Applications of Sulfoxides to Asymmetric Synthesis of Biologically Active Compounds

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Contents

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I. Introduction

The sulfinyl group is now widely used as an important tool to bring about numerous asymmetric transformations. The efficacy of the sulfoxide in diastereoselective auxiliary-induced reactions is mainly due to the steric and stereoelectronic differences existing between the substituents of the stereogenic sulfur atom: a lone electron pair, an oxygen, and two different carbon ligands, which are able to differentiate the diastereotopic faces of a proximal or even remote reaction center. Besides the high configurational stability of the sulfinyl group,[1,2] the existence of several efficient methods to obtain homochiral sulfoxides[3–7] as well as their synthetic versatility has led to a substantial growth of the use of these chiral starting materials in the synthesis of enantiomerically enriched materials over the last two decades. Several major reviews have given evidence of this expansion. Most of them mainly focus on methods for obtaining optically active sulfoxides[3–7] and applications to asymmetric reduction of β-keto sulfoxides,[7] Michael addition of nucleophiles to activated α,β-unsaturated sulfoxides,[8] C–C bond formation using sulfoxide-stabilized carbanions,[4,9–11] or Diels–Alder reactions of vinyl sulfoxides.[7] General surveys on chiral organosulfur compounds also include some aspects of the sulfoxide-directed asymmetric reactions.[12]

Although all these reviews provided a general view of the usefulness of sulfoxides, none of them focused on the importance of their applications to the synthesis of natural products and biologically active compounds. With these considerations in mind, this review is an attempt to present the examples where the enantiomerically pure sulfinyl group has been used successfully to control the stereochemistry of the product in the key step of the total synthesis of biologically active compounds. Moreover, the overall transformations giving rise to the final target molecule are presented. The review is divided into nine sections. The first part deals with the synthetic methods applied mainly after 1992 to obtain optically active sulfoxides. In the following sections, the

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reactions making possible the stereoselective generation of new stereogenic centers by means of sulfoxides are chosen as criteria to present their applications in total synthesis.

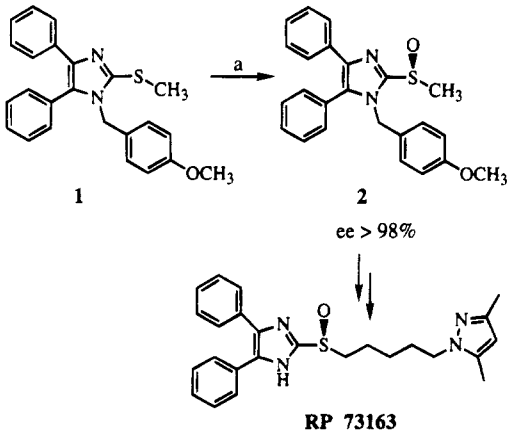
II. Synthesis of Homochiral Sulfoxides

A. Asymmetric Oxidation of Thioethers

Several methods are presently available to obtain optically active sulfoxides: optical resolution, asymmetric oxidation, and asymmetric synthesis. The optical resolution procedure was thoroughly reviewed by Mikolajczyk,[13] and biocatalytic resolutions are acquiring increasing importance in the cases where additional ester[14] or carbinol[15] groups are present in the molecule. Although efficient diastereoselective thioether oxidations have been described[16] with the obtention of optically active sulfoxides, the method was only effectively applied to bornyl derivatives.[15,17] More general are the methods based on asymmetric oxidation and asymmetric synthesis. Recent improvements achieved in both processes are worthy of comment.

The first examples of asymmetric oxidation of sulfides to sulfoxides were independently reported by Kagan[18] and Modena[19] in 1984 by using a modified Sharpless epoxidation reagent [$Ti(OPr^i)_4$/(+)-DET/Bu^tOOH]. Further development of this methodology[20] showed an increase in the optical purity of the resulting sulfoxide by replacing the oxidant by cumene hydroperoxide. In these conditions aryl methyl sulfoxides could be obtained in 86−90% ee. Monosulfoxides derived from 2-methyl-1,3-benzenedithiol[21] or from 2-substituted 1,3-dithianes[22] could also be obtained in an optically active form by this method. Kagan's procedure has been recently applied to a large-scale asymmetric synthesis of a biologically active sulfoxide RP 73163[23] (Scheme 1). The enantioselective oxidation of sulfide **1** to sulfoxide **2** was achieved with the conditions shown in 75% isolated yield and 98% ee on a multigram scale. Subsequent elaboration of the methylsulfinyl side chain allowed the synthesis of RP 73163.

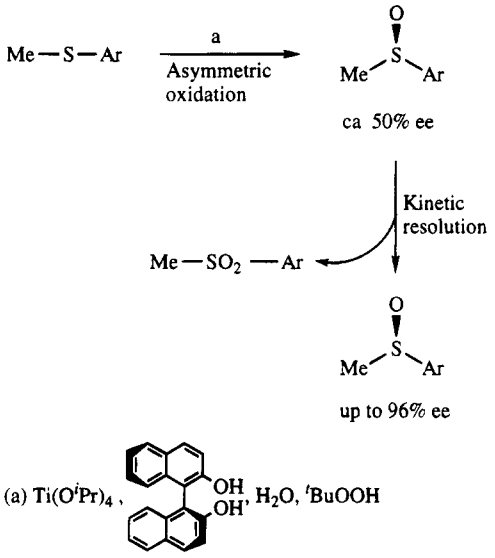
Scheme 1



(a) $Ti(O^iPr)_4$(0.5 eq.), D-DET (1 eq.), $PhC(CH_3)_2OOH$ CH_2Cl_2, -20 °C (75 %)

The use of (*R*)-(+)-binaphthol[24] instead of DET as chiral ligand improved the modest ee (60−70%) achieved in the transformation of some methyl aryl sulfides into sulfoxides (Scheme 2) to a 96% ee by taking advantage of the kinetic resolution process which occurred in a further oxidation step of one of the sulfinyl enantiomers to sulfone.[25] The titanium−binaphthol complex catalyzes not only the asymmetric oxidation but also the kinetic resolution process.

Scheme 2



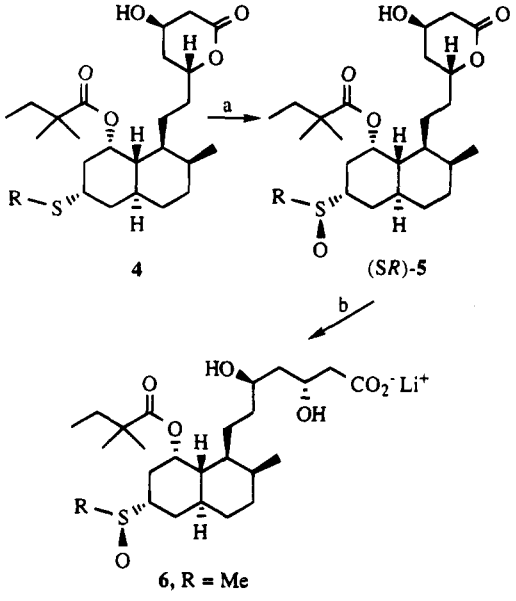
Other catalytic asymmetric oxidations have been effected in the presence of optically active complexes such as chiral (salen)manganese(III) complexes with H_2O_2[26] or iodosobenzene[27] as oxidants. Metalloporphyrins[28] have also been proven to catalyze these enantioselective oxidations. Although high levels of asymmetric induction could be achieved in some specific cases, the enantioselectivity of these catalytic processes is in general modest. Enzymatic oxidation gave very good results in a few cases.[29,19]

More general are the applications of the stoichiometric chiral oxidizing reagents described by Davis.[30] The enantiopure (camphorsulfonyl)oxaziridines and their 8,8-dichloro derivatives **3** (Scheme 3), which are available as both antipodal, gave ee's ranging from 84 to 96%.

Kagan's and Davis's methods have been recently applied to the synthesis of (*R*)-sulfoxide **5**,[31] precursor of the tetrahydromevinic acid derivative **6**, a potential hepatoselective HMG-CoA reductase inhibitor. Diastereoselective oxidation of sulfide **4** afforded a mixture of epimers at the sulfur where that of *SR* configuration was the major. Optimal results for *SR*-sulfoxide were achieved using (−)-**3** for 2-acetoxyethyl sulfide (entry 4), whereas *SS* epimers were obtained as major diastereomers using the corresponding enantiomeric reagents. Saponification of the lactone (*SR*)-**5** gave compound **6**.

The conclusions reached in comparative studies of chemical asymmetric oxidation of epoxy sulfides with a Sharpless-modified reagent and chiral oxaziridine[32] and chemical and microbiological sulfoxidation for the synthesis of optically active vinyl sulfoxides[33] found the three methods complementary, the enantioselectivity in the latter cases being strongly dependent on the structure of substrates.

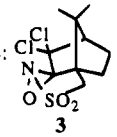
Scheme 3[a]



[a] (a) [Ox]. (b) LiOH, dioxane, 23 °C

Entry	[Ox]	R	Yield (%)	Ratio *SR:SS*
1	A	Me	87	82:18
2	B	Me	100	68:32
3	A	CH_2CH_2OAc	82	78:22
4	B	CH_2CH_2OAc	98	87:13

Method A: (+)-DET, $Ti(O^iPr)_4$, $PhC(CH_3)_2OOH$ CH_2Cl_2, -20 °C

Method B:  , CCl_4, CH_2Cl_2, -20 °C → r.t.

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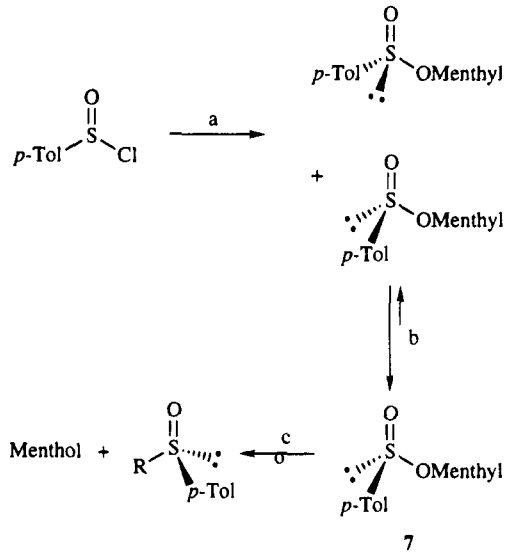
B. Nucleophilic Substitution on Chiral Sulfur Derivatives

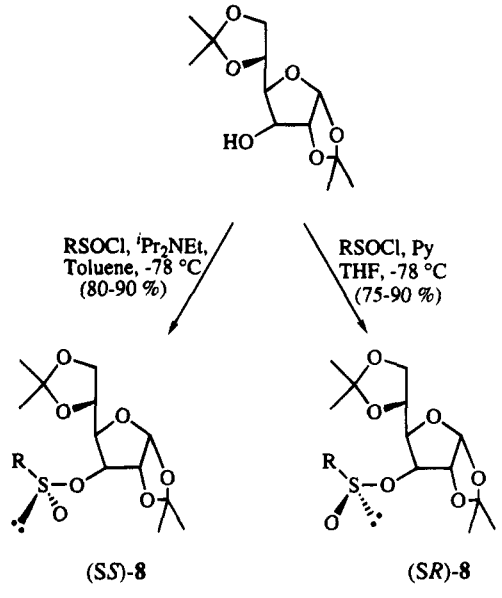
The most widely used approach to enantiomerically pure sulfoxides is the Andersen synthesis[34] based on the nucleophilic substitution on diastereomerically pure (*SS*)-menthyl *p*-toluenesulfinate[35] **7** (Scheme 4) with Grignard reagents which occurs with full inversion of the configuration at sulfur. This classical method has been extensively used to prepare *p*-tolyl alkyl or aryl sulfoxides[2,4,7] and the use of other organometallic nucleophiles, even highly functionalized,[8] has allowed the synthesis of a wide variety of enantiomerically pure sulfoxides. The usefulness of this method is mainly due to the accessibility of the sulfinylating agent, obtained as a mixture of sulfur epimers[34] through esterification of *p*-toluenesulfinyl chloride. This originally described procedure to obtain **7** was further improved and scaled up by equilibrating both sulfur epimers in the presence of hydrochloric acid to displace the equilibrium by

Scheme 4[a]



[a] (a) Menthol, Py, ether, r.t.; (b) Crystallisation in acetone/HCl/-20 °C (80 %); (c) RMgX

Scheme 5

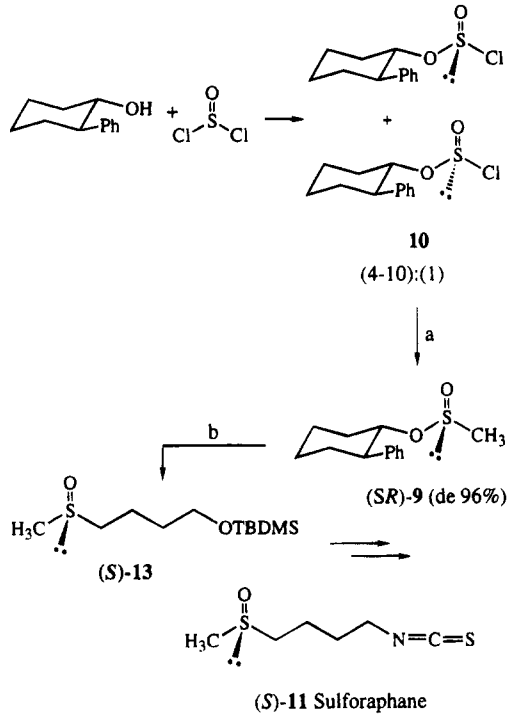


R= Alkyl, Aryl

precipitation of the (*SS*) diastereomer in acetone being thus isolated in 80% yield.[35] This synthesis allowed an easy access to *p*-tolyl sulfoxides.

The selectivity in the formation of chiral epimeric alkane- and arenesulfinates was greatly enhanced by using diacetone D-glucose[36] in the sulfinic acid chloride esterification (Scheme 5). Each sulfur epimer could be obtained as major diastereomer by changing the base present in this esterification step. Further chromatographic separation permitted their obtention in optically pure form. In an Andersen-type synthesis these sulfinyl transfer agents, (*SS*)-**8** and its epimer (*SR*)-**8**, allowed the obtention of enantiomerically pure sulfoxides with both absolute configurations. This agent overcame one of the limitations of the Andersen method opening the access to sulfoxides with substituents different from the *p*-tolyl group.

Scheme 6[a]



[a] (a) $(CH_3)_2Zn$, ether, -78 °C.
(b) ClMg⌇⌇OTBDMS, THF, r.t. (60-80 %)
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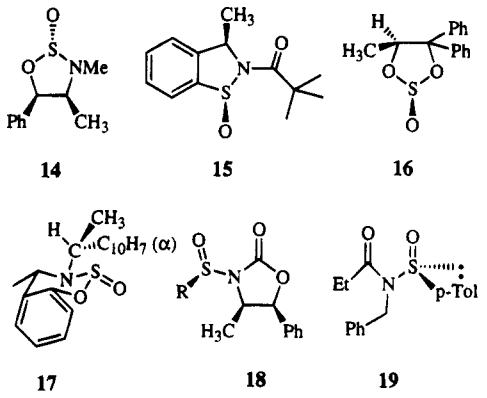
Unequal amounts of diastereomeric sulfinates (4−10:1) were also obtained in the reactions of (1*S*,2*R*)-*trans*-2-phenylcyclohexanol[37] with an excess of arene- or alkanesulfinyl chlorides. An improved asymmetric synthesis of (S*R*)-*trans*-2-phenylcyclohexyl methanesulfinate (**9**)[38] has been achieved by reaction of chlorosulfinates **10** with dimethylzinc (Scheme 6). Interestingly the two epimers **10** resulting from the treatment of the chiral carbinol with thionyl chloride, gave high levels of diastereomeric excess (de 96%) in the formation of (S*R*)-**9**. The utility of this chiral sulfinyl transfer agent has been shown in the synthesis of sulforaphane (*S*)-**11**, a naturally occurring methyl sulfoxide which stimulates the production of carcinogen detoxifying enzymes. Thus, reaction of **9** with Grignard reagent **12** afforded sulfoxide (*S*)-**13** whose transformation into (*S*)-**11** required four additional steps. The *R* enantiomer was synthesized from (1*R*,2*S*)-*trans*-2-phenylcyclohexanol.

Other sulfinyl transfer agents reported (Scheme 7) incorporate chiral auxiliaries such as ephedrine[39] **14**, (*R*)-α-methylbenzylamine[40] **15**, 1,1-diphenyl-1,2-propanediol **16** derived from (S)-ethyl lactate,[41] (*S*)-*O*-[1-[(*S*)-(1-α-naphthylethyl)amino]ethyl]phenol[42] **17** and norephedrine[43] **18**. All these reagents **8**, **9**, and **14**−**18** were designed with the aim of opening the access to dialkyl or alkyl aryl sulfoxides not available from the popular menthyl *p*-toluenesulfinate. A new sulfinyl agent transfer **19** recently developed was obtained from menthyl *p*-toluenesulfinate.[44] *N*-(*p*-Tolylsulfinyl)oxazolidinone **18** and the sulfinimide **19** were developed to circumvent some of the problems encountered with sulfinates related to the nature of the alkoxide leaving group in the nucleophilic substitution. These sulfinylating agents, with an amide anion as leaving group, were shown to be at least 2 orders of magnitude more reactive than the corresponding menthyl sulfinate esters giving rise to the desired sulfoxides when the latter failed. Moreover, compound **19** shows only the stereogenic center of the sulfinyl group. The reactions of compounds **8**, **9**, **15**, **18**, and **19** with nucleophiles such as organolithium or Grignard reagents took place with full inversion of the sulfur configuration, the resulting sulfoxides in most cases being optically pure. With oxathiazolidine *S*-oxide **14**, cyclic sulfite **16**, and amido sulfite **17**, two successive reactions with organometallic compounds provided access to sulfoxides through a double inversion at the original sulfur stereogenic center. The first nucleophilic substitution on **14** was regiospecific regardless of the Grignard reagent used, whereas the regioselectivity of the ring opening on **16** depended on the size of the organometallic employed and could be reversed.

Scheme 7

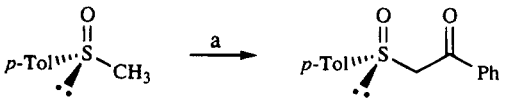


III. Reduction of β-Keto Sulfoxides

A. General Remarks

Acyclic β-keto sulfoxides are readily available by applying the procedure described by Corey[45] to the synthesis of racemic systems based on the reaction of α-sulfinyl anions with esters. The method was first used by Kunieda[46] to prepare optically pure (*R*)-α-(*p*-tolylsulfinyl)acetophenone starting from ethyl benzoate and (+)-(*R*)-methyl *p*-tolyl sulfoxide (**20**, Scheme 8) readily synthesized by Andersen synthesis.[34,35] Over the years, this synthesis has been the most widely used method for the obtention of a great variety of enantiomerically pure acyclic β-keto sulfoxides[7] in spite of the existence of other alternative methods.[47]

Scheme 8

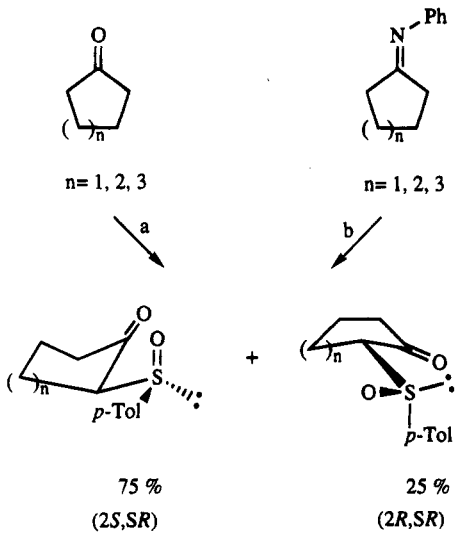


(+)-(*R*)-**20**

(a) (i) $LiNEt_2$, (ii) $PhCO_2Et$ (90 %)

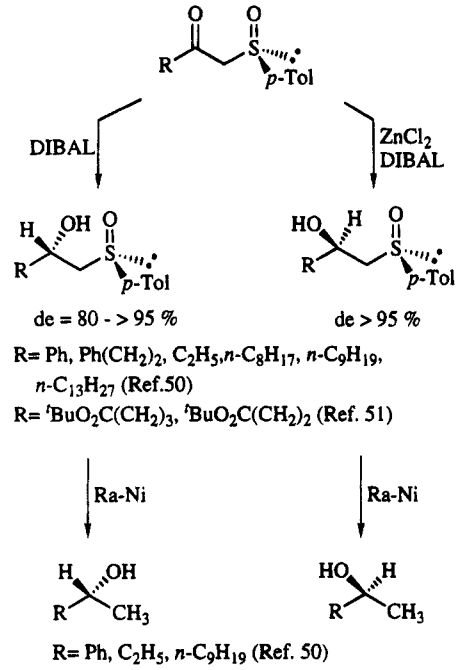
Enantiomerically pure sulfinyl cycloalkanones were easily synthesized by Andersen's synthesis from cycloalkanone enolates[48] or azaenolates derived from

Scheme 9[a]



[a] (a) (i) $^{i}Pr_2NMgBr$, (ii) *p*-$TolSO_2Ment$.; (b) (i) LDA, (ii) *p*-$TolSO_2Ment$, (iii) H_3O^+

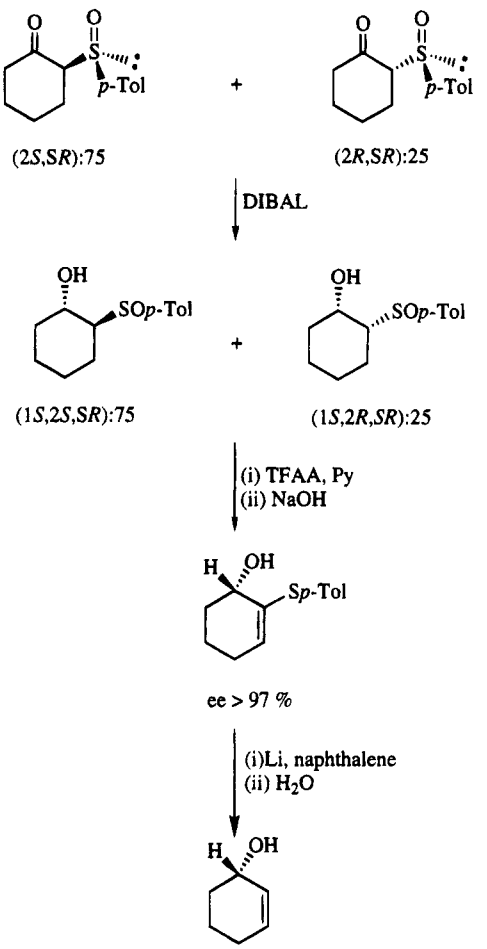
Scheme 10



N-phenylcycloalkanonimines[49] (Scheme 9), as mixtures of C-2 epimers [(2*S*,S*R*)/(2*R*,S*R*) 75/25].

The stereoselectivity of the reduction of β-keto sulfoxides was first investigated by Annunziata and Cinquini[50] with sodium borohydride and lithium aluminum hydride. The diastereomeric excesses obtained were higher in the latter case, the asymmetric induction being in the range 60% to 70%. This reduction process was further investigated and extended to other different reducing agents by Solladié.[51] The best results were obtained with DIBAL which gave mainly the (*S*,S*R*)-β-hydroxy sulfoxide in a highly diastereoselective manner (de ranging from 86% to >95%). The opposite absolute configuration in the new stereogenic hydroxylic carbon was achieved using the system $ZnCl_2$/DIBAL (Scheme 10). Simultaneously, Kosugi[52] found similar results in the $ZnCl_2$/DIBAL reductions of more highly functionalized β-keto sulfoxides. After desulfurization with Raney-nickel optically active *R* and *S* methyl carbinols could be synthesized. A wide variety of enantiomerically pure methyl carbinols could be obtained by applying this methodology as can be seen by the sequence in Scheme 10.

Scheme 11



We further studied the reduction of other acyclic[53] as well as cyclic[48,53,54] β-keto sulfoxides with several nucleophilic and electrophilic hydrides reaching high stereoselectivities. The behavior of all these β-keto sulfoxides in the reductions with DIBAL proved to be very similar and highly diastereoselective. It is interesting to remark that the configuration induced at the new stereogenic center of cyclic derivatives is the same whatever the configuration of the vicinal asymmetric carbon as could be demonstrated upon DIBAL reduction of a 75/25 mixture of (2*S*,S*R*) and (S*R*,S*R*)-2-(*p*-tolylsulfinyl)cyclohexanone (Scheme 11) and transformation of the resulting mixture of hydroxy sulfoxides [(1*S*,2*S*,S*R*)/(1*S*,2*R*,S*R*) 75/25] via Pummerer reaction and basic hydrolysis of the resulting (*S*)-2-(*p*-tolylthio)-2-cyclohexenyl trifluoroacetate into (*S*)-2-(*p*-tolylthio)-2-cyclohexenol.[55] After Li–naphthalene desulfurization 2-cyclohexenol was obtained in enantiomerically pure form.[56]

All these results allowed us to explain the stereoselectivity observed on the basis of the electrophilic character of DIBAL which is able to form an O–Al bond with the more basic sulfinyl oxygen. From this adduct, an intramolecular hydride transfer will take place through the more stable chairlike transition

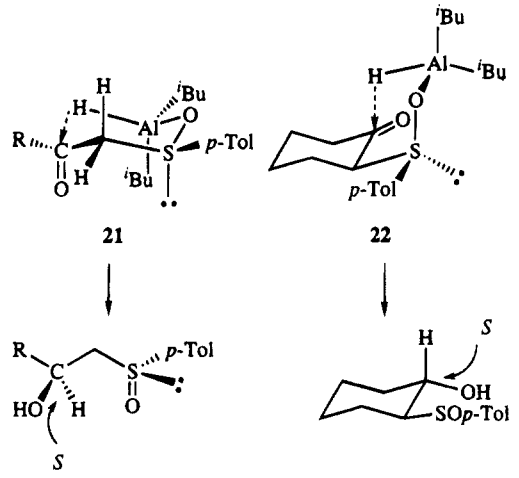


Figure 1. Proposed transition states for hydride transfer in $^{i}Bu_2AlH$ reductions of β-keto sulfoxides.

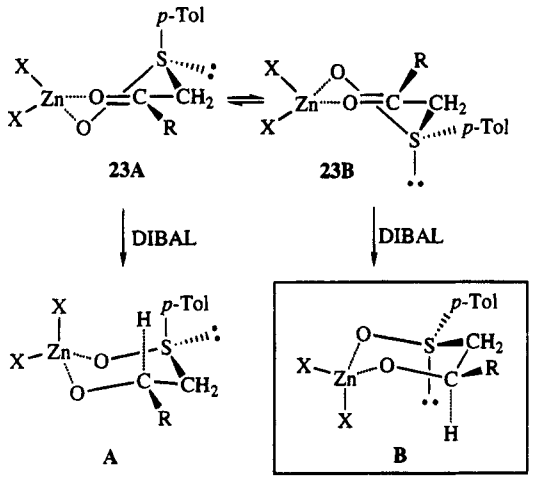


Figure 2. Proposed transition states for hydride transfer in $^{i}Bu_2AlH$ reductions in the presence of ZnX_2.

states **21** and **22**[53] (Figure 1) to give the 1*S* carbinol. The highly stereoselective DIBAL reduction of β,δ-diketo sulfoxides (de > 95%) to the corresponding δ-keto β-hydroxy sulfoxides[57] reinforces this mechanistic model.

The reverse stereoselectivity was attained also with cyclic substrates by addition of DIBAL to a sulfinylcycloalkanone solution containing anhydrous zinc chloride.[53,54] Although $ZnCl_2$ was reported to have a catalytic role in these processes[58] stoichiometric and even larger amounts are generally used.[48,51-54,59,60] Moreover, we found that up to 1.4 equiv of $ZnBr_2$,[60] a better chelating agent, were necessary to get a highly diastereoselective DIBAL reductions on substrates such as α-alkyl-substituted β-keto sulfoxides. When the basicity of the carbonyl oxygen diminished as in the case of 1-phenylethanone 2-sulfinyl derivatives, increasing amounts of ZnX_2 (up to 5 equiv) were essential to achieve useful results. The high asymmetric induction obtained with stoichiometric amounts of ZnX_2 suggested the formation of the chelated species **23** showing a conformational equilibrium between **23A** and **23B** (Figure 2). DIBAL approach to this species both from the top face of **23A** and the bottom face of **23B** gives rise to chairlike transition states **A** and **B**, the latter being more stable due to the absence of destabilizing interactions [**A** shows a (X/*p*-Tol)-1,3-diaxial interaction]. Moreover the approach of the electrophilic hydride from the bottom face of **23B** can be directed by complexation with the lone electron pair of sulfoxide or the pseudo-axial halogen.[58]

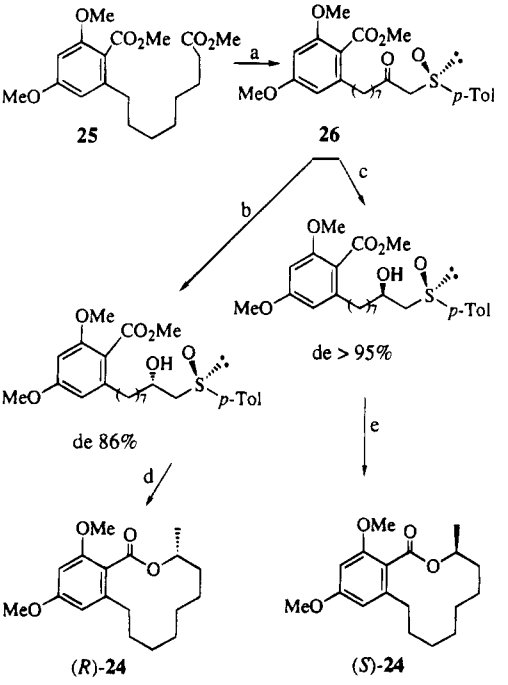
B. Synthesis of Carbinols

The main contribution to the synthesis of optically active secondary carbinols from β-hydroxy sulfoxides is due to Solladié *et al.* Two sets of protocols have been mainly used to the transformation of β-hydroxy sulfoxides resulting in the stereoselective and controlled reduction of β-keto sulfoxides. Methylcarbinols of both configurations could be successfully obtained from esters by applying the reactions sequence outlined in Scheme 10. The second way gives rise to 1,2-diols as will be seen later.

1. Methyl Carbinols

We have achieved the asymmetric total synthesis of two orsellinic acid type macrolides containing a methylcarbinol moiety in their structure by applying the first set of transformations. One of the great advantages of sulfoxides is allowing the asymmetric induction step to be carried out in the very last part of the synthesis via this stereoselective β-keto sulfoxide reduction. The synthesis of the macrolide lasiodiplodin[61] was achieved through its dimethyl ether **24** (Scheme 12). The synthesis was divided in

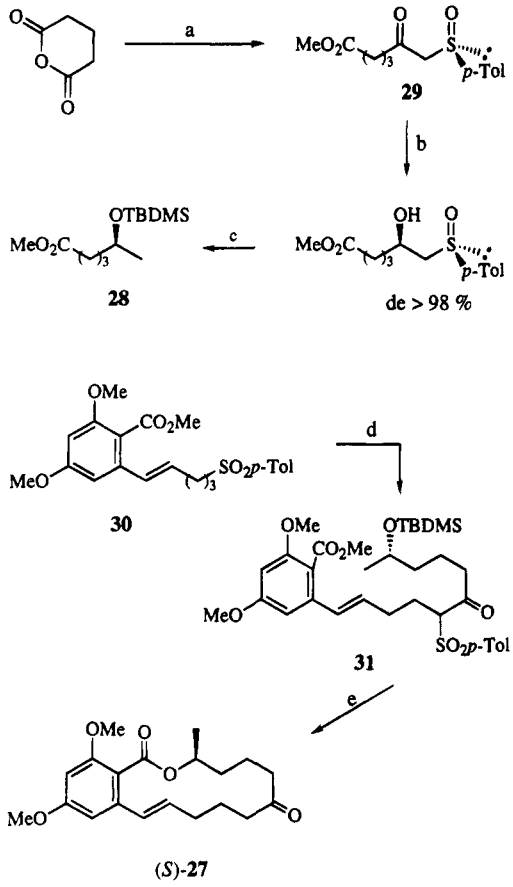
Scheme 12[a]



[a] (a) THF, $LiH_2C-S(=O)-p\text{-Tol}$ (2.2 eq.), -78 °C (85 %); (b) DIBAL, THF, -78 °C (80 %); (c) $ZnCl_2$, THF, DIBAL, r.t. (95 %); (d) (i) Ra Ni (53%), (ii) KOH, Δ (74 %), (iii) Py_2S_2, Ph_3P, PhH (49 %); (e) (i) Ra Ni (70 %), (ii) KOH, Δ (91 %), (iii) Py_2S_2, Ph_3P, PhH (66 %).

two parts: first the synthesis of the achiral diester **25** and then the introduction of the chiral carbinol part via a β-keto sulfoxide functionality. Reduction

Scheme 13[a]



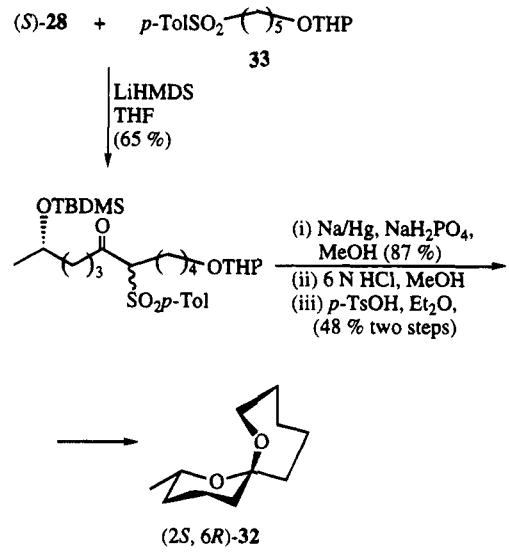
[a] (a) (i) **20**, LDA, THF, -78 →-60 °C, (ii) CH_2N_2 (75 % overall); (b) $ZnCl_2$, DIBAL, THF, -78 °C (80 %); (c) (i)TBDMSCl, imidazole, DMF, r.t. (98 %), (ii) Ra Ni, EtOH, r.t. (89 %); (d) (i) $(Me_3Si)_3NLi$, THF, -78 °C, (ii) **28**, -40 → 0 °C (62 % i+ii); (e) (i) Na/Hg (90 %), (ii) $HS(CH_2)_3SH$, BF_3OEt_2 (78 %), (iii) KOH (84 %), (iv) $(PhO)_2POCl$, Et_3N, DMAP (60 %), (v) IMe, $CaCO_3$ (84 %).

of the β-keto sulfoxide **26** with DIBAL alone gave the expected (*S*,*SR*)-β-hydroxy sulfoxide, while the reduction with DIBAL in the presence of zinc chloride yielded the (*R*,*SR*)-epimer. After desulfurization, both enantiomers of the seco acid were cyclized using the Gerlach method.[62]

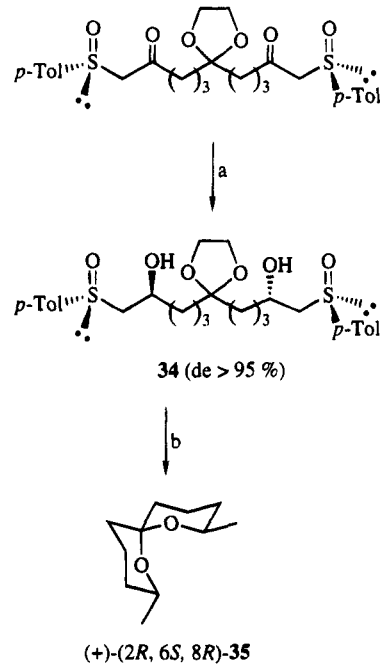
A convergent synthesis was used in the case of dimethyl ether **27**[63] (Scheme 13), a precursor of zearalenone, a naturally occurring macrolide with anabolic and uterotropic properties. The chiral hydroxy ester **28** was prepared by reduction of β-keto sulfoxide **29** readily obtained from glutaric anhydride and further protection and desulfurization. The required natural alcohol configuration was achieved with the $ZnCl_2$/DIBAL reduction system. The sulfonyl anion of the achiral part **30** was coupled with the ester **28** and, after desulfurization and carbonyl protection of **31**, cyclization to zearalenone dimethyl ether **27** was accomplished following Masamune's method.[64]

Hydroxy ester derivative **28** was also the optically active starting material in the synthesis of spiroketal **32**,[65] an insect pheromone. The precursor of **32** was generated by condensation of **28** with sulfone **33** followed by desulfurization and deprotection. The

Scheme 14



Scheme 15[a]



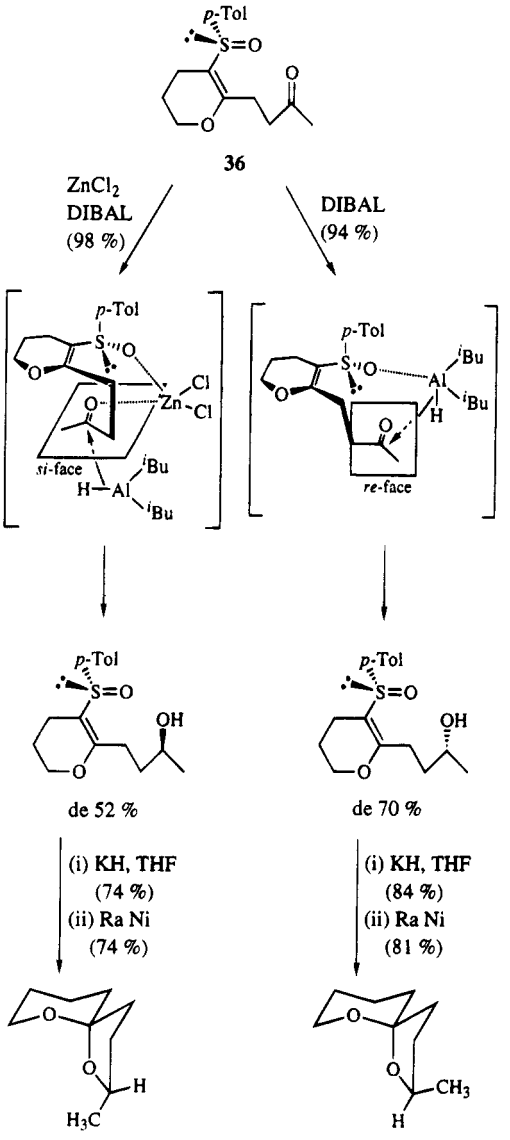
[a] (a) DIBAL, THF, -78 °C (77 %); (b) (i) PPTS, wet acetone, Δ (96 %), (ii) Ra Ni (52 %)

stereochemistry of the cyclization to the acetal, was controlled by the anomeric effect giving the natural C-6-(*R*) configuration of **32** (Scheme 14).

The anomeric effect was also the responsible of the highly stereoselective cyclization observed from dihydroxy disulfoxide **34**[66] (Scheme 15), accessible with both the *S* or *R* configuration at both hydroxylic centers depending on the reduction method utilized in its obtention. Upon treatment in acidic medium, compound **34** evolved into the spiroketal derivative whose desulfurization afforded compound **35**, present in the rectal glandular secretion of certain species of fruit flies. The enantiomer could be sythesized from the dihydroxy disulfoxide resulting from reduction with DIBAL/$ZnCl_2$.

In the field of spiroketal compounds, an example where a remote sulfinyl group was inducing the

Scheme 16

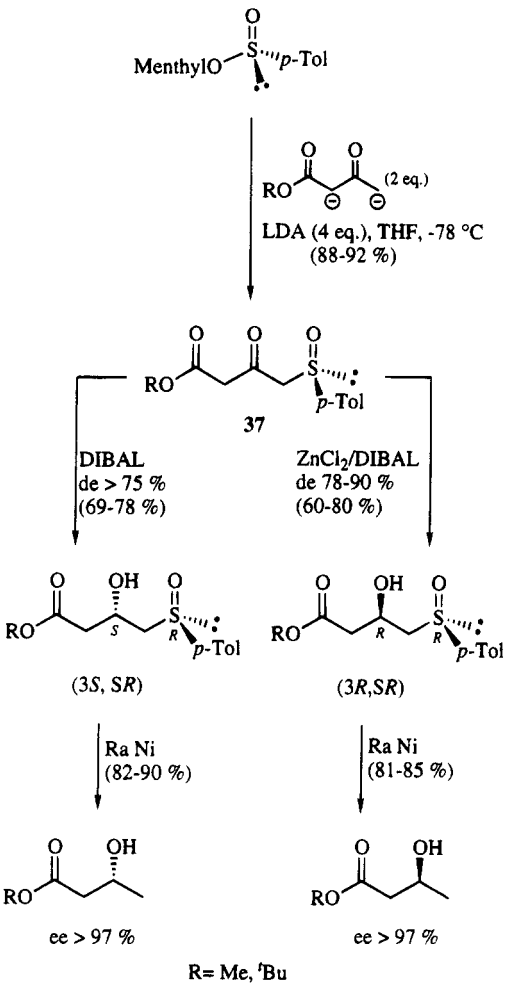


diastereoselective reduction of a carbonyl has been reported[67] (Scheme 16). A 1,6-asymmetric induction in the DIBAL and $ZnCl_2$/DIBAL reductions of β-keto sulfoxide **36** was achieved. Due to the electrophilic nature of DIBAL or the chelating properties of $ZnCl_2$, the reactive species represented bring the ketone functionality very close to the sulfoxide giving rise to a significant asymmetric induction. Both epimers of the cyclic acetal were stereoselectively formed in a Michael-type intramolecular addition.

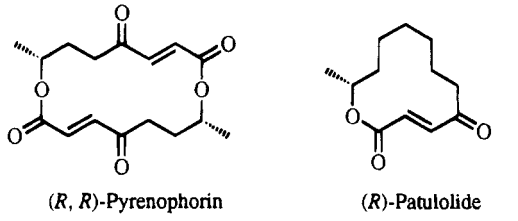
Both enantiomers of 3-hydroxybutyric acid, a useful building block for natural products synthesis, could be obtained by DIBAL or $ZnCl_2$/DIBAL reduction of (*R*)-4-(*p*-tolylsulfinyl)-3-oxobutyric esters **37** prepared in high yield by Andersen synthesis from the dianion of methyl or *tert*-butyl acetoacetate (Scheme 17).[68] Although the diastereoselection of the reduction step was not so high (de 60−80%) probably due to the presence of different chelation sites in the sulfinyl keto ester, diastereomerically pure (*S*,S*R*) and (*R*,S*R*) hydroxy sulfoxides could be isolated and transformed, by desulfurization, into the enantiomerically pure hydroxybutyrate derivatives.

The methylcarbinol moiety present in other natural products such as (*R*,*R*)-pyrenophorin or (*R*)-patulolide[69] (Scheme 18) was also synthesized by applying similar strategies.

Scheme 17



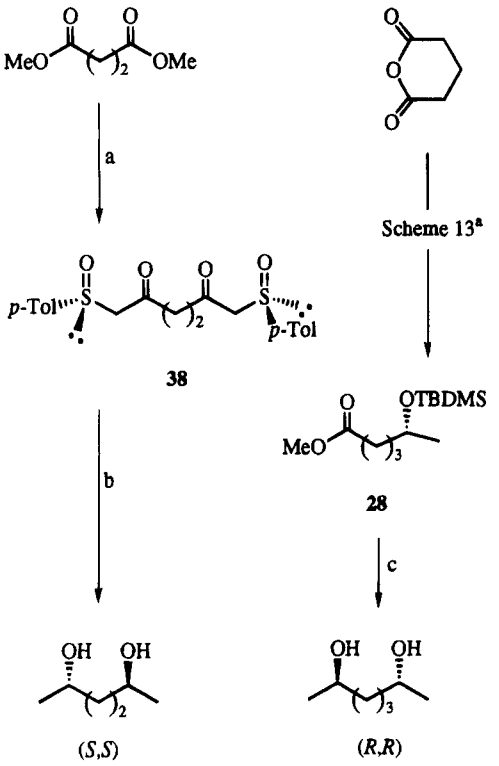
Scheme 18



Both enantiomers of 2,5-hexanediol and 2,6-heptanediol[70] could be obtained in an iterative manner starting from dimethyl succinate or glutaric anhydride (Scheme 19). The formation of the diketo disulfoxide **38** and simultaneous reduction of both carbonyl groups followed by desulfurization allowed for the short synthesis of (*S*,*S*) enantiomer of 2,5-hexanediol. The (*R*,*R*) enantiomer was obtained by using DIBAL in the reduction step. In a stepwise sequence (*R*,*R*)-2,6-heptanediol was synthesized through the intermediacy of protected carbinol **28**.

Bravo[71] synthesized the naturally occurring butanolide **39** ("L-factor") (Scheme 20) from the β-keto sulfoxide **40** through the intermediacy of δ-lactone **41**. Compound **40** was formed as a mixture of epimers in the reaction of *tert*-butyl methyl succinate with (S*R*)-*n*-hexyl *p*-tolyl sulfoxide. DIBAL reduction of this mixture afforded the (4*S*,5*S*,S*R*) diastereomer

Scheme 19[a]



[a] (a) (*R*)-**20** (4 eq.), LDA (60 %); (b) (i) DIBAL, $ZnBr_2$ (2.5 eq.) (75 %, de > 95 %), (ii) Ra-Ni (75 %); (c) (i) (*R*)-**20**, LDA (98 %), (ii) DIBAL (81 %, de > 95 %), (iii) TBAF, (iv) Ra-Ni (70 % two steps)

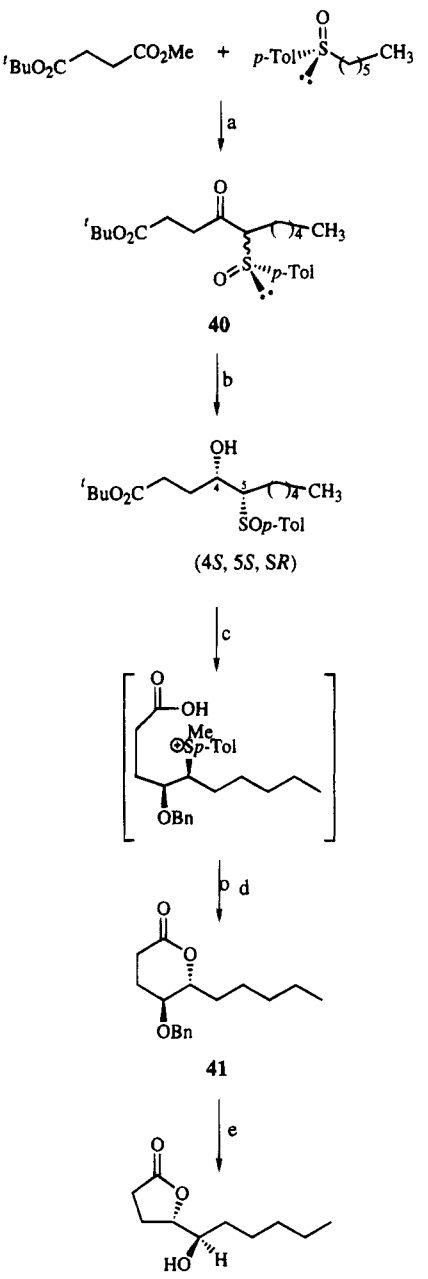
with a 38% isolated yield whose transformation into **41** involved protection of the OH, deoxygenation of the sulfoxide, ester hydrolysis, sulfonium salt formation, and cyclization in the presence of a base. In the later step, the configuration of the stereogenic center was fully inverted. Reductive debenzylation was followed by a spontaneous ring restriction to the butanolide **39**. Although the DIBAL reduction was not highly diastereoselective, the use of α-alkyl β-keto sulfoxide **40** opened the access to alcohols other than methylcarbinols. We improved the methodology by reducing the mixture of diastereomeric α-alkylated β-keto sulfoxides with DIBAL in the presence of a high excess of $ZnBr_2$.[60] After desulfurization, alkylcarbinols could be obtained enantiomerically pure.

2. 1,2-Diols

The protocol allowing the transformation of β-hydroxy sulfoxides into terminal 1,2-diols involved the Pummerer rearrangement followed by desulfurization or $LiAlH_4$ reduction of the resulting hemithioketal. By this means the synthesis of several polyhydroxylated natural products has been achieved.

An interesting short asymmetric synthesis of L-arabinitol was developed[72] as shown in Scheme 21 starting from allylic β-hydroxy sulfoxide **42** obtained by reduction of the β-keto sulfoxide **43**. The stereogenic carbinol moiety induced a high diastereoselectivity in the subsequent double-bond hydroxylation. The resulting triol was easily transformed, by applying the aforementioned methodology into L-penta-*O*-acetylarabinitol.

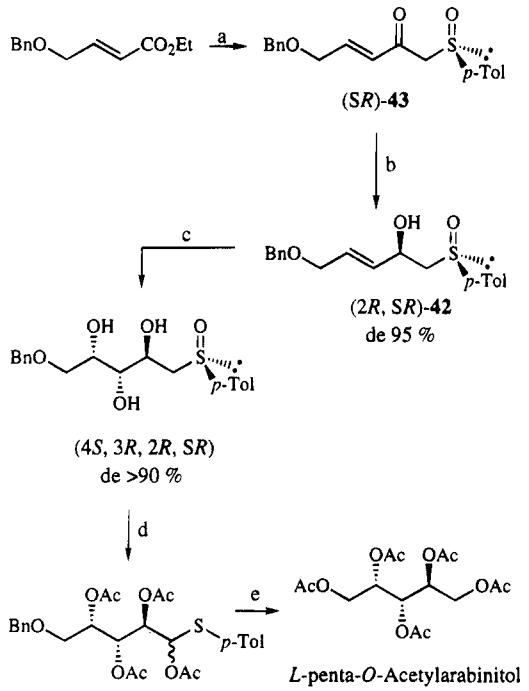
Scheme 20[a]



[a] (a) LDA, THF, -78 °C (88 %); (b) DIBAL (38 %); (c) (i) HNa, BnBr (85 %), (ii) NaI, TFAA (71 %), (iii) AcOH, H_2O, dioxane (89 %), (iv) F_4BOMe_3; (d) ^{t}BuOK, -40 °C; (e) Ra-Ni (93 %).

A similar strategy was used to elaborate the vicinal triol moiety present in aspicilin[73] (**44**). Protected allylic β-hydroxy sulfoxide **45** was submitted to a Pummerer rearrangement and $LiAlH_4$ treatment, before the hydroxylation step that took place with moderate selectivity (Scheme 22). The major diastereomer resulting in this step could be isolated in a 71% overall yield and transformed into the aldehyde **46** by conventional methods. The second necessary synthon **47**, a methylcarbinol, was made from β-keto sulfoxide **48** by DIBAL reduction followed by desulfurization, protection of the hydroxyl, ester reduction, and transformation of the primary carbinol into a phosphonium salt. A Wittig reaction between

Scheme 21[a]

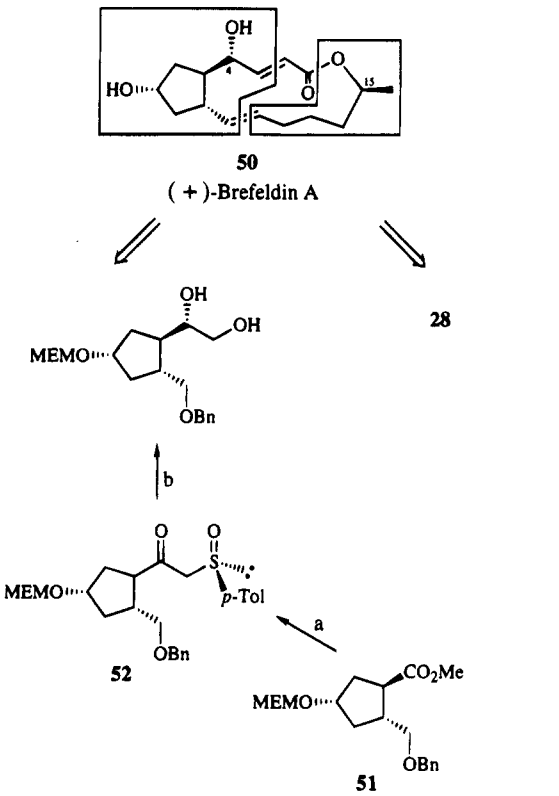


[a] (a) **20**, LDA, THF, 0 °C (60 %); (b) $ZnCl_2$, DIBAL, THF, -78 °C (90 %); (c) 5 % OsO_4, $Me_3N(O)$ (70 %); (d) Ac_2O, AcONa; (e) (i) DIBAL, 0 °C, (ii) Ac_2O, Py, (50%, three steps), (iii) Cyclohexene, Pd/C, (iv) Ac_2O, Py, (80%, two steps).

46 and **47** furnished the *Z* olefin. Reduction of the double bond, saponification of the acetate, and Swern oxidation followed by a Wittig–Horner reaction gave the seco ester **49** which was easily transformed into (−)-aspicilin (**44**).

The 1,2-diol moiety present in several prokaryotic triterpenoids have been prepared by asymmetric

Scheme 23[a]

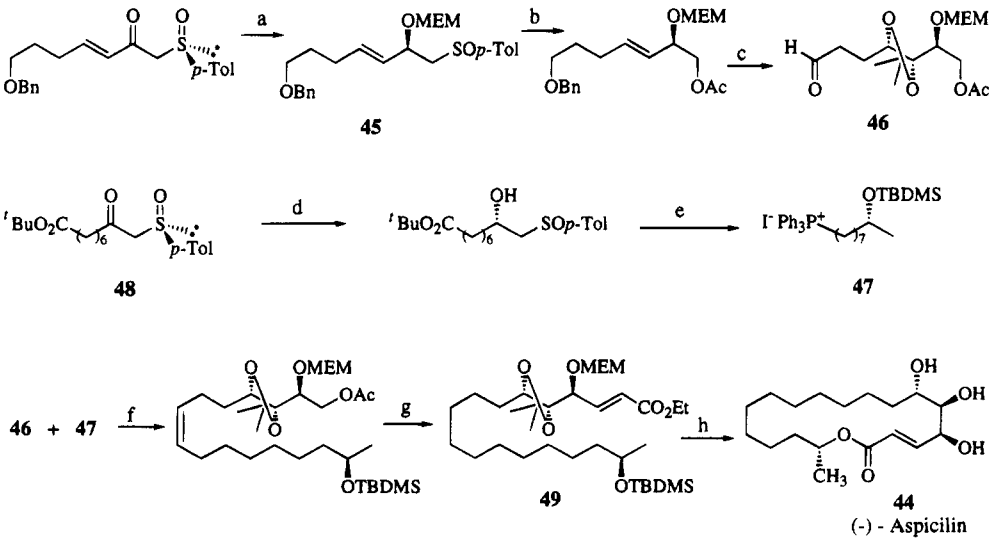


[a] (a) (*R*)-**20**, LDA, -78 °C (99 %); (b) (i) DIBAL (quant. yield), (ii) Ac_2O, AcONa (91 %), (iii) $LiBH_4$ (87 %).

hemisynthesis based on the reduction of β-keto sulfoxides[74] and modification of the sulfinyl group by the Pummerer/reduction ($NaBH_4$) methodology.

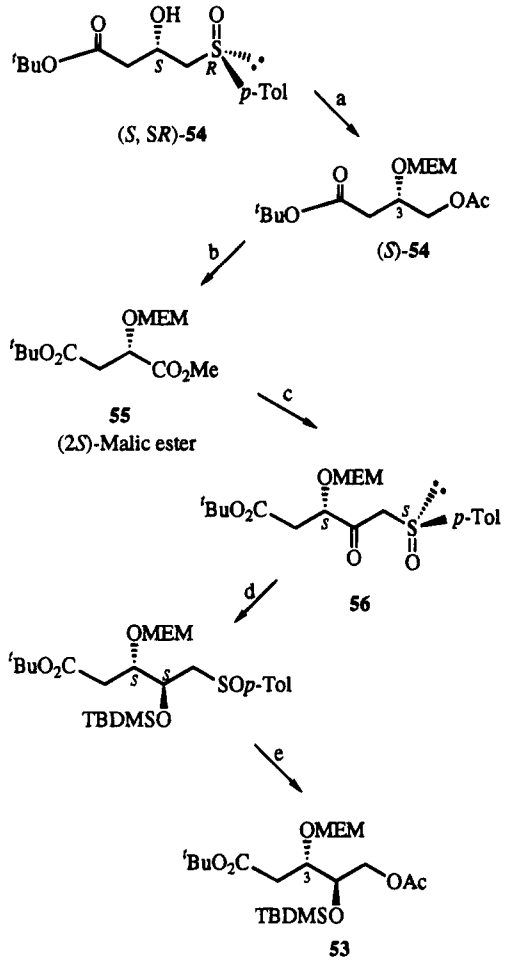
In a recently published synthesis of (+)-brefeldin A[59] (**50**, Scheme 23) the stereogenic centers C-4 and

Scheme 22[a]



[a] (a) (i) $ZnCl_2$, DIBAL (95 %); (ii) MEMCl, $Et(iPr)_2N$ (95 %), (b) (i) Ac_2O, NaAcO (99 %), (ii) $LiAlH_4$, 0 °C (92 %), (iii) Ac_2O, Py (98%); (c) (i) OsO_4 cat., Me_3NO (de 60 %), (85 %, 71 % yield of major diastereomer), (ii) $Me_2C(OMe)_2$, TsOH, DME (98 %), (iii) Ra-Ni (98 %), (iv) $COCl_2$, DMSO, Et_3N (93 %); (d) DIBAL (de > 98 %); (e) (i) Ra-Ni (96 %), (ii) TBDMSCl (95 %), (iii) $LiAlH_4$ (97 %), (iv) PPh_3, imidazole, I_2 (92 %), (v) PPh_3, CH_3CN (87 %); (f) *n*-BuLi (64 %); (g) (i) H_2, Pd/C (90 %), (ii) LiOH, MeOH (90 %), (iii) $(CO_2Cl)_2$, DMSO, Et_3N, (iv) $(EtO)_2P(O)CH_2CO_2Et$; (h) (i) LiOH (90 %), (ii) TBAF (95 %), (iii) 2,5-dichlorobenzoyl chloride, Et_3N, DMAP (55 %), (iv) $BF_3.OEt_2$, $HS(CH_2)_2SH$ (74 %).

Scheme 24[a]

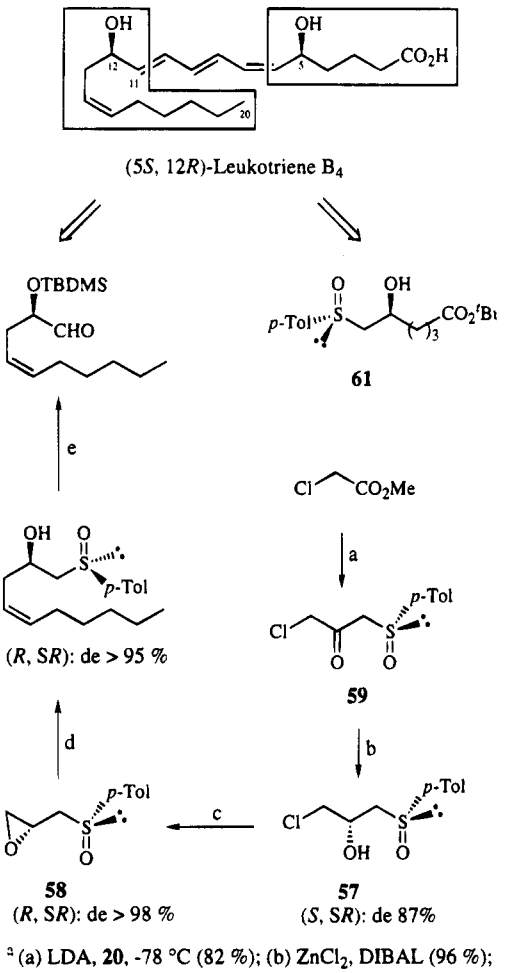


[a] (a) (i) MEMCl, $^{i}Pr_2NEt$, (ii) Ac_2O, AcONa (81 % two steps), (iii) Ra-Ni (91 %); (b) (i) DIBAL (92 %), (ii) PCC, DMF, (iii) CH_2N_2 (80 % two steps); (c) (*S*)-**20**, LDA, -78 °C (86 %); (d) (i) DIBAL (88 %, de > 95 %), (ii) TBDMSCl, imidazole (79 %); (e) (i) Ac_2O, AcONa (82 %), (ii) Ra-Ni (83 %)

C-15 were generated in a stereocontrolled manner from sulfoxides. The latter, a methylcarbinol, proceeded from compound **28** (Scheme 13). The fragment providing the C-4 chiral center was readily made from the ester **51** through the β-keto sulfoxide **52** applying the DIBAL reduction/Pummerer rearrangement/$LiBH_4$ reduction sequence.

An alternative way to chiral 1,2-diols relies on the transformation of chiral α-hydroxy esters into *syn* or *anti* 1,2-diols via β-keto γ-alkoxy sulfoxides.[75] The starting α-hydroxy ester was also made by applying the β-keto sulfoxide reduction methodology. The oxidized form of 2-deoxy-D-ribose derivative[76] **53** could be constructed by applying the β-keto sulfoxide reduction step twice (Scheme 24). The first was used to generate the precursor of C-3 stereogenic carbinol of (*S*,*SR*)-**54** as indicated in Scheme 24. Protection of the carbinol followed by conversion of the carbon supporting sulfoxide into an ester group allowed the synthesis of enantiomerically pure malic ester **55** further transformed into the terminal 1,2-diol moiety of **53** by a sequence involving the formation of a new

Scheme 25[a]



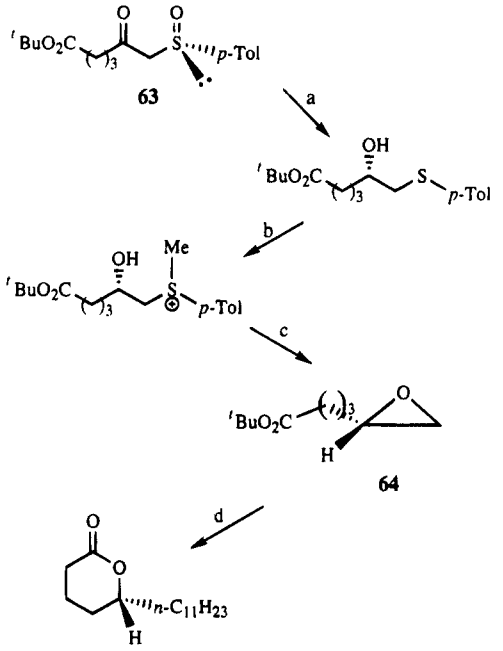
[a] (a) LDA, **20**, -78 °C (82 %); (b) $ZnCl_2$, DIBAL (96 %); (c) K_2CO_3, CH_3CN, H_2O (86 %); (d) Et_2O, -60 °C; (n-$C_5H_{11}CH{=}CH)_2CuCNLi_2$ (**60**); (e) (i) TBDMSCl, imidazole (89 %), (ii) Ac_2O, AcONa (95 %), (iii) $LiAlH_4$, -25 °C (94 %), (iv) PCC, CH_2Cl_2 (84 %).

β-keto sulfoxide **56** followed by DIBAL reduction and transformation of the resulting β-hydroxy sulfoxide into a new 1,2-diol. If the reduction was carried out with DIBAL/$ZnBr_2$, the (3*S*,4*R*)-hydroxy sulfoxide precursor of 2-deoxy-L-xylose was obtained.

3. Epoxides

β-Hydroxy sulfoxides can also be easily transformed into chiral epoxides giving access to a variety of natural products. Cyclization of sulfinyl chlorohydrin **57** (Scheme 25) provided β,γ-epoxy sulfoxide **58** of high optical purity. The required chlorohydrins, prepared by reduction of γ-chloro β-keto sulfoxide **59** were accessible both as (*S*,*SR*) or (*R*,*SR*) diastereomer.[77] The (*R*,*SR*)-**58** epimer was used as starting material in the synthesis of the C-11−C-20 fragment of leukotriene B_4[78] and its (*S*,*SR*) epimer allowed the synthesis of the referible fragment of 12(*S*)-hydroxyeicosatetraenoic acid. Thus, compound (*R*,*SR*)-**58** was reacted with (*E*)-cyanocuprate **60** to give the homoallylic β-hydroxy sulfoxide whose sulfinyl group was transformed into an aldehyde through the sequence Pummerer rearrangement, $LiAlH_4$ reduction, and PCC oxidation. The stereogenic center at C-5 was created also from β-hydroxy sulfoxide **61** by a

Scheme 26[a]



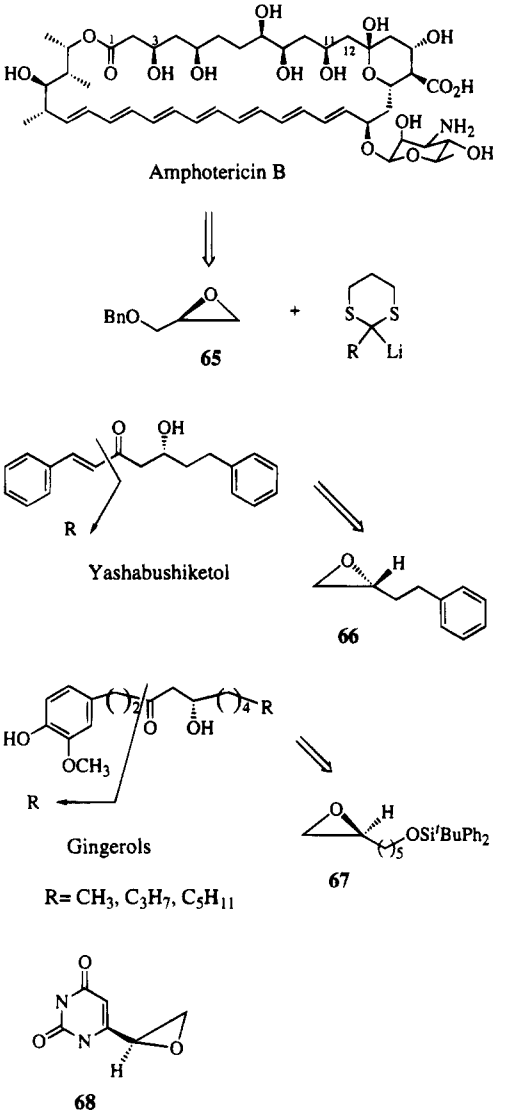
[a] (a) (i) $ZnCl_2$, DIBAL (78%, de>98%) (ii) Zn, Me_3SiCl, Py; (b) Me_3OBF_4, CH_2Cl_2, (c) 5 % NaOH, CH_2Cl_2 (60%, three steps); (d) (i) n-$C_{10}H_{21}MgBr$, CuI, Me_2S, THF, (ii) p-TsOH, benzene (64 %)

similar transformation of the sulfinyl group.[63] Epoxy sulfoxide **58** was also the starting material in the synthesis of the seco-ester precursor of the macrolide recifeiolide[79]

Another route described for the preparation of epoxides from β-hydroxy sulfoxides required sulfinyl reduction to sulfide which could be effected with $LiAlH_4$,[51b] Zn/Me_3SiCl,[52,80,81] t-BuBr,[82] PBr_3,[83] NaI/BF_3,[84] NaI/TFAA,[85] and epoxy ring closure through the intermediacy of a sulfonium salt in the presence of a base (Scheme 26). The strategy was used by Solladié[51b] and Kosugi[52] to enantiomerically pure epoxides. All the synthetic applications which followed the obtention of epoxides relied on the nucleophilic ring opening. The synthesis of δ-lactone **62**, the pheromone responsible for some aspects of the social behavior of the Oriental hornet, was achieved starting from β-keto sulfoxide **63**, transformed into the epoxy ester **64** in 60% overall yield. Treatment of **64** with a Grignard reagent and subsequent lactonization gave enantiomerically pure (*R*)-**62**.

The synthesis of epoxides **65**–**68** represented in Scheme 27, in enantiomerically pure form was described following this protocol. Glycidyl derivative **65** was transformed into the C-1/C-12 unit of the macrolide amphotericin B,[82] the C-3 and C-11 stereogenic centers being those initially formed by applying the diastereoselective β-keto sulfoxide reduction. The aldol functionality present in the structures of (*R*)-yashabushiketol and gingerols were generated from epoxides **66**[80] and **67**,[81] respectively. In the latter case, several cardiotonic principles from ginger could be synthesized from the common precursor **67**. Subsequent epoxy ring opening with the apropriate lithium 1,3-dithiane allowed the incorporation of the latent aldol moiety, which in the example of amphotericin B was further elaborated. The same procedure was applied to the enantiospecific synthesis of compound **68**[83] showing anti-ASFV (African swine fever virus) activity.

Scheme 27

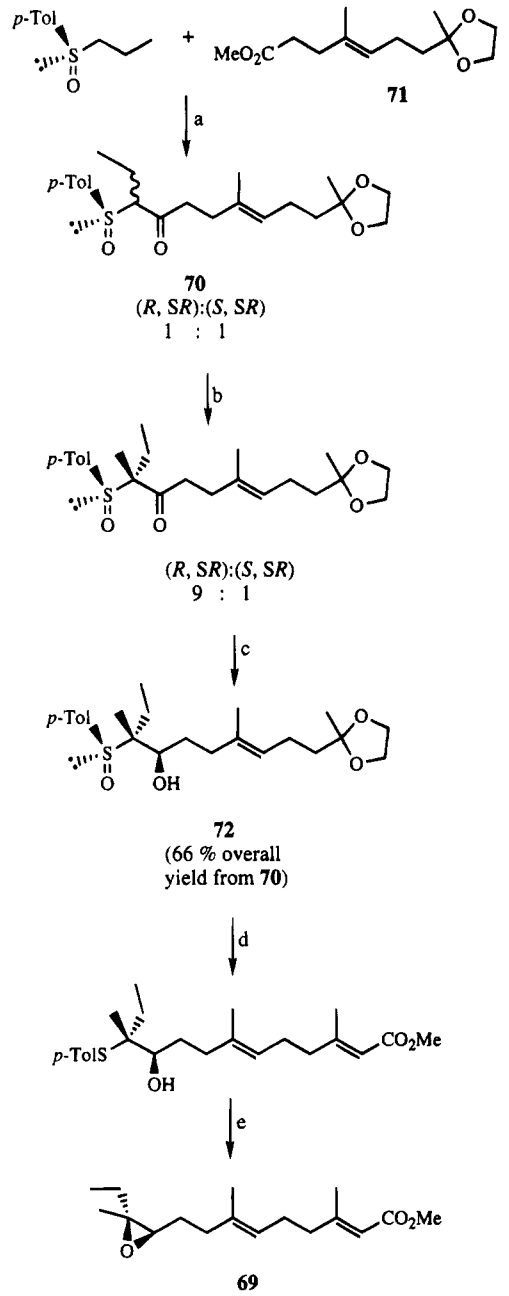


The asymmetric synthesis of juvenile hormone II **69** (Scheme 28) recently reported[85] was based on the diastereoselective alkylation and carbonyl reduction of β-keto sulfoxide **70**. Although compound **70** was generated as a 1:1 mixture of epimers from (*R*)-*n*-propyl *p*-tolyl sulfoxide and ester **71**, its alkylation produced a 9:1 mixture of (*R*,S*R*) and (*S*,S*R*) whose diastereoselective reduction afforded β-hydroxy sulfoxide **72** that was thus obtained in 66% yield from **70**. From **72** natural epoxide **69** was synthesized through the hydroxy sulfide using conventional procedures.

4. Cyclic Carbinols

The applications of diastereoselective reduction of cyclic β-keto sulfoxides to the synthesis of biologically

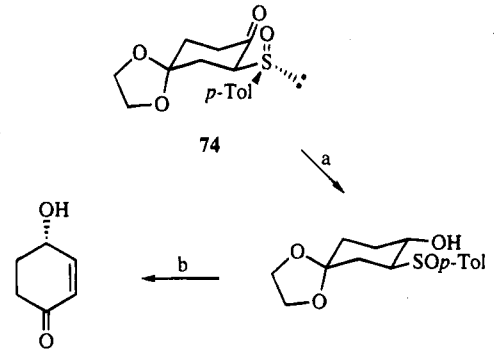
Scheme 28[a]



[a] (a) LDA, THF; (b) NaH, MeI, DMF, r.t.; (c) $ZnCl_2$, DIBAL, THF, -90 °C; (d) (i) Ac_2O, DMAP, CH_2Cl_2, (ii) NaI, $(CF_3CO)_2O$, acetone, (iii) $LiAlH_4$, (iv) PPTS, acetone, (v) $(MeO)_2POCH_2CO_2Me$, NaH, THF, r.t. (50 % four steps); (e) (i) Me_3OBF_4, CH_3NO_2, 0 °C, (ii) MeONa, MeOH (50 % two steps).

active compounds has been far more limited. We reported a short asymmetric synthesis of both enantiomers of 4-hydroxy-2-cylclohexenone **73**,[86] the starting material in the synthesis of ML-236A, compactin and immunosuppresive agent FK-506. Reduction of β-keto sulfoxide **74** with DIBAL and acidic acetal hydrolysis with simultaneous pyrolytic elimination of the sulfoxide on acidic silica gel of the acetylated carbinol gave, after deprotection compound (*S*)-**73** (Scheme 29). The route to the (*R*)-enantiomer required the use of $ZnCl_2$/DIBAL in the reduction step.

Scheme 29[a]



[a] (a) DIBAL (95 %); (b) (i) Ac_2O, AcONa (100 %), (ii) SiO_2, H_2SO_4 (75 %), (iii) K_2CO_3 (95 %).

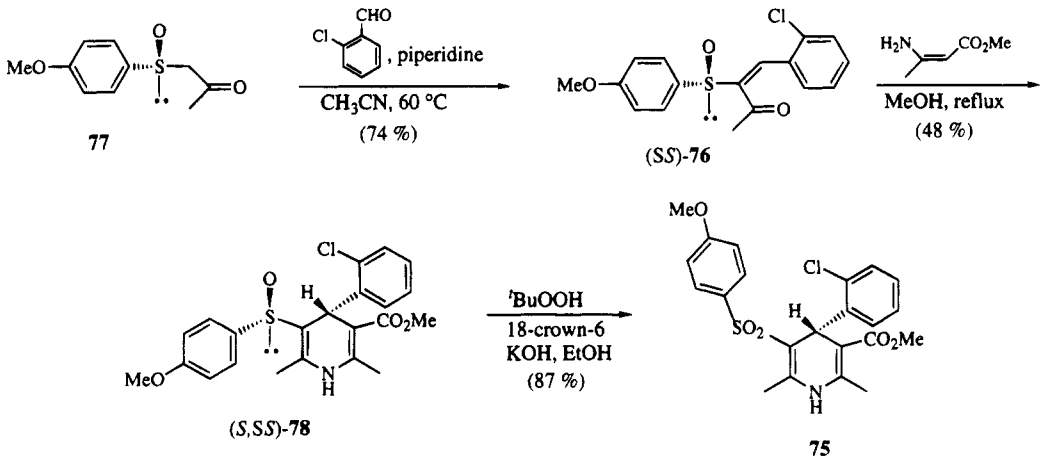
IV. Conjugate Additions to α,β-Unsaturated Sulfoxides

A. C–C Bond Formation

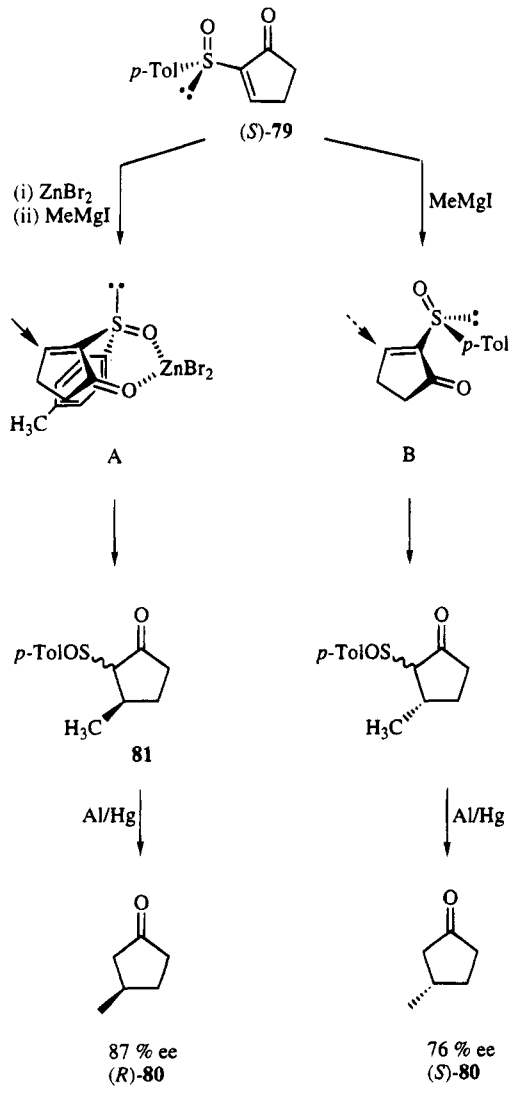
The first asymmetric Michael addition of an enolate ion to acyclic α,β-unsaturated sulfoxides was reported in 1973[87] to proceed with 60% asymmetric induction. Further studies carried out by Posner[88] showed that activation of α,β-ethylenic sulfoxides by an α-carbonyl group enhanced the Michael acceptor character of the substrate, being possible to achieve organometallic β-addition at low temperatures. Nevertheless, on acyclic systems the asymmetric induction did not surpass the 65% except in the reaction between lithium diethyl malonate and (*Z*)-β-styryl *p*-tolyl sulfoxide in THF where a de >95% was achieved.[89] Another exception was found in the synthesis of dihydropyridine **75** (Scheme 30), a potent antihypertensive agent, where the stereogenic center was generated through the Michael addition of methyl 3-aminocrotonate to α,β-unsaturated sulfoxide **76** in a highly diastereoselective manner.[90] The required sulfoxide **76** was prepared by a Knoevenagel reaction from β-keto sulfoxide **77** and 2-chlorobenzaldehyde. Hantzsch reaction of **76** with methyl 3-aminocrotonate produced a single diastereomer (*S*,*SS*)-**78** as a result of the Michael addition followed by cyclization and dehydration. Although the yield of this step was moderate, only *p*-methoxyphenyl methyl sulfoxide was formed as a byproduct as a consequence of a retro-Knoevenagel reaction on **76**. The stereoselectivity of the Michael-type addition was explained by assuming the existence of the reactive conformation represented for (*SS*)-**76** which, on steric grounds, reacted from the opposite side of the bulky aromatic sulfur substituent. Oxidation of the sulfinyl group yielded optically pure **75**.

More general results were obtained in the conjugate additions to cyclic α,β-unsaturated keto sulfoxides. Thus, 2-(*p*-tolylsulfinyl)cyclopentenone **79** (Scheme 31), available in enantiomerically pure form on multigram scale,[91] underwent very efficiently conjugate addition of different organometallic reagents, the resulting diastereoselectivity being dependent on the nature of the reagent and the reaction conditions.[92] The best results were obtained with

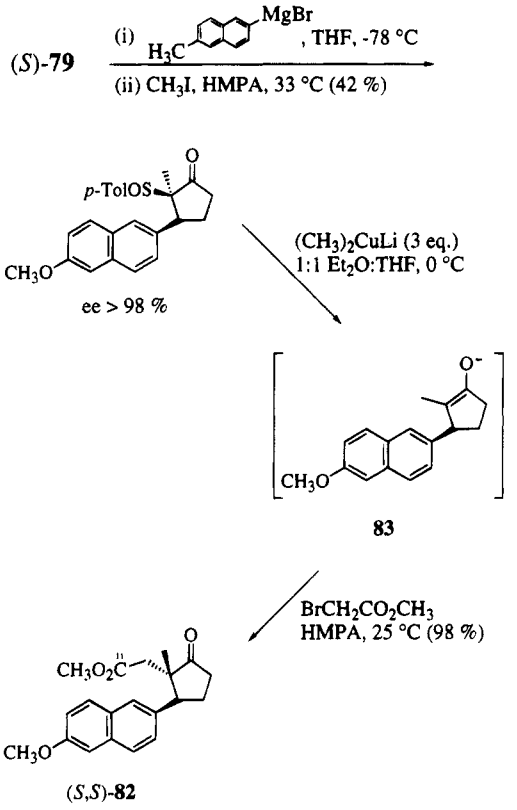
Scheme 30



Scheme 31



Scheme 32

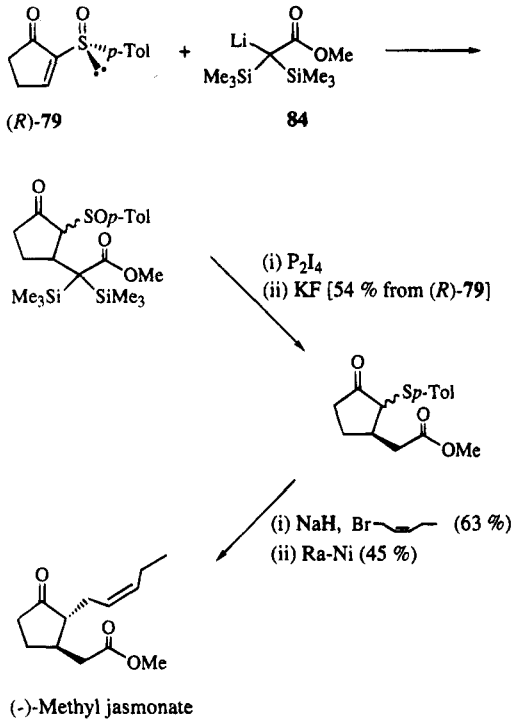


Grignard reagents in the presence of $ZnBr_2$. (*R*)-3-Methylcyclopentanone (**80**) was generated in 87% ee when the enone sulfoxide (*S*)-**79** was treated with $ZnBr_2$ prior to the addition of methylmagnesium iodide, after desulfurization of the resultant conjugate adduct **81**. The observed diastereoselectivity was explained by assuming the formation of a chelate **A** with $ZnBr_2$ where organometallic approach took place from the less-hindered *re* face of the enone. In the absence of divalent metals the sulfinyl enone (*S*)-**79** adopts the **B** *s-cis* conformation shown, now the *si* face approach of the nucleophile being more favored. In these conditions, a similar reaction sequence afforded (*S*)-3-methyl cyclopentanone in 76% ee.

Starting from (*S*)-**79**, several β-substituted cyclopentanones showing biological properties have been synthesized by Posner applying this sulfoxide-directed conjugate addition as a key step.

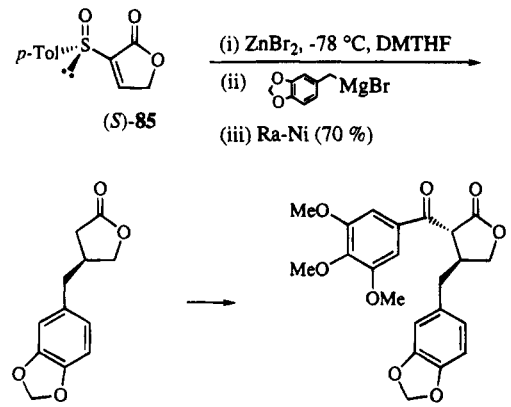
Stereoidal 11-oxoequilenin methyl ether **82**[93] (Scheme 32) was synthesized in a few steps by stereospecific addition of the large (6-methoxy-2-naphthyl)magnesium bromide to (*S*)-**79** followed by trapping of the enolate intermediate with methyl iodide. After dimethylcopper lithium desulfurization to enolate **83** regiospecific and stereospecific alkylation with methyl bromoacetate gave optically pure (*S,S*)-**82**.

Scheme 33



(-)-Methyl jasmonate

Scheme 34



86

(-)-Podorhizon

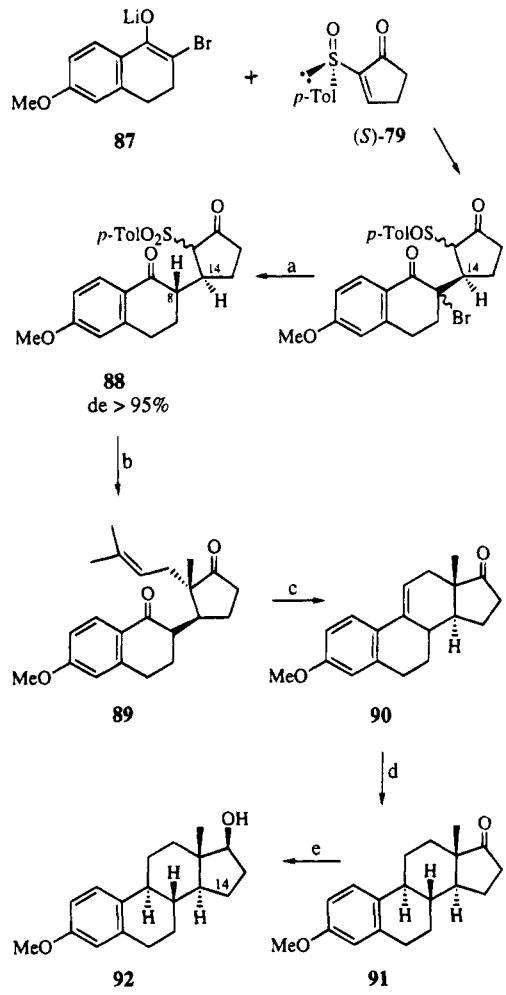
Other enantiomerically pure 3-substituted cyclopentanones, intermediates in the synthesis of steroids,[94] were obtained during $ZnBr_2$-mediated vinylmagnesium bromide conjugate addition to (*S*)-**79**.

The addition of functionalized organometallics such as the α-lithioacetate **84** (Scheme 33) also proceeded with high diastereoselectivity. The transformation of the conjugate adduct into natural methyl jasmonate,[95] an insect sex attractant pheromone, was achieved as indicated through the sequence sulfoxide deoxygenation, desilylation, enolate C-alkylation, and reductive desulfurization.

The stereoselective formation of quaternary stereogenic carbons was also possible via the asymmetric organocopper conjugate addition to 3-substituted sulfinylcyclopentenones. The method was applied to the synthesis of sesquiterpene (+)-α-cuparenone.[96]

Sulfinyl butenolides (*S*)-**85** (Scheme 34) were used as Michael acceptors in the synthesis of optically pure 3-substituted 4-butenolides. Zinc-promoted benzylic

Scheme 35[a]

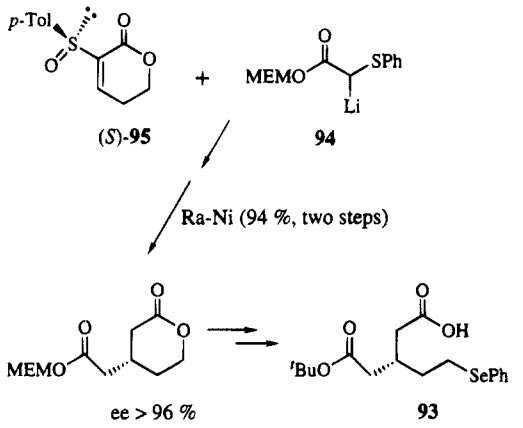


[a] (a) (i) *m*-CPBA, (ii) $TiCl_3$, (iii) $ZnNH_4Cl$ (81 % three steps), (iv) ^tBuOK, ^tBuOH (85 %); (b) (i) NaH, MeI, (ii) Me_2CuLi, $Me_2C{=}CHCH_2Br$ (71 %); (c) (i) O_3, Me_2S (68 %), (ii) $TiCl_3$, Zn/Ag (37 %); (d) CH_3CO_2H, Et_3SiH (90 %); (e) $NaBH_4$

Grignard reagent addition to (*S*)-**85** led, after desulfurization and enolate acylation, to the anticancer podophyllotoxin family agent (−)-podorhizon (**86**).[97]

Total synthesis of the steroidal hormones estrone and estradiol[98] has been achieved by taking advantage of the highly diastereoselective addition of enolates to **79** (Scheme 35). The sense of asymmetric induction depended on the nature of the enolate. The natural configuration of C-14 in the final steroid was created with high asymmetric induction by combining the reaction of α,α-disubstituted enolate **87** with (*S*)-**79**. The resulting diastereoselectivity was a consequence of the reaction between the chelated form of the β-keto sulfoxide and the sterically congested disubstituted enolate. The Michael adduct was converted into β-keto sulfone **88** with a diastereomeric purity >95% by oxidation, reductive dehalogenation, and equilibration. After methylation of **88**, Me_2CuLi-promoted reductive cleavage of the C−S bond afforded an enolate ion whose reaction with 3,3-dimethylallyl bromide led to **89**, easily transformed into **90** after ozonolysis and reductive cyclization of the intermediate keto aldehyde. The yield of the latter step was dependent on the amounts of reactant

Scheme 36



used. Hydrogenation of the double bond gave estrone methyl ether **91** whose carbonyl reduction afforded estradiol derivative **92**, both enantiomerically pure.

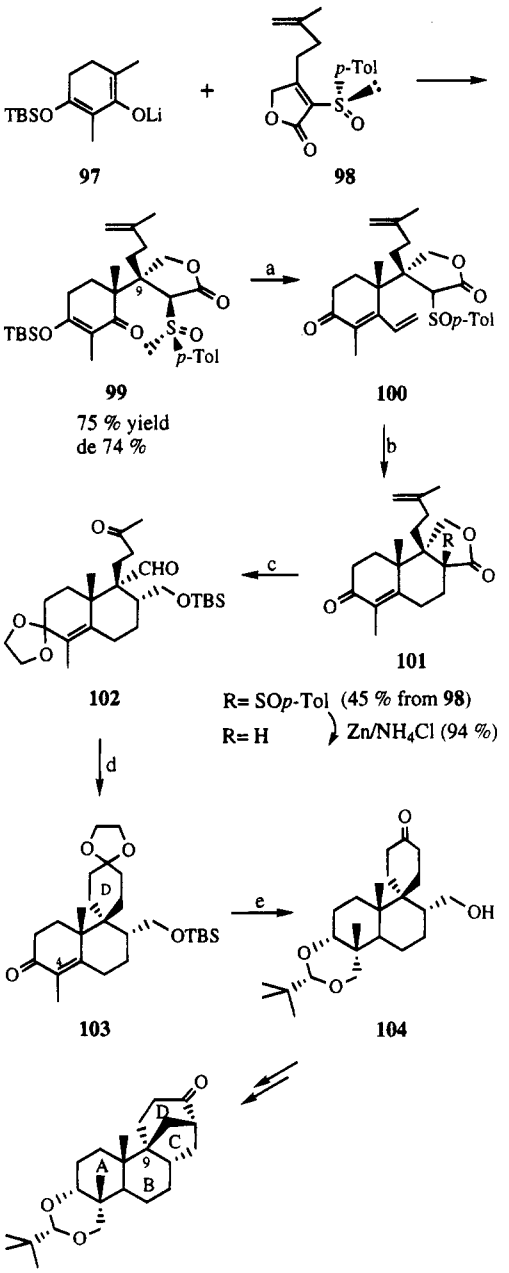
Asymmetric Michael additions of enolates were also carried out on sulfinyl butenolides or pentenolides with variable-facial diastereoselectivities (27 to 96%). The synthetic applications of these reactions were exemplified in the preparation of optically pure 3-substituted glutarate monoesters such as **93**,[99] versatile building blocks in the synthesis of different compounds with biological properties (Scheme 36). Compound **93** was obtained in a few steps from the adduct resulting in the addition of MEM 2-lithioacetate derivative **94** to pentenolide sulfoxide **95**.

The enantioselective total synthesis of the diterpene aphidicolin derivative **96** (Scheme 37) reported by Holton[100] relied on the stereoselective formation of the C-9 quaternary stereogenic center generated in the conjugate addition of lithio enolate **97** to 3-substituted sulfinyl butenolide **98** which took place with 74% de. After vinyllithium addition to compound **99** and HF treatment, cyclization of **100** gave the tricyclic enone **101**. The desulfurized compound was protected, selectively ozonized, reduced to a mixture of diastereomeric triols, protected, and oxidized to keto aldehyde **102**. The D ring of the aphidicolin precursor was made by aldol closure of **102** followed by hydrogenation of the resulting disubstituted olefin and ketal exchange to give enone **103**. The sequence lithium–ammonia reduction with *in situ* formaldehyde trapping, L-Selectride carbonyl reduction and 1,3-diol protection afforded pivalyl derivative **104** whose coversion to pivalyl aphidicoline **96** was already known.

B. C–X Bond Formation

Although asymmetric conjugate addition of nitrogen nucleophiles to α,β-unsaturated sulfoxides[101] was described in 1971, this intermolecular reaction has not been further applied to natural products synthesis probably due to the low reactivity of these simple Michael acceptors. In contrast, the intramolecular version, which took place at lower temperature and higher reaction rates,[102,103] was used in alkaloid synthesis although the asymmetric induction was not as high as that achieved in other sulfinyl-induced processes. Thus, the total synthesis of (*R*)-carnegine (**105**, Scheme 38) reported by Pyne[89,103] was based on the formation of the tetrahydroisoquinoline system

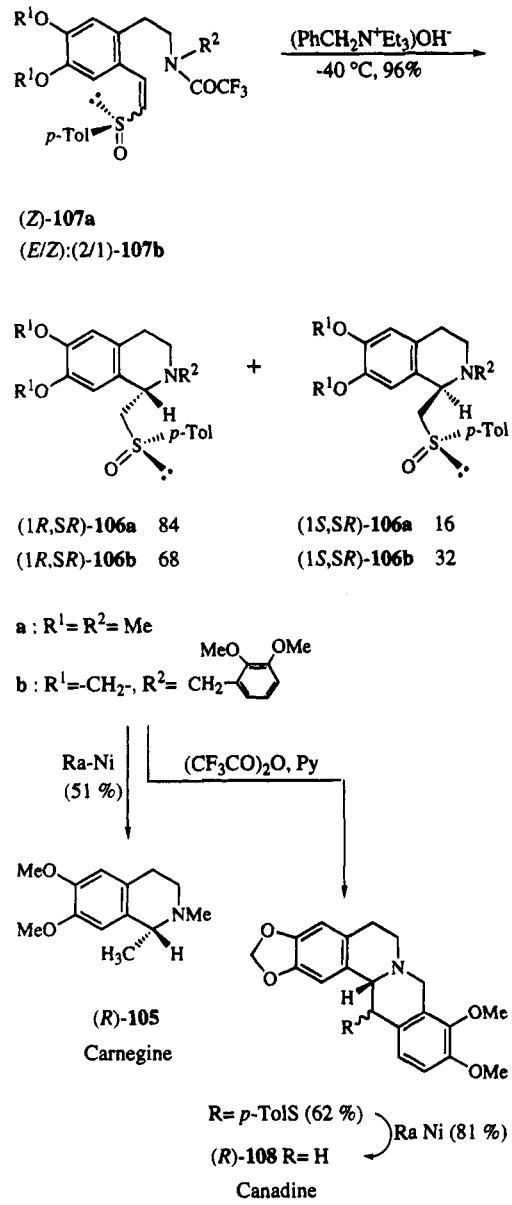
Scheme 37[a]



[a] (a) (i) CH_2=CHLi, Toluene, 25 °C, (ii) HF (76 % two steps); (b) NaOMe, MeOH (100 %); (c) (i) 2-ethoxydioxolane, PPTS, Δ (89 %), (ii) O_3, CH_2Cl_2, -78 °C, Me_2S, (iii) $LiAlH_4$ (100 %), (iv) TBSCl, DMAP, Et_3N, CH_2Cl_2, -78 °C, (v) CrO_3, Py, 25 °C (64 % four steps); (d) (i) KO'Bu, 'BuOH, 0 °C, (ii) H_2, Pd/C, (iii) $HOCH_2CH_2OH$, *p*-TsOH, 0 °C (90 % from **102**); (e) (i) Li, NH_3, CH_2O (70 %), (ii) *L*-selectride, (iii) pivalaldehyde, HF, *p*-TsOH (85 % two steps)

106a upon cyclization of (*Z*)-vinyl sulfoxide **107a** in basic conditions. Although the major diastereomer (1*R*,S*R*)-**106a** was formed in a 68% de, the excellent yield of this intramolecular addition (96%) allowed its isolation in a 78% yield. Desulfurization of (1*R*,S*R*)-**106a** gave the alkaloid carnegine (*R*)-**105**. The use of compound **107b** as starting material allowed the total synthesis of canadine **108**.[102] Thus a 2:1 mixture of (*E*)- and (*Z*)-vinyl sulfoxide isomers

Scheme 38

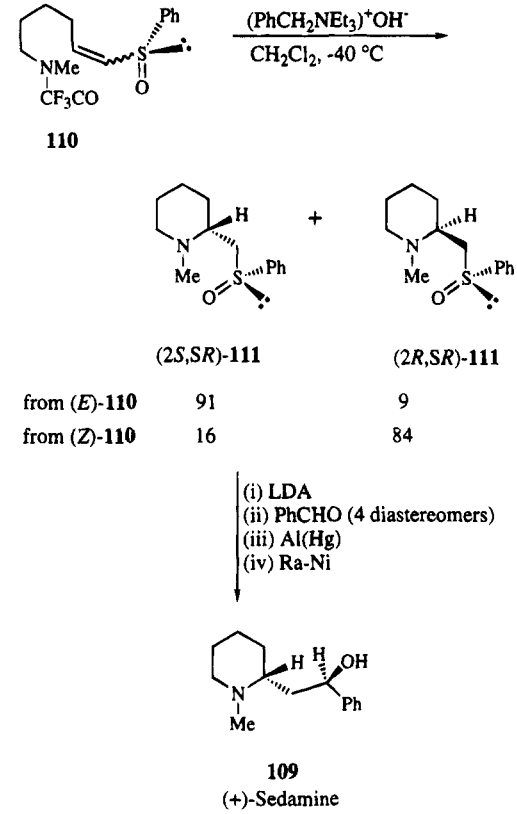


107b was cyclized to the tetrahydroisoquinoline moiety giving rise to a 47% isolated yield of (1*R*,*SR*) epimer **106b** which was converted into (*R*)-canadine **108** via intramolecular Pummerer reaction and desulfurization.

Both enantiomers of sedamine (**109**) were obtained from (*E*)- and (*Z*)-alkenyl sulfoxides **110** respectively (Scheme 39) in a similar way.[89] The diastereoselectivity of the cyclization step was higher for the (*E*) isomer (82% de) than for the (*Z*) derivative (68% de). After separation, diastereomerically pure (2*S*,*SR*)-**111** was transformed into (+)-sedamine and the (2*R*,*SR*) epimer into its enantiomer. The completion of the synthesis required the aldol condensation of the α-sulfinyl carbanion of **111** with benzaldehyde giving rise to a mixture of all the possible diastereomers. After separation and desulfurization sedamine (**109**) was isolated. The synthesis suffers from the low diastereoselectivity of the aldol condensation.

These intramolecular conjugate additions were rationalized assuming a nucleophilic attack of an incipient amino anion generated from the trifluoroacetamide precursor **107** and **110** in the basic conditions utilized. Several stereochemical models, based on steric or stereoelectronic approach control have been proposed to account for the results.[89]

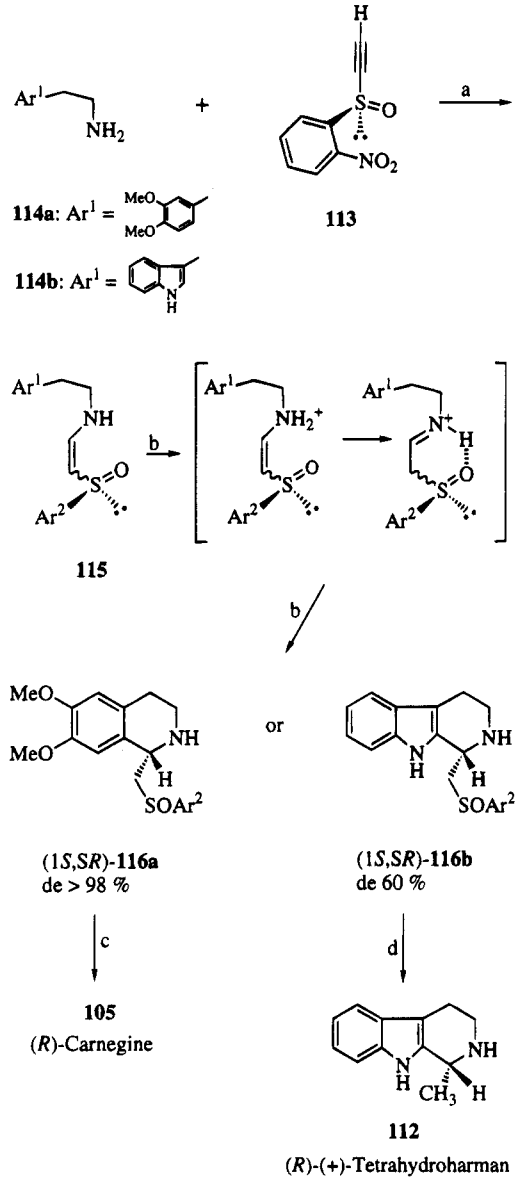
Scheme 39



An alternative strategy to carnegine[104] (**105**) and other alkaloids such as tetrahydroharman[105] (**112**, Scheme 40) has been based on a Michael addition–cyclization sequence starting from (*R*)-ethynyl *o*-nitrophenyl sulfoxide (**113**). The presence of the electron-withdrawing substituent on the aromatic ring increased the Michael acceptor character of **113** which is able to add amines **114a** and **114b** in mild conditions, to generate the α,β-unsaturated sulfoxides **115** which upon acid-induced cyclization of the electron-rich aromatic ring gave the alkaloid precursors **116**. In these cases, the new stereogenic center which was formed in moderate to good diastereoselectivity (60–98% de) did not result from the Michael addition step but from the reaction on the imine as shown in Scheme 40. Thus, the cyclization step took place on the protonated enamine through its iminium ion in equilibrium, the latter having an intramolecular hydrogen bonding which locks the conformation of the sulfinyl group. Reaction of this frozen conformation could explain the observed stereoselectivity, higher when an apolar solvent was used as was the case for the tetrahydroisoquinoline **116a** formation. The transformation of pure diastereomers **116** into the enantiomerically pure natural products only required conventional reactions.

The diastereoselective C–O bond formation by alkoxide ion addition to alkenyl sulfoxides has only been successful in the intramolecular fashion. The levels of asymmetric inductions achieved are better than in the analogue with nitrogen nucleophiles. The reaction has been extensively used by Iwata *et al.* to

Scheme 40[a]

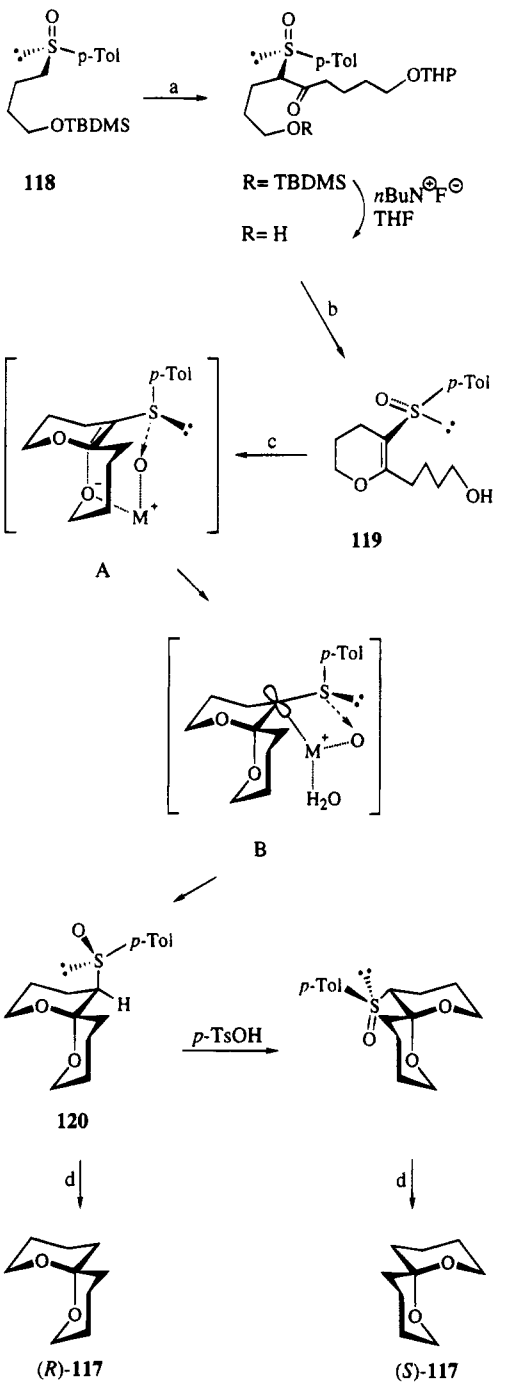


[a] (a) $CHCl_3$, r.t.; (b) TFA, $CHCl_3$, 0 °C, (de > 98 %, 65 % from **115a**) or TsOH, MeOH, -30 °C, (de 60 %, 93 % from **115b**); (c) (i) CH_2O, $NaCNBH_3$, CH_3CN (90 %), (ii) Ra-Ni; (d) Ra-Ni

prepare chiral spiroketals showing different biological properties. The stereochemistry of the dioxaspiro center generated in this process was fully controlled by the configuration at sulfur.[106]

The synthesis of the simplest 1,7-dioxaspiro[5.5]-undecane[107] (**117**, Scheme 41), the major component of sex pheromones produced by the olive fruit fly *Dacus oleae*, was achieved in both configurations by acylation of enantiomerically pure sulfoxide **118** whose transformation into the key intermediate dihydropyranyl derivative **119** required the deprotection of the silyloxy group followed by an acidic treatment giving rise to the intramolecular acetalization and dehydration. The intramolecular Michael addition of the alkoxide ion resulting from **119** in the presence of NaH, allowed for the exclusive formation of the kinetically controlled spiroketal **120** through the more stable associated transition state **A** and intermediate **B** giving the system with the axial

Scheme 41[a]

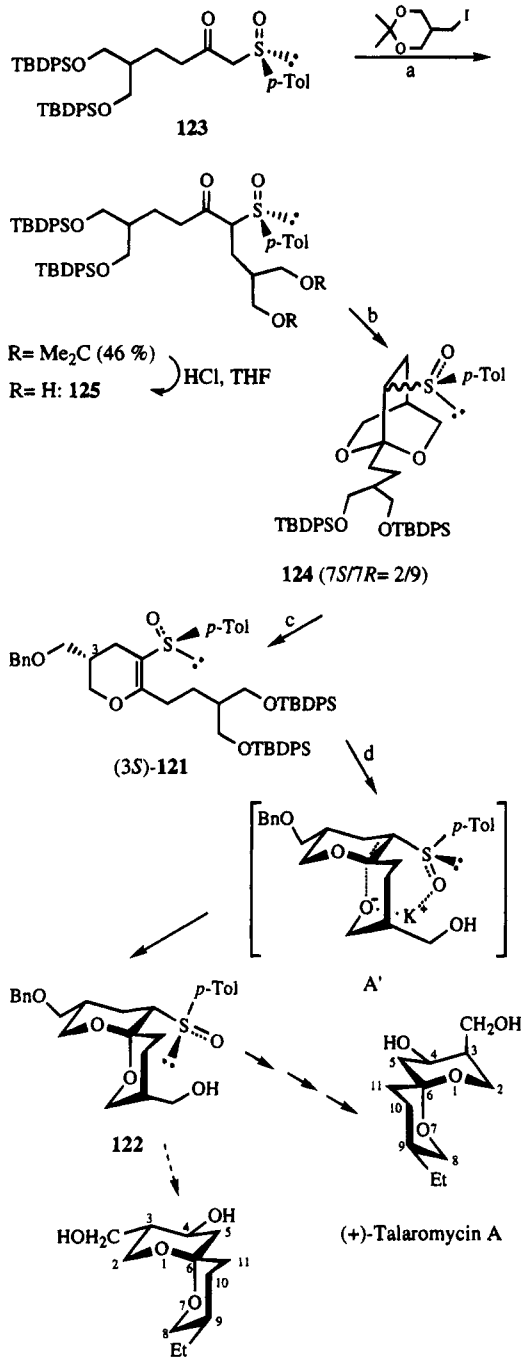


[a] (a) (i) LDA, THF, (ii) MeO_2C-$(CH_2)_4$-OTHP, HMPA, -70 °C (56 %); (b) (i) *p*-TsOH, $MgSO_4$ (68 %), (ii) H_3O^+ (79 %); (c) NaH, r.t. (77 %); (d) Ra Ni

sulfoxide. The spiroketal isomer with the sulfinyl group in the equatorial position was exclusively formed from **120** by isomerization upon treatment with *p*-TsOH which proceeded with inversion of the configuration at the spirocenter through retro-Michael and Michael reactions. Desulfurization of both diastereomers allowed the stereoselective synthesis of both enantiomers of **117**.

The methodology was successfully applied to the preparation of more complex spiroketals such as talaromycins A and B[108] (Scheme 42), toxic metabolites isolated from the fungus *Talaromyces stipitatus*, exhibiting potassium current blocking activity which

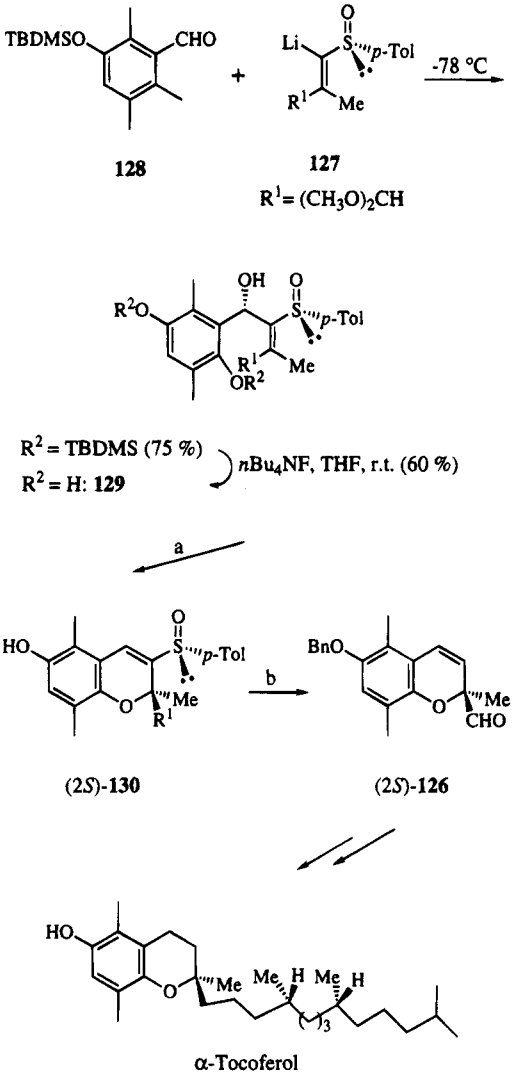
Scheme 42[a]



[a] (a) K_2CO_3, 18-crown-6; (b) $ZnCl_2$, CH_2Cl_2 (94 %); (c) (i) CF_3CO_2H, C_6H_6, then K_2CO_3, MeOH, H_2O, (ii) BnBr, NaH, n-Bu_4NI (66 % two steps); (d) (i) n-Bu_4NF, (ii) KH, THF (87 % two steps)

leads to muscle dysfunction. The synthetic plan relied on the diastereoselective formation of 3-substituted dihydropyran **121**[108,109] and its cyclization to the key intermediate spiroketal **122**. Starting from β-keto sulfoxide **123**, successive alkylation, acetonide hydrolysis and intramolecular acetalization in the presence of $ZnCl_2$ yielded a mixture of C-7 epimeric bicyclic acetals **124**. Diastereoselective cleavage of **124** with trifluoroacetic acid gave a major C-3 epimer of the dihydropyran derivative which after trifluoroacetate hydrolysis and benzylation afforded (3*S*)-**121**.

Scheme 43[a]



[a] (a) MeONa (3 eq.), MeOH, Δ (96 %); (b) (i) Ra-Ni (76 %), (ii) BnBr, K_2CO_3, DMF (87 %), (iii) $CHCl_3$, CF_3CO_2H, H_2O, 40 °C (98 %)

This transformation allowed the asymmetric differentiation of the prochiral 1,3-diol moiety present in **125** by means of the sulfinyl group. A study carried out on model compounds showed the possibility of obtaining the 3*R* epimers by treating the bicyclic sulfinyl acetals with $AlCl_3$. The diastereoselective formation of the spiroketal **122** followed the alkoxide intramolecular Michael addition of the *pro-R* hydroxymethyl group on the deprotected diol, which in this case took place via the chelated transition state **A'**. The protonation of the resulting intermediate from the less-hindered face gave rise to compound **122** having the sulfoxide in the equatorial disposition as a sole diastereomer. The transformation of the spiroketal **122** into talaromycins A and B required conventional procedures. The stereochemistry shown by the natural products resulted in the acid-catalyzed epimerization of the spiranic stereogenic center.[108c]

Several 1,6-dioxaspiro[4.5]decane systems[64] (see Scheme 16) have been obtained by applying a similar key step for the construction of the stereogenic spiro center.

An efficient synthesis of compound **126** (Scheme 43), a key intermediate in the synthesis of α-tocoferol

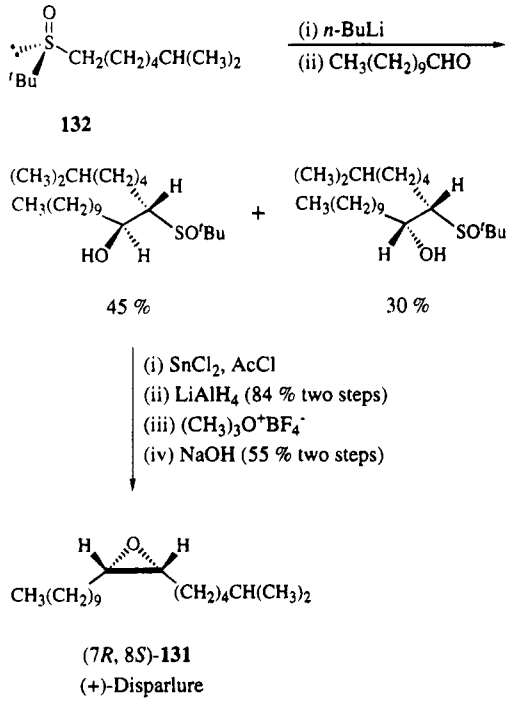
(vitamin E), reported in 1984,[110] used the sulfoxide to induce a high diastereoselectivity in two pivotal steps: addition of lithioalkenyl sulfoxide **127** to aromatic aldehyde **128** and intramolecular reaction of the alkoxide ion resulting from hydroquinone **129** on the allylic alcohol supporting the α,β-unsaturated sulfinyl moiety. Although the first hydroxylic stereogenic center generated was further destroyed, a sole diastereomer was detected in the first reaction as well as in the intramolecular cyclization which took place via S_N2' mechanism in a *syn* stereospecific fashion to give (2*S*)-**130**.

V. Reactions of Sulfoxide-Stabilized Carbanions

A. 1,2-Addition to Carbonyl

Although the addition of simple α-sulfinyl carbanions to aldehydes took place with poor diastereoselectivity,[111] the reaction was used as a key step in the synthesis of (+)-disparlure (**131**),[112] the sex attractant pheromone of the female gypsy moth (Scheme 44). After chromatographic separation of

Scheme 44



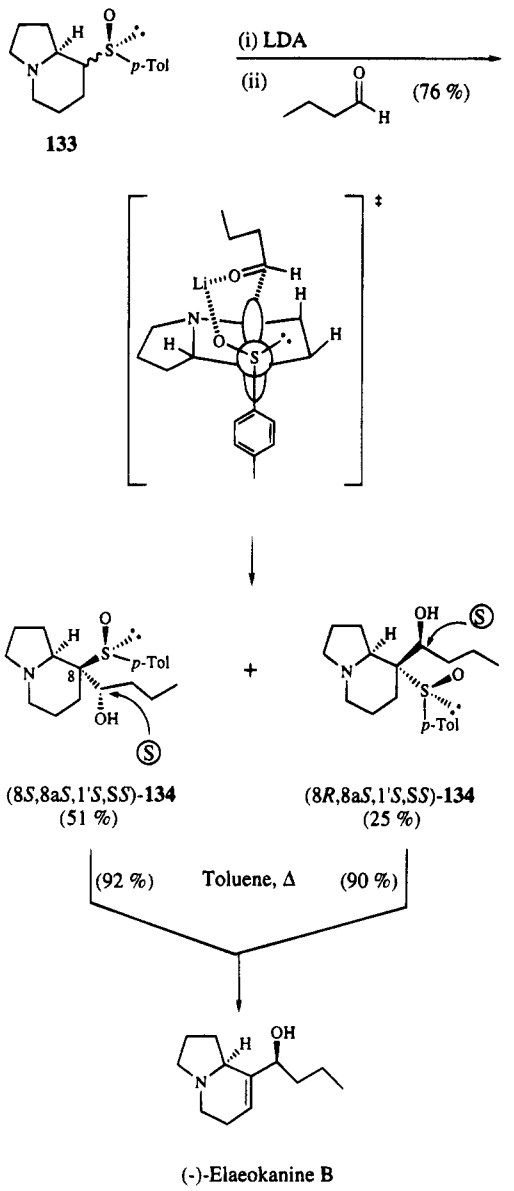
(7*R*, 8*S*)-**131**
(+)-Disparlure

the mixture of hydroxy sulfoxides resulting from the reaction of lithium anion derived from optically pure sulfoxide **132** and undecanal, the epoxide (7*R*,8*S*)-disparlure (**131**) was obtained from the major diastereomer through a sequence involving sulfoxide reduction, and basic cyclization of the sulfonium salt derived from the thioether.

Later on, the stereochemical outcome of the process on both aldehydes and ketones was shown to be highly dependent on the nature of the sulfoxide[113] and the carbonyl derivative,[114] the diastereoselectivity possibly being enhanced by using Zn^{2+} as metal counterion.

A good result was achieved in the reaction between the lithium anion derived from β-sulfinyl amine **133** and butyraldehyde[115] (Scheme 45). Although a mixture of C-8 epimers was formed, only the C-1′ (*S*) configuration was induced. This high asymmetric induction was explained on the basis of the transition state depicted in Scheme 45, where chelation between Li^+ and the sulfinyl and carbonyl oxygens provided a rigid disposition where the approach to the aldehyde is favored from the *si* face to generate the (*S*)-carbinol. The reaction was applied to the total synthesis of alkaloid elaeokanine B by simple dehydrosulfinylation of compounds **134**.

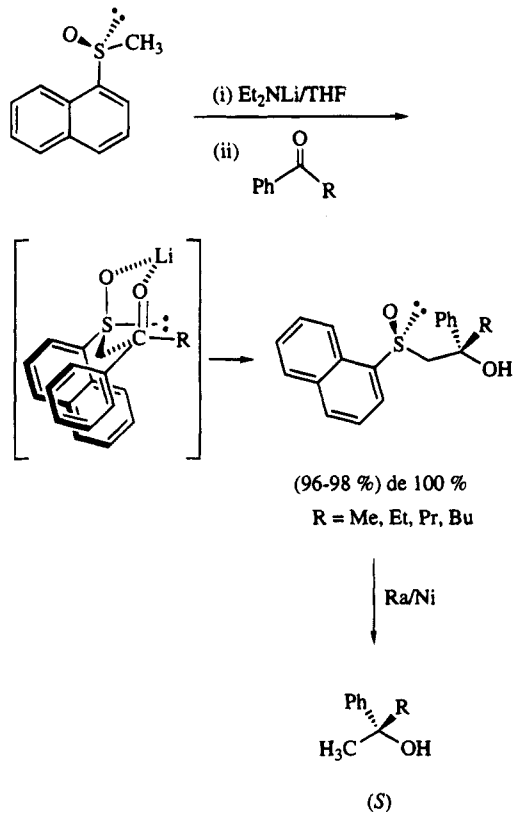
Scheme 45



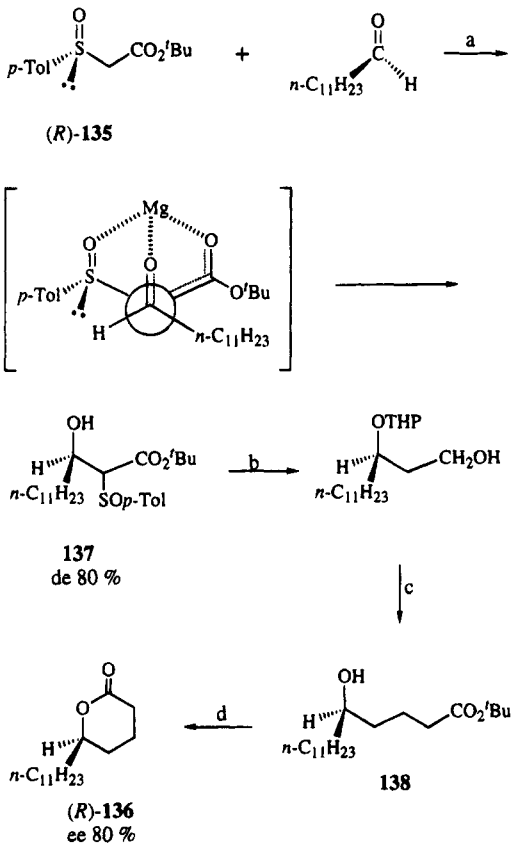
(-)-Elaeokanine B

The use of (*S*)-lithiomethyl 1-naphthyl sulfoxide,[116] instead of *tert*-butyl or aromatic sulfinyl derivatives, has allowed for the exclusive formation of (*S*) tertiary carbinols in the addition to phenyl alkyl ketones (Scheme 46). This high asymmetric induction was explained by assuming a favored approach of the α-sulfinyl anion to the *re* face of the carbonyl group due to the formation of the cyclic transition state represented, strongly stabilized by a $\pi-\pi$ charge transfer interaction between both aromatic rings. The increasing size of the R substituent determined a decrease of the diastereoselection. Despite the achieved improvements, this type of reaction has not

Scheme 46



Scheme 47[a]



[a] (a) ^{t}BuMgBr, THF, -78 °C (100 %); (b) (i) Al/Hg (80 %), (ii) DHP, PPTS (100 %), (iii) $LiAlH_4$; (c) (i) TsCl, Py, (ii) MgI_2, (iii) $LiCH_2CO_2{}^t$Bu; (d) *p*-TsOH

been further applied to natural products synthesis.

Structural modifications of the sulfoxide led to variable stereochemical results.[117] A significant improvement on the diastereoselection was observed with the introduction of a *tert*-butyl ester on the α-carbon. Thus, the aldol-type condensation of (*R*)-*tert*-butyl 2-(*p*-tolylsulfinyl)acetate[118] (**135**, Scheme 47) with aldehydes[119] or ketones in the presence of *tert*-butylmagnesium bromide gave good yields (74–90%) and moderate to good diastereoselection (20–95%). When long-chain aliphatic aldehydes were used, an easy approach to the asymmetric synthesis of insect pheromone lactones[120] such as **136** was described. The adduct **137** resulting in the aldol-type condensation of **135** with dodecanal was desulfurized, protected, and transformed into the seco-ester **138** whose cyclization led to the natural δ-lactone (*R*)-**136** with an 80% ee. This value corresponded to the diastereoselectivity achieved in the condensation step that was explained assuming the evolution of the system through the rigid chelated transition state represented where the enolate approaches the *si* face of the aldehyde from its less hindered face which supports the lone electron pair of the sulfoxide.

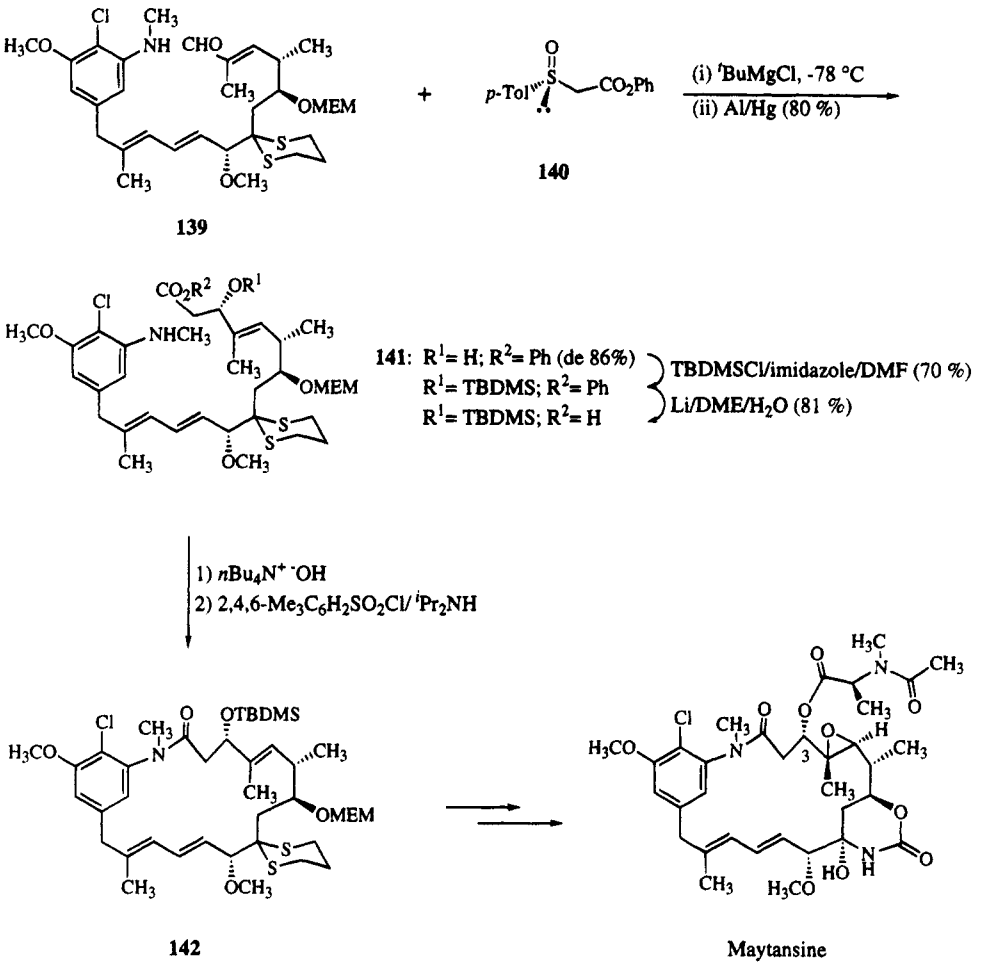
This methodology was applied by Corey[121] to create the C-3 stereogenic carbinol of the antitumor agent maytansine (Scheme 48). The reaction between aldehyde **139** and sulfinyl acetate **140** followed by desulfurization afforded carbinol **141** in a (*R*)/(*S*) epimer ratio 93:7. After silylation and hydrolysis of the phenyl ester, the acid could be separated from the minor epimer. Macrocyclization to lactame **142**, showing the basic maytansine structure, was accomplished from the tetra-*n*-butylammonium salt of the acid using the mixed anhydride with mesitylene sulfonyl acid for carboxyl activation.

An excellent asymmetric indution was reported for the α-lithioalkenyl sulfoxide **127** addition to the aromatic aldehyde **128** (Scheme 43) used in the synthesis of tocoferol[110] previously mentioned.

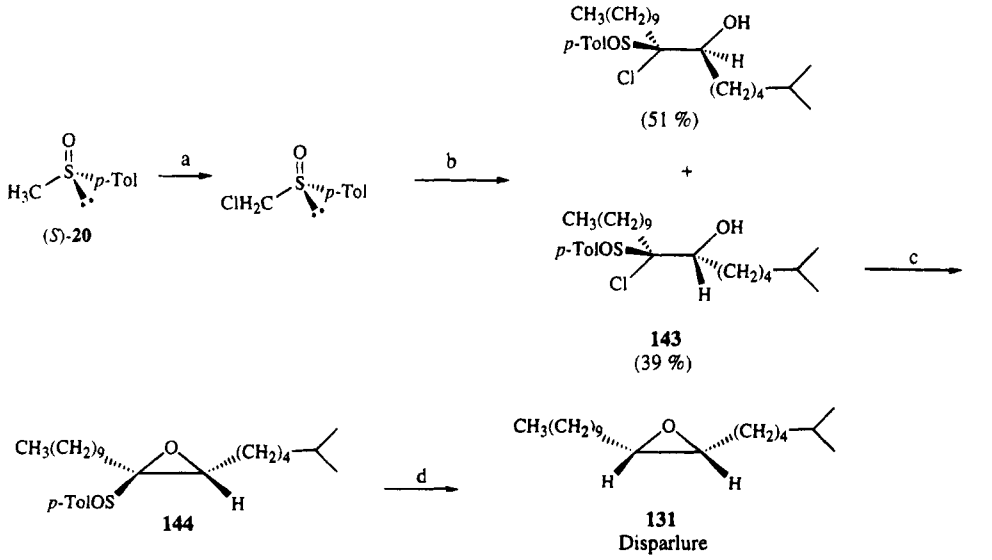
The addition of α-chloro and α-sulfinyl anions to aldehydes or ketones gave poor diastereoselective results.[122] Nevertheless, the reaction was applied to the synthesis of (+)-disparlure (**131**, Scheme 49). The preparation of the starting 1-chloroalkyl *p*-tolyl sulfoxide was described by Yamakawa[123] by NCS chlorination of (*S*)-**20**. After alkylation of chloromethyl *p*-tolyl sulfoxide with 1-iododecane, the addition of the anion derived from the resulting sulfoxide to 6-methyl-1-heptanal gave two epimeric chlorohydrins with complete C-1 asymmetric induction although with low diastereoselectivity in the new hydroxylic center. After separation, the chlorohydrin **143** was cyclized to the α,β-epoxy sulfoxide **144** and desulfurized with *n*-BuLi at −100 °C to disparlure (**131**). The use of these sulfinyl chlorhydrins has been extended to the asymmetric synthesis of α-amino ketones and α-amino aldehydes;[123c] α-hydroxy acids, esters, and amides and α,α′-dihydroxy ketones;[124] α,β-unsaturated γ-hydroxy carbonyl compounds;[125] and α-alkyl amides.[126]

The reactions of chiral α-sulfinyl anions with imines[127] has been reported to proceed with better diastereoselection for simple systems than the analogue reactions on aldehydes. Kagan[127] was the first

Scheme 48



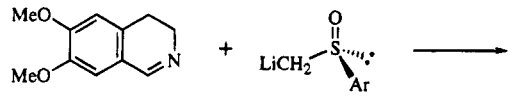
Scheme 49[a]



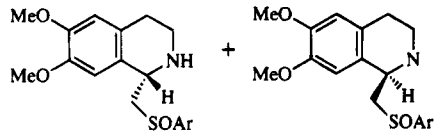
[a] (a) NCS, K_2CO_3, CH_2Cl_2 (94 %); (b) (i) LDA, THF, -50°C, $I(CH_2)_9CH_3$ (77 %), (ii) LDA, $HCO(CH_2)_4{}^iPr$; (c) tBuOK, tBuOH (95 %); (d) *n*-BuLi, -100 °C (55 %).

to point out the strong dependence of the product diastereoselection with the experimental conditions, mainly the temperature. Pyne[128] corroborated this observation in the reaction of α-lithiomethyl phenyl sulfoxide with the imine **145** (Scheme 50). The diastereoselectivity of the process could be inverted by changing the reaction temperature due to an equilibration process although under thermodynamic control the diastereoselection was poorer except in the example shown. Compound **146** generated from (*R*)-methyl *p*-tolyl sulfoxide was used as starting material in the synthesis of the alkaloid tetrahydropalmatine (**147**) achieved after reductive amination, additive Pummerer reaction, and desulfurization.

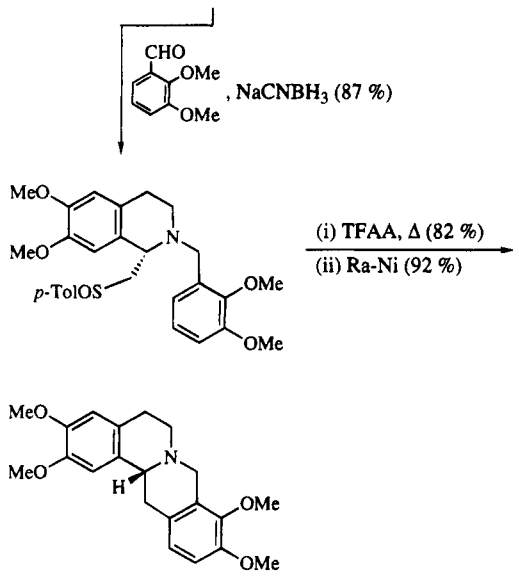
Scheme 50



145



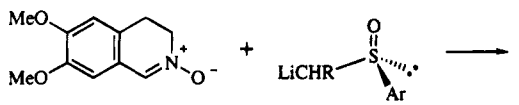
Ar= Ph: T= -45 °C	23	77
Ar= Ph: T= 0 °C	89	11
Ar= *p*-Tol: T= 0 °C	92 (**146**)	8



147

(*R*)-(+)-Tetrahydropalmatine

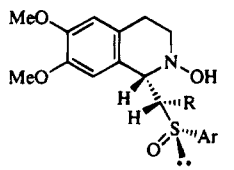
Scheme 51



148

149a: R= Ph; Ar= 

149b: R= H; Ar= *p*-Tol



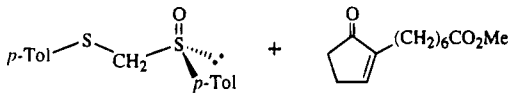
150a: de 92 %
150b: de 84 % (in the presence of quinidine lithium salt)

Different improvements recently reported for the diastereoselective formation of the 1-substituted tetrahydroisoquinoline framework involved the use of nitrones such as **148** (Scheme 51) and α-lithio anions derived from (*R*)-benzyl 2-methoxy-1-naphthyl sulfoxide[129] (**149a**) or (*R*)-*p*-tolyl methyl sulfoxide (**149b**).[130] The addition gave rise to the (1*S*,1′*S*,*SR*)-diastereomer in a 92% de for **150a** and 84% de for **150b**, in this case in the presence of quinidine lithium salt.

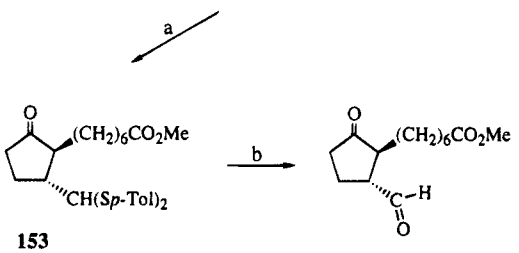
B. Additions to α,β-Unsaturated Compounds

Although the diastereoselective addition of simple α-sulfinyl carbanions to α,β-unsaturated compounds has been studied by several research groups,[4] an important piece of work was devoted to racemic derivatives. The first application of these reactions to asymmetric synthesis was due to Scolastico[131] who described the obtention of a prostaglandin intermediate. The conjugate addition of the anion derived from (*S*)-dithioketal *S*-oxide **151** (Scheme 52) to 2-substi-

Scheme 52[a]



(*S*)-**151** **152**



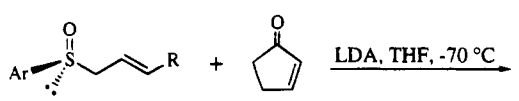
153

[a] (a) (i) *n*-BuLi, THF, HMPT, -78 °C (45 %), (ii) $(Me_2N)_3P$, I_2, KI, MeCN (59 %); (b) I_2, $NaHCO_3$, dioxan-H_2O

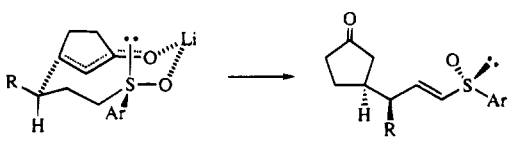
tuted cyclopentenone **152** in the presence of HMPT gave a 52:48 mixture of C-α epimers that were converted into the enantiomerically pure protected aldehyde **153** by sulfinyl deoxygenation. The free aldehyde has been used as starting material in prostanoids synthesis. The high diastereoselectivity achieved in the formation of the stereogenic C-β and C-γ centers seems to be due to the presence of the alkyl substituent at C-2 of the cyclopentenone.

The regiochemical and stereochemical course of the reaction between ambident sulfinylallyl anions and cyclic enones has been deeply studied by Haynes *et al.*[132] The lithium carbanions reacted exclusively by C-3 in a conjugate fashion with 2-cyclopentenone derivatives (Scheme 53). Moreover the diastereo-

Scheme 53

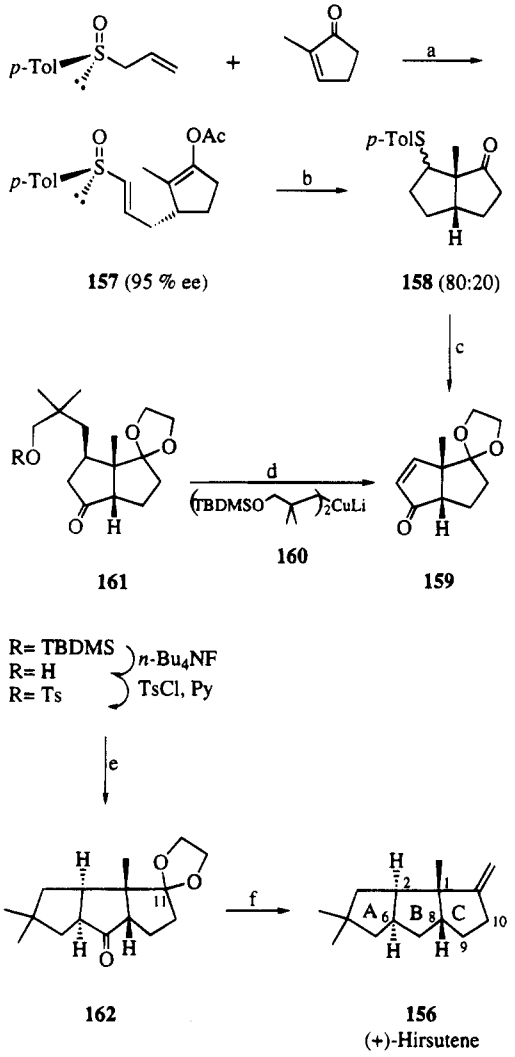


154



155

Scheme 54[a]



[a] (a) (i) LDA, THF, HMPA, -78 °C, (ii) AcCl, -78 °C (84 %); (b) (i) Zn, AcOH (95 %), (ii) $TiCl_4$, AcOH, H_2O, r.t. (86 %); (c) (i) $HOCH_2CH_2OH$, *p*-TsOH, (ii) MCPBA, CH_2Cl_2, 0 °C (90 %, two steps), (iii) DBN, toluene, Δ, (iv) CrO_3, Py (85 %); (d) -30 °C (88 %); (e) NaH, DME (85 % three steps); (f) (i) $NaBH_4$, MeOH (95 %), (ii) $^iPrSO_2Cl$, Et_3N (93 %), (iii) $LiEt_3BH$, toluene (72 %), (iv) *p*-TsOH, THF, MeOH, H_2O (90 %), (v) CH_2=PPh_3 (80 %)

selection of the process was very high even when C-3-substituted allyl sulfoxides with a defined geometry at the double bond such as **154** were used. A model proposed to account for these results was based on the assumption of a central role of the lithium counterion allowing the formation of the *trans*-decalyl-like transition state **155** represented for the reaction of a lithiated (*E*)-2-alkenyl sulfoxide **154** and cyclopentenone, where the substituents occupy the most stable pseudoequatorial positions. The configuration of the new stereogenic allylic carbon depended upon the alkene geometry of the starting allylic sulfoxide.

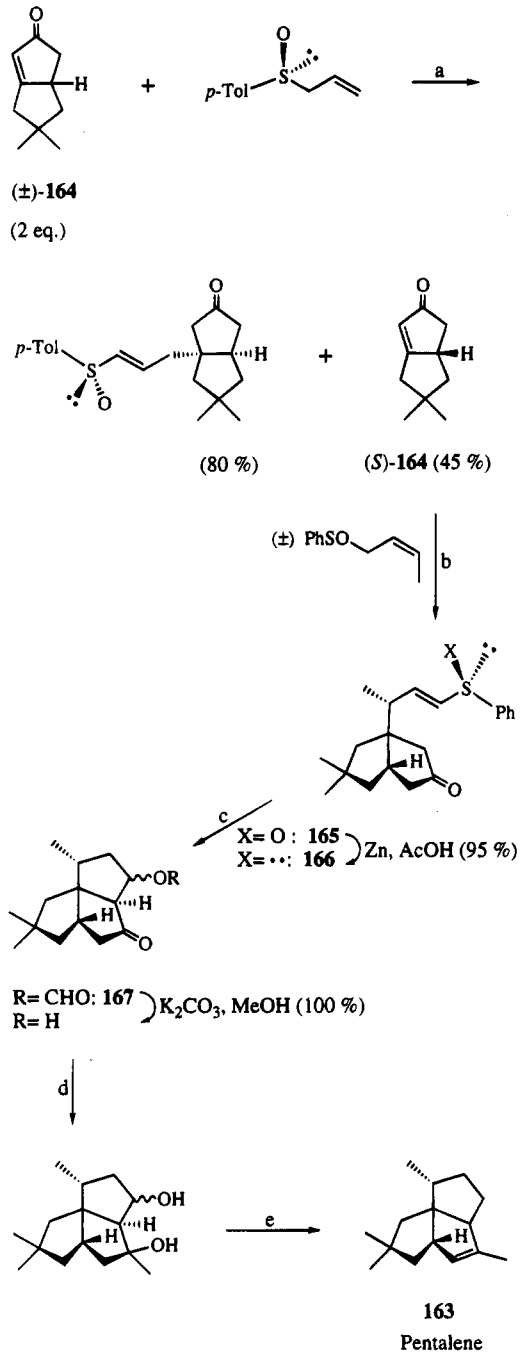
The application of these reactions to asymmetric synthesis of natural products was mainly due to Hua. The first example published was the total synthesis of the sesquiterpene hirsutene (**156**, Scheme 54).[133] Two crucial reactions, previously explored on different compounds,[134] were used in the formation of the B and C rings of the natural product. The highly diastereoselective addition of the anion resulting in the treatment of (*S*)-allyl *p*-tolyl sulfoxide with LDA to 2-methylcyclopentenone was the key step allowing the creation of the stereogenic C-8. The enolate initially formed after this addition was quenched with acetyl chloride to give **157** in 84% yield and 95% ee. The second crucial process was an efficient hydrolytic ring closure involving the vinyl thioether moiety, which resulted in the sulfoxide deoxygenation, and the enol acetate to afford the bicyclic derivative **158**, precursor of the B and C rings. The creation of the A ring involved the obtention of enone **159** which required the protection of the keto group of **158**, sulfur oxidation, pyrolytic sulfoxide elimination, and allylic oxidation. 1,4-Addition of cuprate **160** to enone **159** followed by cyclization of the tosylate resulting from **161**, afforded the tricyclic precursor **162** whose transformation into natural hirsutene (**156**) required the ketone reduction and Wittig reaction on the deprotected carbonyl at C-11.

A similar methodology was applied to the total synthesis of pentalenene **163**.[135] In this case, the reaction between the enantiomerically pure sulfinyl allylic anion and racemic enone **164** allowed the kinetic resolution of the latter, whose (*S*) enantiomer was thus recovered unreacted in a 45% isolated yield (Scheme 55). A new kinetic resolution was effected with racemic *cis*-crotyl phenyl sulfoxide lithium anion and (*S*)-**164**. The resulting addition product **165** was isolated optically pure in a 82% yield. After reduction to the vinyl sulfide **166** the hydrolytic ring closure took place upon treatment with HCO_2H/CF_3CO_2H to give formate **167**. The obtention of pentalenene **163** was achieved from **167** after hydrolysis, methyl magnesium bromide addition, deoxygenation of the secondary carbinol through the phosphorylation/deoxyphosphorylation sequence, and dehydration of the tertiary carbinol.

When the anion resulting from (*E*,*SR*)-1-butenyl *p*-tolyl sulfoxide was reacted with 2-cyclohexenone,[15] a major 1,4-addition product with the 1′*S*,3*R* configuration was formed. The configuration induced at C-1′ was the opposite to that expected according to previous results obtained from anions proceeding from allylic sulfoxides and cyclopentenones.[132] Although the diastereoselectivity of the process was 90%, no pure diastereomers could be isolated. The mixture was transformed into the juvenile sesquiterpene hormone (+)-juvabione.

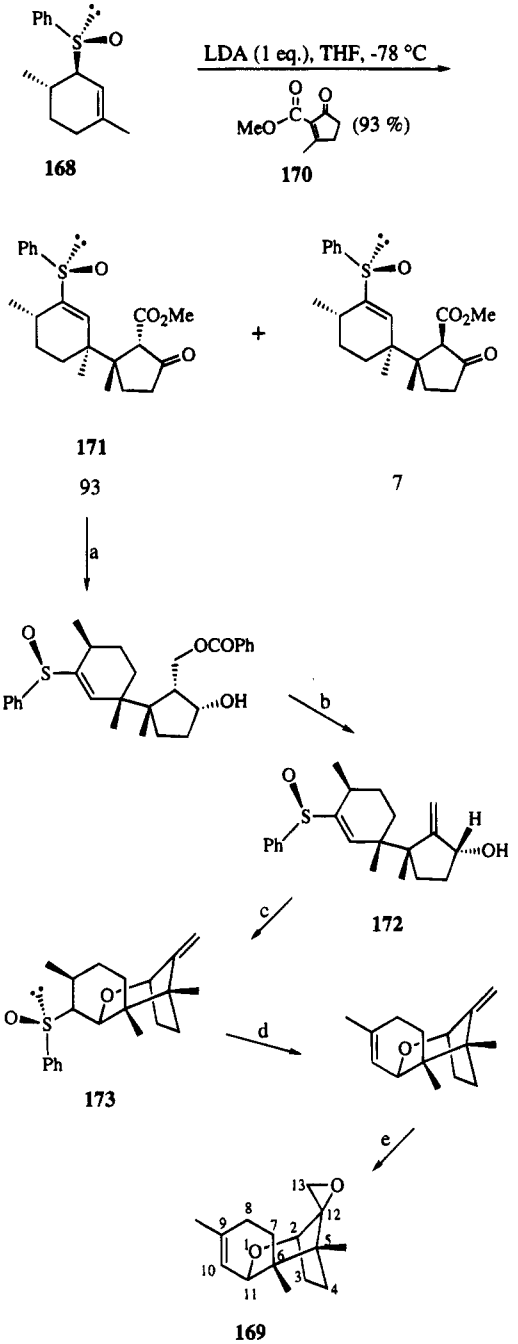
The use of a cyclic allyl sulfoxide such as **168** (Scheme 56) as a carbanion precursor allowed the synthesis of enantiomerically pure 12,13-epoxytrichothec-9-ene[136] (**169**), a compound showing a wide range of biological properties. The C-5 and C-6 stereogenic centers were simultaneously created in the 1,4-addition of the anion derived from **168** to the 3-methyl-substituted enone **170**. Although the 3-methyl substituent on the enone hampered the reaction, the carboxymethyl group activated **170**, giving rise to the addition product in a 93% yield. Although a mixture of epimers at C-12 was formed, compound **171**, resulting in the protonation of the intermediate enolate from the less hindered face, was

Scheme 55[a]



[a] (a) LDA (1 eq.), -78 °C; (b) LDA (2 eq.), THF, -78 °C (91 %); (c) 88 % HCO_2H/CF_3CO_2H, 60 °C (60 %); (d) MeMgBr (4 eq.), 0 °C (70 %); (e) (i) $(Me_2N)_2POCl$, Et_3N, DMAP (96 %), (ii) Li, ^{t}BuOH, $EtNH_2$/THF (97 %), (iii) BF_3.OEt (99 %)

Scheme 56[a]

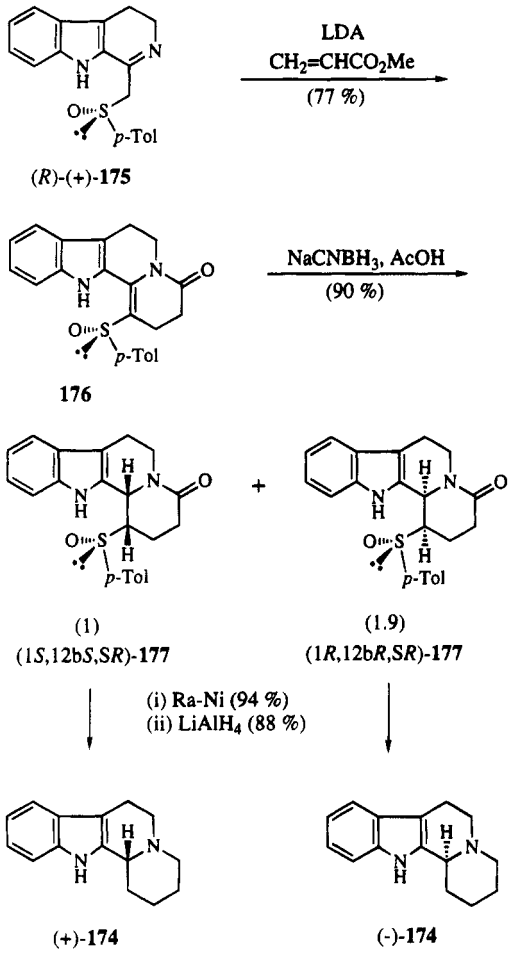


[a] (a) (i) $LiBH_4$, THF, 25 °C (67 %), (ii) PhCOCN, Et_3N (70 %); (b) (i) PCC, CH_2Cl_2 (85 %), (ii) DBN, toluene, 80 °C (82 %), (iii) $CeCl_3/NaBH_4$ (92 %); (c) KOH, ^{t}BuOH (84 %); (d) DABCO, 250 °C, 1,3,5-trimethylbenzene (70 %); (e) MCPBA, Na_2HPO_4 (50 %)

the major. Compound **171** was further converted into the tricyclic precursor **172** by applying a sequencial reduction, monoprotection, PCC oxidation, pyrolytic ester elimination, and reduction. The last step produced a 9:1 mixture of epimeric carbinols where **172** was the major. An intramolecular Michael-type reaction afforded the pyran ring present in **173** whose transformation into the epoxytrichothecene **169** required sulfoxide pyrolysis and epoxidation.

Hua also reported the asymmetric synthesis of different cyclic alkaloids showing an indolizidine skeleton where the nitrogen atom ring juncture was constructed through the tandem 1,4-addition/ring closure reactions of chiral α-sulfinyl ketimine anions with α,β-unsaturated esters and further reduction of the resulting β-sulfinyl enamides.[137] Although the latter step was only moderatly diastereoselective, the method was applied to the synthesis of indolo quinolizidine derivatives **174** (Scheme 57) and yohimban alkaloids (Scheme 58) from both enantiomers of sulfinyl ketimine **175**. Thus, addition of the anion derived from sulfoxide (*R*)-**175** to methyl acrylate occurred from the α-carbon of the sulfoxide to give an enolate whose evolution to an aza enolate facili-

Scheme 57



tates the ring closure, providing the sulfinyl enamide **176**. Although $NaCNBH_3$ in AcOH reductions of simpler sulfinyl enamides took place in a higly diastereoselective manner, compound **176** in the same conditions evolved into a 1.9:1 mixture of diastereomeric **177**. After separation, both stereoisomers were desulfurized to the enantiomers of **174**.

When the Michael acceptor was methyl 1-cyclohexenecarboxylate (Scheme 58) the addition of (*S*)-**175** anion gave, after separation, a 42% yield of (15*R*,20*S*,*SR*)-**178** and a 5% of (15*S*,20*R*,*SR*)-**178**. Desulfurization and reduction of **178** afforded both enantiomers of alloyohimban. The C-3 epimer could be obtained from sulfinyl enamide (15*R*,20*S*,*SR*)-**178** by $NaCNBH_3$/AcOH reduction prior to desulfurization and reduction. The enamide reduction step occurred only with a moderate stereoselectivity.

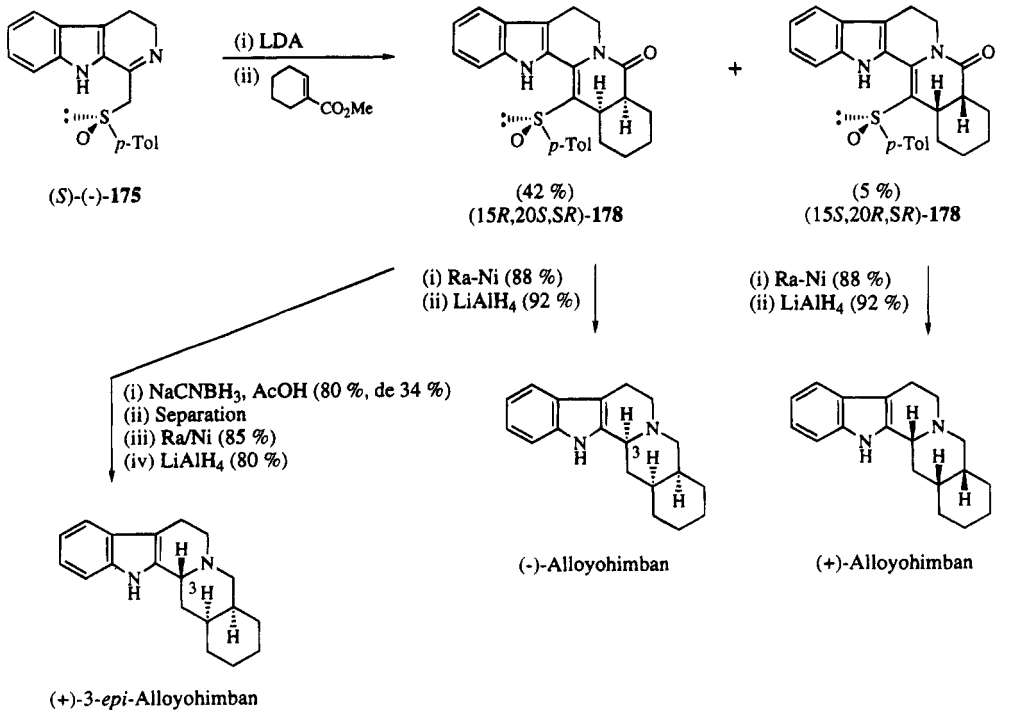
Another application of these processes was devoted to the synthesis of slaframine and 6-epislaframine (Scheme 59).[138] 3-Substituted sulfinyl ketimine (*SR*)-**179** was the starting material giving rise after *n*-BuLi treatment and methyl α-amidoacrylate addition to the C-6 epimeric indolizidinones **180**. After separation, both epimers were converted into the natural products in four steps, the first of which (Raney nickel/H_2 desulfurization and hydrogenation) generated a new stereogenic center at C-2 with the (*S*) configuration.

VI. Pummerer Rearrangement

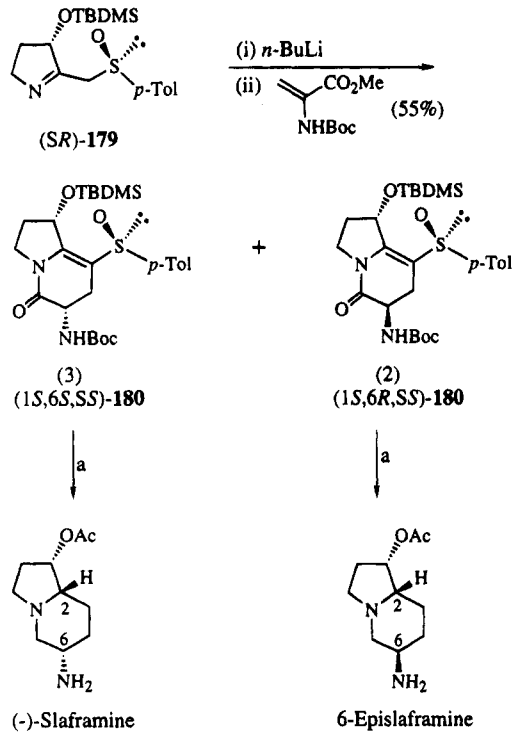
A. Alkyl Sulfoxides

The reaction discovered by Pummerer,[139] consisting of transformation of sulfoxides bearing α-hydrogens in α-acyloxy sulfides by treatment with acid anhydrides (see Scheme 21), has been widely used in synthesis. From the stereochemical point of view, this is a self-immolative asymmetric process where the chirality at sulfur is transferred to the α carbon. Unfortunately, the extent of asymmetric induction reported for the classical Pummerer rearrangement

Scheme 58



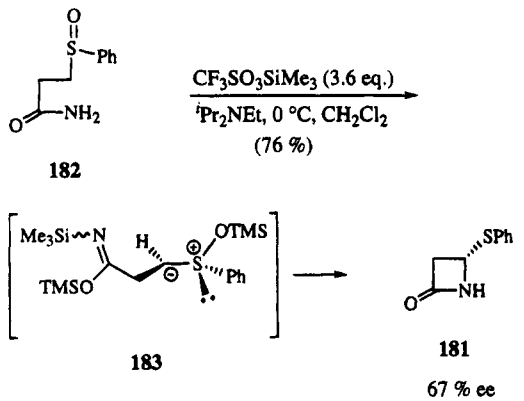
Scheme 59[a]



[a] (a) (i) Ra-Ni, H_2 (76 %), (ii) BH_3.THF (61 %), (iii) n-Bu_4NF, Ac_2O, Py (87 %), (iv) Me_3SiI, (69 %)

by different authors[140,141] never exceeded 30% ee except in one example where the addition of DCC to the reaction medium improved the ee to 70%[142] although a low chemical yield (10%) was achieved. A similar asymmetric induction but a better yield has been reported for the trimethylsilyl methanesulfonate-promoted Pummerer reaction used in the synthesis of β-lactam **181**, a precursor of some penicillin antibiotics (Scheme 60).[143] Conversion of enantio-

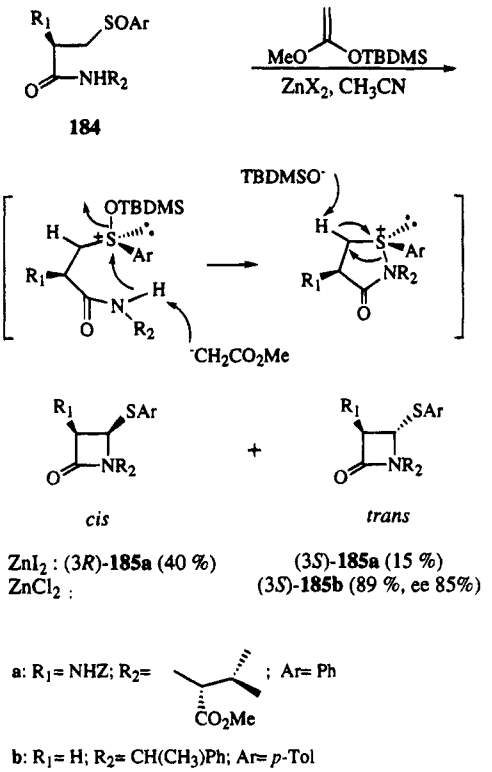
Scheme 60



merically pure amido sulfoxide **182** (the absolute configuration was not indicated) into compound **181** (67% ee) was achieved in a 76% yield. Although the mechanism of this reaction is not fully understood, the authors suggested the formation of the silyloxy sulfonium ylide intermediate **183** whose ring closure afforded the β-lactam.

A biomimetic synthesis of β-lactams based on a Pummerer-type reaction induced by an O-silylated ketene acetal has been described by Kita *et al.*[144]

Scheme 61



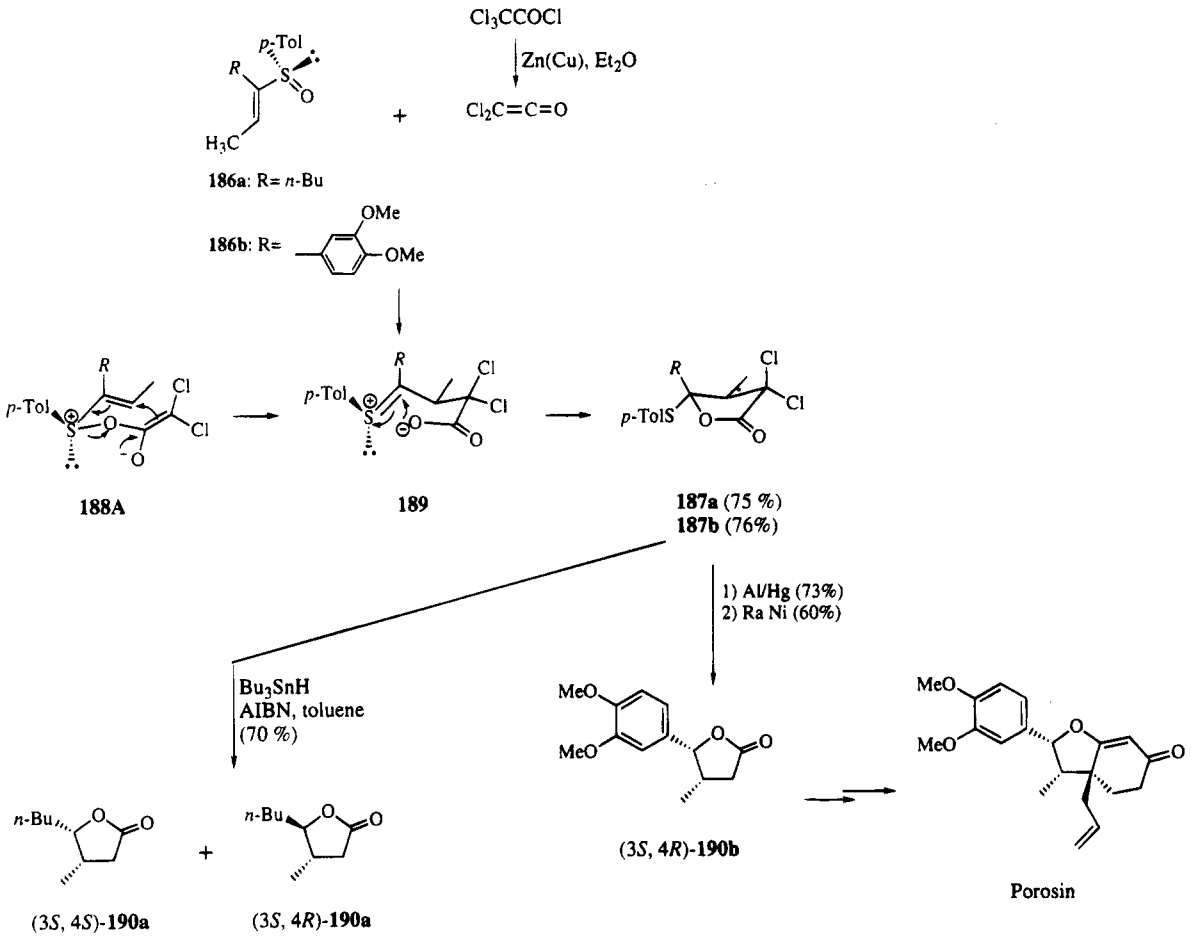
Thus, a 37:63 mixture of sulfoxides **184a** (Scheme 61), epimers at sulfur, was treated with ketene methyl *tert*-butyldimethylsilyl acetal in the presence of catalytic amounts of ZnI_2 to give a 40% of *cis*-substituted β-lactam (3*R*)-**185a** and a 15% of the *trans* isomer (3*S*)-**185a**. An improved application of this asymmetric cyclization procedure in the field of β-lactams required the use of $ZnCl_2$[145] instead of ZnI_2 as catalyst. Thus from enantiomerically pure sulfoxide **184b** the $ZnCl_2$-catalyzed reaction afforded β-lactam (3*S*)-**185b** in up to 85% ee. Similar results were obtained from different sulfoxides without the stereogenic center on the amide group allowing the proposal of the evolution of the system through the intermediates represented on Scheme 61, where the diastereoselectivity of the process is exclusively controlled by the chirality at sulfur.

Other Pummerer-type reactions promoted by ketene *tert*-butyldimethylsilyl acetal[146] on simple sulfoxides were further shown to proceed with a high degree of asymmetric induction giving rise to α-silyloxy sulfides with 86–88% ee in the absence of ZnI_2. A mechanistic investigation, whose preliminary results were recently published,[147] seems to be in progress.

B. Vinyl Sulfoxides

Better results were reported for the additive Pummerer-type reaction which occurs on vinylic sulfoxides. In 1981, Marino[148] described a new and efficient lactonization procedure based on the reaction of vinyl sulfoxides with dichloroketene generated in situ from trichloroacetyl chloride in the presence of zinc–copper couple. When carried out on an α,β-disubstituted alkenyl sulfoxide[149] or a trisubstituted one[150] the method produced optically pure γ-butyrolactones, the sulfur chirality being transferred up to three

Scheme 62

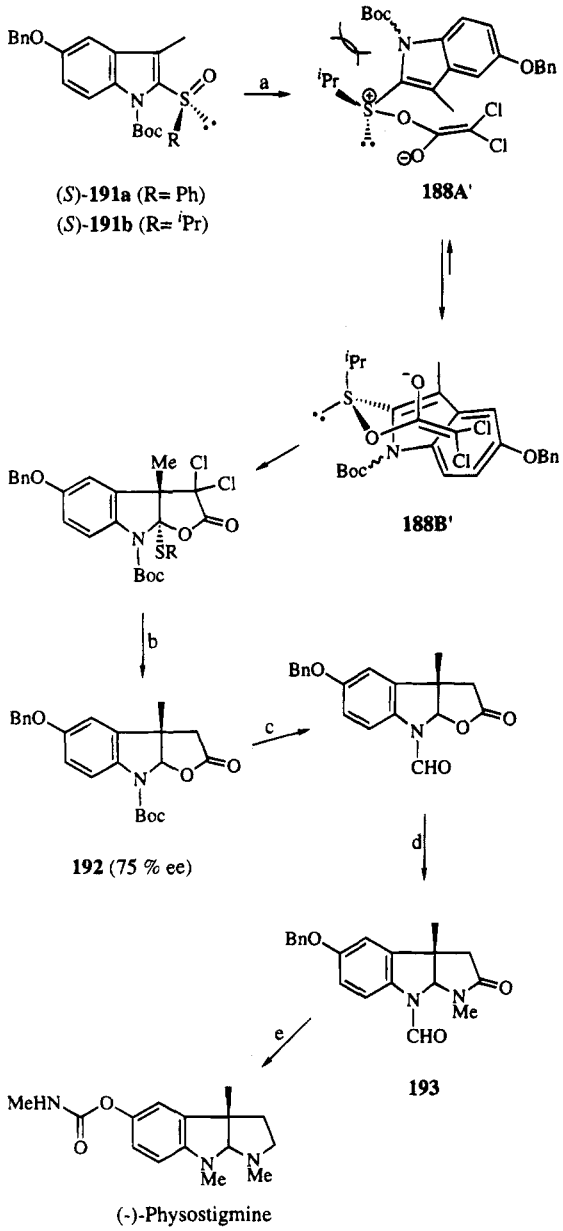


contiguous stereogenic carbons. The applications focused obviously on the synthesis of natural butyrolactones or their derivatives. One of the first examples corresponded to the obtention of oak lactones.[147] As shown in Scheme 62, (*R*)-vinyl sulfoxide **186a** gave rise to dichlorolactone **187a** in an enantiospecific way. This is an intramolecular process involving the activation of the sulfinyl group by the electrophilic dichloroketene followed by a 3,3-sigmatropic rearrangement initiated by the enolate **188A** leading to a Pummerer-type intermediate **189**. In an intramolecular fashion the intermediate **189** is trapped by the carboxylate anion. On the basis of further results obtained from methyl sulfoxides,[151] the resulting enantioselectivity was rationalized by assuming that intermediate **188A** adopts the conformation represented where the bulky tolyl group is in an equatorial disposition. Cyclization of **189** took place faster than rotation around C−C bond. After reductive desulfurization and dechlorination, compound **187a** yielded the C-4 epimeric oak lactones **190a** in enantiomerically pure form. The last step was not stereoselective giving rise to a mixture of C-4 epimers. In a later application of the method to the synthesis of lactone **190b**, a direct precursor of the neolignan porosin[152] starting from vinyl sulfoxide **186b**, a stepwise dechlorination and desulfurization of the dichlorolactone **187b** circumvented the problem of the epimerization at C-4. The stereoselectivity of the Raney nickel desulfurization step was shown to be highly dependent on the activation of Raney nickel and the temperature. In this case at 0 °C and with freshly prepared reagent, diastereomerically pure (3*S*,4*R*)-**190b** was obtained in a 60% yield.

In an application to the synthesis of (−)-physostigmine, an alkaloid isolated from the Calabar bean used in the treatment of the myastenia gravis and glaucoma, Marino[151] encountered that only aryl sulfoxides are able to give the lactonization in an enantiospecific fashion, but the indolyl phenyl sulfoxide **191a** (Scheme 63), a diaryl sulfoxide, was not reactive enough toward the electrophilic dichloroketene. Thus, physostigmine had to be synthesized starting from isopropyl sulfoxide **191b** whose lactonization followed by desulfenylation and dechlorination, gave lactone **192** with a 75% ee. This precursor was protected as *N*-formyl derivative before being converted into lactam **193** upon $MeNH_2/H_2SO_4$ treatment. After lactam and formamide reduction, hydrogenolysis of the benzyl group, and carbamate formation, natural (−)-physostigmine was generated. According to the stereochemical model previously proposed (Scheme 62), the unnatural (+)-enantiomer was expected. This surprising result was explained by considering the presence of a indolyl sulfoxide system in the intermediate equivalent to **188A** where the conformation **188A′** exhibits a destabilizing 1,2-diequatorial interaction between the BOC and isopropyl group which determines the evolution through the conformation **188B′**.

A formal synthesis of (−)-serriconine (Scheme 64), the sex pheromone of the cigarette beetle, was recently reported[153] from butyrolactone **194**. The starting vinyl sulfoxide **195** reacted with dichlo-

Scheme 63[a]

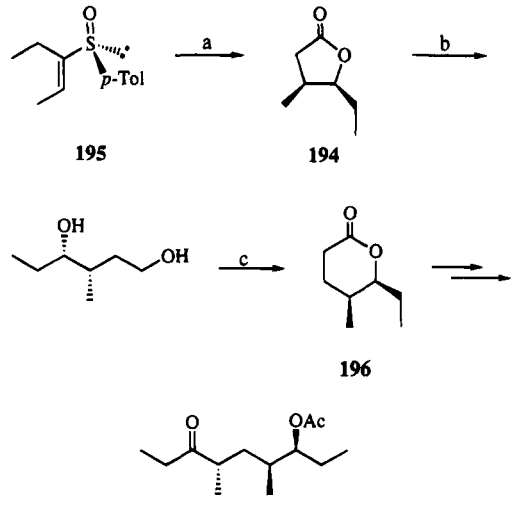


[a] (a) Cl_3CCOCl, Zn/CuCl (58 %); (b) Bu_3SnH, AIBN (84 %); (c) (i) HCOOH, (ii) MeCOOCHO (94 %); (d) (i) $MeNH_2$, (ii) H_2SO_4 (68 %); (e) (i) BH_3.THF (64 %), (ii) Ra-Ni, (iii) Na, MeNCO (60 % two steps)

roketene as expected, and after aluminum amalgam and Raney nickel treatment, **194** was obtained as a single diastereomer and enantiomer. The intermediate δ-lactone **196**, which had been already transformed into the natural product, was synthesized after reduction of **194** and homologation of the diol followed by hydrolysis and lactonization.

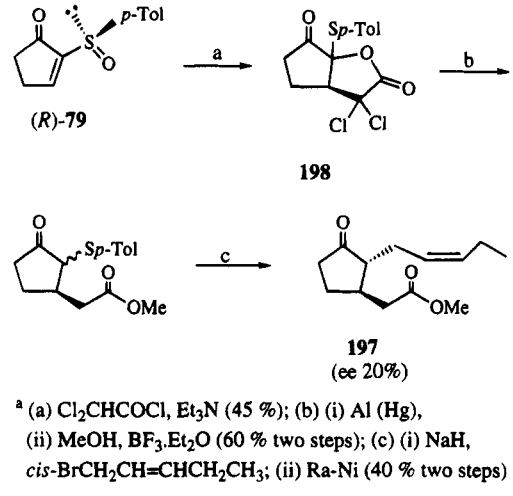
The use of this additive Pummerer-type rearrangement on 2-(*p*-tolylsulfinyl)cyclopentenone [(*R*)-**79**] allowed a short synthesis of methyl jasmonate,[154] **197** a perfume essence (Scheme 65). In this case, the dichlorolactone **198** was dechlorinated and esterified, and the remaining sulfenyl group was utilized to introduce a 2-pentenyl chain. In this case the process was only moderately stereoselective giving a methyl jasmonate with a 20% ee.

Scheme 64[a]



[a] (a) (i) Cl_3CCOCl, Zn/Cu (96 %), (ii) Al (Hg) (84 %), (iii) Ra-Ni (66 %); (b) $LiAlH_4$ (98 %); (c) (i) *p*-TsCl, Py, (ii) NaCN (67 %), (iii) KOH, Δ, (iv) *p*-TsOH (89 %)

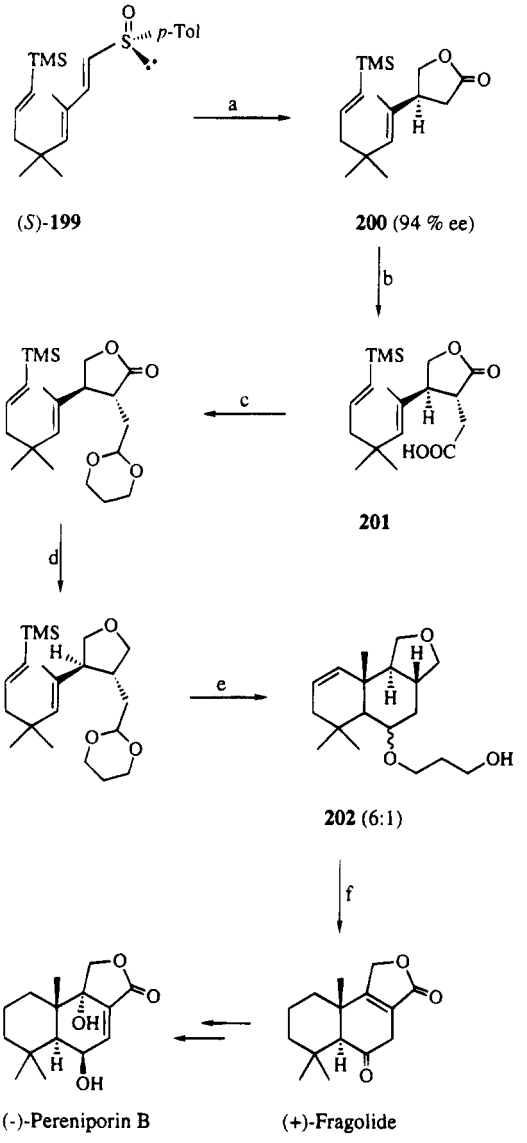
Scheme 65[a]



[a] (a) $Cl_2CHCOCl$, Et_3N (45 %); (b) (i) Al (Hg), (ii) MeOH, $BF_3.Et_2O$ (60 % two steps); (c) (i) NaH, *cis*-$BrCH_2CH{=}CHCH_2CH_3$; (ii) Ra-Ni (40 % two steps)

The method has been extended to the synthesis of other systems with an increasing number of stereogenic centers taking advantage of the stereoselective modifications that could be made from the γ-butyrolactone moiety. Thus, the stereogenic centers present in sesquiterpene lactones such as (+)-fragolide[155] (Scheme 66) were generated by using the (*S*)-vinyl sulfoxide **199** to create the adequate configuration at C-3 of the butyrolactone **200** which was formed with a 94% ee. Lactone enolate alkylation proceeded stereoselectively to give the *trans* isomer precursor of the lactonic acid **201** which was converted into a mixed anhydride to effect the carboxyl reduction. After Swern oxidation, acetalization of the resulting aldehyde could only be achieved without desilylation by using propanediol/Me_2SO_4/DMF. The lactone ring was reduced to the tetrahydrofuran system prior to Lewis acid-catalyzed bicyclization, leading to a 6:1 mixture of epimers **202**, showing the tricyclic skeleton of drimane sesquiterpenes. The key bicyclization step took place from the terminal vinylsilane moiety through a cationic mechanism with high

Scheme 66[a]

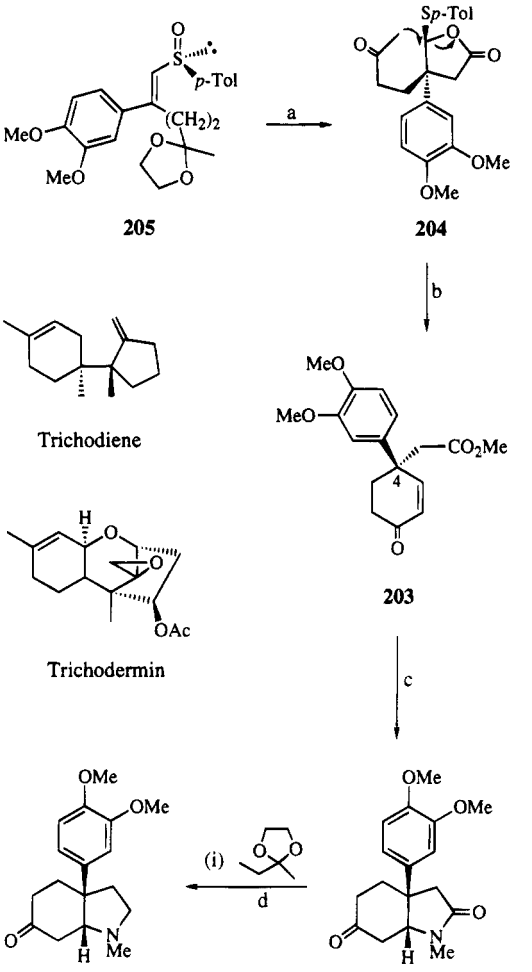


[a] (a) (i) Cl_3CCOCl, Zn/Cu (89 %), (ii) Bu_3SnH, AIBN (89 %); (b) (i) LDA, -78 °C, ICH_2CO_2Me (82 %), (ii) LiOH, MeOH, H_2O (92 %); (c) (i) $^tBuOCOCl$, Et_3N, $NaBH_4$ (77 %), (ii) $(COCl_2)_2$, DMSO (85 %), (iii) Me_2SO_4, DMF, $HO(CH_2)_3OH$, 4 A zeolites (97 %); (d) (i) $LiAlH_4$ (100 %), (ii) *p*-TsCl, Py (84 %); (e) $TiCl_4$ (5 eq.), CH_2Cl_2, -78 °C (85 %); (f) (i) $(COCl_2)_2$, DMSO (73 %), (ii) Piperidinium acetate PhH, Δ (85 %), (iii) $(COCl_2)_2$, DMSO (89 %), (iv) H_2, Pd/C (100 %), (v) $RuCl_3$, $NaIO_2$ (77 %) (vi) $PhMe_3NBr_3$, (vii) DBU (45 % two steps)

stereoselection. Further elaboration to (+)-fragolide involved removal of the remanent acetal, Swern oxidation, hydrogenation of the olefin, and oxidation. Other sesquiterpenic lactones such as (−)-pereniporin B could be made from (+)-fragolide.

An asymmetric synthesis of (+)-mesembrine (Scheme 67) via 4,4-disubstituted 2-cyclohexenones **203** was recently published;[156] it relies upon the creation of the C-4 stereogenic center from a γ-butyrolactone precursor **204**. The adequately functionalized vinyl sulfoxide **205** was the chiral source. Its transformation into γ-tolylthio γ-lactone **204** was achieved after dichloroketene cycloaddition and dechlorination upon treatment with Zn/AcOH which also effected deacetalization. An intramolecular aldol condensation and esterification afforded the required cyclohexenone **203**, easily converted into the natural (−)-mesembrine through the *N*-methyl lactam formation on the enone moiety, and protection of the carbonyl group before reducing the lactam carbonyl. By applying the same strategy to a methylphenyl instead of 3,4-dimethoxyphenyl-substituted vinyl sulfoxide analogue to **205**, sesquiterpenes such as trichodiene or trichodermine were accessible.

Scheme 67[a]

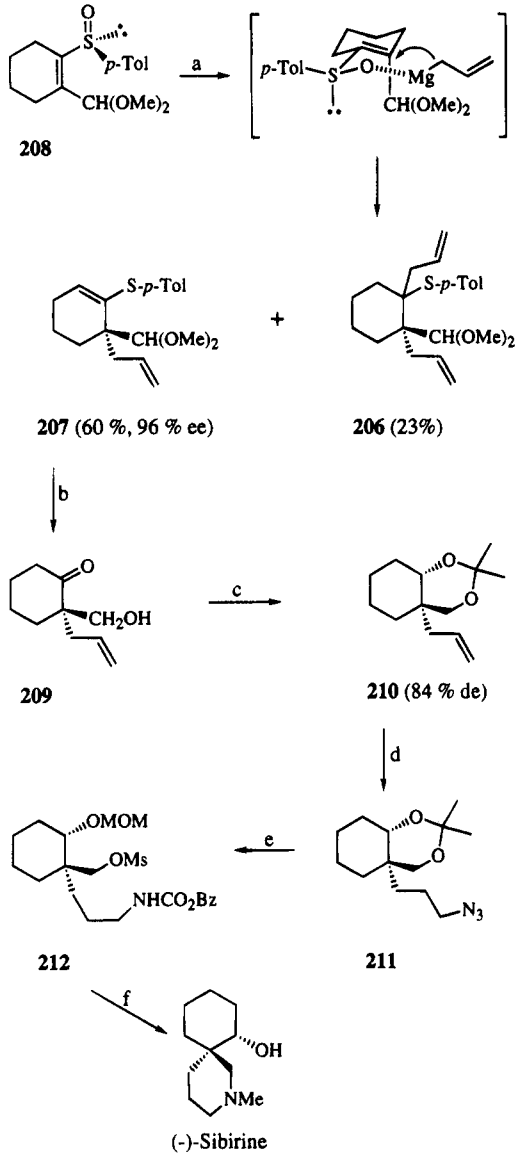


[a] (a) (i) Cl_3CCOCl, Zn/Cu, (ii) Zn, AcOH (47 % two steps); (b) (i) K_2CO_3, MeOH, (ii) CH_2N_2 (65 %); (c) $MeNH_2$, THF (83 %); (d) (i) PTS, (ii) $LiAlH_4$, (iii) H^+, NH_4OH (79 % three steps)

This lactonization procedure has been successfully extended to polycyclic vinyl sulfoxides[157] the *endo* or *exo* lactonization on bicyclo[2.2.1]heptane being possible to achieve in a highly diastereoselective manner.

Another stereoselective Pummerer-type reaction of vinyl sulfoxides described was on the basis of the treatment with allylmagnesium bromide[158] to give diallylated sulfides. Acyclic vinyl sulfoxides behave as a 1,2-dication equivalent, giving rise mainly to 1,2-diallylated sulfides similar to **206** (Scheme 68) whereas cyclic vinyl sulfoxides produced significant amounts of vinyl sulfides as **207**. The reaction was

Scheme 68[a]



[a] (a) CH_2=$CHCH_2MgBr$, THF, -78 °C → r.t.; (b) (i) TsOH, acetone (92 %), (ii) $NaBH_4$, MeOH (83 %), (iii) HCl, MeCN, Δ (62 %); (c) (i) $Zn(BH_4)_2$, (de 84%); (ii) Dimetoxy propane, TsOH (95 % two steps); (d) (i) $BH_3.Me_2S$, H_2O_2 (75 %), (ii) $MeSO_2Cl$, Py (87 %), (iii) NaN_3, *n*-BuNI (90 %); (e) (i) H_2, Pd/C, (ii) $ClCO_2CH_2Ph$, K_2CO_3, (iii) $MeSO_2Cl$, Py, 0 °C, (iv) MOMCl, $^iPr_2NEt$ 62 % four steps); (f) (i) KH (92 %), (ii) $LiAlH_4$, (iii) HCl, 10 °C (70 % two steps)

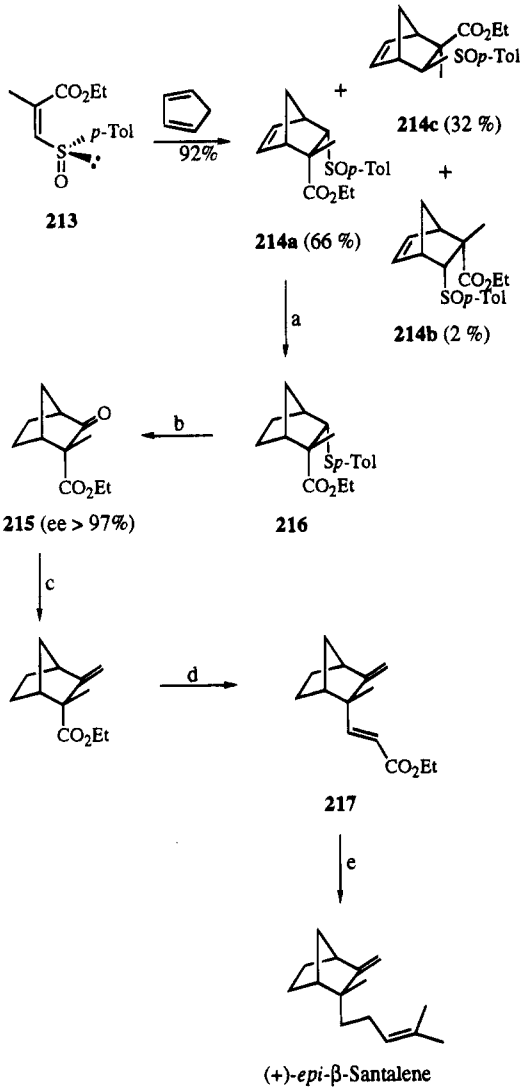
successfully applied to the diastereoselective creation of the quaternary carbon present in the alkaloid (−)-sibirine.[159] Thus cyclohexenyl sulfoxide **208** underwent the Pummerer-type reaction upon treatment with an excess of the Grignard reagent affording vinyl sulfide **207** in a 60% yield and 96% ee. This high enantioselectivity was explained by assuming the initial coordination of the allylmagnesium bromide with both the sulfinyl oxygen and the acetal to form an species which evolves mainly from the *si* face through the transition state depicted in Scheme 68. Compound **207** was converted into (−)-sibirine through a reaction sequence which involved deacetalization, reduction, and vinyl thioether hydrolysis to cyclohexanone **209**. Diastereoselective reduction of **209** (84% de) was followed by acetalization and diastereomer separation to isolate **210**. After hydroboration the resulting primary alcohol was mesylated and reacted with sodium azide to afford **211**. Catalytic reduction of the azide gave an amine without the acetonide moiety. Amine protection, primary alcohol mesylation and protection of the secondary one produced **212** whose KH treatment afforded the azaspiro skeleton present in sibirine, easily accessible by carbamate reduction and carbinol deprotection.

VII. Diels–Alder Cycloaddition

A. Sulfinyl Dienophiles

The first stereochemical study of Diels–Alder reaction with optically active alkenyl sulfoxides was carried out by Maignan[160] on the cycloaddition between (*R*)-vinyl *p*-tolyl sulfoxide and cyclopentadiene with discouraging results. They showed the existence of four diastereomers with a poor stereoselectivity (*endo/exo* 2 and facial selectivity 2−4) probably due to the lack of dienophile reactivity which required energetic reaction conditions favoring the thermodynamic control process. Subsequent efforts focused on the design of sulfinyl dienophiles bearing additional electron-withdrawing groups on the double bond such as ketones,[161] esters,[16,162] and sulfones.[16] Although the cycloadditions of these doubly activated dienophiles still proceeded with low *endo/exo* selectivity, a serious improvement of the facial selectivity was achieved in both cases. Moreover, Koizumi[162b] showed that the presence of $ZnCl_2$ in the reaction of ethyl 2-(*p*-tolylsulfinyl)acrylate with cyclopentadiene slightly changed the *endo/exo* ratio but produced a significant increase of the facial selectivity yielding the adducts of opposite configuration with respect to those formed in thermal conditions. The adducts resulting from the reaction between (−)-(*Z*,*R*)-ethyl 2-methyl-3-(*p*-tolylsulfinyl)propenoate (**213**) and cyclopentadiene in thermal conditions (Scheme 69) were used to prepare santalene-type sesquiterpenes.[163] The cycloaddition afforded a mixture of *endo* (**214a** and **214b**) and *exo* (**214c**) adducts, the π-facial diastereoselectivity being 100% for the *exo* cycloaddition and 94% for the *endo*.[162a] After chromatographic separation, compound **214a** was converted into (+)-epi-β-santalene through a sequence starting with the double-bond hydrogenation and sulfoxide reduction. Keto ester **215** was obtained from thioether **216** in 97% ee by NCS treatment and then oxidative hydrolysis. Methylenation of **215** proved to be difficult being only achieved by applying Nozaki's method. Ester reduction and PCC oxidation followed by Emmons–Horner condensation afforded compound **217** further transformed into the natural sesquiterpene epi-β-santalene applying an ionic double-bond reduction and repetitive ester reduction, PCC oxidation, and Wittig condensation. The *exo* adduct **214c** allowed the asymmetric synthesis of an intermediate conducting to (−)-β-santalol. Although both natural products were accessible in enantiomerically pure form, the applicability of the Diels–

Scheme 69[a]

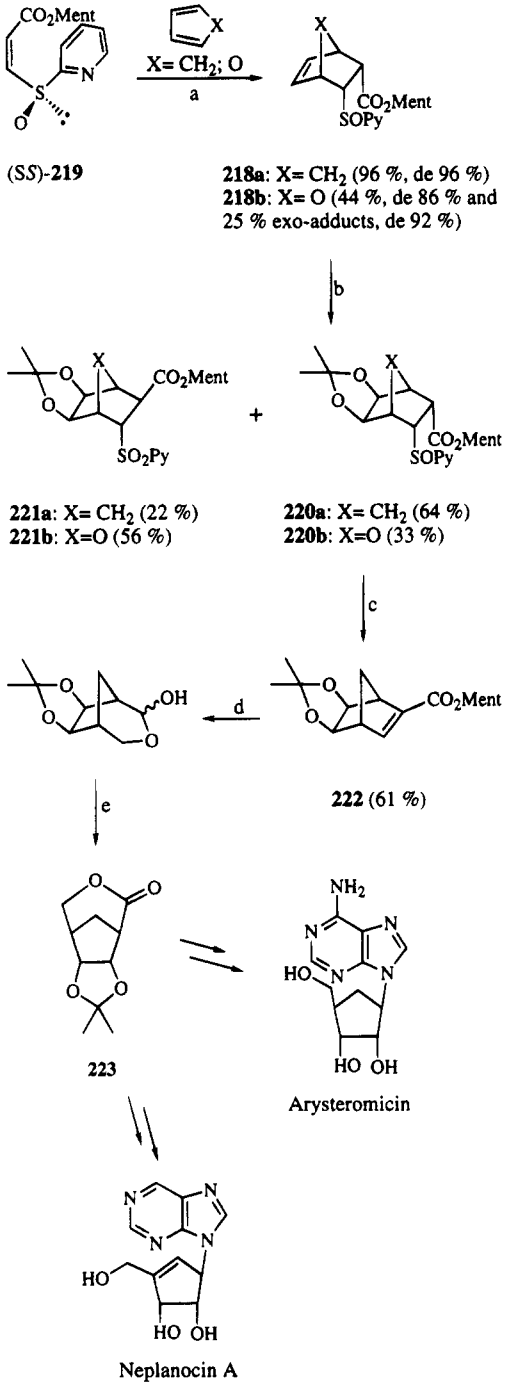


[a] (a) (i) H_2, Pd/C, (ii) $TiCl_3$ (92 % two steps); (b) (i) NCS, (ii) $CuCl_2$, CuO, acetone, H_2O (85 % two steps); (c) $CH_2Br_2/Zn/TiCl_4$ (40 %); (d) (i) DIBAL (100 %), (ii) PCC (90 %), (iii) $(EtO)_2POCH_2CO_2Et$, BuLi (96 %); (e) (i) Et_3SiH, $[(PPh_3)_3RhCl]$, (ii) EtOH (100 %), (iii) DIBAL, (iv) PCC, (v) $Ph_3P{=}C(CH_3)_2$ (51 % three steps)

Alder methodology remained limited to the reactive cyclopentadiene.

In order to further improve the reactivity of the dienophile a stronger electron-withdrawing substituent on the sulfinyl function was introduced. A study on ethyl 3-(2-pyridylsulfinyl)acrylates,[164] carried out on racemic series, showed an enhancement of the dienophile reactivity, higher when a NO_2 or CF_3 group was present in the pyridine substituent, in such a way that the reaction proceeded even with furan which is known to be a low reactive diene. The cycloadditions on menthyl 3-(2-pyridylsulfinyl)acrylates[165] showed that the configuration of the new stereogenic centers generated was controlled by the sulfinyl group and not by the menthyl moiety. This was also pointed out by De Lucchi[16b] who described the formation of adducts with the opposite configuration of the new stereogenic centers using *SS* and *SR* alkenyl sulfoxides having the same bornyl enantiomer as sulfur ligand. Recent results on chiral 1-(alkylsulfinyl)-2-nitroalkenes[166] as dienophiles corroborated this observation.

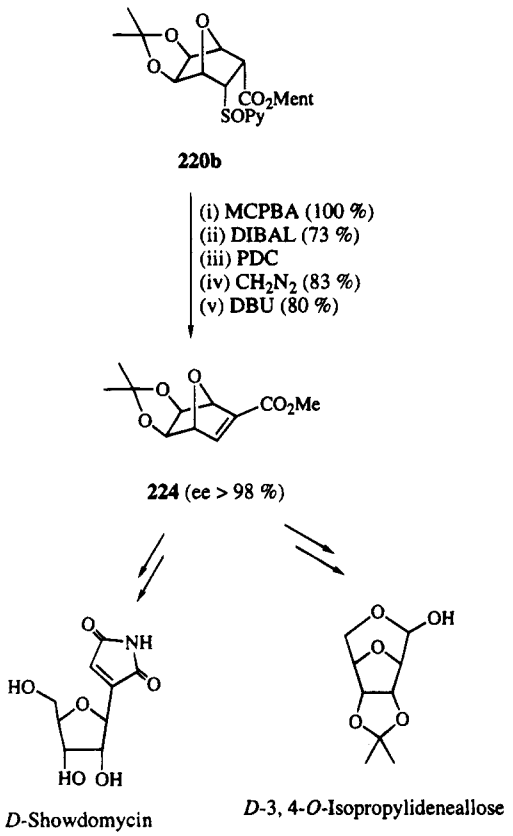
Scheme 70[a]



[a] (a) Et_2AlCl; (b) (i) OsO_4, Me_3NO, (ii) $Me_2C(OMe)_2$, TsOH; (c) (i) MCPBA, (ii) DBU; (d) (i) O_3, Me_2S, (ii) $LiAlH_4$, (iii) $NaIO_4$ (60 % three steps); (e) CrO_3, Py

Even better results were obtained in the reactions of these chiral acrylates with cyclopentadiene in the presence of Et_2AlCl.[167] Thus, a single *endo* adduct **218a** (96% de) was obtained from (*SS*)-menthyl 3-(2-pyridylsulfinyl)acrylate (**219**) in the Et_2AlCl-catalyzed reaction (Scheme 70). Compound **218a** was used as starting material in an approach to the carbocyclic nucleosides (−)-aristeromycin and (−)-neplanocin A.[168] Thus **218a** was subjected to OsO_4

Scheme 71



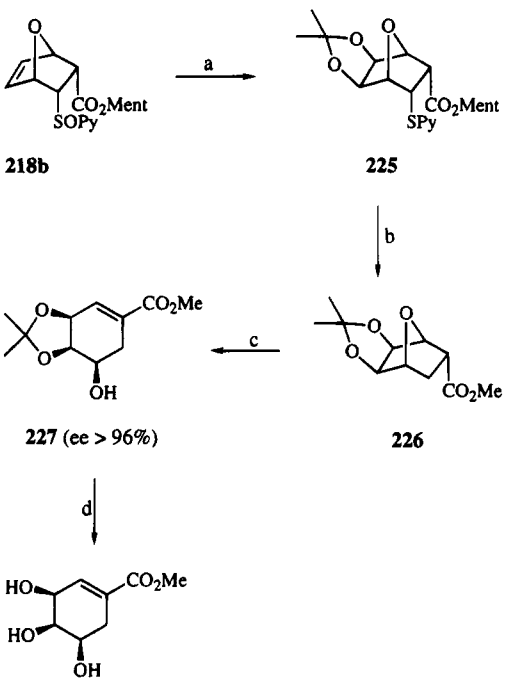
oxidation followed by ketalization to furnish sulfoxide **220a** (64%) and a 22% of sulfone **221a**. After sulfoxide oxidation on **220a**, DBU elimination on the resulting sulfone afforded unsaturated ester **222** along with epimerized sulfone **221a**. The vinyl ester was ozonized and reduced, and the resulting vicinal diol was cleaved yielding an anomeric mixture of lactols transformed into lactone **223** by Collins oxidation. The obtention of bicyclic lactone **223** constitutes a formal total asymmetric synthesis of arysteromycin and neplanocin A since it had been previously used as intermediate in the synthesis of these natural products.

In a similar strategy, compound **218b** obtained as major *endo* adduct in the reaction between (*SS*)-**219** and furan[165] (Scheme 70) was transformed into enantiomerically pure methyl ester **224** (Scheme 71), a common key intermediate in the synthesis of D-showdomycin and D-3,4-isopropylideneallose,[169] through sulfinyl derivative **220b**.

The same cycloadduct **218b** was used as starting material in the asymmetric synthesis of (+)-methyl 5-epishikimate[170] (Scheme 72). This application required the sulfoxide reduction prior to hydroxylation and protection to compound **225**, followed by carboxylate reduction, desulfurization, reoxidation, and methylation to carboxylic ester **226**. Cleavage of the oxide bridge gave precursor **227** in a 96% ee. Deprotection of the carbinols yielded methyl 5-epishikimate.

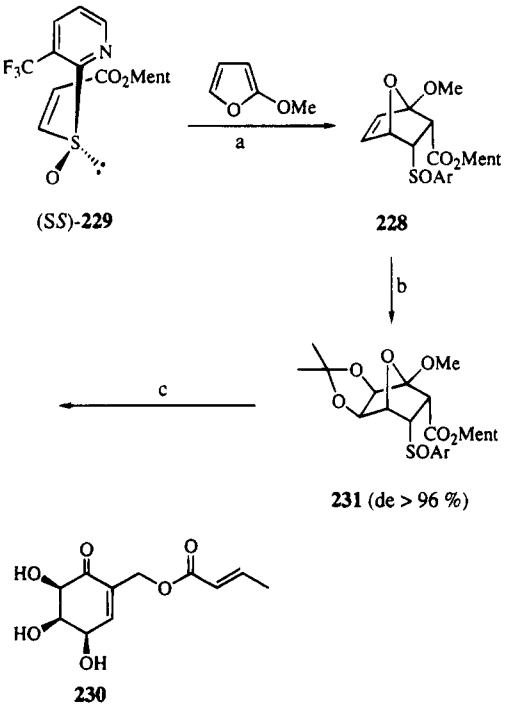
The 2-methoxyfuran *endo* adduct **228** resulting from (*SS*)-[(trifluoromethyl)pyridyl]sulfinyl acrylate **229** (Scheme 73) allowed the asymmetric synthesis of glyoxalase I inhibitor **230**.[171] The crude adduct **228** was almost exclusively formed in thermal and mild

Scheme 72[a]



[a] (a) (i) $TiCl_3$ (84 %), (ii) OsO_4, Me_3NO, (iii) $Me_2C(OMe)_2$, TsOH (92 %); (b) (i) $LiAlH_4$ (79 %), (ii) Ra-Ni (92 %), (iii) CrO_3, Py, (iv) CH_2N_2 (80 %); (c) $LiN(SiMe_3)_2$ (58 %); (d) AcOH (96 %)

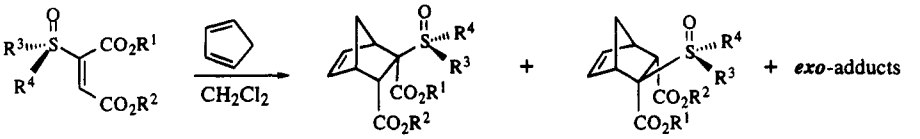
Scheme 73[a]



[a] (a) Toluene, 0 °C, 6 days; (b) (i) OsO_4, Me_3NO, (ii) $(CH_3)_2C(OMe)_2$, *p*-TsOH (72 % three steps); (c) (i) $TiCl_3$, EtOH, (ii) $LiAlH_4$ (78 % two steps), (iii) *trans*-$(CH_3CH{=}CHCO)_2O$, Py (100 %), (iv) *m*-CPBA (85 %), (v) CF_3COOH, (62 %)

conditions. OsO_4 oxidation followed by acetalization afforded the *exo*-diol derivative **231** in a 96% de. Diastereomerically pure sulfoxide **231**, obtained by

Table 1. Diels–Alder Reactions of Sulfinyl Maleates 234 with Cyclopentadiene



234 235-I 235-II

endo

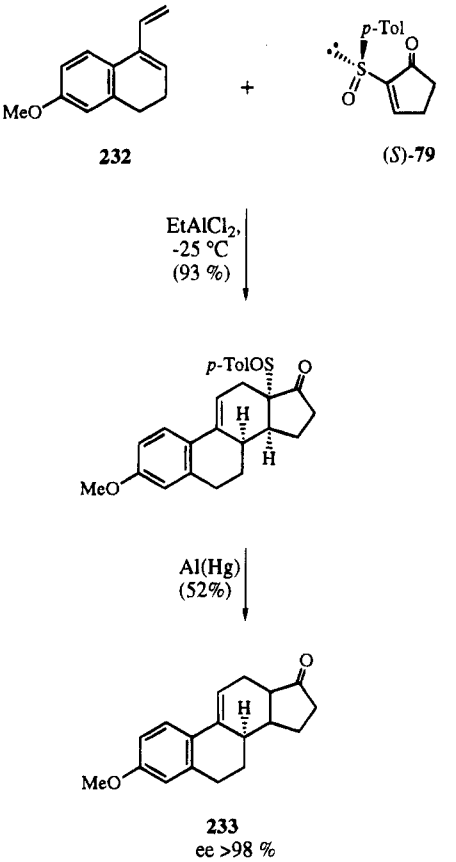
Dienophile	Lewis acid	T °C	t (h)	*endo*		*exo*
				235-I	235-II	
234a: R^1= R^2= Me; R^3= :; R^4= 10-isobornyl	$ZnCl_2$	-20	2.5	a: 94	a: 0	6
234b: R^1= ^{t}Bu; R^2= Me; R^3= *p*-Tol; R^4= :	$ZnBr_2$	-20	7	b: 6	b: 89	5
234c: R^1= Bn; R^2= Me; R^3= *p*-Tol; R^4= :	$ZnBr_2$	-20	5	c: 6	c: 91	3
234c: R^1= Bn; R^2= Me; R^3= *p*-Tol; R^4= :	$TiCl_4$	-78	2	c: 83	c: 13	4
234c: R^1= Bn; R^2= Me; R^3= *p*-Tol; R^4= :	$Eu(fod)_3$	-20	2	c: 66	c: 3	31

recrystallization, was reduced with $TiCl_3$ and then $LiAlH_4$ to provide a primary carbinol readily transformed into the crotyl ester. Sulfide oxidation yielded a sulfoxides mixture (10:1) which upon CF_3COOH treatment afforded enantiomerically pure natural product **230**. The facial diastereoselectivity of these processes has been explained on steric factors, assuming the diene approach from the less hindered face of the dienophilic double bond of the alkenyl sulfoxides whose reactive conformation depends on the dienophile structure and on reaction conditions.[172] Thus, in thermal conditions, dienophiles such as **229** must react through the *s-trans* conformation represented, favored from steric and dipolar factors, being the diene approach favored from the less hindered face *syn* to the lone pair on sulfur.

Good to excellent π-facial diastereoselectivities as well as good *endo/exo* selectivities were achieved in the reactions of cyclopentadiene with a variety of monoactivated vinyl sulfoxides such as 1-sulfinyl-2-nitro-[166] or 2-sulfonyl-[16] substituted alkenes and 2-(*p*-tolylsulfinyl)-2-cycloalkenones.[173] In the latter cases, the cycloaddition between (*S*)-2-(*p*-tolylsulfinyl)-cyclopentenone (**79**) and an acyclic diene such as Dane's diene **232** (Scheme 74) carried out in the presence of $EtAlCl_2$[174] gave a sole *endo* diastereomer with excellent yield. After desulfurization, the steroidal precursor **233** was obtained enantiomerically pure.

The use of sulfinyl maleates as chiral equivalents of acetylene dicarboxylate has also been reported.[175–177] A significant increase of the reactivivity was observed as a consequence of the doubly activated system present in these sulfinyl dienophiles **234** (Table 1), cycloadditions being possible to achieve even at −78 °C for **234c** in the presence of $TiCl_4$ with both cyclic and acyclic dienes.[176] The *endo/exo* selectivity also increased. Cycloaddition of (*SR*)-**234a**[177] and (*SS*)-**234b**[175] with cyclopentadiene in the presence of zinc halides (Table 1) afforded mainly *endo* adducts **235a-I** and **235b-II**, respectively, with the opposite configuration at the new stereocenters due to the different absolute configurations of the starting sulfoxide. The high π-facial diastereoselection achieved from **234c**[176] in the presence of $ZnBr_2$ was opposite to that found with $TiCl_4$ and $Eu(fod)_3$.

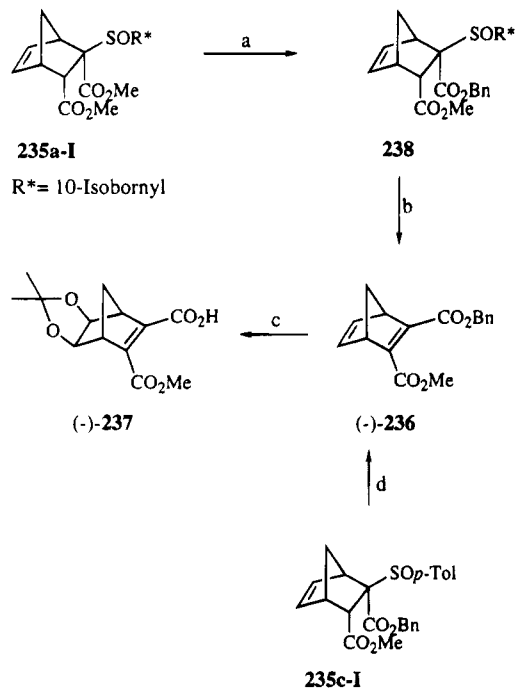
Scheme 74



233
ee >98 %

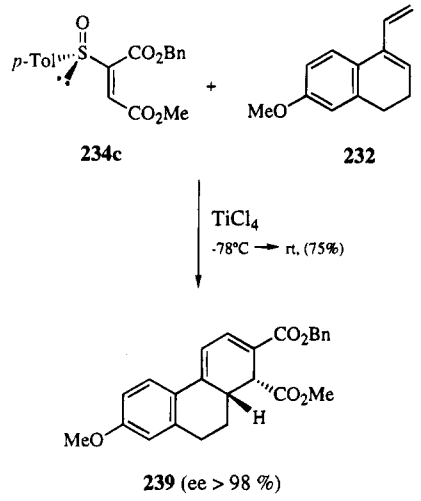
Transformation of adducts **235a-I**[177] and **235b-II**[176] into both enantiomers of the diester **236** (Scheme 75) demonstrated the utility of sulfinyl maleates as chiral acetylene dicarboxylate equivalents. Moreover, half ester (−)-**237**, obtained from **235a-I**, has been used as a starting material in the synthesis of carbocyclic nucleosides. Thus, partial demethylation of **235a-I** and further benzylation yielded **238** which upon treatment with DBU afforded (−)-**236**. A more direct access to compound (−)-**236** involved the pyrolytic elimination of the sulfinyl group from Diels–Alder adduct **235c-I**.[176] After *cis* hydroxylation, diol protection, and debenzylation, half ester (−)-**237** was obtained in enantiomerically pure form. From cy-

Scheme 75[a]



[a] (a) (i) $AlBr_3$, Me_2S (100 %), (ii) BrBn, NaH, 18-crown-6 (86 %); (b) DBU, PhH (89 %); (c) (i) OsO_4, Me_3NO, (ii) $(MeO)_2C(CH_3)_2$, *p*-TsOH (70 % two steps), (iii) 5 % Pd/C, cyclohexa-1,3-diene (50 %); (d) DBU, toluene (59 %)

Scheme 76



cloadduct **235c-II**, the enantiomeric half ester (+)-**237** was accessible in few steps.

Similarly high diastereoselective cycloadditions were found in the reactions of maleate **234c** with acyclic dienes.[176] In these cases the resulting cycloadducts underwent spontaneous sulfoxide elimination, giving in most cases enantiomerically pure cyclohexadienes. The regioselectivity of the cycloaddition was fully controlled by the sulfinyl group but the regiochemistry of the pyrolytic elimination depended on the substitution of the resulting cyclohexadiene from cycloadducts resulting from 1-substituted dienes. The use of Dane's diene **232** (Scheme 76) allowed an easy access to compound **239** readily transformable into steroidal structures. The formation of **239** in enantiomerically pure form in the presence of $TiCl_4$ showed that the cycloaddition occurred with very high regioselectivity, *endo* selectivity, and π-facial diastereoselectivity.

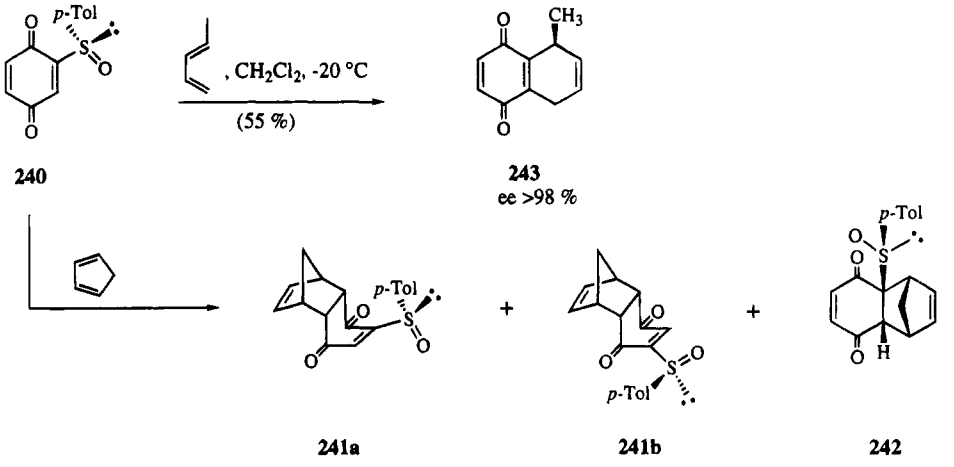
Enantiomerically pure sulfinyl maleimides[178] turned out to be powerful dienophiles reacting with cyclopentadiene and furan in a highly *endo* and π-facial diastereoselective manner.

We have reported the synthesis[179,180] and model studies of Diels–Alder reactions[179,181] of homochiral sulfinyl quinones. The study, carried out on the simplest (*S*)-2-(*p*-tolylsulfinyl)-*p*-benzoquinone (**240**, Scheme 77) with cyclopentadiene revealed a remarkable behavior of this ambident dienophile being possible to control both the chemoselectivity and π-facial diastereoselectivity of the cycloaddition by choosing the reaction conditions. In thermal conditions and in the presence of Lewis acids at −20 °C the cycloaddition took place on the unsubstituted C_5–C_6 dienophilic double bond with total *endo* selectivity and moderate to good π-facial diastereoselectivity (de ranging from 20 to 82%). Moreover, this π-facial diastereoselectivity was the opposite in thermally catalyzed or $Eu(fod)_3$-catalyzed reactions (**241a** was the major adduct) or in the presence of $BF_3{\cdot}OEt_2$ (**241b** was mainly formed). These results showed that the sulfinyl group is able to exert even a remote control on the approaching diene probably as a consequence of the existence of a different reactive conformation around the C-2–S bond in the different conditions employed.

When $ZnBr_2$[182] was used, the cycloaddition with cyclopentadiene took place on the C_5–C_6 dienophilic double bond at low temperature, whereas at 40 °C an *endo* adduct **242** (de > 96%) resulting from reaction on the sulfinyl substituted C-2–C-3 double bond could be isolated in a 60% yield. This result could be a consequence of the effectiveness of $ZnBr_2$ as chelating agent which strongly activates the substituted double bond through a double association between the carbonyl and sulfinyl oxygens. Thus, the chemoselectivity of the process could also be controlled. Acyclic dienes, such as piperylene, also reacted through the substituted double bond to produce an adduct which spontaneously suffered the pyrolytic elimination of the sulfoxide. Compound **243** obtained both in thermal and catalytic conditions from **240** and 1,3-pentadiene was shown to be enantiomerically pure. These results demonstrated that the initial cycloaddition had taken place in a highly regio- and diastereocontrolled manner. As a consequence of the tandem Diels–Alder reaction/pyrolytic elimination, enantiomerically pure sulfinyl quinones could act as synthetic chiral equivalents of the unknown triple-bonded quinones.

In order to apply these excellent results to the synthesis of natural products, sulfinylquinone derivative **244** (Scheme 78) was synthesized. Its reaction with diene **245** allowed an easy access to optically active tricyclic quinone **246** (ee 84% in thermal conditions) after the pyrolytic elimination of the sulfoxide.[183] Racemic derivative **246** had already been transformed into different terpenic quinones such as Royleanone. Thus this simple procedure gives the entrance to a formal synthesis of such sesquiterpenic quinones.

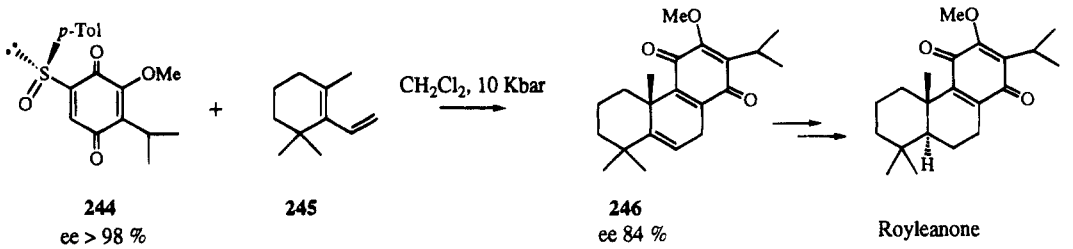
Scheme 77[a]



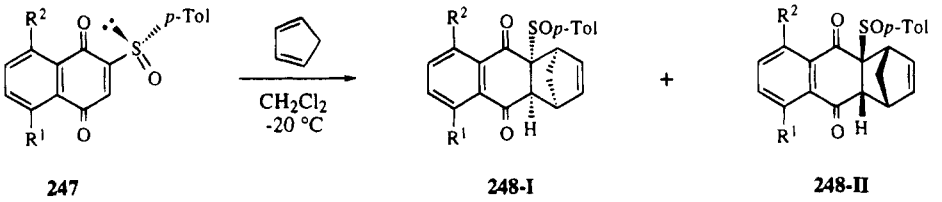
Lewis Acid	Solvent	T °C	241a	241b	242	yield (%)
---------	$CHCl_3$	-20	72	28	0	95
$BF_3.OEt_2$	$CHCl_3$	-20	10	90	0	89
$Eu(fod)_3$	CH_3CN	-20	91	9	0	62
$ZnBr_2$	CH_2Cl_2	-20	50	40	10	a
$ZnBr_2$	CH_2Cl_2	40	0	0	100	60

[a] yield not determined

Scheme 78



Scheme 79

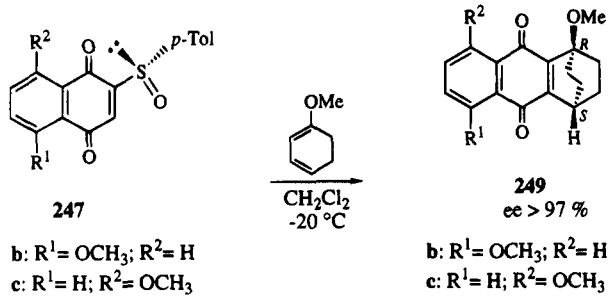


a: $R^1 = R^2 = H$
b: $R^1 = OCH_3$; $R^2 = H$
c: $R^1 = H$; $R^2 = OCH_3$

Dienophile	Lewis Acid	248-I	248-II	yield (%)
247a	-------	94	6	92
"	$ZnBr_2$	0	100	84
247b	-------	90	10	90
"	$ZnBr_2$	0	100	81
247c	-------	95	5	94
"	$ZnBr_2$	40	60	80

Enantiomerically pure (*S*)-2-(*p*-tolylsulfinyl)-1,4-naphthoquinones **247a–c** (Scheme 79),[184] with only one reactive double bond which supports the sulfoxide, have also been shown to evolve in a highly *endo* and π-facial diastereoselective manner with cyclic dienes. Diels–Alder adducts of opposite configuration in the new stereogenic centers **248-I** and **248-II** could be obtained by adequate choice of the reaction conditions. The diastereoselectivity was only low in the case of reaction of **247c** in the presence of $ZnBr_2$.

Scheme 80



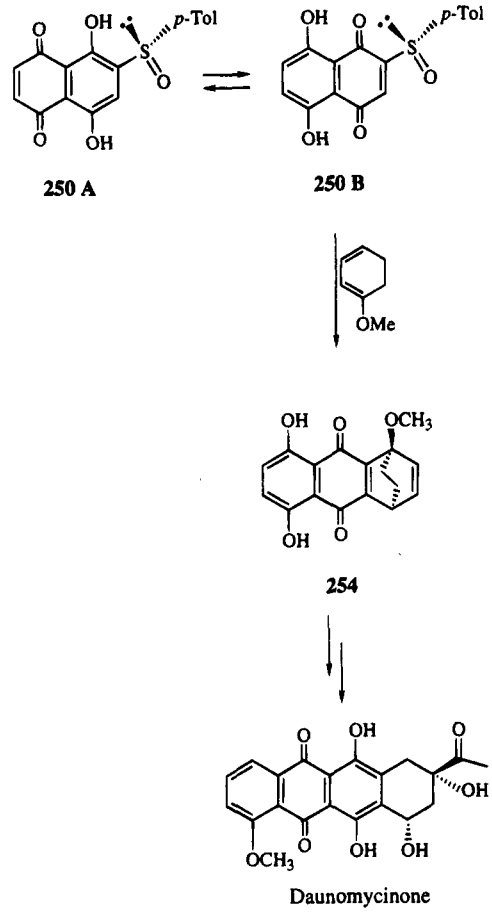
b: $R^1 = OCH_3$; $R^2 = H$
c: $R^1 = H$; $R^2 = OCH_3$

b: $R^1 = OCH_3$; $R^2 = H$
c: $R^1 = H$; $R^2 = OCH_3$

With juglone derivatives **247b** and **247c** the regiochemistry of the cycloaddition with 1-methoxy-1,3-cyclohexadiene was fully controlled by the sulfinyl group (Scheme 80). Thermal reactions afforded compounds (1*R*,4*S*)-**249b** and (1*S*,4*R*)-**249c** enantiomerically pure through the tandem Diels–Alder cycloaddition/sulfoxide pyrolytic elimination which took place in situ.

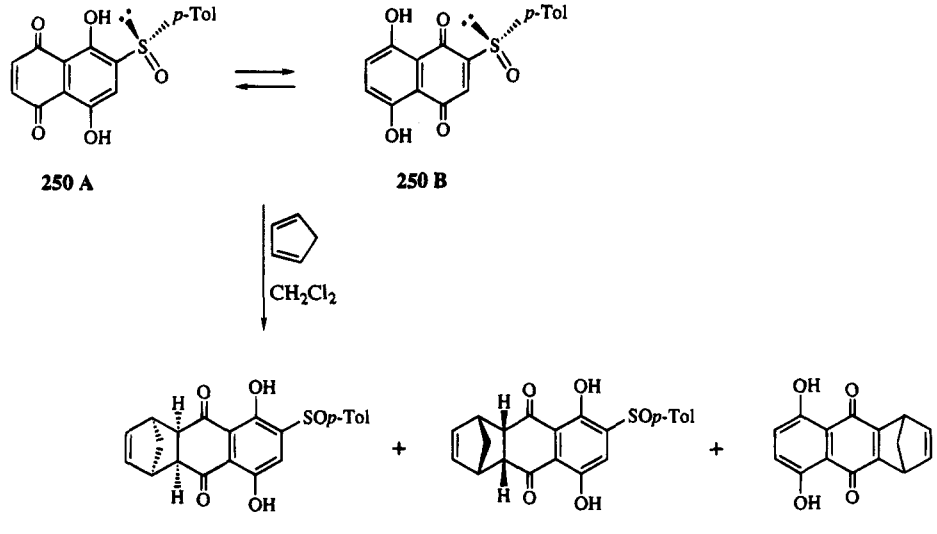
Interestingly, (*S*)-(*p*-tolylsulfinyl)naphthazarin **250**[185] (Scheme 81) presented the tautomeric equilibrium expected in these 4,8-dihydroxy-1,4-naphthoquinonic systems which make them ambident dienophiles. The behavior of **250** in the Diels–Alder cycloaddition with cyclopentadiene[186] also reflected the existence of two different tautomers **250A** and **250B** in the equilibrium. Thus, different mixtures of diastereomeric adducts **251** and **252**, resulting from cycloaddition on tautomer **250A**, and compound **253**, resulting in the tandem cycloaddition/pyrolytic elimination from **250B**, were formed depending on the Lewis acid present in the reaction medium. We could find conditions (BF_3·OEt_2) to shift the equilibrium toward **250A** achieving the exclusive evolution of this tautomer. Moreover, in this experiment, one of the diastereomers **251** was formed in a 40% de. Taking into account the long distance existing between the chiral sulfinyl group and the dienophilic double bond in the reactive tautomer **250A** this was a surprising result which suggested the existence of factors other than steric ones in the control of the diene approach to these quinones.

Scheme 82



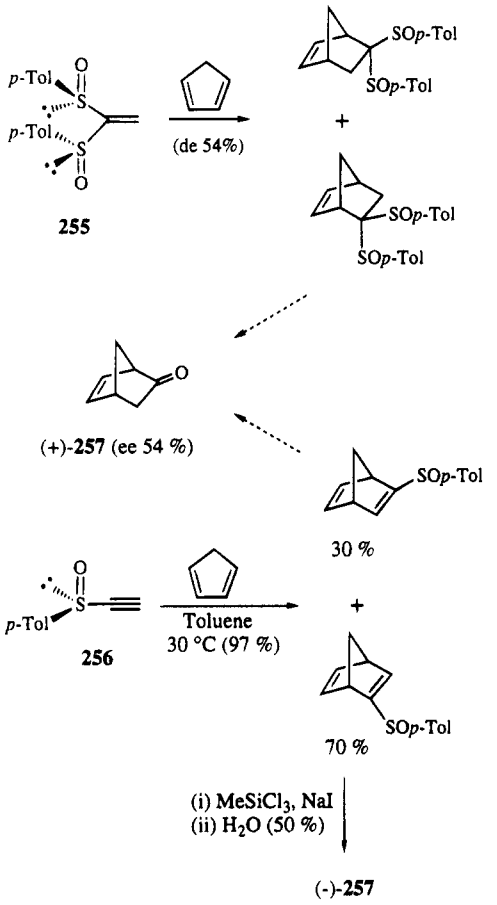
Encouraged by these results, we undertook the reaction of **250** with 1-methoxycyclohexadiene (Scheme 82), obtaining in this case the product resulting from the exclusive cycloaddition on **250B**. The compound

Scheme 81

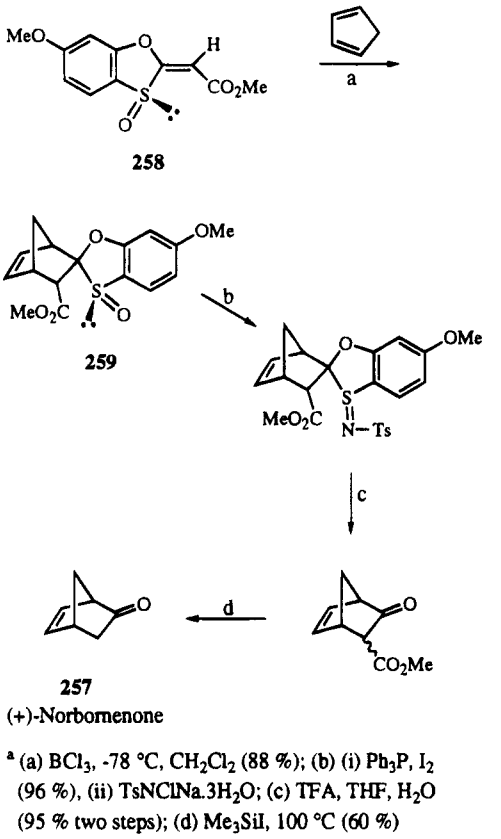


Lewis Acid	251	252	253
--------	40	20	40
$ZnBr_2$	25	20	55
$BF_3.OEt_2$	70	30	0

Scheme 83



Scheme 84[a]



[a] (a) BCl_3, -78 °C, CH_2Cl_2 (88 %); (b) (i) Ph_3P, I_2 (96 %), (ii) TsNClNa.$3H_2O$; (c) TFA, THF, H_2O (95 % two steps); (d) Me_3SiI, 100 °C (60 %)

254 was formed in enantiomerically pure form. Its racemate had been transformed into the antitumor antibiotic daunomycinone. Presently, we are developing a synthetic approach to this anthracyclinone in the optically active form.

The sulfinyl group has allowed the design of simple chiral ketene equivalents such as **255**[187] and **256**[188] (Scheme 83). Their cycloadditions with cyclopentadiene occurred with moderate diastereoselectivity enabling the obtention of (+)-norbornenone (**257**) in a 54% ee from **255**, and both enantiomers of **257** from the separable 70:30 mixture of the adducts resulting from dienophile **256**.

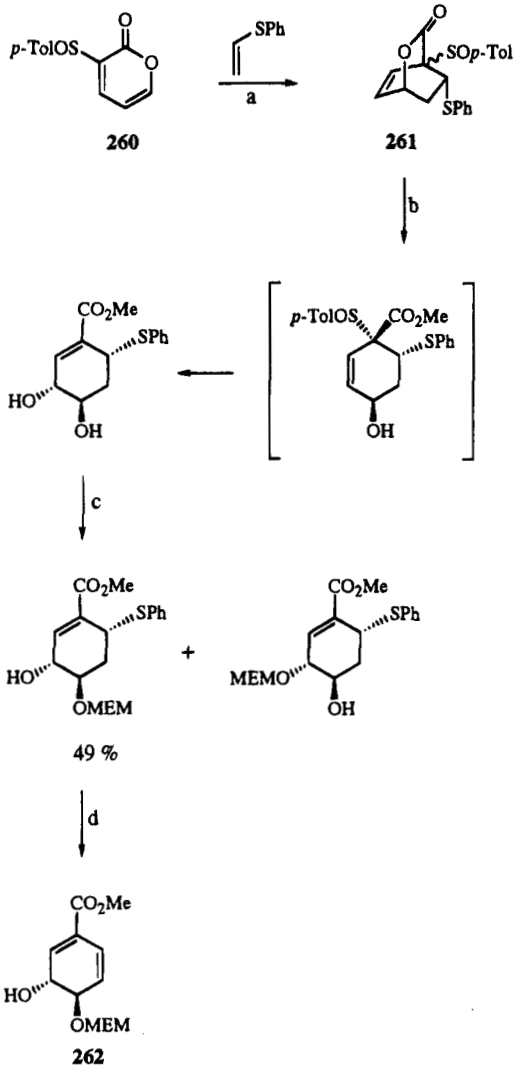
The chiral keto ester ketene equivalent **258**[189] gave better results in its cycloaddition with cyclopentadiene which proceeded with complete *endo* and π-facial diastereoselectivity at −78 °C in the presence of BCl_3 (Scheme 84). The resulting adduct **259** was converted into (+)-norbornenone (**257**) by transforming the sulfoxide in the sulfinylimine, a group which allowed the easy hydrolysis of the bicyclic acetal. Further keto ester hydrolysis and decarboxylation afforded (+)-**257**.

B. Sulfinyl Dienes

In contrast to the efforts devoted to the study of dienophiles bearing a sulfoxide, only few examples of the use of sulfinyl dienes in asymmetric synthesis are known despite the report of Evans,[190] published in 1972, describing the application of the adduct resulting in the cycloaddition of racemic 1-butadienyl phenyl sulfoxide and an electron-rich dienophile in the synthesis of the alkaloid hasubanan. This pioneering work was followed by a study on 1-(acylamino)-4-sulfinyl-substituted dienes[191] exhibiting an excellent Diels–Alder reactivity with electron-deficient dienophiles and high *endo* selectivity being the regioselectivity controlled by the acylamino substituent. Later on, Posner[192] showed that 2-(*p*-tolylsulfinyl)dihydropyrone **260** (Scheme 85) underwent inverse electron demand cycloadditions in different experimental conditions depending on the dienophiles. The adduct **261**[193] resulting from phenyl vinyl thioether at high pressure, gave a stereoselective access to chorismic acid derivative **262** after lactone ring opening with simultaneous [2,3]-sigmatropic rearrangement of the sulfoxide, followed by OH protection, thioether oxidation, and sulfoxide elimination. Although the synthesis was completed in a racemic version, (*S*)-2-(*p*-tolylsulfinyl)dihydropyrone could only be obtained in its optically active form in small amount by a not easily reproducible method.

The first data available concerning the face selectivity of these reactions were reported by Overman *et al.* and referred to conformationally rigid systems.[194] High *endo* and π-facial diastereoselections were observed in the cycloaddition between 5-alkenyl-1,3-oxathiole 3-oxides and *N*-phenylmaleimide. A similarly high *endo* but opposite face diastereoselection was described for the Diels–Alder reactions of 2,5-dimethylthiophene *S*-oxide.[195] All these data corresponded to racemic derivatives. With respect to the use of enantiopure sulfinyl dienes, after the pioneering paper of Hoffmann[196] describing the synthesis of (*SR*)-1-(*p*-tolylsulfinyl)-1,3-butadiene, no other reports appeared until 1988, which is when Okamura[197] synthesized the tricyclic sesquiterpene

Scheme 85[a]

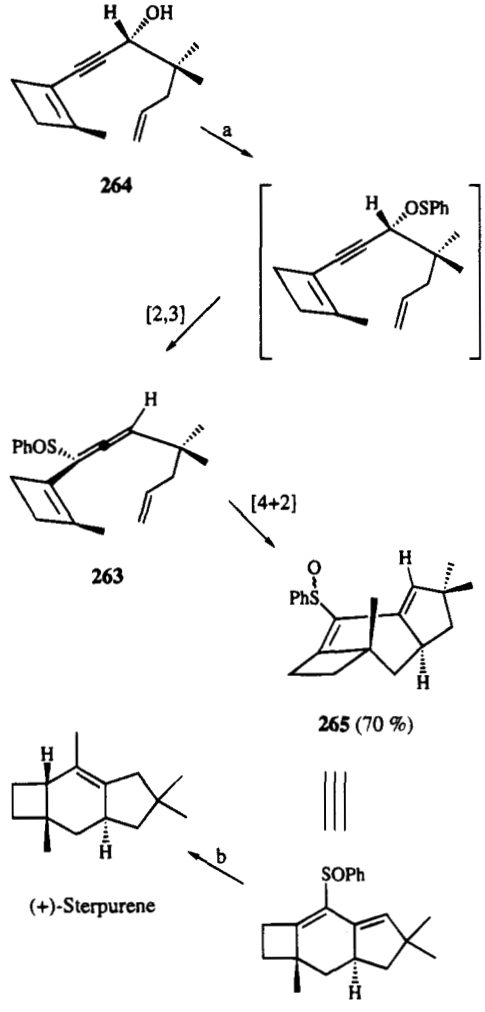


[a] (a) 6.8 Kbar (98 %); (b) NaOMe; (c) MEMCl; (d) (i) MCPBA (86 %), (ii) Benzene, 85 °C (68 %)

(+)-sterpurene (Scheme 86) through a completely stereoselective intramolecular Diels–Alder reaction taking place on vinyl allenic sulfoxide **263**. Compound **263** was easily prepared from enantiomerically pure propargylic alcohol **264** upon treatment with phenyl sulfenyl chloride and subsequent sulfenate-sulfoxide rearrangement. The intramolecular [4 + 2] process occurred with complete enantio- and diastereoselectivity and the whole transformation showed an efficient central–axial–central chiral element transfer where the sulfoxide did not play an essential role. The sulfinyl group of adduct **265** was substituted by a methyl and transformed into enantiomerically pure (+)-sterpurene by diene reduction.

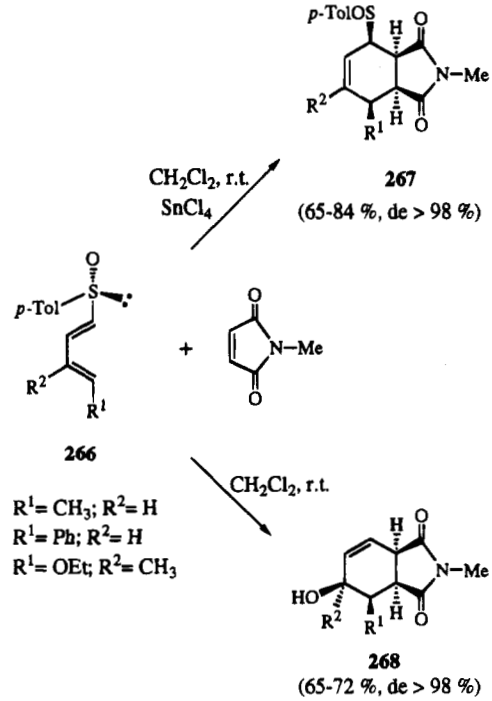
Later, we described the synthesis of enantiomerically pure differently substituted 1-(*p*-tolylsulfinyl)-1,3-butadienes[198] (*R*)-**266** (Scheme 87). We undertook a study on their behavior as dienes in Diels–Alder cycloadditions and we found a diminished reactivity due to the presence of the sulfoxide at C-1. Nevertheless, a high *endo* and π-facial diastereoselectivity was achieved in their rections with *N*-methyl maleimide. Our stereochemical results were in agreement with Overman's reports[194] being possible to isolate

Scheme 86[a]

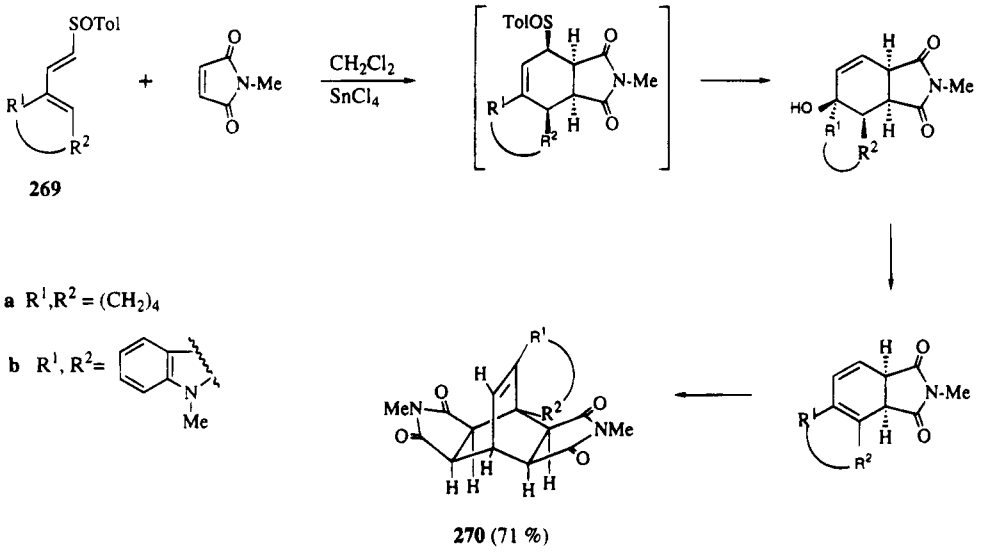


[a] (a) PhSCl, Et_3N, CH_2Cl_2, -78 °C → r.t.; (b) (i) MeMgBr, Ni(dppp)Cl_2, THF, Δ (62 %), (ii) Na/NH_3, ^tBuOH, -78 °C (69 %)

Scheme 87



Scheme 88



enantiomerically pure *endo* adducts **267** in the presence of $SnCl_4$. Moreover, the tandem Diels–Alder cycloaddition/[2,3]-sigmatropic rearrangement which took place on the allylic sulfinyl group of the adducts **267** when the reactions were carried out in the absence of Lewis acids, occurred with complete enantio and diastereoselectivity directed by the sulfoxide opening an easy access to optically pure *all-cis*-substituted cyclohexenols **268**.[199]

When 1-*p*-tolylsulfinyl dienes with an endocyclic double bond such as **269** were used, the reaction with an excess of maleimide yielded the all *cis*-substituted bicyclo[2.2.2]octene derivatives **270** (Scheme 88).[200] The formation of **270** was a consequence of the in situ stereoselective evolution of the initially formed Diels–Alder adducts through a tandem sulfoxide–sulfenate rearrangement/dehydration/[4 + 2] cycloaddition.

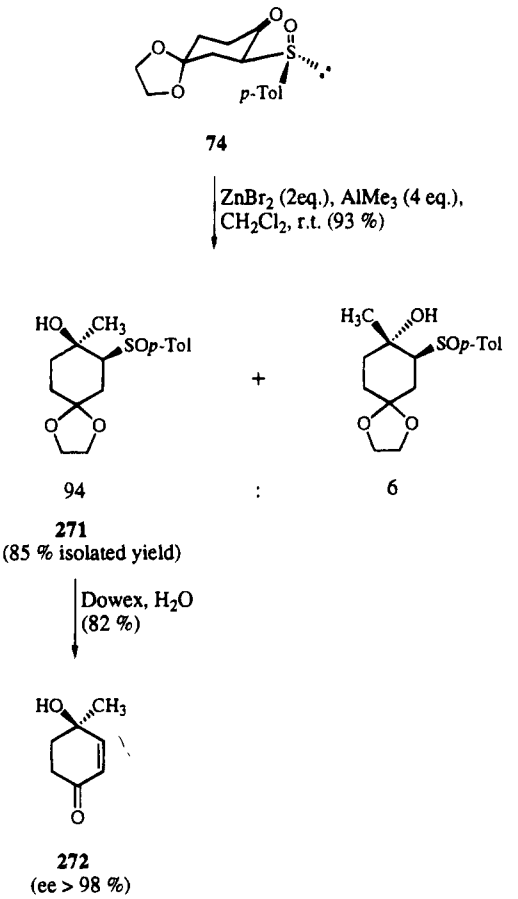
The synthesis of enantiomerically pure 2-sulfinyl-substituted 1,3-butadienes have been reported recently.[201] Good diasterofacial selectivities were also reported for their cycloadditions with different dienophiles.[202] These few results augur well the future of the chiral dienes.

VIII. Miscellaneous

The sulfinyl group has shown a high efficiency as chiral inducer in organometallic additions to both acyclic[203] and cyclic[204] β-keto sulfoxides. The best diastereoselection was achieved with organoalanes on cyclic systems. Thus, the addition of $AlMe_3$ in the presence of $ZnBr_2$ to 2-(*p*-tolylsulfinyl)-1,4-cyclohexanedione derivative **74** (Scheme 89) led to the diastereoselective formation of hydroxy sulfoxide **271** that could be isolated pure in an 85% yield. Its transformation into (*R*)-4-hydroxy-4-methyl-2-cyclohexenone (**272**),[205] a volatile component of some plants, was easily achieved in one pot/two steps by hydrolysis of the acetal and instantaneous elimination of the sulfoxide.

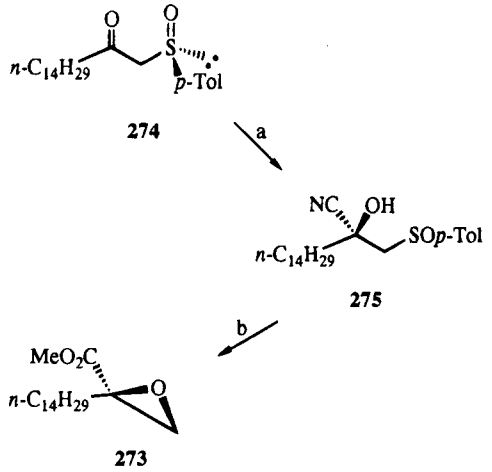
Other efficient nucleophilic additions to β-keto sulfoxides relied upon the use of other aluminum derivatives such as Et_2AlCN. The synthesis of enantiomerically pure cyanohydrins derived from both

Scheme 89



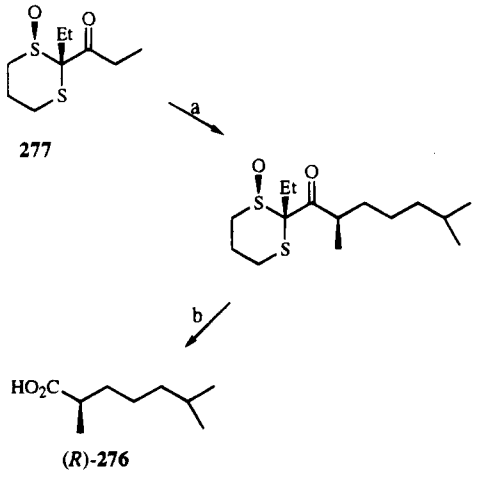
acyclic[206] and cyclic[207] systems has been achieved with a high degree of asymmetric induction. The reaction has been successfully applied to the synthesis of 2-alkylglycidic acid derivatives such as methyl (*R*)-palmoxirate (**273**, Scheme 90). The Et_2AlCN addition to β-keto sulfoxide **274** occurred in a diastereospecific fashion leading to the exclusive formation of cyanohydrin **275** easily converted into the natural epoxy derivative **273** through the treatment with HCl and MeOH which produced the transformation of the nitrile into the ester group with simultaneous sulfoxide reduction. After sulfonium

Scheme 90[a]



[a] (a) Et_2AlCN, toluene, 0 °C (92 %); (b) (i) HCl, MeOH, Δ (78 %), (ii) $Me_3O^+BF_4^-$, (iii) K_2CO_3 (87 %)

Scheme 91[a]



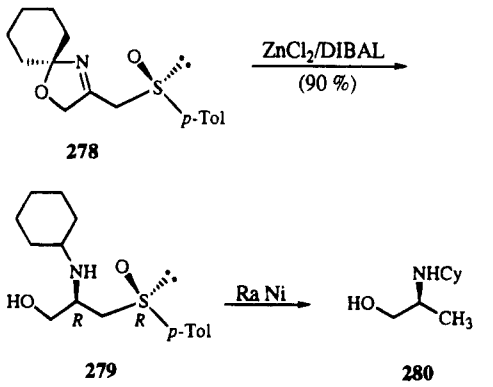
[a] (a) LiHMDS, DMPU, -78 °C, 4-methyl iodopentane (57 %); (b) NaOH (10 % aq.) (39 %)

salt formation, cyclization afforded compound **273**.

Page described the use of 1,3-dithiane *S*-oxide (DITOX) derivatives as combined chiral auxiliaries and building blocks in a variety of asymmetric transformations[22,208] which took place with a high diastereoselection. The application of enantiomerically pure DITOX[22,209] to the synthesis of natural (*R*)-2,6-dimethylheptanoic acid (**276**, Scheme 91) has been recently reported.[210] Thus alkylation of (*SR*,2*R*)-2-ethyl-2-propanoyl-1,3-dithiane 1-oxide (**277**) produced only one diastereomer whose base-mediated hydrolysis led to (*R*)-**274** though in low yield.

Diastereoselective reductions of β-imino sulfoxides were achieved with high diastereoselection on both cyclic[211] and acyclic[212] systems. Starting from α-sulfinyl ketimines[213] such as (*SR*)-[cyclohexanespiro-2′-(3′-oxazoline)-4′-yl]methyl *p*-tolyl sulfoxide **278**[214] the DIBAL/$ZnCl_2$ reduction of the ketimine group led to the exclusive formation of the (*R*,*SR*)-derivative **279** whose desulfurization yielded optically pure (*S*)-*N*-cyclohexylalalinol (**280**, Scheme 92).

Scheme 92



IX. Conclusions/Future

With few exceptions, the sulfoxides act as chiral inducers in the reactions mentioned giving good to excellent asymmetric inductions. The key to the success is related to the steric and electronic differences between the substituents at sulfur, as mentioned in the introduction, as well as the conformational behavior of the sulfinyl group which is able to react through a rigid conformation. The nature of the reactive conformation of the sulfoxide is strongly dependent on the nature of the substituents at C-α and/or C-β. The presence in the reaction medium of metallic atoms in the reagents or in an added catalyst, which may undergo a bonding interaction with the sulfinyl oxygen, could dramatically modify the nature of the reactive conformation, in many cases being able to achieve products of opposite configurations from a common starting material by changing the reaction conditions.

The total syntheses arising from these diastereoselective reactions are completed by taking advantage of the versatility of the sulfinyl group which is also able to give tandem reactions sequences in some special cases, as pointed out in this review article. In some cases a short synthesis of a natural product could be achieved. In general, the stereogenic center induced by the sulfoxide is able to direct the stereochemistry of further transformations necessary to complete a total synthesis.

Besides the reactions considered, other processes are emerging at the moment. The intermolecular hetero-Diels–Alder cycloaddition[215] with α,β-unsaturated carbonyl compounds bearing a sulfoxide on the double bond as well as the related intramolecular process,[216] the asymmetric ene reaction,[217] and asymmetric radical reactions involving sulfoxides[218] should be mentioned. The finding of conditions to get highly diastereoselective processes of this type should extend the already wide use of sulfoxides in asymmetric synthesis.

Some shy efforts in the field of asymmetric catalysis by using sulfoxides as chiral ligands should also be mentioned.[219]

X. Acknowledgments

This review arose from the investigations on reductions of β-keto sulfoxides and Diels–Alder reactions with both sulfinyl quinones and sulfinyl dienes. I thank the Dirección General de Investigación Cien-

tífica y Técnica (DGICYT), Ministerio de Educación y Ciencia (Spain) for financial support. I am grateful to Professor J. L. García Ruano for careful reading the manuscript and Ana I. Mateo for the drawings.

XI. References

(1) (1) Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319.
(2) Solladié, G. *Synthesis* **1981**, 185–196.
(3) Andersen, K. K. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; John Wiley & Sons: New York, 1988; Chapter 3, pp 56–94.
(4) Walker, A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 961–998.
(5) Solladié, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, Chapter 3, pp 148–170.
(6) Kresze, G. In *Methoden der Organischen Chemie* (Houben-Weyl); Klamann, D., Ed.; Georg Thieme Verlag: Stuttgart, 1985; pp 669–886.
(7) Solladié, G.; Carreño, M. C. In *Organosulphur Chemistry. Synthetic Aspects*; Page, P. C. B., Ed.; Academic Press: New York, 1995; Chapter 1, pp 1–47.
(8) (a) Posner, G. H. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; John Wiley & Sons: New York, 1988; Chapter 16, pp 823–849. (b) Posner, G. H. *Acc. Chem. Res.* **1987**, 20, 72. (c) Posner, G. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, pp 225–241.
(9) Solladié, G. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, pp 157–199.
(10) Cinquini, M.; Cozzi, F.; Montanari, F. In *Organic Sulfur Chemistry, Theoretical and Experimental Advances*; Bernardi, F., Csizmadia, G., Mangini, A., Eds.; Elsevier: Amsterdam, 1985.
(11) Hua, D. H. In *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; JAI Press: London, 1992; Vol. 1, p 249.
(12) (a) Mikolajczyk, M.; Drabowicz, J. In *Topics in Stereochemistry*; Allinger, N., Eliel, E., Wilen, S., Eds.; Wiley: New York, 1982; Vol. 13, pp 333–468. (b) Barbachyn, M. R.; Johnson, C. R. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 4, pp 227–261.
(13) Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; John Wiley & Sons: New York, 1988; pp 233–378.
(14) Burguess, K.; Henderson, I. *Tetrahedron Lett.* **1989**, *30*, 3633.
(15) Watanabe, H.; Shimizu, H.; Mori, K. *Synthesis* **1994**, 1249.
(16) (a) De Lucchi, O.; Lucchini, V.; Valle, G.; Modena, G. *J. Chem. Soc., Chem. Commun.* **1985**, 878. (b) De Lucchi, O.; Lucchini, V.; Marchioro, C.; Valle, G.; Modena, G. *J. Org. Chem.* **1986**, *51*, 1457.
(17) Arai, Y.; Matsui, M.; Koizumi, T. *Synthesis* **1990**, 320.
(18) Pitchen, P.; Dunach, E.; Deshmukh, N. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188.
(19) Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325.
(20) (a) Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135. (b) Kagan, H. B.; Rebiere, F. *Synlett* **1990**, 643.
(21) Cashman, J. R.; Olsen, L. D.; Boyd, D. R.; McMordie, R. A. S.; Dunlop, R.; Dalton, H. *J. Am. Chem. Soc.* **1992**, *114*, 8772.
(22) Page, P. C. B.; Gareh, M. T.; Porter, R. A. *Tetrahedron: Asymmetry* **1993**, *4*, 2139.
(23) Pitchen, P.; France, C. J.; McFarlane, I. M.; Newton, C. G.; Thompson, D. M. *Tetrahedron Lett.* **1994**, *35*, 485.
(24) Komatsu, N.; Nishibayashi, Y.; Sugita, T. Uemora, S. *Tetrahedron Lett.* **1992**, *33*, 5391.
(25) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529.
(26) Palucki, M.; Hanso, P.; Jacobsen, N. E. *Tetrahedron Lett.* **1992**, *33*, 7111.
(27) (a) Noda, K.; Hoyosa, N.; Nakai, K.; Katsuki, T. *Tetrahedron Lett.* **1994**, *35*, 1887. (b) Noda, K.; Hoyosa, N.; Irie, R.; Yamashita, Y.; Katsuki, T. *Tetrahedron* **1994**, *32*, 9609.
(28) (a) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628. (b) Naruta, T.; Tani, F.; Maruyama, K. *Tetrahedron: Asymmetry* **1991**, *2*, 533. (c) Halterman, R. L.; Jan, S. T.; Nimmons, H. C. *Synlett* **1991**, 791. (d) Chiang, L. C.; Konishi, K.; Aida, T.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1992**, 254.
(29) (a) Holland, H. *Chem. Rev.* **1988**, *88*, 473. (b) Colonna, S.; Gaggero, N.; Casella, L.; Carrea, G.; Pasta, P. *Tetrahedron: Asymmetry* **1992**, *3*, 95. (c) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1094. Secundo, F.; Carrea, G.; Dallavalle, S. G.; Franzosi, G. *Tetrahedron: Asymmetry* **1993**, *4*, 1981.
(30) (a) Davis, F. A.; Reddy, R. T.; Weismiller, M. C. *J. Am. Chem. Soc.* **1989**, *111*, 5964. (b) Davis, F. A.; Reddy, R. T.; Han, W.; Carroll, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 1428.
(31) Poss, K. M.; Chao, S. T.; Gordon, E. M.; McCann, P. J.; Santafianos, D. P.; Traeger, S. C.; Varma, R. K.; Washburn, W. N. *Tetrahedron Lett.* **1994**, *21*, 3461.
(32) Rayner, C. M.; Sin, M. S.; Westwell, A. D. *Tetrahedron Lett.* **1992**, *33*, 7237.
(33) Rossi, C.; Fauve, A.; Madesclaire, M.; Roche, D.; Davis, F. A.; Reddy, R. T. *Tetrahedron: Asymmetry* **1992**, *3*, 629.
(34) (a) Andersen, K. K. *Tetrahedron Lett.* **1962**, 93. (b) Andersen, K. K.; Gaffield, W.; Papanikolau, N. E.; Foley, J. W.; Perkins, R. I. *J. Am. Chem. Soc.* **1964**, *86*, 5637.
(35) Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173.
(36) (a) Fernández, I.; Llera, J. M.; Alcudia, F. *Tetrahedron Lett.* **1991**, *32*, 7229. (b) Fernández, I.; Khiar, N.; Llera, J. M.; Alcudia, F. *J. Org. Chem.* **1992**, *57*, 6789. (c) Fernández, I.; Khiar, N.; Alcudia, F. *Tetrahedron Lett.* **1994**, *37*, 5719.
(37) Whitesell, J. K.; Wong, M.-S. *J. Org. Chem.* **1991**, *56*, 4552.
(38) Whitesell, J. K.; Wong, M.-S. *J. Org. Chem.* **1994**, *59*, 597.
(39) (a) Wudl, F.; Lee, T. B. K. *J. Am. Chem. Soc.* **1973**, *95*, 6349. (b) Benson, S. C.; Snyder, J. K. *Tetrahedron Lett.* **1991**, *32*, 5885.
(40) (a) Wills, M.; Butlin, R. J.; Linney, I. D. *Tetrahedron Lett.* **1992**, *33*, 5427. (b) Linney, I. D.; Tye, H.; Wills, M.; Butlin, R. J. *Tetrahedron Lett.* **1994**, *35*, 1785.
(41) (a) Rebiere, F.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *30*, 3659. (b) Rebiere, F.; Samuel, O.; Ricard, L.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 5991.
(42) Hiroi, K.; Sato, S.; Kitayama, R. *Chem. Pharm. Bull.* **1983**, *31*, 3471.
(43) Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D. *J. Am. Chem. Soc.* **1992**, *114*, 5977.
(44) Alonso, R.; García Ruano, J. L.; Noheda, P.; Zarzuelo, M. M. *Tetrahedron: Asymmetry* **1995**, *6*, 1133.
(45) (a) Corey, E. J.; Chaykowski, M. *J. Am. Chem. Soc.* **1962**, *84*, 866; (b) **1965**, *87*, 1345.
(46) Kunieda, N.; Nokami, J.; Kinoshita, M. *Chem. Lett.* **1974**, 369.
(47) Schneider, F.; Simon, R. *Synthesis* **1986**, 582.
(48) Carreño, M. C.; García Ruano, J. L.; Rubio, A. *Tetrahedron Lett.* **1987**, *28*, 4861.
(49) Carreño, M. C.; García Ruano, J. L.; Pedregal, C.; Rubio, A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1335.
(50) Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Chem. Soc., Perkin Trans 1* **1979**, 1687.
(51) (a) Solladié, G.; Greck, C.; Demailly, G.; Solladié-Cavallo, A. *Tetrahedron Lett.* **1982**, *23*, 5047. (b) Solladié, G.; Greck, C.; Demailly, G. *Tetrahedron Lett.* **1985**, *26*, 435.
(52) Kosugi, H.; Konta, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1985**, 211.
(53) Carreño, M. C.; García Ruano, J. L.; Martín, A. M.; Pedregal, C.; Rodríguez, J. H.; Rubio, A.; Sánchez, J.; Solladié, G. *J. Org. Chem.* **1990**, *55*, 2120.
(54) Bueno, A. B.; Carreño, M. C.; García Ruano, J. L.; Peña, B.; Rubio, A.; Hoyos, M. A. *Tetrahedron* **1994**, *50*, 9355.
(55) Bueno, A. B.; Carreño, M. C.; García Ruano, J. L.; Rubio, A. *Tetrahedron: Asymmetry* **1992**, *3*, 251.
(56) Bueno, A. B.; Carreño, M. C.; García Ruano, J. L.; Hamdouchi, C. *Tetrahedron: Asymmetry* **1995**, *6*, 1237.
(57) Solladié, G.; Ghiatou, N. *Tetrahedron Lett.* **1992**, *33*, 1605.
(58) Solladié-Cavallo, A.; Suffert, J.; Adib, A.; Solladié, G. *Tetrahedron Lett.* **1990**, *31*, 6649.
(59) Solladié, G.; Lohse, O. *J. Org. Chem.* **1993**, *58*, 4555.
(60) (a) Barros, D.; Carreño, M. C.; García Ruano, J. L.; Maestro, M. C. *Tetrahedron Lett.* **1992**, *33*, 2733. (b) García Ruano, J. L.; Fuerte, A.; Maestro, M. C. *Tetrahedron: Asymmetry* **1994**, *5*, 1443.
(61) Solladié, G.; Rubio, A.; Carreño, M. C.; García Ruano, J. L. *Tetrahedron: Asymmetry* **1990**, *1*, 187
(62) Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1982**, *65*, 2563.
(63) Solladié, G.; Maestro, M. C.; Rubio, A.; Pedregal, C.; Carreño, M. C.; García Ruano, J. L. *J. Org. Chem.* **1991**, *56*, 2317.
(64) Kaito, T.; Masamune, S.; Toyoda, T. *J. Org. Chem.* **1982**, *47*, 1612.
(65) Solladié, G.; Almario, A.; Colobert, F. *Synlett* **1992**, 167.
(66) Solladié, G.; Huser, N. *Tetrahedron: Asymmetry* **1994**, *5*, 255.
(67) (a) Iwata, C.; Moritani, Y.; Sugiyama, K.; Fujita, M.; Imanishi, T. *Tetrahedron Lett.* **1987**, *28*, 2255. (b) Iwata, C.; Moritani, Y.; Sugiyama, K.; Izaki, H.; Kuroki, T.; Imanishi, T. *Chem. Pharm. Bull.* **1988**, *36*, 4785.
(68) Solladié, G.; Almario, A. *Tetrahedron Lett.* **1992**, *33*, 2477.
(69) Solladié, G.; Gerber, C. *Synlett* **1992**, 449.
(70) Solladié, G.; Huser, N.; García Ruano, J. L.; Adrio, J.; Carreño, M. C.; Tito, A. *Tetrahedron Lett.* **1994**, *35*, 5297.
(71) Bravo, P.; Resnati, G.; Viani, F.; Arnone, A. *Tetrahedron* **1987**, *43*, 4635.
(72) (a) Solladié, G.; Hutt, J.; Frechou, C. *Tetrahedron Lett.* **1987**, *28*, 61. (b) Solladié, G.; Frechou, C.; Hutt, J.; Demailly, G. *Bull. Soc. Chim. Fr.* **1987**, 827.
(73) Solladié, G.; Fernández, I.; Maestro, M. C. *Tetrahedron Lett.* **1991**, *32*, 509. (b) Solladié, G.; Fernández, I.; Maestro, M. C. *Tetrahedron: Asymmetry* **1991**, *32*, 801.
(74) Peiseler, B.; Rohmer, M. *J. Chem. Soc., Perkin Trans 1* **1991**, 2449.
(75) Solladié, G.; Almario, A. *Tetrahedron Lett.* **1994**, *35*, 1937.
(76) Solladié, G.; Almario, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1717.

(77) Solladié, G.; Hamdouchi, C.; Vicente, M. *Tetrahedron Lett.* **1988**, *29*, 5929.
(78) Solladié, G.; Hamdouchi, C.; Ziani-Cherif, C. *Tetrahedron: Asymmetry* **1991**, *2*, 457.
(79) Solladié, G.; Kovenski, J.; Colobert, F. *Tetrahedron: Asymmetry* **1993**, *4*, 2173.
(80) Solladié, G.; Ziani-Chérif, C.; Jesser, F. *Tetrahedron Lett.* **1992**, *33*, 931.
(81) Solladié, G.; Ziani-Chérif, C. *J. Org. Chem.* **1993**, *58*, 2181.
(82) Solladié, G.; Hutt, J. *Tetrahedron Lett.* **1987**, *28*, 797.
(83) Botta, M.; Saladino, R.; Gambacorta, A.; Nicoletti, R. *Tetrahedron: Asymmetry* **1990**, *1*, 441.
(84) Vankar, Y. D.; Rao, T. *Tetrahedron Lett.* **1985**, *26*, 2717.
(85) Kosugi, H.; Kanno, O.; Uda, H. *Tetrahedron: Asymmetry* **1994**, *5*, 1139
(86) Carreño, M. C.; García Ruano, J. L.; Garrido, M.; Ruiz, M. P.; Solladié, G. *Tetrahedron Lett.* **1990**, *31*, 6653.
(87) Tsuchihashi, G.; Mitamura, S.; Inoue, S.; Ogura, K. *Tetrahedron Lett.* **1973**, 323.
(88) Posner, G. H.; Mallamo, J. P.; Miura, K. *J. Am. Chem. Soc.* **1981**, *103*, 2886.
(89) Pyne, S. G.; Bloem, P.; Chapman, S. L.; Dixon, C. E.; Griffith, R. *J. Org. Chem.* **1990**, *55*, 1086.
(90) Davis, R.; Kern, J. R.; Kurz, L. J.; Pfister, J. R. *J. Am. Chem. Soc.* **1988**, *110*, 7873.
(91) Frye, L. L.; Kogan, T. P.; Mallamo, J.; Posner, G. H. *Org. Synth.* **1985**, *64*, 196.
(92) Posner, G. H.; Mallamo, J. P.; Hulce, M.; Frye, L. L. *J. Am. Chem. Soc.* **1982**, *104*, 4180.
(93) Posner, G. H.; Mallamo, J. P.; Miura, K. *J. Am. Chem. Soc.* **1981**, *103*, 2886.
(94) Posner, G. H.; Hulce, M.; Mallamo, J. P.; Drexler, S. A.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 5246.
(95) Posner, G. H.; Asirvatham, E. *J. Org. Chem.* **1985**, *50*, 2591.
(96) Posner, G. H.; Kogan, T. P.; Hulce, M. *Tetrahedron Lett.* **1984**, *25*, 383.
(97) Posner, G. H.; Kogan, T. P.; Haines, S. R.; Frye, L. L. *Tetrahedron Lett.* **1984**, *25*, 2627.
(98) Posner, G. H.; Switzer, C. *J. Am. Chem. Soc.* **1986**, *108*, 1239.
(99) Posner, G. H.; Weitzberg, M.; Hamill, T. G.; Asirvatham, E.; Cun-Heng, H.; Clardy, J. *Tetrahedron* **1986**, *42*, 2919.
(100) (a) Holton, R. A.; Kim, H.-B. *Tetrahedron Lett.* **1986**, *27*, 2191. (b) Holton, R. A.; Kennedy, R. M.; Kim, H.-B.; Krafft, M. E. *J. Am. Chem. Soc.* **1987**, *109*, 1597.
(101) Abbot, D. J.; Colonna, S.; C. J. Stirling *J. Chem. Soc., Chem. Commun.* **1971**, 471.
(102) Pyne, S. *Tetrahedron Lett.* **1987**, *28*, 4737.
(103) Pyne, S.; Chapman, S. L. *J. Chem. Soc., Chem. Commun.* **1986**, 1688.
(104) Lee, A. W. M.; Chan, W. H.; Lee, Y.-K. *Tetrahedron Lett.* **1991**, *32*, 6861.
(105) Lee, A. W. M.; Chan, W. H.; Tao, Y.; Lee, Y. K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 477.
(106) (a) Iwata, C. Hattori, K.; Uchida, S.; Imanishi, T. *Tetrahedron Lett.* **1984**, *25*, 2995. (b) Iwata, C.; Hattori, K.; Kuroki, T.; Uchida, S.; Imanishi, T. *Chem. Pharm. Bull.* **1988**, *36*, 2909.
(107) (a) Iwata, C.; Fujita, M.; Hattori, K.; Uchida, S.; Imanishi, T. *Tetrahedron Lett.* **1985**, *26*, 2221. (b) Iwata, C.; Fujita, M.; Kuroki, T.; Hattori, K.; Uchida, S.; Imanishi, T. *Chem. Pharm. Bull.* **1988**, *36*, 3257.
(108) (a) Iwata, C.; Fujita, M.; Moritani, Y.; Hattori, K.; Imanishi, T. *Tetrahedron Lett.* **1987**, *28*, 3135. (b) Iwata, C.; Maezaki, N.; Hattori, K.; Fujita, M.; Moritani, Y.; Takemoto, Y.; Tanaka, T.; Imanishi, T. *Chem. Pharm. Bull.* **1993**, *41*, 339. (c) Iwata, C.; Maezaki, N.; Hattori, K.; Fujita, M.; Moritani, Y.; Takemoto, Y.; Tanaka, T.; Imanishi, T. *Chem. Pharm. Bull.* **1993**, *41*, 946.
(109) Iwata, C.; Fujita, M.; Moritani, Y.; Sugiyama, K.; Hattori, K.; Imanishi, T. *Tetrahedron Lett.* **1987**, *28*, 3131.
(110) Solladié, G.; Moine, G. *J. Am. Chem. Soc.* **1984**, *104*, 6097.
(111) (a) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1971**, *93*, 5303. (b) Tsuchihashi, G.; Iriuchijima, S.; Ishibashi, M. *Tetrahedron Lett.* **1972**, 4605. (c) Pyne, S.; Boche, G. *J. Org. Chem.* **1989**, *54*, 2663. (d) Kusuda, S.; Ueno, Y.; Toru, T. *Tetrahedron* **1994**, *50*, 1045.
(112) Farnum, D. G.; Veysoglu, T.; Cardé, A. M. *Tetrahedron Lett.* **1977**, 4009.
(113) Demailly, G.; Greck, C.; Solladié, G. *Tetrahedron, Lett.* **1984**, *25*, 4113.
(114) Pyne, S.; Boche, G. *J. Org. Chem.* **1989**, *54*, 2663.
(115) Hua, D. H.; Bharati, S. N.; Robinson, P. D.; Tsujimoto, A. *J. Org. Chem.* **1990**, *55*, 2128.
(116) Sakuraba, H.; Ushiki, S. *Tetrahedron Lett.* **1990**, *31*, 5349.
(117) Annunziata, R.; Cinquini, M.; Cozzi, F.; Gilardi, A.; Poli, G.; Scolastico, C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 255.
(118) Mioskowski, C.; Solladié, G. *J. Chem. Soc., Chem. Commun.* **1977**, 162.
(119) Mioskowski, C.; Solladié, G. *Tetrahedron* **1980**, *36*, 227.
(120) Solladié, G.; Matloubi-Moghadam, F. *J. Org. Chem.* **1982**, *47*, 91.
(121) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Cho, H.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6613.
(122) Abushanab, E.; Reed, D.; Suzuki, F.; Sih, C. J. *Tetrahedron Lett.* **1978**, *19*, 3415.
(123) (a) Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *Tetrahedron Lett.* **1988**, *29*, 313. (b) Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *Tetrahedron Lett.* **1988**, *29*, 2851.(c) Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3130.
(124) Satoh, T.; Onda, K.; Yamakawa, K. *J. Org. Chem.* **1991**, *56*, 4129.
(125) Satoh, T.; Motohashi, S.; Tokutake, N.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2966.
(126) Satoh, T.; Motohashi, S.; Kimura, S.; Tokutake, N.; Yamakawa, K. *Tetrahedron Lett.* **1993**, *34*, 4823.
(127) Ronan, B.; Marchalin, S.; Samuel, O.; Kagan, H. B. *Tetrahedron Lett.* **1988**, *29*, 6101.
(128) Pyne, S. G.; Dikic, B. *J. Org. Chem.* **1990**, *55*, 1932.
(129) Pyne, S.; Hajipour, A. R.; Prabakaran, K. *Tetrahedron Lett.* **1994**, *35*, 645.
(130) Murahashi, S.; Sun, J.; Tsuda, T. *Tetrahedron Lett.* **1993**, *34*, 2645.
(131) Colombo, L.; Gennari, C.; Resnati, G.; Scolastico, C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1284.
(132) (a) Binns, M. R.; Chai, O. L.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *Tetrahedron Lett.* **1985**, *26*, 1565, 1569. (b) Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *J. Am. Chem. Soc.* **1988**, *110*, 5411. (c) Haynes, R. K.; Katsifis, A. G.; Vonwiller, S. C.; Hambley, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5423.
(133) (a) Hua, D. H.; Sinai-Zingde, G.; Venkataraman, S. *J. Am. Chem. Soc.* **1985**, *107*, 4088. (b) Hua, D. H.; Venkataraman, S.; Ostrander, R. A.; Sinai, G.-Z.; McCann, P. J.; Coulter, M. J.; Xu, M. R. *J. Org. Chem.* **1988**, *53*, 507.
(134) Hua, D. H.; Venkataraman, S.; Coulter, M. J.; Sinai-Zingde, G. *J. Org. Chem.* **1987**, *52*, 719.
(135) Hua, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 3835.
(136) Hua, D. H.; Venkataraman, S.; Chan-Yu-King, R.; Paukstelis, J. V. *J. Am. Chem. Soc.* **1988**, *110*, 4741.
(137) Hua, D. H.; Bharathi, S. N.; Panangadan, J. A. K.; Tsujimoto, A. *J. Org. Chem.* **1991**, *56*, 6998.
(138) Hua, H. D.; Park, J.-G.; Katsuhira, T.; Bharathi, S. N. *J. Org. Chem.* **1993**, *58*, 2144.
(139) Pummerer, R. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1401.
(140) Numata, T.; Oae, S. *Tetrahedron Lett.* **1977**, *18*, 1337.
(141) Mikolajczyk, M.; Zatorski, A.; Grzejszczak, S.; Costisella, B.; Midura, W. *J. Org. Chem.* **1978**, *43*, 2518.
(142) Numata, T.; Itoh, O.; Oae, S. *Tetrahedron Lett.* **1979**, *20*, 1869.
(143) Kaneko, T.; Okamoto, Y.; Hatada, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1511.
(144) Kita, Y.; Tamura, O.; Miki, T.; Tono, H.; Shibata, N.; Tamura, Y. *Tetrahedron Lett.* **1989**, *30*, 729.
(145) Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimori, C.; Matsumoto, K. *Tetrahedron Lett.* **1995**, *36*, 115.
(146) Kita, Y.; Shibata, N.; Yoshida, N. *Tetrahedron Lett.* **1993**, *34*, 4063.
(147) (a) Kita, Y.; Shibata, N.; Yoshida, N.; Fukui, S.; Fujimori, C. *Tetrahedron Lett.* **1994**, *35*, 2569. (b) Kita, Y.; Shibata, N.; Fukui, S.; Fujita, S. *Tetrahedron Lett.* **1994**, *35*, 9733.
(148) Marino, J. P.; Neisser, M. *J. Am. Chem. Soc.* **1981**, *103*, 7687.
(149) Marino, J. P.; Pérez, A. D. *J. Am. Chem. Soc.* **1984**, *106*, 7644.
(150) Marino, J. P.; Fernández de la Pradilla, R. *Tetrahedron Lett.* **1985**, *26*, 5381.
(151) (a) Marino, J. P.; Kim, M.-W.; Lawrence, R. *J. Org. Chem.* **1989**, *54*, 1784. (b) Marino, J. P.; Bogdan, S.; Kimura, K. *J. Am. Chem. Soc.* **1992**, *114*, 5566.
(152) Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *Synthesis* **1987**, 1088.
(153) Ferreira, J. T. B.; Marques, J. A.; Marino, J. P. *Tetrahedron: Asymmetry* **1994**, *5*, 641.
(154) Posner, G. H.; Asirvatham, E.; Ali, S. *J. Chem. Soc., Chem. Commun.* **1985**, 542.
(155) Burke, S. D.; Shankaran, K.; Helber, M. J. *Tetrahedron Lett.* **1991**, *32*, 4655.
(156) Kosugi, H.; Miura, Y.; Kanna, H.; Uda, H. *Tetrahedron: Asymmetry* **1993**, *4*, 1409.
(157) Arjona, O.; Fernández, P.; Fernández de la Pradilla, R.; Morente, M.; Plumet, J. *J. Org. Chem.* **1993**, *58*, 3172.
(158) Iwata, C.; Maezaki, N.; Kurumada, H.; Fukuyama, H.; Sugiyama, K.; Imanishi, T. *J. Chem. Soc., Chem. Commun.* **1991**, 1408.
(159) Imanishi, T.; Kurumada, H.; Maezaki, N.; Sugiyama, K.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1991**, 1409.
(160) Maignan, C.; Raphael, R. A. *Tetrahedron* **1983**, *39*, 3245.
(161) Maignan, C.; Guessous, A.; Rouessac, F. *Tetrahedron Lett.* **1986**, *27*, 2603.
(162) (a) Koizumi, T.; Hakamada, I.; Yoshii, E. *Tetrahedron Lett.* **1984**, *25*, 87. (b) Arai, Y.; Kuwayama, S.; Takeuchi, Y.; Koizumi, T. *Tetrahedron Lett.* **1985**, *26*, 6205.

(163) (a) Arai, Y.; Yamamoto, M.; Koizumi, T. *Chemistry Lett.* **1986**, 1225. (b) Arai, Y.; Yamamoto, M.; Koizumi, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 467.
(164) Takayama, H.; Hayashi, K.; Takeuchi, Y.; Koizumi, T. *Heterocycles* **1986**, *24*, 2137.
(165) Takayama, H.; Iyobe, A.; Koizumi, T. *J. Chem. Soc., Chem. Commun.* **1986**, 771.
(166) (a) Fuji, K.; Tanaka, K.; Abe, H.; Itoh, A.; Node, M.; Taga, T.; Miwa, Y.; Shiro, M. *Tetrahedron: Asymmetry* **1991**, *2*, 179. (b) Fuji, K.; Tanaka, K.; Abe, H.; Matsumoto, K.; Harayama, T.; Ikeda, A.; Taga, T.; Miwa, Y.; Node, M. *J. Org. Chem.* **1994**, *59*, 2211.
(167) Arai, Y.; Hayhasi, Y.; Yamamoto, M.; Takayema, H.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3133.
(168) Arai, Y.; Hayashi, Y.; Yamamoto, M.; Takayama, H.; Koizumi, T. *Chem. Lett.* **1987**, 185.
(169) Takayama, H.; Iyobe, A.; Koizumi, T. *Chem. Pharm. Bull.* **1987**, *35*, 433.
(170) Takahashi, T.; Iyobe, A.; Arai, Y.; Koizumi, T. *Synthesis* **1989**, 189.
(171) Takayama, H.; Hayashi, K.; Koizumi, T. *Tetrahedron Lett.* **1986**, *27*, 5509.
(172) Koizumi, T.; Arai, Y.; Takayama, H. *Tetrahedron Lett.* **1987**, *28*, 3689.
(173) Alonso, I.; Carretero, J. C.; García Ruano, J. L. *Tetrahedron Lett.* **1989**, *30*, 3853.
(174) Alonso, I.; Carretero, J. C.; García Ruano, J. L.; Martin Cabrejas, L. M.; López-Solera, I.; Raithby, P. *Tetrahedron Lett.* **1994**, *35*, 9461.
(175) (a) Alonso, I.; Carretero, J. C.; García Ruano, J. L. *Tetrahedron Lett.* **1991**, *32*, 947. (b) Alonso, I.; Cid, M. B.; Carretero, J. C.; García Ruano, J. L. *Tetrahedron: Asymmetry* **1991**, *2*, 1193.
(176) (a) Alonso, I.; Carretero, J. C.; García Ruano, J. L. *J. Org. Chem.* **1993**, *58*, 3231; (b) **1994**, *59*, 1499.
(177) (a) Arai, Y.; Hayashi, K.; Koizumi, T. *Tetrahedron Lett.* **1988**, *29*, 6143. (b) Arai, Y.; Matsui, M.; Koizumi, T. *Synthesis* **1990**, 320.
(178) Arai, Y.; Matsui, M.; Koizumi, T. *J. Org. Chem.* **1991**, *56*, 1983.
(179) Carreño, M. C.; García Ruano, J. L.; Urbano, A. *Tetrahedron Lett.* **1989**, *30*, 4003.
(180) (a) Carreño, M. C.; García Ruano, J. L.; Mata, J. M.; Urbano, A. *Tetrahedron* **1990**, *47*, 605. (b) Carreño, M. C.; García Ruano, J. L.; Urbano, A. *Synthesis* **1992**, 651.
(181) Carreño, M. C.; García Ruano, J. L.; Toledo, M. A.; Urbano A. *Tetrahedron Lett.* **1994**, *35*, 9759.
(182) Carreño, M. C.; García Ruano, J. L.; Remor, C. Z.; Toledo, M. A.; Urbano, A. Unpublished results.
(183) Carreño, M. C.; García Ruano, J. L.; Toledo, M. A.; Urbano, A. Unpublished results.
(184) Carreño, M. C.; García Ruano, J. L.; Urbano, A. *J. Org. Chem.* **1992**, *57*, 6870.
(185) Carreño, M. C.; García Ruano, J. L.; Urbano, A. *Tetrahedron* **1994**, *50*, 5013.
(186) Carreño, M. C.; García Ruano, J. L.; Urbano, A. *Tetrahedron Lett.* **1994**, *35*, 3789.
(187) Arai, Y.; Kuwayama, S.; Takeuchi, Y.; Koizumi, T. *Synth. Commun.* **1986**, *16*, 233.
(188) Maigan, C.; Belkasmioui, F. *Tetrahedron Lett.* **1988**, *29*, 2823.
(189) Martynow, J.; Dimitroff, M.; Fallis, A. G. *Tetrahedron Lett.* **1993**, *34*, 8201.
(190) Evans, D. A.; Bryan, C. A.; Sims, C. L. *J. Am. Chem. Soc.* **1972**, *94*, 2891.
(191) Overman, L. E.; Petty, C. B.; Ban, T.; Huang, G. T. *J. Am. Chem. Soc.* **1983**, *105*, 6335.
(192) Posner, G. H.; Harrison, W. *J. Chem. Soc., Chem. Commun.* **1985**, 1785.
(193) Posner, G. H.; Haces, A.; Kinter, C. M.; Harrison, W. *J. Org. Chem.* **1987**, *52*, 4836.
(194) (a) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 2630. (b) Fisher, M. J.; Herhe, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4625.
(195) Naperstkow, A. M.; Macaulay, J. B.; Newlands, M. J.; Fallis, A. G. *Tetrahedron Lett.* **1989**, *30*, 5077.
(196) Hoffmann, R. W.; Goldmann, S.; Maak, N.; Geueke, K. J. *Chem. Ber.* **1978**, *113*, 831.
(197) (a) Gibbs, R. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1988**, *110*, 4062. (b) Gibbs, R. A.; Bartels, K.; Lee, R. W. K.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 3717.
(198) (a) Solladié, G.; Ruiz, P.; Colobert, F.; Carreño, M. C.; García Ruano, J. L. *Synthesis* **1991**, 1011. (b) Solladié, G.; Maugein, N.; Moreno, I.; Almario, A.; Carreño, M. C.; García Ruano, J. L. *Tetrahedron Lett.* **1992**, *33*, 4561. (c) Paley, R. S.; Lafontaine, J. A.; Ventura, M. P. *Tetrahedron Lett.* **1993**, *34*, 3663. (d) Paley, R. S.; de Dios, A.; Fernández de la Pradilla, R. *Tetrahedron Lett.* **1993**, *34*, 2429.
(199) Arce, E.; Carreño, M. C.; Cid, M. B.; García Ruano, J. L. *J. Org. Chem.* **1994**, *59*, 3421.
(200) Carreño, M. C.; Cid, M. B.; Colobert, F.; García Ruano, J. L.; Solladié, G. *Tetrahedron: Asymmetry* **1994**, *5*, 1439.
(201) (a) Aversa, M. C.; Bonnacorsi, P.; Giannetto, P.; Jafari, S. M. A.; Jones, D. N. *Tetrahedron: Asymmetry* **1992**, *3*, 701. (b) Bonfand, E.; Gosselin, P.; Maignan, C. *Tetrahedron Lett.* **1992**, *33*, 2347. (c) Bonfand, E.; Gosselin, P.; Maignan, C. *Tetrahedron: Asymmetry* **1993**, *4*, 1667.
(202) (a) Adams, H.; Jones, N. D.; Aversa, M. C.; Bonaccorsi, P.; Giannetto, P. *Tetrahedron Lett.* **1993**, *34*, 6481. (b) Aversa, M. C.; Bonaccorsi, P.; Giannetto, P.; Jones, N. D. *Tetrahedron: Asymmetry* **1994**, *5*, 805. (c) Gosselin, P.; Bonfand, E.; Hayes, P.; Retoux, R.; Maignan, C. *Tetrahedron: Asymmetry* **1994**, *5*, 781.
(203) (a) Carreño, M. C.; García Ruano, J. L.; Maestro, M. C.; Pérez, M. *Tetrahedron* **1993**, *49*, 11099.
(204) (a) Bueno, A. B.; Carreño, M. C.; Fischer, J.; García Ruano, J. L.; Peña, B.; Peñas, L.; Rubio, A. *Tetrahedron Lett.* **1991**, *32*, 3191. (b) Bueno, A. B.; Carreño, M. C.; García Ruano, J. L. *An. Quim.* **1994**, *90*, 442.
(205) Bueno, A. B.; Carreño, M. C.; García Ruano, J. L. *Tetrahedron Lett.* **1995**, *36*, 3737.
(206) (a) García Ruano, J. L.; Martín-Castro, A. M.; Rodríguez, J. H. *Tetrahedron Lett.* **1991**, *32*, 3195. (b) García Ruano, J. L.; Martín-Castro, A. M.; Rodríguez, J. H. *J. Org. Chem.* **1992**, *57*, 7235.
(207) Escribano, A.; García Ruano, J. L.; Martín-Castro, A. M.; Rodríguez, J. H. *Tetrahedron* **1994**, *50*, 7567.
(208) Page, P. C. B.; Allin, S. M.; Collington, E. W.; Carr, R. A. E. *J. Org. Chem.* **1993**, *58*, 6902.
(209) (a) Page, P. C. B.; Namwindwa, E. S.; Klair, S. S.; Westwood, D. *Synlett* **1990**, 457. (b) Page, P. C. B.; Namwindwa, E. S. *Synlett* **1991**, 80.
(210) Page, P. C. B.; Allin, S. M.; Collington, E. W.; Carr, R. A. E. *Tetrahedron Lett.* **1994**, *35*, 2607.
(211) Carreño, M. C.; Domínguez, E.; García Ruano, J. L. Pedregal, C.; Rodríguez, J. H. *Tetrahedron* **1991**, *47*, 10035.
(212) García Ruano, J. L.; Lorente, A.; Rodríguez, J. H. *Tetrahedron Lett.* **1992**, *33*, 5637.
(213) Hua, D. H.; Khiar, N.; Zhang, F.; Lambs, L. *Tetrahedron Lett.* **1992**, *33*, 7751.
(214) Khiar, N.; Fernández, I.; Alcudia, F.; Hua, D. H. *Tetrahedron Lett.* **1993**, *34*, 699.
(215) (a) Gosselin, P.; Bonfand, E.; Hayes, P.; Retoux, R.; Maignan, C. *Tetrahedron: Asymmetry* **1994**, *5*, 781. (b) Hayes, P.; Maignan, C. *Synlett* **1994**, 409.
(216) Hiroi, K.; Umemura, M.; Fujisawa, A. *Tetrahedron Lett.* **1992**, *33*, 7161.
(217) Hiroi, K.; Umemura, M. *Tetrahedron* **1993**, *49*, 1831.
(218) (a) Toru, T.; Watanabe, Y.; Tsuaka, M.; Ueno, Y. *J. Am. Chem. Soc.* **1993**, *115*, 10464. (b) Mesmaeker, A.; Waldner, A.; Hoffmann, P.; Mindt, T. *Synlett* **1993**, 871. (c) Renaud, P.; Bourquard, T. *Tetrahedron Lett.* **1994**, *35*, 1707. (d) Renaud, P.; Carrupt, P. A.; Gerster, M.; Schenk, K. *Tetrahedron Lett.* **1994**, *35*, 1703.
(219) Carreño, M. C.; Maestro, M. C.; Martín Cabrejas, L. M.; García Ruano, J. L. *Tetrahedron: Asymmetry* **1993**, *4*, 727.

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