Russian Chemical Reviews **69** (5) 367 – 408 (2000) © 2000 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2000v069n05ABEH000561

Sulfones and sulfoxides in the total synthesis of biologically active natural compounds

E N Prilezhaeva

Contents

I.	Introduction	367
II.	Brief characterisation of reactions applicable in the synthesis of natural compounds based on the use of sulfones and sulfoxides	368
III.	Syntheses based on α-sulfonyl or α-sulfinyl carbanions	369
IV.	Formation of C=C bonds by thermolysis of sulfoxides	390
V.	Syntheses based on reactions of unsaturated sulfones and sulfoxides	392
VI.	Conclusion	403

Abstract. Data on the use of sulfones and sulfoxides in total stereo-, regio- and enantioselective syntheses of natural compounds published over the last 15–20 years are discussed and classified into the most important types of reactions. The bibliography includes 420 references.

I. Introduction

Sulfonyl- and sulfinyl-containing intermediates and their precursors are finding increasing use in the synthesis of natural compounds because these groups satisfy the requirements of sophisticated multistage transformations. In this review, the most important requirements are stated based on the concepts proposed by the eminent chemist and populariser of science, E Block.[1]

These functional groups should be:

(1) readily accessible;
(2) highly reactive;
(3) able to effect asymmetric induction;
(4) readily removable at a particular stage of the synthesis.

Sulfoxides and sulfones are rather readily available compounds. Methods for their synthesis both from the corresponding sulfides and other precursors have been well developed.[2–5]

Owing to their high reactivity, sulfoxides and sulfones can induce the stereo-, regio- and enantioselective formation of new C–X bonds and, what is particularly important, of C–C bonds.

Enantiomerically pure sulfoxides are excellent mediators in the asymmetric synthesis. The fact that the sulfur atom in sulfoxides containing different substituents is an ideal asymmetry center (Montanari[6] was the first to note this fact back in the 1970s) is not the only reason. The ability of the sulfinyl group to form chelates due to complexation with other polar groups in the molecule as well as with catalysts is used in enantioselective syntheses resulting in $1 \rightarrow 2$, $1 \rightarrow 3$ and more distant asymmetry transfer.[5,7–13] The wide application of chiral sulfoxides is also favoured by the availability of convenient methods for their preparation in enantiomerically pure *S*- or *R*-forms.[5,12]

Sulfonyl groups do not possess inherent asymmetry and are substantially less active complex-forming agents. However, due to their specific bulk and electronic properties, these compounds can perform regio- and stereocontrol. Reactions of sulfones proceed under rather mild conditions, which makes it possible to retain chiral carbon centres (even those located in the vicinity of the sulfonyl group) throughout the process.

A wide variety of chemoselective procedures for the removal of sulfonyl and sulfinyl groups are available (see, for example, Ref. 14). Classical heterogeneous reduction with Raney nickel (Ra/Ni) continues to be used. Mild heterogeneous desulfonation (desulfination) with metal amalgams (primarily with Na/Hg) is also often employed. However, the majority of modern procedures involve homogeneous processes, *viz*., reactions of transition metal salts, palladium(0) complexes or solutions of alkali metals in ammonia. Since the use of lanthanides have attracted growing interest in recent years,[15,16] mild desulfonation with SmI_2 is rather often used (see, for example, Refs 16–19). Reductive desulfurisation, elimination of sulfenic and sulfinic acids to form C=C bonds and double elimination of hydroxy and sulfonyl groups from substituted sulfones can readily be performed. Although the sulfonyl fragment is a poor leaving group (see, for example, Ref. 20), conditions were found under which this group in some compounds can be replaced by the attacking reagents.

In spite of the fact that synthetic applications of sulfones have been surveyed (see, for example, Refs 21 and 22), the data on the use of these compounds in the synthesis of natural products remain to be systematised. Applications of particular types of sulfones, such as γ-hydroxyvinyl sulfones[23,24] and sulfolenes,[25,26] for these purposes have been described. Examples of the use of sulfones were cited in reviews devoted to syntheses of selected groups of natural compounds (juvenile hormones[27] and linear polyprenols[28,29]). Recently, Carreno[12] has reported a comprehensive analysis of the uses of chiral sulfoxides in asymmetric syntheses of biologically active compounds. Therefore, in the present review the attention is focused on sulfonyl-containing and racemic sulfinyl-containing precursors and intermediates without special reference to asymmetric synthesis, all the more so since the stereochemistry of all chiral centres has not always been reported in the original studies. Yet another aim of this review is to

E N Prilezhaeva N D Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prosp. 47, 117913 Moscow, Russian Federation. Fax (7-095) 135 53 28. Tel. (7-095) 939 36 21

Received 24 November 1999
Uspekhi Khimii **69** (5) 403 – 446 (2000); translated by T N Safonova

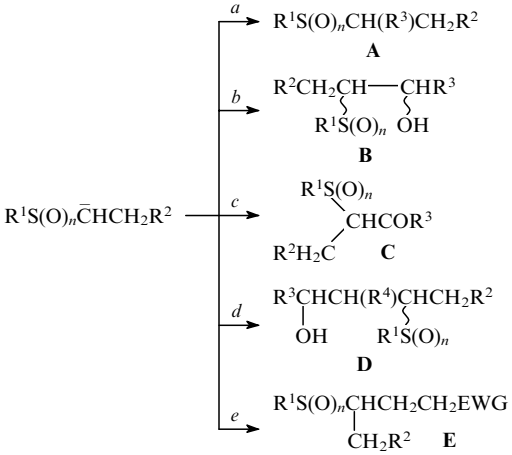
demonstrate how successfully sulfones and sulfoxides complement each other in syntheses of natural compounds.

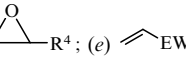
II. Brief characterisation of reactions applicable in the synthesis of natural compounds based on the use of sulfones and sulfoxides

Even a brief analysis of reactions of sulfoxides and sulfones gives an idea of their wide synthetic potential. These compounds can provide the basis for the erection of the building for the synthesis of natural compounds. Fuchs and coworkers [24] compared this building to a majestic pyramid.

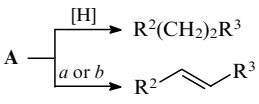
Reactions of carbanions stabilised by α-sulfonyl or (to a lesser extent) α-sulfinyl groups are often used in the synthesis of natural compounds. Among various reagents used for α-deprotonation,[30,31] lithium bases (for example, alkyllithium compounds or lithium diisopropylamide LDA) predominate. In this review, these species will be sometimes described as C-lithiated species in accordance with the original reports although this is not quite correct. It has been rigorously proved [32] that in the crystalline state of sulfur-containing alkyllithium compounds, the metal atom is bound to the oxygen atom of the sulfonyl (sulfinyl) group rather than to the α-carbon atom. However, this fact is not reflected in their reactions in solution. Electrophilic reagents attack exclusively the carbon atom unlike their reactions with carbanions stabilised by the carbonyl group. Alkylation with alkyl or cycloalkyl halides, tosylates or mesylates (Scheme 1, path *a*) affords

Scheme 1



n = 1, 2; (*a*) R^3X, X = Hal, OTs, OMs (Ms = $MeSO_2$); (*b*) R^3CHO; (*c*) $R^3CO_2R^4$; (*d*)  ; (*e*)  EWG, EWG is an electron-withdrawing group.

sulfones or sulfoxides **A** and their reductive desulfurisation leads to the elongation of a saturated chain. Elimination of fragments of acids RSO_nH (n = 1 or 2) from derivatives **A** results in the formation of the C=C bond. For most sulfones, this process occurs under rather drastic conditions. Many sulfoxides eliminate sulfenic acid upon mild thermolysis, which provided the basis for a method of introduction of C=C bonds with *E* configuration into complex molecules proposed by Trost.[33–35]

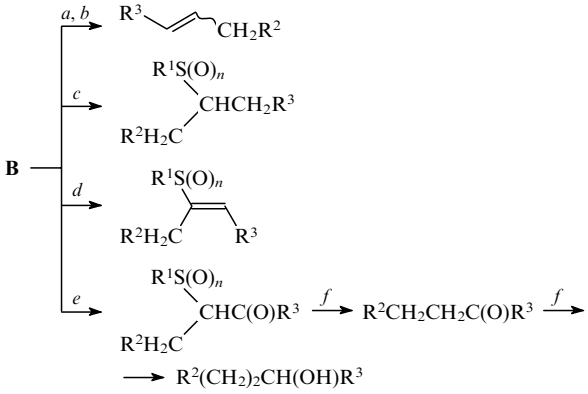


(*a*) *n* = 2, B:; (*b*) *n* = 1, Δ.

Reactions with carbonyl compounds or oxiranes lead to the 1,2-addition at the carbonyl group (Scheme 1, paths *b* and *c*) or to the oxirane-ring opening (path *d*). Reactions of α-sulfonyl carbanions with aldehydes are of particular importance because the resulting epimeric mixtures of 2-hydroxy sulfones **B** (*n* = 2) serve as an inexhaustible source for the construction of new functional groups, *viz*., vinylsulfonyl, oxosulfonyl, saturated hydroxy or oxo groups.

Of prime importance is the Julia olefination resulting in stereoselective construction of the C=C bond with either the *E* (Ref. 36) or *Z* (Ref. 37) configuration following acylation of the hydroxy group (Scheme 2, paths *a* and *b*).

Scheme 2



(*a*) *n* = 2, Ac_2O; (*b*) Na/Hg; (*c*) *n* = 1, 2; (*d*) *n* = 2, B:; (*e*) *n* = 2, [O]; (*f*) [H].

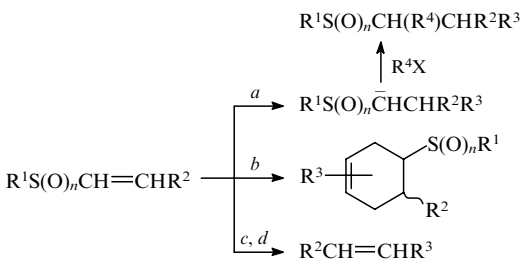
The most important precursors in the asymmetric synthesis, *viz*., 2-hydroxy sulfoxides (**B**, *n* = 1),[12] must be used only in enantiomerically pure form. Therefore, these compounds are generally prepared by selective reduction according to Solladie [38,39] starting from 2-oxo sulfoxides **C**. The most convenient procedure for the synthesis of the latter involves the reaction of α-sulfinyl carbanions with the carbonyl groups of esters (Scheme 1, path *c*).

α-Sulfonyl(sulfinyl) carbanions, being active C-nucleophiles, readily react with various electron-deficient multiple bonds (Scheme 1, path *e*).

Either aryl or (more rarely) *tert*-butyl groups generally serve as substituents R^1 in sulfonyl(sulfinyl) fragments. This is dictated not only by the necessity of providing conditions for regiospecific deprotonation but also for kinetic reasons. For example, benzenesulfenic acid is eliminated upon thermolysis of sulfoxides at substantially lower temperatures than methanesulfenic acid.[40]

Among unsaturated precursors, vinyl sulfones are worthy of particular attention. Fuchs and coworkers [23,24] believed that these sulfones are ideal starting compounds (superior even to enones) for sophisticated syntheses. New C–C bonds are formed upon addition of C-nucleophiles (predominantly metal alkyls) at the activated C=C bonds of vinyl sulfones followed by the reaction of electrophiles with the resulting α-sulfonyl carbanionic centre (Scheme 3, path *a*). Reactions of the C=C bonds of ene sulfoxides with C-nucleophiles occur successfully, if additional acceptors, for example, carbonyl groups, are introduced into the sulfoxide molecules. Reactions of heteronucleophiles with ene sulfoxides

Scheme 3



n = 1, 2; (*a*) R^3M (M = Li, MgX); (*b*)  ; (*c*) *n* = 2, R^3MgX, Ni(II) or Fe(III); (*d*) B:.

and ene sulfones (see Section V.1.b) as well as the Diels–Alder [4+2] cycloaddition (Scheme 3, path *b*) are also widely used. Cross-coupling of vinyl sulfones with Grignard reagents in the presence of transition metal salts makes it possible to replace the sulfonyl group according to Julia,[41] the C=C bonds being unaffected (Scheme 3, paths *c* and *d*).

Linear and cyclic polyunsaturated structures are successfully constructed with the use of various 1,3-dienes generated from substituted 3-sulfolenes by cheletropic elimination of SO_2.[26]

Allyl sulfoxides and, particularly, allyl sulfones are very reactive compounds. Due to abstraction of the labile allylic hydrogen, these compounds readily form ambident carbanions, which can undergo alkylation both at the α- and (more rarely) γ-positions. In the presence of palladium catalysts or Lewis acids, the sulfonyl group in allyl sulfones is replaced by various nucleophiles.[42,43] Because of the wide diversity of their transformations, Trost[44] has named allylic sulfones 'organic chameleons'.

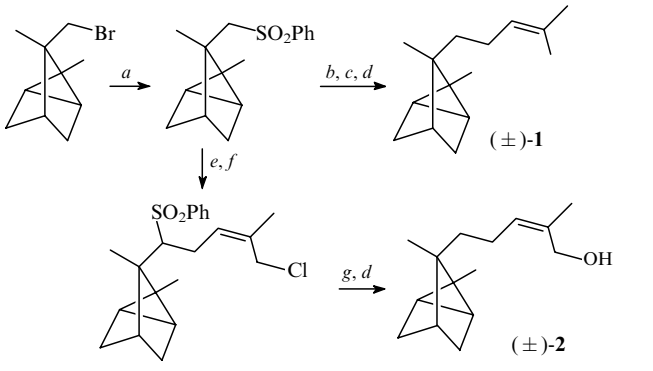
Of rearrangements of sulfoxides and sulfones, the Mislow–Evans sulfenyl–sulfenate rearrangement[45,46] (which is used for the formation of hydroxy allylic fragments), the Pummerer reaction[47,48] (which has many applications, but is predominantly used for the construction of cyclic molecules) and the Ramberg–Bäcklund reaction[49,50] (which is used for the introduction of C=C bonds) are most commonly used in the synthesis of natural compounds. Because of a great body of information on syntheses involving rearrangements of sulfoxides and sulfones, these processes cannot be considered in this review in detail.

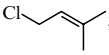
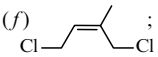
III. Syntheses based on α-sulfonyl or α-sulfinyl carbanions

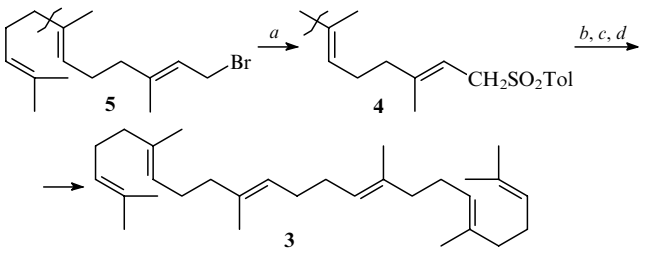
1. Alkylation

a. Alkylation followed by reductive removal of sulfur-containing groups

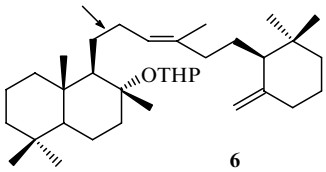
The simplest procedure for the formation of new C–C bonds involves alkylation of α-sulfonyl or α-sulfinyl carbanions followed by reductive removal of sulfur-containing groups. This strategy was used for the first time in the syntheses of components of essential oils, *viz*., racemic α-santalene [(±)-**1**] and α-santalol [(±)-**2**],[51] as well as for the preparation of a pure *trans*-isomer of squalene (**3**)[52] by alkylation of the anion of farnesyl phenyl sulfone (**4**) with farnesyl bromide (**5**). This procedure is often used for the coupling of complex polyfunctional fragments containing numerous chiral centres. Recently, this method has been used for the preparation of intermediates **6**–**8** in the synthesis of ambrein (the intermediate **6**[53]), polysubstituted biologically active furan compounds, *viz*., calicogorgins A and C (the intermediates **7a** and **7b**, respectively[54]), and the antibiotic mycotrienin (the intermediate **8**[55]) (the sites of coupling are indicated by arrows).



(*a*) $PhSO_2Na$, DMF; (*b*) Bu^nLi, THF, hexamethylphosphorous triamide (HMPT); (*c*) ; (*d*) Na/Hg, EtOH; (*e*) Bu^nLi; (*f*) ; (*g*) AcO^-.

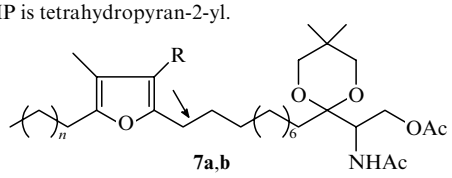


(*a*) $TolSO_2Na$ (Tol = 4-MeC_6H_4) (97%); (*b*) Bu^nLi; (*c*) **3**; (*d*) Et_2NLi, −78 °C.



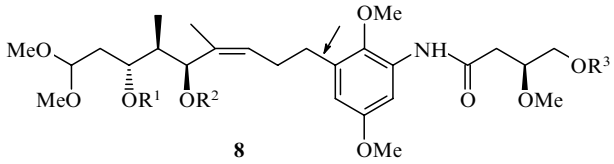
6

THP is tetrahydropyran-2-yl.



7a,**b**

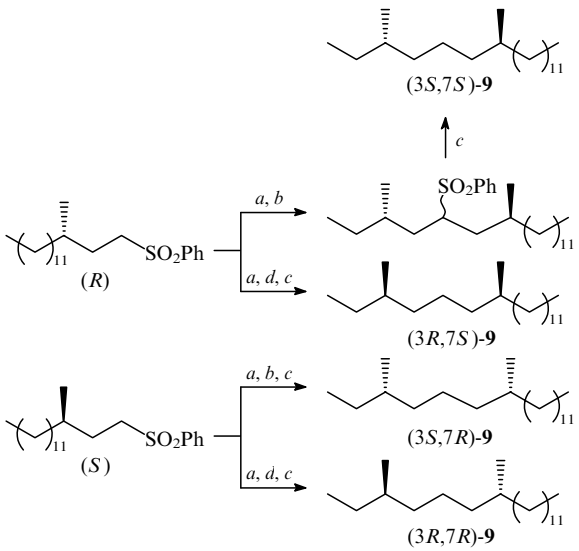
n = 1, R = Me (**a**); *n* = 2, R = H (**b**).

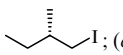
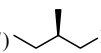


8

R^1–R^3 are protective groups.

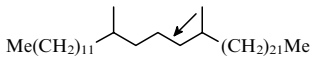
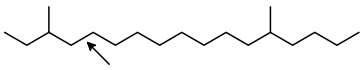
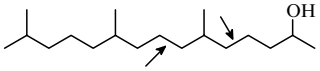
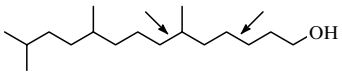
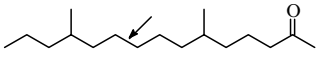
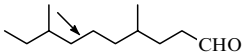
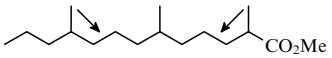
This procedure can also be used for the construction of linear enantiomerically pure pheromones, both saturated and containing isolated C=C bonds. Mori and coworkers[56–64] performed convergent syntheses of pheromones (*ee* 97%–98%) starting from two or more enantiomerically pure building blocks. If the absolute configuration of the natural pheromone was unknown, all possible enantiomers were synthesised in amounts sufficient for biological assays. Below are presented the syntheses of four possible enantiomers of 3,7-dimethylnonadecane (**9**), which is a pheromone of tortricid *Agromyza frontella* (an alfalfa pest).[56]



(*a*) Bu^nLi; (*b*) ; (*c*) Na/Hg, EtOH; (*d*) .

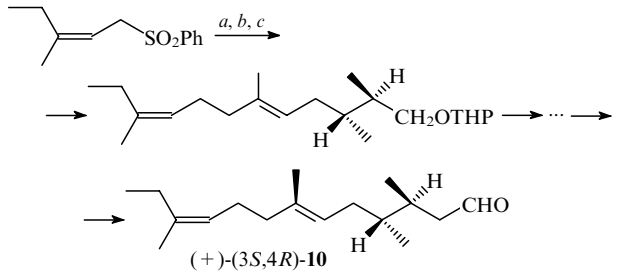
Other pheromones synthesised by Mori and coworkers with the use of alkylation–desulfonylation methodology are listed in Table 1 (the coupling sites are indicated by arrows).

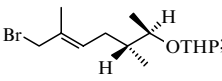
Table 1. Pheromones synthesised by alkylation – desulfurisation.

Name	Structure	Absolute configuration of natural pheromone	Biological characteristic	Number of possible enantiomers (the number of enantiomers synthesised)	Ref.
13,17-Dimethylnonatriacontane		unknown	kairomone for wasp *Trichogramma nubiale*	4 (4)	57
3,13-Dimethylheptadecane		"	sex pheromone of western false hemlock looper *Nepytia freemani*	4 (4)	63
6,10,14-Trimethylpentadecan-2-ol		(2*R*,6*R*,10*R*) [a]	pheromone of rice moth *Corcyra cephalonica*	8 (8)	58
6,10,13-Trimethyltetradecan-1-ol		unknown	aggregation pheromone of predatory stink bug *Stiretrus anchorago*	4 (4)	59
6,12-Dimethylpentadecan-2-one		"	female-produced sex pheromone of banded cucumber beetle *Diabrotica balteata* Le Conte	4 (4)	60
4,8-Dimethyldecanal		(4*R*,8*R*)	aggregation pheromone of red-flour beetle *Tribolium castaneum*	4 (2) [b]	61
Methyl 2,6,10-trimethyltridecanoate		unknown	sex pheromone of stink bug *Euschistus heros*/*E.obscurus*	8 (8)	62

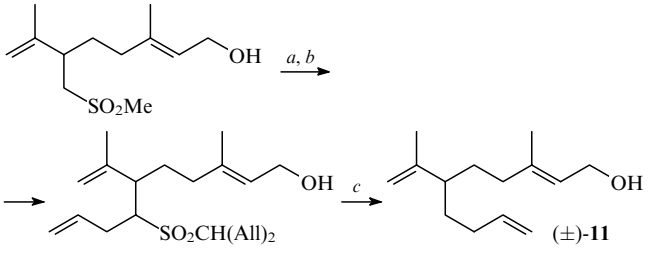
[a] Preliminary data of biological studies. [b] In the study,[61] enantiomers inactive with respect to *Tribolium castaneum*, but active with respect to other species *Tribolium* were prepared.

Pheromones whose molecules contain double bonds were constructed by alkylation – desulfonylation starting from allylic sulfones and (or) allyllic halides. This procedure was used for the preparation of enantiomerically pure faranal (**10**), which is the pheromone of Pharaoh's ant.[64]



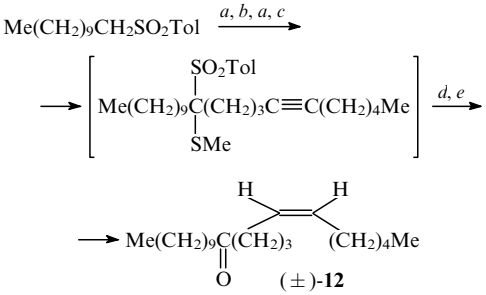
(*a*) Bu^{n}Li; (*b*)  (*c*) Na/Hg, EtOH.

The synthesis of the pheromone of California scale (±)-**11** in the racemic form required the use of a threefold excess of allyl bromide because deprotonation and, correspondingly, alkylation of the initial methyl sulfone occurred non-regiospecifically.[65]



All = $CH_2CH=CH_2$; (*a*) Bu^{n}Li; (*b*) 3 equiv. of BrAll; (*c*) Na/NH_3.

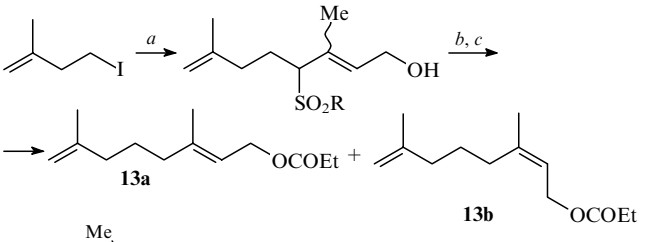
In the synthesis of the sex pheromone of Douglas fir tussock moth **12**, α-thiylation followed by hydrolysis was used for the simultaneous formation of the oxo group and removal of the sulfonyl group; the C=C bond was formed by stereospecific hydrogenation of the triple bond.[66]

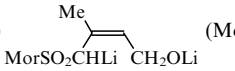


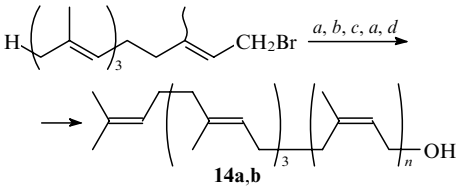
(*a*) Bu^{n}Li; (*b*) 2 equiv. of $Me(CH_2)_4C\equiv C(CH_2)_3I$; (*c*) $(MeS)_2$; (*d*) $CuCl_2$, SiO_2; (*e*) H_2, 5% $Pd/BaSO_4$.

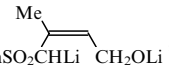
An elegant method for stepwise alkylation developed by Moiseenkov and coworkers [28, 67–70] makes it possible to synthesise polyunsaturated natural molecules by C_5-homologation. Lithiated δ-hydroxyallylic or saturated sulfones (including those containing a chiral centre) and the corresponding unsaturated terpenoid halides served as the starting compounds. This methodology was used for the preparation not only of relatively small molecules [for example, the pheromone components of San-Jose scale, *viz*., α-neryl and α-geranyl propionates (**13a**,**b**)[67]], but also of long-chain natural regulators, such as polyprenol- and dolichol-like alcohols **14**[68] or **15**.[69] The addition of a crown ether, *viz*., dibenzo-18-crown-6 (DB-18-C-6), to a solution of sodium in liquid ammonia in the stage of reductive desulfonation made it

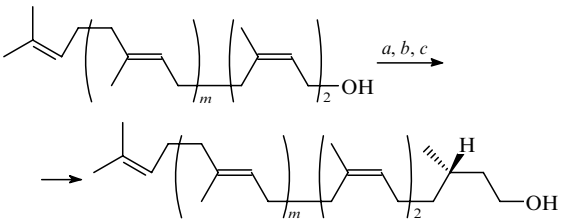
possible to suppress the undesirable allylic isomerisation of the adjacent C=C bond.[70]

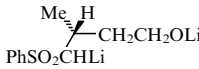


(*a*)  (Mor is morpholinyl); (*b*) Na/NH_3, DB-18-C-6; (*c*) EtCOCl.

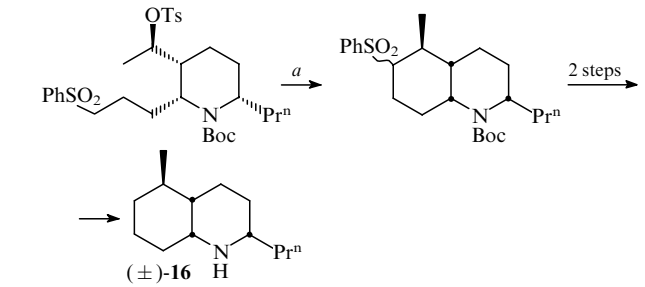


n = 1 (**a**), 2 (**b**); (*a*) ; (*b*) Na/NH_3; (*c*) PBr_3, Py; (*d*) Na/NH_3, DB-18-C-6.

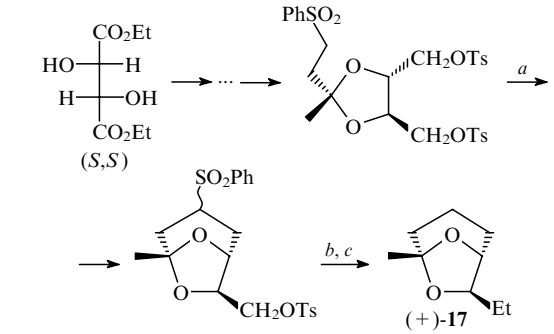


m = 2 (**a**), 3 (**b**); (*a*) PBr_3; (*b*) ; (*c*) Na/NH_3.

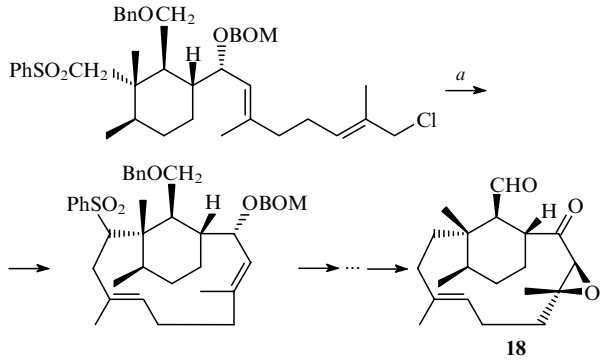
Intramolecular alkylation–reductive desulfonylation leads to ring closure. This procedure was used for the synthesis of racemic pumiliotoxin C (**16**), which is contained in excretions of arrow-poison frog,[71] the bicyclic pheromone (+)-*exo*-brevicomin (**17**) in



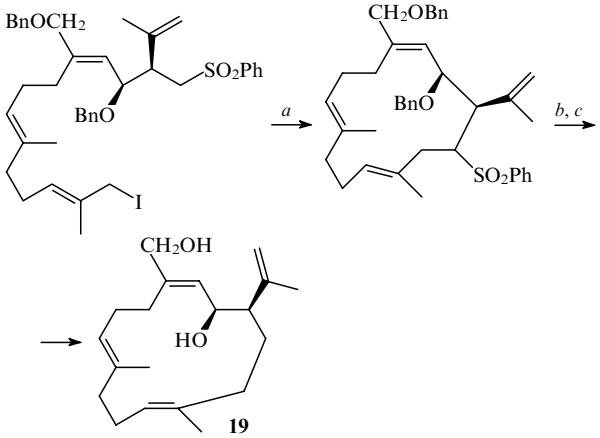
Boc is *tert*-butoxycarbonyl; (*a*) Bu^nLi, HMPT, −78→20 °C.



(*a*) Bu^nLi, THF, −78 °C; (*b*) Me_2CuLi, Et_2O, Me_2S; (*c*) Na, EtOH, THF.



BOM — $BnOCH_2$; (*a*) potassium bis(trimethylsilyl)amide (potassium hexamethyldisilazanide, KHMDS), THF.

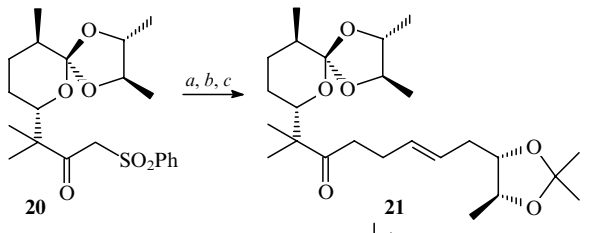


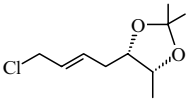
(*a*) KHMDS; (*b*) Na_2HPO_4, Na/Hg, MeOH, 0 °C; (*c*) CF_3CO_2H, CH_2Cl_2, −70 °C.

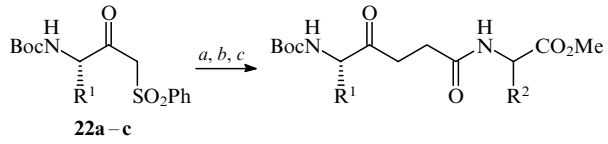
the enantiomerically pure form starting from (*S*,*S*)-(−)-diethyl tartrate,[72] phomactin D (**18**), which is a 12-membered PAF antagonist,[73] and the 14-membered carbocycle 7(8)-deoxyasperdiol (**19**), which is a synthetic precursor of the widespread cembranoid antitumor agent asperdiol.[74]

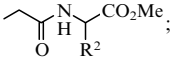
However, attempts to perform macrocyclisation of the halogenosulfone in the synthesis of an analogue of terpenoid **19** failed.[75]

Intramolecular alkylation was used in the total synthesis of 21-membered heterocyclic antibiotics (+)-trienomycins A and F[76] and for the construction of the *AB* ring system of taxol.[77]



(*a*) Bu^nLi, DMSO, KI; (*b*) ; (*c*) Al/Hg, EtOH.

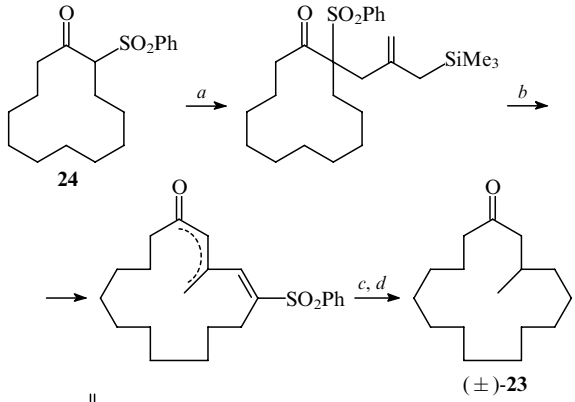


R^1 = Me (**a**), Pr^i (**b**), 4-$MeOC_6H_4CH_2OC_6H_4CH_2O$ (PMBO) (**c**); R^2 = D-Pr^i, L-Pr^i, D-Bn, L-4-$HOC_6H_4CH_2$; (*a*) K_2CO_3, DMF; (*b*) Br ; (*c*) SmI_2, THF, MeOH, −78 °C, 20 min (50%–98%).

Unlike the above-mentioned studies in which alkylation was generally performed with the use of bromides or iodides, the enantiomerically controlled construction of the C(1)–C(17) fragment in the total synthesis of ionophoric boromycin was carried out using the mild reaction of a chloride with an anion generated from the 2-oxosulfonyl group.[78]

Oxo sulfone **20** serves as an example of additional activation of the α-sulfonyl carbanionic centre in alkylation. The sulfone **20** was used as the starting material in the synthesis of compound **21**, which is the key intermediate for the preparation of the antibiotic (±)-aplasmomycin.[79] Amino-acid-derived oxo sulfones **22a–c** were successfully used in the peptide synthesis.[80]

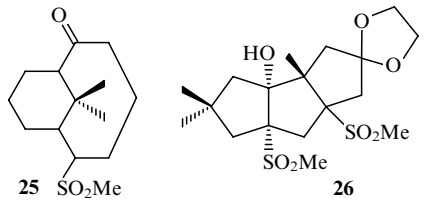
Cyclic ketones containing the sulfonyl group at the α-position undergo three-carbon ring expansion when a fluoride anion acts on the products of alkylation of enolates of these ketones with silicon-containing allylic iodides or mesylates [$Me_3SiCH_2(XCH_2)C=CH_2$], which generate trimethylenemethane.[81] Trost and coworkers[82] used this procedure for the preparation of muscone **23** from 2-sulfonylcyclododecanone **24** in high yield.



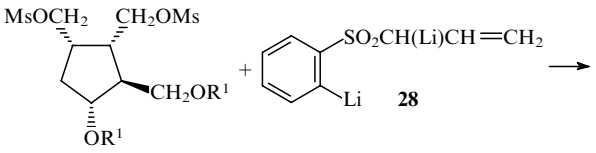
(*a*) Me_3Si X (X = I, OSO_2Me), NaH, NaI, DME;

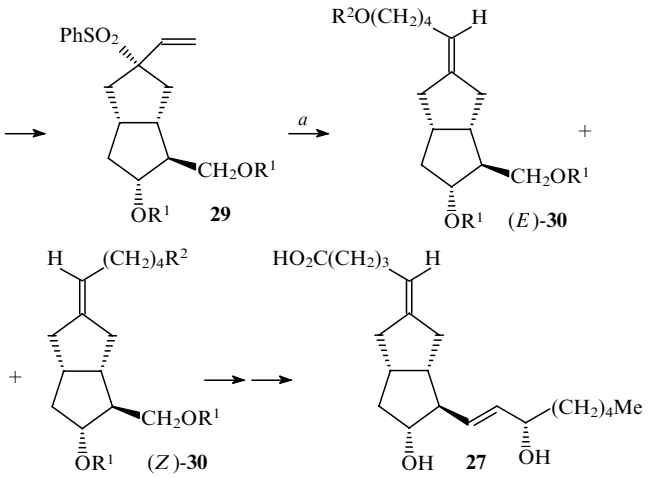
(*b*) Bu^n_4NF, THF; (*c*) H_2, 5% $Pd/BaSO_4$; (*d*) Na/Hg, Na_2HPO_4, H_2O.

The application of more complex oxosulfonyl precursors made it possible to construct sterically hindered systems of the 11,11-dimethylbicyclo[5.3.1]undecane series, such as compound **25**, which is the key intermediate in the synthesis of taxane derivatives,[83] as well as to prepare fused cyclopentanoids of the type **26**, which serve as the starting compounds for the preparation of hirsutene, hirsutic acid and coriolin.[84]



The formal total synthesis of carba-prostacyclin (**27**), which is an analogue of prostacyclin, was reported.[85] The compound **27** is more stable, but exhibits no lesser activity in the inhibition of blood coagulation. The allylic sulfone dianion **28** was alkylated with enantiomerically pure mesylate of substituted hydroxycyclopentane. The necessary side chains were introduced into compound **29** by reactions with the corresponding lithium cuprates. The reactions were accompanied by the replacement of the

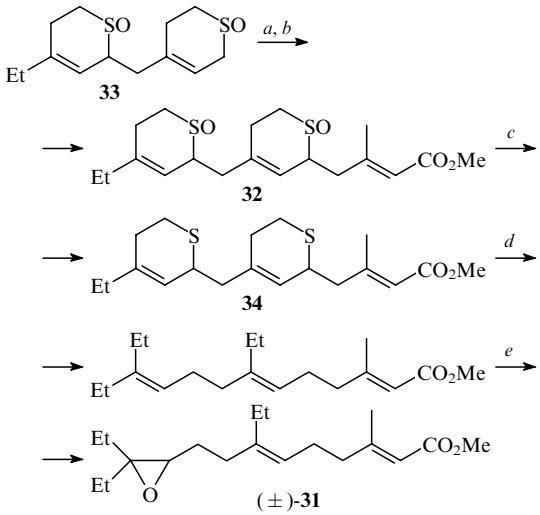




R^1 = $SiMe_2Bu^t$; (*a*) $LiCu[(CH_2)_3OR^2]_2$; R^2 = CH(Me)OEt.

sulfonyl group and migration of the C=C bond to form a mixture of (*Z*)- and (*E*)-isomers of compound **30**. The latter is the key intermediate in the synthesis of carba-prostacyclin (**27**).

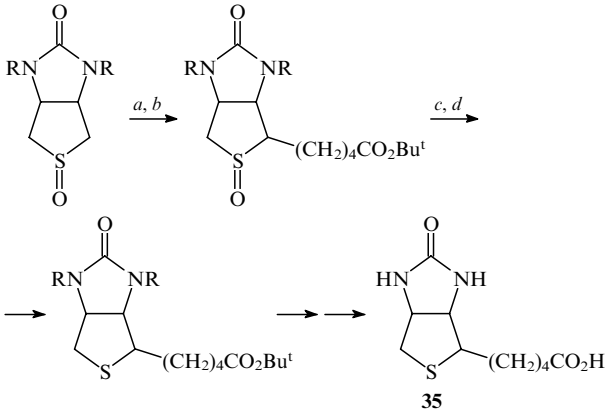
As to α-sulfinyl carbanions, the simplest alkylation – reductive desulfinylation procedure is rather rarely used in the synthesis of natural compounds. However, the racemic juvenile hormone **31** was synthesised by two-step reduction of the compound **32**, which is an alkylation product of disulfoxide **33**, *via* intermediate dithioether **34**.[86]



(*a*) LDA; (*b*) Br CO_2Me; (*c*) $SnCl_2$, AcCl, DMF;

(*d*) Ra/Ni, DMSO; (*e*) *m*-chloroperbenzoic acid (MCPBA).

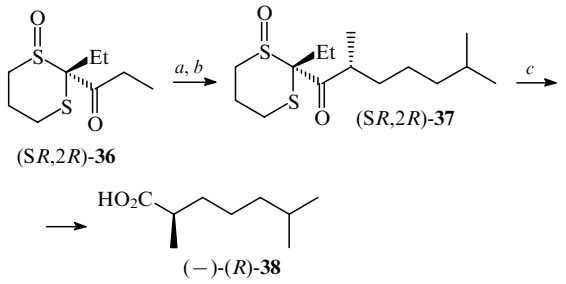
In the total synthesis of racemic biotin **35**,[87] an intermediate obtained by alkylation of a sulfoxide was reduced to sulfide.

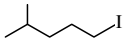


R = Bn, All; (*a*) MeLi; (*b*) $I(CH_2)_4CO_2Bu^t$; (*c*) $TiCl_3$; (*d*) HBr.

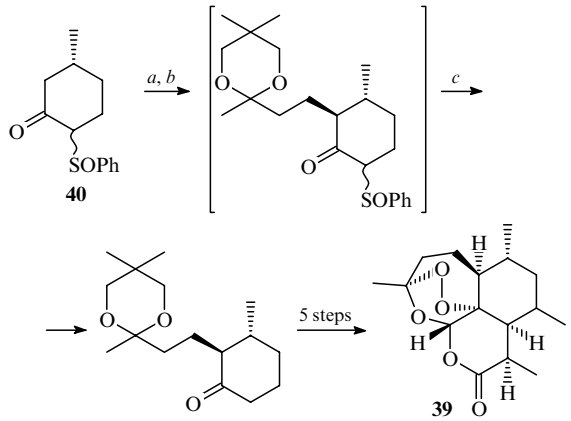
Deprotection of the amino and carboxy groups was performed in two steps to produce (±)-biotin **35**.

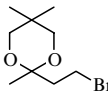
The reactions given below exemplify the use of alkylation of the anions derived from oxo sulfoxides upon deprotonation at the α-position with respect to the carbonyl group. Due to the induction exerted by the sulfinyl group, alkylation of an enantiomerically pure derivative of 1,3-dithiane 1-oxide (**36**) proceeded selectively to form compound **37**. Its hydrolysis afforded natural (−)-(*R*)-2,6-dimethylheptanoic acid [(−)-(*R*)-**38**].[88]



(*a*) $(Me_3Si)_2NLi$; (*b*) ; (*c*) NaOH (39%).

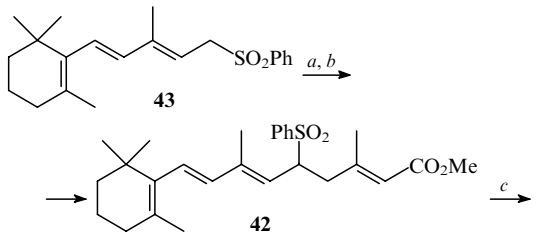
The total synthesis of an antimalarial drug, *viz*., sesquiterpenoid (+)-artemisinin (**39**), was carried out starting from sulfoxide **40**,[89] which had been prepared from pulegone. The sulfinyl group acts as an activating agent that promotes alkylation of enolate.

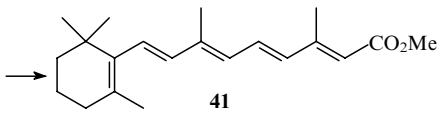


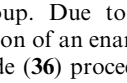
(*a*) 2 equiv. of LDA, HMPT, THF, −35 °C; (*b*) ; (*c*) Al/Hg.

b. Alkylation of α-sulfonyl carbanions followed by elimination of sulfinic acid

Homoallylic sulfones are promising starting compounds for the introduction of C=C bonds by alkylation of α-sulfonyl carbanions followed by elimination of sulfinic acid. Julia and Arnould[90] were the first to use this approach in the synthesis of natural compounds. These authors performed a convergent (C_{15} + C_5)-synthesis of methyl retinoate (**41**) related to vitamin A starting from β-ionone. The key step of this scheme involves dehydrosulfinylation of homoallylic sulfone **42** prepared by alkylation of





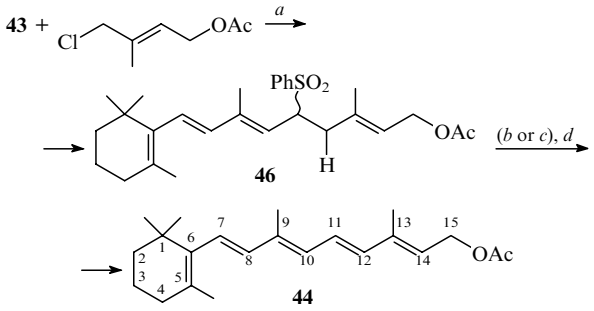
(*a*) Bu^nLi; (*b*) Br ; (*c*) K_2CO_3, MeOH (73%).

sulfone **43**. However, the *E*-configurations of all C=C bonds of the final reaction product **41** have not been established reliably.[90]

This study[90] gave impetus to intensive investigations aimed at developing a sulfonyl procedure for the preparation of vitamin A as retinol acetate (**44**) (the results were surveyed in Ref. 91). This approach seemed to be promising owing to a small number of steps and the possibility of recycling of the sulfinate eliminated. The most essential results were obtained by researchers of Rhone–Poulenc[92,93] and of Hoffman–LaRoche.[94,95] Two versions of the convergent (C_{15} + C_5) schemes (Scheme 4, paths I

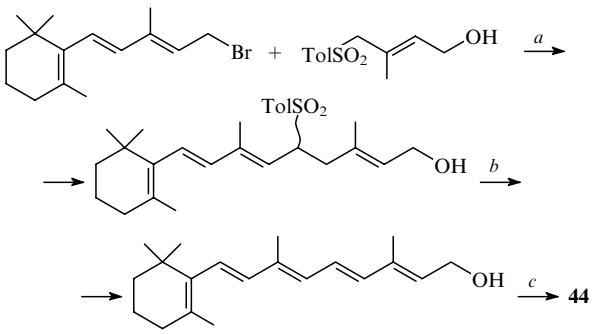
Scheme 4

Path I



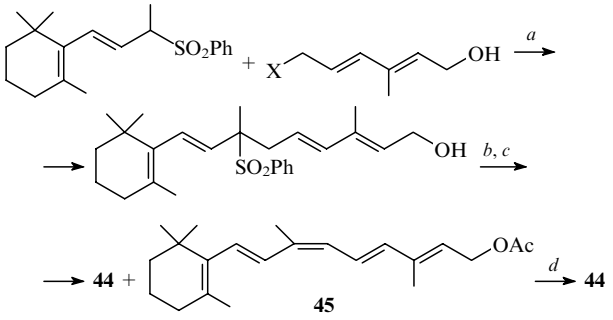
(*a*) Bu^tOK, THF; (*b*) Pr^iONa, C_6H_{14}, 30 °C, 1 h (82%–86%); (*c*) EtONa, EtOH, Δ, 13 h (83%), (*d*) Ac_2O, Py.

Path II

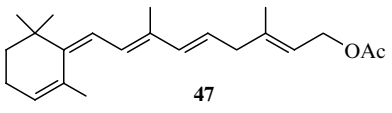


(*a*) LDA, THF; (*b*) $NaNH_2$, NH_3 (liquid), −30 °C, 50 min (85%); (*c*) Ac_2O, Et_3N.

Path III

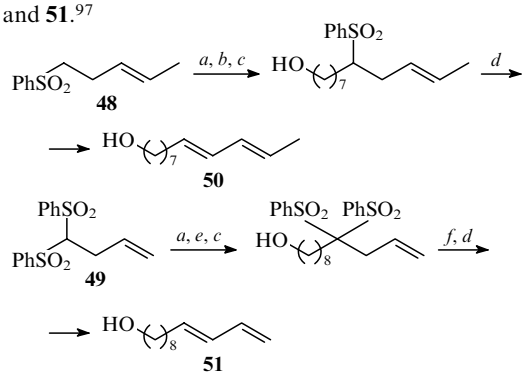


X = Cl, Br; (*a*) Bu^tOK; (*b*) NaOH, Me_2NH, 20 °C, 16 h (75%) (ratio **44** : **45** ~ 1 : 2); (*c*) AcCl, Py; (*d*) $PdCl_2$ (70%).



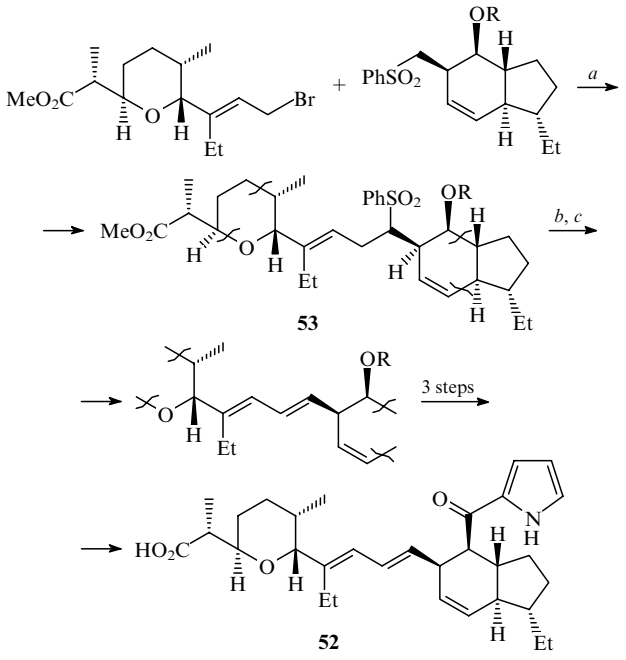
and II)[92,93,95] and the (C_{13} + C_7) scheme 4 (path III)[94] were developed together with several procedures for the elimination of sulfinic acid. The major difficulties were associated with the formation of an admixture of the biologically inactive isomer **45** with the (*Z*)-C(9)=C(10) bond and the isomer **47**. Apparently, the isomer **45** was formed as a result of isomerisation of the intermediate sulfone **46**, whereas the isomer **47** was formed upon prolonged action of a base. The best results were obtained with the use of mild heterogeneous elimination of sulfinic acid (Pr^iONa, hexane, path I *b*). However, isolation of pure retinol acetate (**44**) requires recrystallisation.[92] Other procedures for elimination (path I *c*, path II *e* and path III *h*) call for a number of additional operations. Thus upon desulfonylation with a solution of NaOH in Me_2NH, the content of the isomer **45** in the reaction mixture reached 34%. After isomerisation under the action of $PdCl_2$ and recrystallisation, pure retinol acetate was obtained in 70% yield. None of the sulfonyl procedures has been used in industry, at least, before 1984.[96]

In the case of less complex molecules, for example, in the formation of (*E*,*E*)-1,3-dienes, the reactions are not accompanied by isomerisation. Therefore, (*E*)-homoallylic sulfones of the types **48** and **49** are convenient starting compounds. Elimination of sulfinic acid was used in the synthesis of pheromone components **50** and **51**.[97]



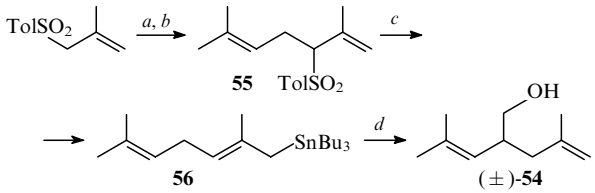
(*a*) Bu^nLi; (*b*) THPO$(CH_2)_7$I; (*c*) H_3O^+; (*d*) Bu^tOK, Bu^tOH, Δ;
(*e*) THPO$(CH_2)_8$I; (*f*) Na/Hg.

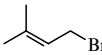
In the total convergent synthesis of the ionophore antibiotic indanomycin **52**,[98] the formation of the (*E*,*E*)-diene bridge between two cyclic fragments of the molecule occurred as elimination of sulfinic acid involving only the hydrogen atom of the acyclic part of the intermediate sulfone **53**.



R = $SiMe_2Bu^t$; (*a*) LDA, THF, −78 °C (97%);
(*b*) triton B ($BnMe_3NOH$), MeOH, 40 °C; (*c*) CH_2N_2, Et_2O, 0 °C.

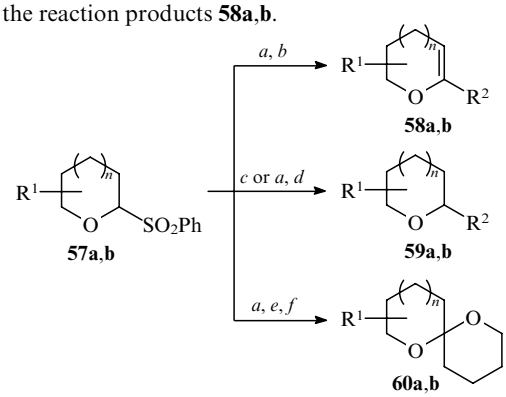
The synthesis of racemic lavandulol (±)-**54** involved formal replacement of the sulfonyl group.[99] The intermediate sulfone **55** was hydrostannylated simultaneously with the elimination of sulfinic acid. The subsequent reaction of stannane **56** with trioxane in the presence of boron trifluoride etherate was accompanied by elimination of Bu^n_3SnH and migration of the double bond.



(*a*) Bu^nLi; (*b*)  (97%); (*c*) Bu^n_3SnH, AIBN (azobisisobutyronitrile) (97%); (*d*) $(CH_2O)_3$, $Et_2O \cdot BF_3$ (57%).

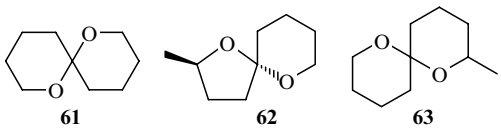
c. Alkylation of α-sulfonyl carbanions with synchronous elimination of sulfinic acid

For saturated molecules, alkylation of α-sulfonyl carbanions with elimination of sulfinic acid is exemplified by the reaction of alkylating reagents with α-carbanions derived from 2-sulfonyl-substituted cyclic ethers, *viz*., tetrahydropyrans or tetrahydrofurans **57a**,**b**. The sulfonyl groups in tetrahydropyrans and tetrahydrofurans facilitate α-deprotonation. However, Ley and coworkers[100] found that an intermediate formed in the course of the subsequent reaction with an electrophile is stabilised due to synchronous elimination of sulfinic acid. Apparently, the driving force for this process is the formation of the endocyclic C=C bond in the reaction products **58a**,**b**.



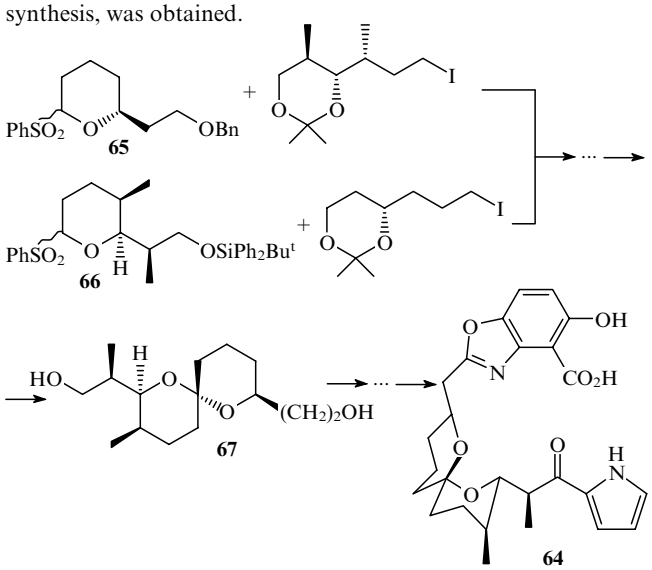
n = 0 (**a**), 1 (**b**); (*a*) Bu^nLi; (*b*) R^2X; (*c*) R^2MgX, $ZnBr_2$;
(*d*) R^2X, $C_{10}H_8Na$; (*e*) $I(CH_2)_4OTHP$; (*f*) H_3O^+.

The reactions with Grignard reagents in the presence of zinc salts or with alkyl halides in the presence of sodium naphthalenide afforded tetrahydro derivatives **59a**,**b**, which are the formal replacement products of the sulfonyl group, instead of dihydropyrans or dihydrofurans **58a**,**b**. The reactions of the sulfones **57** with electrophiles containing a protected hydroxy group at the ω-position are of considerable interest for the synthesis of certain natural compounds. These reactions afford spiroketals **60** because the hydroxy group of the substituent in the intermediate **58** immediately reacts with the nucleophilic double bond after deprotection in an acidic medium. The simplest examples of this approach are the syntheses of 1,7-dioxaspiro[5.5]undecane (**61**), which is a component of the pheromone of *Dacus Olea*[101] and of the so-called fruit flies particularly widespread in tropical countries,[102] as well as the syntheses of analogous compounds **62** and **63**.[101]



61 **62** **63**

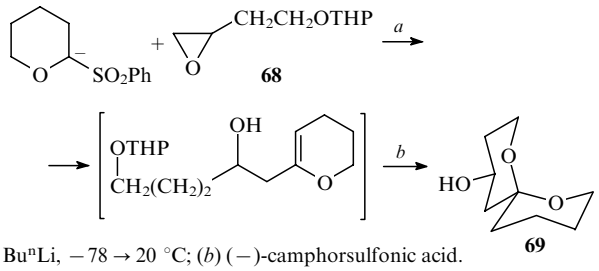
The construction of the spiroketal fragment in the total enantioselective synthesis of an ionophore routiennocin (**64**), which is a carrier of divalent cations, presented a more difficult problem.[103] This problem was solved with the use of alkylation of the anions derived from sulfonyltetrahydropyrans **65** or **66**. In both cases, spiroketal **67**, which is the necessary precursor in this synthesis, was obtained.



65 **66** **67** **64**

Total syntheses of polyfunctional macrolides of the avermectin–melbemycin family, which were discovered about 20 years ago,† present a major achievement by Ley and coworkers. These compounds exhibit a very broad spectrum of antiparasitic, including antihelminthic, activities, and their use in medical practice is recognised to be an impressive breakthrough.[104]

Ley and coworkers started their studies in this field with the development of a procedure for the synthesis of substituted spiroketals by reactions of anions generated from 2-sulfonyltetrahydropyrans with new reagents, *viz*., alkoxy-substituted epoxides of the type **68**. For example, this procedure was used for the synthesis of a minor component (**69**) of the pheromone of olive moth.[105]



68 **69**

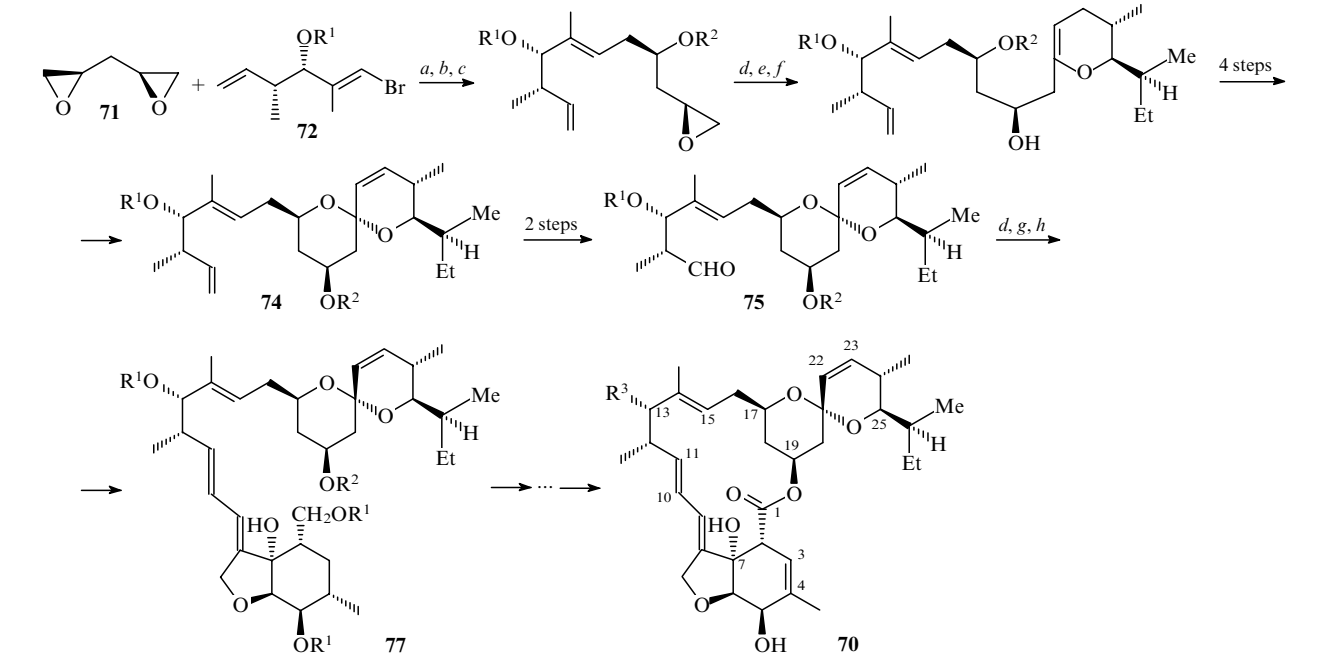
(*a*) Bu^nLi, $-78 \rightarrow 20$ °C; (*b*) (−)-camphorsulfonic acid.

Syntheses of the most important representatives of this series, *viz*., avermectin B1a (**70**)[106] and melbemycin β_1 (as the aglycone),[107] are characterised by the elegant and versatile applications of sulfonyl and other building blocks.

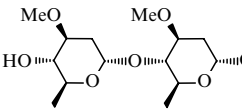
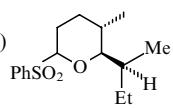
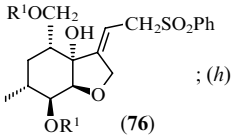
The key steps of the total synthesis of avermectin (**70**) containing 30 stereogenic centres, five C=C bonds with a fixed configuration and numerous functional groups are given in Scheme 5. In particular stages of the synthesis, the intermediates were compared with the degradation products of natural avermectin. The first step of the synthesis of the macrolide **70** involved

† Avermectin was isolated from actinomycete MA-46650 in 1978.[104]

Scheme 5

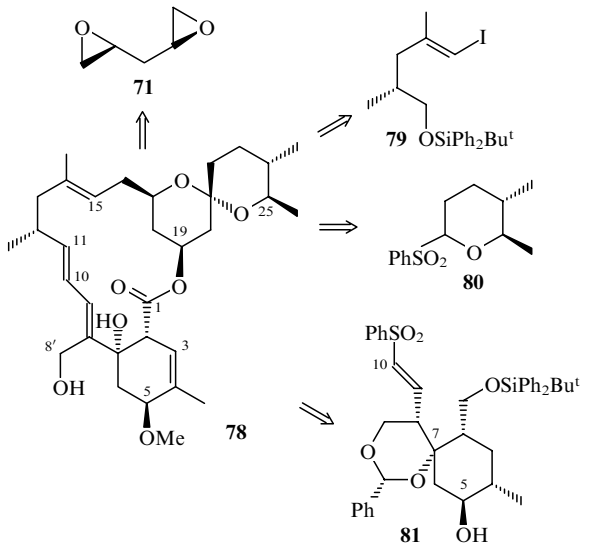


71 **72** **74** **75** **77** **70**

R^1 and R^2 are protective groups; R^3 = ; (*a*) Bu^tLi; (*b*) Me_3Al; (*c*) Bu^tMe_2SiCl, DMAP (4-dimethylaminopyridine), Et_3N, DMF; (*d*) Bu^nLi; (*e*)  (**73**); (*f*) $BF_3 \cdot Et_2O$; (*g*)  (**76**); (*h*) Na/Hg.

the reaction of enantiomerically pure diepoxide **71** [an important synthon for the C(17)–C(19) fragment] with a vinylic bromide **72** to form a substituted epoxide. Subsequent reactions with substituted 2-sulfonyltetrahydropyran **73** followed by transformations required for the formation of the C(22)=C(23) bond afforded spiroketal **74**, which is the 'northern' [C(11)–C(25)] hemispherical fragment of the macrolide **70**. The terminal C=C bond in the compound **74** was converted into the aldehyde group in two steps. The reaction of the intermediate **75** with the anion generated from allylsulfonyl synthon **76** resulted in the formation of the (*E*)-C(10)=C(11) bond (the Julia olefination, Section III.2.a). Compound **77** contained ~12% of an admixture of the (*Z*)-C(10)=C(11) isomer. The completion of the synthesis involved the macrolactonisation of the intermediate **77** following oxidation at C(1) with simultaneous formation of the C(3)=C(4) bond and the attachment of the disaccharide residue R^3, which was obtained from oleandrose, at C(13).

The synthesis of a somewhat less complex molecule, *viz*., melbemycin β_1 (**78**), was carried out according to an analogous scheme.[107] The major synthons in this scheme are either identical to compounds used for the preparation of avermectin (**70**) (for example, diepoxide **71**) or differ only in the functional groups (synthons **79**, **80** and **81** correspond to compounds **72**, **73** and **76**, respectively). The formation of spiroketal is also a fundamental step in the construction of the 'northern' fragment. The coupling of the 'northern' and 'southern' fragments to form the (*E*)-C(10)=C(11) bond was performed by the reaction of the aldehyde group of the 'northern' fragment with the α-sulfonyl carbanion of the 'southern' fragment. This reaction is not the standard olefination procedure according to Julia because the C(9)=C(10) double bond is converted into the required C(10)=C(11) bond.[107]

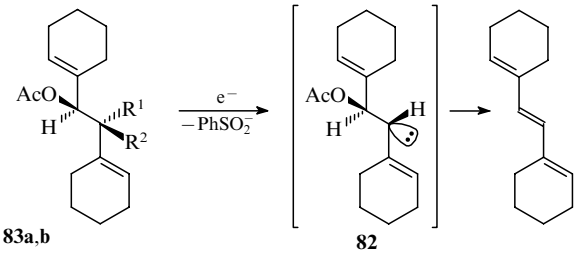


The common feature in the syntheses of the macrolides **70** and **78** is the method of formation of the trisubstituted C(14)=C(15) bond. This bond is introduced upon reactions with the halide synthons **72** or **79**. This makes it possible to circumvent the difficulties encountered in earlier studies (see Section III.2.a) in attempting to construct this bond with the use of sulfonyl or sulfinyl precursors.

2. Addition to oxygen-containing electrophiles

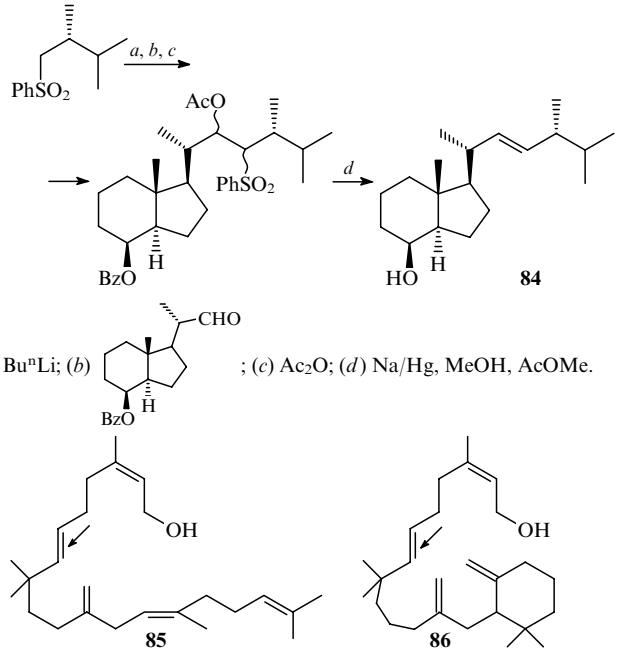
a. Addition of α-sulfonyl carbanions to carbonyl groups of aldehydes and ketones

Lythgoe [108] and Kocienski [109–111] have shown that an important problem of olefination (coupling of synthons with the stereospecific formation of the C=C bond) can be solved by reductive elimination of 2-hydroxy sulfones, which are prepared by the reactions of aldehydes with α-sulfonyl carbanions, proposed by Julia and Paris.[36] This procedure is an excellent alternative to the phosphonate Wittig method. The optimum conditions for olefination were found, *viz*., acetylation or benzoylation of the hydroxy group and reductive elimination with sodium amalgam in a mixture of methanol with tetrahydrofuran or ethyl acetate.[112] In studies of the scope and limitations of this reaction, it was demonstrated that *E*-disubstituted double bonds can be formed with a stereoselectivity of ~ 80% – 100%. The stereoselectivity is enhanced in the case of chain branching at the β-position with respect to the double bond, whereas a substituent at the α-position hinders the reaction.[113] Trisubstituted C=C bonds are formed with difficulty and the stereoselectivity of this process is low, whereas attempts to obtain tetrasubstituted C=C bonds failed.[109] Since the stereochemistry of the initial acyloxy sulfone (*threo*-, *erythro*- or a mixture of both forms) has no effect on the stereoselectivity of the formation of the C=C bond, it was suggested that this process occurs *via* a common intermediate **82** formed upon reductive elimination of the sulfinate anion or from the diastereomers **83a** or **83b**.[109, 113] The intermediate **82** is long-lived enough to assume the conformation favourable for elimination of the acyloxy anion. This may not be the case with ketones exerting steric hindrances, which explains the fact that olefination with the use of acyloxysulfonyl derivatives prepared from ketones is not always successful. Recently, a more intricate mechanism of the olefination has been proposed.[114] However, none of the suggested reaction schemes was confirmed by quantitative methods, for example, by kinetic methods.



R^1 = H, R^2 = SO_2Ph (**a**); R^1 = SO_2Ph, R^2 = H (**b**).

Below are summarised the results of the use of this methodology in the syntheses of natural compounds performed by Kocienski and Lythgoe with their coworkers. This procedure was used for the formation of the (*E*)-C=C bond in the alcohol **84**, which is the key intermediate in the synthesis of calciferol,[115] and for the preparation of different modifications of vitamin D,

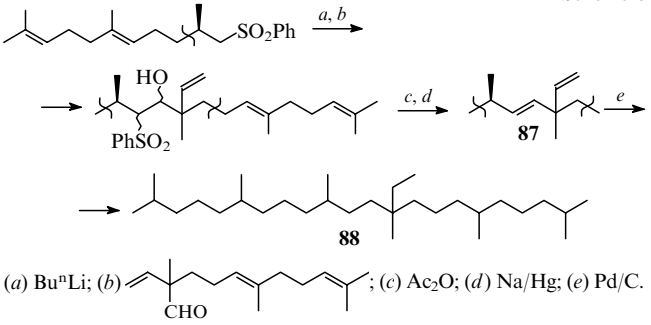


(*a*) Bu^nLi; (*b*) ; (*c*) Ac_2O; (*d*) Na/Hg, MeOH, AcOMe.

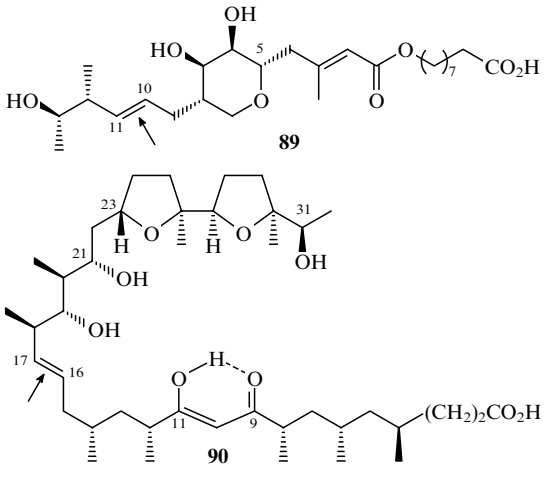
including α-hydroxy vitamin D_3 (see Ref. 116) and vitamin D_4.[117] (More recently,[118] 25-hydroxy vitamin D_2 was prepared according to an analogous procedure with the use of ethylmagnesium bromide instead of BuLi for deprotonation). This scheme was applied to the synthesis of the major C_{25} segments (**85** and **86**) for the preparation of the antibiotics moenocinol[119] and diumycinol,[120] respectively.

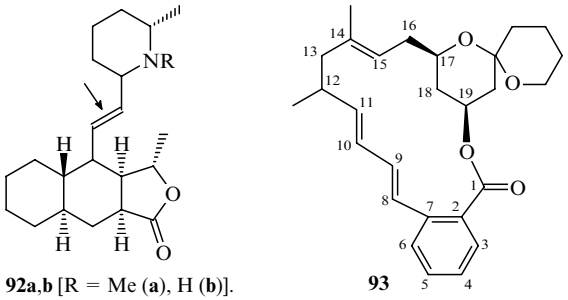
Later, the Julia olefination (which is sometimes called the Julia–Kocienski or the Julia–Lythgoe olefination) has found wide application in the synthesis. Thus this procedure was used in the synthesis of botryococcene **87** (Scheme 6), which is an algae hydrocarbon. The compound **87** has a specific branched structure. The product of its exhaustive hydrogenation (**88**) is a promising biological marker in petroleum production.[121]

Scheme 6



Olefination is the major stage in the total syntheses of a number of biologically active long-chain compounds. This reaction has been used in the formation of the (*E*)-C(10)=C(11) bond in the antibiotic pseudomonic acid C (**89**),[122, 123] the C(16)=C(17) bond in the antibiotic ionomycin (**90**) responsible for the transport of Ca^{2+} ions[124, 125] and the C(7)=C(8) bond in the diene fragment of curacin (**91**) exhibiting antitumor activity.[126] To construct the double bond between the piperidine and decahydronaphthalene fragments in the synthesis of alkaloids (+)-himbacine (**92a**) and (+)-himbeline (**92b**), the aldehyde and sulfonyl groups should be bound to the pyrimidine and decahydronaphthalene synthons, respectively,[127] otherwise steric hindrance to olefination occurs. One of the double bonds of the 1,3-diene system of indanomycin was also formed according to this procedure.[128]





The Julia olefination is often used for the introduction of C=C bonds into the starting compounds which are subsequently employed in total syntheses. For example, double bonds in the following fragments were formed according to this procedure: in the C(1)–C(22) fragment for the construction of immunodepressant FK,[129] in the C(22)–C(31) fragment of an intermediate for the macrolide antibiotic roxaticin[130] and in the triene group of the C(10)–C(27) fragment used in the synthesis of the immunodepressant rapamycin.[131, 132] In the total synthesis of the antitumor macrolide aplyronine, coupling by the reaction of the α-sulfonyl anion with the aldehyde group was employed twice.[133] When the C(3)–C(17) fragment was constructed in the synthesis of boromycin, the intermediate 2-hydroxysulfonyl unit was used for the stereoselective formation of the hydroxy group rather than for the introduction of the double bond.[134]

The Julia olefination was also used in the total syntheses of the majority of macrolides of the avermectin — melbemycin group, for example, of avermectin B1a (Ley *et al.*,[106] Hanessian *et al.*[135] and White *et al.*[136]), as well as of the simplest compound of this group, *viz.*, melbemycin β_3 (**93**), which served as the favourite subject in earlier synthetic studies performed by Kocienski,[137] Baker[138] and Barrett[139] with their coworkers.

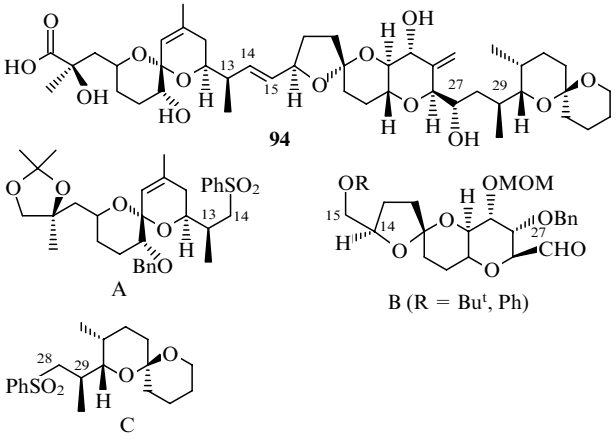
The Julia procedure was used for the coupling of large fragments which have been synthesised beforehand and already contained the required chiral centres. Macrolactonisation was performed in the final stage of the synthesis. In the synthesis of these very complex systems, the previously established regularities hold on the whole. The formation of the disubstituted C(10)=C(11) bond occurs most readily and with a high stereoselectivity, particularly, when the aldehyde group is bound to the C(11) atom of the 'northern' fragment, while the sulfonyl group is bound to the C(10) atom of the 'southern' fragment.[106, 137] When the functional groups are located in the reverse order, the results are somewhat worse.[135, 138] When the ketone was used in place of the aldehyde for the formation of the C(8)=C(9) bond of avermectin B1a [the carbonyl group at the C(8) atom of the 'southern' fragment and the sulfonyl group at the C(9) atom of the 'northern' fragment],[136] the reaction was complicated by lactonisation of the intermediate. The formation of the trisubstituted C(14)=C(15) bond with the use both of the ketone[136] and aldehyde[139] versions of olefination occurs in low yield and affords an admixture of an undesirable regioisomer. With the aim of constructing this bond, more sophisticated approaches, though also based on reactions of sulfoxides and sulfones, were applied.[136, 139]

Kocienski was the first to note[109] that the use of olefination for the preparation of large amounts of compounds is hampered by the necessity of consuming a considerable amount of amalgam for desulfonation. Presently, a number of procedures free of this drawback are available. Thus it is believed[140] that reduction with magnesium in ethanol upon catalysis with mercuric chloride occurs due to *in situ* formation of magnesium amalgam. It was also recommended to use SmI_2 in THF[141] or HMPA.[141, 142] In the latter case, a trisubstituted double bond is successfully formed from ketones and primary sulfones, though only in low-molecular-weight model compounds.

Reactions of α-sulfonyl anions with aldehyde groups have also been used for the coupling of bulky, *e.g.*, cycloaliphatic, segments. This coupling not necessarily involved the formation of the C=C bond, but sometimes occurs through hydroxy- or oxo-functionalised saturated units.

The key steps in a multistep (more than 100 steps) enantio- and stereospecific total synthesis of okadaic acid **94**, which is a

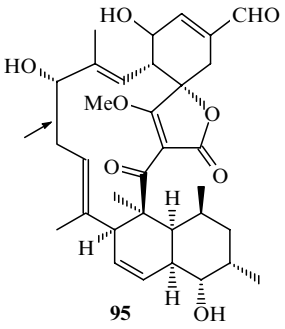
potential antitumor drug,‡ involved couplings of the segments A, B and C, which have been prepared according to the retrosynthetic approach, in the order (B + C) + A (the atomic numbering scheme corresponds to that used for okadaic acid).[144–147]



MOM is methoxymethyl.

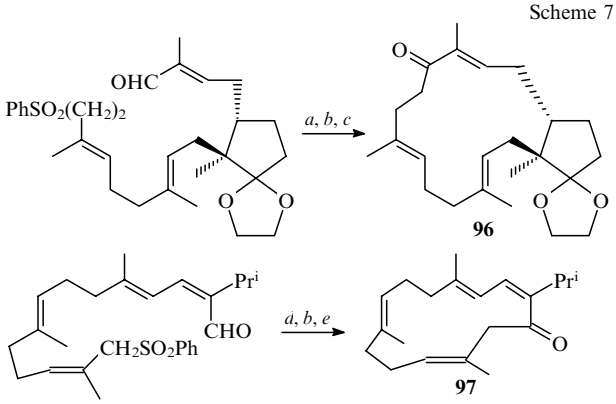
D-Glucose derivatives served as chiral pools for the construction of the segments A, B and C. The OH group at C(27) was obtained by transformation of the 2-hydroxysulfonyl grouping formed by the reaction of the aldehyde group of the segment B with the anion from the sulfone C, and the C(14)=C(15) double bond was formed according to Julia with the participation of the sulfonyl centre of the segment A. The stereoselective introduction of the methyl groups at C(13) in the segment A [145] and at C(29) in the segment C [147] was performed according to 'heteroconjugate addition' to α-silyl vinyl sulfones developed by Isobe and coworkers (this procedure will be considered in more detail in Section V.1). The final steps in the total synthesis of acid **94** with the construction of all its 17 chiral centres involve deprotection of the functional groups and conversion of 1,2-acetonide into the hydroxy acid.

The use of intramolecular reactions of α-sulfonyl carbanions with aldehydes [148–151] is exemplified by the synthesis of tetronolide **95**, which is the aglycone of the antitumor antibiotic tetrocarcin,[148,149] as well as by the construction of a bicyclo[13.3.0]octadecane core **96** for the synthesis of terpestacin and of a 14-membered core **97** for the preparation of sarcophytol A.[150] Syntheses of the compounds **96** and **97** involved oxidation of hydroxy groups to carbonyl groups followed by reductive removal of the sulfonyl group (Scheme 7), while the synthesis of the compound **95** additionally involved stereospecific reduction of the carbonyl group to the hydroxy group. Attempts to use this approach in the synthesis of the antitumour antibiotic lankacidin were unsuccessful. Apparently, this is associated with the use of the imidazolesulfonyl group.[152]



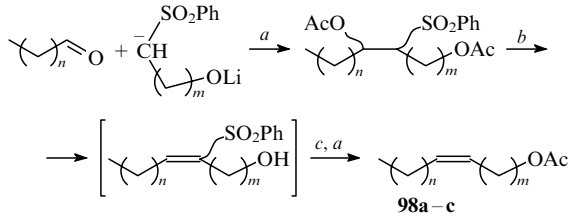
‡ It was believed [143] that acid **94** and its esters isolated from marine algae are toxins, which cause mortality of the gastroenteritis type as a result of diarrhetic shellfish poisoning.

Scheme 7

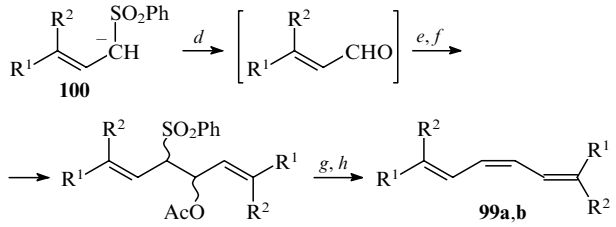


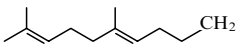
(*a*) LiHMDS, PhH, 25 °C; (*b*) oxidation; (*c*) Al/Hg; (*d*) LiHMDS, PhH, 22 °C, 5 min; (*e*) SmI_2, THF.

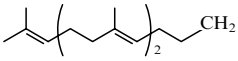
The *Z*-olefination method, which has also been developed by Julia,[37] is applied more rarely than the *E*-version. In this case, a mixture of diastereomeric acyloxy sulfones generated originally was treated with a strong base followed by desulfonylation of an intermediate (*Z*)-vinyl sulfone to form (*Z*)-alkene. This procedure was used for the preparation of components of the pheromones **98a–c** [98% of the (*Z*)-isomers],[37] dehydro-(*Z*)-12-squalene (**99a**) and (*Z*)-16-phytoene (**99b**) (in both cases, the selectivity was ~ 87%).[153] In the latter case, the aldehyde component was generated *in situ* by oxidation of a portion of the α-sulfonyl carbanions **100**.



$n = 2, m = 7$ (**a**); $n = 1, m = 8$ (**b**); $n = 3, m = 8$ (**c**).

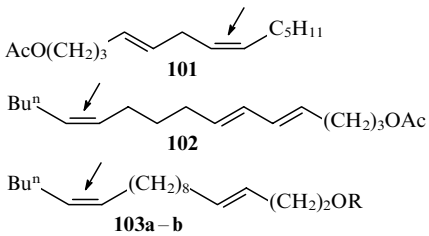


99a: R^1 = , R^2 = Me;

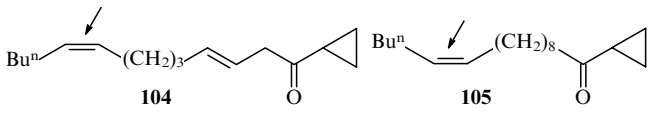
99b: R^1 = , R^2 = Me;

(*a*) Ac_2O; (*b*) NaOH; (*c*) $Na_2S_4O_6$; (*d*) MoO_5, Py, HMPT; (*e*) **100**; (*f*) Ac_2O, Et_3N; (*g*) NaH, THF; (*h*) Bu^nMgX, $Ni(acac)_2$.

Later on, Moiseenkov and Nefedov with coworkers [154–156] slightly improved the procedure for *Z*-olefination and applied it to the synthesis of trideca-(4*E*),(7*Z*)-dien-1-yl acetate (**101**) (the potato moth pheromone) [155] and (*E*,*Z*)- and (*E*,*E*,*Z*)-acetogenin



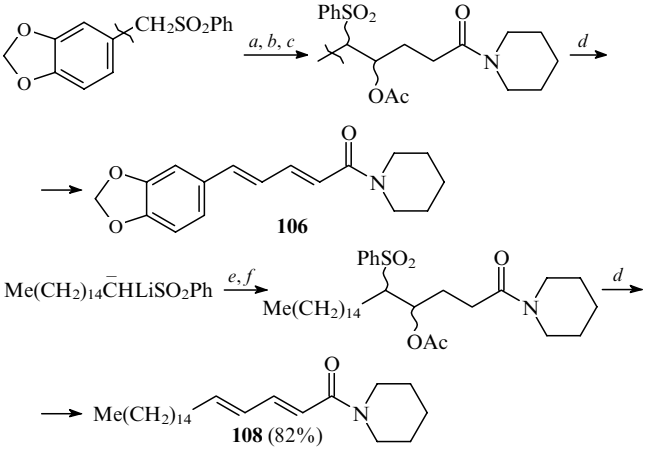
R = Ac (**a**), H (**b**).



104 **105**

pheromones **102** and **103a**,**b**.[155] The previously unknown cyclopropane ketones **104** and **105** served as the key compounds in the syntheses of the latter compounds (in the schemes, the double bonds formed with the use of the α-sulfonyl carbanions are indicated by arrows).

Otera and coworkers [157–160] elaborated a procedure for the transformation of ethers of 2-hydroxy sulfones through double elimination. This procedure extends the possibilities of application of reactions of sulfonyl carbanions with aldehydes. Initially, acyloxy or alkoxy groups in esters and ethers of 2-hydroxy sulfones are eliminated under the action of a strong base (generally, Bu^{t}OK) followed by dehydrosulfinylation of vinyl sulfone to form the acetylene bond. If allylic isomerisation can occur in the stage of generation of unsaturated sulfone, an *E*,*E*-diene system is formed. The latter procedure has been used [159] for the preparation of piperine **106**, which is one of the components of black pepper, starting from the aldehyde **107**. Yet another natural dienamide, *viz*., trichonine (**108**), was also prepared according to this procedure [85%, 10% and 5% of the (2*E*,4*E*)-, (2*E*,4*Z*)- and (2*Z*,4*E*)-isomers, respectively].[160]

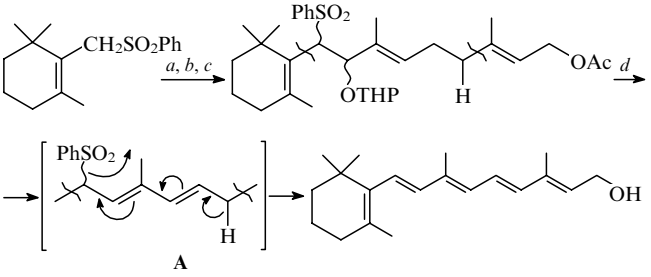


106

108 (82%)

(*a*) Bu^{n}Li; (*b*) OHC–(**107**); (*c*) Ac_2O; (*d*) Bu^{t}OK, Bu^{t}OH; (*e*) **107**; (*f*) Ac_2O, Py.

An ingenious convergent (C_{10} + C_{10}) scheme for the synthesis of vitamin A was also developed.[161, 162] Tetrahydropyran-2-yl ethers of 2-hydroxy sulfones proved to be the starting compounds of choice for this sequence of reactions. In the first step, the second allylic bond was established with respect to the sulfonyl group. Elimination of sulfinic acid from the intermediate **A** occurred with the participation of the remote allylic hydrogen atom at C(12). The resulting vitamin A contained > 85% of the all-*trans* isomer;



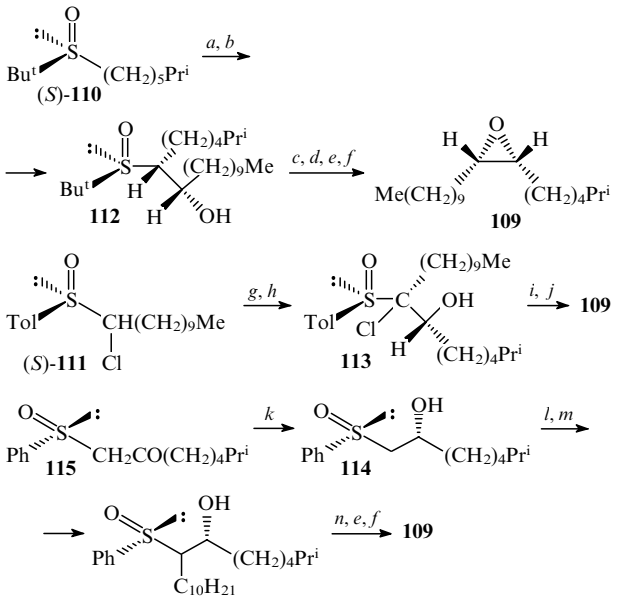
A

(*a*) Bu^{n}Li; (*b*) OHC–OAc; (*c*) O–, H^+; (*d*) MeOK, cyclo-C_6H_{12}, 35 °C.

this amount is substantially greater than those obtained with the use of other sulfonyl methods (see Section III.1.b).

b. Addition of α-sulfinyl carbanions to carbonyl groups of aldehydes and ketones

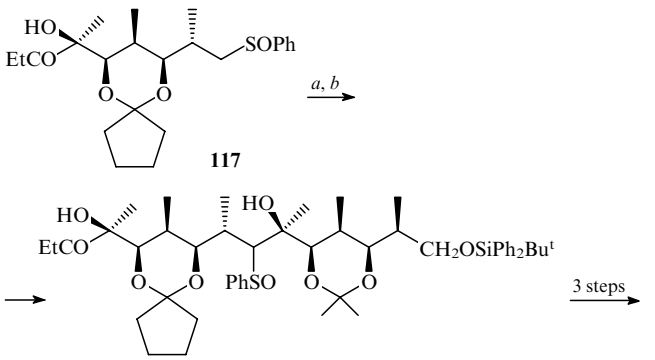
As mentioned above (Section II), epimeric mixtures of 2-hydroxy sulfoxides formed in the reactions of aldehydes with α-sulfinyl carbanions are rather rarely used in the synthesis of natural products. The synthesis of the enantiomerically pure pheromone (+)-(7*R*,8*S*)-disparlure (**109**) by the reaction of the corresponding aldehydes with enantiomerically pure (*S*)-*tert*-butyl 6-methylheptyl sulfoxide (**110**) [163] or (*S*)-α-chlorododecyl tolyl sulfoxide (**111**) is one of a few examples.[164]



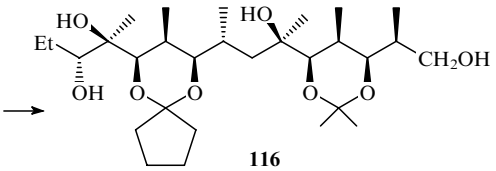
(*a*) Bu^{t}Li; (*b*) Me$(CH_2)_9$CHO (45%); (*c*) $SnCl_2$, AcCl; (*d*) $LiAlH_4$; (*e*) Me_3OBF_4; (*f*) NaOH; (*g*) LDA; (*h*) Pr$^i(CH_2)_4$CHO (39%); (*i*) Bu^{t}OK, Bu^{t}OH; (*j*) Bu^{n}Li, THF, −100 °C; (*k*) Bu^n_2AlH; (*l*) MeLi; (*m*) $C_{10}H_{21}I$; (*n*) Zn, Me_3SiCl.

The total yield of the compound **109** was low because hydroxy sulfoxides **112** and **113** were obtained as mixtures of diastereomers. The procedure with the use of enantiomerically pure 2-hydroxy sulfoxide **114**, which is prepared by stereoselective reduction of oxo sulfoxide **115**, is approximately twice as efficient.[165]

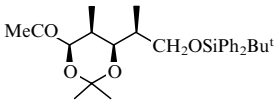
The ratio of the diastereomers in a mixture of 2-hydroxy sulfoxides depends on the nature of substituents in the initial sulfoxide and aldehyde. Stork and coworkers [166] reported that the reaction of sulfoxide **117** with ketone **118**, which was used in a rather simple synthesis of protected chiral polyol **116** containing all 10 asymmetric centres of the secoacid of the aglycone of erythromycin, afforded a mixture of 2-hydroxy sulfoxides containing 80% of the target epimer. Compound **119** was obtained [the C(1)–C(12) fragment with the required configuration; the

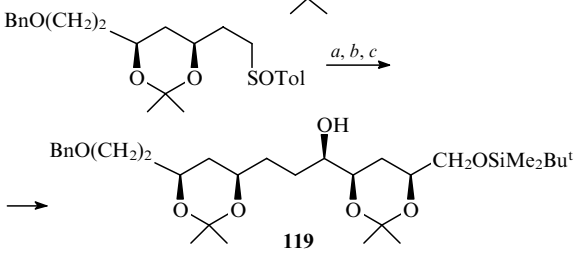


117

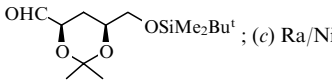


116

(*a*) 3 equiv. of LDA; (*b*)  (**118**).

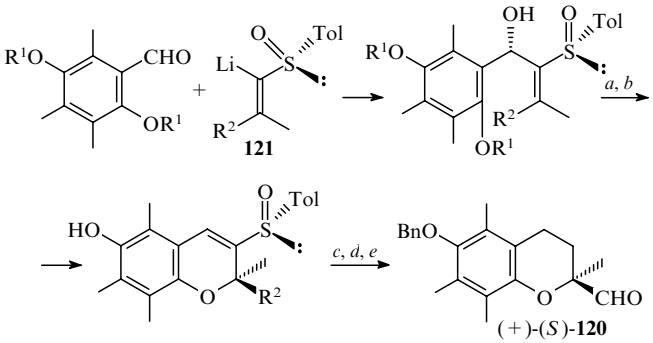


119

(*a*) Bu^nLi, THF; (*b*)  ; (*c*) Ra/Ni, Me_2CO.

admixture of another isomer was < 7%] in the course of construction of the aglycone of amphotericin B.[167]

The formation of the benzyl ether of (*S*)-chroman-2-carbaldehyde [(+)-(*S*)-**120**], which is the key intermediate in the synthesis of vitamin E,[168] proceeded exclusively stereo- and enantioselectively due apparently to the influence of the adjacent C=C bond on the carbanionic centre of lithiated sulfoxide **121**.

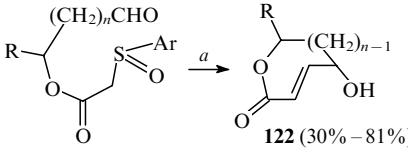


(+)-(*S*)-**120**

$R^1 = SiMe_2Bu^t$; $R^2 = (MeO)_2CH$; (*a*) Bu^n_4NF; (*b*) MeONa, MeOH; (*c*) Ra/Ni; (*d*) BnBr, K_2CO_3; (*e*) CF_3CO_2H, H_2O.

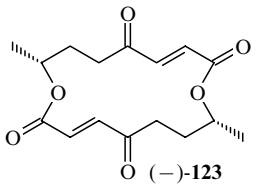
The stereo- and enantioselectivity of the reactions of α-sulfinyl carbanions with aldehydes increases in the presence of alkoxycarbonyl groups adjacent to the carbanionic centre.[12] This can be demonstrated by syntheses of enantiomerically pure pheromone lactams [169] and maytansin [170] exhibiting antitumour activity.

Macrocyclic lactones of the type **122**, in particular, 16-membered (−)-pyrenophorin (**123**), were synthesised [171] using intramolecular ring closure based on the reaction of the α-sulfinyl



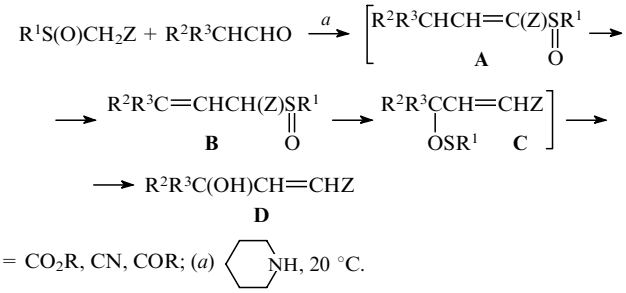
122 (30% – 81%)

Ar = 4-ClC_6H_4; R = H, Me; *n* = 8, 10; (*a*) , MeCN, 20 °C, 2 – 6 days.



(−)-**123**

carbanion with the aldehyde group. This reaction proceeds under very mild conditions and occurs according to a more complex mechanism rather than the ordinary 1,2-addition at the carbonyl group; this is typical of sulfoxides containing an electron-withdrawing group at the α-position. It is believed that this reaction proceeds *via* α,β-unsaturated sulfoxide **A**, which undergoes allylic isomerisation to sulfoxide **B** followed by the sulfoxide – sulfenate rearrangement to sulfenate **C**. In the presence of bases, the latter gave the reaction product **D**.[172 – 174]



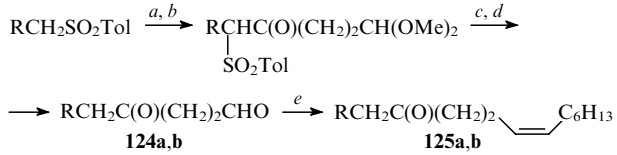
Z = CO_2R, CN, COR; (*a*) , 20 °C.

Since α-sulfinyl-substituted carbonyl compounds are most commonly used as the starting materials in this reaction, the latter is abbreviated to SPAC (Sulfoxide Piperidine and Carbonyl).

c. Reactions of α-sulfonyl carbanions with esters

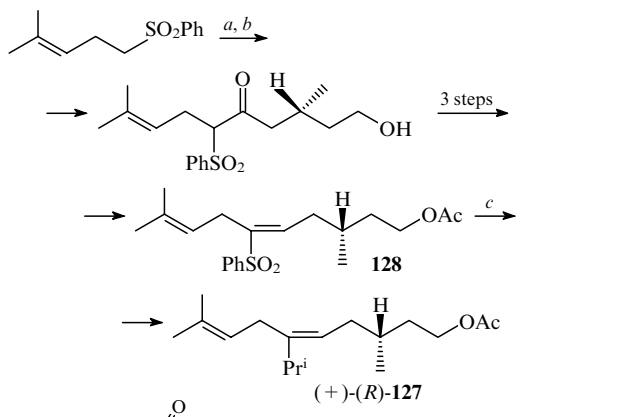
If a molecule contains both the aldehyde and ester groups, the former is the first to react with the α-sulfonyl carbanion, as is the case, for example, in the synthesis of alternaric acid [175] or the antibiotic A-8558G.[176]

In the absence of such competition, the reactions involving ester groups, including lactone groupings, proceed readily. Reactions of α-sulfonyl carbanions with esters were used for the construction of the intermediates **124a**,**b** in the syntheses of components of pheromones of peach moth, *viz*., of (*Z*)-eicos-13-en-10-one (**125a**) and (*Z*)-nonadec-12-en-9-one (**125b**).[177] Julia and coworkers [178] prepared the pheromone of yellow scale (**127**) starting from enantiomerically pure lactone (*R*)-**126**. In this synthesis, advantages were taken of yet another interesting reaction, which has been discovered in the same laboratory,[41] *viz*., the replacement of the sulfonyl group in the intermediate **128** under the action of isopropylmagnesium chloride in the presence of $FeCl_3$.



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

R = C_8H_{17} (**a**), C_7H_{15} (**b**); (*a*) LDA; (*b*) $MeO_2C(CH_2)_2CH(OMe)_2$; (*c*) Al/Hg; (*d*) 3% HCl, H_2O; (*e*) $C_6H_{13}C=PPh_3$.

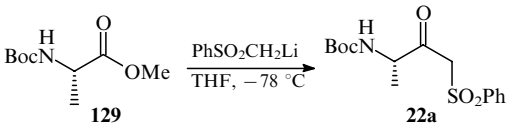


(+)-(*R*)-**127**

(*a*) Bu^nLi; (*b*)  [(*R*)-**126**]; (*c*) Pr^iMgCl, $FeCl_3$.

The reaction of the sulfonyl anion with the ester group served as the key step [179] in the stereocontrolled synthesis of pseudoannonacin A.

The oxo sulfone **22a**, which is the reaction product of lithiated methyl phenyl sulfoxide with protected alanine methyl ester **129**,[180] was used in the synthesis of isosteres of peptides.[80]



129 **22a**

The reaction of α-sulfonyl anions with esters was used as the key step in the construction of the macrolide brefeldin A (**130**) (which is related to prostaglandin and is a highly active fungicidal and antitumour drug,[181,182]) and of the corresponding secoacid **131**.[183]

The compound **130** was prepared both in racemic and optically active forms, whereas the acid **131** was obtained only in the optically active form. In all three cases, the lower branch was constructed *via* substituted oxo sulfones **132**–**134** using similar procedures (Scheme 8).

The phosphonate method was used for the construction of the (*E*)-C(10)=C(11) bond in brefeldin (**130**),[181,182] while Trost *et al.*[183] made use of the Julia methodology to form this bond in compound **131**§ following reduction of the oxo group in the intermediate **134** to the hydroxy group. The C(2)=C(3) bond and the chiral centre at C(4) were generated with the use of various procedures for the introduction of the sulfinyl group [181,183] followed by thermolysis. This methodology is described in more detail in Section IV.

The intramolecular reactions under consideration have also been used for the synthesis of polycyclic terpenoids, for example, trinoranastreptene [185] or precursors for guaiane terpenoids.[186,187] A general procedure for the synthesis of terpenoids with fused medium-sized rings involving intramolecular reactions of α-sulfonyl carbanions with esters was also proposed.[188]

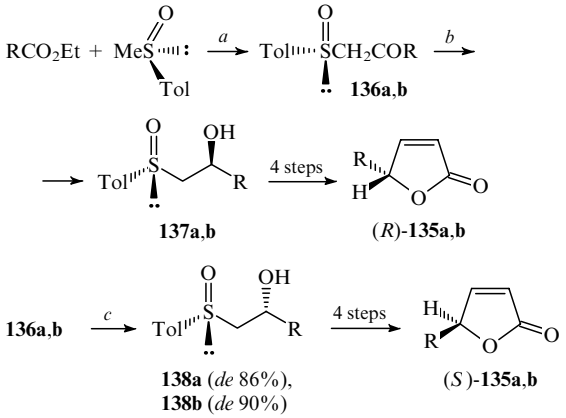
§An analogous procedure was used for the construction of the lower branch in more recent syntheses of brefeldin.[184]

d. Reactions of α-sulfinyl carbanions with esters

Owing to the development of enantioselective procedures for the reduction of oxo sulfoxides,[12,27] which can be readily prepared by reactions of α-sulfinyl carbanions with esters, enantiomerically pure chiral 2-hydroxy sulfoxides became readily accessible compounds and found wide use in asymmetric synthesis, including the preparation of biologically active compounds.[12]

Thus 4-substituted butenolides **135a**,**b** both with the *R*- and *S*-configurations of the asymmetric centre were prepared from the same oxo sulfoxide **136a** or **136b**.[189]

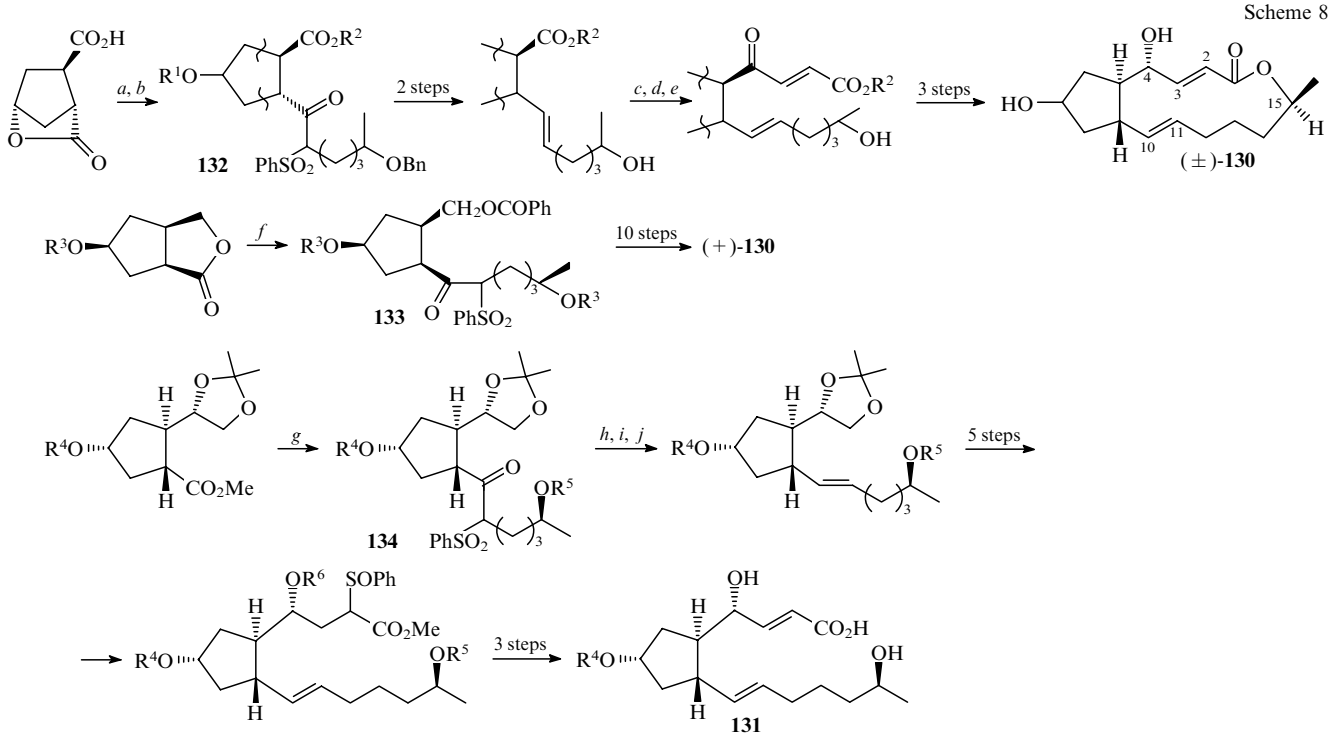
The high enantioselectivity in the synthesis of 2-hydroxy sulfoxides **137a**,**b**, which are required for the preparation of *R*-enantiomers of butenolides **135a**,**b**, was achieved by the addition of $ZnCl_2$ in the course of hydride reduction of the oxo sulfoxides **136a**,**b**. In this case, a rigid chelate complex of zinc



R = Bu^t (**a**), C_8H_{17} (**b**); (*a*) LDA; (*b*) Bu^i_2AlH, $ZnCl_2$; (*c*) Bu^i_2AlH.

involving both functional groups of the oxo sulfoxide was formed as a result of which the hydride attack occurred from the required side. Reduction of the oxo sulfoxides **136a**,**b** without addition of

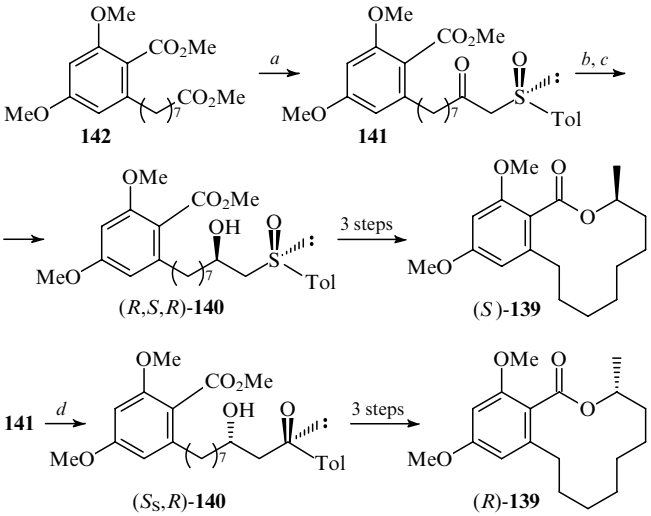
Scheme 8



R^1–R^5 are protective groups; (*a*) $PhSO_2\bar{C}H(CH_2)_3CH(OBn)Me$; (*b*) R^2Cl, $EtPr^i_2N$; (*c*) Me_2SO, NaOH; (*d*) $BrCH_2CO_2Me$; (*e*) Δ; (*f*) $PhSO_2\bar{C}H(CH_2)_3CH(OR^3)Me$; (*g*) $PhSO_2\bar{C}H(CH_2)_3CH(OR^5)Me$ (90%–96%); (*h*) $NaBH_4$; (*i*) Ac_2O; (*j*) Na/Hg, Na_2HPO_4 (65%).

$ZnCl_2$ afforded hydroxy sulfones **138a**,**b** with a high diasteroeselectivity. The latter were transformed into the *S*-enantiomers of the butenolides **135a**,**b**.

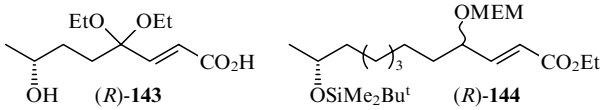
An analogous approach was used in the synthesis of macrolides for the preparation of enantiomerically pure diethers of lasiodiplodins, (*R*)- and (*S*)-**139**.[190] Epimeric 2-hydroxy sulfoxides **140** were synthesised by the reduction of oxo sulfoxide **141** in the presence or in the absence of $ZnCl_2$. It should be noted that when the compound **141** was prepared from diester **142** and the chiral sulfinyl anion, only the methoxycarbonyl group of the aliphatic chain was involved in the reaction, while the methoxycarbonyl group in the aromatic ring remained intact and was subsequently used for the construction of the macrolide lactone fragment.



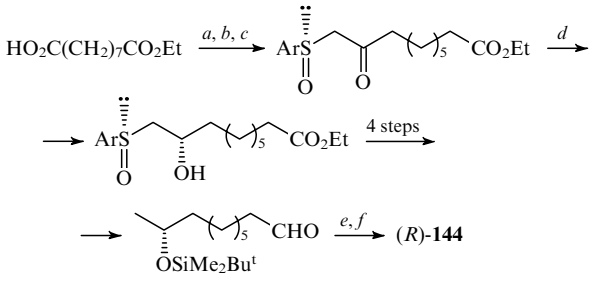
(*a*) 2.2 equiv. of $LiCH_2S(O)Tol$, THF, −78 °C; (*b*) $ZnCl_2$;

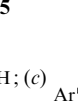
(*c*) Bu^i_2AlH, 20 °C (*de* > 95%); (*d*) Bu^i_2AlH, THF, −78 °C, (*de* 86%).

Chiral sulfinyl groups of 2-hydroxy sulfoxides served as inductors in diastereospecific syntheses of the protected secoacids **143** and **144** representing degradation products of the macrolides (*R*,*R*)-pyrenophorin and (*R*)-patulolide A, respectively.[191] The γ-hydroxy-α,β-unsaturated fragment of the secoacid **144** was constructed by the SPAC-type reaction of aldehyde **145** with the ethyl sulfinylacetate anion.[172–174]



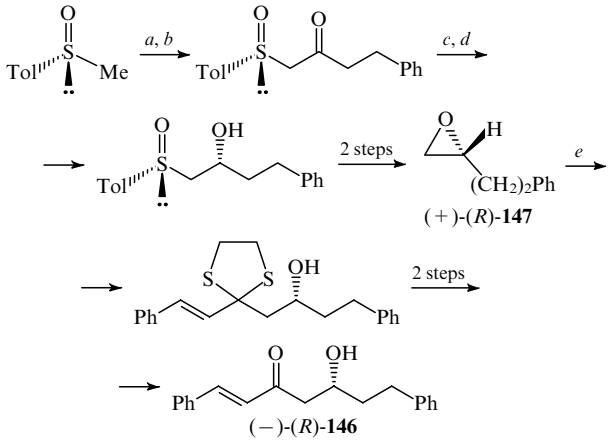
MEM is (2-methoxyethoxy)methyl.



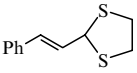
(*a*) $(COCl)_2$, PhH; (*b*) ; (*c*) ; (*d*) Bu^i_2AlH,

THF, −78 °C; (*e*) $PhS(O)CH_2CO_2Et$, , MeCN;
(*f*) $MeOCH_2CH_2OCH_2Cl$.

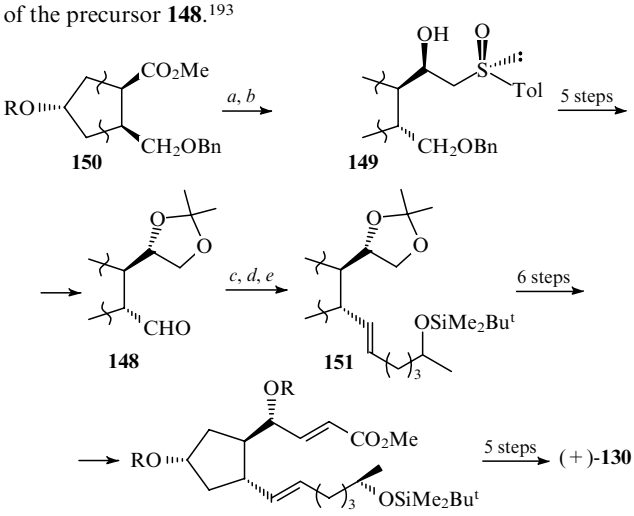
In the synthesis of (−)-(*R*)-yashabushiketol **146**, which is a rare representative of natural compounds containing a chiral hydroxy group at the β-position with respect to the carbonyl group, the hydroxysulfonyl intermediate was converted into the target ketol through the formation and cleavage of chiral epoxide **147**.[192]



(*a*) LDA, THF, −78 °C; (*b*) $Ph(CH_2)_2CO_2Me$ (87%), [(+)-(*R*)];

(*c*) $ZnCl_2$; (*d*) Bu^i_2AlH; (*e*) Bu^nLi, .

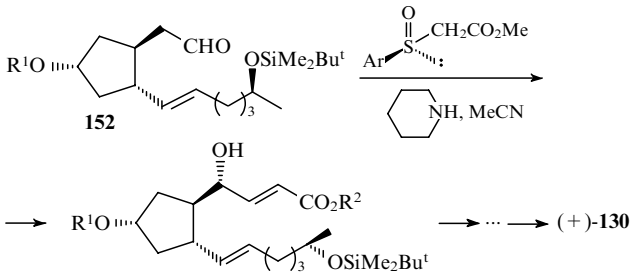
Syntheses of brefeldin A (**130**) performed predominantly with the use of sulfinyl-containing intermediates or auxiliary reagents are presented below. Solladie *et al.*[193] prepared a chiral cyclopentane precursor **148** with the use of enantiomerically pure 2-hydroxy sulfoxide **149**, which had been synthesised from substituted cyclopentane **150** in two steps. The formation of chiral centres at C(4) and C(15) in the brefeldin molecule was completely controlled by the sulfinyl group of the compound **149**. The (*E*)-C(10)=C(11) bond in the fragment **151** was formed using the Julia olefination with the participation of the aldehyde group of the precursor **148**.[193]



R = MEM; (*a*) 2 equiv. of $LiCH_2S(O)Tol$; (*b*) Bu^i_2AlH, $ZnCl_2$;

(*c*) ; (*d*) Ac_2O, Py; (*e*) Na/Hg (80%).

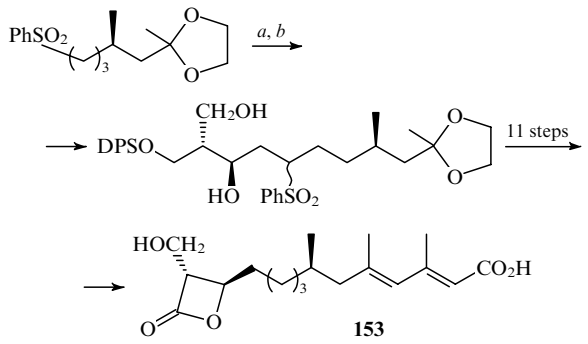
Two analogous schemes proposed by Corey (R^1 = MOM, Ar = Tol, R^2 = Me)[194] and Nokami (R^1 = MEM, Ar = 4-ClC_6H_4, R^2 = Et)[195] for the construction of the γ-hydroxy-α,β-unsaturated C(4)–C(15) fragment of the brefeldin molecule are based on a simplified approach using the SPAC reaction. These schemes involve the reaction of aldehyde **152** with chiral arylsulfonylacetates in the presence of piperidine as the key step.

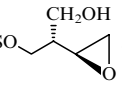


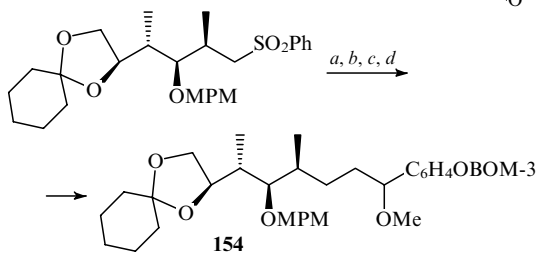
A new approach to the synthesis of carbohydrates [196] and to the preparation of (+)-nonactic and 8-*epi*-nonactic acids, which served as the starting compounds in the synthesis of the macrolide antibiotic nonactin,[197] was developed using 2-hydroxy sulfoxides as precursors. A modification of this method involving the reaction of homochiral sulfinyl ketones with Et_2AlCN made it possible to prepare alkylglycidic acids with *ee* 97% and a highly reactive hypoglycemic agent (+)-(*R*)-palmoxirate.[198]

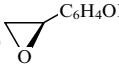
e. Reactions of α-sulfonyl carbanions with oxiranes

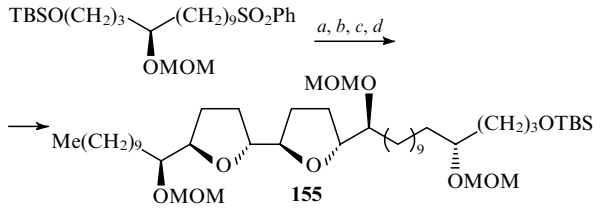
Reactions of α-sulfonyl carbanions with oxiranes give rise to γ-hydroxysulfones (see Scheme 1, path *d*). Both the intermolecular and intramolecular versions of these reactions are applied to the synthesis of natural compounds. These reactions are often used in the initial stages of syntheses of polyfunctional molecules, such as an inhibitor of cholesterol biosynthesis **153**,[199] compound

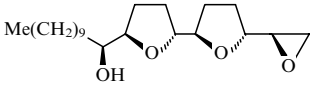


DPSO = Bu^tPh_2SiO; (*a*) EtMgBr; (*b*) Bu^nLi, DPSO .



MPM = 4-$MeOC_6H_4CH_2$; (*a*) 2 equiv. of Bu^nLi; (*b*) ; (*c*) Na/Hg; (*d*) MeI, KOH.

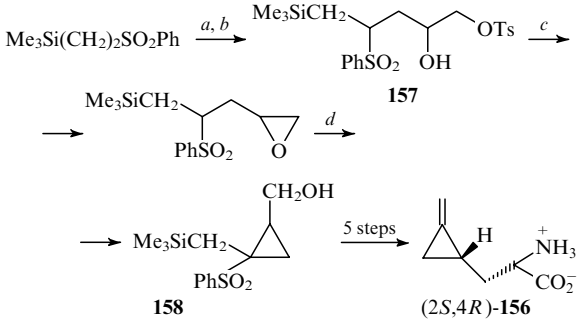


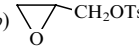
TBS = Bu^tMe_2Si; (*a*) Bu^nLi; (*b*) ,

DME, 20 °C; (*c*) MOMCl, Pr^i_2NEt; (*d*) Na/Hg, EtOH.

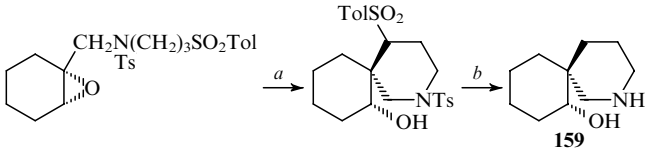
154 (which is a fragment of the tumour promoter debromoaplysiatoxin) [200] and the key fragment **155** for the construction of the antitumour acetogenin (+)-bullatacin.[201]

In the total synthesis of the amino acid hypoglycine A (**156**) containing a methylenecyclopropane fragment, epoxide-ring opening was employed twice.[202] The intermediate **157** was constructed by intermolecular reaction with an α-sulfonyl carbanion, whereas the three-membered ring in the key compound **158** was formed by an intramolecular reaction.

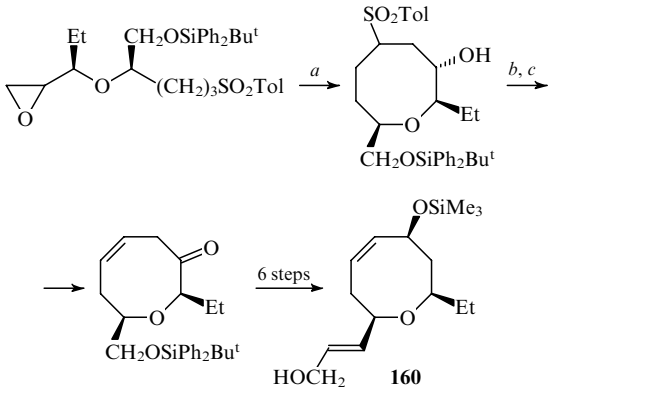


(*a*) Bu^nLi; (*b*) ; (*c*) K_2CO_3, MeOH, THF; (*d*) LDA, THF.

The synthesis of the enantiomerically pure piperidine alkaloid (+)-nitramine (**159**) [203] is yet another example of a ring closure through the intramolecular epoxide-ring opening. Oxirane was used for the preparation of the intermediate **160** in the formal synthesis of (+)-laurencin isolated from red algae.[204] The latter compound is the acetogenin with the Δ^4-oxocene skeleton.



(*a*) 2 equiv. of Bu^nLi (64%); (*b*) Na/Hg, Na_2HPO_4 (74%).



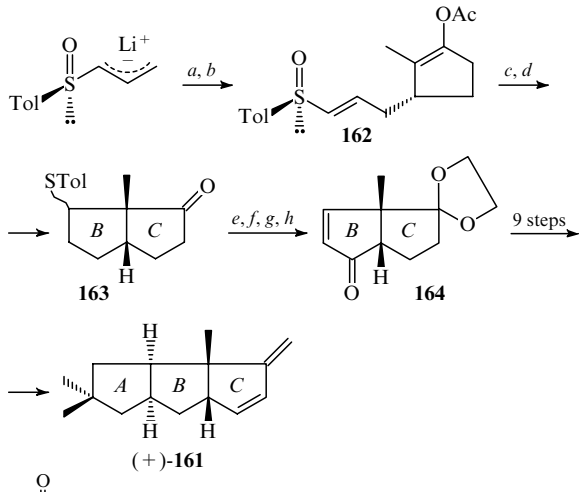
(*a*) LDA, THF, −65 °C; (*b*) oxidation; (*c*) diazabicycloundecene (DBU).

3. Reactions of α-sulfinyl and α-sulfonyl carbanions with C−C multiple bonds

a. Addition of α-sulfinyl carbanions to activated multiple bonds

The addition of α-sulfinyl carbanions to activated multiple bonds in the synthesis of natural compounds has been primarily studied by Hua and coworkers. The key step of these reactions involves the Michael addition of enantiomerically pure ambident carbanions, which are prepared from allylic sulfoxides or their nitrogen analogues, *viz*., α-sulfinyl ketimines, to double bonds most commonly activated by carbonyl groups. In classical investigations by Haynes and coworkers,[205, 206] it was demonstrated with model compounds that the reactions of lithiated allylic sulfoxides with substituted cyclopentenones occur exclusively as the stereoselective addition to the double bond, while the carbonyl group remains intact.

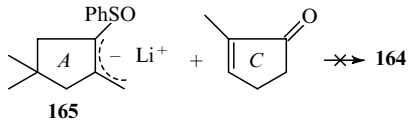
The first line of investigations performed by Hua and coworkers [207–211] was devoted to the addition of allylsulfinyl anions to enones. The total enantioselective synthesis of hirsutene (**161**) (a tricyclic biogenetic precursor of the polyquinanes coriolin and hirsutic acid ¶) is a typical example of this approach. In the first stage, the (*S*)-allylsulfinyltolyl carbanion added to 2-methylcyclopent-2-enone.[207] Reduction of the reaction product **162** to sulfide followed by cyclisation afforded substituted hexahydropentalenone **163** containing the rings *B* and *C* of hirsutene. The compound **163** was transformed in several steps and then the construction of the ring *A* was completed on the basis of bicyclic enone **164**. Attempts to perform this synthesis starting from the cyclic allylsulfinyl anion **165** failed [208] because the anions of cyclic sulfoxides of this type reacted with 2-methylcyclopent-2-enone to



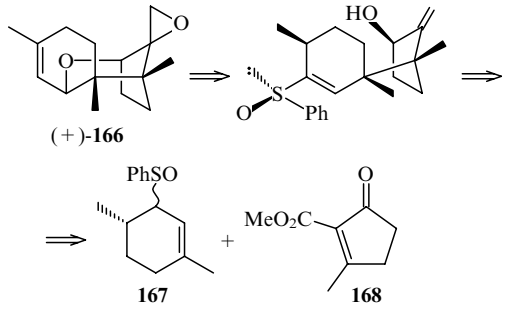
(*a*)  ; (*b*) AcCl; (*c*) Zn, AcOH; (*d*) $TiCl_4$, AcOH;

(*e*) $(HOCH_2)_2$, TsOH; (*f*) MCPBA; (*g*) diazabicyclononene (DBN);

(*h*) pyridinium chlorochromate (PCC).

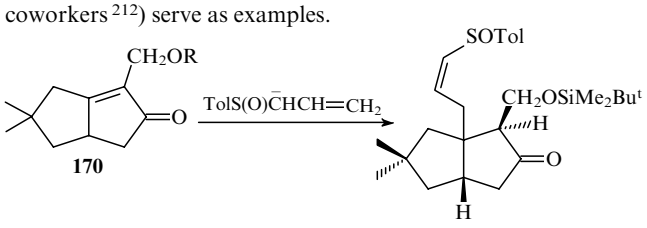


form only undesirable γ-adducts. However, the molecule of equally complicated (+)-12,13-epoxytrichocet-9-ene (**166**) possessing high biological activity was constructed starting from cyclic allylic sulfoxide **167** according to a procedure which was chosen based on retrosynthetic analysis.[209] In this case, cyclopentenone **168** additionally activated with the methoxycarbonyl group was used. An analogous, but somewhat more complicated procedure made it possible to perform the total synthesis of (+)-pentalenene related to antitumour pentalenolactone.[210]

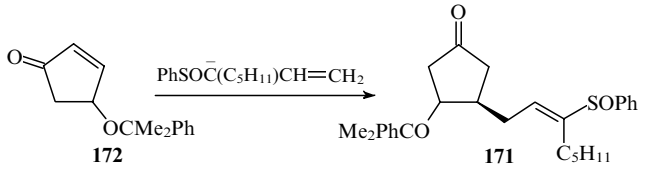


¶ Another version of the sulfonyl approach to polyquinanes is shown in Scheme 8.[184]

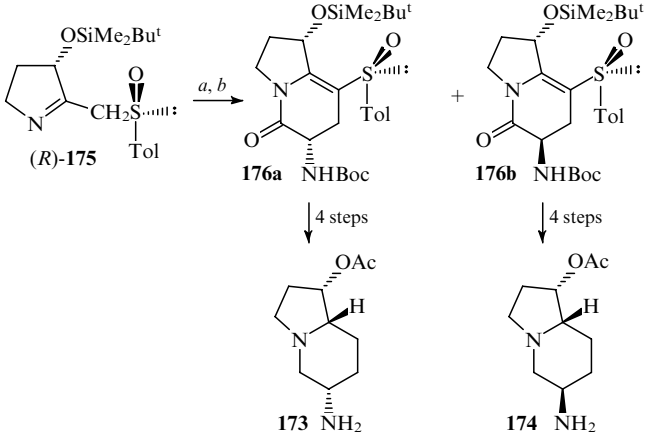
Bulky substituents in the cyclic enone do not hinder the stereoselective addition of the allylsulfinyl carbanion to the double bond. The preparation of compound **169**, which is the key intermediate in the synthesis of methyl ester of (±)-pentalenolactone E, from bicyclic enone **170** [211] or the construction of the prostaglandin precursor **171** from enone **172** (Pivnitskii and coworkers [212]) serve as examples.

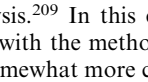


R = $SiMe_2Bu^t$.

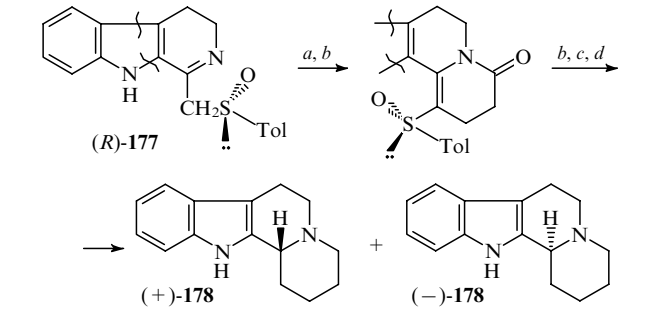


The second line of investigations performed by Hua and coworkers dealt with the construction of molecules of polycyclic alkaloids based on reactions of carbanions from chiral sulfinyl ketimines with α,β-unsaturated esters followed by (sometimes synchronous) cyclisation. Thus the total syntheses of parasympathomimetic agents (−)-slaframine (**173**) and (−)-6-*epi*-slaframine (**174**) were performed starting from the sulfoxide (*R*)-**175** anion and *N*-protected methyl 2-aminoacrylate.[213] The diastereomers **176a** and **176b** were obtained in a ratio of 3 : 2.



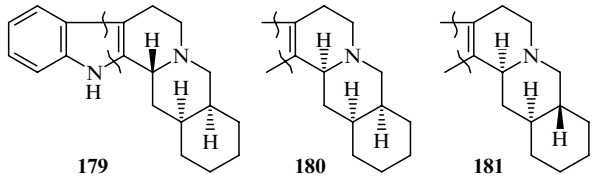
(*a*) Bu^nLi; (*b*)  .

An analogous reaction of the anion of tricyclic (*R*)-α-sulfinyl ketimine **177** with methyl acrylate was used for the preparation of epimers of indolo[2,3-*a*]quinolizidine, *viz*., (+)- and (−)-**178** (the ratio was 1 : 1.9). The key step in the synthesis of pentacyclic



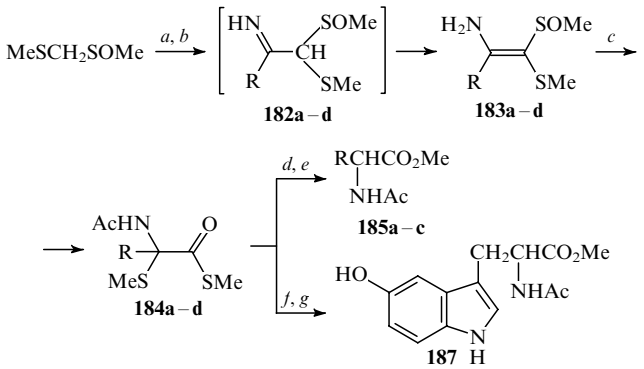
(*a*) LDA, ; (*b*) $NaCN \cdot BH_3$; (*c*) Ra/Ni; (*d*) $LiAlH_4$.

yohimbane alkaloids **179**–**181** involves the reaction of (*S*)-**177** with methoxycarbonylcyclohexene.[214]



179 **180** **181**

A general procedure for the synthesis of esters of racemic α-amino acids[215] is based on the addition of a carbanion generated from methyl methylthiomethyl sulfoxide at the C≡N bond of nitriles. The unstable adducts **182a**–**d** were isomerised through a prototropic shift to form enamino sulfoxides **183a**–**d**. The Pummerer rearrangement under the action of Ac_2O yielded compounds **184a**–**d** from which racemic phenylglycine, alanine and valine derivatives (**185a**–**c**, respectively) were prepared. Treatment of the compound **184d** with substituted phenylhydrazine hydrochloride **186** afforded racemic *N*-acetyl-5-hydroxytryptophan methyl ester (**187**).[215]

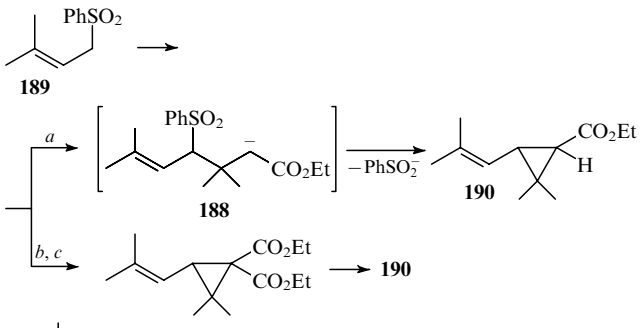


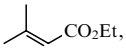
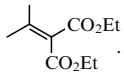
R = Ph (**a**), Me (**b**), Pr^i (**c**), $(MeO)_2CH(CH_2)_2$ (**d**); (*a*) NaH, THF, 20 °C; (*b*) RCN; (*c*) Ac_2O; (*d*) R = Ph, Me, Pr^i; MeOH, Et_3N; (*e*) Ra/Ni; (*f*) R = $(MeO)_2CH(CH_2)_2$, 4-$BnOC_6H_4NHNH_2 \cdot HCl$ (**186**); (*g*) Ra/Ni, EtOH.

b. Reactions of α-sulfonyl carbanions with activated C=C bonds

Specific transformations of anionic intermediates formed as a result of addition of α-sulfonyl anions to activated double bonds have found use in the synthesis of natural products.

Martel *et al.*[216] found that the addition of α-sulfonyl carbanions generated from 3-methylbut-2-en-1-yl sulfones to esters of α,β-unsaturated acids afforded cyclisation products of the initially anionic intermediates rather than the usual adducts. Thus the intermediate **188** formed from sulfone **189** and ethyl 3-methylbut-2-enoate is stabilised through cyclisation with 1,3-elimination of the sulfonyl anion to produce ethyl *trans*-chrysanthemate (**190**),[217]

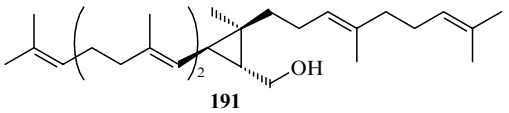


(*a*) , Bu^tOK, THF; (*b*) EtMgBr, $CuCl_2$, THF; (*c*) .

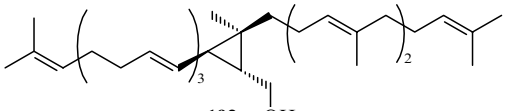
which is a component of natural insecticides, *viz*., pyrethroids. The optimum conditions for this reaction involve the use of components taken in a ratio sulfone : THF : Bu^tOK = 1 : 2 : 3. A large number of aryl and alkyl chrysanthemates were synthesised according to this procedure.[218] Some of these compounds are more active insecticides than natural pyrethroids.

Julia and coworkers[219] prepared the ester **190** by the reaction of the sulfone **189** with ethylmagnesium bromide and then with diethyl isopropylidenemalonate.

Later on, Campbell *et al.*[220] demonstrated that the reactions of anions generated from *E*-isomers of polyunsaturated sulfones with esters of polyunsaturated acids under conditions proposed by Martel and coworkers[218] were not accompanied by isomerisation of double bonds. This procedure was used for the preparation of the key compounds in the biosynthesis of terpenoids, *viz*., (+)-presqualene alcohol (**191**) and (+)-prephytoene alcohol (**192**). In this study, the structure of natural prephytoene alcohol was also established.

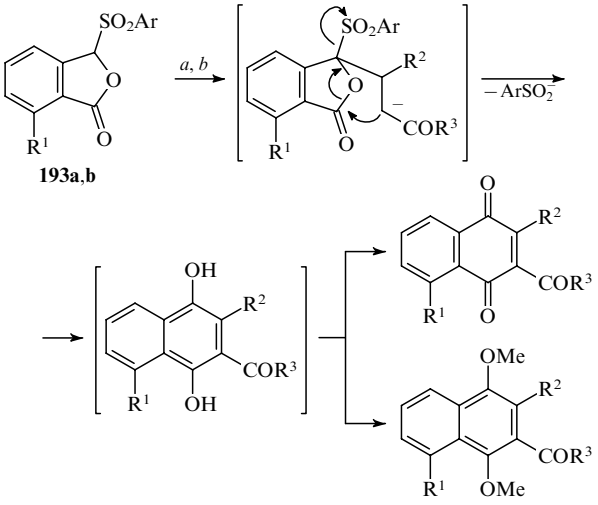


191



192

Reactions of α,β-unsaturated carbonyl compounds with α-sulfonyl carbanions generated from 3-oxo-1,3-dihydroisobenzofuran-1-yl phenyl sulfone (**193a**) ('phthalide sulfone') and its analogues play an important role in the synthesis of biologically active compounds. Hauser and Rhee[221] studied reactions of the model compounds **193a**,**b** with linear enones or α,β-unsaturated esters and demonstrated that the resulting carbanionic intermediate is stabilised in the course of cyclisation through elimination of the sulfinate anion. The resulting 1,4-dihydroxy-naphthalene is readily oxidised to naphthoquinone, whereas methylation prevents oxidation. Apparently, the driving force for this process is the formation of a thermodynamically favourable aromatic structure.

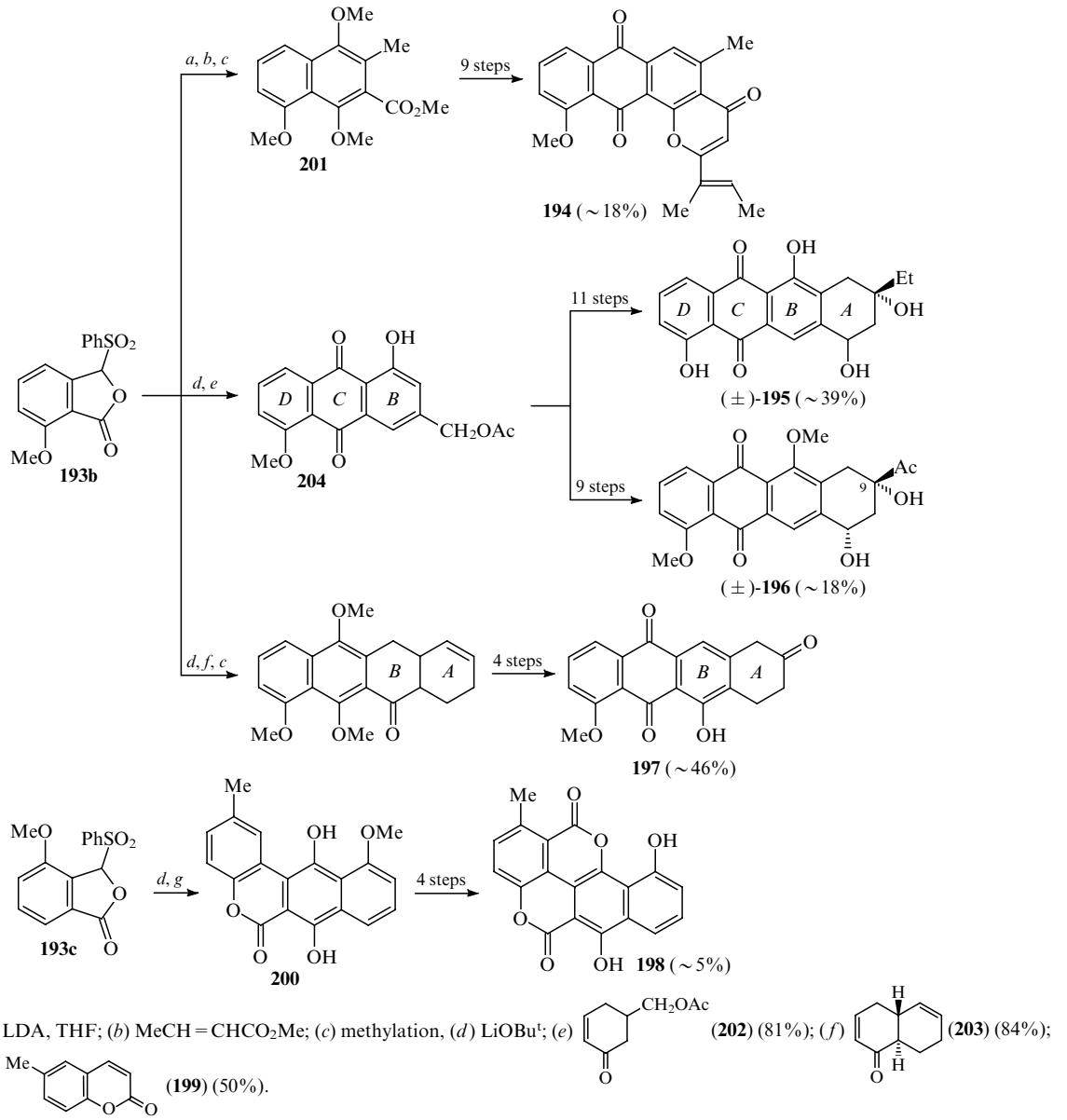


193a,**b**

R^1 = H (**a**), OMe (**b**); R^2 = H, Me; R^3 = OEt, Me; (*a*) LDA, THF, −78 °C; (*b*) $R^2CH=CHCOR^3$.

Owing to the possibilities of varying the structures of analogues of phthalide sulfone **193a** and, especially, of α,β-unsaturated carbonyl compounds, a flexible and rather versatile procedure was developed for stereoregular aromatic annelation, which is strictly controlled by the structures of the starting compounds. This method was successfully used by Hauser

Scheme 9



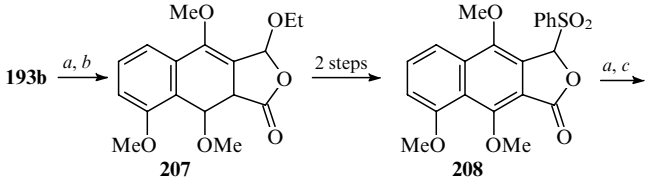
(*a*) LDA, THF; (*b*) MeCH=CHCO$_2$Me; (*c*) methylation, (*d*) LiOBu^t; (*e*) (**202**) (81%); (*f*) (**203**) (84%);

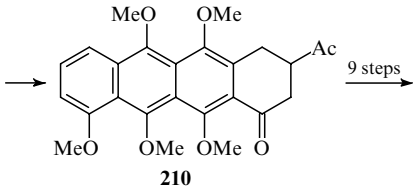
(*g*) (**199**) (50%).

et al.[222–234] and by other researchers [235–238] and assumed particular importance in the synthesis of aglycones of antitumour antibiotics, for example, compounds **194**–**198**. Selected stages of the total syntheses of these compounds are shown in Scheme 9. The key reactions of the anions prepared from phthalide sulfones **193** with α,β-unsaturated carbonyl compounds generally proceed with high yields. (The exception is the reaction of phthalide sulfone **193c** with lactone **199** producing compound **200** in a yield of only 50%.) However, the multistep character of subsequent transformations impairs the efficiency of the process as a whole. Thus in the total synthesis of the antibiotic of the anthra[1,2-*b*]pyran series, *viz*., *O*-methylkidamycinone **194**, starting from phthalide sulfone **193b** and methyl methacrylate,[222] a naphthalene derivative **201** was converted into the final antibiotic **194** in nine steps. The use of cyclic enones (such as compounds **202** or **203**) as Michael acceptors is much more efficient. Thus the reaction of phthalide sulfone **193b** with 5-acetoxymethylcyclohex-2-enone (**202**) afforded the anthraquinone derivative **204** in 81% yield.[223, 224] Despite the fact that 11 steps were required to build up the ring *A* and to obtain the final product, *viz*., γ-citromycinone (±)-**195**, the total yield was ~ 39%. A comparatively low yield of (±)-dimethyl-6-deoxydaunomycin (±)-**196** prepared from the same precursor **204** was attributed to the formation of an admixture of its C(9)-epimer in the final stage.[224] The use of the simplest bicyclic enone **203** made it possible to perform a five-step synthesis of a tetracyclic triketone **197** in good yield. The latter is a versatile precursor for the preparation of daunomycinones.[225]

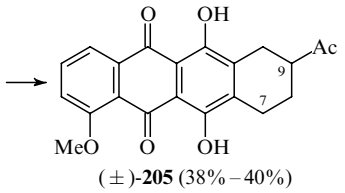
An exceptional interest in the synthesis of antibiotics of the anthracyclinone series (see, for example, Ref. 239) arises from their high biological activity. Thus since the 1970s [239] to the present, daunomycin and adrianomycin obtainable by microbiological methods find use in medicine as antitumour drugs.[240]

Hauser *et al.*[227, 228] have developed additional ways of improving procedures with the use of monocyclic enones. Thus the convergent synthesis of (±)-7,9-dideoxydaunomycinone (**205**) was performed in a rather high yield.[227] In the first stage, the anion generated from phthalide sulfone **193b** reacted with 5-ethoxy-2,5-dihydrofuran-2-one (**206**). Then the reaction product **207** was converted into phthalide sulfone **208** in two steps. The subsequent reaction of the anion generated from **208** with 5-acetylcyclohex-2-enone **209** afforded the tetracyclic product **210**, which was converted into the target 7,9-dideoxydaunomycinone (±)-**205**.

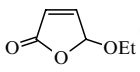
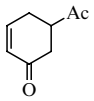




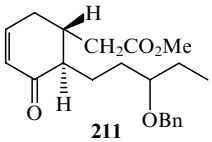
210



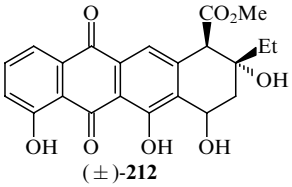
(±)-**205** (38%–40%)

(*a*) LDA; (*b*)  (**206**); (*c*)  (**209**).

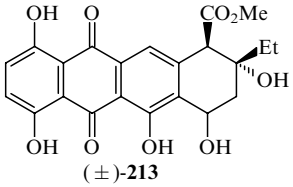
Disubstituted cyclohexenone **211** served as the starting compound in the synthesis of racemic aklavinone (**212**) and pyrromycinone (**213**).[228]



211

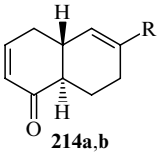


(±)-**212**

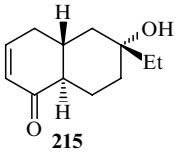


(±)-**213**

Further progress in the application of bicyclic enones to annelation was achieved [229–234] once procedures for the synthesis of compounds **214a**,**b** and **215**, which contain substituents corresponding to the substituents in the rings *A* of anthracyclinones, had been developed.



214a,**b**

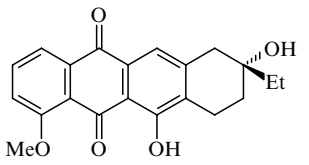


215

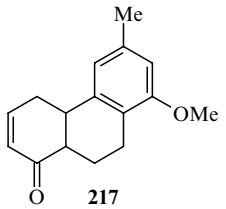
R = Ac (**a**), Et (**b**).

Thus a new more efficient procedure was proposed [232] for the preparation of racemic aklavinone [(±)-**212**] starting from readily available compounds, *viz*., phthalide sulfone **193b** and enone **214b** (the total yield was ~ 17% with respect to 2-ethylacrolein used as the starting compound for the preparation of the enone **214b**). The first regio- and enantiospecific synthesis of a compound of the anthracyclinone series, *viz*., the preparation of (−)-(*R*)-7,11-dideoxy-13-deoxydaunomycinone (**216**) from the anion of phthalide sulfone **193d** and enantiomerically pure enone **215**, was performed.[233]

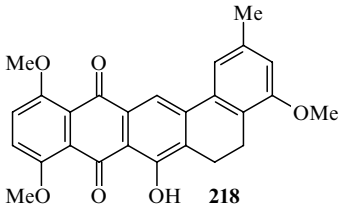
Compound (±)-**218** possessing the nonlinear benzo-[*a*]naphthacene skeleton was synthesised starting from phthalide sulfone **193b** and tricyclic enone **217**.[234] In this study, yet another problem was solved. Thus the nature and arrangement of the substituents in the *A* rings of the natural pigments G2N and G2A were established.



(−)-(*R*)-**216**

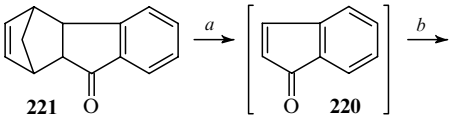


217

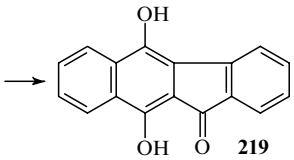


218

The procedure for annelation proposed by Hauser has been extended to the preparation of antibiotics containing five-membered rings. This procedure was used for the synthesis of compound **219**, which is a close analogue of kinafluorenone.[235] For this purpose, the anion prepared from **193a** was brought into reaction with indenone **220**, which had been synthesised *in situ* by flash pyrolysis of its adduct with cyclopentadiene (**221**).



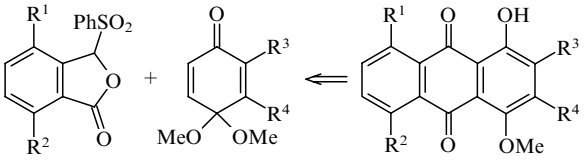
221 **220**



219

(*a*) flash pyrolysis (>95%); (*b*) **193a**, $LiOBu^t$, −60 °C (73%).

Syntheses of natural 1,4-dihydroxyanthraquinones **222** using reactions of the anions generated from phthalide sulfones **223** with monoketals of substituted benzoquinones **224** provide other examples of annelation according to Hauser.[236]



223 **224** **222**

R^1–R^4 = Alk.

(±)-Daunomycinone was synthesised analogously from the sulfone **193a** and analogues of benzoquinone monoketals **224**.[237] The reaction of the anion of 5,6-methylenedioxyphthalide sulfone with methyl methacrylate afforded functionally substituted naphthalenes necessary for the synthesis of lignins.[238]

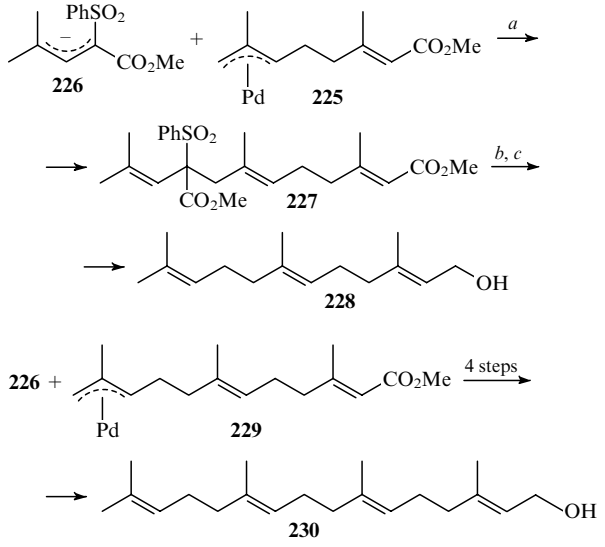
c. π-Allylic alkylation with α-sulfonyl carbanions

Among processes with the use of Pd(0) complexes, π-allylic alkylation occupies a prominent place. In these reactions, soft nucleophiles react with allylic Pd(0) complexes as the cationoid components. These complexes can be prepared from allylic compounds containing good leaving groups, such as acyloxy or sulfonyl groups. This procedure became popular due to mild reaction conditions and high stereospecificity. The reaction can be performed either with the use of stoichiometric amounts of a Pd(0) complex in a basic medium or as a catalytic process in neutral or

weakly basic media. In the latter case, the Pd(0) complex can be prepared *in situ* from a Pd^{2+} salt. The introduction of phosphine or other ligands allows one to change the regio- and stereochemistry of the reaction (see the reviews [241–243]).

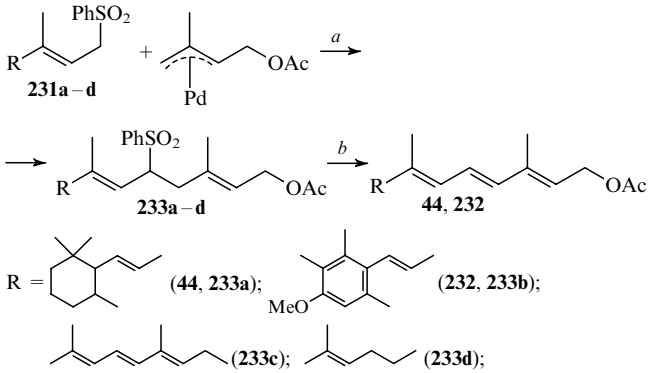
In these processes, α-sulfonyl carbanions activated with the adjacent oxo, carboxy or sulfonyl groups or (more rarely) with the allylic bond are widely used along with other C-nucleophiles.

Trost and Weber [244] were the first to use this procedure for the synthesis of biologically active compounds and they transformed simple terpenoids into more complex compounds. The reaction of an allylic palladium complex prepared from methyl geraniate **225** with the ambident anion, which has been synthesised by the reaction of methyl 4-methlyl-2-phenylsulfonylbut-3-enoate (**226**) with NaH in THF, followed by transformation of the reaction product **227** afforded farnesol (**228**). An analogous reaction of the anion **226** with the allylic Pd(0) complex **229** afforded all-*trans*-geranylgeraniol (**230**).



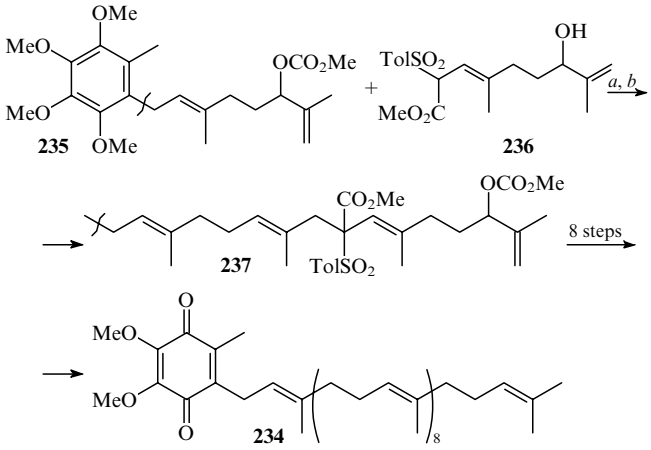
(*a*) dppe is 1,2-bis(diphenylphosphino)ethane, THF, 25 °C (65%); (*b*) Bu^i_2AlH, MePh, −40 °C; (*c*) Li, $EtNH_2$ −78 °C.

A π-allylic version of the synthesis of retinol acetate (**44**, 67% of the *trans* isomer) was carried out [245] using the reaction of the anion generated from substituted allylic sulfone **231a** with the Pd(0) prenylacetate complex in the presence of an excess of triphenylphosphine. Its aromatic analogue **232** exhibiting antitumour activity was synthesised analogously. In the case of sulfones containing acyclic substituents R, the reactions stopped at the stage of formation of compounds **233c**,**d**.



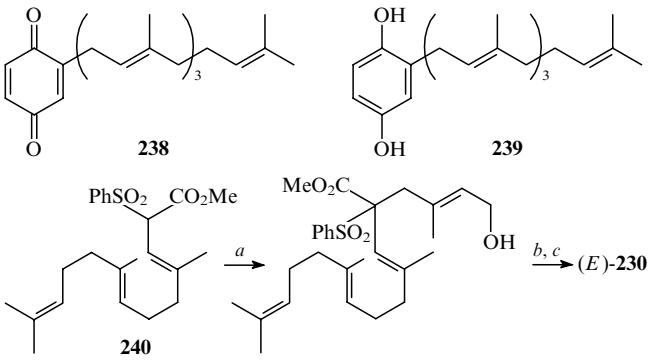
(*a*) NaH, THF, PPh_3; (*b*) EtONa, EtOH.

Tsuji was the first to propose a catalytic version of this reaction [242, 246] and he recommended to employ *O*-methoxycarbonyl as the leaving group. This procedure was used for the preparation [247] of ubiquinone-10 (**234**), which is the coenzyme Q_{10} exhibiting cardiovascular activity, and its analogues. Compound **235** containing an allylic *O*-methoxycarbonyl group was brought into the reaction with the anion of an activated sulfone **236** containing an allylic hydroxy group, which was employed to form a new allylic *O*-methoxycarbonyl group in the intermediate **237**. The iterative reaction with the sulfone **236** and the formation of the MeO_2CO group made it possible to build up a polyunsaturated chain. The last stage of the process involved oxidation of the aromatic ring to the quinoid one.



(*a*) 5 mol. % of $Pd(PPh_3)_4$, THF; (*b*) MeOCOCl, $Et_2NC_6H_4$, Py, PhH.

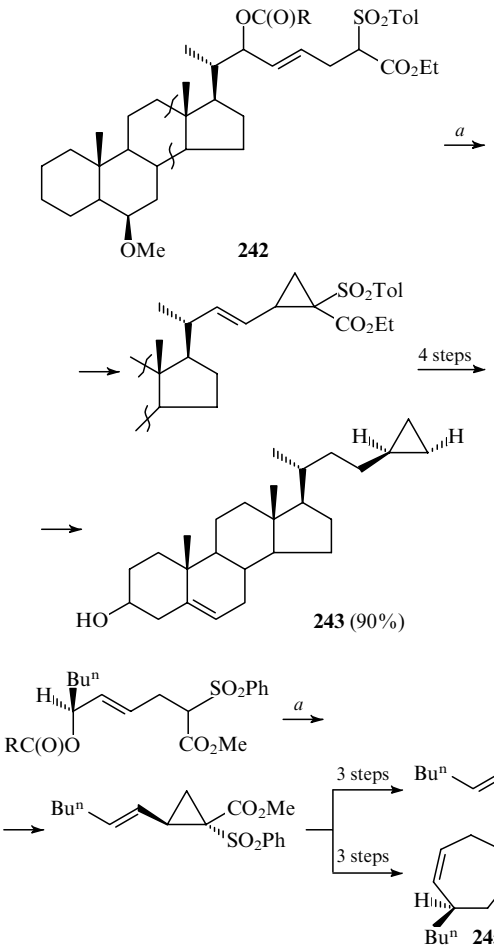
Natural compounds exibiting analgesic activity, *viz*., tetraprenylquinone **238** and -quinol **239**, were prepared analogously.[248] The synthesis of *trans*,*trans*,*trans*-geranylgeraniol (**230**) from α-sulfonyl-substituted ester **240** and oxirane **241** was also performed using the catalytic version.[249] In this scheme, the metal-complex catalysis was used for the regiospecific opening of the oxirane ring.



(*a*)  (**241**), 5 mol. % of $Pd(PPh_3)_4$, THF, 25 °C (90%); (*b*) PhSH, Cs_2CO_3; (*c*) $LiBHEt_3$, THF, 5 mol. % of $PdCl_2$(dppp) [dppp is 1,3-bis(diphenylphosphino)propane] (100% *E*).

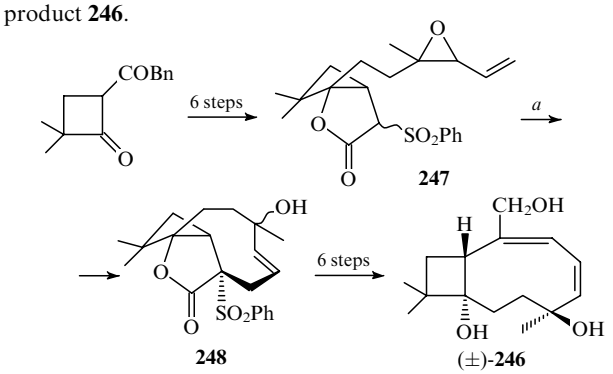
The catalytic procedure has assumed utmost importance in intramolecular cyclisations, which offers outstanding possibilities for the construction (including diastereocontrol) of carbo- and heterocycles (see the reviews [250, 251]).

Thus the diastereoselective introduction of a cyclopropane ring into the steroid molecule was performed by the reaction of the carbanion generated from the sulfonyl(ethoxycarbonyl) fragment of compound **242** with the π-allylic Pd complex generated in the same molecule. The final product, *viz*., glaucasterol (**243**), contains a three-membered ring at C(24)–C(25).[252] 2-(Hex-1-en-1-yl)-1-methoxycarbonyl-1-phenylsulfonylcyclopropane was synthesised analogously. The latter compound served as the starting material for the synthesis of dictyopterene A (**244**) containing a three-membered ring and of a seven-membered dictyopterene B (**245**).[253]



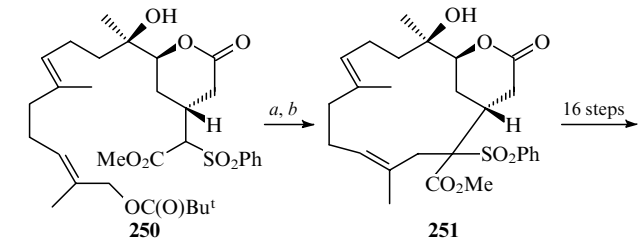
R = 2,4-$Cl_2C_6H_3$; (*a*) DBU, THF, $Pd(dppe)_2$.

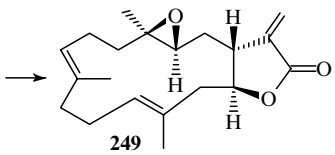
Examples of the construction of more complex carbocycles are considered below. Bicyclic (±)-punctaporonin B (**246**) was synthesised in 12 steps starting from substituted cyclobutanone.[254] The palladium-catalysed reaction of the allyloxirane fragment of compound **247** with the activated α-sulfonyllactone fragment afforded the intermediate **248**, which was converted into the target product **246**.



(*a*) $Pd(Ph_3P)_4$, dppe, THF, 60 °C.

In the synthesis of 14-membered (±)-isolobophytolide (**249**), the methoxycarbonyl(phenylsulfonyl) carbanion served as the anionic component of the initial compound **250** and the pivalate

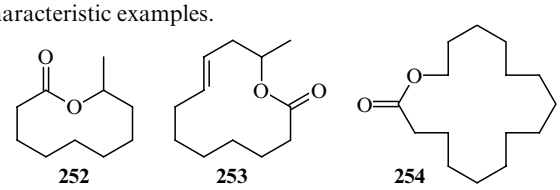




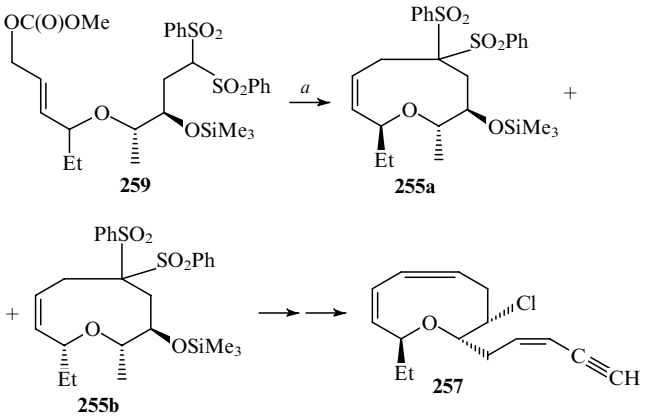
(*a*) *O*,*N*-bis(trimethylsilyl)acetamide, $Pd(Ph_3P)_4$, dppe, THF; (*b*) Bu^n_4NF.

anion served as the leaving group. The resulting macrocyclic intermediate **251** was transformed into the target product **249**.[255]

Cyclisation catalysed by palladium complexes is of particular importance for the preparation of medium-size heterocycles, which are widespread in nature, but which have previously been difficultly accessible.[256–261] The construction of the key intermediates in the synthesis of natural lactones, *viz*., 10-membered phoracantholide (**252**),[256] 12-membered recifeiolide (**253**)[257] and 16-membered exaltolide (**254**),[258] from acyclic precursors serve as characteristic examples.

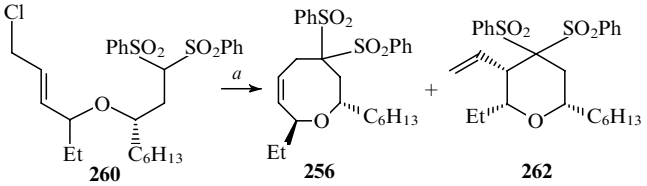


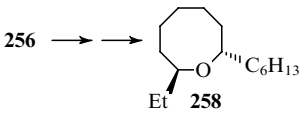
The construction of nine- and eight-membered functionally substituted cyclic ethers **255a**,**b** and **256**, which are precursors of oxonins **257** and **258** isolated from the algae *Laurencia*, presented a substantially more difficult problem. The regio- and stereochemical direction of cyclisation of the acyclic precursors **259** and **260** is determined by the site of attack of the anion generated from the sulfone on the allyl palladium fragment and depends on the nature of the leaving group and, especially, on the ligand used. Thus the methoxycarbonyloxy group and triethyl phosphite appeared to be the best leaving group and ligand, respectively, for the ring closure in compound **259** required for the construction of the skeleton of nine-membered brasilenyne (**257**). The ratio of the cyclisation products, *viz*., *trans*–*trans*-**255a** (similar to the natural isomer) and undesirable *cis*–*trans*-**255b**, was 14 : 1.[259]

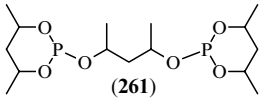


(*a*) 5 mol. % of $Pd_2(dba)_3$ (dba is dibenzylideneacetone), 50 mol. % of $P(OEt)_3$, $CHCl_3$, THF.

A chloride anion and bisphosphite **261** appeared to be the best leaving group and ligand, respectively, in the stereoconvergent synthesis of compound **256**, which is a precursor of enantiomerically pure (−)-lauthisan (**258**).[260] Because of the formation of

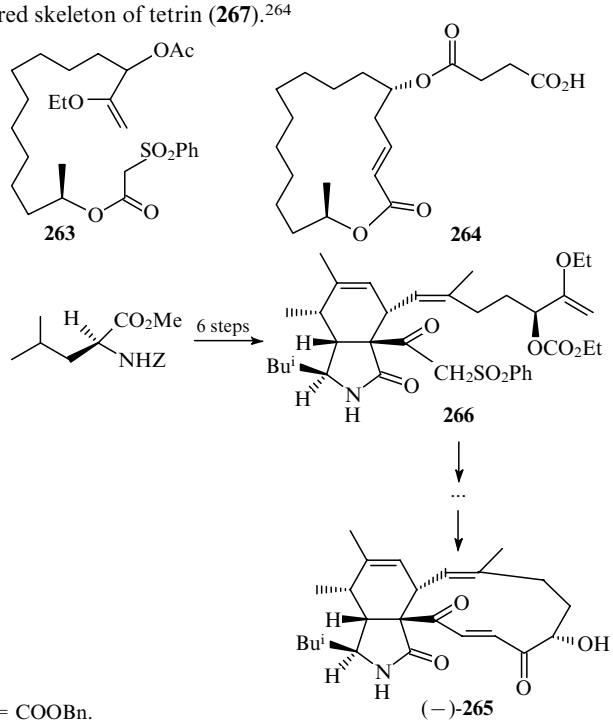




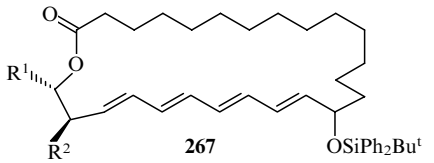
(*a*) 5 mol. % of $Pd_2(dba)_3$, $CHCl_3$, KH,  (**261**), THF – dioxane, 80 °C.

the six-membered cyclic products **262**, the yield of the eight-membered reaction product **256** was only 70%.[260]

The construction of more complex heterocycles, *viz*., macrolides of the cytochalasin series, which possess high membrane-transport and a broad spectrum of other biological activities, presented a particularly interesting problem. Trost and coworkers performed a 12-step synthesis of the model antibiotic A 22667718 (**264**) starting from undecynal *via* the intermediate **263**,[262] a 9-step synthesis of (−)-aspochalasin [(−)-**265**] from *N*-protected leucine ester *via* the precursor **266**[263] and construction of the 26-membered skeleton of tetrin (**267**).[264]

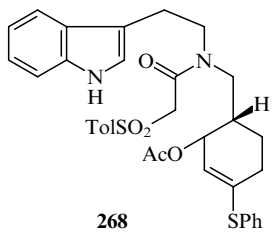


Z = COOBn.

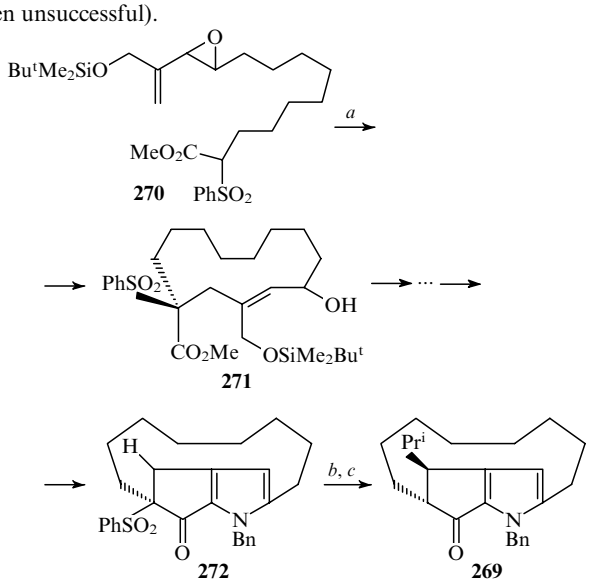


R^1, R^2 = H, Me.

A precursor of pentacyclic alloyohimbone was synthesised analogously using the Pd(0)-catalysed ring closure in compound **268** with the acetoxy group serving as the leaving group.[265]



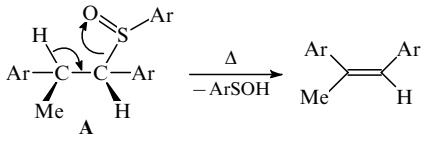
A 12-step synthesis of the skeleton of the macrocyclic antitumour compound roseophillin (**269**) is yet another example of the high efficiency of palladium-catalysed cyclisation.[266] Acyclic compound **270** was transformed into the cyclic precursor **271** by the reaction of the methoxycarbonylsulfonylfragment with the allylpalladium complex incorporating the oxirane ring. The groups that activate the anionic centre were not removed following cyclisation and they were employed in subsequent transformations. Thus the ester group was used in the construction of tricyclic sulfone **272**. The benzenesulfonyl group in compound **272** is homoallylic and hence it was readily eliminated in the presence of Bu^tOK as sulfinic acid. Simultaneously, the isopropyl group was attached to the adjacent carbon atom by the action of dimethylisopropylzincmagnesium chloride on the C=C bond of the enone formed (attempts to use more traditional cuprates have been unsuccessful).



(*a*) [Pd(0)] (85%); (*b*) an excess of Bu^tOK; (*c*) $Me_2Pr^iZnMgCl$ (51%).

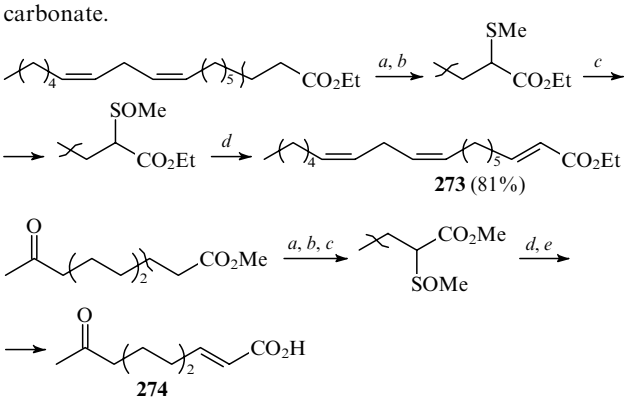
IV. Formation of C=C bonds by thermolysis of sulfoxides

In many cases, thermal elimination of sulfenic acid from sulfoxides leads to the formation of (*E*)-C=C bonds. In 1960, Kingsbury and Cram[267] suggested that at moderate temperatures this process occurs according to a concerted mechanism *via* a transition state **A**. More recently,[268] this suggestion was confirmed by kinetic studies.



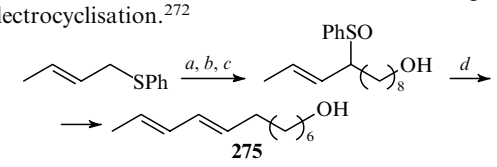
A modification of this reaction proposed by Trost *et al*.[33–35,40,269,270] has been widely used predominantly for the introduction of (*E*)-C=C bonds at the α,β-position with respect to the carbonyl groups of ketones or esters. This procedure is convenient because a one-pot sulfenylation – sulfinylation – dehydrosulfenylation sequence can be used. Initially, an alkylthio group is introduced at the α-position with respect to the electron-withdrawing group under the action of disulfide in a basic medium. The alkylthio group is readily oxidised to the sulfinyl group, which is removed by thermolysis, most commonly, upon boiling in toluene. All steps are carried out under mild conditions; the presence of functional groups in the molecule does not hinder this process. The temperature required for dehydrosulfenylation depends on the substrate structure. Sometimes, it is necessary to add a thiophilic scavenger. This method for the directed introduction of (*E*)-C=C bonds advantageously supplements the Julia olefination and dehydrosulfinylation of homoallylic sulfones.

The synthesis of components of bee pheromones is the first example of the use of the sulfenylation – sulfinylation – dehydrosulfenylation sequence for the preparation of natural compounds.[270] Ethyl linoleate served as the starting compound for the preparation of the attractant **273**. (*E*)-9-Oxodec-2-enoic acid (**274**) (the queen substance, *viz*., the attractant of the queen bee and simultaneously the pheromone of termites) was prepared from an azelaic acid ester. In both cases, thermolysis was performed by boiling in toluene with the addition of calcium carbonate.

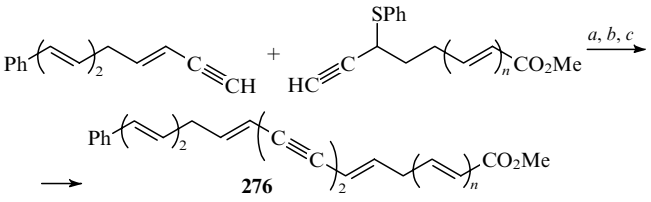


(*a*) cyclo-$C_6H_{11}NPr^iLi$; (*b*) MeSSMe, THF, HMPT, −78 °C; (*c*) oxidation; (*d*) PhMe, $CaCO_3$, 110 °C, 16 h; (*e*) H_3O^+.

The sulfinyl groups located at the allylic or propargyl positions are also readily eliminated under conditions of thermolysis because the resulting conjugated diene and enyne systems are thermodynamically favourable. This procedure was used for the preparation of dodeca-8,10-dien-1-ol (**275**)[271] (the major component of the pheromone of apple fruit moth) and polyunsaturated esters **276**, which are the key compounds in the synthesis of natural unsaturated endiandric acids involving mild cascade electrocyclisation.[272]

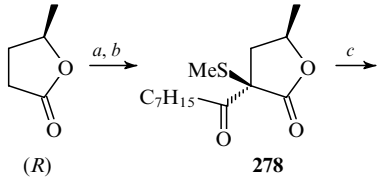


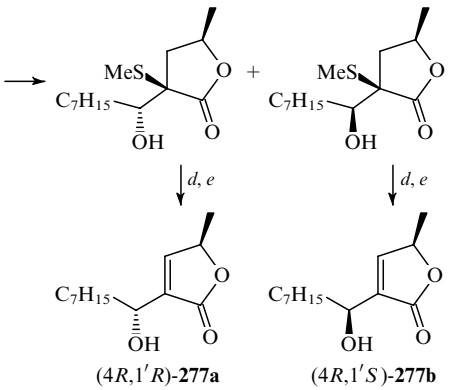
(*a*) LDA; (*b*) $Br(CH_2)_8OH$; (*c*) $ArCO_3H$; (*d*) PhMe, NEt_3, Δ.



n = 0, 1; (*a*) $Cu(OAc)_2$, Py, EtOH; (*b*) MCPBA; (*c*) PhMe, 50 °C, Δ.

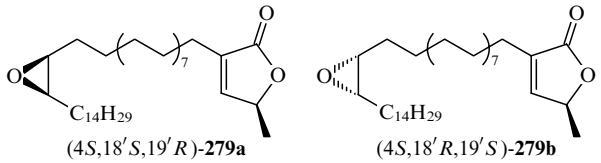
Endocyclic C = C bonds can also be readily constructed by this procedure. For example, all four possible enantiomers of the natural CoA inhibitor, *viz*., acaterin (**277**), with an acetogenin-type skeleton were prepared. The latter is a promising anti-atherosclerosis drug.[273] The (4*R*,1′*R*) absolute configuration was assigned to the natural inhibitor. Both compound (+)-**277a** and its C(1′)-epimer **277b** were prepared by thermolysis (after oxidation) of substituted valerolactones isolated from a mixture of reduction products of compound **278**. The second pair of epimers of the compound **277** was synthesised according to the same procedure starting from (*S*)-γ-valerolactone.



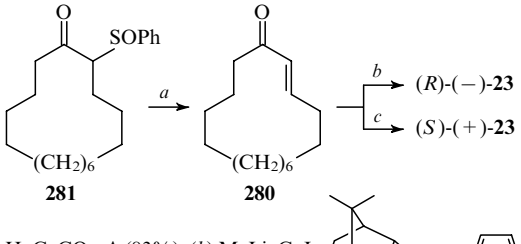


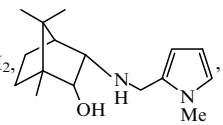
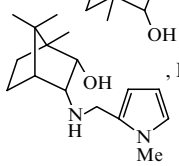
(*a*) LDA, $MeSSO_2Me$; (*b*) LDA, $C_7H_{15}COCl$; (*c*) $NaBH_4$, THF, H_2O; (*d*) oxidation; (*e*) PhMe, $CaCO_3$, Δ, 3 h.

An analogous procedure for the introduction of the endocyclic C = C bond was used [274] in the synthesis of compounds **279a**,**b**, which were supposed to correspond to stereoisomers of a more complex acetogenin, *viz*., epoxyrollin A. However, the ^{13}C NMR and mass spectra of both stereoisomers **279a**,**b** differed from those of the natural product.

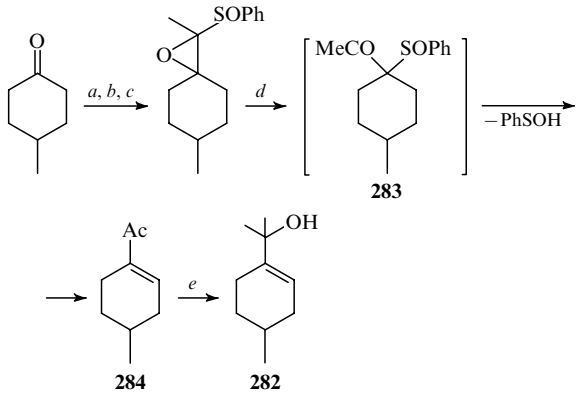


A short elegant synthesis of (+)-(*R*)- and (−)-(*S*)-muscones **23** involved asymmetric methylation of the C = C bond of the enone **280** in the presence of D- or L-camphor derivatives, respectively.[275] The enone **280** was prepared by elimination of benzenesulfenic acid from the oxo sulfoxide **281**.



(*a*) PhH, $CaCO_3$, Δ (83%); (*b*) MeLi, CuI_2, , PhMe, THF (*ee* 100%); (*c*) MeLi, CuI_2, , PhMe, THF (*ee* 100%).

8-Hydroxymenth-3-ene (**282**), which is a component of mint essential oil, was prepared according to a general procedure for the transformation of saturated ketones to enones proposed by Taber and Gunn.[276] In the first step, α-chloroethylsulfinyl carbanion was added to the carbonyl group of 4-methylcyclohexanone to form epoxide. When distilled, the latter underwent spontaneous isomerisation to give unstable oxo sulfoxide **283**, which readily eliminated sulfenic acid. The addition of MeLi to enone **284** completed the process.

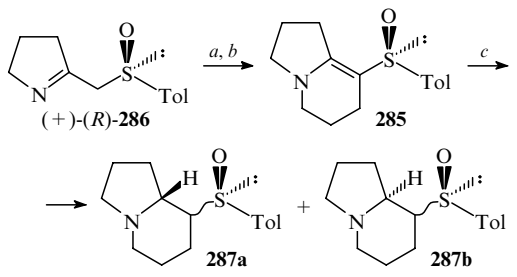


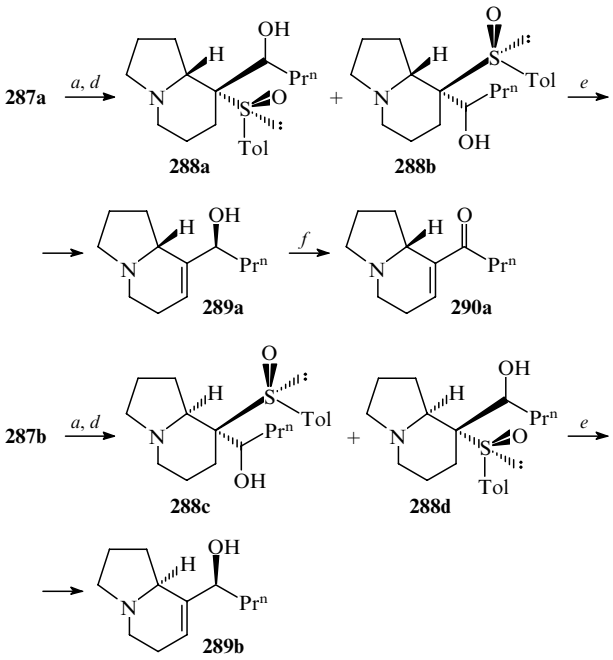
(*a*) LDA, THF; (*b*) MeCH(Cl)SOPh; (*c*) NaOH (90%); (*d*) Δ, $CaCO_3$; (*e*) MeLi.

If the sulfonyl group is located in the aliphatic chain, the direction and the rate of hydrogen abstraction upon thermolysis depend predominantly on its acidity.[35,269] However, thermolysis of steroid sulfoxides is a stereocontrolled process due apparently to the unique features of this system of rigidly fused rings. Thus attempts to introduce the C(15)=C(16) bond into the estrone molecule according to a conventional procedure [starting from C(16)-selenoxide[277]] failed, but this bond was constructed upon prolonged heating of the methyl ether of C(16)-(phenylsulfinyl)estrone in the presence of triphenyl phosphite, which is an active thiophilic scavenger.[40] Elimination of sulfenic acid from the *A* ring of 5α- or 5β-cholestanes occurred under standard conditions.[278] The dependence of the direction and rate of thermolysis on the stereochemistry of the sulfur atom was observed for the first time in the case of bulky thermally stable (*R*)- and (*S*)-adamantylsulfinyl groups, which are not able to undergo stereomutation. This made it possible to develop procedures for the selective synthesis of difficultly accessible 5α- or 5β-cholest-2-enes and cholest-3-enes.[276]

The formation of C=C bonds by thermolysis of sulfoxides was also used in more sophisticated synthetic sequences. For example, this reaction served as a stage in the construction of brefeldin A (**130**)[181,183] and in the synthesis of hirsutene[207] (in the latter case, thermolysis was carried out in an alkaline medium according to a procedure reported previously[279]). Other examples will be considered below.

In the course of the total enantioselective synthesis of indolizine alkaloids elaeokanines A and B, Hua *et al.*[280] used a large number of approaches based on reactions of sulfinyl-containing intermediates. Enamino sulfoxide **285** was prepared by alkylative annelation in the reaction of 1,3-diiodopropane with the anion of (+)-(*R*)-sulfinyl ketimine **286**. Reduction of the reaction product afforded a mixture of all four possible epimeric indolizine sulfoxides represented in pairs as **287a** and **287b**. The reaction of each of these epimers with butanal in the presence of lithium diisopropylamide proceeded quantitatively, the C(8a) chiral centre, which is essential for the subsequent synthesis, remaining unchanged. Thermolysis of a 2 : 1 mixture of hydroxy sulfoxides **288a** and **288b** gave the single product, *viz.*, hydroxyindolizine **289a** with the





(*a*) LDA; (*b*) $I(CH_2)_3I$; (*c*) $NaBH_4$, **287a** : **287b** (1 : 1); (*d*) Pr^nCHO; (*e*) 110 °C, PhMe (~80%); (*f*) PCC (>90%).

C(7)=C(8) bond. Oxidation of the hydroxy group of **289a** resulted in (+)-elaeokanine A (**290a**). (−)-Elaeokanine B (**289b**), which is (unlike elaeokanine A) a hydroxy derivative, was prepared by thermolysis of hydroxy sulfoxides **287c**,**d** obtained by the reaction of butanal with the diastereomers **287b**.

V. Syntheses based on reactions of unsaturated sulfones and sulfoxides

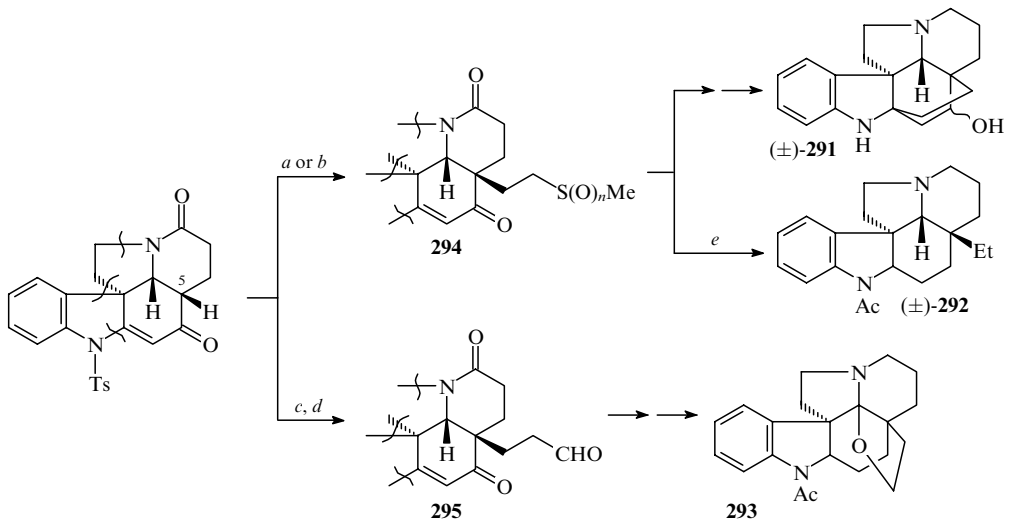
1. Addition at the C=C bonds

a. Addition of C-nucleophiles

The synthesis of racemates of alkaloids (**291**–**293**) of the *Aspidosperma* family from a single pentacyclic precursor provides an example of the use of unsaturated sulfones and sulfoxides as acceptors of C-nucleophiles for the transformation of the basic skeleton, which has been constructed beforehand.[281–283] Owing to the high acidity of the hydrogen atom at C(5) of the enone fragment, the carbanion can readily be generated and involved in the Michael addition to methyl vinyl sulfone, methyl 1-methylthiovinyl sulfoxide or methyl vinyl sulfoxide. Subsequent modifications of the adducts **294** and **295** involved the formation of additional rings in the alkaloids 4-hydroxyaspidofractinine (**291**) and 1-acetylaspidoalbidine (**293**) and the introduction of the ethyl group at position 5 in 1-acetylaspidospermidine **292** (Scheme 10).

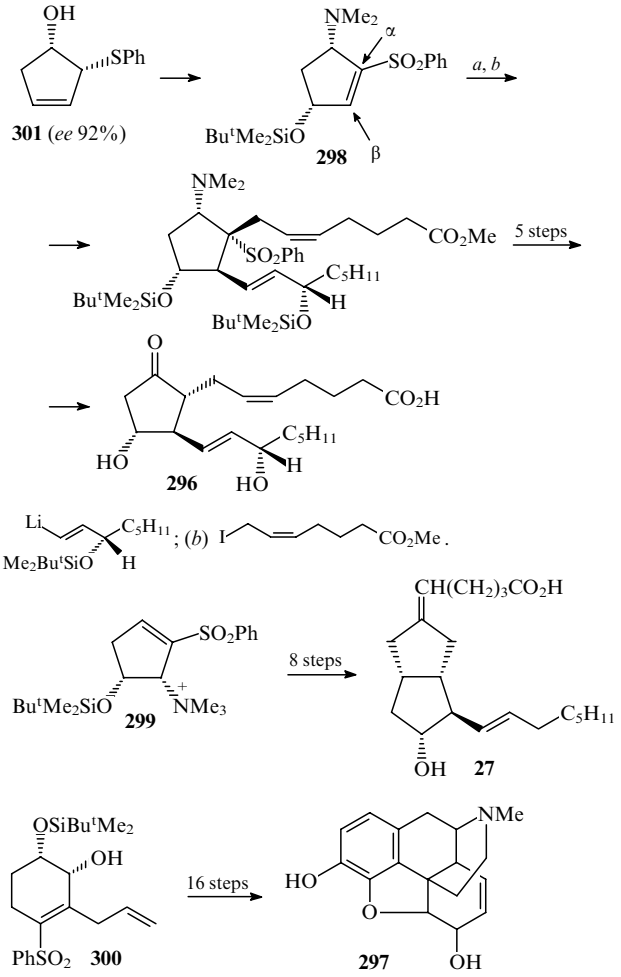
Vinyl sulfones have found substantially wider application due to the fundamental studies of Fuchs and coworkers, which have been surveyed in detail in their reviews.[23,24] Hence, these studies will be considered in this review only briefly. Fuchs and coworkers have developed convenient procedures for the synthesis of substituted cycloalkenyl sulfones, including enantiomerically pure sulfones, containing a free or substituted hydroxy group at the γ-position. In the case of vinyl sulfones, unlike enones, the attack of even hard nucleophiles (for example, alkyllithium) occurs exclusively at the C=C bonds following a Michael addition. Owing to the high nucleophilicity of the resulting α-sulfonyl carbanion compared to enolate, the addition can be combined with a subsequent reaction of the newly formed α-sulfonyl carbanion with an internal or external electrophile resulting in additional functionalisation. The presence of γ-hydroxy groups in these vinyl sulfones allows one to control the stereochemistry of the process.

Scheme 10

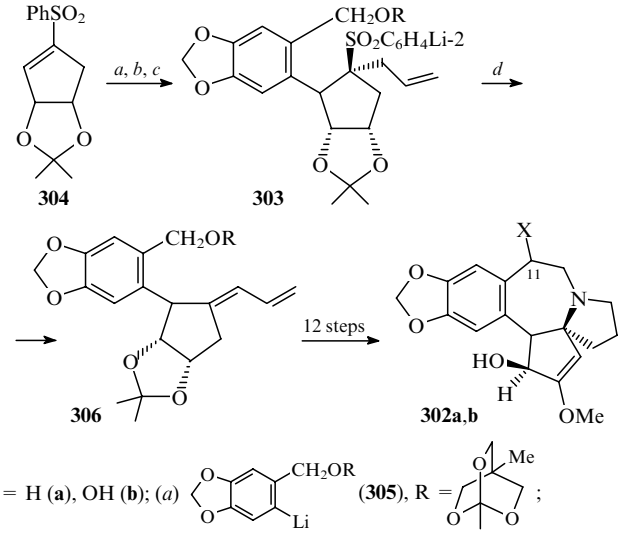


(*a*) $CH_2=CHSO_2Me$, Bu^tOK, Bu^tOH, $n = 2$; (*b*) $CH_2=CHSOMe$, LDA, $n = 1$; (*c*) $CH_2=C(SOMe)SMe$, LDA; (*d*) $HClO_4$, H_2O; (*e*) Ra/Ni, $n = 1$.

The scheme given below outlines in general convergent total syntheses of natural or related compounds, *viz*., (−)-prostaglandin E_2 (**296**),[284] (+)-carbacyclin (**27**)[285] and (±)-morphine (**297**),[286] carried out by Fuchs and coworkers. The key steps of these syntheses involve β-addition – α-alkylation of cycloalkenyl sulfones **298** – **300** (in the scheme, the sites of the α- and β-attacks are indicated by arrows).



The synthesis of prostaglandin **296** from the vinyl sulfone **298** involves only seven steps (the total yield was 13% with respect to 2-phenylthiocyclopent-3-enol **301** with *ee* 92%).[284] The preparation of racemic cephalotaxine **302a**[287, 288] is worthy of notice as an example of more complicated syntheses. The scheme under consideration is of interest from the viewpoint of the diversity of chemical transformations. The lithiated intermediate **303** prepared from vinyl sulfone **304** by consecutive reactions with the lithium derivative **305**, allyl bromide and then with Bu^nLi contains the homoallylic sulfonyl group, which is spontaneously eliminated as lithium sulfinate. The *exo*-1,3-diene group of the reaction product **306** is used in one of the major steps of subsequent transformations to produce cephalotaxine, *viz*., for the construction of the seven-membered heterocycle. A modification of this procedure afforded 11-hydroxycephalotaxine (**302b**). However, this method, despite its elegant character, is unsuitable for the preparation of optically active forms of compounds **302a**,**b**.[287, 288]

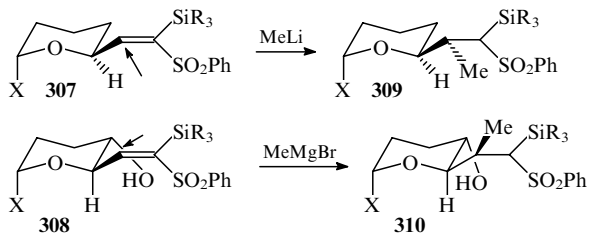


X = H (**a**), OH (**b**); (*a*) (**305**), R = ;

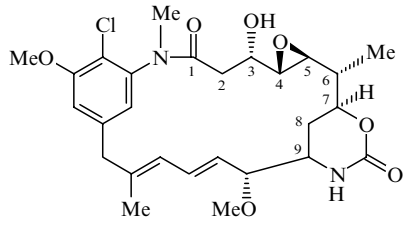
(*b*) $BrCH_2CH=CH_2$; (*c*) Bu^nLi; (*d*) 20 °C, $-PhSO_2Li$.

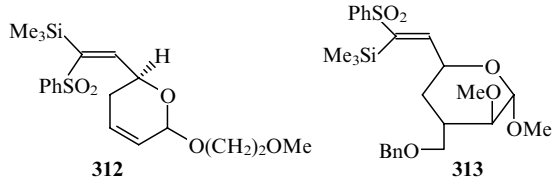
A procedure for the 'heteroconjugate addition' developed by Isobe[289] made it possible to solve a very important problem of the efficient stereocontrol in the construction of new acyclic C−C bonds enabling, simultaneously, further carbon-chain elongation. This method was tested using model pyranosides containing α-silylated vinylsulfonyl substituents at C(5). In this case, D-glucopyranose derivatives serve as chiral pools.

Owing to the bulky α-silyl substituent, the substrate molecule adopts a conformation in which the direction of the attack of the nucleophilic reagent [*syn* or *anti* with respect to the H atom at C(5)] depends both on the nature of the reagent and the sub-

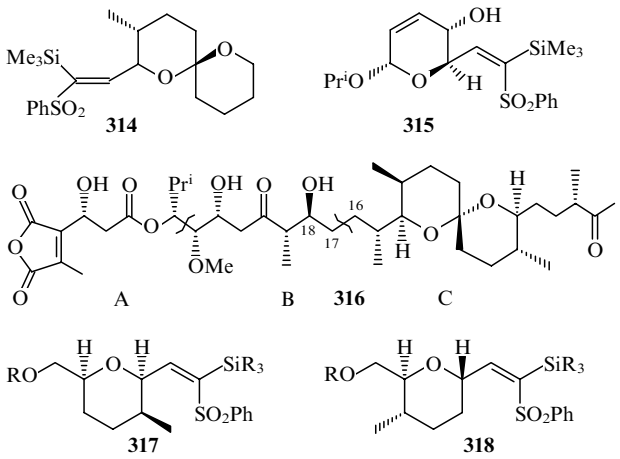


stituents in the pyran ring, which can form chelates with nucleophiles. In the absence of polar substituents (compound **307**), the reaction with alkyllithium proceeds exclusively as *syn*-alkylation.[290] The presence of the hydroxy group at C(4) in compound **308** and the use of a Grignard reagent provide conditions for exclusive *anti*-alkylation due to the formation of a chelate with the reagent.[291] Subsequent chain elongation in the intermediates **309** and **310** was performed predominantly by alkylation of the α-sulfonyl carbanion after desilylation. This method was used for the introduction of the *syn*-methyl group at position 6 in the total syntheses of maysine and *N*-methylmaysenine[292] as well as of racemic maytansinol (**311**)[293] and (−)-maytansinol.[294] Vinyl sulfones **312** and **313** were used as the starting compounds for the construction of the C(4)−C(9) fragment. In the total synthesis of okadaic acid (**94**), vinyl sulfones **314** and **315** were used for the introduction of the *anti*-C(13)-methyl group and the *syn*-C(29)-methyl group into the segments *A*[145] and *C*,[147] respectively.





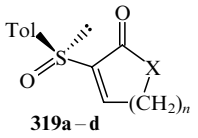
α-Silylated vinylsulfonyl groups at C(6) of the pyran ring were used for 'pseudoenantiomeric' addition.[295] In the total synthesis of tautomycin (**316**), compounds **317** and **318** were employed for the spiro-fusion of rings pseudoenantiomeric with respect to okadaic acid as well as for the introduction of the methyl group at position 3 of the segment *C*. The segments *C* and *B* were coupled



R = $SiMe_2Bu^t$.

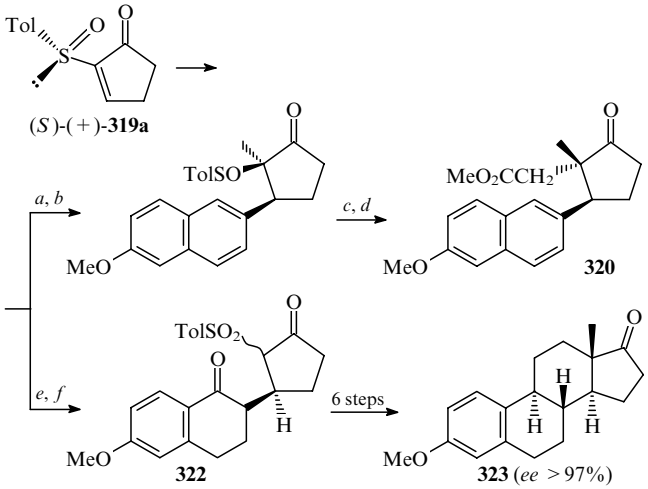
by the reaction of the C(16)-sulfonyl carbanion of the former with the C(17),C(18)-epoxide of the latter in the presence of $BF_3 \cdot Et_2O$. Esterification with the segment *A* completed the synthesis.[296, 297]

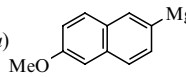
Studies by Posner *et al.*[11, 298] have played a decisive role in the development of asymmetric synthesis based on reactions of C-nucleophiles with enantiomerically pure vinyl sulfoxides. These reactions made use of enantiomerically pure 2-(sulfinyl)-cycloalkenones **319a**,**b** or 2-(sulfinyl)alkenolides **319c**,**d** as the substrates. Convenient procedures for the synthesis of these compounds were devised. The carbonyl group activates the double bond thus promoting Michael-type addition of C-nucleophiles. The stereochemistry of addition can be controlled by adding chelating agents. Thus conditions for the *Si*-attack of the nucleophile are created in the presence of $ZnBr_2$, which binds the sulfinyl and carbonyl groups to form a rigid chelate. In the absence of this additive, *Re*-attack predominantly occurs.

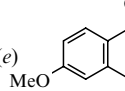


X = CH_2, n = 1 (**a**), 2 (**b**);
X = O: n = 1 (**c**), 2 (**d**).

Posner and coworkers used not only organometallic compounds but also lithium enolates as nucleophiles. The high optical purity of the resulting compounds was attained by varying the reaction parameters and using enantiomerically pure precursors. Thus the formal synthesis of the methyl ether of (*S*,*S*)-11-oxoequilenin was carried out starting from (*S*)-(+)-2-(tolylsulfinyl)cyclopent-2-enone [(*S*)-(+)-**319a**] *via* the secosteroid **320**.[299, 300] The reaction of the same vinyl sulfone **319a** with lithium enolate **321** gave rise to the Michael addition product **322** with a diastereoselectivity of 91%–94%. The latter compound was converted in six steps into methyl ether of estradiol (**323**) with *ee* > 97%.[301]

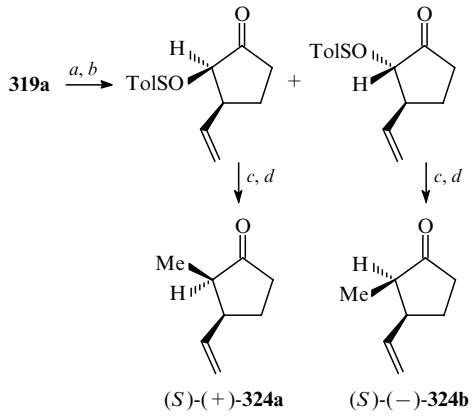


(*a*) 

, THF, −78 °C; (*b*) MeI, HMPT; (*c*) Me_2CuLi, Et_2O, 0 °C; (*d*) $BrCH_2CO_2Me$, HMPT, 25 °C; (*e*) 

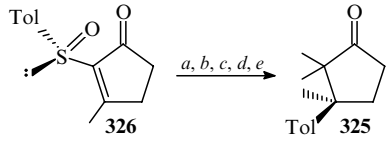
(**321**); (*f*) MCPBA.

Vinylation of vinyl sulfone **319a** in the presence of $ZnBr_2$ followed by methylation afforded a mixture of diastereomers of trisubstituted cyclopentanones. Reductive desulfinylation of the latter made it possible to obtain enantiomerically pure substituted cyclopentanones **324a**,**b**, which are required for the synthesis of steroids.[302]



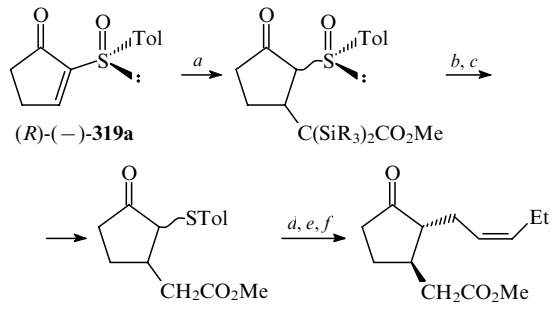
(*a*) $ZnBr_2$; (*b*) $CH_2=CHMgBr$; (*c*) MeI; (*d*) Al/Hg.

Quaternary chiral centres can be generated using 3-alkyl-substituted tolylsulfonylcyclopentenone as the starting compound.[303] For example, vinyl sulfone **326** was used in the stereoconvergent synthesis of the sesquiterpene (+)-α-cuparenone (**325**); however, the *ee* value of the resulting product was only 70%.



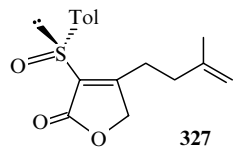
(*a*) Tol_2CuLi; (*b*) MCPBA; (*c*) Bu^tOK; (*d*) MeI; (*e*) Me_2CuLi, MeI.

The five-step synthesis of enantiomerically pure (−)-methyl jasmonate with *ee* > 98% was carried out [304] starting from vinyl sulfone (*R*)-(−)-**319a**.



(*a*) $(R_3Si)_2C(Li)CO_2Me$; (*b*) P_2I_4; (*c*) KF; (*d*) NaH; (*e*) $BrCH_2$—CH=CH—Et; (*f*) Ra/Ni.

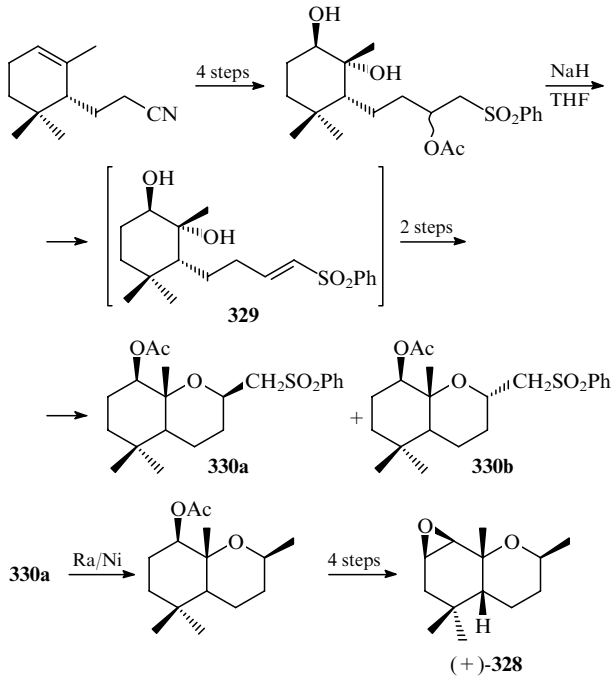
Using enantiomerically pure (*S*)-(+)-tolylsulfinylbutenolide **319c** [305] or -pentenolide **319d** [306] as the starting compounds in the reactions with a Grignard reagent in the presence of $ZnBr_2$ or with substituted lithium enolates, enantiomerically pure antitumour (−)-podarhizon and 3-substituted esters of glutaric acids, respectively, were prepared. Holton *et al.*[307] used an analogous reaction and vinyl sulfoxide **327** as the starting compound in the formal total synthesis of aphidicolin, which exhibits *in vitro* activity against the virus *Herpes simplex*.



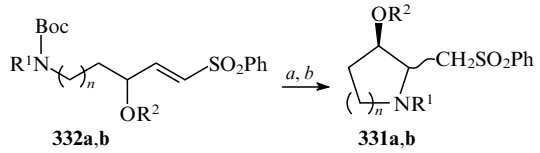
b. Addition of heteronucleophiles

In the synthesis of natural products, reactions of vinyl sulfones or vinyl sulfoxides with alkoxides or amines resulting in the construction of C—O or C—N bonds were used almost exclusively in the intramolecular versions regardless of the nature of the acceptor.

Thus the key step of the 15-step enantioselective total synthesis of the pheromone (1*R*,3*S*,6*R*,9*S*,10*S*)-9,10-epoxytetrahydroedulan (+)-**328** involved cyclisation of hydroxyvinyl sulfone **329** yielding compounds **330a**,**b** in a ratio of 3.5:1.[308]

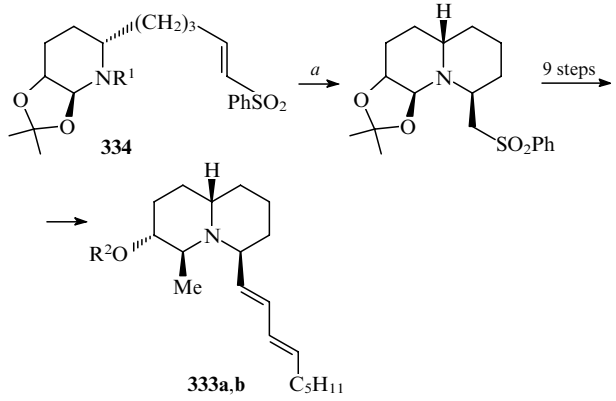


In the synthesis [309] of 2,3-disubstituted pyrrolidines **331a** and piperidines **331b** (the starting materials in the synthesis of biologically active compounds) from acyclic alkoxy- and hydroxy-substituted aminovinyl sulfones **332a**,**b**, cyclisation proceeded also nonstereoselectively. The best *cis*-stereoselectivity (~ 80%) was achieved with the use of the hydroxy derivatives **332a**. The protection of the hydroxy group (the best results were obtained with $R^3 = Pr^i_3Si$) favours *trans*-stereoselectivity.



n = 1 (**331a**), 2 (**331b**); R^1 = H, $(CH_2)_2CO_2Me$; R^2 = H (**332a**), Pr^i_3Si (**332b**); (*a*) CF_3CO_2H, CH_2Cl_2; (*b*) Et_2NH, THF, −78 °C.

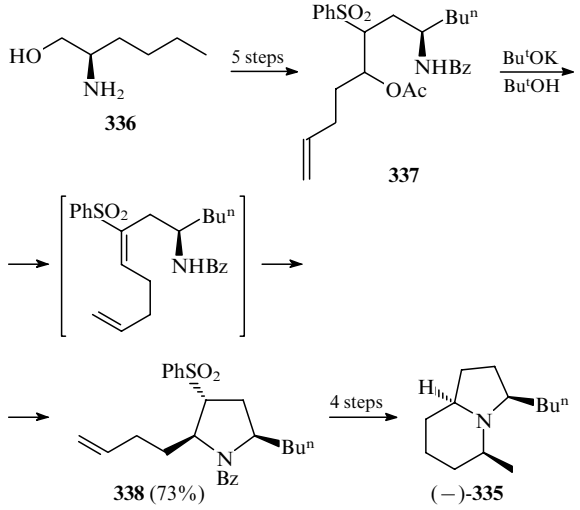
In more rigid systems, for example, in the synthesis of the alkaloids clavepictines A and B **333a**,**b** from monocyclic com-



R^1 = Troc (trityloxycarbonyl); R^2 = Ac (**a**), H (**b**); (*a*) 10% C/Pd, THF, NH_4OAc, 20 °C, 48 h (94%).

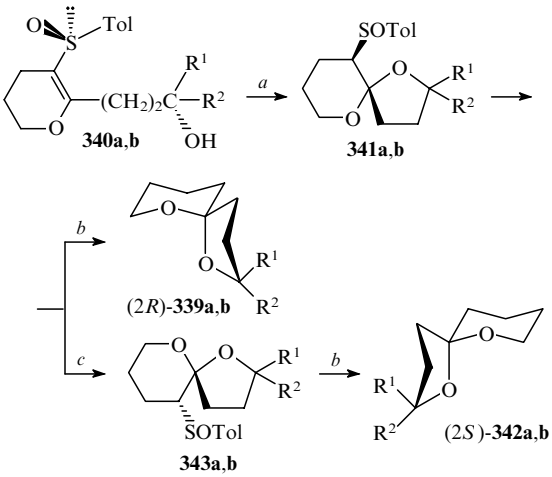
pound **334**, cyclisation through β-amination of the double bond of the vinylsulfone fragment occurs with a high stereoselectivity.[310]

In the synthesis of (−)-monomorine **335**, 5-*endo-trig* cyclisation of compound **337** prepared from norleucinol **336** took place also in a highly stereoselective manner.[311] The construction of the second ring from the monocyclic intermediate **338** occurred through intramolecular reductive amination.



Intramolecular addition of heteronucleophiles at the C=C bonds of vinyl sulfoxides plays a considerable role in the asymmetric synthesis.[12]

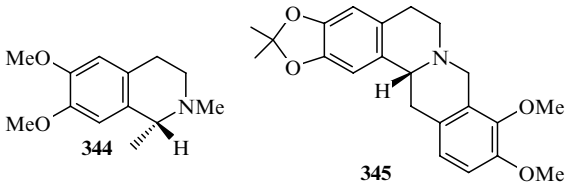
In the series of studies performed by Iwata *et al.*,[312–315] the addition of remote hydroxy groups to the vinyl sulfoxide fragment was used for the construction of enantiomerically pure dioxaspirodecanes and -undecanes, which are the major components of pheromones of many insects. The enantioselectivity of spirocyclisation is achieved owing to the asymmetric induction of the chiral sulfinyl group due to which this method has advantages over some others.[100, 101] Dioxaspirodecanes (2*R*)-**339a**,**b**, which are pheromones of the wasp *Paravespula vulgaris*,[312, 313] were prepared by the action of KH on 5-hydroxydihydropyran sulfoxides **340a**,**b** followed by reductive desulfination of the reaction products **341a**,**b**. Two other diastereomers of the pheromone, *viz*., **342a**,**b**, were synthesised by isomerisation of the cyclisation product in an acidic medium followed by reductive desulfination of isomeric sulfoxides **343a**,**b**. The closure of the six-membered rings by an analogous intramolecular reaction afforded (*R*)- and (*S*)-1,7-dioxaspiro[5.5]undecanes **61**[313, 314] and more complex molecules of talaromycins A and B, which are metabolites of the toxic mushroom *Talaramyces stipitatus*.[315]



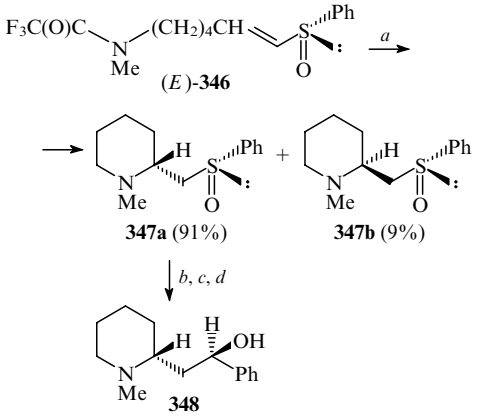
R^1 = H, R^2 = Me (**a**); R^1 = Me, R^2 = H (**b**); (*a*) KH, THF, −78 °C; (*b*) Ra/Ni, MeOH; (*c*) TsOH.

Solladie *et al.*[168] used cyclisation involving a remote hydroxy group and the C=C bond of the chiral vinylsulfinyl fragment of the molecule as one of the steps in the above-considered synthesis of a vitamin E precursor, *viz*., (+)-(*S*)-**122**.

Polycyclic alkaloids, such as (+)-carnegine (**344**) and (+)-canadine (**345**), can be prepared by intramolecular amination of vinylsulfinyl bonds in spite of the fact that this process is not always stereoselective.[316, 317]

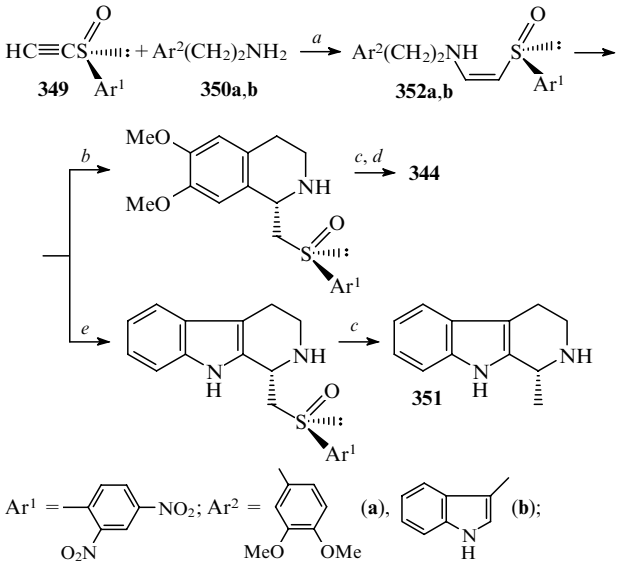


Monocyclic (+)- and (−)-sedamines were synthesised[316] from linear precursors, *viz*., substituted (*E*)- and (*Z*)-alkenyl sulfoxides. Thus cyclisation of the sulfoxide (*E*)-**346** followed by chain elongation in the reaction of the α-sulfinyl carbanion of diastereomer **347a** with benzaldehyde and reductive desulfinylation of the reaction product afforded (+)-sedamine (**348**). (−)-Sedamine was prepared according to the same procedure starting from the (*Z*)-isomer of the sulfoxide **346**.



(*a*) $PhCH_2NEt_3OH$, −40 °C; (*b*) LDA; (*c*) PhCHO; (*d*) Ra/Ni.

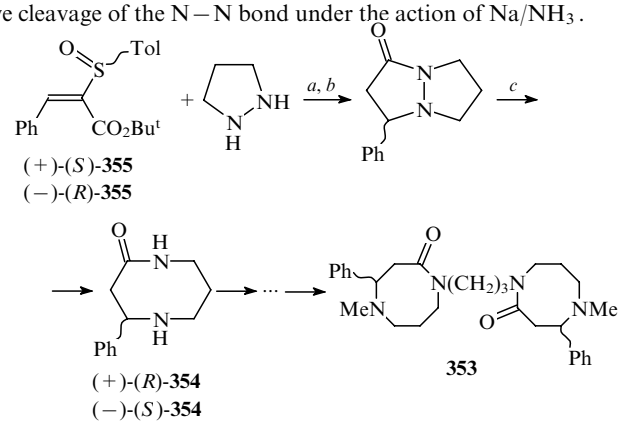
An alternative procedure for the preparation of carnegine (**344**) was developed[318] based on the reaction of enantiomerically pure (*R*)-2,4-dinitrophenylethynyl sulfoxide (**349**) containing the highly electrophilic triple bond with 2-(3,4-dimethoxyphenyl)-



(*a*) 20 °C; (*b*) **350a**, CF_3CO_2H, 0 °C, 100%; (*c*) Ra/Ni; (*d*) CH_2O, $NaCNBH_3$; (*e*) **350b**, TsOH, MeOH, −30 °C (70%).

ethylamine (**350a**). The tricyclic alkaloid (+)-tetrahydroharman (**351**) was prepared with a rather high selectivity starting from amine **350b** containing the indole substituent *via* the vinyl sulfoxide **352b**.

Intermolecular addition of a nitrogen nucleophile to the vinylsulfinyl bond was used in the synthesis of structurally unique (*R*,*R*)- and (*S*,*S*)-homalines **353** from epimeric 4-phenyl-1,5-diazacyclooctan-2-ones [(*R*)-(+)-**354**) and (*S*)-(−)-**354**].[319] The reaction of pyrazolidine with enantiomerically pure substituted (*R*)- or (*S*)-(*E*)-vinyl sulfoxides **355** in an excess of Bu^{t}OK followed by the removal of the sulfinyl group under the action of SmI_2 afforded bicyclic compounds. The target products were prepared from these bicyclic compound in two steps after reductive cleavage of the N—N bond under the action of Na/NH_3.

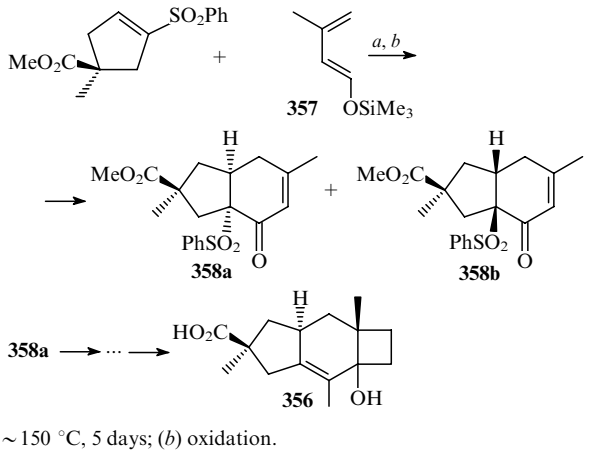


(*a*) Bu^{t}OK; (*b*) SmI_2; (*c*) Na/NH_3.

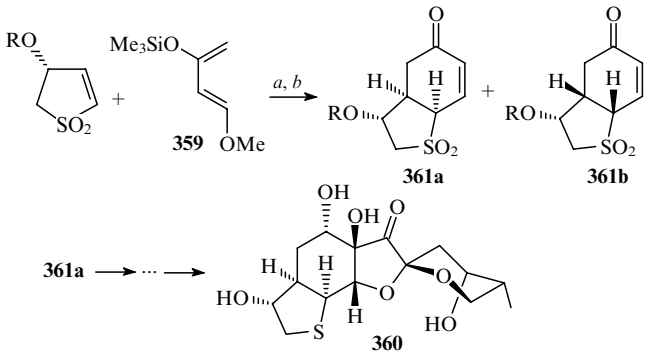
2. The Diels – Alder reaction

a. Sulfonyl- and sulfinyl-containing dienophiles

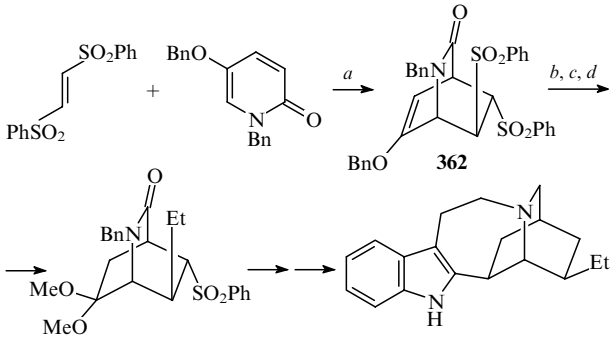
The high reactivity of vinyl sulfones as dienophiles in [4 + 2] cycloaddition reactions was reported in the 1960s. Ethyl vinyl sulfone readily enters into Diels – Alder reactions not only with electron-rich dienes (the reaction with cyclopentadiene is exothermic), but also with electron-deficient dienes (for example, with hexachlorocyclopentadiene [320]). More recently, owing to the fact that the adducts of vinyl sulfones can readily undergo reductive desulfonation, the latter have found application as equivalents of nonactivated alkenes and alkynes, which are difficult to introduce into the [4 + 2] cycloaddition reactions.[321, 322] However, the Diels – Alder reactions are rather rarely used for the preparation of biologically active compounds due apparently to their low stereoselectivity. The first step of the synthesis of sesquiterpenoid sterpuric acid (**356**) involved cycloaddition of cyclic vinyl sulfone to the highly electrophilic Danishefsky diene (**357**).[323, 324] The ratio between the target isomer **358a** and the undesirable isomer **358b** was ~ 2 : 1 (the total yield of the final product was 11%). The reaction of 3-silyloxy-2-sulfolene with diene **359**, which is the key



(*a*) ~150 °C, 5 days; (*b*) oxidation.



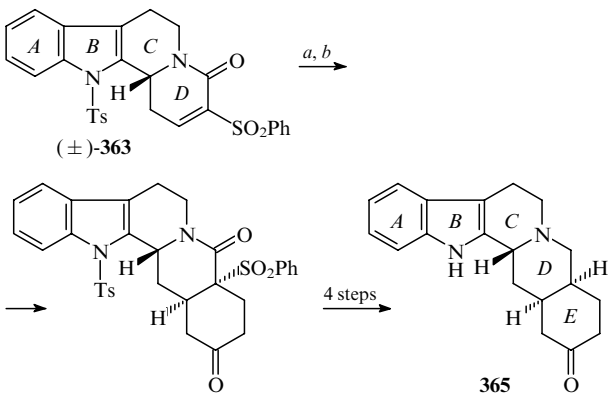
R = Pr^i_3Si; (*a*) 170 – 180 °C, 48 h; (*b*) Py · TsOH, Δ (82% – 85%).



(*a*) 150 °C, 8 days; (*b*) 2 M HCl, $(MeO)_3CH$; (*c*) KOH, THF; (*d*) EtCuMgI.

step in the formal synthesis of breynolide (**360**), also proceeded nonselectively to form a mixture of adducts **361a**,**b**.[325] (*E*)-1,2-Bis(diphenylsulfonyl)ethene is a more efficient dienophile. Its reaction with 5-benzoyloxy-2-pyridone proceeded with a higher selectivity and was used in the synthesis of racemic ibogamine *via* the adduct **362** (the total yield was 14%).[326, 327]

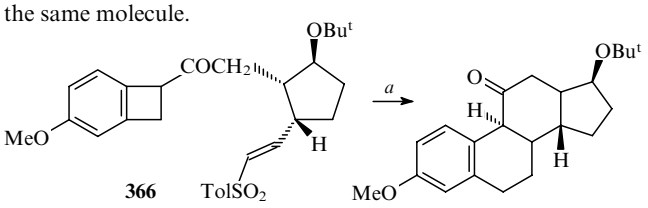
In the absence of catalysts, [4 + 2] cycloaddition involving vinyl sulfones proceeds at rather high temperature. The use of catalysts makes it possible to use milder reaction conditions and to enhance the selectivity. Thus the selectivity of the Diels – Alder reaction of tetracyclic vinyl sulfone **363** with diene **364** in the presence of $EtAlCl_2$ at 0 °C was higher than 90%. Such strategy for the ring buildup made it possible to perform the C(15)- and C(20)-enantioselective synthesis of racemic alkaloid 3-*epi*-alloyohimbone (**365**) with a skeleton similar to that of reserpine.[328]



(*a*) (**364**), $EtAlCl_2$, 0 °C; (*b*) 0.5 M HCl.

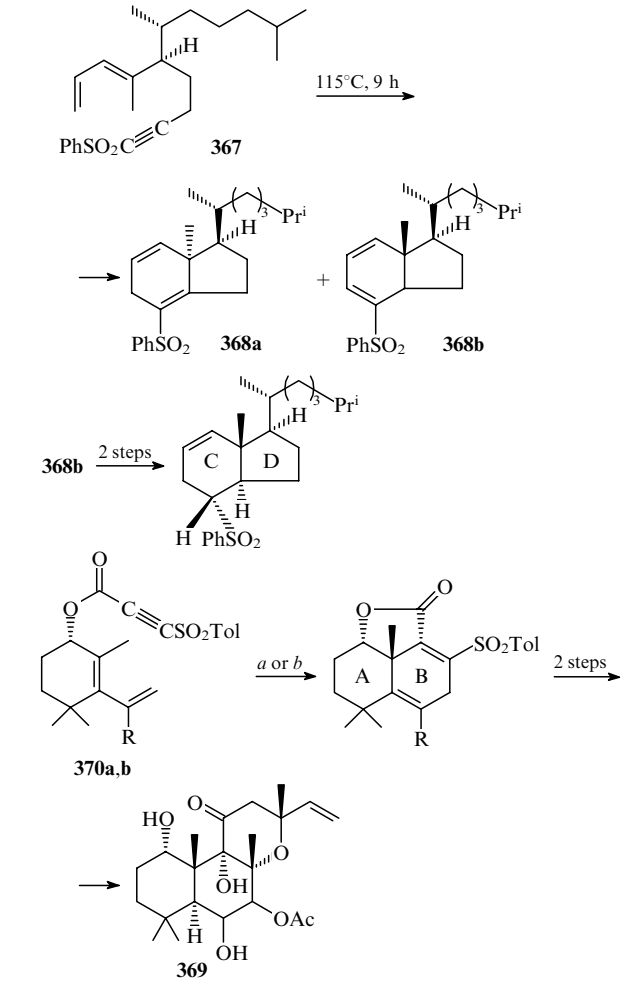
An application of intramolecular [4 + 2] cycloaddition involving α,β-unsaturated sulfonyl fragments has been described. Thus the stereospecific construction of the skeleton of *cis* – *anti* – *cis*-estrone was carried out [329] by the reaction of the *o*-quinodimethane fragment formed upon pyrolysis of the benzocyclo-

butane moiety of compound **366** with the vinylsulfonyl group of the same molecule.

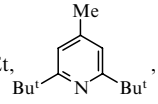


(*a*) 195 °C, 1,2-$Cl_2C_6H_4$, 6 h (~62%).

Based on their experience on intramolecular Diels–Alder reactions of polyene sulfones,[330] Craig *et al.*[331] attempted to use this approach in the synthesis of vitamin D_3 and its analogues, which have attracted growing interest because of the discovery of new pharmacological properties of these compounds.[332] However, the construction of the block *CD* for the synthesis of vitamin D_3 can be performed[333] only starting from compound **367** containing the highly reactive sulfonylethynyl fragment. Selective hydrogenation of one of the C=C bonds in the major reaction product **368b** afforded the key intermediate in the synthesis of vitamin D_3, *viz.*, sulfone containing the rings *CD*. Corey *et al.*[334–336] used ethynylsulfonyl precursors for the construction of the rings *AB* of forskolin (**369**) possessing valuable pharmacological properties. Owing to the additional activation of the triple bonds in compounds **370a**,**b** with ester groups, cyclisation occurred in the absence of a catalyst under mild conditions with a high enantioselectivity.

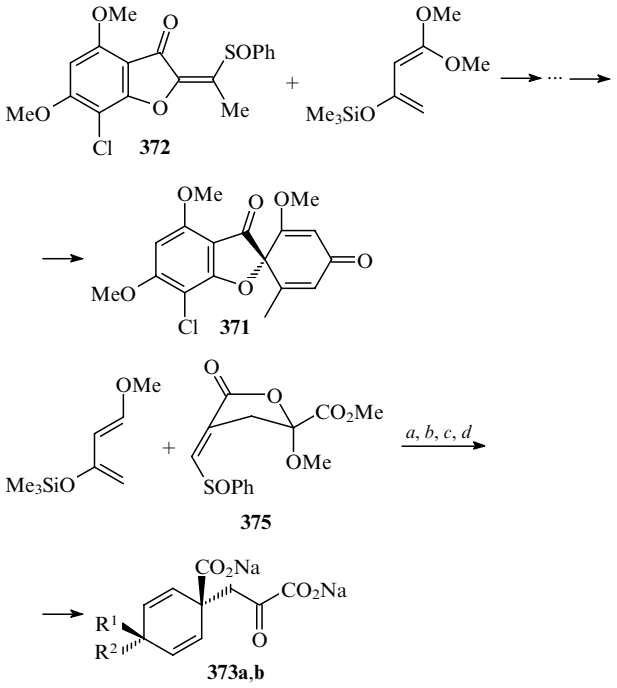


R = H (**a**), OCO_2Et (**b**); (*a*) R = H, CH_2Cl_2, 23 °C, 36 h (64%, *ee* 97%);

(*b*) R = OCO_2Et, , 95 °C, 48 h (65%, *ee* 93%).

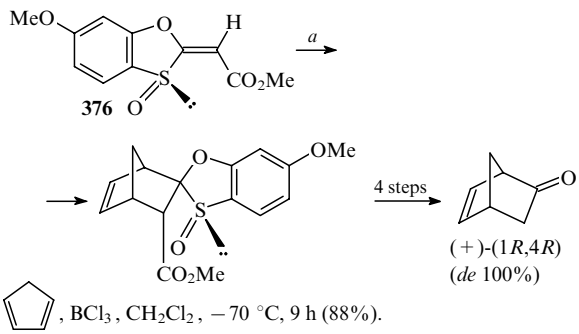
The introduction of activating groups and the addition of catalysts, which allow one to perform the Diels–Alder reactions under milder conditions, are particularly necessary if less reactive vinyl sulfoxides are used as dienophiles.

The Diels–Alder synthesis involving polyfunctional racemic vinyl sulfoxides was applied, for example, in the preparation of (±)-dehydrogriseofulvin (**371**)[337] starting from the sulfoxide **372** or sodium salts of prephenates **373** *via* the intermediates **374a**,**b**, which were generated from the sulfoxide **375**.[338] When surveying his investigations, Danishefsky particularly emphasised these studies.[339] The reactions of vinyl sulfoxides even with Danishefsky's silyloxydienes necessitated prolonged heating and were accompanied by elimination of sulfenic acid.



R^1 = OH, R^2 = H (**a**); R^1 = H, R^2 = OH (**b**); (*a*) 100 °C, 20 h; (*b*) AcOH, AcOEt; (*c*) BBN (9-borabicyclononane); (*d*) NaOH.

The development of procedures for efficient asymmetric synthesis starting from enantiomerically pure sulfinyl-containing dienophiles presented the major problem. The search for the optimum reaction conditions and for the chiral sulfinyl dienophile of choice for the synthesis of (+)-(1*R*,4*R*)- and (−)-(1*S*,4*S*)-enantiomers of norborn-4-enone was carried out using the [4+2] cycloaddition of cyclopentadiene to (+)-(*R*)-tolyl vinyl sulfoxide[340] and its analogues[341, 342] as examples. The full selectivity was achieved only with the use of a more complex compound, *viz.*, a ketene equivalent **376**. The reaction of the latter with cyclopentadiene in the presence of BCl_3 at −70 °C gave only one adduct, which was transformed into (+)-(1*R*,4*R*)-norborn-4-enone.[343] The reaction proceeded selectively due to the formation



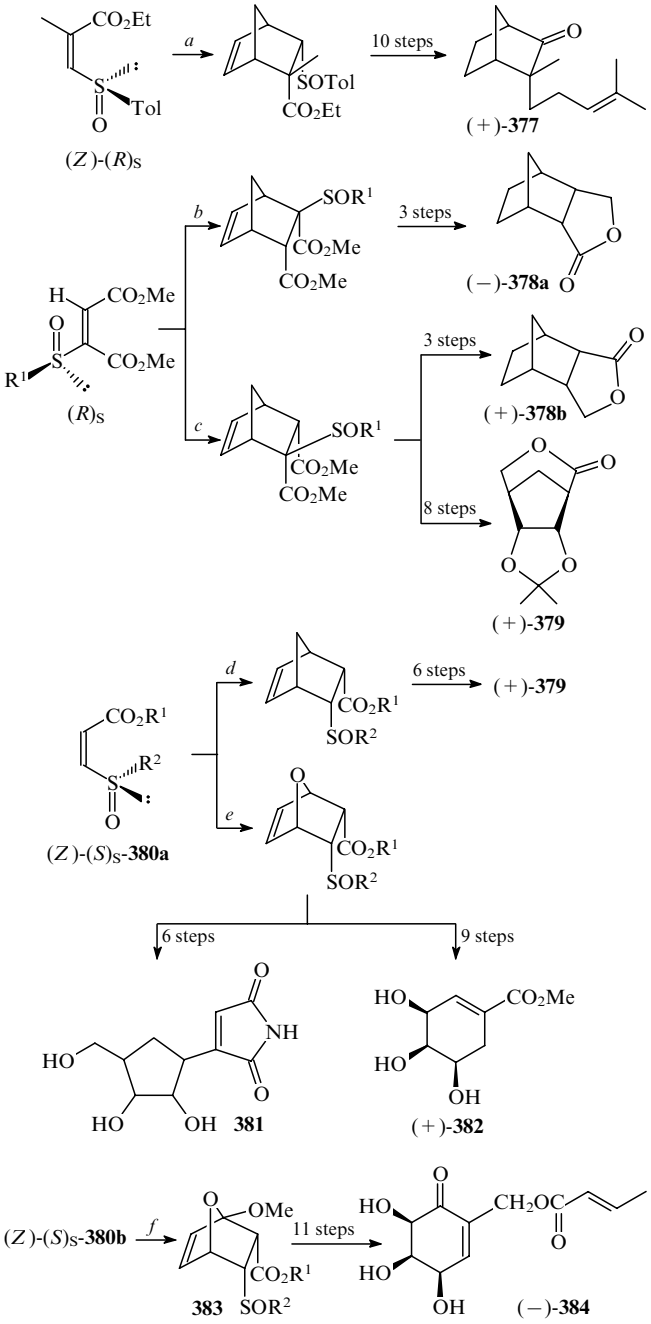
(*a*) , BCl_3, CH_2Cl_2, −70 °C, 9 h (88%).

of a BCl_3 chelate with both the sulfinyl and methoxycarbonyl groups of the substrate. It should be noted that the noncatalytic reaction afforded a mixture of all possible enantiomeric adducts.

Koizumi and coworkers [344–347] made a major contribution to the development of procedures for the asymmetric synthesis of natural compounds starting from chiral sulfinyl-containing dienophiles.

The synthesis of (+)-*epi*-β-santalene **377** involved the reaction of cyclopentadiene with ethyl (*Z*)-(*R*)$_S$-2-methyl-3-(tolylsulfinyl)-prop-2-enoate (Scheme 11).[344, 345] In this synthesis, the reaction

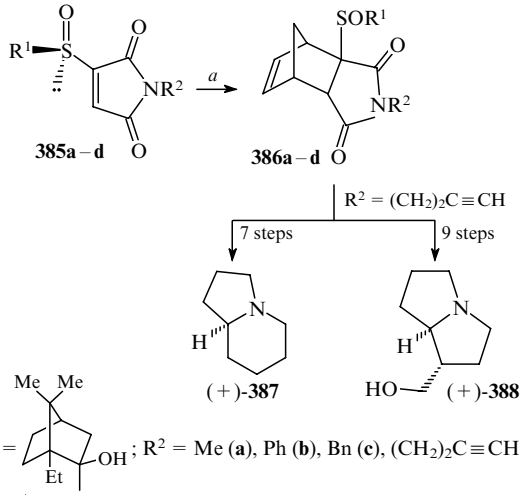
Scheme 11

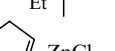


R^1 = menthyl: R^2 = 2-pyridyl (**380a**), R^2 = 3-trifluoromethyl-2-pyridyl (**380b**); (*a*) , 90 °C, 6 h (87%); (*b*) , 25 °C, 19 h (87%); (*c*) , $ZnCl_2$, −20 °C, 3.5 h (94%); (*d*) , Et_2AlCl, −78 °C (94%); (*e*) , Et_2AlCl, −78 °C (~70%); (*f*) , 0 °C, 6 days (~100%).

temperature can be noticeably decreased and the enantioselectivity of the reaction can be enhanced in the presence of an additional (compared to tolyl vinyl sulfoxide) electron-withdrawing substituent at the C=C bond of the vinyl sulfoxide. The influence of the second alkoxycarbonyl group in dimethyl (*R*)$_S$-(menthylsulfinyl)-maleate makes a reaction with cyclopentadiene at room temperature highly enantioselective. This was used for the preparation of the enantiomerically pure bicyclic lactone **378a**, which is the starting compound in the synthesis of various natural products.[346] The application of zinc salts as catalysts allows one to perform the reactions at low temperatures. However, in this case an isomeric adduct is formed. This adduct can be transformed into either lactone **378b** or 'the Ono lactone' (**379**), which is an important precursor in the synthesis of natural compounds, for example, of carbocyclic nucleosides.[347] The lactone **379** can also be synthesised starting from the adduct of menthyl (*S*)$_S$-3-(2-pyridylsulfinyl)acrylate (**380a**) with cyclopentadiene, which was prepared in high yield in the presence of Et_2AlCl.[348] Recently,[349] this adduct has been used in the total synthesis of the alkaloid *cis*-trikentrin B. The selectivity of condensation of compound **380a** with the less active dienophile furan is lower. However, this reaction was used for the preparation of D-showdomycin **381** and methyl *epi*-shikimate **382**.[350] The sulfoxide **380b** with a 3-trifluoromethyl-2-pyridyl group is a 'champion' among dienophiles of this series. Its adduct with 2-methoxyfuran, *viz*., compound **383**, which was formed in quantitative yield at 0 °C in the absence of a catalyst, was employed in the synthesis of a glyoxylase I inhibitor (**384**) (Scheme 11).[351]

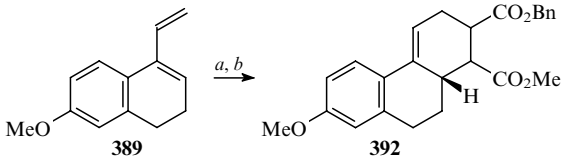
Chiral *N*-substituted sulfinylmaleimides **385a–d** are efficient dienophiles. These compounds react with cyclopentadiene in the presence of $ZnCl_2$ at low temperature to form almost exclusively *exo*-adducts **386a–d** in quantitative yields.[352] The adduct **386d** was used [353] for the preparation of the bicyclic alkaloids (+)-indolizidine **387** and (+)-laburnine **388**.

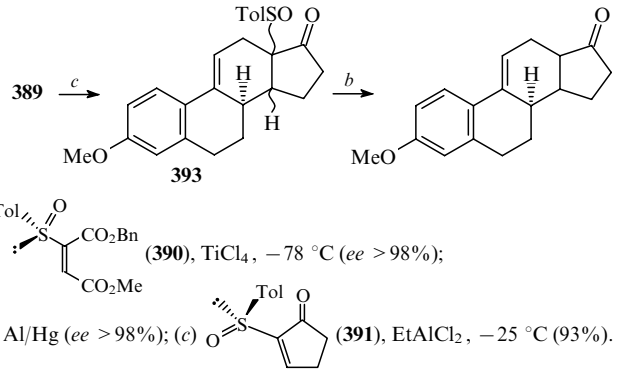


R^1 = ; R^2 = Me (**a**), Ph (**b**), Bn (**c**), $(CH_2)_2C{\equiv}CH$ (**d**);

(*a*) , $ZnCl_2$, −78 °C (95%–100%).

The search for new types of electron-rich dienes holds promise. This will extend the scope of synthetic applications of sulfinyl-containing dienophiles. For example, condensation of 'Dane's diene' (**389**) with the sulfinyl-substituted ester of maleic acid **390** [354] or with sulfinyl-substituted cyclopentenone **391** [355] afforded the adducts **392** and **393**, respectively, which are precursors in the steroid synthesis, with a high diastereoselectivity.





The reaction of the diene **389** with the sulfoxide **390** was accompanied by spontaneous elimination of sulfenic acid.

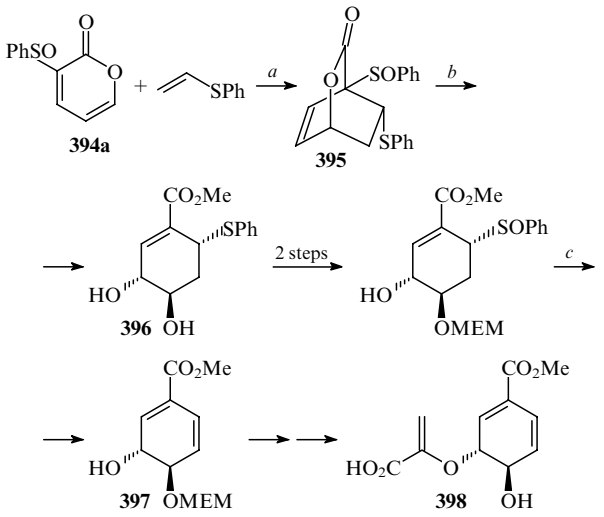
b. Sulfonyl- and sulfinyl-containing dienes

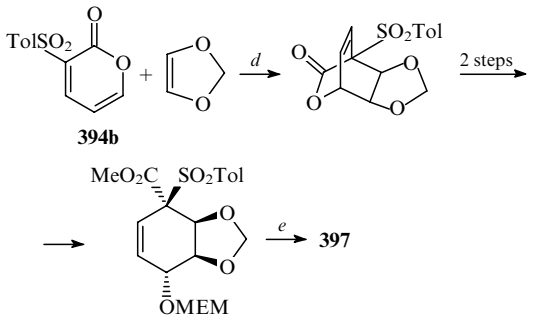
As yet, sulfonyl-substituted and, particularly, enantiomerically pure sulfinyl-substituted dienes have received little use in the synthesis of natural products.

Evans[356] was the first to propose a tandem [4 + 2] cycloaddition of a racemic sulfinyl-containing diene and the sulfonyl-sulfenate rearrangement of the adduct using the synthesis of a derivative of the hasubanan series as an example.

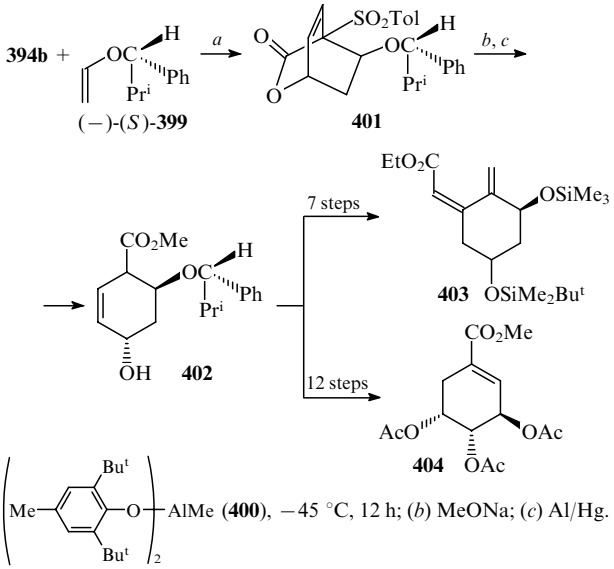
More recently, Posner and coworkers (see the review[357]) performed systematic studies of the Diels–Alder reactions of 3-sulfinyl- (**394a**) and 3-sulfonyl-2-pyrones (**394b**) with electron-rich dienophiles, such as vinyl ethers or vinyl sulfides. Unlike other substituted pyrones whose Diels–Alder reactions proceed only at high temperatures (resulting in the degradation of the initially formed adducts), the pyrones **394a**,**b** at low temperatures (sometimes at high pressure) give polysubstituted bicyclic lactones, which are excellent starting compounds for the preparation of various natural products.

Thus the reaction of the sulfinyl-substituted pyrone **394a** with ethyl vinyl sulfide proceeded stereoselectively to form[358] the *endo*-adduct **395**, which was converted into tetrasubstituted cyclohexene **396** through the sulfoxide-sulfenate rearrangement under conditions of alkaline methanolysis. Subsequent transformations afforded substituted cyclohexadiene **397**, which is the key intermediate in the synthesis of (±)-chorismic acid (**398**). A shorter synthetic path for the cyclohexadiene **397** is based on the reaction of sulfonylpyrone **394b** with 1,3-dioxole.[359]



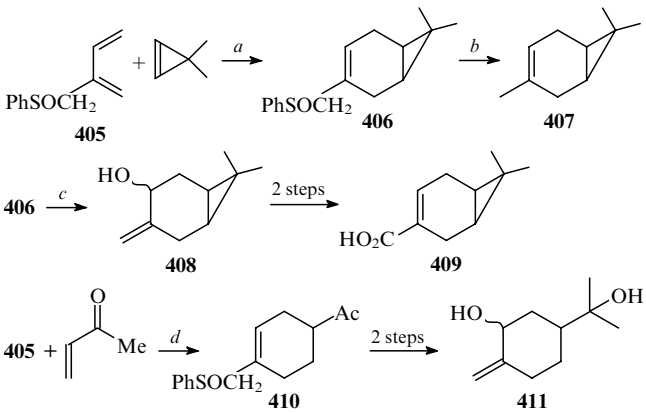


Posner and coworkers performed asymmetric syntheses of a number of enantiomerically pure natural compounds by introducing sulfonylpyrone **394b** into the Diels–Alder reaction with optically pure vinyl ether (−)-(*S*)-**399**[360–362] catalysed by Lewis acid **400**.[360] The transformation of the *endo*-adduct **401**, which was obtained with a high stereoselectivity, afforded trisubstituted cyclohexene (−)-**402**. A somewhat lower stereoselectivity was achieved when this reaction was carried out in the absence of a catalyst at 25 °C.[361] The cyclohexene **402** served as the starting compound for the preparation of the key intermediate **403** (the total yield was 62%) in the total synthesis of 1α,25α-didehydroxyvitamin D_3 as well as for the synthesis of methyl (−)-tri-*O*-acetyl-4-*epi*-shikimate (**404**) (the total yield was 23.4%, *ee* >98%).



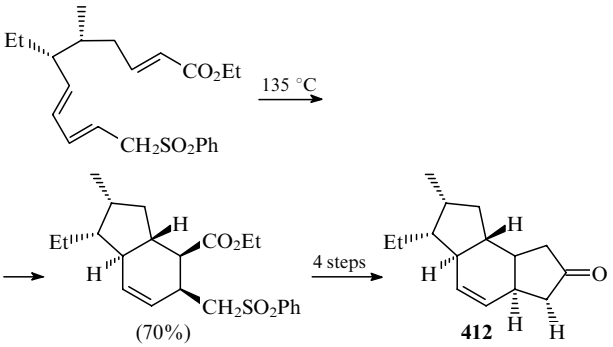
Readily available racemic 2-(phenylsulfinylmethyl)buta-1,3-diene (**405**) is an active diene.[363] This compound reacted with dimethylcyclopropene to give a mixture of *exo*- and *endo*-adducts **406**. After reductive desulfinylation, the *exo*-adduct was converted into Δ^3-carene (**407**). The sulfoxide-sulfenate rearrangement of compound **406** under the action of $P(OEt)_3$ afforded the hydroxy derivative **408** from which racemic chaminic acid (**409**) was prepared. Thermal condensation of the diene **405** with methyl vinyl ketone gave rise to a mixture of 1,4- and 1,3-substituted cyclohexenes in a ratio of 3 : 1. The adduct **410** was converted into racemic $\Delta^{1(7)}$-menthene-2,8-diol (**411**) in three steps.

Sulfonyl- and sulfinyl-substituted diene units can be involved in intramolecular [4 + 2] cycloaddition. For example, this procedure was used for the preparation of compound **412**, which is an

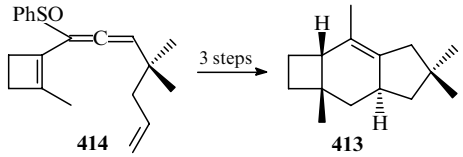


(*a*) 80 °C, 5 kbar; (*b*) Li, NH_3 (liquid); (*c*) $P(OEt)_3$; (*d*) PhH, 80 °C.

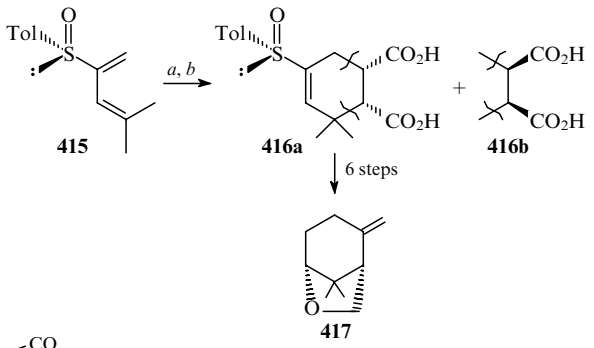
important fragment in the total synthesis of the macrolide ikarugamycin.[364]



A short synthesis of sesquiterpenoid (+)-sterpurene (**413**) was carried out[365] using the cascade intramolecular [4 + 2] cycloaddition involving the diene system of sulfinyl-substituted tetraene **414**.



Convenient procedures for the preparation of enantiomerically pure 2-sulfinyl-substituted butadienes have been developed recently.[366, 367] The transformation of the *endo*-adduct (**416a**) of diene **415** with maleic anhydride in the synthesis of monoterpenoid (−)-(1*S*,5*R*)-karahana ether (**417**) (*ee* > 93%) is the first example of an asymmetric synthesis of a natural product with the use of such dienes.[368]



(*a*) , THF, Δ; (*b*) Na_2CO_3, H_2O (90%), (**416a** : **416b** = 4 : 1).

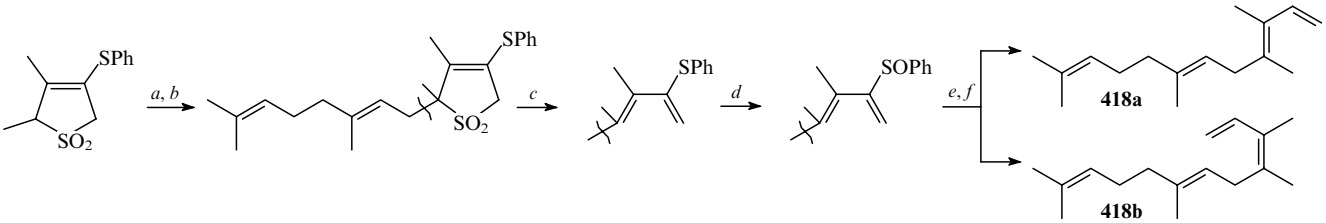
3. Syntheses based on elimination of SO_2 from 2,5-dihydrothiophene 1,1-dioxides (3-sulfolenes)

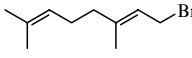
3-Sulfolenes readily eliminate SO_2 to form substituted buta-1,3-dienes. This process is the cheletropic ring-opening reaction which obeys the Woodward – Hoffmann rule and occurs under conditions of pyrolysis, sometimes in the presence of bases. The introduction of substituents into the sulfolene ring, which can be readily performed, for example, by alkylation at the α-position, followed by thermolysis allows one to prepare various buta-1,3-dienes starting from 3-sulfolenes. These butadienes can be used in the synthesis of polyunsaturated linear and carbocyclic natural compounds. Thus the homofarnesene components of the fire-ant trail pheromone **418a**,**b** were prepared[369] from 2,3-dimethyl-4-(phenylthio)-3-sulfolene (Scheme 12). Polysubstituted thiophene **419** was converted into 3-sulfolene **420** by electrolytic reduction followed by oxidation at the sulfur atom.[370] The compound **420** was subjected to *in situ* thermolysis resulting in a mixture of a juvenoid methoprene **421** and its (2*Z*,4*E*)-isomer.

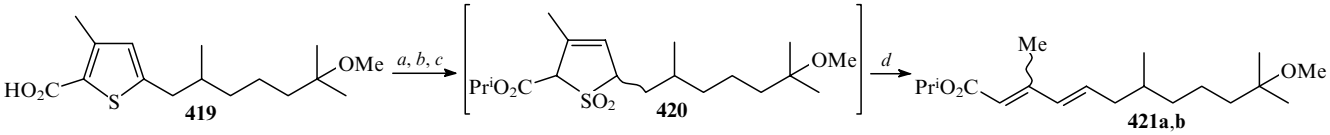
Sulfolene **422** was used as the starting material[371] for the preparation of tricyclic compound **423** containing the taxane ring system. 3-Methyl-3-sulfolene served as the starting compound in many syntheses of natural compounds, for example, of open-chain α-sinensal (**424**) (an important contributor to the odour of the Chinese orange oil)[372] or bicyclic terpenoids of the eudesmane series **425** – **427**.[373] In the latter cases, the intramolecular Diels – Alder reactions proceeded with extremely high stereoselectivities (Scheme 13).

The use of nitrogen-containing dienophilic groups (for example, imine or enamide groups) in the intramolecular Diels – Alder reactions opens up the way to the construction of racemic alkaloids (Scheme 14). Apparently, the first to be performed was the short synthesis of racemic elaeokanine A (**289a**) *via* the

Scheme 12

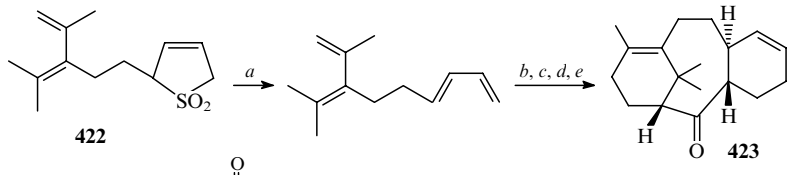


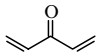
(*a*) Bu^nLi; (*b*) ; (*c*) $LiAlH_4$; (*d*) oxidation; (*e*) chromatographic separation; (*f*) Bu^nLi, Et_2O, NaOH.

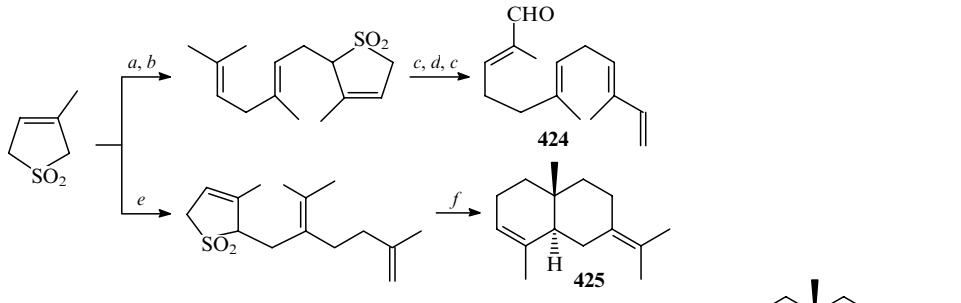


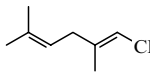
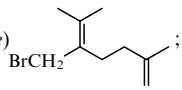
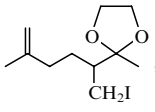
(*a*) $2e^-$; (*b*) Pr^iOH, H^+ (84%); (*c*) MCPBA; (*d*) PhMe, Δ.

Scheme 13



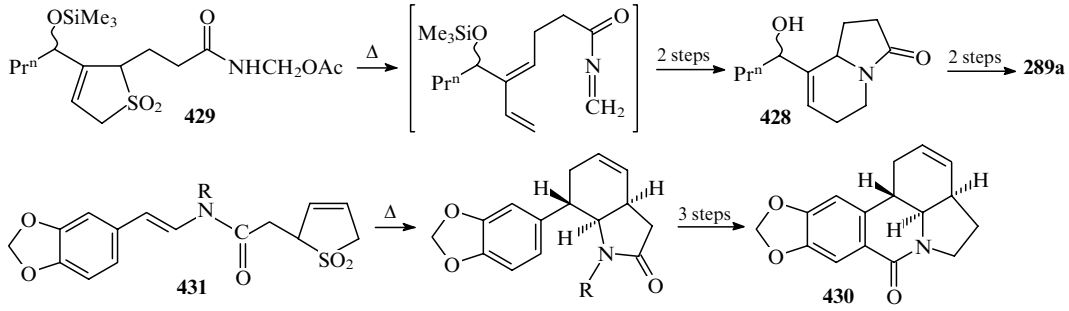
(*a*) PhMe, Δ, 50 min; (*b*)  ; $ZnCl_2$; (*c*) BF_3 , Et_2O; (*d*) PhMe, Δ; (*e*) NaOH.



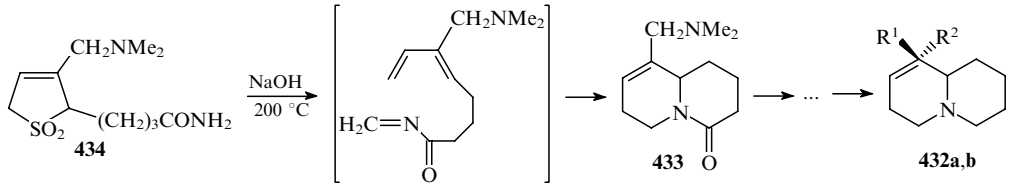
(*a*) LiHMDS; (*b*)  ; (*c*) oxidation; (*d*) Δ; (*e*)  ; (*f*) 80 °C; (*g*)  ; (*h*) MeMgBr; (*i*) $Ph_3P=CH_2$.

intermediate **428** starting from the sulfolene **429.**[374] Elimination of SO_2 and cyclisation were carried out by passing compound **429** through a heated column (370–390 °C) filled with glass helices. Martin *et al.*[375] performed the formal total synthesis of pentacyclic lycorine (a natural plant-growth inhibitor, which is an important alkaloid of the *Amaryllidacae* family) *via* the key precursor lycorane **430**. Sulfolene-containing enamide **431** was used as the starting compound. Short syntheses of racemic lupinine **432a** and epilupinine **432b** were performed starting from bicyclic compound **433**, which has been prepared by pyrolysis and the intramolecular Diels–Alder reaction of disubstituted sulfolene **434**.[376] Analogous conversions of the precursors **435a**,**b**,

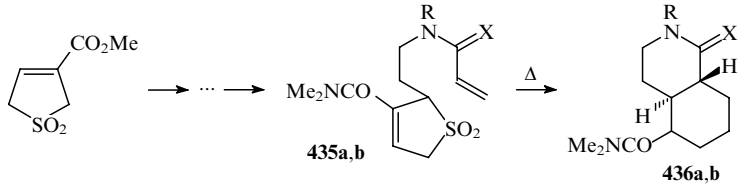
Scheme 14



R = $CH_2C_6H_4OMe$-4.



R^1 = CH_2OH, R^2 = H (**a**); R^1 = H; R^2 = CH_2OH (**b**).

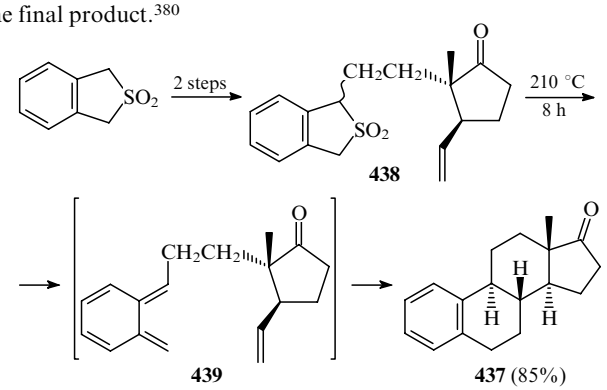


R = $CH_2CH=CH_2$, X = CH_2 (**a**); R = Bn, X = O (**b**).

which have been prepared from 3-methoxycarbonyl-3-sulfolene, afforded the bicyclic systems **436a**,**b**. The latter served as the starting compounds in the synthesis of heteroyohimboids.[377]

The sulfolene grouping has also been used as a protective group in modifications of vitamin D_3. For the purpose of introducing methyl groups at C(6) and C(19)[378] or the fluorine atom at C(19),[379] an adduct of vitamin D_3 with SO_2 at its 1,3-diene fragment has been initially prepared. After completion of the required transformations, the adduct was decomposed by mild thermolysis.

In the total synthesis of racemic estra-1,3,5(10)-trien-17-one (**437**), a mixture of epimers of substituted 1,3-dihydrobenzo[*c*]-thiophene 2,2-dioxide **438** was used as the precursor. This mixture gave rise to the quinodimethane intermediate **439** upon thermal elimination of SO_2, which underwent stereospecific cyclisation to the final product.[380]



VI. Conclusion

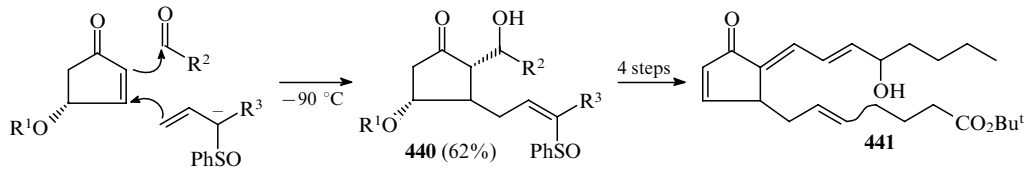
Among reactions of sulfoxides and sulfones playing an important role in the synthesis of natural compounds, alkylation of carbanions obtained from these compounds or the Julia olefination became conventional processes. However, the improvement of these procedures is still in progress. Thus the use of dimethoxyethane as the solvent in the first stage of the Julia olefination[381] in combination with SmI_2 (see Refs 141 and 142) made it possible to construct trisubstituted C=C bonds, which previously failed, for example, in the synthesis of macrolides of the avermectin–melbemycin series.[136, 139]

One would expect that considerable study will be given to the enhancement of the stereoselectivity of catalytic Diels–Alder reactions, particularly, involving nonracemic sulfinyl dienes and dienophiles, to the use of new asymmetric building blocks, for example, chiral (*ee* 95%–99%) allylic sulfones synthesised recently,[382] and to the development of π-allylic alkylation catalysed by transition metals based on the strategy of the transfer of the reaction centre to the remote functional group (for example, in the synthesis of tetracyclic (−)-dendrobine)[383] with the participation of sulfinyl-containing nucleophiles.

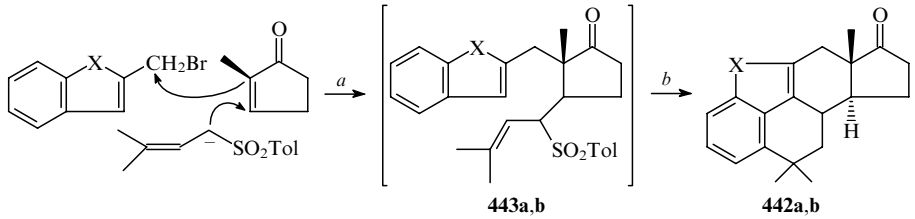
Convergent syntheses (Fuchs[23] took an active part in popularisation of this method) have found a rather wide application in the reactions considered in this review. More modern methodologies, which allow one to perform one-pot syntheses of complex compounds, are not used so often. These procedures are said to be consecutive or tandem processes,[384–386] cascade reactions,[387] processes with the use of counterattacking reagents[388] or polycomponent condensations.[389] The examples of multicomponent reactions considered below demonstrate that this approach to the synthesis of natural compounds is fruitful.

Thus three-component cyclisation of an allylsulfinyl anion with a substituted cyclopentenone and an aldehyde afforded compound **440**. Modification of the latter made it possible to synthesise the prostaglandin derivative **441**.[390] Epithio- and epoxyestratetraenones **442a**,**b**[391] were synthesised by three-component cyclisation involving the allylsulfonyl anion, which made it possible to construct the steroid skeleton with a high stereoselectivity without isolation of the intermediates **443a**,**b**. The synthesis of the alkaloids apoyohimbines **444a**,**b**[392] was based on the cascade process involving the Pictet–Spengler reaction of substituted tryptamines with a sulfolene-containing aldehyde, elimination of SO_2 from the intermediates **445a**,**b** and the intramolecular Diels–Alder reaction. This allows one to perform one-steps introduction of the methoxycarbonyl group at C(22) yielding a pentacyclic reaction product with the stereochemistry of the natural compound (Scheme 15).

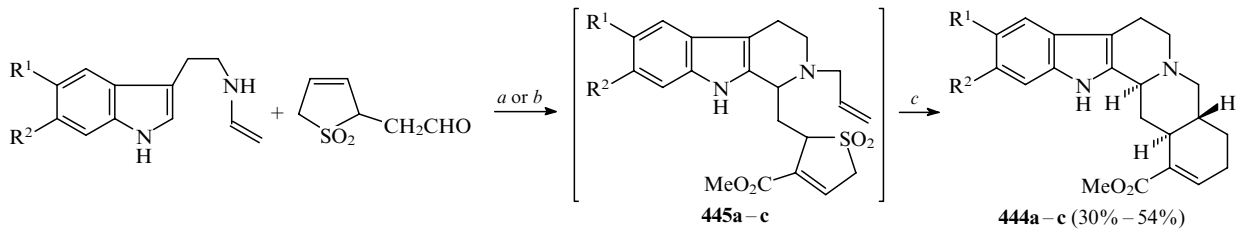
Scheme 15



R^1 = $SiMe_2Bu^t$, R^2 = CH=CHCH(OR¹)$(CH_2)_3$Me; R^3 = $(CH_2)_3CO_2Bu^t$.



X = S (**a**, 92%), O (**b**, 87%); (*a*) DMF, −78 °C; (*b*) $AlCl_3$, 0 °C, 10 min.



R^1 = R^2 = H (**a**); R^1 = OMe, R^2 = H (**b**); R^1 = R^2 = OMe (**c**); (*a*) AcOH, 20 °C, R^1 = H, OMe; R^2 = OMe; (*b*) R^1 = R^2 = H, CF_3CO_2H, 20 °C; (*c*) PhMe, Δ, 18 h.

The area of these investigations would be expected to expand in the near future.

When this review had been prepared for publication, the results of new studies devoted to the applications of sulfoxides and sulfones to the synthesis of natural compounds appeared. The most interesting of them are briefly considered below.

Conventional alkylation–desulfonylation of α-sulfonyl carbanions [393–397] (including those prepared from oxiranes [398]) along with an interesting version of reductive alkylation of 1,1-di(sulfone) with lithium naphthalenide, allyl bromide or sodium amalgam [399] were used for the construction of C–C bonds. Endocyclic C=C bonds were formed by pyrolysis of oxo sulfoxides.[400,401] In addition to the coupling of fragments through the (*E*)-C=C bonds using the classical olefination according to M Julia in the construction of natural molecules,[402–404] the increasing popularity has acquired a modification of this procedure developed by S Julia [405] using model compounds (see Refs 406–417 and references cited therein). The procedure elaborated by S Julia involves the reactions of aldehydes with anions generated from 2-benzothiazolyl sulfones whose participation makes it possible to perform olefination as a one-pot process. Double bonds between the pyrrole rings in natural compounds are formed by successive treatment of a mixture of a sulfone and an aldehyde with DBU and PBu^n_3.[408] The reactions of α-sulfonyl anions [409,410] or anions of chiral sulfoxides [411] with carbonyl compounds were used for binding fragments through the CH_2CO or $CH_2CH(OH)$ groups. Unsaturated sulfones were involved in cyclisation of acyclic γ-hydroxyvinyl sulfones,[412–414] metallation of vinyl sulfones at the C=C bond followed by the introduction of a substituent [415,416] and [4 + 2] cycloaddition of ethynyl sulfones to *N*-Boc-pyrrole.[417,418] Free-radical $Ni(acac)_2$-catalysed arylation of optically active sulfoxide with $Ph_3ZnMgCl$ was also reported.[419] The one-pot diastereoselective synthesis of a complex polycyclic compound by cascade cyclisation involving sulfones or sulfoxides under conditions of radical catalysis was described.[420]

References

1. E Block *J. Chem. Educ.* **48** 814 (1971)
2. S Patai, Z Rappoport, C J M Stirling (Eds) *The Chemistry of Sulfoxides and Sulfones* (New York; London; Chichester: Wiley, 1988)
3. T Durst, in *Comprehensive Organic Chemistry* Vol. 3 (Eds D Barton, W D Ollis) (Oxford: Pergamon Press, 1979)
4. G Krecze, K Shank, in *Methoden der Organischen Chemie (Houben-Weil)* Vol. E-11 (Ed. E Klemann) (Stuttgart: Georg Thieme, 1985) p. 669, 1182
5. E N Prilezhaeva, in *Poluchenie i Svoistva Organicheskikh Soedinenii Sery* (Synthesis and Properties of Organic Compound of Sulfur) (Ed. L I Belen'kii) (Moscow: Khimiya, 1998) p. 115
6. F Montanari, in *Organic Sulfur Chemistry* (Ed. C J M Stirling) (London: Butterworth, 1975) p. 181
7. G Solladie *Synthesis* 185 (1981)
8. G Solladie *Chimia* **38** 233 (1984)
9. G Solladie, in *Asymmetric Synthesis* Vol. 2 (Ed. J D E Morrison) (New York: Academic Press, 1983) p. 184
10. G H Posner, in *Asymmetric Synthesis* Vol. 2 (Ed. J D E Morrison) (New York: Academic Press, 1983) p. 225
11. G H Posner, H Mallarmo, K Miura, M Hulce, in *Asymmetric Reactions and Processes in Organic Chemistry* (Eds E L Eliel, G H Otsuka) (Washington, DC: American Chemical Society, 1982) p. 139
12. M C Carreno *Chem. Rev.* **95** 1717 (1995)
13. G H Solladie, in *Comprehensive Organic Synthesis* Vol. 6 (Eds B M Trost, J E Fleming) (Oxford: Pergamon, 1991) p. 148
14. L I Belen 'kii, in *Khimiya Organicheskikh Soedinenii Sery. Obshchie Voprosy* (The Chemistry of Organic Compounds of Sulfur. General Problems) (Ed. L I Belen'kii) (Moscow: Khimiya, 1988) p. 191
15. H B Kagan, M Sasaki, J Collin *Pure Appl. Chem.* **60** 1725 (1988)
16. G A Molander *Chem. Rev.* **92** 29 (1992)
17. G A Molander, G Hahn *J. Org. Chem.* **51** 1135 (1986)
18. R Pontikis, J Wolf, C Monneret, J-C Florent *Tetrahedron Lett.* **36** 3523 (1995)
19. M Oikawa, W Oikawa, A Ichihara *Tetrahedron Lett.* **34** 4797 (1993)
20. X Creary *J. Org. Chem.* **50** 5080 (1985)
21. N S Simpkins *Tetrahedron* **46** 6951 (1990)
22. N S Simpkins *Sulfones in Organic Synthesis* (New York: Pergamon Press, 1993)
23. T F Braish, P L Fuchs *Chem. Rev.* **86** 903 (1986)
24. Z Jin, P C Vandort, P L Fuchs *Phosphorus Sulfur Silicon Relat. Elem.* **95/96** 1 (1994)
25. T E Bezmenova *Khimiya Tiofen-1,1-dioksidov* (The Chemistry of Thiophene-1,1-dioxides) (Kiev: Naukova Dumka, 1981) p. 690
26. T E Bezmenova *Fiziologicheski Aktivnye Veshchestva* (Physiologically Active Compounds) (Kiev: Naukova Dumka, 1985) No. 17, p. 63
27. A V Lozanova, A M Moiseenkov *Khim. Prir. Soedin.* 133 (1986) [a]
28. N Ya Grigor'eva, V V Veselovsky, A M Moiseenkov *Khim.-Farm. Zh.* **21** 845 (1987) [b]
29. N Ya Grigor'eva, O A Pinsker *Usp. Khim.* **63** 177 (1994) [*Russ. Chem. Rev.* **63** 169 (1994)]
30. A Krief *Tetrahedron* **36** 2531 (1980)
31. F M Stoyanovich, in *Khimiya Organicheskikh Soedinenii Sery. Obshchie Voprosy* (The Chemistry of Organic Compounds of Sulfur. General Problems) (Ed. L I Belen'kii) (Moscow: Khimiya, 1988) p. 128
32. G Boche *Angew. Chem., Int. Ed. Engl.* **28** 277 (1989)
33. B M Trost, T N Salzmann *J. Am. Chem. Soc.* **95** 6840 (1973)
34. B M Trost, W P Conway, P E Stege, T J Dietsche *J. Am. Chem. Soc.* **96** 7165 (1974)
35. B M Trost *Chem. Rev.* **78** 363 (1978)
36. M Julia, J-M Paris *Tetrahedron Lett.* 4833 (1973)
37. M Julia, J-P Stacino *Tetrahedron* **42** 2469 (1986)
38. G Solladie, C Greck, G Demailly, A Solladie-Cavallo *Tetrahedron Lett.* **23** 5047 (1982)
39. G Solladie, G Demailly, C Greck *Tetrahedron Lett.* **26** 435 (1985)
40. B M Trost, T N Salzmann, K Hiroi *J. Am. Chem. Soc.* **98** 4887 (1976)
41. J L Fabre, M Julia, J N Verpeaux *Tetrahedron Lett.* **23** 2469 (1982)
42. B M Trost, M R Ghadiri *J. Am. Chem. Soc.* **106** 7260 (1984)
43. B M Trost, M R Ghadiri *J. Am. Chem. Soc.* **108** 1098 (1986)
44. B M Trost *Bull. Chem. Soc. Jpn.* **61** 107 (1988)
45. D A Evans, G C Andrews *Acc. Chem. Res.* **7** 147 (1974)
46. R W Hoffmann *Angew. Chem., Int. Ed. Engl.* **18** 563 (1979)
47. A M Moiseenkov, V A Dragan, V V Veselovsky *Usp. Khim.* **60** 1255 (1991) [*Russ. Chem. Rev.* **60** 643 (1991)]
48. O De Lucchi, U Miotti, G Modena *Org. React.* **40** 157 (1991)
49. L A Paquette *Org. React.* **25** 1 (1977)
50. F S Guziec Jr , L J SanFilippo *Tetrahedron* **44** 6241 (1988)
51. M Julia, P Ward *Bull. Soc. Chim. Fr.* 3065 (1973)
52. P A Grieco, Y Masaki *J. Org. Chem.* **39** 2135 (1974)
53. H Tanimoto, T Oritani *Tetrahedron* **53** 3527 (1997)
54. D I MaGee, J D Leach, T C Mallais *Tetrahedron Lett.* **38** 1289 (1997)
55. J S Panek, C E Masse *J. Org. Chem.* **62** 8290 (1997)
56. K Mori, J Wu *Liebigs Ann. Chem.* 213 (1991)
57. K Mori, J Wu *Liebigs Ann. Chem.* 83 (1992)
58. K Mori, H Harada, P Zagatti, A Cork, D R Hall *Liebigs Ann. Chem.* 259 (1991)
59. K Mori, J Wu *Liebigs Ann. Chem.* 783 (1991)
60. K Mori, Y Igarashi *Liebigs Ann. Chem.* 717 (1988)
61. K Mori, H Takikawa *Liebigs Ann. Chem.* 497 (1991)
62. K Mori, N Murata *Liebigs Ann. Chem.* 1153 (1994)
63. H Takikawa, Y Shirai, M Kobayashi, K Mori *Liebigs Ann. Chem.* 1965 (1996)
64. K Mori, H Ueda *Tetrahedron Lett.* **22** 461 (1981)
65. V A Dragan, V V Veselovsky, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim.* 1143 (1989) [c]
66. Y Murata, K Inomata, H Kinoshita, H Kotake *Bull. Chem. Soc. Jpn.* **56** 2535 (1983)
67. A M Moiseenkov, R I Ishchenko, V V Veselovsky, V N Odinokov, E V Polunin, B G Kovalev, B A Cheskis, G A Tolstikov *Khim. Prir. Soedin.* 422 (1989) [a]

68. V A Koptenkova, V V Veselovsky, M A Novikova, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim.* 817 (1987) [c]
69. V V Veselovsky, V A Koptenkova, M A Novikova, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim.* 2052 (1989) [c]
70. E V Polunin, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim.* 1568 (1983) [c]
71. N A LeBel, N Balasubramanian *J. Am. Chem. Soc.* **111** 3363 (1989)
72. Y Masaki, K Nagata, Y Serizawa, K Kaji *Tetrahedron Lett.* **23** 5553 (1982)
73. H Miyaoka, Y Saka, S Miura, Y Yamada *Tetrahedron Lett.* **37** 7107 (1996)
74. J A Marshall, D G Cleary *J. Org. Chem.* **51** 858 (1986)
75. C P Astles, E J Thomas *J. Chem. Soc., Perkin Trans. 1* 845 (1997)
76. A B Smith III, J Barbosa, W Wong, J L Wood *J. Am. Chem. Soc.* **117** 10 777 (1995)
77. D Crich, S Natarajan, J Z Crich *Tetrahedron* **53** 7139 (1997)
78. J D White, M A Avery, S C Choudhry, O P Dhingra, M Kang, A J Whittle *J. Am. Chem. Soc.* **105** 6517 (1983)
79. J D White, T R Vedananda, M Kang, S C Choudhry *J. Am. Chem. Soc.* **108** 8105 (1986)
80. B Lygo, C N Rudd *Tetrahedron Lett.* **36** 3577 (1995)
81. B M Trost *Chem. Soc. Rev.* **11** 141 (1982)
82. B M Trost, J E Vincent *J. Am. Chem. Soc.* **102** 5680 (1980)
83. B M Trost, H Hiemstra *J. Am. Chem. Soc.* **104** 886 (1982)
84. B M Trost, D P Curran *J. Am. Chem. Soc.* **103** 7380 (1981)
85. H-J Gais, W A Ball, J Bund *Tetrahedron Lett.* **29** 781 (1988)
86. J-P Demoute, D Hainaut, E Toromanoff *C. R. Hebd. Seances Acad. Sci., Ser. C* **277** 49 (1973)
87. S Lavielle, S Bory, B Moreau, M J Luche, A Marquet *J. Am. Chem. Soc.* **100** 1558 (1978)
88. P C B Page, S M Allin, E W Collington, R A E Carr *Tetrahedron Lett.* **35** 2607 (1994)
89. M A Avery, W K M Chong, C J White *J. Am. Chem. Soc.* **114** 974 (1992)
90. M Julia, D Arnould *Bull. Soc. Chim. Fr. II* 746 (1973)
91. R S H Liu, A E Asato *Tetrahedron* **40** 1931 (1984)
92. P Chabardes, J P Decor, J Varygnat *Tetrahedron* **33** 2799 (1977)
93. P S Marchand, M Rosenberger, G Saucy, P A Wehrli, H Wong, L Chambers, M P Ferro, W Jackson *Helv. Chim. Acta* **59** 387 (1976)
94. A Fischli, H Mayer, W Simon, H-J Stoller *Helv. Chim. Acta* **59** 397 (1976)
95. G L Olson, H-C Cheung, K D Morgan, C Neukom, G Saucy *J. Org. Chem.* **41** 3287 (1976)
96. O Isler, F Kienzle, in *Kirk-Othmer Encyclopedia of Chemical Technology* Vol. 24 (New York: Wiley, 1984) p. 146
97. C Herve du Penhoat, M Julia *Tetrahedron* **42** 4807 (1986)
98. K C Nicolau, D P Papahatjis, D A Claremon, R L Magolda, R E Dolle *J. Org. Chem.* **50** 1440 (1985)
99. Y Ueno, S Aoki, M Okawara *J. Chem. Soc., Chem. Commun.* 683 (1980)
100. D S Brown, M Bruno, R J Davenport, S V Ley *Tetrahedron* **45** 4293 (1989)
101. S V Ley, B Lygo, A Wonnacott *Tetrahedron Lett.* **26** 535 (1985)
102. M T Fletcher, W Kitching *Chem. Rev.* **95** 789 (1995)
103. D Diez-Martin, N R Kotecha, S V Ley, S Mantegani, J C Menendez, H M Organ, A D White, B J Banks *Tetrahedron* **48** 7899 (1992)
104. H G Davies, R H Green *Chem. Soc. Rev.* **20** 211 (1991)
105. C Greck, P Grice, S V Ley, A Wonnacott *Tetrahedron Lett.* **27** 5277 (1986)
106. S V Ley, A Armstrong, D Diez-Martin, M J Ford, P Grice, J G Knight, H C Kolb, A Madin, C A Marby, S Mukherjee, A N Shaw, A M Z Slawin, S Vile, A D White, D J Williams, M Woods *J. Chem. Soc., Perkin Trans. 1* 667 (1991)
107. S V Ley, N J Anthony, A Armstrong, M Gabriella Brasca, T Clarke, D Culshaw, C Greck, P Grice, A B Jones, B Lygo, A Madin, R N Sheppard, A M Z Slawin, D J Williams *Tetrahedron* **45** 7161 (1989)
108. B Lythgoe *Chem. Soc. Rev.* **9** 449 (1980)
109. P J Kocienski *Chem. Ind.* 548 (1981)
110. P J Kocienski *Phosphorus Sulfur Silicon Relat. Elem.* **24** 477 (1985)
111. P J Kocienski, in *Comprehensive Organic Synthesis* Vol. 6 (Eds B M Trost, J E Fleming) (Oxford: Pergamon, 1991) p. 967
112. P J Kocienski, B Lythgoe, S Ruston *J. Chem. Soc., Perkin Trans. 1* 829 (1978)
113. P J Kocienski, B Lythgoe, I Waterhouse *J. Chem. Soc., Perkin Trans. 1* 1045 (1980)
114. G E Keck, K A Savin, M A Weglarz *J. Org. Chem.* **60** 3194 (1995)
115. P J Kocienski, B Lythgoe, D A Roberts *J. Chem. Soc., Perkin Trans. 1* 834 (1978)
116. P J Kocienski, B Lythgoe, I Waterhouse *Tetrahedron Lett.* 4419 (1979)
117. P J Kocienski, B Lythgoe, S Ruston *J. Chem. Soc., Perkin Trans. 1* 1290 (1979)
118. J W Morzycki, H K Schnoes, H F De Luca *J. Org. Chem.* **49** 2148 (1984)
119. P J Kocienski, M Todd *J. Chem. Soc., Perkin Trans. 1* 1777 (1983)
120. P J Kocienski, M Todd *J. Chem. Soc., Perkin Trans. 1* 1783 (1983)
121. N M Hird, T V Lee, T M Leigh, J R Maxwell, T M Peakman *Tetrahedron Lett.* **30** 4867 (1989)
122. G E Keck, D F Kachensky, E J Enholm *J. Org. Chem.* **49** 1462 (1984); **50** 4317 (1985)
123. D R Williams, J L Moore, M Yamada *J. Org. Chem.* **51** 3916 (1986)
124. S Hanessian, N G Cooke, B DeHoff, D Sakito *J. Am. Chem. Soc.* **112** 5276 (1990)
125. D A Evans, R L Dow, T L Shih, J M Takacs, R Zahler *J. Am. Chem. Soc.* **112** 5290 (1990)
126. H Ito, N Imai, K Takao, S Kobayashi *Tetrahedron Lett.* **37** 1799 (1996)
127. D J Hart, W-L Wu, A P Kozikowski *J. Am. Chem. Soc.* **117** 9369 (1995)
128. M P Edwards, S V Ley, S G Lister, B D Palmer, D J Williams *J. Org. Chem.* **49** 3503 (1984)
129. Y Morimoto, A Mikami, S Kuwabe, H Shirahama *Tetrahedron Lett.* **32** 2909 (1991)
130. Y Mori, M Asai, J Kawade, H Furukawa *Tetrahedron* **51** 5315 (1995)
131. S-H Chen, R F Horvath, J Joglar, M J Fisher, S J Danishefsky *J. Org. Chem.* **56** 5834 (1991)
132. R F Horvath, R G Linde II, C M Hayward, J Joglar, D Yohannes, S J Danishefsky *Tetrahedron Lett.* **34** 3993 (1993)
133. H Kigoshi, K Suenaga, T Mutou, T Ishigaki, T Atsumi, H Ishiwata, A Sakakura, T Ogawa, M Ojika, K Yamada *J. Org. Chem.* **61** 5326 (1996)
134. S Hanessian, D Delorme, P C Tyler, G Demailly, Y Chapleur *Can. J. Chem.* **61** 634 (1983)
135. S Hanessian, A Ugolini, P J Hodges, P Beaulieu, D Dube, C Andre *Pure Appl. Chem.* **59** 299 (1987)
136. J D White, G L Bolton, A P Dantanarayana, C M J Fox, R N Hiner, R W Jackson, K Sakuma, U S Warrier *J. Am. Chem. Soc.* **117** 1908 (1995)
137. P J Kocienski, S D A Street, C Yeates, S F Campbell *J. Chem. Soc., Perkin Trans. 1* 2171 (1987)
138. R Baker, M J O'Mahony, C J Swain *J. Chem. Soc., Chem. Commun.* 1326 (1985)
139. A G M Barrett, R A E Carr, S V Attwood, G Richardson, N D A Walshe *J. Org. Chem.* **51** 4840 (1986)
140. G H Lee, H K Lee, E B Choi, B T Kim, C S Pak *Tetrahedron Lett.* **36** 5607 (1995)
141. M Ihara, S Suzuki, T Taniguchi, Y Tokunaga, K Fukumoto *Synlett* 859 (1994)
142. I E Marko, F Murphy, S Dolan *Tetrahedron Lett.* **37** 2089 (1996)
143. M Norte, A Padilla, J J Fernandez, M L Souto *Tetrahedron* **50** 9175 (1994)
144. M Isobe, Y Ichikawa, D-L Bai, H Masaki, T Goto *Tetrahedron* **43** 4767 (1987)
145. Y Ichikawa, M Isobe, D-L Bai, T Goto *Tetrahedron* **43** 4737 (1987)
146. Y Ichikawa, M Isobe, T Goto *Tetrahedron* **43** 4749 (1987)
147. Y Ichikawa, M Isobe, H Masaki, T Kawai, T Goto, C Katayama *Tetrahedron* **43** 4759 (1987)
148. K Takeda, M Urahata, E Yoshii, H Takayanagi, H Ogura *J. Org. Chem.* **51** 4735 (1986)
149. K Takeda, E Kawanishi, H Nakamura, E Yoshii *Tetrahedron Lett.* **32** 4925 (1991)
150. K Takeda, A Nakajima, E Yoshii *Synlett* 249 (1995)

151. D R Williams, P J Coleman, C R Nevill, L A Robinson *Tetrahedron Lett*. **34** 7895 (1993)
152. A S Kende, K Liu, I Kaldor, G Dorey, K Koch *J. Am. Chem. Soc*. **117** 8258 (1995)
153. M Capot, T Cuvigny, C Herve du Penhoat, M Julia, G Loomis *Tetrahedron Lett*. **28** 6273 (1987)
154. N M Ivanova, B A Cheskis, A M Moiseenkov, O M Nefedov *Izv. Akad. Nauk, Ser. Khim*. 2362 (1992) [c]
155. N M Ivanova, B A Cheskis, A M Moiseenkov, O M Nefedov *Izv. Akad. Nauk SSSR, Ser. Khim*. 2521 (1991) [c]
156. A M Moiseenkov, B A Czeskis, N M Ivanova, O M Nefedov *J. Chem. Soc., Perkin Trans. 1* 2639 (1991)
157. T Mandai, T Yanagi, K Araki, Y Morisaki, M Kawada, J Otera *J. Am. Chem. Soc*. **106** 3670 (1984)
158. J Otera, H Misawa, K Sugimoto *J. Org. Chem*. **51** 3830 (1986)
159. T Mandai, T Moriyama, K Tsujimoto, M Kawada, J Otera *Tetrahedron Lett*. **27** 603 (1986)
160. T Moriyama, T Mandai, M Kawada, J Otera, B M Trost *J. Org. Chem*. **51** 3896 (1986)
161. J Otera, H Misawa, T Mandai, T Onishi, S Suzuki, Y Fujita *Chem. Lett,* 1883 (1985)
162. J Otera, H Misawa, T Onishi, S Suzuki, Y Fujita *J. Org. Chem*. **51** 3834 (1986)
163. D G Farnum, T Veysoglu, A M Carde, B Duhl-Emsviller, A Taylor, T A Pancoast, T J Reitz, R T Carde *Tetrahedron Lett*. 4009 (1977)
164. T Satoh, T Oohara, Y Ueda, K Yamakawa *Tetrahedron Lett*. **29** 313 (1988)
165. T Sato, T Ytoh, T Fujisawa *Tetrahedron Lett*. **28** 5677 (1987)
166. G Stork, I Paterson, F K C Lee *J. Am. Chem. Soc*. **104** 4686 (1982)
167. S Masamune, P Ma, H Okumoto, J W Ellinghoe, Y Ito *J. Org. Chem*. **49** 2834 (1984)
168. G Solladie, G Moine *J. Am. Chem. Soc*. **106** 6097 (1984)
169. G Solladie, F Matloubi-Moghadam *J. Org. Chem*. **47** 91 (1982)
170. E J Corey, L O Weigel, A R Chamberlin, H Cho, D H Hua *J. Am. Chem. Soc*. **102** 6613 (1980)
171. J Nakami, T Taniguchi, S Gomyo, T Kakihara *Chem. Lett*. 1103 (1994)
172. S Yamagiwa, H Sato, N Hoshi, H Kosugi, H Uda *J. Chem. Soc., Perkin Trans. 1* 570 (1979)
173. R Tanikaga, Y Nozaki, T Tamura, A Kaji *Synthesis* 134 (1983)
174. K Burgess, I Henderson *Tetrahedron Lett*. **30** 4325 (1989)
175. H Tabuchi, T Hamamoto, S Miki, T Tejima, A Ichihara *J. Org. Chem*. **59** 4749 (1994)
176. K J Hale, J Cai *Tetrahedron Lett*. **37** 4233 (1996)
177. T Yoshida, S Saito *Bull. Chem. Soc. Jpn*. **55** 3047 (1982)
178. T E Alvarez, T Cuvigny, C Herve du Penhoat, M Julia *Tetrahedron* **44** 119 (1988)
179. S Hanessian, T A Grillo *J. Org. Chem*. **63** 1049 (1998)
180. B Lygo *Synlett* 793 (1992)
181. A Bartlett, F R Green III *J. Am. Chem. Soc*. **100** 4858 (1978)
182. H-J Gais, T Leed *Angew. Chem., Int. Ed. Engl*. **23** 145 (1984)
183. B M Trost, J Lynch, P Renaut, D H Steinman *J. Am. Chem. Soc*. **108** 284 (1986)
184. D F Taber, L J Silverberg, E D Robinson *J. Am. Chem. Soc*. **113** 6630 (1991)
185. S H Kang, W J Kim, Y B Chae *Tetrahedron Lett*. **29** 5169 (1988)
186. A M Moiseenkov, B T Zhuzbaev, V V Veselovsky, K M Turdybekov, A V Buevich, S M Adekenov, Yu T Struchkov *Izv. Akad. Nauk, Ser. Khim*. 126 (1993) [c]
187. V V Veselovsky, B T Zhuzbaev, A M Moiseenkov *Mendeleev Commun*. 167 (1992)
188. E L Grimm, M L Coutu, S Levac, in *The 16th International Symposium on the Organic Chemistry of Sulfur (ISOCS) (Abstracts of Reports), Merseburg, 1994* p. 119
189. G Solladie, C Frechou, G Demailly, C Greck *J. Org. Chem*. **51** 1912 (1986)
190. G Solladie, A Rubio, M C Carreno, J L Garcia Ruano *Tetrahedron Asymmetry* **1** 187 (1990)
191. G Solladie, C Gerber *Synlett* 449 (1992)
192. G Solladie, C Ziani-Cherif, F Jesser *Tetrahedron Lett*. **33** 931 (1992)
193. G Solladie, O Lohse *J. Org. Chem*. **58** 4555 (1993)
194. E J Corey, P Carpino *Tetrahedron Lett*. **31** 7555 (1990)
195. J Nokami, M Ohkura, Y Dan-oh, Y Sakamoto *Tetrahedron Lett*. **32** 2409 (1991)
196. G Solladie, J Hutt, C Frechou *Tetrahedron Lett*. **28** 61 (1987)
197. G Solladie, C Dominguez *J. Org. Chem*. **59** 3898 (1994)
198. J L Garcia Ruano, A M Martin Castro, H Rodriguez *J. Org. Chem*. **59** 533 (1994)
199. K Mori, Y Takahashi *Liebigs Ann. Chem*. 1057 (1991)
200. P-u Park, C A Broca, B F Johnson, Y Kishi *J. Am. Chem. Soc*. **109** 6205 (1987)
201. H Naito, E Kawahara, K Maruta, M Maeda, S Sasaki *J. Org. Chem*. **60** 4419 (1995)
202. J E Baldwin, R M Adlington, D Bebbington, A T Russell *Tetrahedron* **50** 12015 (1994)
203. D Tanner, H M He *Tetrahedron* **45** 4309 (1989)
204. M T Mujica, M M Afonso, A Galindo, J A Palanzuela *Synlett* 983 (1996)
205. M R Binns, R K Haynes, A G Katsifis, P A Schober, S C Vonwiller *J. Am. Chem. Soc*. **110** 5411 (1988)
206. R K Haynes, A G Katsifis, S C Vonwiller, T W Hambley *J. Am. Chem. Soc*. **110** 5423 (1988)
207. D H Hua, G Sinai-Zingde, S Venkataraman *J. Am. Chem. Soc*. **107** 4088 (1985)
208. D H Hua, S Venkataraman, R A Ostrander, G-Z Sinai, P J McCann, M J Coulter, M R Xu *J. Org. Chem*. **53** 507 (1988)
209. D H Hua, S Venkataraman, R Chan-Yu-King, J V Paukstelis *J. Am. Chem. Soc*. **110** 4741 (1988)
210. D H Hua *J. Am. Chem. Soc*. **108** 3835 (1986)
211. D H Hua, M J Coulter, I Badejo *Tetrahedron Lett*. **28** 5465 (1987)
212. L L Vasil'eva, V I Mel'nikova, E T Gaidullina, K K Pivnitskii *Zh. Org. Khim*. **19** 941 (1983) [d]
213. D H Hua, J-G Park, T Katsuhira, S N Bharathi *J. Org. Chem*. **58** 2144 (1993)
214. D H Hua, S N Bharathi, J A K Panangadan, A Tsujimoto *J. Org. Chem*. **56** 6998 (1991)
215. K Ogura, G Tsuchihashi *J. Am. Chem. Soc*. **96** 1960 (1974)
216. J Martel, C Huynh, E Toromanoff, G Nomine *Bull. Soc. Chim. Fr*. 982 (1967)
217. J Martel, C Huynh *Bull. Soc. Chim. Fr*. 985 (1967)
218. L Velluz, J Martel, G Nomine *C.R. Hebd. Seances Acad. Sci., Ser. C* **268** 2199 (1969)
219. M Julia, A Guy-Rouaoult *Bull. Soc. Chim. Fr*. 1411 (1967)
220. R V M Campbell, L Crombie, D A R Findley, R W King, G Pattenden, D A Whiting *J. Chem. Soc., Perkin Trans. 1* 897 (1975)
221. F M Hauser, R P Rhee *J. Org. Chem*. **43** 178 (1978)
222. F M Hauser, R P Rhee *J. Org. Chem*. **45** 3061 (1980)
223. F M Hauser, D Mal *J. Am. Chem. Soc*. **106** 1862 (1984)
224. F M Hauser, P Hewawasam, D Mal *J. Am. Chem. Soc*. **110** 2919 (1988)
225. F M Hauser, S Prasanna, D W Combs *J. Org. Chem*. **48** 1328 (1983)
226. F M Hauser, D W Combs *J. Org. Chem*. **45** 4071 (1980)
227. F M Hauser, S Prasanna *J. Am. Chem. Soc*. **103** 6378 (1981)
228. F M Hauser, D Mal *J. Am. Chem. Soc*. **106** 1098 (1984)
229. F M Hauser, D Mal *J. Am. Chem. Soc*. **105** 5688 (1983)
230. F M Hauser, V M Baghdanov *Tetrahedron* **40** 4719 (1984)
231. F M Hauser, S Prasanna *Tetrahedron* **40** 4711 (1984)
232. F M Hauser, P Hewawasam, Y S Rho *J. Org. Chem*. **54** 5110 (1989)
233. F M Hauser, R A Tommasi *J. Org. Chem*. **56** 5758 (1991)
234. F M Hauser, Y Caringal *J. Org. Chem*. **55** 555 (1990)
235. D Mal, N K Hazra *Tetrahedron Lett*. **37** 2641 (1996)
236. R A Russell, N W Warrener *J. Chem. Soc., Chem. Commun*. 108 (1981)
237. M G Dolson, B L Chenard, J S Swenton *J. Am. Chem. Soc*. **103** 5263 (1981)
238. A I Meyers, W B Avila *J. Org. Chem*. **46** 3881 (1981)
239. Y Tamura, M Sasho, S Akai, A Wada, Y Kita *Tetrahedron* **40** 4539 (1984)
240. M D Mashkovskii *Lekarstvennye Sredstva* (Medicinals) (Moscow: Novaya Volna, 1996) Vol. 2, p. 2615
241. B M Trost *Tetrahedron* **33** 2615 (1977)
242. J Tsuji *Tetrahedron* **42** 4361 (1986)
243. J Tsuji *Palladium Reagents in Catalysis* (New York: Wiley, 1995)

244. B M Trost, L Weber *J. Org. Chem.* **40** 3617 (1975)
245. P S Manchand, H S Wong, J F Blount *J. Org. Chem.* **43** 4769 (1978)
246. J Tsuji, I Shimizu, I Minami, Y Ohashi, T Sugiura, K Takahashi *J. Org. Chem.* **50** 1523 (1985)
247. D Eren, E Keinan *J. Am. Chem. Soc.* **110** 4356 (1988)
248. R Bouzbouz, B Kirschleger *Synthesis* 714 (1994)
249. R Bouzbouz, B Kirschleger *Synlett* 763 (1994)
250. B M Trost *Angew. Chem., Int. Ed. Engl.* **28** 1173 (1989)
251. A Heumann, M Reglier *Tetrahedron* **51** 975 (1995)
252. J P Genet, G M Gaudin *Tetrahedron* **43** 5315 (1987)
253. F Colobert, J P Genet *Tetrahedron Lett.* **26** 2779 (1985)
254. A S Kende, I Kaldor, R Aslanian *J. Am. Chem. Soc.* **110** 6265 (1988)
255. J A Marshall, R C Andrews, L Lebioda *J. Org. Chem.* **52** 2378 (1987)
256. B M Trost, T R Verhoeven *J. Am. Chem. Soc.* **101** 1595 (1979)
257. B M Trost, T R Verhoeven *Tetrahedron Lett.* 2275 (1978)
258. B M Trost, T R Verhoeven *J. Am. Chem. Soc.* **99** 3867 (1977)
259. A Brandes, H M R Hoffmann *Tetrahedron* **51** 145 (1995)
260. H M R Hoffmann, A Brandes *Tetrahedron* **51** 155 (1995)
261. J Pohlmann, C Sabater, H M R Hoffmann *Angew. Chem., Int. Ed. Engl.* **37** 633 (1998)
262. B M Trost, S J Brickner *J. Am. Chem. Soc.* **105** 568 (1983)
263. B M Trost, M Ohmori, S A Boyd, H Okawara, S J Brickner *J. Am. Chem. Soc.* **111** 8281 (1989)
264. B M Trost, J T Hane, P Metz *Tetrahedron Lett.* **27** 5695 (1986)
265. S A Godleski, E V Villhauer *J. Org. Chem.* **51** 486 (1986)
266. A Furstner, H Weintritt *J. Am. Chem. Soc.* **120** 2817 (1998)
267. C A Kingsbury, D J Cram *J. Am. Chem. Soc.* **82** 1810 (1960)
268. T Yoshimura, E Tsukurimishi, Y Iizuka, H Mizuno, H Isaji, C Shimasaki *Bull. Chem. Soc. Jpn.* **62** 1891 (1989)
269. B M Trost, K K Leung *Tetrahedron Lett.* 4197 (1975)
270. B M Trost, T N Salzmann *J. Org. Chem.* **40** 148 (1975)
271. J H Babler, R A Haack *J. Org. Chem.* **47** 4801 (1982)
272. K C Nicolaou, R E Zipkin, N A Petasis *J. Am. Chem. Soc.* **104** 5558 (1982)
273. K Ishigami, T Kitahara *Tetrahedron* **51** 6431 (1995)
274. H Konno, H Makabe, A Tanaka, T Oritani *Tetrahedron* **52** 9399 (1996)
275. K Tanaka, H Ushio, Y Kawabata, H Suzuki *J. Chem. Soc., Perkin Trans. 1* 1445 (1991)
276. D F Taber, B P Gunn *J. Org. Chem.* **44** 450 (1979)
277. J R Williams, J D Leber *Synthesis* 427 (1977)
278. D N Jones, A C F Edmonds, S D Knox *J. Chem. Soc., Perkin Trans. 1* 459 (1976)
279. S I Goldberg, M S Sahli *J. Org. Chem.* **32** 2059 (1967)
280. D H Hua, S N Bharathi, P D Robertson, B A Tsujimoto *J. Org. Chem.* **55** 2128 (1990)
281. T Ohnuma, T Oishi, Y Ban *J. Chem. Soc., Chem. Commun.* 301 (1973)
282. K Seki, T Ohnuma, T Oishi, Y Ban *Tetrahedron Lett.* 723 (1975)
283. Y Ban, T Ohnuma, K Seki, T Oishi *Tetrahedron Lett.* 727 (1975)
284. R E Donaldson, P L Fuchs *J. Am. Chem. Soc.* **103** 2108 (1981)
285. D K Hutchinson, P L Fuchs *J. Am. Chem. Soc.* **109** 4755 (1987)
286. J E Toth, P R Hamann, P L Fuchs *J. Org. Chem.* **53** 4694 (1988)
287. T P Burkholder, P L Fuchs *J. Am. Chem. Soc.* **110** 2341 (1988)
288. T P Burkholder, P L Fuchs *J. Am. Chem. Soc.* **112** 9601 (1990)
289. M Isobe, in *Perspectives of Organic Chemistry of Sulfur* Vol. 28 (Eds B Zwanenberg, A J H Klunder) (Amsterdam: Elsevier, 1987) p. 209
290. M Isobe, M Kitamura, T Goto *Tetrahedron Lett.* 3465 (1979)
291. M Isobe, Y Ichikawa, Y Funabashi, S Mio, T Goto *Tetrahedron* **42** 2863 (1986)
292. M Kitamura, M Isobe, Y Ichikawa, T Goto *J. Org. Chem.* **49** 3517 (1984)
293. M Isobe, M Kitamura, T Goto *J. Am. Chem. Soc.* **104** 4997 (1982)
294. M Kitamura, M Isobe, Y Ichikawa, T Goto *J. Am. Chem. Soc.* **106** 3252 (1984)
295. Y Jiang, M Isobe *Tetrahedron* **52** 2877 (1996)
296. Y Jiang, Y Ichikawa, M Isobe *Tetrahedron* **53** 5103 (1997)
297. K Tsuboi, Y Ichikawa, Y Jiang, A Naganawa, M Isobe *Tetrahedron* **53** 5123 (1997)
298. G H Posner *Acc. Chem. Res.* **20** 72 (1987)
299. G H Posner, J P Mallamo, K Miura *J. Am. Chem. Soc.* **103** 2886 (1981)
300. G H Posner, M J Chapdelaine, C M Lentz *J. Org. Chem.* **44** 3661 (1979)
301. G H Posner, C Switzer *J. Am. Chem. Soc.* **108** 1239 (1986)
302. G H Posner, M Hulce, J P Mallamo, S A Drexler, J Clardy *J. Org. Chem.* **46** 5244 (1981)
303. G H Posner, T P Kogan, M Hulce *Tetrahedron Lett.* **25** 383 (1984)
304. G H Posner, E Asirvatham *J. Org. Chem.* **50** 2589 (1985)
305. G H Posner, T P Kogan, S R Haines, L L Frye *Tetrahedron Lett.* **25** 2627 (1984)
306. G H Posner, M Weitzberg, T G Hamill, E Asirvatham, H Cun-Heng, J Clardy *Tetrahedron* **42** 2919 (1986)
307. R A Holton, R M Kennedy, H B Kim, M E Krafft *J. Am. Chem. Soc.* **109** 1597 (1987)
308. K Mori, S Aki, M Kido *Liebigs Ann. Chem.* 83 (1993)
309. J C Carretero, R G Arrayas, I S de Gracia *Tetrahedron Lett.* **37** 3379 (1996)
310. N Toyooka, Y Yotsui, Y Yoshida, T Momose *J. Org. Chem.* **61** 4882 (1996)
311. M B Berry, G J Rowlands, D Craig, P S Jones *Chem. Commun.* 2141 (1997)
312. C Iwata, K Hattori, S Uchida, T Imanishi *Tetrahedron Lett.* **25** 2995 (1984)
313. C Iwata, Y Moritani, K Sugiyama, M Fujita, T Imanishi *Tetrahedron Lett.* **28** 2255 (1987)
314. C Iwata, M Fujita, K Hattori, S Uchida, T Imanishi *Tetrahedron Lett.* **26** 2221 (1985)
315. C Iwata, M Fujita, Y Moritani, K Hattori, T Imanishi *Tetrahedron Lett.* **28** 3135 (1987)
316. S G Pyne, P Bloem, S L Chapman, C E Dixon, R Griffith *J. Org. Chem.* **55** 1086 (1990)
317. S G Pyne, S L Chapman *J. Chem. Soc., Chem. Commun.* 1688 (1986)
318. A W M Lee, W H Chan, Y Tao, Y K Lee *J. Chem. Soc., Perkin Trans. 1* 477 (1994)
319. N Itoh, H Matsuyama, M Yoshida, N Kamagata, M Iyoda *Bull. Chem. Soc. Jpn.* **68** 3121 (1995)
320. E N Prilezhaeva, L V Tsymbal, M F Shostakovskii *Dokl. Akad. Nauk SSSR* **138** 122 (1961) [c]
321. O De Lucci, G Modena *Tetrahedron* **40** 2585 (1984)
322. O De Lucci, L Pasquato *Tetrahedron* **44** 6755 (1988)
323. L A Paquette, H-S Lin, M J Coghlan *Tetrahedron Lett.* **28** 5017 (1987)
324. L A Paquette, H-S Lin, B P Gunn, M J Coghlan *J. Am. Chem. Soc.* **110** 5818 (1988)
325. S F Martin, B G Anderson, D Daniel, A Gaucher *Tetrahedron* **53** 8997 (1997)
326. C Herdeis, C Hartke *Heterocycles* **29** 287 (1989)
327. C Herdeis, C Hartke-Karger *Liebigs Ann. Chem.* 99 (1991)
328. D Gomez-Pardo, J d'Angelo *Tetrahedron Lett.* **33** 6637 (1992)
329. T Kametani, M Aizawa, H Nemoto *Tetrahedron* **37** 2547 (1981)
330. D Craig, D A Fischer, O Kemal, A Marsh, T Plessner, A M Z Slawin, D J Williams *Tetrahedron* **47** 3095 (1991)
331. M C Clasby, D Craig, A Marsh *Angew. Chem., Int. Ed. Engl.* **32** 1444 (1993)
332. G-D Zhu, W H Okamura *Chem. Rev.* **95** 1877 (1995)
333. M C Clasby, D Craig, A A Jaxa-Chamiec, J Y Q Lai, A Marsh, A M Z Slawin, A J P White, D J Williams *Tetrahedron* **52** 4769 (1996)
334. E J Corey, P Da Silva Jardine, T Mohri *Tetrahedron Lett.* **29** 6409 (1988)
335. E J Corey, P Da Silva Jardine, J C Rohloff *J. Am. Chem. Soc.* **110** 3672 (1988)
336. E J Corey, P Da Silva Jardine *Tetrahedron Lett.* **30** 7297 (1989)
337. S Danishefsky, F J Walker *J. Am. Chem. Soc.* **101** 7018 (1979)
338. S Danishefsky, M Hirama, N Fritsch, J Clardy *J. Am. Chem. Soc.* **101** 7013 (1979)
339. S Danishefsky *Tetrahedron* **53** 8689 (1997)
340. C Maignan, R A Raphael *Tetrahedron* **39** 3245 (1983)
341. Y Arai, S Kuwayama, Y Takeuchi, T Koizumi *Synth. Commun.* **16** 233 (1986)
342. C Maignan, F Belkasmioui *Tetrahedron Lett.* **29** 2823 (1988)

343. J Martynow, M Dimitroff, A G Fallis *Tetrahedron Lett*. **34** 8201 (1993)
344. Y Arai, M Yamamoto, T Koizumi *Chem. Lett*. 1225 (1986)
345. Y Arai, M Yamamoto, T Koizumi *Bull. Chem. Soc. Jpn*. **61** 467 (1988)
346. Y Arai, K Hayashi, M Matsui, T Koizumi, M Shiro, K Kuriyama *J. Chem. Soc., Perkin Trans. 1* 1709 (1991)
347. Y Arai, Y Hayashi, M Yamamoto, H Takayema, T Koizumi *J. Chem. Soc., Perkin Trans. 1* 3133 (1988)
348. T Takayama, A Isobe, T Koizumi *Chem. Pharm. Bull*. **35** 433 (1987)
349. M Lee, I Ikeda, T Kawabe, S Mori, K Kanematsu *J. Org. Chem*. **61** 3406 (1996)
350. T Takahashi, A Isobe, Y Arai, T Koizumi *Synthesis* 189 (1989)
351. H Takayama, K Hayashi, T Koizumi *Tetrahedron Lett*. **27** 5509 (1986)
352. Y Arai, M Matsui, T Koizumi, M Shiro *J. Org. Chem*. **56** 1983 (1991)
353. Y Arai, T Kontani, T Koizumi *Chem. Lett*. 2135 (1991)
354. I Alonso, J C Carretero, J L Garcia Ruano *J. Org. Chem*. **59** 1499 (1994)
355. I Alonso, J C Carretero, J L Garcia Ruano, L M Martin Cabrejas, I Lopez Solera, P Raithby *Tetrahedron Lett*. **35** 9461 (1994)
356. D A Evans, C A Bryan, C L Sims *J. Am. Chem. Soc*. **94** 2891 (1972)
357. G H Posner *Pure Appl. Chem*. **62** 1949 (1990)
358. G H Posner, A Haces, W Harrison, C M Kinter *J. Org. Chem*. **52** 4836 (1987)
359. G H Posner, T D Nelson *Tetrahedron* **46** 4573 (1990)
360. G H Posner, C M Kinter *J. Org. Chem*. **55** 3967 (1990)
361. G H Posner, D G Wettlaufer *J. Am. Chem. Soc*. **108** 7373 (1986)
362. G H Posner, D G Wettlaufer *Tetrahedron Lett*. **27** 667 (1986)
363. V V Veselovsky, Z G Makarova, A I Lutsenko, N A Shpiro, V M Zhulin, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim*. 810 (1988) [c]
364. M J Kurth, D H Burns, M J O'Brien *J. Org. Chem*. **49** 731 (1984)
365. R A Gibbs, K Bartels, R W K Lee, W H Okamura *J. Am. Chem. Soc*. **111** 3717 (1989)
366. M C Aversa, A Barattucci, P Bonaccorsi, P Giannetto, D N Jones *J. Org. Chem*. **62** 4376 (1997)
367. P Gosselin, E Bonfand, C Maignan *Synthesis* 1079 (1996)
368. P Gosselin, E Bonfand, C Maignan *J. Org. Chem*. **61** 9049 (1996)
369. S S P Chou, W H Lee *Synthesis* 219 (1990)
370. A V Lozanova, V P Gul'tyai, A N Karaseva, A M Moiseenkov *Izv. Akad. Nauk SSSR, Ser. Khim*. 1370 (1983) [c]
371. J D Winkler, H S Kim, S Kim *Tetrahedron Lett*. **36** 687 (1995)
372. S R Desai, V K Gore, S V Bhat *Synth. Commun*. **20** 523 (1990)
373. T S Chou, S G Lee, N K Yao *Tetrahedron* **45** 4113 (1989)
374. H F Schmitthenner, S M Weinreb *J. Org. Chem*. **45** 3372 (1980)
375. S F Martin, C-y Tu, M Kimura, S H Simonsen *J. Org. Chem*. **47** 3634 (1982)
376. T Nomoto, H Takayama *Heterocycles* **23** 2913 (1985)
377. J Leonard, S P Fearnley, D M B Hickey *Synlett* 272 (1992)
378. S Yamada, T Suzuki, H Takayama *Tetrahedron Lett*. **22** 3085 (1981)
379. Y Iwasaki, M Shimizu, T Hirosawa, S Yamada *Tetrahedron Lett*. **37** 6753 (1996)
380. K C Nicolaou, W E Barnette, P Ma *J. Org. Chem*. **45** 1463 (1980)
381. D J Hart, W L Wu *Tetrahedron Lett*. **37** 5283 (1996)
382. B M Trost, M G Organ, G A O'Doherty *J. Am. Chem. Soc*. **117** 9662 (1995)
383. B M Trost, A S Tasker, G Rüther, A Brandes *J. Am. Chem. Soc*. **113** 670 (1991)
384. T L Ho *Tandem Organic Reactions* (New York: Wiley, 1992)
385. L F Tietze, U Beifuss *Angew. Chem., Int. Ed. Engl*. **32** 131 (1993)
386. R A Bunce *Tetrahedron* **51** 13103 (1995)
387. D P Curran, H Liu, H Iosien, S-B Ko *Tetrahedron* **52** 11385 (1996)
388. J R Hwu, S-C Tsay *Chem. Commun*. 161 (1998)
389. G H Posner *Chem. Rev*. **86** 831 (1986)
390. J Nokami, T Ono, S Wakabayashi, A Hazato, S Kurozumi *Tetrahedron Lett*. **26** 1985 (1985)
391. J P Adams, I Bowler, M A Collins, D N Jones, S Swallow *Tetrahedron Lett*. **31** 4355 (1990)
392. J Leonard, A B Hague, M F Jones *Tetrahedron Lett*. **38** 3071 (1997)
393. C E Masse, M Yang, J Solomon, J S Panek *J. Am. Chem. Soc*. **120** 4123 (1998)
394. H Miyoka, Y Isaji, Y Kajiwara, I Kunimune, Y Yamada *Tetrahedron Lett*. **39** 6503 (1998)
395. C H Heathcock, R C D Brown, T C Norman *J. Org. Chem*. **63** 5013 (1998)
396. K Domon, H Takikawa, K Mori *Eur. J. Org. Chem*. 981 (1999)
397. Y Shirai, M Seki, K Mori *Eur. J. Org. Chem*. 3139 (1999)
398. Y Mori, K Yaegashi, H Furukawa *J. Org. Chem*. **63** 6200 (1998)
399. A Fürstner, T Gastner, J Rust *Synlett* 29 (1999)
400. H Kosugi, J Ku, M Kato *J. Org. Chem*. **63** 6939 (1998)
401. A Sinha, Sa C Sinha, Su C Sinha, E Keinan *J. Org. Chem*. **64** 2381 (1998)
402. D A Evans, P H Carter, E M Carreira, A B Charette, J A Prunet, M Lautens *J. Am. Chem. Soc*. **121** 7540 (1999)
403. H M Eng, D C Myles *Tetrahedron Lett*. **40** 2275 (1999)
404. N Toyooka, M Okamura, H Takahata *J. Org. Chem*. **64** 2182 (1999)
405. J B Baudin, G Harean, S A Julia, O Ruel *Tetrahedron Lett*. **32** 1175 (1991)
406. P R Blakemore, P J Kocienski, S Marzcak, J Wicha *Synthesis* 1209 (1999)
407. J A Lafontaine, D P Provencal, C Gardelli, J W Leahy *Tetrahedron Lett*. **40** 4145 (1999)
408. T Kakiuchi, H Kinoshita, K Inomato *Synlett (Spec. Issue)* 901 (1999)
409. L A Paquette, L Barriault, D Pissarnitski *J. Am. Chem. Soc*. **121** 4542 (1999)
410. A Arnone, P Bravo, W Panzeri, F Viani, M Zanda *Eur. J. Org. Chem*. 117 (1999)
411. G Solladig, N Wilb, C Bauder *Eur. J. Org. Chem*. 3021 (1999)
412. J C Carretero, R G Arrayes *Synlett* 49 (1999)
413. J C Carretero, R G Arrayes, I S de Gracia *Tetrahedron Lett*. **38** 8537 (1997)
414. J de Vicente, R G Arrayes, J Canada, J C Carretero *Synlett* 53 (2000)
415. J G Urones, I S Marcos, N M Garrido, P Basabe, S G San Feliciano, R Coca, D Diez *Synlett* 1364 (1998)
416. O Arjona, F Iradier, J Plumet, M P Martinez-Alcazar, H Hernvndez-Cano, I Fonseca *Tetrahedron Lett*. **39** 6741 (1999)
417. C D Jones, N S Simpkins, G M P Giblin *Tetrahedron Lett*. **39** 1021; 1023 (1998)
418. L E Brieaddy, F Liang, P Abraham, J R Lee, F I Garroll *Tetrahedron Lett*. **39** 5321 (1998)
419. I N Houpis, A Molina, I Dorziotis, R A Reamer, R P Volante, P J Reider *Tetrahedron Lett*. **38** 7131 (1997)
420. P Devin, L Fensterbank, M Malacria *J. Org. Chem*. **63** 6764 (1998)

[a] — *Chem. Nat. Compd. (Engl. Transl.)*
[b] — *Chem. Pharm. J. (Engl. Transl.)*
[c] — *Russ. Chem. Bull. (Engl. Transl.)*
[d] — *Russ. J. Org. Chem. (Engl. Transl.)*
[e] — *Dokl. Chem. Technol., Dokl. Chem. (Engl. Transl.)*