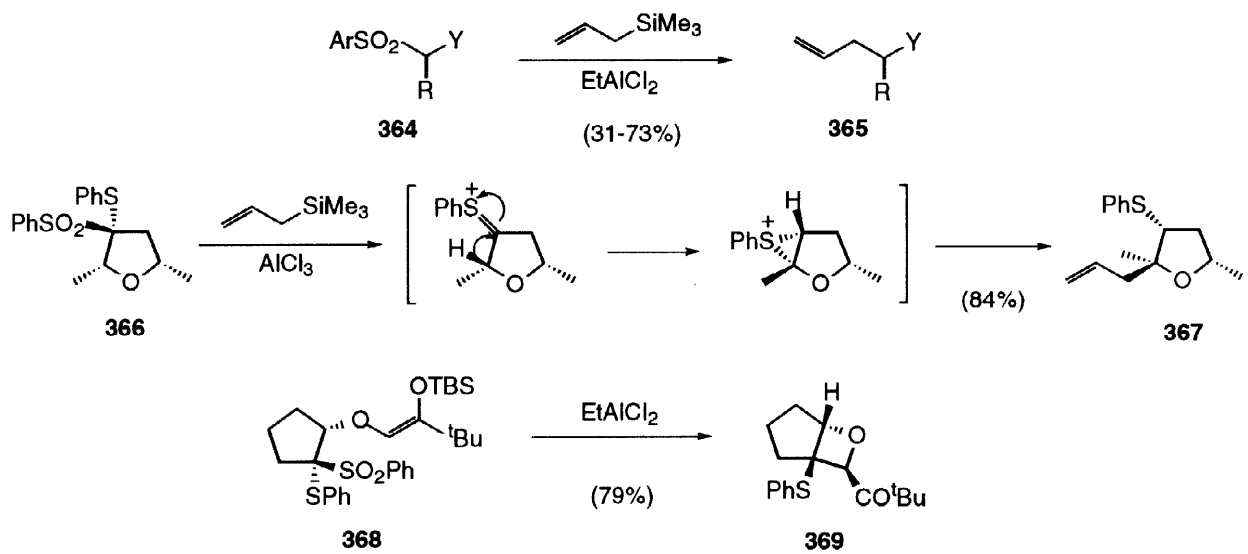
The Trost and Mikhail ketone homologation is based on the *in situ* treatment of α-methoxy-β-hydroxy sulfones **362**, prepared by addition of 1-lithio-1-methoxymethyl phenyl sulfone **361** to cyclobutanones and cyclopentanones, with diethylaluminium chloride.[236] The use of zirconium or hafnium tetrachloride in the rearrangement step of hydroxy sulfones **362** gives good yields of α-methoxyketones **363** from alkyl aryl ketones, dialkyl ketones and cycloalkanones.[237,238] This homologation procedure has been applied to the preparation of (-)-dihydroconduritol C and *meso*-dihydroconduritol D.[238]



361 **362** **363**

Scheme 125

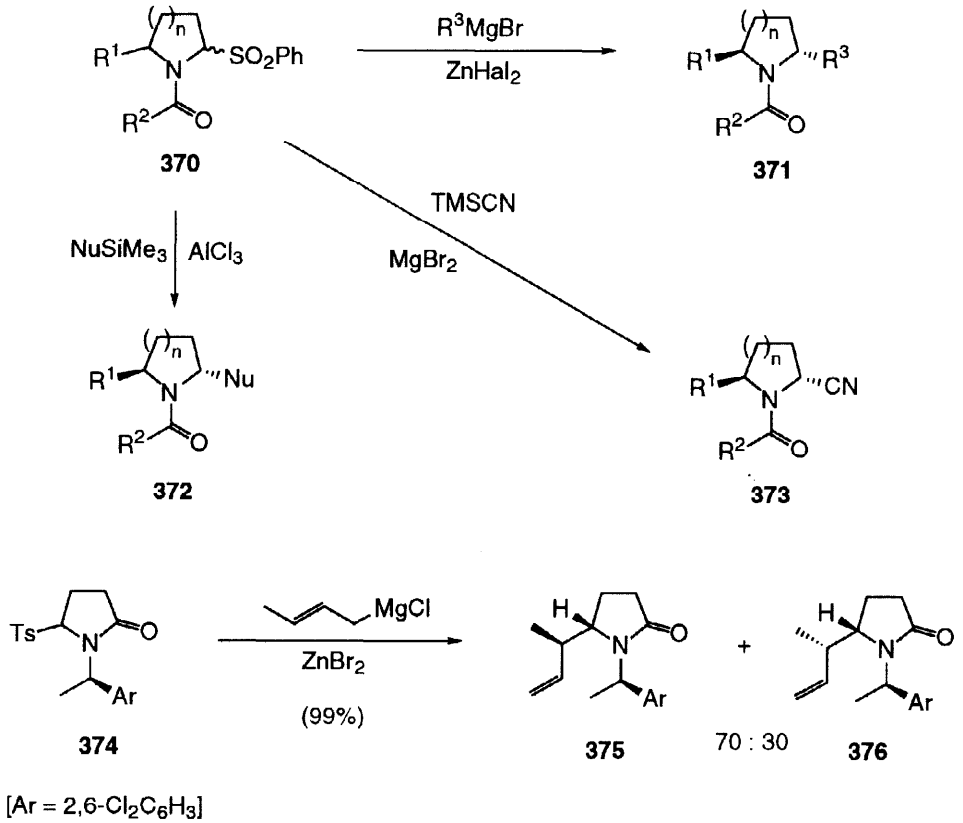
α-Phenylthio ketones can also be obtained using this homologation procedure.[236] α-Seleno- and α-thio-substituted sulfones **364** react with allyltrimethylsilane with ethylaluminium dichloride as the Lewis acid, to give homoallylic selenides and sulfides **365**, respectively[239] (Scheme 126). However, in the case of the sulfone **366**, the allylation takes place at the α-position of the tetrahydrofuran ring giving product **367**, probably by the formation of a thionium ion which undergoes a [1,2]-hydride migration and subsequent nucleophilic attack by allyltrimethylsilane[240] (Scheme 126). Silyl enol ethers can act as nucleophiles in the intramolecular ethylaluminium dichloride-promoted alkylation reactions of α-phenylthio sulfones,[241] and is similar to that previously described by Craig *et al.* for α-alkoxy sulfones[234,235] (see Scheme 123). Bicyclic ketooxetane **369** has only been obtained from the cyclopentanone derivative **368**[241] (Scheme 126), and in the case of the corresponding cyclohexanone derivative, a 1,2-hydride shift is observed instead of alkylation.



364 **365** **366** **367** **368** **369**

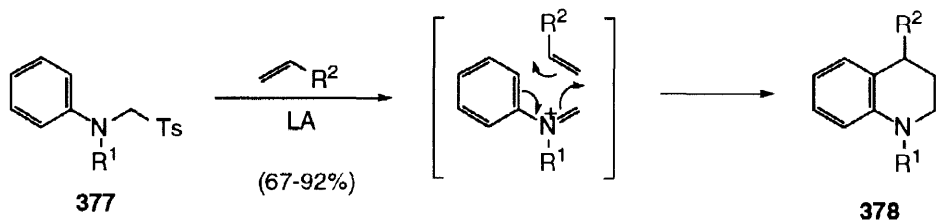
Scheme 126

α-Sulfonyl substituted *N*-acylated pyrrolidines and piperidines **370** can be alkylated at the α-position with Grignard reagents in the presence of a zinc halide, or with silyl enol ethers, silyl ketene acetals, allyl silanes and trimethylsilyl cyanide in the presence of a Lewis acid, *via* *N*-acyliminium intermediates[229d,242,243] (see, for instance, compounds **371-373** in Scheme 127). These methods have been employed in the syntheses of the two natural pyrrolidine alkaloids, norruspoline and ruspolinone, as well as for the lactam **375**, an intermediate in the total synthesis of indolizidine alkaloids (-)-205A and (-)-235B[244] (Scheme 127).



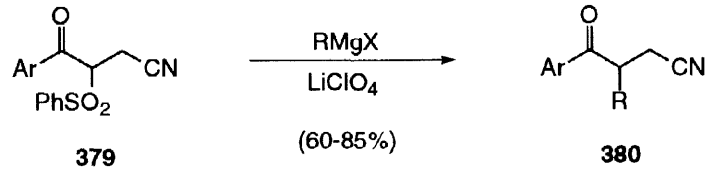
Scheme 127

α-Arylaminosulfones **377** react with olefins in the presence of Lewis acids ($SnCl_4$, $TiCl_4$ or $BF_3{\cdot}OEt_2$) providing tetrahydroquinolines **378** through a [4+2]-cycloaddition pathway[245] (Scheme 128).



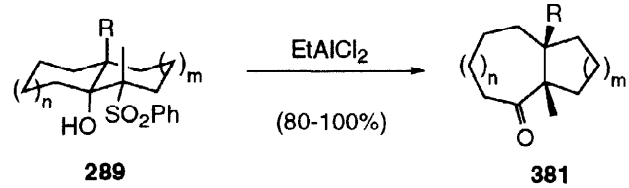
Scheme 128

Lithium perchlorate mediates in the substitution of the phenylsulfonyl group in β-ketosulfones of the type **379** in the reaction with Grignard reagents to afford α-alkylated ketones **380**[246] (Scheme 129).



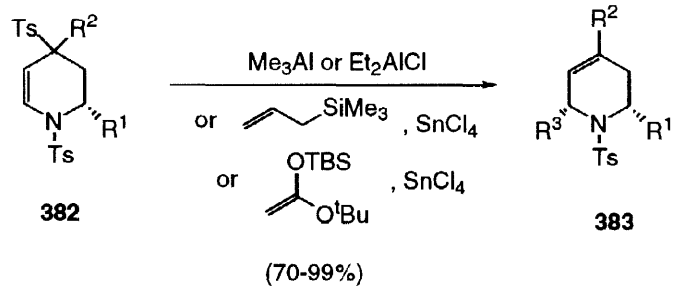
Scheme 129

Bicyclic *trans*-β-hydroxy sulfones **289**, obtained by samarium diiodide promoted intramolecular alkylation of ketosulfones **288** (see Scheme 98), undergo pinacol type rearrangement in the presence of ethylaluminium dichloride to give bicyclic ketones **381**, with very high regioselectivity[183] (Scheme 130). The rearrangement takes place through a *trans* periplanar arrangement between the migrating bond and the sulfonyl leaving group.



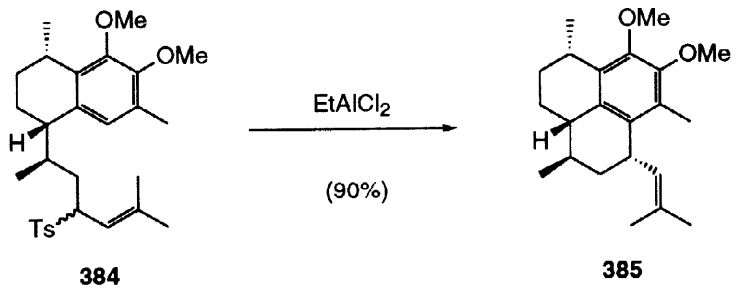
Scheme 130

Allylic sulfones can undergo alkylative desulfonylation by organometallic compounds in the presence of transition metals (see Section 5.3) or Lewis acids.[247] Craig *et al.* have studied this substitution reaction with 4-tosyl-substituted tetrahydropyridines **382**, which undergo a S_N1' process with allyltrimethylsilane or silyl enol ethers, in the presence of tin tetrachloride, to afford 2,6-*cis*-dialkylated 1,2,5,6-tetrahydropyridines **383**[248] (Scheme 131).



Scheme 131

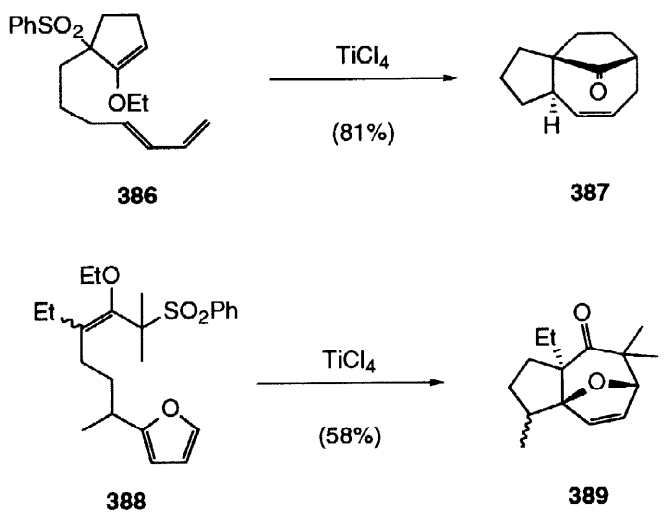
The intramolecular electrophilic attack of an allylic sulfone to an arene, catalysed by a Lewis acid, has been used by Kocienski *et al.* in the synthetic approach to the diterpene pentose glycosides, pseudopterosins.[249] In the final step to give the aglycone section **385**, allylic sulfone **384** is stereoselectively alkylated by the arene in the presence of ethylaluminium dichloride[249a,b] (Scheme 132).



384 385

Scheme 132

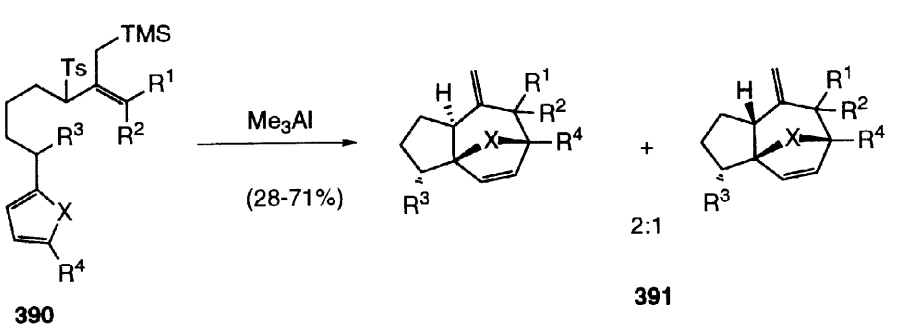
β-Functionalised allylic sulfones have been used by Harmata *et al.* as 2-ethoxyallyl cations in [4+3] intramolecular cycloaddition reactions providing an *endo* transition state, with titanium tetrachloride as catalyst.[250] This strategy has been used in the synthesis of cycloheptanoids and cyclooctanoids. Thus, sulfones **386**[251] and **388**[252] give, after cyclisation in the presence of the above catalyst, the products **387** and **389**, respectively (Scheme 133).



386 387

388 389

Scheme 133



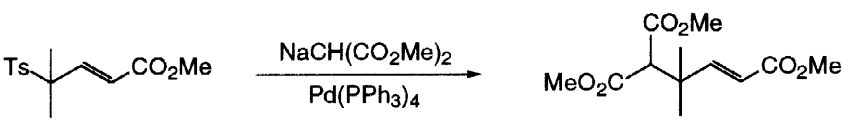
390 391

Scheme 134

When the allylic sulfone **390** bears a trimethylsilylmethyl group at the 2-position relative to the sulfone moiety, treatment with trimetylaluminium as the Lewis acid provides a *ca.* 2:1 mixture of cycloadducts **391** with an *exo*-cyclic olefinic bond[253] (Scheme 134).

5.3. Transition metal-catalysed nucleophilic displacements

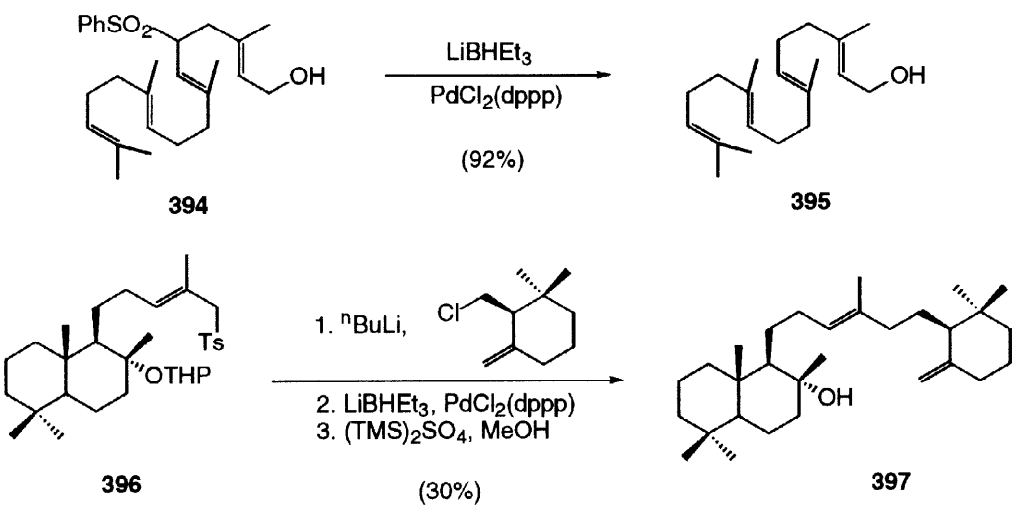
Allylic sulfones can be desulfonylated by Grignard reagents using copper(II) acetylacetonate[254] or copper(I) cyanide[255] as catalysts. Tetrakis(triphenylphosphine) palladium(0) catalyses the cleavage of the carbon-sulphur bond to afford a π-allyl complex, which undergoes nucleophilic attack by stabilised carbanions such as sodium malonate.[256] Nickel(0) complexes, generated *in situ* by the reaction of nickel chloride with triphenylphosphine, give similar results to those of palladium(0).[257] Molybdenum hexacarbonyl as the catalyst favors the α-attack by the nucleophile.[258] In the case of the α,α-dimethylated sulfone **392** derived from methyl γ-tosyl crotonate, the nucleophilic substitution at the α-position by sodium malonate with palladium(0) catalysis, occurs regioselectively to yield compound **393**[259] (Scheme 135).



392 (60%) **393**

Scheme 135

Palladium-catalysed lithium triethylborohydride reduction[260] has been widely used for the reaction of allylic sulfones *via* regioselective substitution at the α-position of the sulfonyl group, by a hydride. As representative examples are the syntheses of all-*trans*-geranylgeraniol **395** from compound **394**,[261,262] 2-tetraprenyl benzoquinol and benzoquinone,[263] the sex pheromones of the green flagellate *chlamydomonas* lurlenic acid and lurlenol,[264] (+)-ambrein **397** from compound **396**[265] and the inhibitor of topoisomerase II elenic acid[266] (Scheme 136).

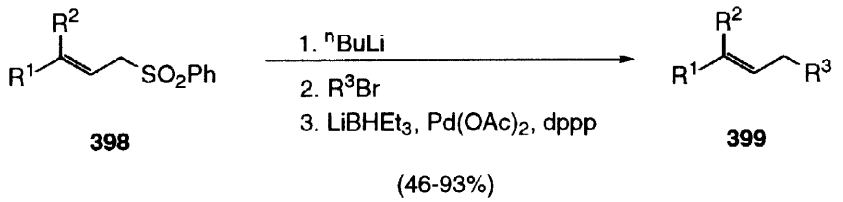


394 **395**

396 **397**

Scheme 136

An integrated chemical process based on alkylation of allylic sulfones **398** and reductive desulfonylation using palladium(0)-catalysed lithium diethylborohydride conditions allows the one-pot synthesis of olefins **399**[267] (Scheme 137). Lithium borohydride[268] and formic acid[269] have also been used as sources of the hydride anion.

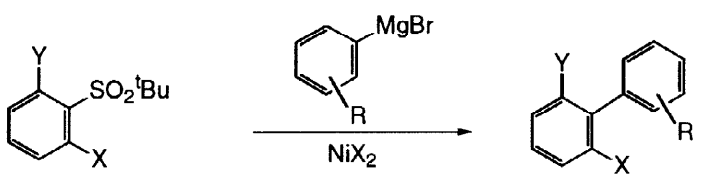


398 **399**

(46-93%)

Scheme 137

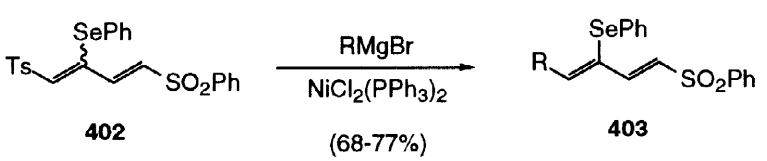
Vinyl and dienyl sulfones can be desulfonylated by Grignard reagents in the presence of nickel or iron salts.[270] Aryl *tert*-butyl sulfones **400** can be transformed into biaryls **401** by nickel salt catalysed coupling with arylmagnesium bromides[271] (Scheme 138).



400 (20-95%) **401**

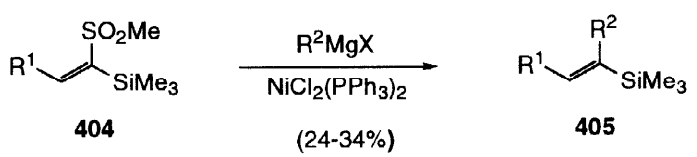
Scheme 138

The dienyl 1,4-bis-sulfone **402**, obtained by selenosulfonylation of an enyne sulfone, has been stereoselectively transformed into dienyl sulfones **403** by nickel-catalysed coupling with Grignard reagents[272] (Scheme 139).



402 (68-77%) **403**

Scheme 139



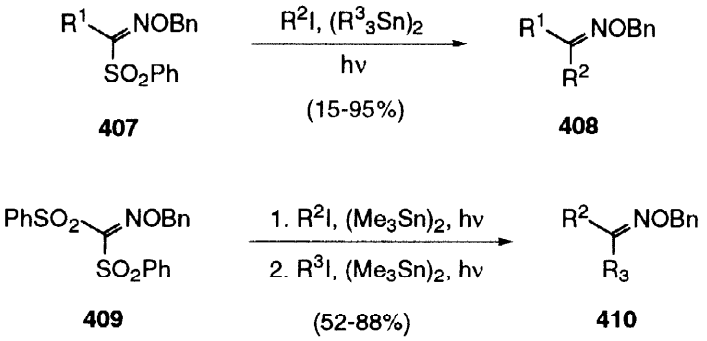
404 (24-34%) **405**

Scheme 140

α-Silylated vinyl sulfones **404** are transformed into vinylsilanes **405** by reaction with alkyl Grignard reagents in the presence of a nickel catalyst in high stereoselectivity (>96%) but in low yields, due to competition with the corresponding reduction process[273] (Scheme 140).

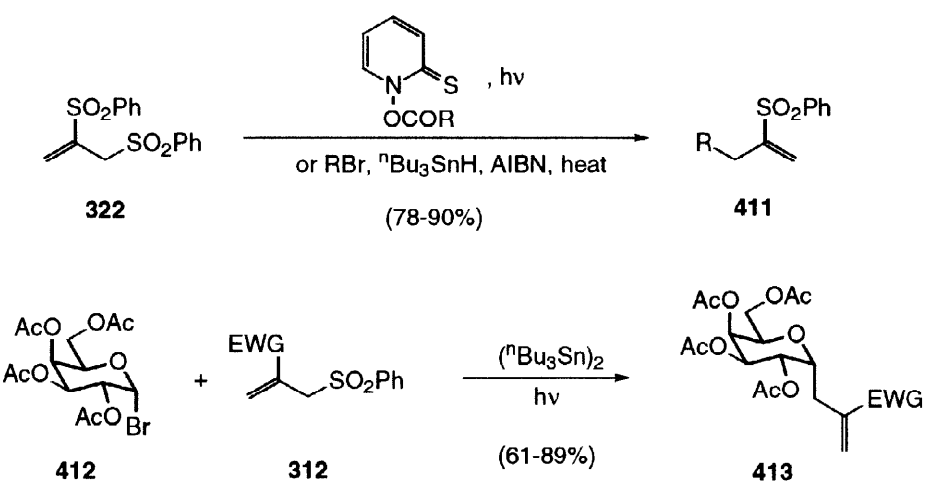
5.4. Radical-mediated displacements

Desulfonylation by means of carbon or tin free radicals usually occurs with allylic and vinylic sulfones. Phenylsulfonyl oxime ethers **407** have recently been alkylated by free radicals, formed from alkyl iodides and bis(trialkyltin), to give oxime ethers **408**.[274] The double substitution on disulfones **409** affords the corresponding products **410**, which after acidic hydrolysis give the expected acyclic or cyclic ketones[275] (Scheme 141).



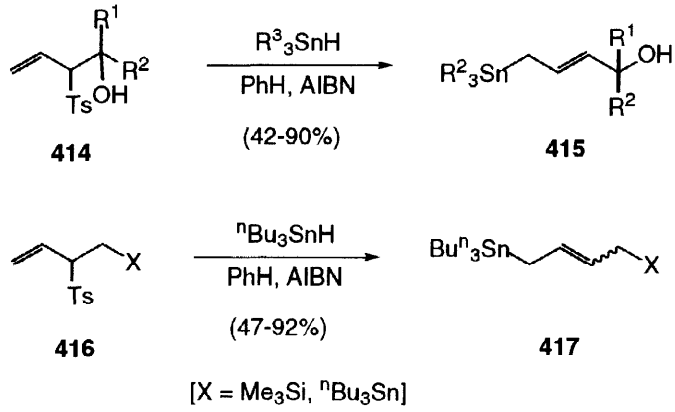
Scheme 141

Trost *et al.* have used alkyl radicals, generated by the Barton method, in the nucleophilic substitution of 2,3-bis(phenylsulfonyl)-1-propene (**322**). The conventional tributyltin hydride method also works nicely to give the corresponding products **411**[211] (Scheme 142). Tris(trimethylsilyl)silane has also been used as mediator in the radical substitution of different allylic sulfones by alkyl groups.[276] 6-Bromosugars (for instance compound **412**) react through the anomeric radical with allylic sulfones of the type **312**, in the presence of hexabutyldistannane, under photolytic conditions, to give the corresponding α-*C*-allylated sugars **413**[278] (Scheme 142).



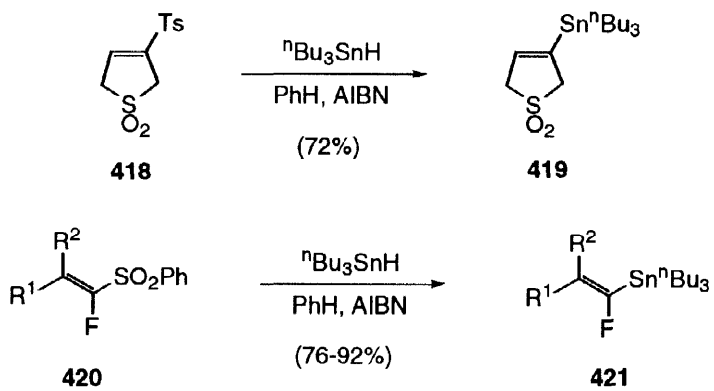
Scheme 142

Tributyltin hydride reacts regioselectively with allylic sulfones, under free radical conditions, to give rearranged allylstannanes according to a S_N2' mechanism.[279] This procedure has been applied to the preparation of functionalised allylstannanes which are interesting intermediates in organic synthesis.[280] Some representative examples are sulfones **414** and **416**, which give compounds **415**[281] and **417**,[282] respectively. In the first case, compounds **415** are obtained exclusively as the *E*-diastereomers, but in the second case a *ca.* 2:1 mixture of *E*:*Z* diastereomers is isolated (Scheme 143).



Scheme 143

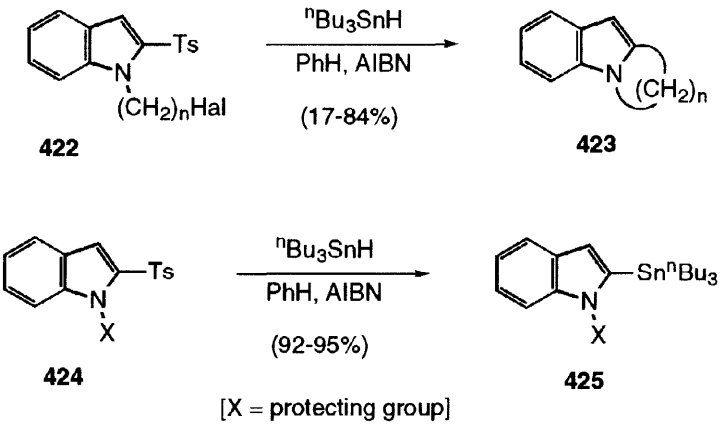
Vinyl sulfones undergo substitution by reaction with tributyltin hydride affording vinylstannanes, either by an addition-elimination mechanism or by an electron transfer process.[283] This procedure has been applied to the synthesis of the sulfolene **419** fron the sulfone **418**, a precursor of 2-tributylstannyl-1,3-butadiene[284] (see Section 7.2) and 1-fluorovinylstannanes **420**, precursors of fluoroolefins **421** by Stille coupling reactions[285] (Scheme 144).



Scheme 144

Caddick *et al.* have studied the radical substitution of the tosyl group in 2-tosylindoles **422** and **424** by means of alkyl[286] and stannyl[287] radicals in intra and intermolecular processes, respectively (Scheme 145). 2-Tosylimidazoles also undergo radical intramolecular displacement to give [1,2-a]-fused imidazoles.[288] The

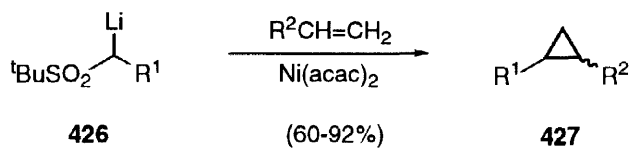
stannylation process can be carried out with aromatic and other heteroaromatic sulfones to provide organostannanes.[287]



Scheme 145

6. ELIMINATION REACTIONS

The β-elimination of the sulfinate anion is one of the simplest methods for desulfonylating organic molecules to generate a double or triple carbon-carbon bond. Simple δ-elimination or double β-elimination can be used for the formation of dienic systems. However, α-elimination reactions are scarce, because α-sulfonyl carbanions are stable intermediates and have no tendency to undergo α-eliminative processes. The only known example has been that described by Julia *et al.* using a nickel(II) acetylacetonate catalyst in the presence of olefins to afford the corresponding cyclopropanes as a mixture of *cis/trans* diastereomers[289] (Scheme 146).



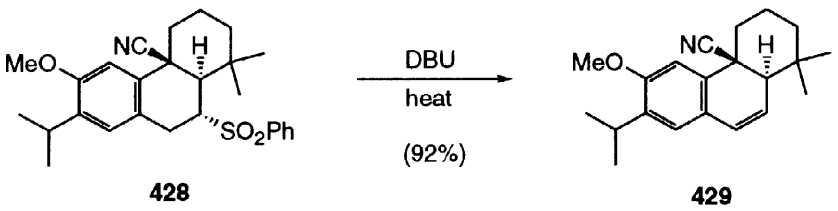
Scheme 146

6.1. β-Elimination reactions

This type of elimination process can take place under ionic, generally basic conditions, or radical conditions.

6.1.1. Alkyl and vinyl sulfones

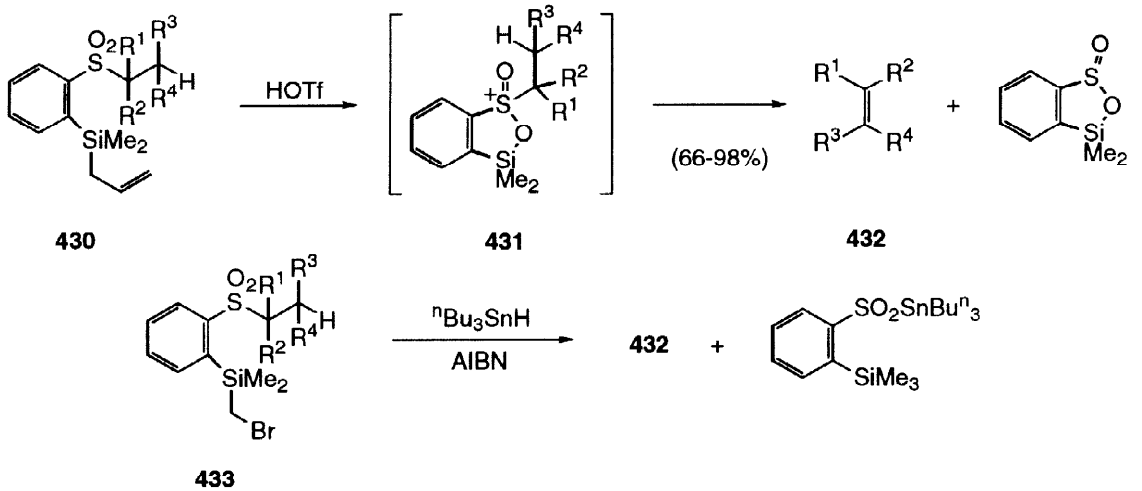
Simple alkyl sulfones can not be dehydrosulfinylated easily unless the new double carbon-carbon bond is conjugated with some unsaturated group already present in the molecule.[290] In the case of the synthesis of pisiferol, the alkyl sulfone **428**, obtained by intramolecular Diels-Alder reaction of a vinyl sulfone with an *o*-quinodimethane, is finally heated with DBU at 130°C to give the conjugate alkene **429**[291] (Scheme 147).



428 429

Scheme 147

Alkyl aryl sulfones **430** bearing a silyl group *ortho* relative to the sulfone group undergo intramolecular oxygen silylation forming a cyclic sultinium species **431**, which readily eliminates to provide olefins (Scheme 148). The sulfone elimination proceeds under mild conditions with or without the presence of activated β-protons in the substrate.[292a] When the sulfone bears an allyl[292b] or a (bromomethyl)dimethylsilyl[293] moiety **433**, free radical species can be generated by treatment with AIBN and tributyltin hydride, the 1,2-elimination taking place *via* a intramolecular β-sulfonyl hydrogen abstraction[193] (Scheme 148).

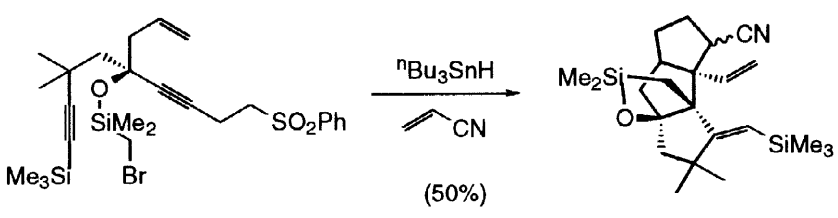


430 431 432

433 432

Scheme 148

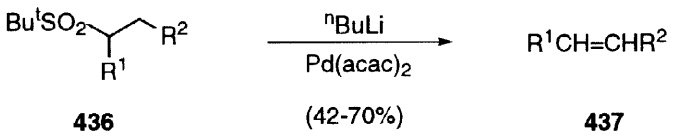
The triquinane derivative **435** is formed through a radical cascade from compound **434** in which, after cyclisation, a final radical β-elimination of the phenylsulfonyl group takes place (Scheme 149).



434 435

Scheme 149

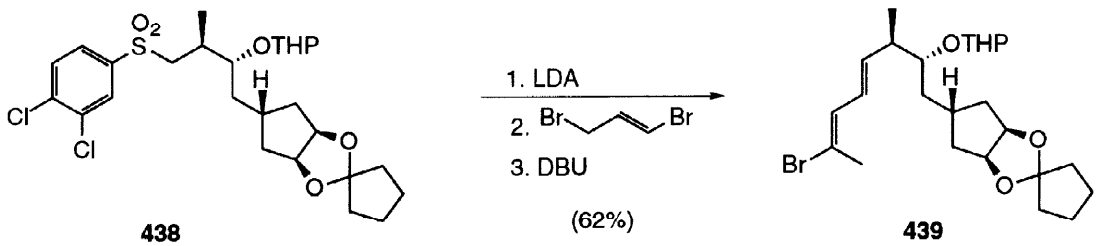
Lithiated *tert*-butyl alkyl sulfones **436** undergo β-elimination in the presence of a catalytic amount of palladium acetylacetonate in boiling THF, without isomerisation of the alkene **437**[295] (Scheme 150).



436 437

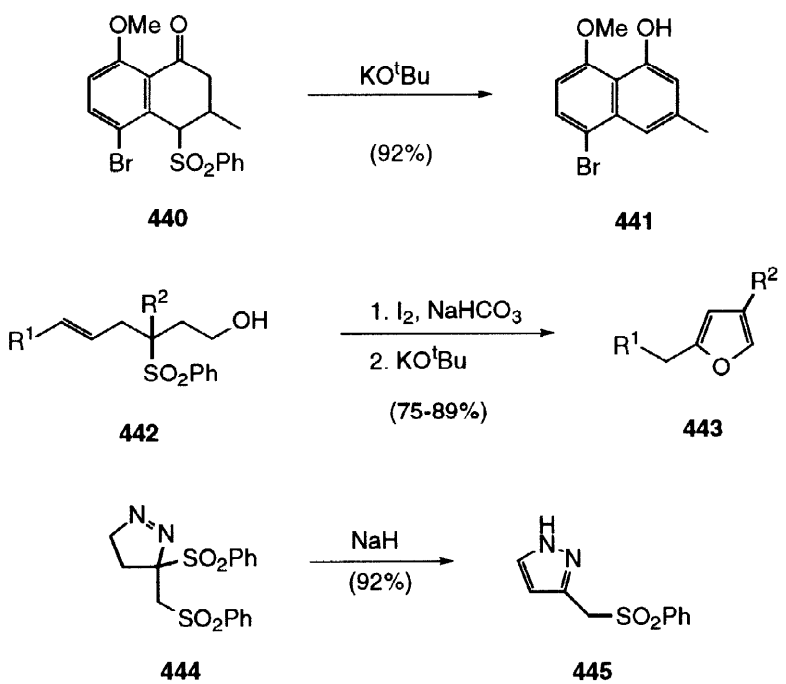
Scheme 150

In the case of sulfone **438**, its allylation with (*E*)-1,3-dibromo-2-butene followed by dehydrosulfonylation with DBU in refluxing toluene affords the diene **439**,[296] a precursor in the total synthesis of the antimitotic agent for cancer chemotherapy, rhizoxin D (Scheme 151).



438 439

Scheme 151



440 441

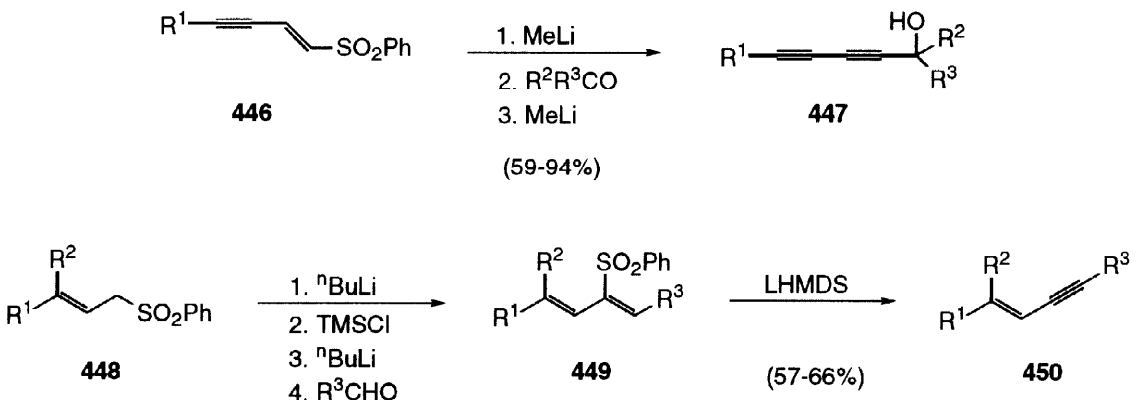
442 443

444 445

Scheme 152

Some examples in which the dehydrosulfinylation step affords aromatic and heteroaromatic systems are summarised in Scheme 152. The benzylic sulfone **440**, obtained by Michael addition to methyl crotonate followed by intramolecular acylation, is aromatised with potassium *tert*-butoxide to give naphthol **441**, a useful building block for the construction of naphthylisoquinoline alkaloids.[297] Allylated β-hydroxy sulfones **442** give, after iodoetherification followed by treatment with potassium *tert*-butoxide, the furans **443**.[298] Pyrazole **445** is obtained by sodium hydride treatment of the pyrazoline **444**, formed in the 1,3-dipolar cycloaddition of diazomethane to 2,3-bis(phenylsulfonyl)-1-propene (**322**).[299]

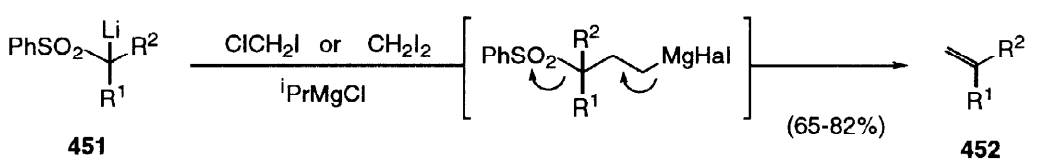
Vinyl sulfones give acetylenes under strongly basic conditions. This methodology has been used for the syntheses of diynes[300] and enynes.[301] Thus, from conjugated enyne sulfones **446**, their α-lithiation followed by reaction with carbonyl compounds and finally treatment with methyllithium, the (*E*)-diynols **447** are formed[300] (Scheme 153). Dienyl sulfones **449**, generated *in situ* by Peterson olefination from allylic sulfones **448**, undergo final elimination to lead to a one-pot synthesis of enynes **450**[301] (Scheme 153).



Scheme 153

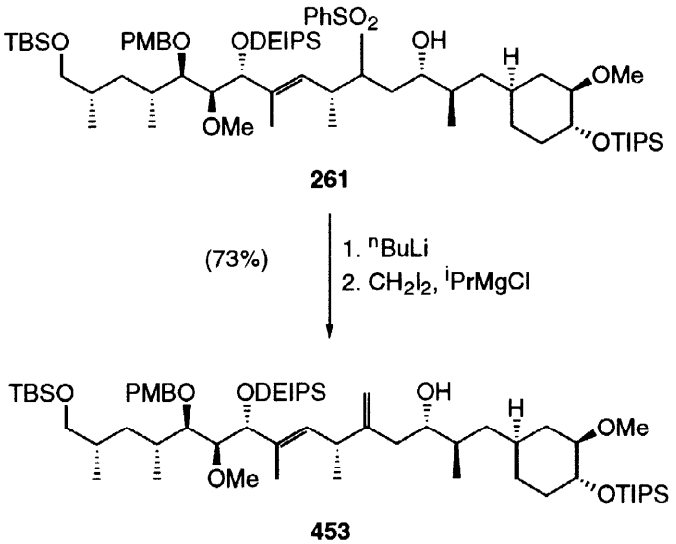
6.1.2. Olefination of alkyl sulfones

A direct replacement of the sulfone group in an alkyl sulfone by a methylene or alkylidene group can be achieved in an one-pot process based on the alkylation of lithiated sulfones **451** with 1-haloalkylmagnesium halides, followed by a β-elimination process. This simple and direct olefination reaction is usually carried out with carbenoids derived from chloroiodomethane or diiodomethane, in the case of the methylenation process, affording olefins **452**[302] (Scheme 154).



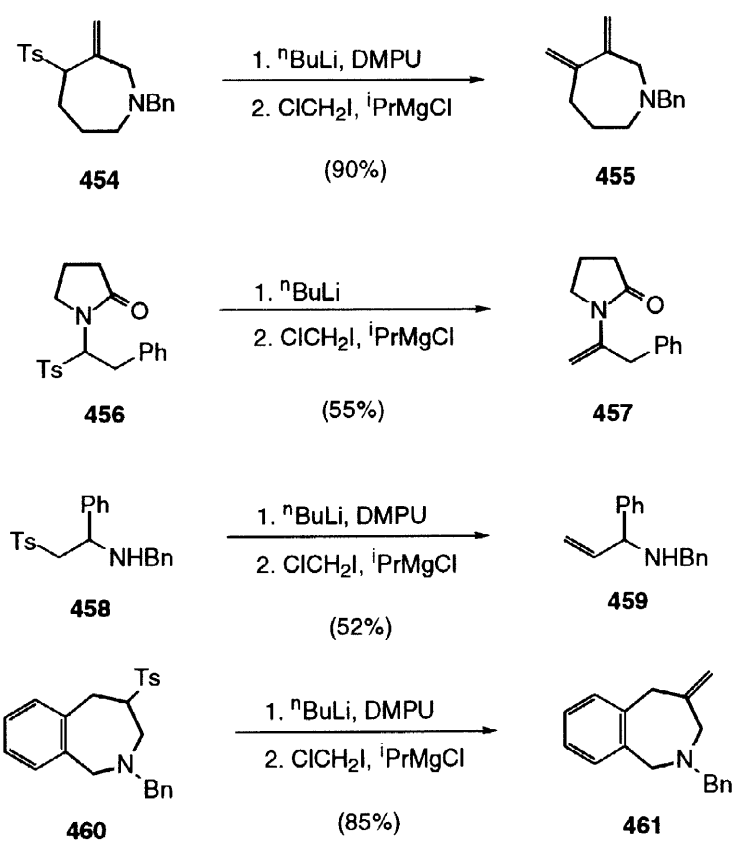
Scheme 154

The same strategy has been used for the preparation of the compound **453** used in the total synthesis of (-)-rapamycin[51] by Schreiber *et al.*[161b] (Scheme 155). This method gives better yields of final ketone **262** than the corresponding oxidative desulfonylation (see Scheme 87).



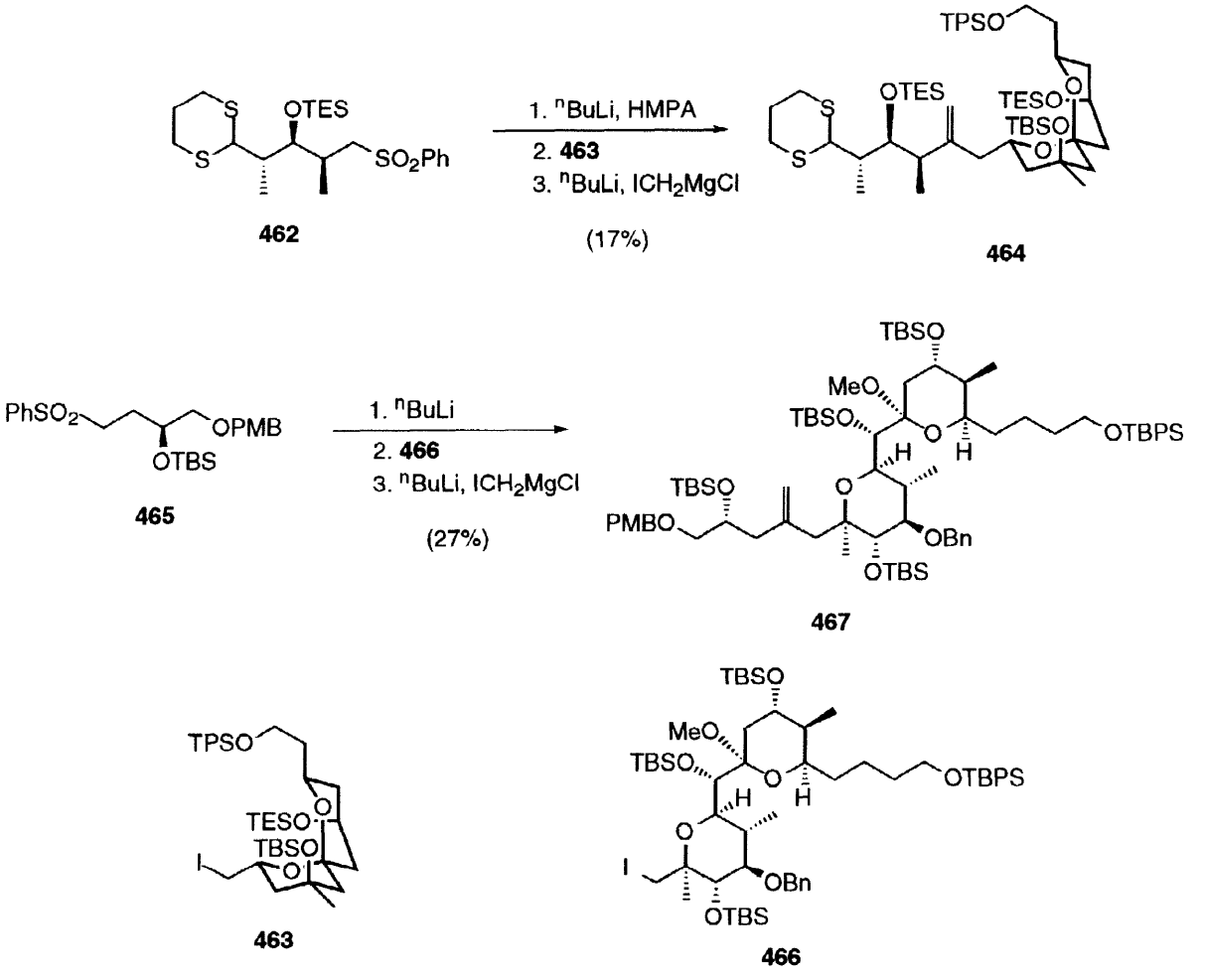
Scheme 155

The allylic sulfone **454** has been transformed into the outer ring diene **455** in good yield.[86b] α-Amido-**456**[180b] or β-amino-alkyl[74] sulfones **458** and **460** have also been methylenated to give the enaminone **457**[180b] or allylic amines **459** and **461**[74] (Scheme 156).



Scheme 156

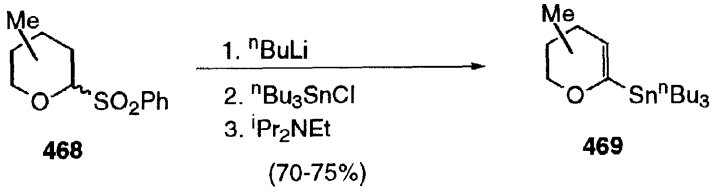
In the synthesis of the C1-C17 spiroketal **464** of the sponge metabolite spongistatin, Smith *et al.* couple the sulfone **462** with the iodide **463**, followed by a Julia methylenation[303] (Scheme 157). The same strategy has been used for the preparation of the C29-C48 subtarget **467** by using the sulfone **465** and the iodide **466**[304] (Scheme 157).



Scheme 157

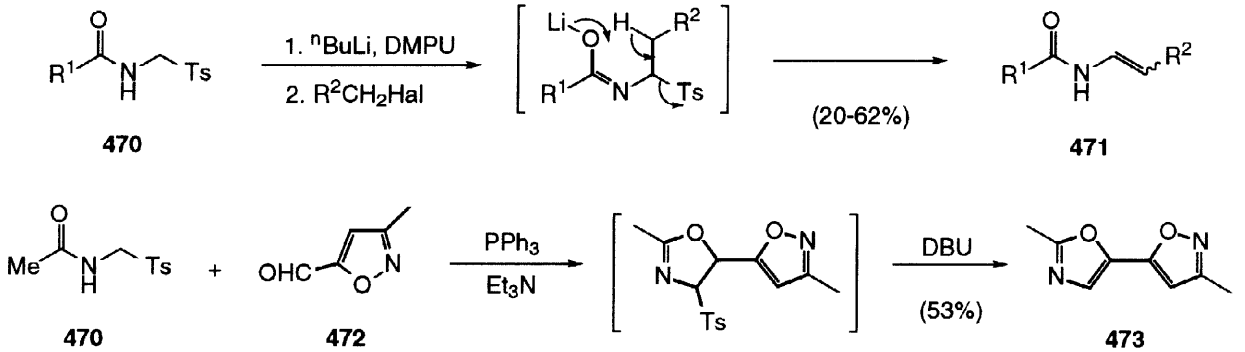
6.1.3. α-Functionalised alkyl sulfones

Cyclic α-alkoxy sulfones **468** have been transformed into vinylstannanes **469** by β-elimination of benzenesulfinic acid with Hünig base (Scheme 158). These products **469** are coupled to give C_2-symmetric bis-dihydropyrans used in the enantioselective and regioselective protection of glycerol.[305] Related stannyl dihydropyrans have also been used for the preparation of organolithium derivatives by tin-lithium exchange.[306]



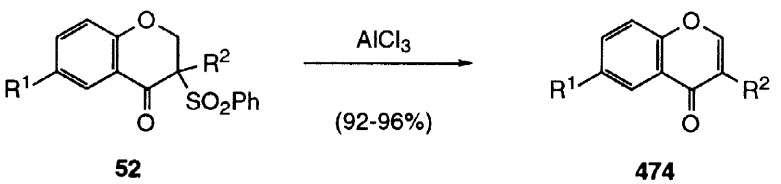
Scheme 158

When α-nitrogenated alkyl sulfones derived from primary amides **470** are lithiated and alkylated at the α-position, they suffer spontaneous β-elimination, probably through an intramolecular process, to provide *N*-acyldienamides **471**[180] (Scheme 159). In the case of the *N*-methyl derivatives, the dehydrosulfinylation is carried out using potassium *tert*-butoxide.[307] The isoxazole-oxazole unit **473** of the anti-bacterial compound BRL 49467 has been prepared by the reaction of **470** (R^1 = Me) with the aldehyde **472** in the presence of triphenylphosphine, followed by DBU-promoted dehydrosulfinylation[308] (Scheme 159).



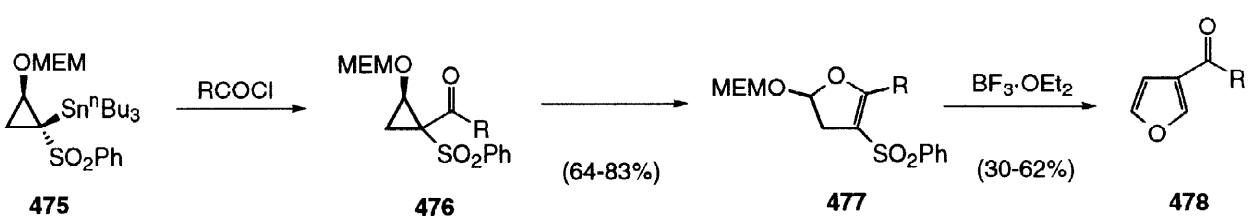
Scheme 159

The dihydrosulfinylation of β-ketosulfones is favoured by the formation of α,β-unsaturated ketones. Isoflavones **474** are obtained when sulfones **52** are treated with aluminium trichloride as Lewis acid; base-promoted elimination fails in this case [35] (Scheme 160).



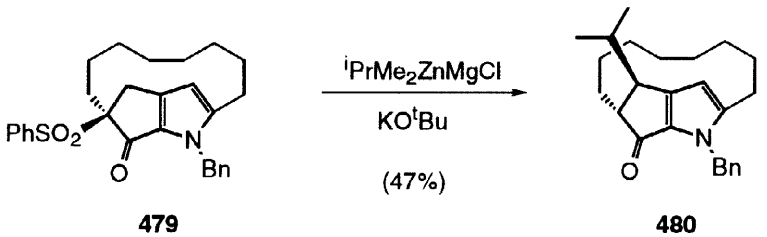
Scheme 160

Cyclopropyl sulfones **476**, obtained by acylation of the stannyl precursor **475**, give dihydrofurans **477**, which are transformed into 3-acylfurans **478** by treatment with boron trifluoride etherate[309] (Scheme 161).



Scheme 161

The macrotricyclic core **480** of the potent antitumor agent, roseophilin, is formed from the β-ketosulfone **479** upon elimination of the sulfone group with potassium *tert*-butoxide in the presence of a isopropylzincate, which is compatible with the basic conditions used and gives stereoselective Michael addition onto the resulting unstable enone[310] (Scheme 162).



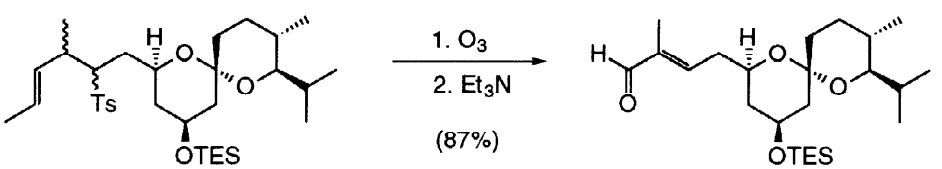
479 **480**

Scheme 162

6.1.4. β-Functionalised alkyl sulfones

The presence of an electron-withdrawing group at the β-position of an alkyl sulfone favours a base-promoted β-elimination reaction. Another important process is the fluoride-induced β-elimination reaction which occurs in the case of β-silylated or β-stannylated sulfones.

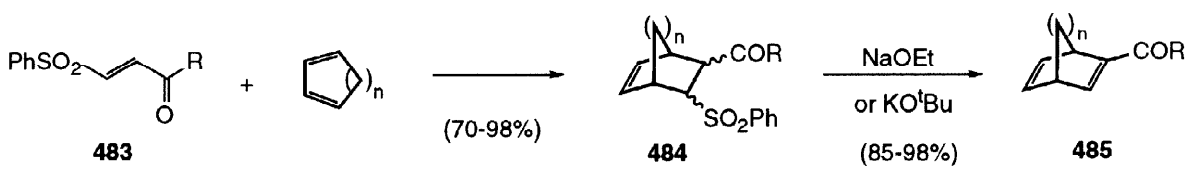
Carbonyl compounds, esters, lactones and amides substituted at the β-position by a sulfone group are easily dehydrosulfinylated , usually under basic conditions. In the synthesis of the C10-C25 northern moiety of 22,23-dihydroavermectin B_{1b}, the aldehyde **482** is prepared from the sulfone **481** by ozonolysis and tetraethylamine-mediated β-elimination[311] (Scheme 163).



481 **482**

Scheme 163

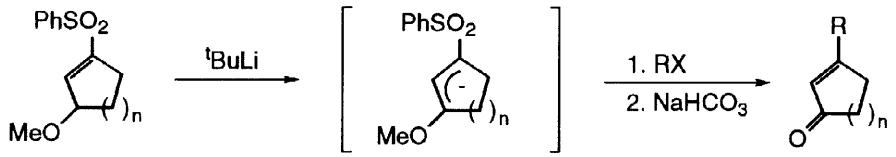
(*E*)-β-Phenylsulfonyl enones **483** are useful dienophiles and behave as synthetic equivalents of α,β-acetylenic ketones. The basic elimination by means of sodium ethoxide or potassium *tert*-butoxide on the resulting adducts **484** yields the corresponding enones **485**[312a] (Scheme 164). For β-aroyl-α,β-unsaturated ketones **483** (R = Ar) Nazarov cyclisation occurs on treatment with triflic acid affording indanones, which give indenones after reaction with DBU.[312b]



483 **484** **485**

Scheme 164

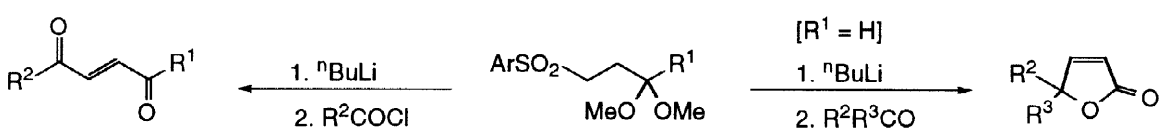
β-Substituted cyclic enones **487** can be prepared by alkylation of anions of γ-methoxy vinyl sulfone **486** with different electrophiles followed by basic hydrolysis[313] (Scheme 165). Acyclic γ-benzyloxy allyl sulfone anions react with aldehydes and alkyl halides at the α-position in respect to the sulfone group giving, after hydrolysis, the corresponding butenolides and furans.[314] All these anions can be considered β-acylvinyl anion equivalents.[315]



486 **487**

Scheme 165

Lithiated 3-tosylpropanal and 4-tosyl-2-butanone dimethyl acetals **488** have also been used as β-acylvinyl anion equivalents of acrolein and methyl vinyl ketone, for the synthesis of unsaturated 1,4-dicarbonyl compounds **489** and α,β-butenolides **490**[316a] (Scheme 166). In the case of dilithiated 3-tosylpropanal, the corresponding dialkylation followed by hydrolysis of the acetal functionality and final 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-mediated dehydrosulfinylation gives the expected β,β-disubstituted acrolein derivatives.[60] In β-tosylated carboxylic acids, it is not necessary to protect the carboxylic group, as the corresponding dianions behave as β-acylvinyl anion equivalents[315] for α,β-unsaturated carboxylic acids. They have been used in the synthesis of butenolides by the reaction with carbonyl compounds, and of 1,4-enedicarbonyl compounds by acylation and of α,β-unsaturated esters by alkylation.[316b,c] The homoenolate derived from **488** (R1 = OMe), 3-phenylsulfonyl orthopropionate, has also been used as a β-anionic acrylate synthon for the syntheses of butenolides[316d] and α,β-unsaturated δ-lactones, such as cytotoxic styryl lactones, goniodiol and 9-deoxygoniopypyrones.[316e-k]



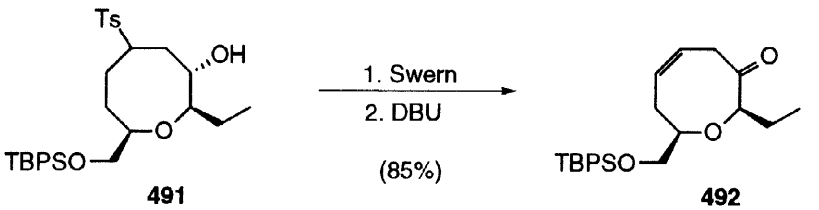
489 **488** **490**

Scheme 166

In the formal synthesis of (+)- and (-)-laurencin the cyclic γ-hydroxy sulfone **491** (or its enantiomer) is transformed into the corresponding α,β-unsaturated ketone **492** (or its enantiomer) by a tandem oxidation-DBU elimination[317] (Scheme 167).

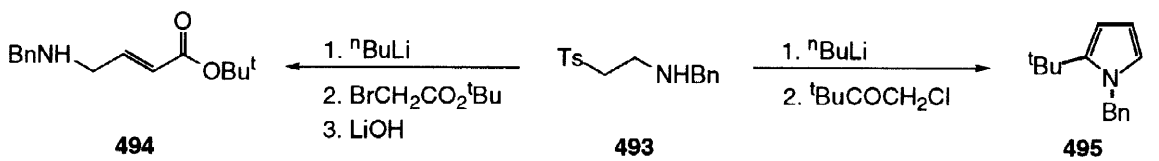
The alkylation of the monoanion derived from β-aminoalkyl sulfone **493** with *tert*-butyl bromoacetate or with *tert*-butyl chloromethyl ketone gives, after treatment with lithium hydroxide, the GABA derivative **494** or directly the pyrrol **495**, respectively[74] (Scheme 168). Pyrroles **497** can also be prepared by the dipolar addition of isocyanoacetate to vinyl sulfones **496** followed by potassium *tert*-butoxide elimination[318a-d] (Scheme 169),

or by addition to β-nitrosulfones in the presence of DBU.[318e] 3-Acylpyrroles **499** have been prepared through a [4+1] annulation reaction of the sulfonyl diene **498** with amines, to give *trans*-3,4-disubstituted pyrrolidines, followed by dehydrosulfinylation with sodium methoxide and air oxidation[319] (Scheme 169).



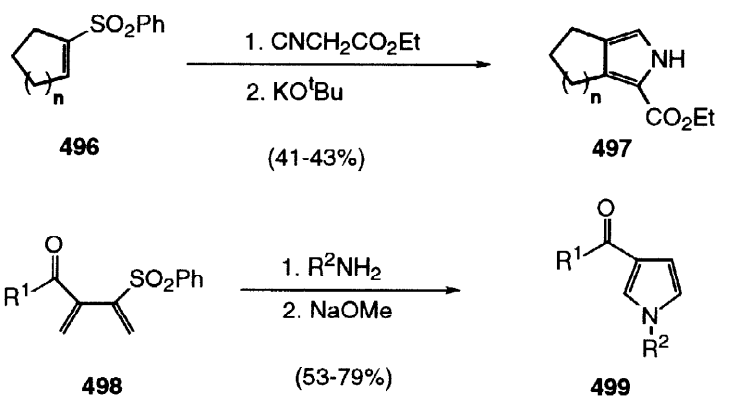
491 **492**

Scheme 167



494 **493** **495**

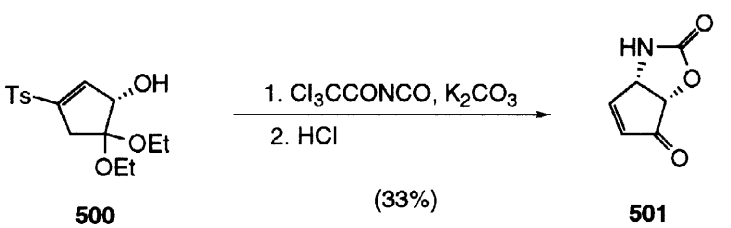
Scheme 168



496 **497** **498** **499**

Scheme 169

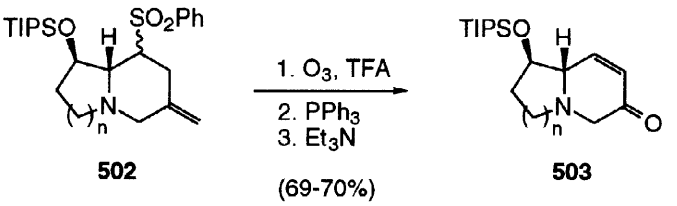
The oxazolidinone **501**, a precursor of the glycosidase inhibitor amannostatin A,[320] is obtained in high optical purity from an intramolecular Michael addition of an *in situ* generated carbamate to the vinyl sulfone in **500** followed by deprotection of the ketal in acidic media with concomitant dehydrosulfinylation[321] (Scheme 170).



500 **501**

Scheme 170

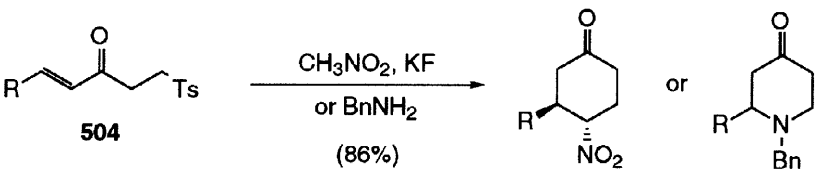
In recent syntheses of polyhydroxylated quinolizidines[322] and indolizidines,[323] alkaloid sulfones of the type **502** are transformed into α,β-unsaturated cyclohexenones **503** by ozonolysis of the methylene group followed by dehydrosulfinylation (Scheme 171).



502 **503**

Scheme 171

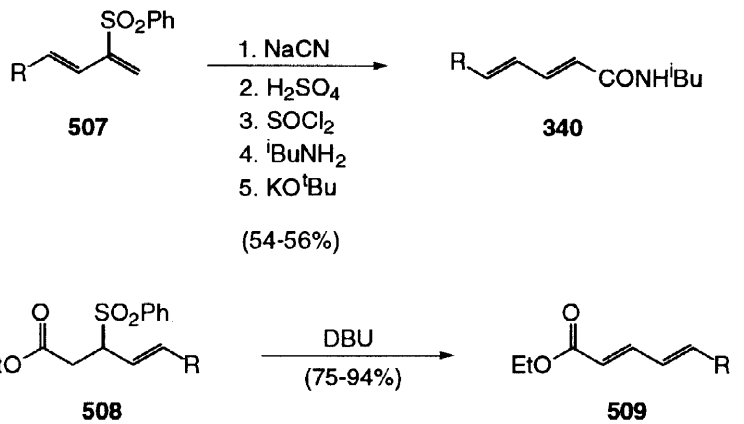
Divinyl ketones are trapped by the treatment of β-keto sulfones, of the type **504**, with nucleophiles, such as nitromethane and potassium fluoride or benzylamine, to give cyclohexanones **505** or **506**, respectively[324a] (Scheme 172). This methodology has been studied on a solid support, the resin being released in a recyclable sulfinate form.[324b]



504 **505** **506**

Scheme 172

Michael addition reactions of sodium cyanide or nitroalkanes to 2-phenylsulfonyl 1,3-dienes[2d] **507**, in the presence of DBU, allows the stereoselective synthesis of naturally occurring (2*E*,4*E*)-dienamides,[325] dienoates[325a] or dien-2-ones[325b] and dienals **340**.[325b] Scheme 173 shows the preparation of dienamides **340** (R^1 = H, R^2 = Bu^i).[325a] Sulfones **508**, obtained by Claisen rearrangement of γ-hydroxyvinyl sulfones, are transformed into (2*E*,4*E*)-dienoates **509** by DBU-mediated elimination[326] (Scheme 173).

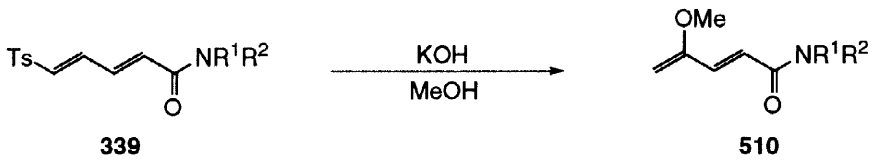


507 **340**

508 **509**

Scheme 173

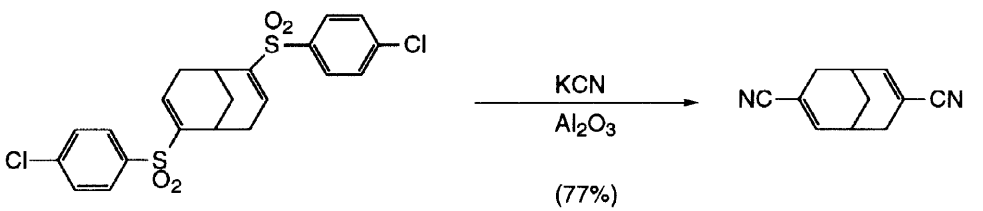
(2*E*, 4*E*)-5-Tosyl-2,4-pentanedienamides **339**, which have been used as δ-acyldienyl cation equivalents[315] for the synthesis of dienamides, add methoxide at the γ-position and after dehydrosulfinylation give (2*E*)-4-methoxy-2,4-pentadienamides **510** (Scheme 174). These amides behave as electron-rich dienes in Diels-Alder reactions.[328]



339 **510**

Scheme 174

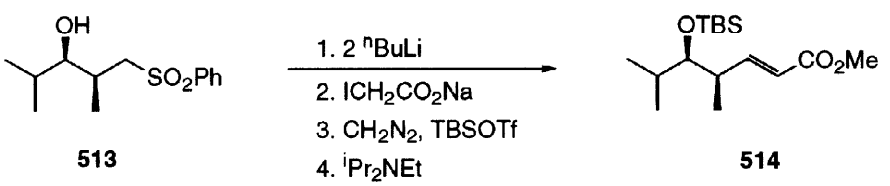
The dinitrile **512**, precursor of barbaralanes, has been prepared by tandem Michael addition of potassium cyanide-dehydrosulfinylation from the vinylic sulfone **511**[328] (Scheme 175).



511 **512**

Scheme 175

The alkylation of sulfonyl carbanions with α-halogeno carboxylic acids or derivatives followed by base-promoted dehydrosulfinylation is a very common strategy for the stereoselective synthesis of α,β-unsaturated carboxylic acids or derivatives. The synthesis of the ester **514**, a segment of the antibiotic pristinamycin PIIA[329a] and PIIB,[329b] is based on the alkylation of the sulfone **513** with sodium iodoacetate followed by esterification and Hünig base treatment (Scheme 176).

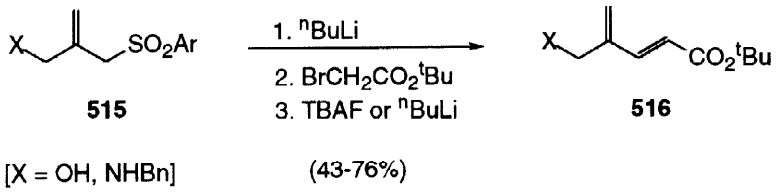


513 **514**

(40%)

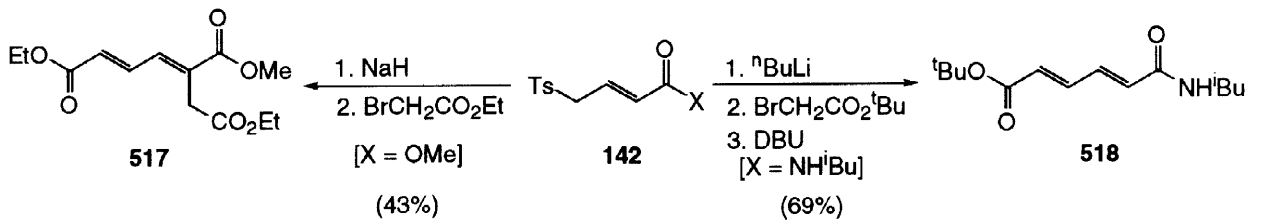
Scheme 176

Allylic sulfones of the type **515** bearing hydroxy[330] or amino[86] groups (X = OH, NH_2) have been transformed into 2,4-pentadienoates **516** by lithiation and alkylation with *tert*-butyl bromoacetate and basic β-elimination with tetrabutylammonium fluoride (TBAF)[330] or butyllithium[86] (Scheme 177).



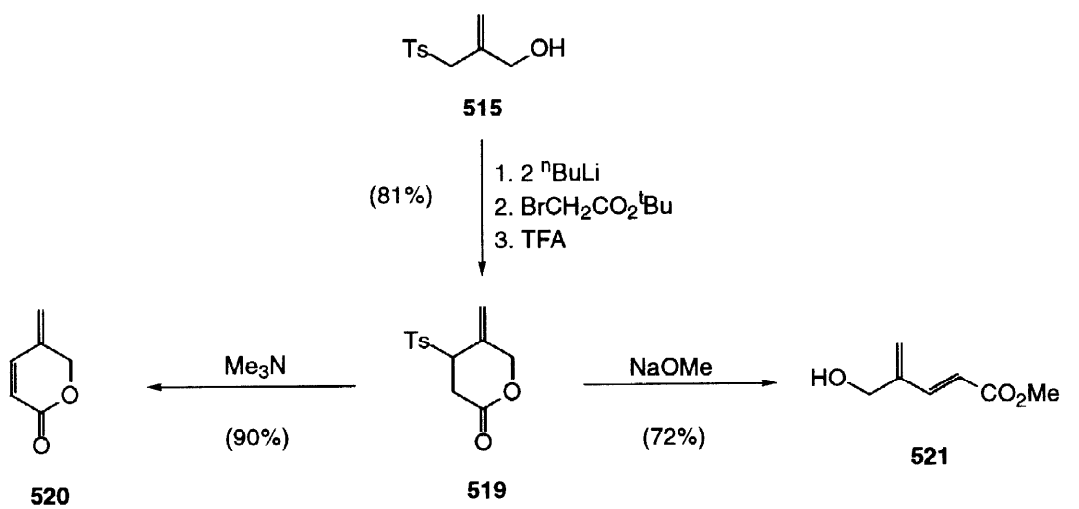
Scheme 177

Allylic sulfones with crotonoate structure **142** (X = OMe,[259] NHiBu[88]) react with bromoacetates in the presence of sodium hydride (X = OMe) or butyllithium (X = NHiBu). In the first case, the dialkylation followed by *in situ* dehydrosulfinylation gives the dienic triester **517**,[259] whereas in the second case, the alkylated sulfone is treated with DBU providing the product **518**[88] (Scheme 178).



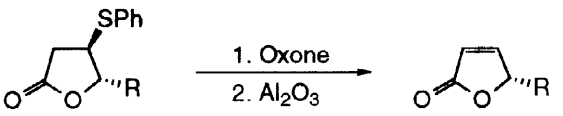
Scheme 178

When the starting sulfone contains a hydroxy group at the γ-position, the alkylation with bromoacetates or related halides followed by dehydrosulfinylation can be applied to the synthesis of α,β-unsaturated δ-lactones.[331a] In the case of 2-(tosylmethyl)-2-propen-1-ol (**515**, X = OH), lactone **519** furnishes either the dienic lactone **520**, when it is treated with trimethylamine, or the dienic ester **521** (related to **516**) on reaction with sodium methoxide[85] (Scheme 179).



Scheme 179

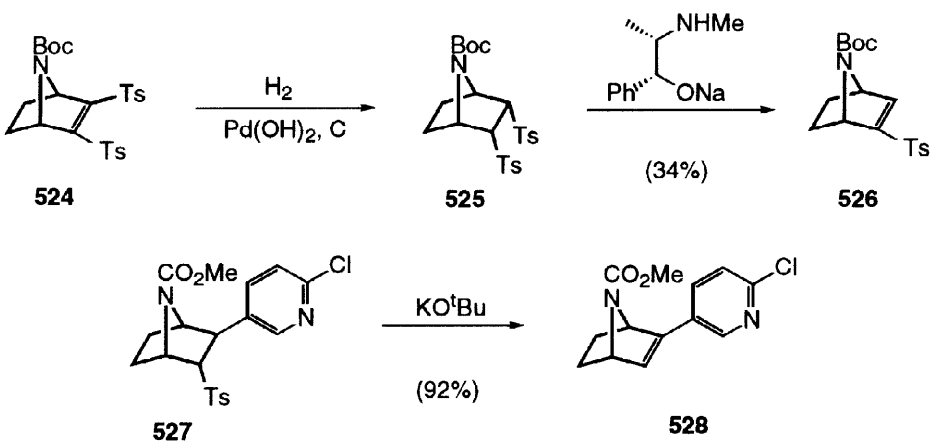
The final step in the asymmetric synthesis of butenolides from 3-phenylthio substituted γ-lactones **522** is based on their oxidation to give sulfones followed by basic elimination[331b] (Scheme 180). Chiral butenolides have also been prepared by alkylation of β-ketosulfones with ethyl bromoacetate, followed by reduction with bakers yeast, lactonisation and dehydrosulfinylation with DBU.[11]



522 (72-95%) **523**

Scheme 180

Vicinal bis-sulfones can be dehydrosulfinylated to give vinyl sulfones by strong bases. The bis-sulfone **525**, obtained by hydrogenation of the starting material **524**,[332a] undergoes a novel type of asymmetric elimination on treatment with the sodium alkoxide of (1*R*,2*S*)-ephedrine to afford the vinyl sulfone **526** in 60% ee[332a] (Scheme 181). This compound is a key intermediate in the synthesis of the alkaloid, epibatidine.[77] Another route to prepare epibatidine is based on the dehydrosulfinylation of the sulfone **527** with potassium *tert*-butoxide, followed by hydrogenation of the obtained compound **528**[332c] (Scheme 181).



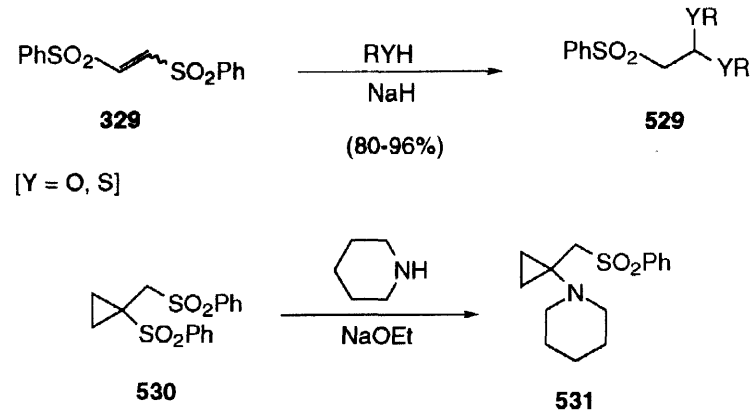
524 **525** **526**

527 **528**

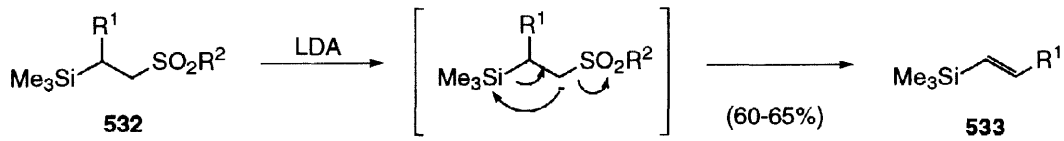
Scheme 181

Acetals or thioacetals derived from 2-sulfonylacetaldehyde **529** can be prepared from (*Z*)- or (*E*)-bis(phenylsulfonyl)ethylene **329** by reaction with sodium alkoxides or thioalkoxides, according to a tandem addition-elimination-addition process[333a] (Scheme 182). In the case of the 1,2-bis-sulfone **530**, the reaction with piperidine in ethanolic sodium ethoxide gives the elimination-addition product **531**[333b] (Scheme 182).

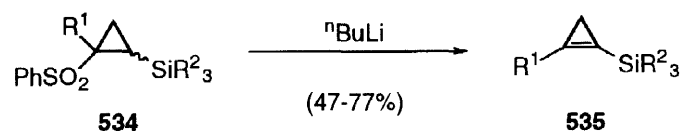
The treatment of β-trimethylsilylalkyl sulfones **532** with strong bases, such as LDA, causes elimination-rearrangement to give mainly vinylsilanes **533**[334] (Scheme 183). Cyclopropenes bearing a silyl group **535** are prepared by radical addition of iodoalkyl sulfones to vinylsilanes, followed by cyclisation to afford cyclopropyl sulfones **534** and treatment with butyllithium[335] (Scheme 184).



Scheme 182

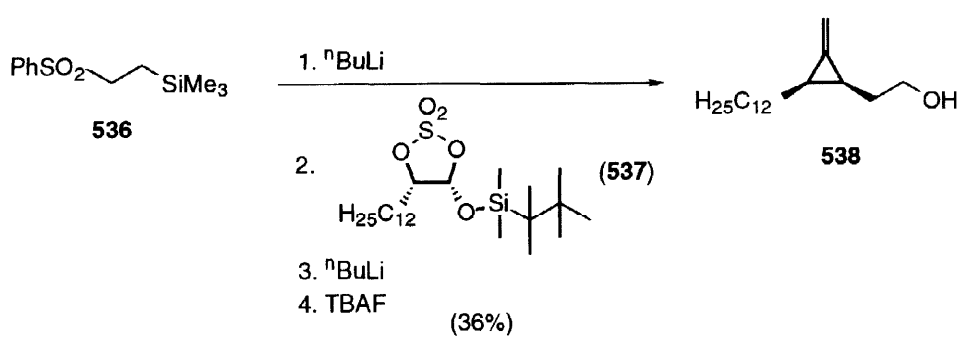


Scheme 183



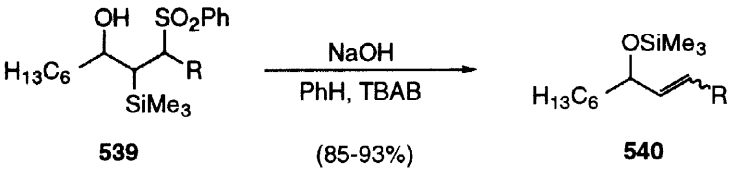
Scheme 184

However, the most important reaction of β-silyl-[336] or β-stannyl-alkyl[337] sulfones is the β-elimination affording alkenes. Methylenecyclopropanes can be prepared by reaction of lithiated β-(trimethylsilyl)ethyl phenyl sulfone **536** with epoxides, followed by fluoride induced phenylsulfonyltrimethylsilane elimination.[338] In the case of enantiopure cyclic sulfates, such as **537**, the reaction has been applied to the synthesis of enantiopure methylenecyclopropane **538**[339] (Scheme 185).



Scheme 185

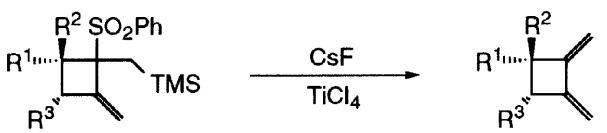
γ-Hydroxy-β-trimethylsilyl sulfones **539**, obtained by reaction of (α,β-epoxyalkyl)silanes with α-sulfonyl anions, are transformed into *O*-trimethylsilyl derivatives of allylic alcohols **540** using sodium hydroxide with phase-transfer catalysis[340] (Scheme 186).



539 (85-93%) **540**

Scheme 186

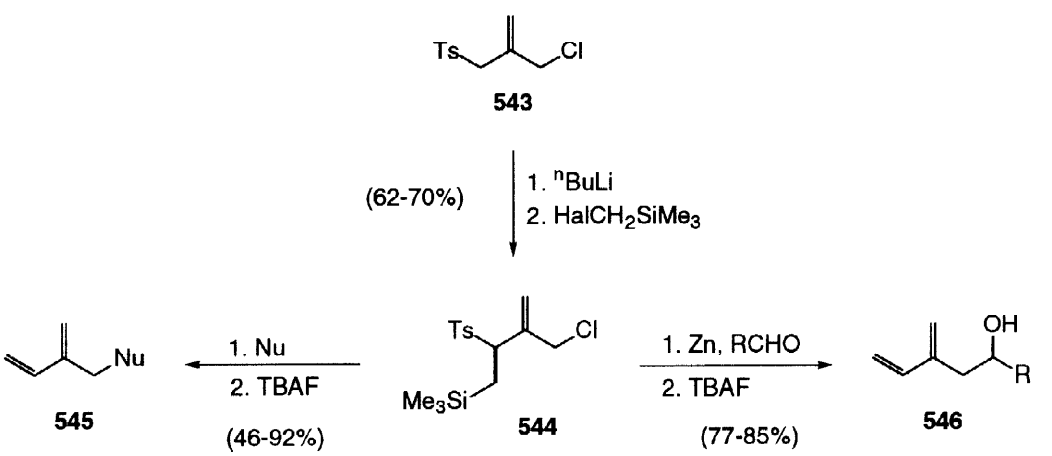
Di-*exo*-methylenecyclobutanes **542** are obtained by fluoride-induced β-elimination of the corresponding β-silyl sulfone **541**, in the presence of titanium tetrachloride at low temperature, in order to avoid isomerisation of the exocyclic carbon-carbon double bonds[341] (Scheme 187).



541 (63-81%) **542**

Scheme 187

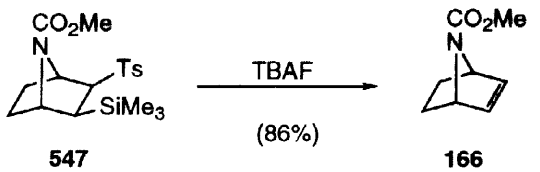
2-(Chloromethyl)-3-tosylpropene (**543**) is a useful reagent for the general synthesis of functionalised 2-substituted 1,3-dienes. The alkylation of the monolithium derivative with bromo- or iodo-methyltrimethylsilane gives the β-silyl sulfone **544**, which reacts with carbo and heteronucleophiles or aldehydes under Barbier conditions to provide dienes **545** or **546**, respectively, after treatment with TBAF[86,342] (Scheme 188).



545 (46-92%) **544** (77-85%) **546**

Scheme 188

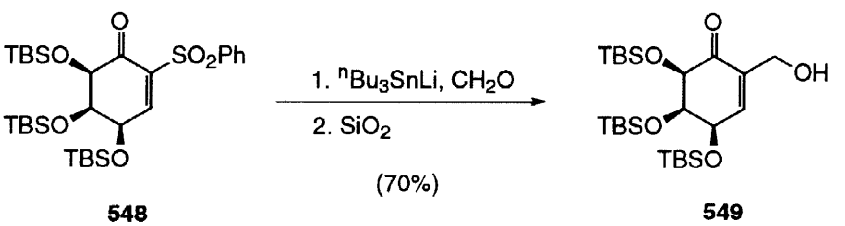
Diels-Alder adducts of 1-(phenylsulfonyl)-2-trimethylsilylacetylene acting as acetylene equivalents, give cyclohexa-1,4-dienes after reduction of the formed vinylsilane and fluoride-promoted β-elimination.[343] This strategy has been used in the case of the synthesis of 7-azabicycloheptene **166**, which is prepared by β-elimination of the silyl sulfone **547** and is a precursor of the alkaloid epibatidine after palladium-catalysed hydroarylation[103b] (Scheme 189). The same synthesis can be carried out with the corresponding β-stannyl sulfone.[344]



547 **166**

Scheme 189

In the total synthesis of a glyoxalase I inhibitor and of its precursor (-)-KD16-U1, the key intermediate **549** is prepared by Michael addition of tributylstannyllithium to vinyl sulfone **548** and trapping of the corresponding anion with formaldehyde. The β-elimination of the tributylstannyl and sulfone groups takes place by treatment with silica gel[345] (Scheme 190).

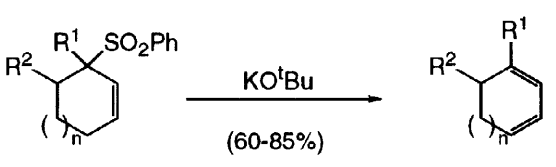


548 **549**

Scheme 190

6.2. High order elimination reactions

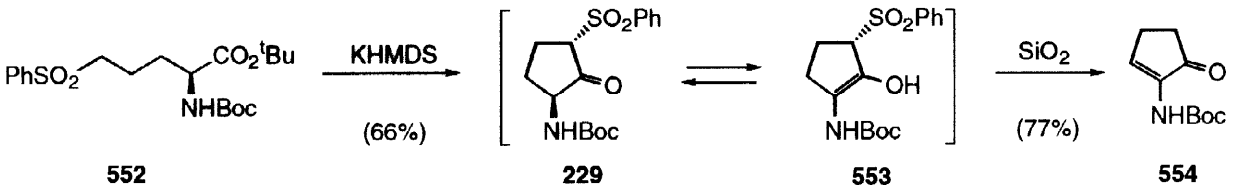
δ-Elimination of sulfinic acids promoted by bases has been studied with acyclic β-substituted sulfones[346a] and applied to the synthesis of dienamides or dienoates.[346b] In the case of acyclic allylic sulfones **550**, treatment with potassium *tert*-butoxide affords cyclic dienes **551**[347] (Scheme 191).



550 **551**

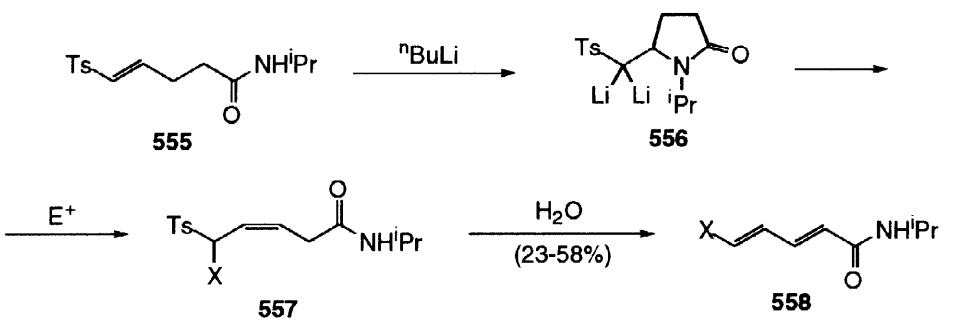
Scheme 191

The cyclic sulfone **229**, obtained by cyclisation of the δ-phenylsulfonyl amino acid **552**, is transformed into the cyclopentenone **554** through a δ-elimination process of compound **553** by silica gel[49c] (Scheme 192).



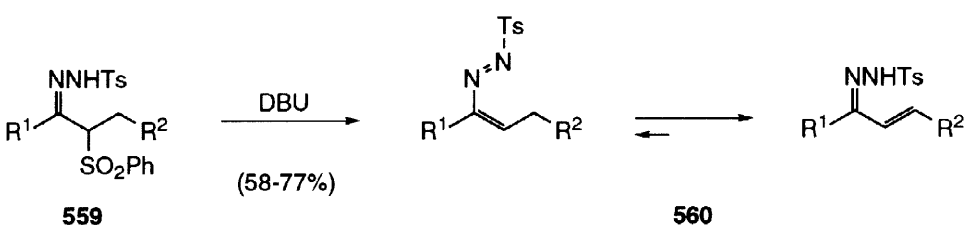
Scheme 192

The vinyl sulfone **555**, obtained by iodosulfonylation-dehydroiodination of 4-pentenoic acid and further amidation, is dilithiated to the lactam **556** to give, after reaction with aldehydes, alkyl halides or propylene oxide as electrophilic reagents (E^+), the corresponding dienamides **558**. The formation of intermediates of the type **557**, which undergo δ-dehydrosulfinylation during the work-up, is proposed in order to explain the formation of the dienamides **558**[37b,348] (Scheme 193). Intermediates **557** have been intercepted in deuterolysis or hydrolysis experiments of dianion **556**.



Scheme 193

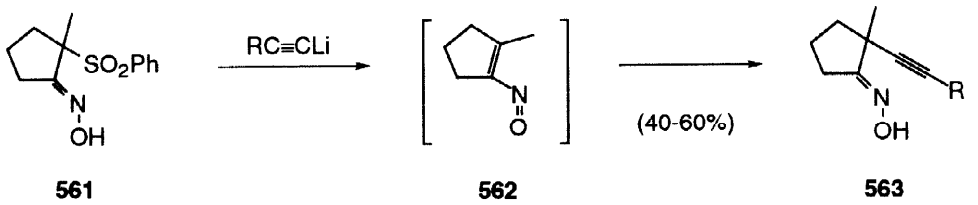
β-Ketosulfone tosylhydrazones **559** undergo 1,4-elimination of benzenesulfinic acid by means of DBU to give α,β-unsaturated ketone tosylhydrazones **560**[349] (Scheme 194).



Scheme 194

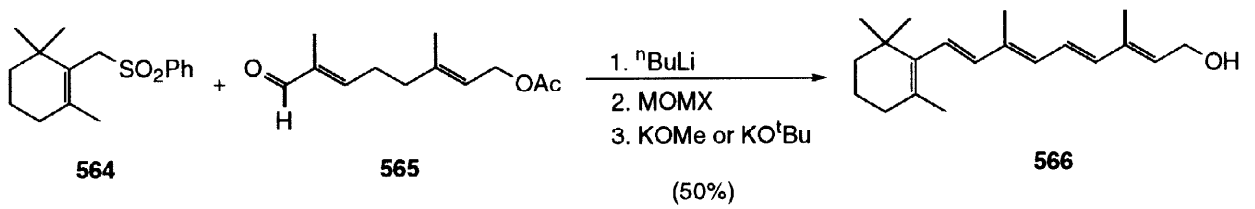
In the case of the cyclopentanoid β-ketoxime sulfone derivative **561**, the 1,4-elimination process takes place in the presence of lithium acetylides, generating a vinyl nitroso species **562**, which undergoes conjugate addition to alkynylated products **563**[350] (Scheme 195).

The synthesis of vitamin A **566**, by means of the cyclogeranylsulfone **564** and the aldehyde **565**,[351] has been recently improved through a one-pot procedure under basic conditions. The last step consists of a double elimination process of MOMOH and benzenesulfinic acid by a 1,6-elimination process[352] (Scheme 196).



561 562 563

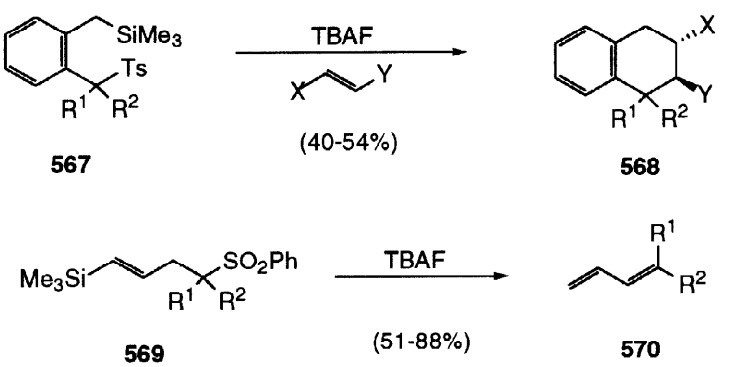
Scheme 195



564 565 566

Scheme 196

1,4-Eliminations on δ-silyl benzylic or allylic sulfones can be carried out by means of tetrabutylammonium fluoride, as in the case of β-silyl sulfones. For benzylic systems **567**, *o*-quinodimethanes are formed and trapped with dienophiles[353] (Scheme 197). (*E*)- and (*Z*)-1-(phenylsulfonyl)-4-trimethylsilyl-2-butenes **569**, obtained by successive alkylation of the corresponding lithiated sulfones, are transformed into dienes **570**[354] (Scheme 197).



567 568

569 570

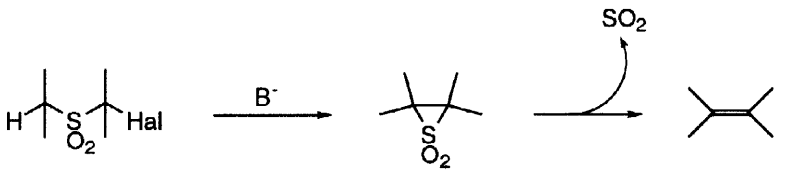
Scheme 197

7. SO_2 EXTRUSION PROCESSES

In this section, the carbon-carbon double bond formation reaction, by the elimination of SO_2, the Ramberg-Bäcklung rearrangement (RBR), reactions of episulfones as well as other olefination procedures will be discussed. The formation of dienes by pyrolytic 1,4-elimination of SO_2 from dihydrothiophene dioxides or sulfolenes is an important strategy for Diels-Alder reactions. Pyrolysis of other cyclic sulfones and radical fragmentation are processes which allow carbon-carbon single bond formation.

7.1. Olefin formation

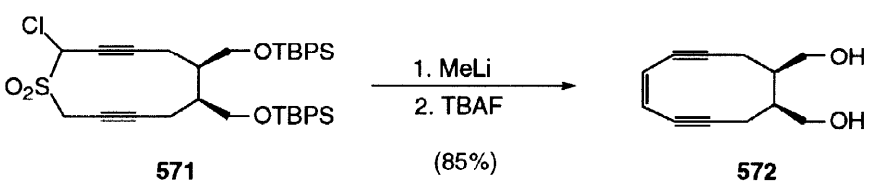
The **RBR**[1d] is the base-mediated regiospecific conversion of a α-halogeno sulfone into an alkene by the intermediacy of episulfones[355a] (Scheme 198).



Scheme 198

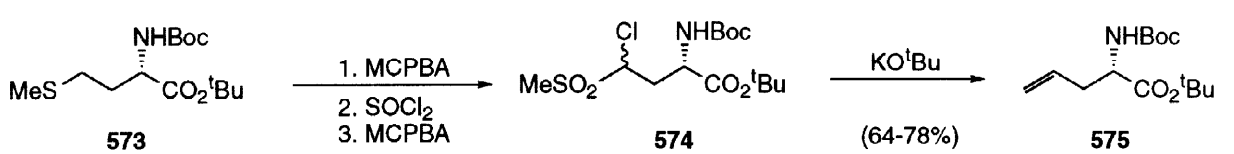
Intermediate episulfones can be prepared by other methods and their thermal decomposition to give alkenes takes place in a stereospecific manner. However, their treatment with bases can give mixtures of *Z*- and *E*-olefins due to episulfone epimerisation. The reaction can also be carried out with dialkyl sulfones by *in situ* chlorination with potassium hydroxide or *tert*-butoxide and carbon tetrachloride (Meyers method).[355b] The applicability of this method is rather limited to the preparation of stilbenes and 1,1-diarylalkenes. The new RBR employs alumina-supported potassium hydroxyde-dibromodifluormethane-*tert*-butanol as reagent, so α- and α'-hydrogen-bearing sulfones can be converted into alkenes in good yields.[356] Halogens as leaving groups as well as sulfinates can be used.

The RBR has been applied to the synthesis of cyclopentenes related to prostaglandins, strained bicyclic alkenes, enediynes related to esperamicin, calicheamicin and neocarzinostatin, and (+)-eremantholide A.[1d] The yield is very low (12%) in the preparation of the water-soluble DNA-cleaving 10-membered cyclic enediyne **572** by Nicolau *et al.*, using the RBR of α-chlorosulfone **571** with methyllithium, due to the formation of the open enediyne[357] (Scheme 199). Dipropargylic or diallylic sulfones have been transformed into acyclic enediynes[358] or 1,3,5-hexatrienes[359] by a modified one-pot RBR.



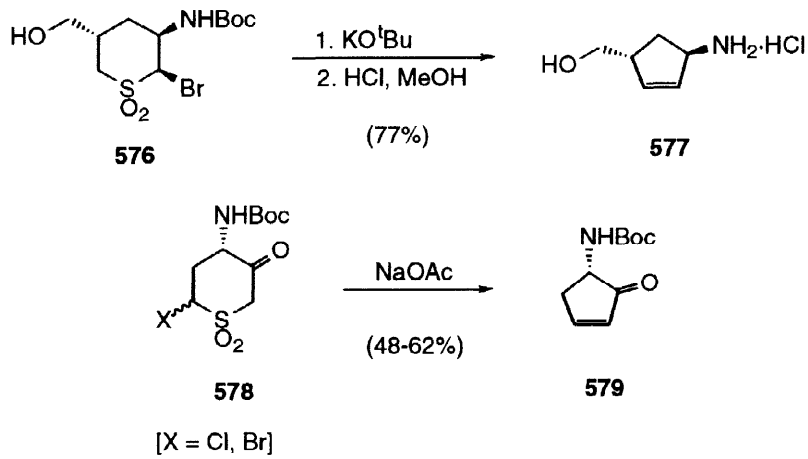
Scheme 199

The protected L-allylglycine **575** has been prepared from the methionine derivative **573** by oxidation to the corresponding sulfoxide, chlorination and then oxidation to the α-chloro sulfone **574**. Treatment with potassium *tert*-butoxide should be carried out at -78 to -30°C in order to avoid epimerisation of the α-amino acid so obtained[360] (Scheme 200).



Scheme 200

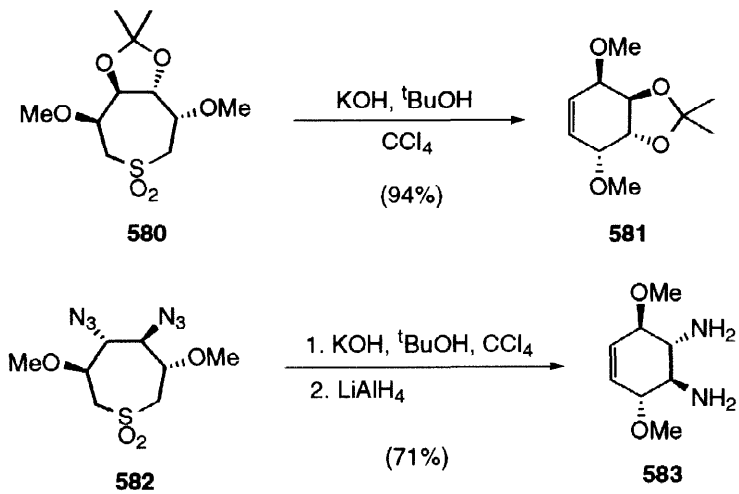
A new approach to the carboxylic nucleoside *trans*-carbovir **577** is based on the RBR of the cyclic α-bromo sulfone **576**[361] (Scheme 201). The aminocyclopentanone **579** has been prepared by the same approach from sulfones **578** but using sodium acetate as base in order to avoid racemisation[362] (Scheme 201).



576 **577**

Scheme 201

The (-)-condutirol E derivative **581**[363] and the 2,3-diamino derivatives **583**[364] have been prepared by Meyers RBR of thiepane dioxides **580** and **582**, respectively (Scheme 202).

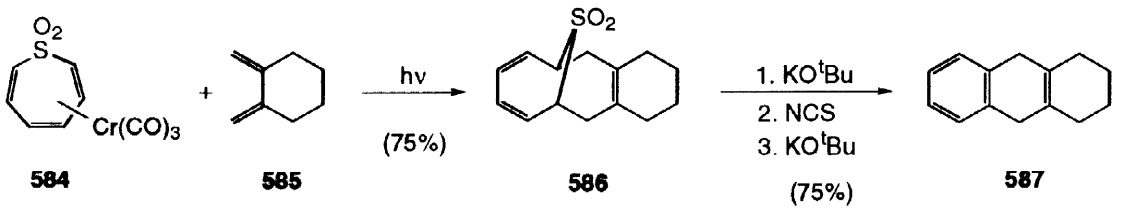


580 **581**

582 **583**

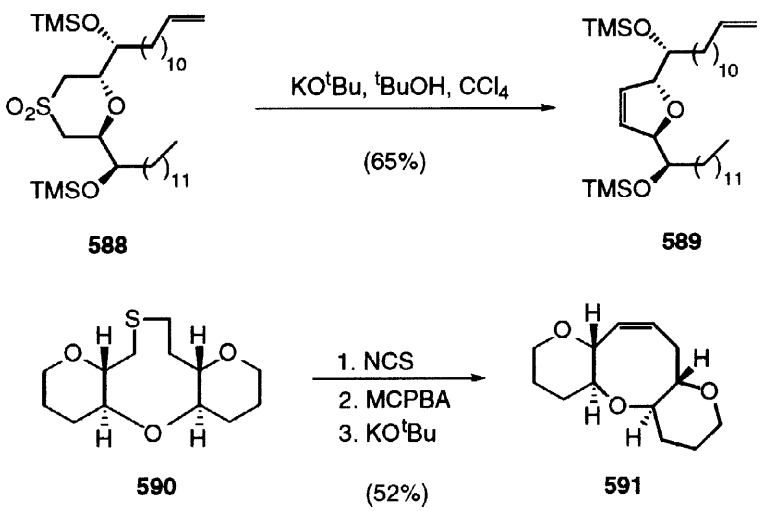
Scheme 202

A novel benzoannulation sequence, based on chromium(0)-promoted [6π + 4π] cycloaddition followed by a RBR, gives benzo-fused polycyclic products. Scheme 203 shows the cycloaddition of the thiepin 1,1-dioxide **584** with the diene **585** to give cycloadduct **586**, which after RBR affords the hexa-hydroantracene **587**.[365]



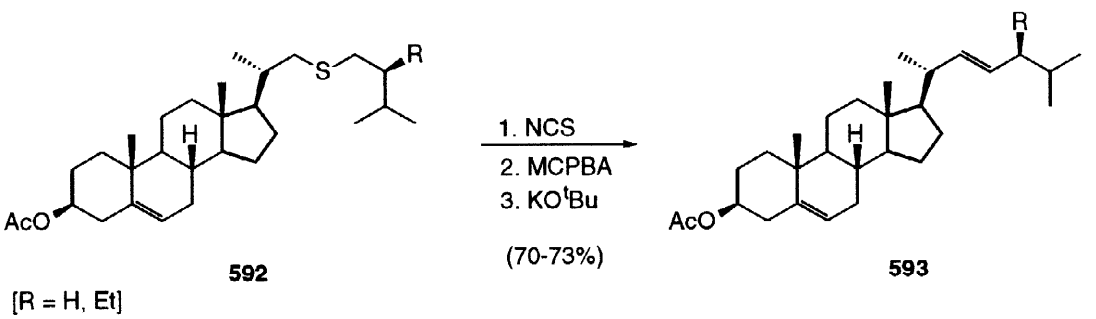
Scheme 203

The tetrahydrofuran ring of acetogenins has been prepared by a one-pot RBR of 1,4-oxathiane **588** to give the dihydrofuran **589**[366] (Scheme 204). Other medium-size polyethers, such as the **591**, have been prepared by this olefination procedure[567] (Scheme 204).



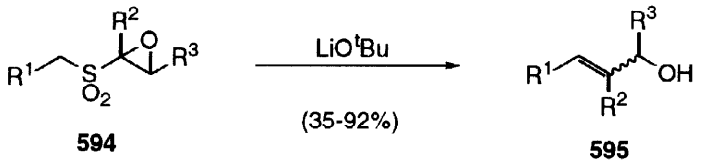
Scheme 204

The side-chain of sterols, such as **593**, has been stereoselectively prepared by RBR of α-chloro sulfones, derived from sulfides **592**, by a chlorination-oxidation sequence[368] (Scheme 205). This strategy has been used in the formal synthesis of the plant-growth factor bassinolide.[62]



Scheme 205

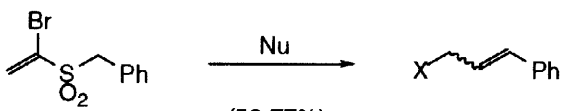
When the starting sulfone has functional groups in one of the chains, the RBR can be used for the synthesis of functionalised alkenes. In the case of α,β-epoxysulfones **594**, simple treatment with strong bases, specially lithium *tert*-butoxide, gives mainly (*E*)-allylic alcohols **595** with good yields and high stereoselectivity[369] (Scheme 206).



594 **595**

Scheme 206

A novel tandem conjugate addition-RBR[370] has been applied to the preparation of allylic amines, ethers and sulfides from α-bromo-α,β-unsaturated sulfones. Different carbo and heteronucleophiles react with compound **596** affording the corresponding functionalised olefins **597** directly[371] (Scheme 207).

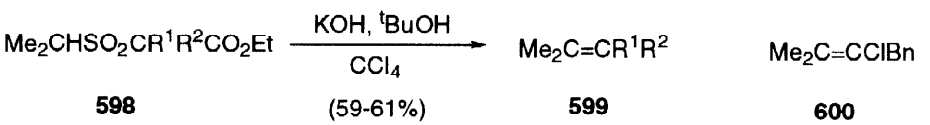


596 **597**

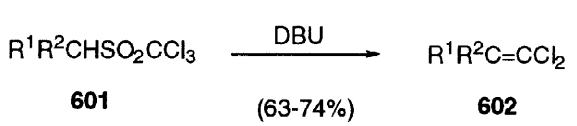
[Nu = NaOMe, KSBu, RNH_2, NH_3, $MeCNa(CO_2Me)_2$]

Scheme 207

Decarboxylative RBR has been observed in the case of α-(isopropylsulfonyl)carboxylic esters **598** under Meyers' conditions. Hydrolysis and decarboxylation take place to yield mainly the corresponding alkenes **599**. When the ester has a benzyl group, the chloroalkene **600** is the only product obtained[372] (Scheme 208). When the RBR is carried out with trichloromethyl sulfones **601** in the presence of DBU as base, the corresponding dichloroalkenes **602** are obtained (Scheme 208). On the contrary, the reaction with trifluoromethyl sulfones fails.[373]



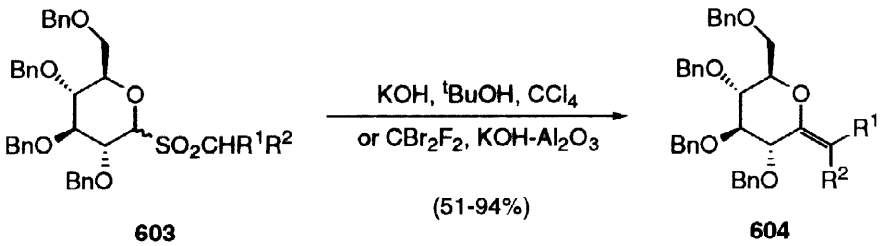
598 **599** **600**



601 **602**

Scheme 208

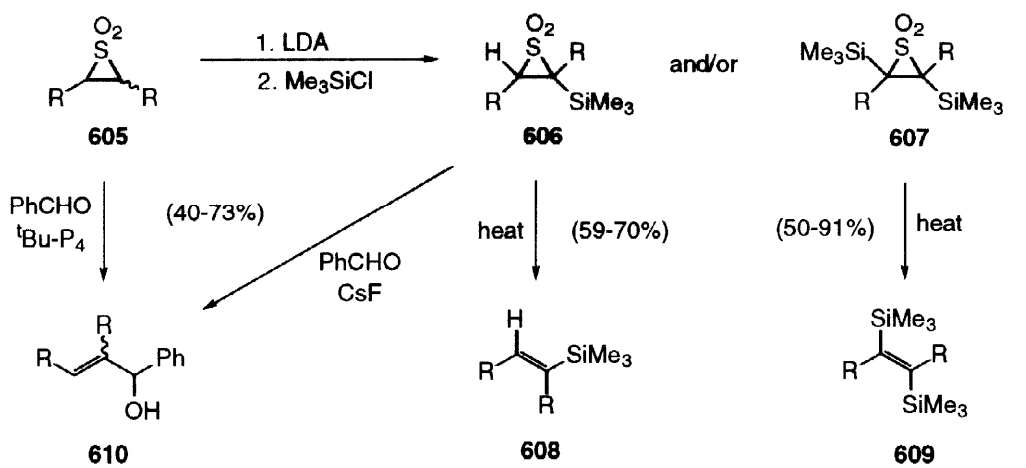
Recent work of Taylor *et al.*[374] and of Belica and Franck[375] describe the application of RBR to the syntheses of *C*-alkylidene glycosides. Treatment of *S*-glycoside dioxides under the Meyers[355b] or Chan[356] conditions affords methylidene or alkylidene sugars derived from glucose, galactose, mannose, xylose, fucose or ribose. Scheme 209 shows the case of glucose derivatives **604**, prepared from **603**, which are obtained mainly with (*Z*)-configuration.[374a]



603 **604**

Scheme 209

Episulfones **605** can be prepared using RBR conditions. The reaction of α,β-unsaturated sulfones with iodotri-methylsilane followed by *in situ* quenching with ethylene glycol gives iodosulfones, which are finally treated with potassium *tert*-butoxide at low temperature to give episulfones **605**.[355a,376] These three-membered cyclic sulfones can be deprotonated with LDA and reacted with chlorotrimethylsilane to give the corresponding silylated sulfones **606** or **607**, which can then be stereoselectively transformed into the vinylsilanes **608** or **609**, by brief thermolysis in refluxing toluene.[377] When monosilylated episulfones **606** are treated with cesium fluoride or with the Schwesinger's ^{t}Bu-P$_4$-phosphazene base and benzaldehyde, allylic alcohols **610** are obtained (Scheme 210). The monosilylation of the corresponding carbanions gives mixtures of diastereomers suggesting unstable α-sulfonyl carbanions, however, the disilylated products are obtained as *trans*-isomers because of steric reasons.

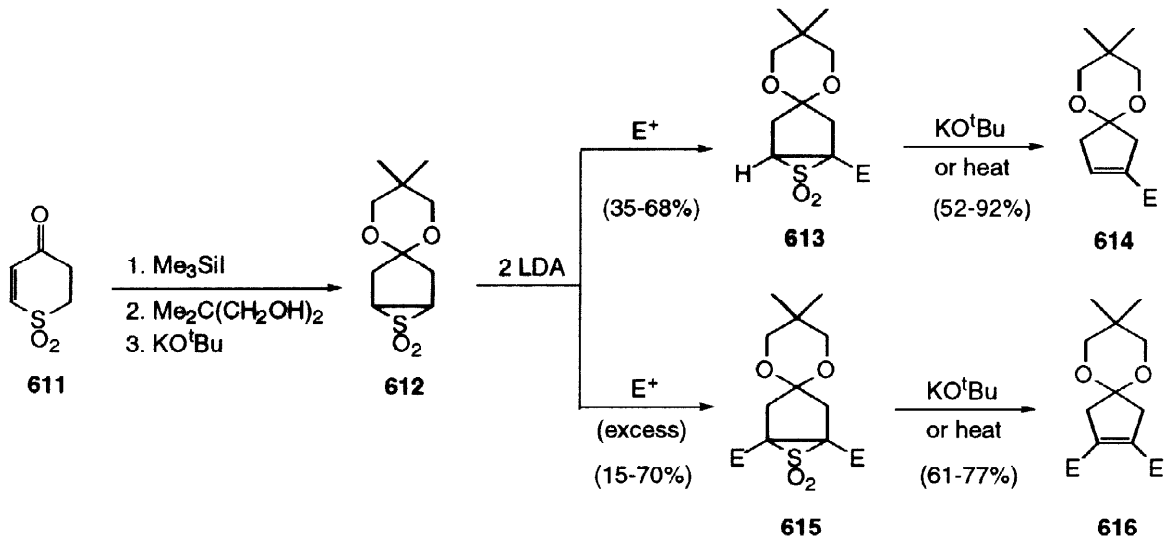


605 **606** **607**

610 **608** **609**

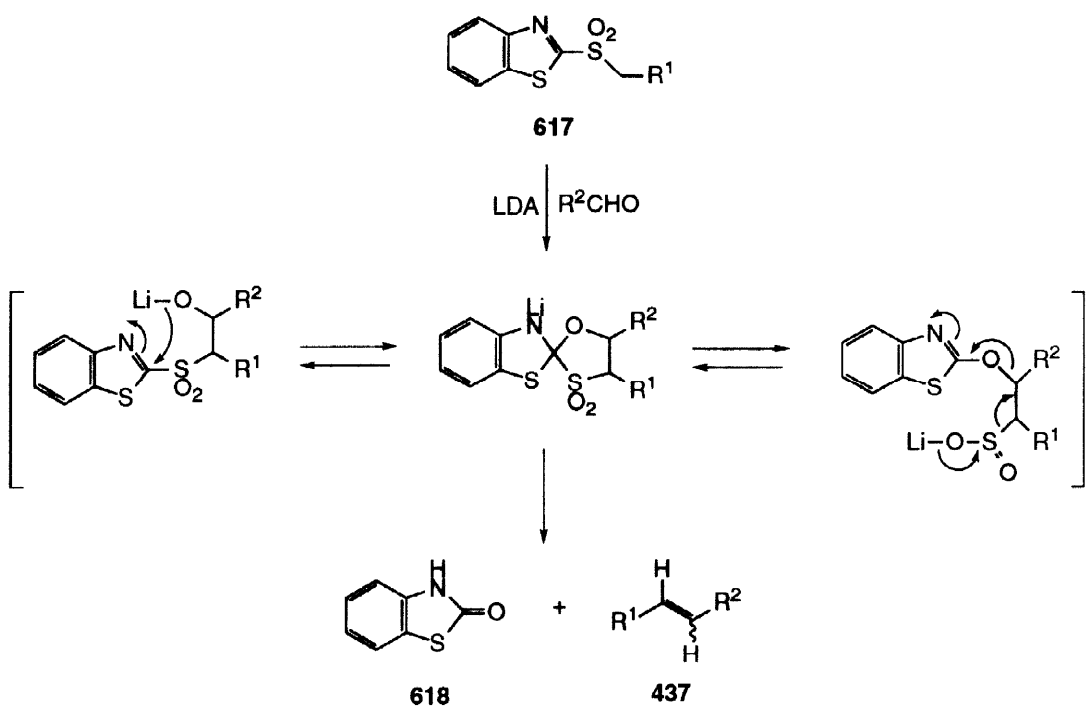
Scheme 210

Episulfone **612**, prepared from the enone **611** by RBR,[376] can be dilithiated in the presence of chlorosilanes or chlorostannanes to afford mainly products **613** and even **615**, when a large excess of electrophile is used. These episulfones are converted into the corresponding alkenes **614** or **616** in boiling THF or by potassium *tert*-butoxide[378] (Scheme 211).



611 **612** **613** **614** **615** **616**

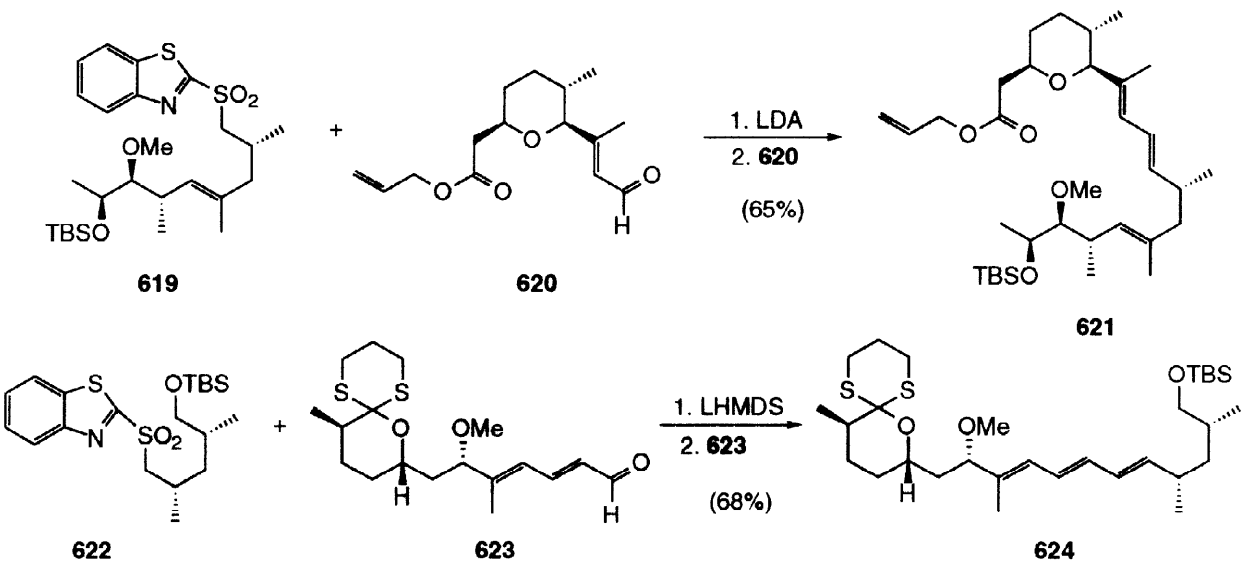
Scheme 211



617 **618** **437**

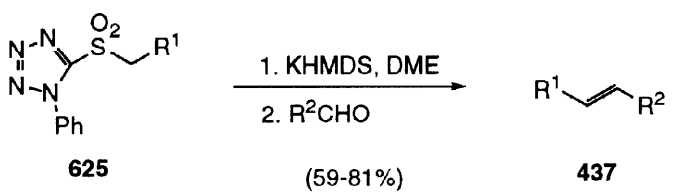
Scheme 212

Another type of synthesis of olefins in which the extrusion of sulfur dioxide is involved, is the reaction of carbonyl compounds with lithium derivatives of alkyl benzothiazolyl (BT) sulfones **617**.[140] The proposed mechanism for this transformation consists of the condensation of the corresponding α-sulfonyl carbanion with an aldehyde followed by intramolecular addition of the alkoxide to the carbon-nitrogen double bond and final elimination of SO_2 and benzothiazolone **618** to yield the olefin **437** (Scheme 212). This Julia olefination has been used by Kocienski *et al.* in the synthesis of the conjugated diene segment of herboxidiene A[139a] and the conjugated triene segment of rapamycin.[139b] The BT-sulfone **619** is lithiated and allowed to react with the aldehyde **620** giving the diene **621** stereoselectively[139a] (Scheme 213). In the synthesis of the C10-C26 fragment of rapamycin[51] the BT-sulfone **622** is lithiated and reacted with the dienal **623** to afford the triene **624** stereoselectively[139b] (Scheme 213). Ley *et al.* have recently used this strategy for the synthesis of okadaic acid.[235]



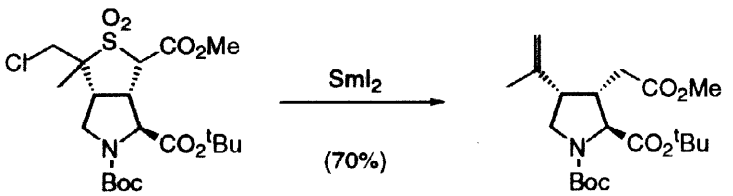
Scheme 213

High stereoselectivities are only obtained in special cases, such as in the formation of conjugated dienes. However, some lithiated BT-sulfones are unstable giving undesirable self-condensation products. Although other heterocyclic sulfones such as 2-pyridyl and 2-pyrimidyl sulfones have been tried, similar results have been obtained.[140c] A recent extensive study with other heterocyclic derivatives such as 1-isoquinolinolyl, 1-methyl-2-imidazolyl, 4-methyl-1,2,4-thiazol-3-yl and 1-phenyl-1*H*-tetrazol-5-yl (PT), demonstrated that the last heterocyclic substituent gives the best yields and stereoselectivities in *trans*-1,2-disubstituted alkenes **437**. The PT-sulfones **625** give higher *E/Z* ratio when KHMDS or NHMDS are used as bases and 1,2-dimethoxyethane as solvent[379] (Scheme 214).



Scheme 214

A novel desulfonylation is based on the treatment of the β-chlorosulfone **626** with samarium diiodide. Chlorine atom extrusion with concomitant ring opening and double bond formation is followed by SO_2 reductive α-elimination to give the kainate **627**[380] (Scheme 215).



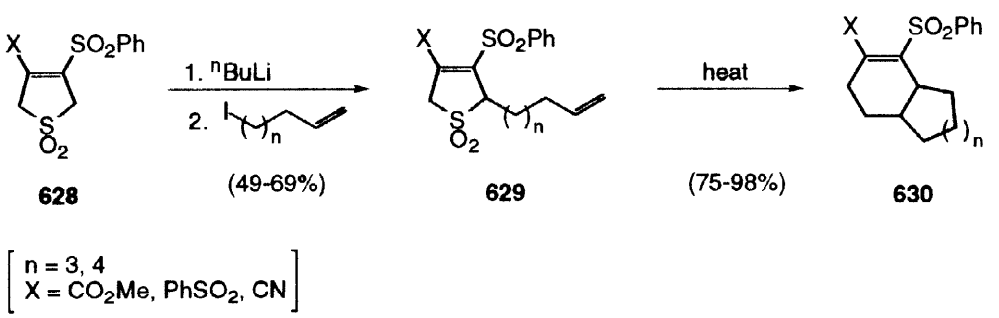
626 **627**

Scheme 215

7.2. Diene formation

Chelotropic extrusion of SO_2 from substituted or fused 3-sulfolenes constitutes a general method[1d] for the preparation of cyclic and acyclic dienes or *o*-quinodimethanes, which are usually trapped *in situ* with dienophiles in Diels-Alder cycloadditions. The extrusion of SO_2 can be accomplished by thermolysis or by treatment with lithium aluminium hydride as well as by ultrasonically dispersed potassium. The last method is more convenient in the case of 2,2,5,5-tetrasubstituted 3-sulfolenes, using water or *tert*-butanol as a proton source, to give the corresponding dienes.[381]

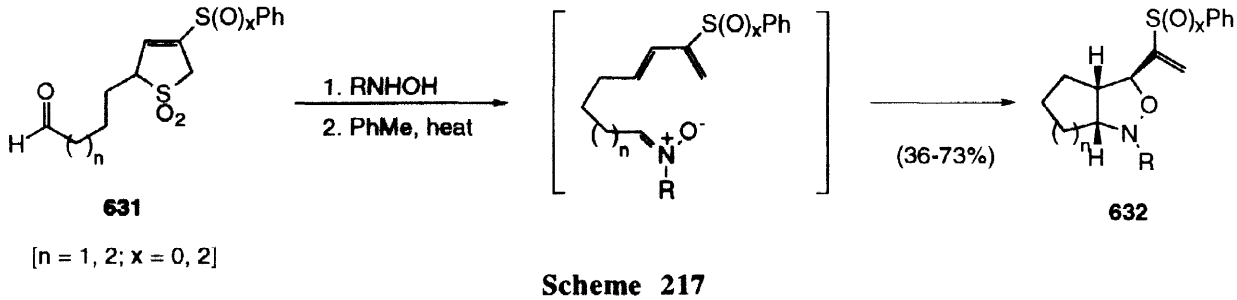
The thermolysis of substituted sulfolenes has been extensively studied for the preparation of functionalised 1,3-dienes[382] and their inter- and intra-molecular Diels-Alder reactions. Sulfolenes **629**, obtained by alkylation of the dianions derived from substituted sulfolenes **628**, at the 2-position, with 5-iodo-1-pentene or 6-iodo-1-hexene, can be transformed into hydroindenes or hydronaphthalenes **630** in refluxing xylene by an intramolecular Diels-Alder reaction[383] (Scheme 216).



628 (49-69%) **629** (75-98%) **630**

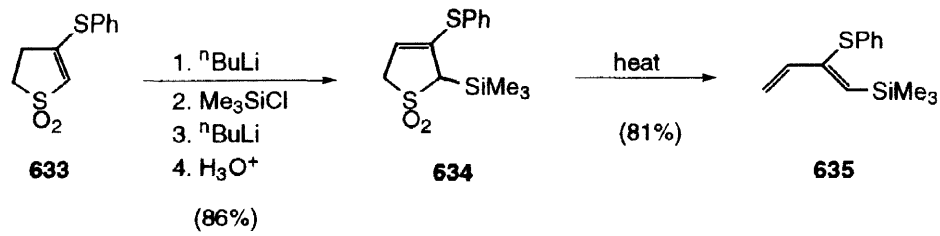
Scheme 216

In the case of aldehydes **631**, the corresponding nitrones are prepared by condensation with alkylhydroxylamines, which upon heating undergo an intramolecular 1,3-dipolar cycloaddition, giving the fused bicyclic isoxazolidines **632**[384] (Scheme 217).



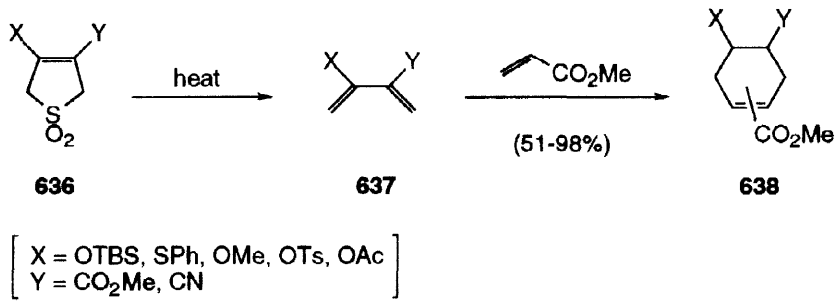
Scheme 217

(*Z*)-2-(Phenylthio)-1-(trimethylsilyl)-1,3-butadiene **635** has been prepared by distillation of the sulfolene **634**, which is obtained from compound **633** by silylation and isomerisation (Scheme 218). In the Diels-Alder reaction of diene **635** with *N*-phenylmaleimide the corresponding *endo*-adduct is obtained.[385]



Scheme 218

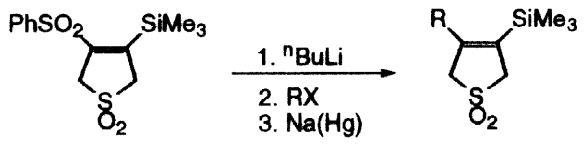
Several 3,4-disubstituted 3-sulfolenes **636** are good precursors for the corresponding dienes **637**, which have been trapped by methyl acrylate to give the expected products **638** (Scheme 219). The order of *para*-directing ability for different substituents is OTBS > CN > SPh > OMe ≈ CO_2Me > OTs > OAc.[386]



Scheme 219

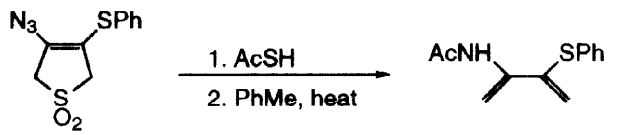
The syntheses of 2-alkyl-3-(trimethylsilyl)-1,3-butadienes are based on the alkylation of the sulfolene **639** and reductive desulfonylation to sulfolenes **640**, followed by thermolysis[387] (Scheme 220).

2-Acetamido-3-phenylthiobuta-1,3-diene **642** and its sulfoxide or sulfone derivatives have been prepared from 3-azido-4-phenylthio-3-sulfolene **641**[388] (Scheme 221). Its reaction with unsymmetrical dienophiles demonstrates that the *para*-directing ability of the substituents on the 2,3-disubstituted dienes follows the order AcNH > $PhSO_2$ > PhS > PhSO. In the presence of a Lewis acid, the regioselectivity can be reversed or enhanced.



639 **640**

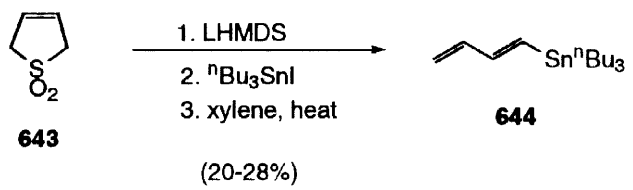
Scheme 220



641 (40%) **642**

Scheme 221

(*E*)-1,3-Butadienyl(tributyl)stannane **644** has been prepared in a two-step procedure by lithiation of 3-sulfolene **643**, reaction with tributylstannyl iodide and finally, heating in xylene[389] (Scheme 222). The regioisomeric 2-tributylstannyl-1,3-butadiene has been prepared by distillation of the sulfolene **419**[284] (see Scheme 144).

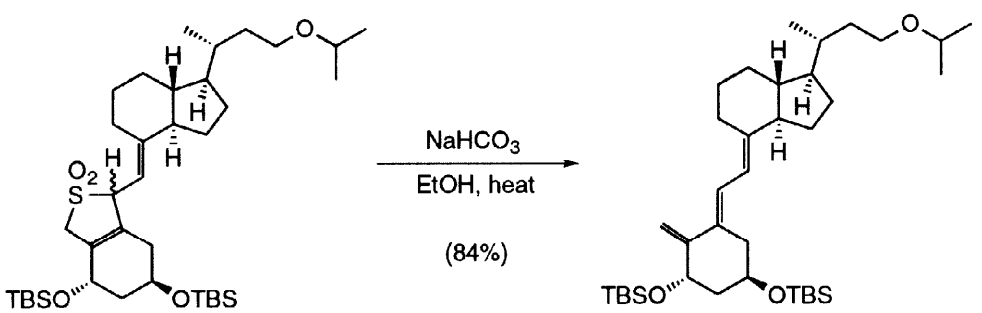


643 **644**

(20-28%)

Scheme 222

The conjugated triene fragment, present in vitamin D_3 and related compounds, can be protected by cycloaddition with SO_2 and liberated again by extrusion. This strategy has been used in the preparation of compound **646**, from material **645**, which is a precursor of MC 1090 involved in the *in vitro* metabolism of calcitroic acid[390] (Scheme 223).

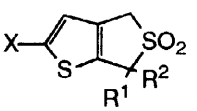


645 **646**

(84%)

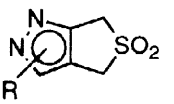
Scheme 223

The preparation of *o*-quinodimethanes by SO_2 extrusion from benzo-fused thiophene 1,1-dioxides, is usually carried out in the presence of dienophiles and has been applied to the synthesis of polycyclic systems.[1d,391] The study of the preparation and reactivity of heterocyclic derivatives of *o*-quinodimethane has attracted wide attention.[392] The required sulfolenes are easily prepared either by construction of the heterocycle onto a suitable activated sulfolene or by building the sulfolene ring onto the preformed heterocycle, the former being the method most used. The chelotropic extrusion of SO_2 requires higher temperatures for fused than for simple sulfolenes. Storr *et al.* have prepared thiophene **647** and pyrazole **648** fused sulfolenes, which on heating at 200°C liberate the corresponding heterocyclic *o*-quinodimethanes, which are trapped by dienophiles to give the corresponding adducts in variable yields.[393] Unsubstituted thiophene derivative **647** (X = R^1 = R^2 = H) has also been prepared by Chou *et al.*[394] as well as the corresponding pyrazoles **648** (R = H, Ph).[395]



647

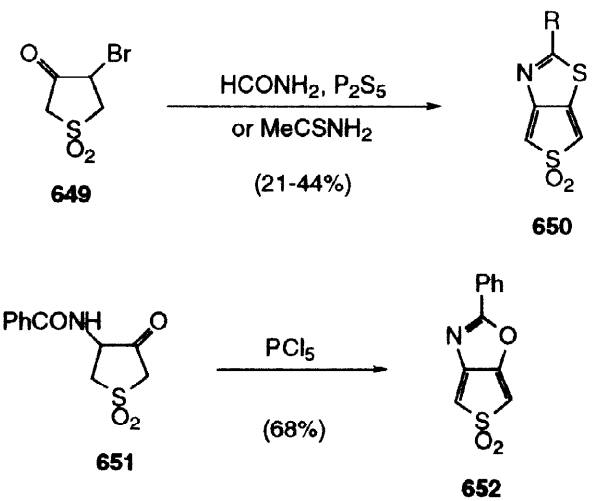
[X = H, CO_2Me; R^1, R^2 = H, Me]



648

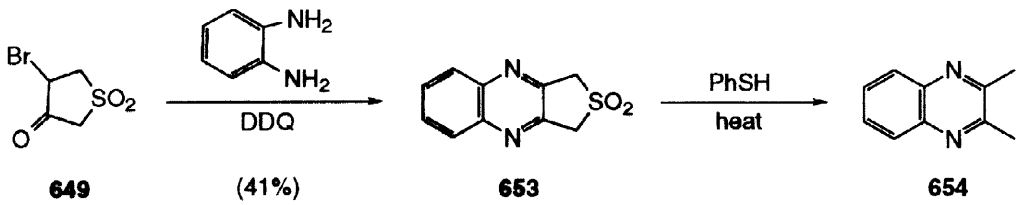
[R = Me, COPh]

o-Dimethylene thiazoles can be prepared from the corresponding thiazole-fused 3-sulfolenes **650**, which are easily obtained by reaction of sulfolene **649** with formamide and phosphorous pentasulfide or thioacetamide[396] (Scheme 224). For the corresponding oxazole **652**, the reaction of the starting material **649** fails and the process has to be performed using the sulfolene **651**[397] (Scheme 224).



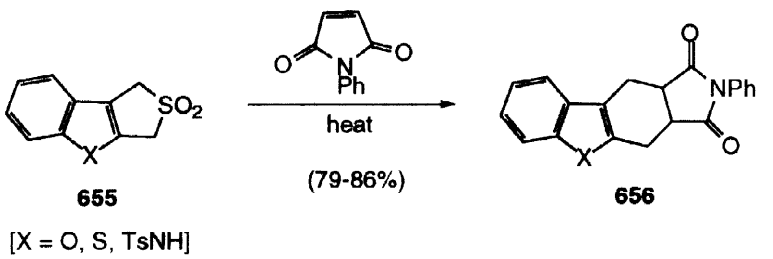
Scheme 224

From compound **649** the quinoxaline derivative **643** can be prepared, but requires very high temperatures for the generation of the corresponding *o*-quinodimethane which after hydrogen abstraction from thiophenol gives the dimethyl derivative **654**[398] (Scheme 225).



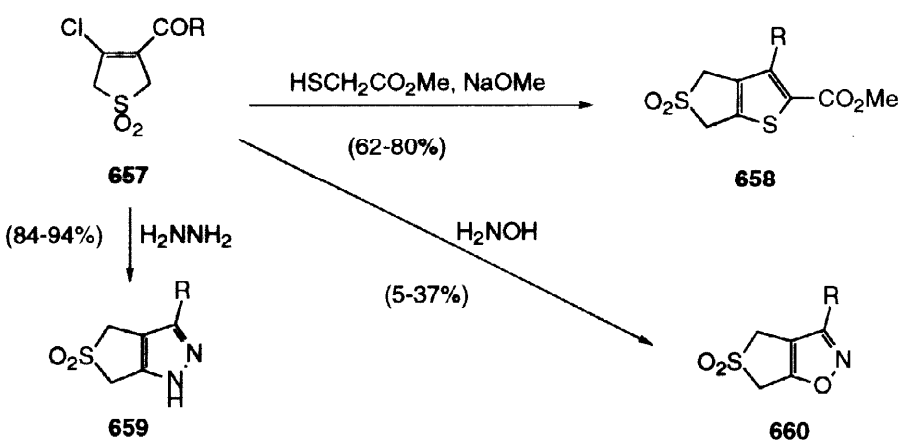
Scheme 225

Benzotrieno-3-sulfolene, benzofurano-3-sulfolene and *N*-tosylindolo-3-sulfolene **655** have been prepared from sulfolene and been decomposed at 150°C in the presence of *N*-phenylmaleimide to afford the expected adducts **656**[399] (Scheme 226).



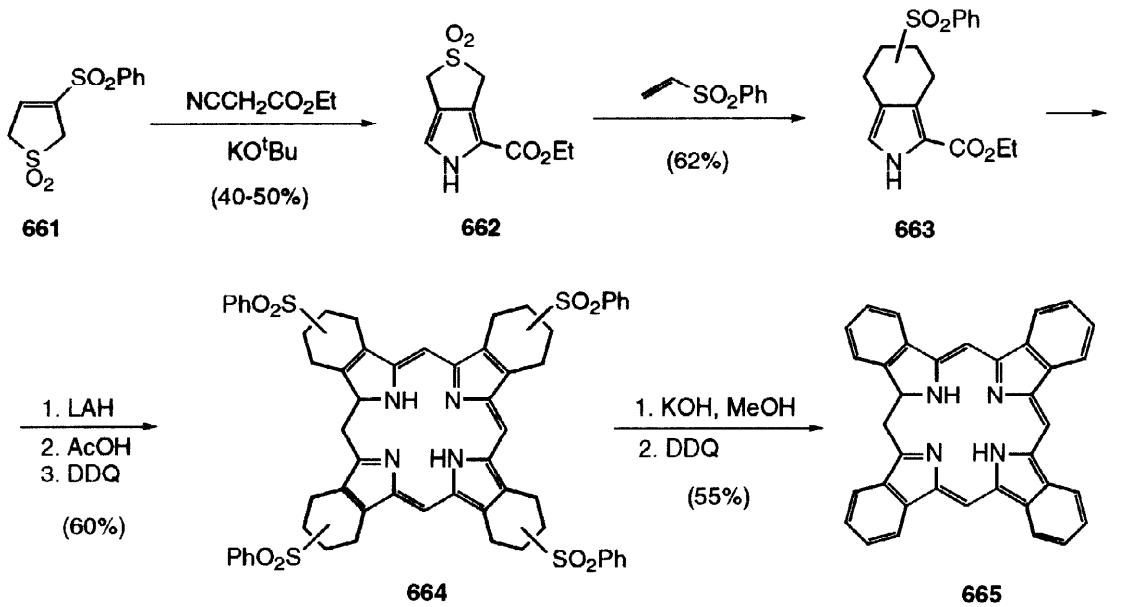
Scheme 226

Tso *et al.* add thiophene, pyrazole and isoxazole rings (**658-660**) to substituted sulfolenes **657** and heat the products in toluene in a sealed tube (170-200°C) with *N*-phenylmaleimide, to obtain the corresponding adducts in high yields[400] (Scheme 227). From the same sulfolenes **657**, the corresponding isothiazole derivatives have been prepared, in 56-61% yield, by successive reactions with thioglycolate and then hydroxylamine.[401]



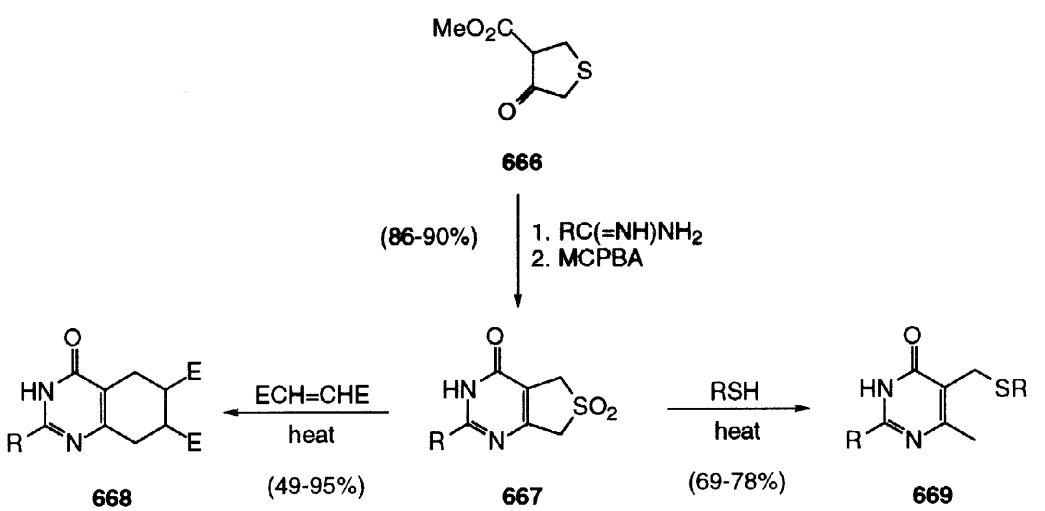
Scheme 227

The pyrrolo-fused 3-sulfolene **662** has been prepared from the vinyl sulfone **661** by dipolar cycloaddition of ethyl isocyanoacetate.[318] Cycloaddition reactions can be carried out without protection of the nitrogen atom, in refluxing 1,2,4-trichlorobenzene. Adducts **663** resulting from the reaction of vinyl sulfone have been tetramerised to a mixture of porphyrins **664**, which after basic β-elimination of benzenesulfinic acid and aromatisation give the corresponding tetrabenzoporphyrin **665**[402] (Scheme 228).



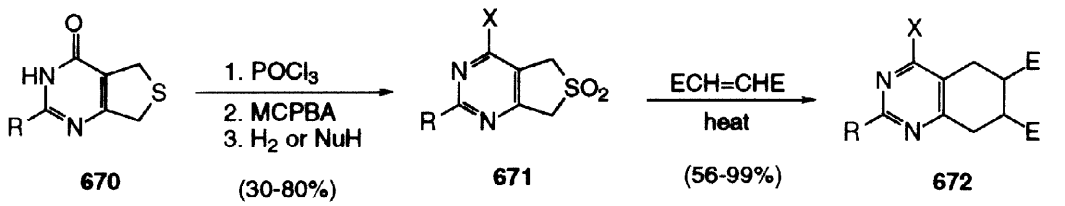
Scheme 228

Pyrimidone-fused 3-sulfolenes **667** have been prepared from the keto ester **666** by reaction with amidines[403] (Scheme 229). The intermediate pyrimidone *o*-quinodimethane obtained by heating compound **667** has been trapped with dienophiles or thiols, through a Michael addition, to give products **668** and **669**, respectively (Scheme 229).



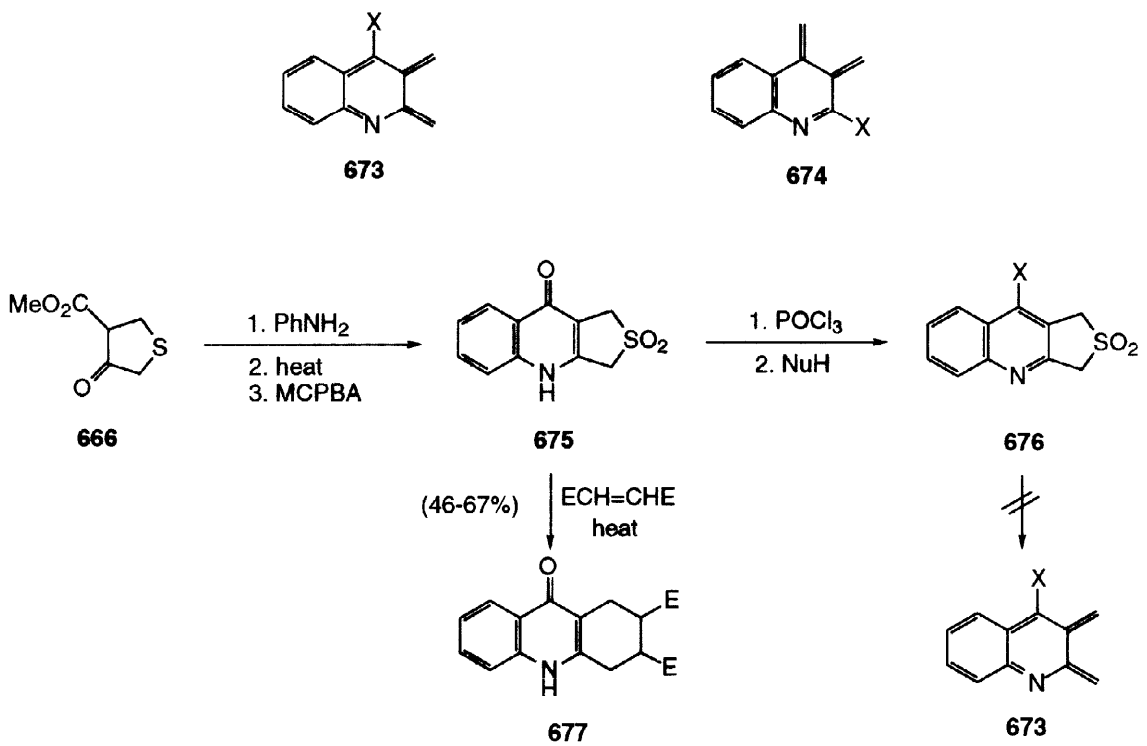
Scheme 229

The related pyrimidine-fused 3-sulfolenes **671** have been obtained from the intermediate pyrimidones **670**, from the starting material **666** above, by treatment with phosphorous oxytrichloride followed by oxidation and nucleophilic substitution or dehalogenation. Thermal extrusion of SO_2 from compound **671** requires higher temperatures than 4-pyrimidone derivatives (*ca.* 215°C), the corresponding *o*-quinodimethane intermediates being trapped with *N*-phenylmaleimide or dimethyl fumarate as dienophiles[404] (Scheme 230).



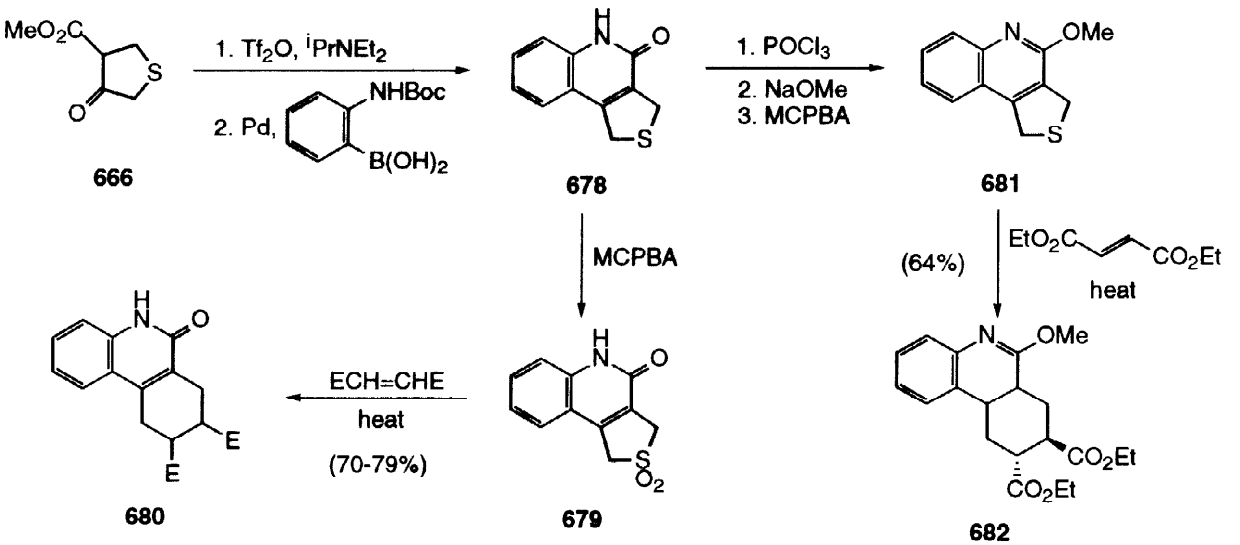
Scheme 230

In the case of quinolines, 2,3- and 3,4-quinoline *o*-quinodimethanes **673** and **674** can be generated by thermolysis. The preparation of the corresponding precursors for compounds **673** and **674** has also been carried out by Storr *et al.* from the keto ester **666**. Attempts to extrude SO_2 from 2,3-quinoline-fused sulfolenes **676** fail. However, quinolone **675** reacts with *N*-phenylmaleimide and diethyl fumarate in refluxing 1,2,4-trichlorobenzene, to give Diels-Alder adducts **677**[405] (Scheme 231).



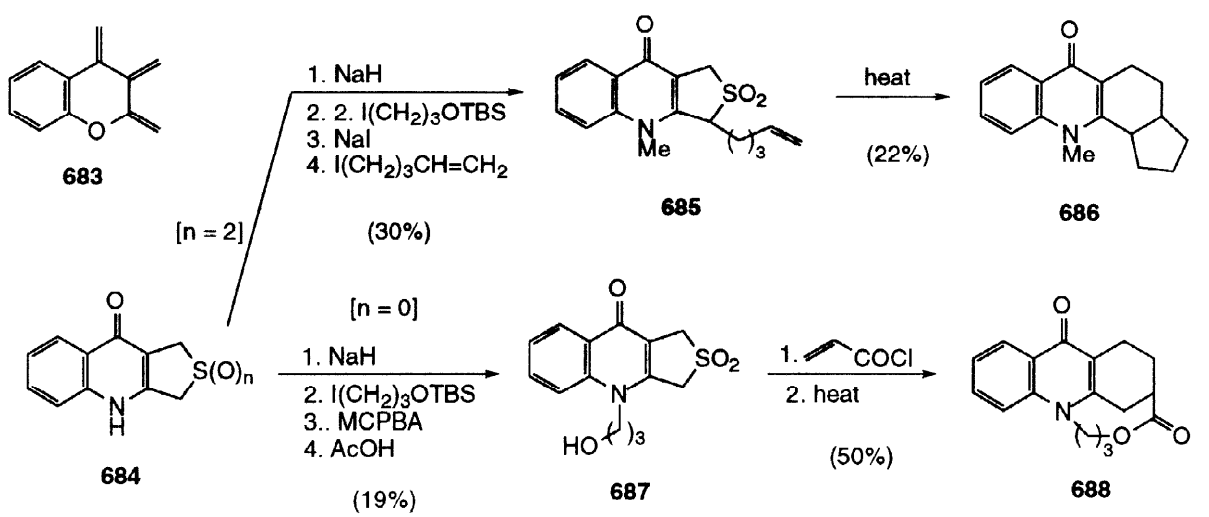
Scheme 231

3,4-Fused quinolines and quinolones are also prepared from the enol triflate of compound **666** by Suzuki coupling with a boronic acid to give the quinolone **678**, which by oxidation to the sulfolene **679** and heating in the presence of dienophiles gives the expected adducts **680**. The methoxyquinoline **681** (easily prepared from compound **678** by successive chlorination, nucleophilic substitution and oxidation) generates the *o*-quinodimethane **674**, in refluxing 1,2,4-trichlorobenzene, which can be trapped with diethyl fumarate[405] (Scheme 232). The same strategy has been used for the coumarin *o*-quinodimethane **683**.[405b]



Scheme 232

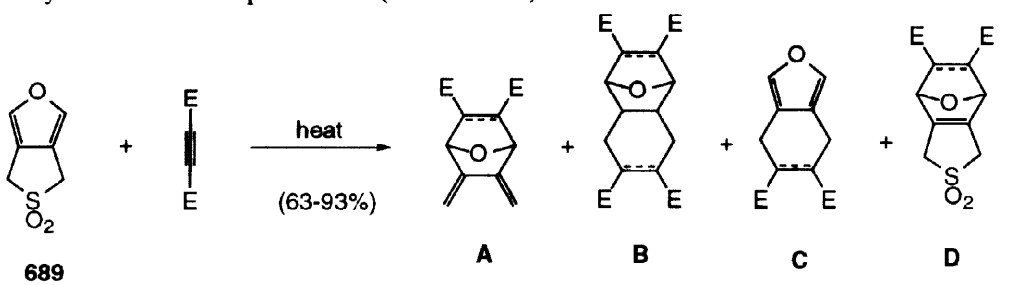
Substituted 4-quinolone-fused 3-sulfolene **685** and **687**, alkylated at the α-position relative to the sulfone group and/or at the nitrogen atom, respectively, are prepared from compound **684** by deprotonaton/alkylation processes followed by oxidation in the second case. Heating compounds **685** and the acrylate derivative of **687** gives the corresponding quinolono-*o*-quinodimethane intermediates, which undergo intramolecular Diels-Alder reactions affording the adducts **686** and **688**, respectively[406] (Scheme 233).



Scheme 233

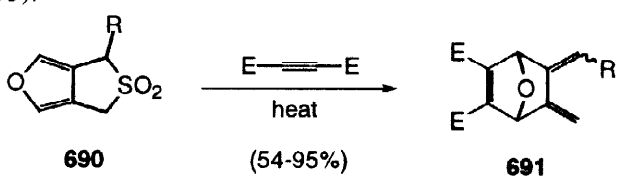
Isoquinolino-*o*-quinodimethanes from isoquinolino-3-sulfones have been generated at 210°C and trapped with dienophiles in intra and intermolecular Diels-Alder reactions.[406b]

Takayama *et al.* have studied the preparation of furan-fused 3-sulfolenes and their reactivity in inter and intramolecular Diels-Alder reactions.[392b] The unsubstituted 3,4-fused furan derivative **689** gives four types of cycloadducts **A-D** depending upon the dienophile and the reaction conditions. In the case of dimethyl acetylenedicarboxylate (DMAD) and dimethyl fumarate, mixtures of adducts **A** (furan cycloaddition-SO_2 extrusion) and **B** (furan and sulfolene tandem cycloaddition) are obtained, compound **A** being in the majority. For dimethyl maleate, fumaronitrile or *N*-phenylmaleimide cycloadducts **A** and **C** (cycloaddition to sulfolene) are formed at 150°C. Finally, in the case of maleic anhydride, *exo*-cycloadduct **D** (furan cycloaddition) is isolated in 60% yield at room temperature[407] (Scheme 234).



Scheme 234

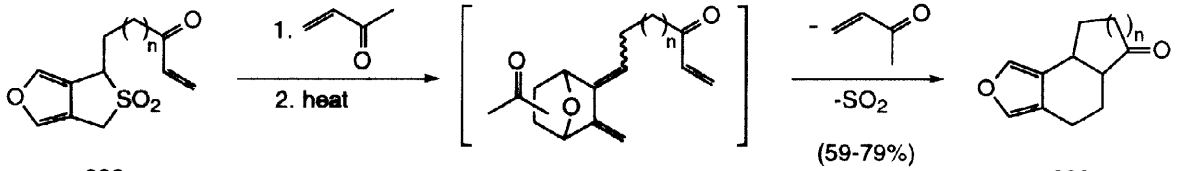
1-Substituted furan-fused 3-sulfolenes react with DMAD or dimethyl maleate or fumarate to give mixtures of cycloadducts similar to those from the unsubstituted derivatives **689**. 1-Acetyl and 1-nitro furansulfolenes react with dienophiles through the furan ring.[408] However, when the substitution is at the α-position with respect to the SO_2 group, such as in compound **690**, the *exo*-dienes **691** are obtained as a mixture of diastereomers[409] (Scheme 235).



[R = ^{n}Bu, PhCO, CyCO, $EtCO_2$]

Scheme 235

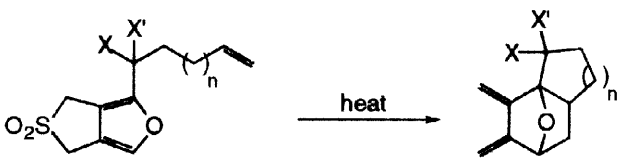
Intramolecular Diels-Alder reactions have been studied of 4-substituted compounds **690** having an alkyl chain containing a terminal olefin [R = $(CH_2)_3CH{=}CH_2$] or a α,β-unsaturated ketone **690** [R = $(CH_2)_{n+1}COCH{=}CH_2$] as dienophiles. In the first case only decomposition products are observed but in the latter case the reaction is carried out in the presence of methyl vinyl ketone giving adducts **692** (Scheme 236). Methyl vinyl ketone participates as a dienophile with the furan at room temperature and after heating at 180°C the intramolecular Diels-Alder with the sulfolene occurs together with a final retro-Diels-Alder to recover the furan moiety. When the dienophile is at the 1-position of the furan ring the cycloaddition of compounds **693** takes place with the furan. Subsequent SO_2 extrusion in refluxing xylene affords the products **694** stereoselectively[411] (Scheme 237).



690 692

[n = 1, 2]

Scheme 236

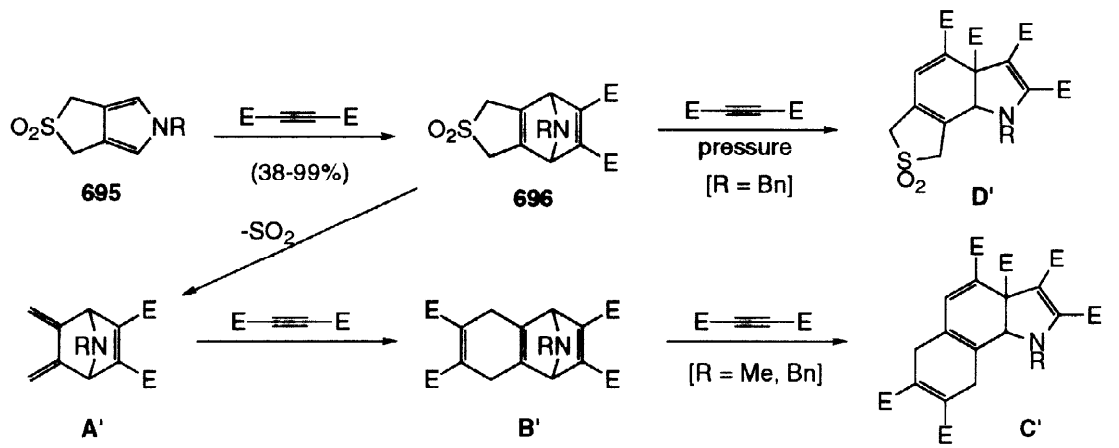


693 694

[n = 1, 2]

Scheme 237

The pyrrole-fused sulfolenes **695** behave in a similar manner to the furan derivatives or the substituted compounds **662**, depending on the nucleophile[402] (see Scheme 228). They react with DMAD to give four adducts **A'-D'** depending upon the reaction conditions and the *N*-substituent. Thus, in the case of the *N*-benzyl derivative at 100°C, adducts **A'** and **C'** are obtained, whereas at 140°C only **C'** is formed for both the *N*-benzyl and *N*-methyl derivatives. At high pressure (12 kbar) the *N*-benzyl derivative gives product **D'** only. When there is an electron-withdrawing group on the nitrogen atom only product **B'** is formed[412a,b] (Scheme 238). The formation of the different products can be explained by the initial formation of the pyrrole cycloadduct **696**, which after SO_2 extrusion gives **A'**. Compound **A'** then reacts with another DMAD molecule to afford the product **B'**. If the group R is an alkyl one, **B'** reacts with DMAD to give compound **C'**, by a double Michael-type reaction. Finally, under high pressure compound **696** reacts with DMAD to give the product **D'**.



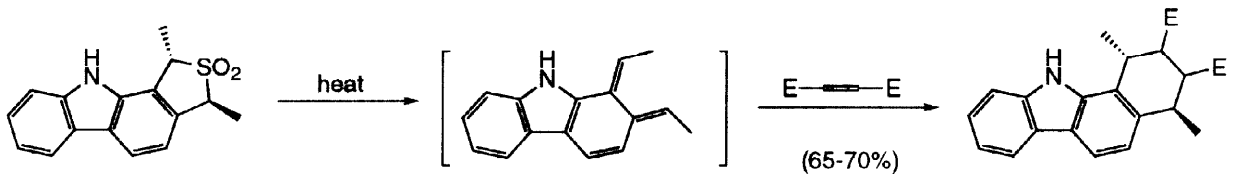
695 696 D'

A' B' C'

Scheme 238

In the reaction of compound **695** (Scheme 238) with olefinic dienophiles, a sequential process takes place involving, (a) a Diels-Alder reaction on the pyrrol moiety, (b) a chelotropic elimination of SO_2, (c) a Diels-Alder reaction of the resulting diene and (d) a retro Diels-Alder reaction to give 4,5,6,7-tetrahydroisoindoles of type **663** in good yields.[412c]

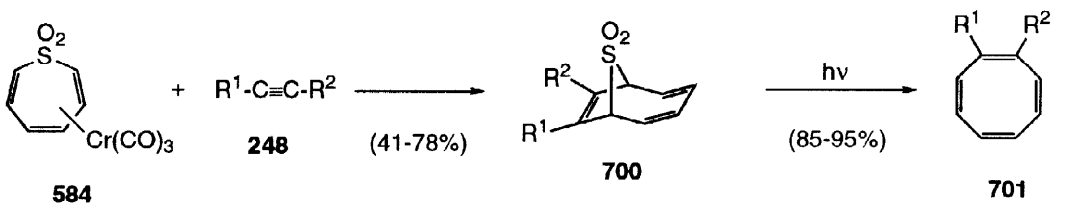
A recent preparation of carbazole-1,2-quinodimethane **698** has been described from the sulfolene **697** with SO_2 extrusion by heating in refluxing 1,2,4-trichlorobenzene in the presence of *N*-phenylmaleimide or dimethyl fumarate, to give the corresponding adducts **699**[413] (Scheme 239).



697 **698** **699**

Scheme 239

A convenient synthesis of 1,2-disubstituted cyclooctatetraenes **701** is based on the photoactivated SO_2 extrusion of cycloadducts **700**, obtained by a [6 + 2] cycloaddition of the thiepin dioxide complex **584** with internal alkynes[414] (Scheme 240).



584 **700** **701**

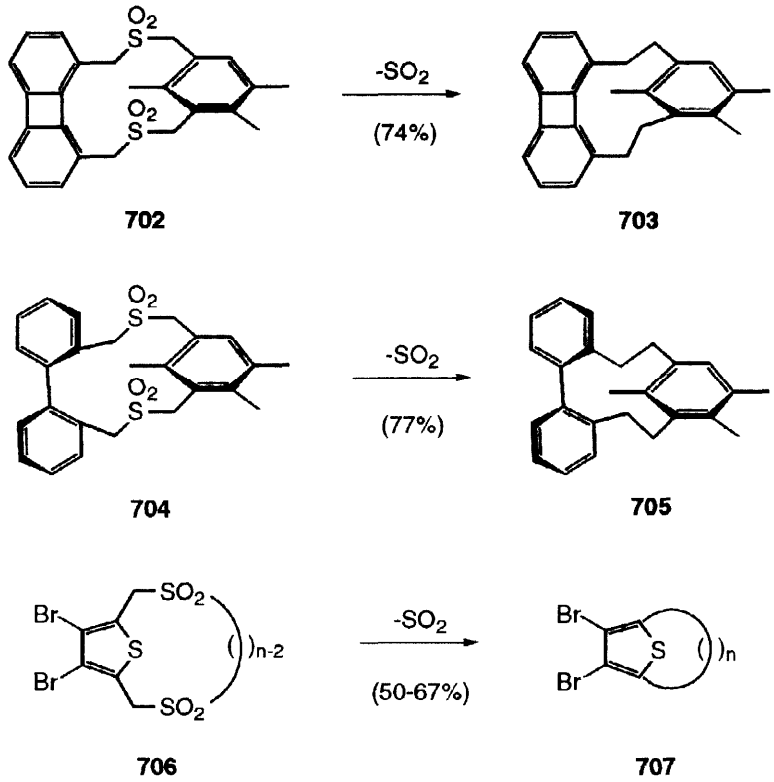
Scheme 240

7.3. Carbon-carbon bond formation

In this section, the extrusion of SO_2 under thermal or radical conditions to generate carbon-carbon single bonds, will be studied. Under pyrolytic conditions some allylic or benzylic sulfones can extrude SO_2 in an inter or intramolecular process involving radical intermediates. Recent applications of this methodology are the preparation of the chiral *syn*-[2.2]biphenylenophane **703** and [2.2]biphenylophane **705** from disulfones **702** and **704**, respectively, by vacuum pyrolysis[415] (Scheme 241). Thiophenophanes **707** have also been prepared by pyrolysis of the corresponding disulfones **706**[416] (Scheme 241).

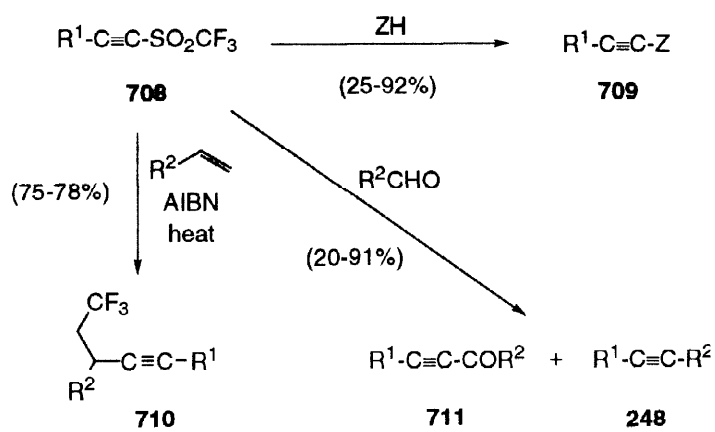
Fuchs *et al.* have recently described the spontaneous radical decomposition of acetylenic triflones **708** to give trifluoromethyl and acetylenic radicals and SO_2. In the presence of unactivated hydrocarbons, the corresponding alkynylation of carbon-hydrogen bonds takes place, whereas with olefins, both radicals are added to give products **709** and **710**, respectively[717] (Scheme 242). The reactions can be carried out at room temperature or by heating in the presence of AIBN or *via* photochemical activation. As substrates, alkanes, ethers, sulfides, alkyl chlorides and terminal or cyclic olefins have been used. The mechanism of the process has

been studied using $^{13}C2$ labelled phenyl ethynyl triflone and is summarised in Scheme 243 for the case of THF.[418] The alkylation can also be carried out with aldehydes to give a mixture of acetylenic ketones **711** and alkylated acetylenes **248** *via* the intermediacy of acyl radicals[419] (Scheme 242). Organic iodides undergo chemospecific alkynylation with triisopropylsilylacetylene triflone under photochemical irradiation. Many functional groups are compatible with this reaction for primary, secondary and tertiary iodides.[420]



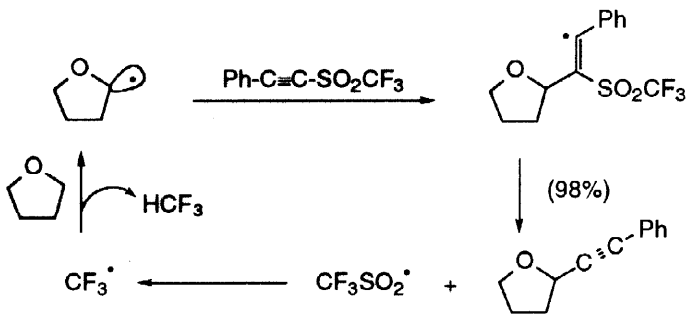
702 **703** **704** **705** **706** **707**

Scheme 241



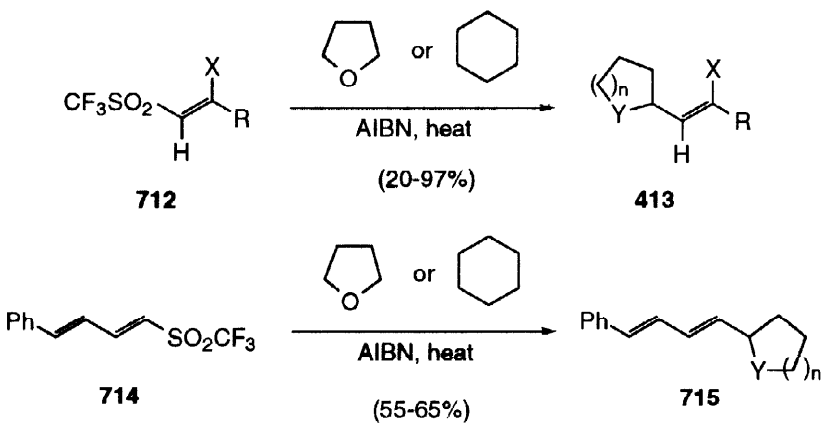
708 **709** **710** **711** **248**

Scheme 242



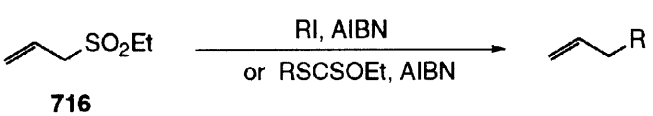
Scheme 243

The same carbon-hydrogen activation can be achieved with β-functionalised vinyl triflones **712** and the dienyl triflone **714** to give the corresponding compounds **713** and **715**.[421] Most of the reactions proceed with high yield and stereospecificity (retention of configuration). β-Substituents can be phenyl, halogens (iodine, bromine and fluorine), benzoate, ethylcarbonate and phthalimide (Scheme 244).



Scheme 244

The generation of carbon-carbon double bonds by allylation of alkyl iodides is usually carried out with allyl stannanes. Recently, a new radical allylation of alkyl iodides uses allyl ethyl sulfone **716** as the source of radicals, in the presence of AIBN.[422] This allylation reaction can also be carried out with dithiocarbonates.[423] The allylic sulfone **716** decomposes to give an ethylsulfonyl radical which looses SO_2 to give the ethyl radical. This species traps either iodine or xanthate to generate the corresponding radical R·, which is finally allylated by the sulfone **716** (Scheme 245).



Scheme 245

8. CONCLUDING REMARKS

This review has shown the synthetic significance of sulfones in their widespread use in total synthesis of many natural products and important synthetic target molecules. The high work of sulfones in synthesis is due not only to the great variety of reactions that they can undergo as intermediates, but also because of their final synthetic transformations into different types of functional groups, as well as in the creation of new carbon-carbon bonds. The development of a great variety of desulfonylation strategies during the last eight years has expanded enormously the use of sulfones in synthesis. It can be concluded that sulfones enjoy good health and will continue to be successfully used until the appearance of the next review on the subject.

Acknowledgements

The authors acknowledge the Dirección General de Investigación Científica y Técnica (DGICYT) of the Spanish Ministerio de Educación y Cultura (MEC) for generous and continuous financial support.

Apendix. Abbreviations

Ac: acetyl
acac: acetylacetonate
ADPP: 1,1'-(azodicarbonyl)dipiperidine
AIBN: azoisobutyronitrile
Bn: benzyl
Boc: *tert*-butyloxycarbonyl
BOM: benzyloxymethyl
BT: benzothiazol
CSA: camphorsulfonic acid
Cy: cyclohexyl
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ: dichlorodicyanoquinone
DEIPS: diethylisopropylsilyl
DIBAL: diisobutylaluminium hydride
DMAD: dimethyl acetylenedicarboxylate
DME: dimethoxyethane
DMF: dimethylformamide
DMPU: *N,N'*-dimethylpropyleneurea
DMTr: di-(*p*-methoxyphenyl)phenylmethyl
dppp: 1,3-bis(diphenylphosphino)propane
E: alkoxycarbonyl
EWG: electron-withdrawing group
GABA: γ-aminobutyric acid
HMDS: hexamethyldisilylamine
HMPA: hexamethylphosphorotriamide
JPK: Julia-Paris-Kocienski
KHMDS: potassium hexamethyldisilazane

LA: Lewis acid
LAH: lithium aluminium hydride
LDA: lithium diisopropylamide
LHMDS: lithium hexamethyldisilazane
MCPBA: *m*-chloroperbenzoic acid
MEM: methoxyethoxymethyl
MOM: methoxymethyl
MoOPH: oxodiperoxymolybdenumpyridine hexamethylphosphoramide
MP: 4-methoxybenzylidene
Ms: methanosulfonyl (mesyl)
MTM: methylthiomethyl
NCS: *N*-chlorosuccinimide
NHMDS: sodium hexamethyldisilazane
NMO: *N*-methylmorpholine *N*-oxide
PEG: polyethyleneglycol
PG: prostaglandine
Piv: *tert*-butylcarbonyl (pivaloyl)
PMP: *p*-methoxyphenyl
PNB: *p*-nitrobenzyl
PNBz: *p*-nitrobenzoyl
PPTS: Pyridinium *p*-toluenesulfonate
PT: 1-phenyl-1*H*-tetrazol-5-yl
Py: pyridine
Ra-Ni: Raney nickel
RBR: Ramberg-Bäcklund rearrangement
SEM: β-trimethylsilylethoxymethyl
SET: single electron transfer
T: thymine
TBAF: tetrabutylammonium fluoride
TBDPS = TBPS: *tert*-butyldiphenylsilyl
TBS: *tert*-butyldimethylsilyl
TES: triethylsilyl
Tf: trifluoromethylsulfonyl (triflyl)
TFAA: trifluoroacetic anhydride
THF: tetrahydrofuran
THP: tetrahydropyranyl
TIPS: 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane
TMS: trimethylsilyl
Tol: *p*-methylphenyl
Ts: *p*-toluenesulfonyl
Z: benzyloxycarbonyl

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Biographical sketch

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