Russian Chemical Reviews **70** (8) 641 – 653 (2001) © 2001 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2001v070n08ABEH000630

1,3-Dipolar cycloaddition reactions of nitrile oxides in the synthesis of natural compounds and their analogues

A I Kotyatkina, V N Zhabinsky, V A Khripach

Contents

I.	Introduction	641
II.	Methods for the generation of nitrile oxides	641
III.	Methods for the transformations of isoxazoles and 4,5-dihydroisoxazoles	641
IV.	Intermolecular 1,3-dipolar cycloaddition reactions of nitrile oxides	643
V.	Intramolecular 1,3-dipolar cycloaddition reactions of nitrile oxides	647
VI.	Syntheses based on enantiocontrolled 1,3-dipolar cycloaddition reactions of nitrile oxides	649

Abstract. The published data on the use of 1,3-dipolar cycloaddition reactions of nitrile oxides in the synthesis of natural compounds and their analogues are systematised and reviewed. The bibliography includes 145 references.

I. Introduction

The cycloaddition of nitrile oxides to alkynes and alkenes is the most popular approach to the synthesis of isoxazoles and 4,5-dihydroisoxazoles.[1–7] Isoxazoles and 4,5-dihydroisoxazoles are used as intermediates in total syntheses of natural compounds. The fact that these compounds represent equivalents of definite functional groups can be exploited in different steps of the synthesis. On the other hand, isoxazoles and 4,5-dihydroisoxazoles are relatively stable compounds and remain intact in the course of multistep transformations.

The present review is devoted to the synthesis of natural compounds based on reactions of nitrile oxides with dipolarophiles with subsequent transformations of the adducts formed.

II. Methods for the generation of nitrile oxides

Nitrile oxides are usually unstable and prone to dimerisation resulting in the corresponding furoxans.[8] Therefore, they are usually generated *in situ* by dehydration of primary nitro compounds by phenyl isocyanate[9] or by dehydrohalogenation of hydroximoyl chlorides or bromides by triethylamine.[10] Hydroximoyl chlorides are generated from oximes by chlorination with chlorine, *N*-chlorosuccinimide (NCS),[11] nitrosyl chloride, sodium hypochlorite[12] or *tert*-butyl hypochlorite.[13] A procedure for the synthesis of functionalised and non-functionalised hydroximoyl chlorides, which involves treatment of nitroalkanes or conjugated nitroalkenes with titanium(IV) chloride, has been developed.[14]

Several modified procedures for the generation of nitrile oxides, *e.g.*, dehydration of nitroalkanes by toluene-*p*-sulfonic acid,[15] benzenesulfonyl chloride or ethyl chloroformate in the presence of triethylamine[16] were developed in the 1980's. All these reactions are carried out at elevated temperatures. The use of di-*tert*-butyl pyrocarbonate and catalytic amounts of *N*,*N*-dimethylaminopyridine (DMAP) allows the dehydration of nitroalkanes under much milder conditions.[17]

Chloramine T is effective for the generation of nitrile oxides from oximes.[18] This reaction is usually carried out by heating an aldoxime and an alkene in ethanol in the presence of chloramine T. Its role consists in the chlorination of aldoxime to hydroximoyl chloride. Subsequent elimination of HCl by treatment with a base results in nitrile oxide. Nitrosyl chloride or aqueous sodium hypochlorite can be used instead of chloramine T.[12]

Thermolysis of furoxans, which represent cyclic dimers of nitrile oxides, occurs under drastic conditions and is therefore seldom used;[19] thermal generation of nitrile oxides from hydroximoyl chlorides by boiling in toluene is used far more often.[20] This method was used, in particular, for the synthesis of fullereno-4,5-dihydroisoxazoles.[21]

A new method for the generation of nitrile oxides by microwave irradiation of hydroximoyl chlorides in the presence of dipolarophiles has recently been proposed. This procedure includes cycloaddition of nitrile oxides to weak dipolarophiles, such as nitriles[22] and polycyclic aromatic compounds (*e.g.*, phenanthrene, anthracene, pyrene, *etc.*) in the absence of solvents.[23] The yields of cycloaddition products exceed severalfold those obtained under standard conditions, whereas the reaction time is reduced to 3 – 10 minutes against ~ 24 h under standard conditions.

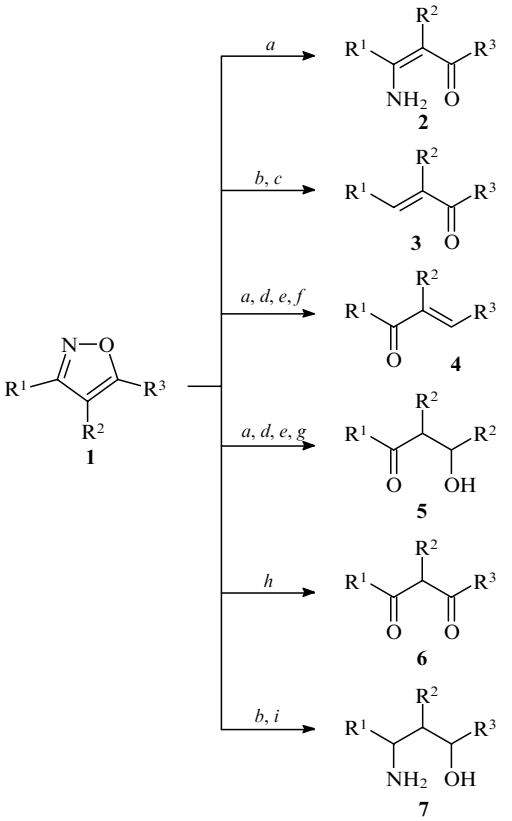
Nitrile oxides are generated from *O*-trimethylsilylhydroximoyl chlorides by treatment with potassium fluoride in acetonitrile at ~ 20 °C (see Ref. 24) or from hydroximoyl chlorides using molecular sieves (3 – 5 Å) in CH_2Cl_2.[25] In the latter case, the cycloadducts are formed in high yields, while no furoxans are formed at all.

III. Methods for the transformations of isoxazoles and 4,5-dihydroisoxazoles

Methods for the transformations of isoxazoles (**1**) and 4,5-dihydroisoxazoles are based on the lability of the N – O bond and are extremely diverse. In this section, we shall consider the main classes of compounds generated from the 1,3-dipolar cycloaddition adducts of nitrile oxides and the methods for their transformation with special emphasis on novel approaches.

A I Kotyatkina, V N Zhabinsky, V A Khripach Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, ul. Acad. Kuprevicha 5/2, 220141 Minsk, Belarus. Fax (37-517) 264 86 47. Tel. (37-517) 263 76 13. E-mail: vz@ns.iboch.ac.by (A I Kotyatkina, V N Zhabinsky) Tel. (37-517) 264 86 47. E-mail: khripach@ns.iboch.ac.by (V A Khripach)
Received 19 October 2000
Uspekhi Khimii **70** (8) 730 – 743 (2001); translated by R L Birnova

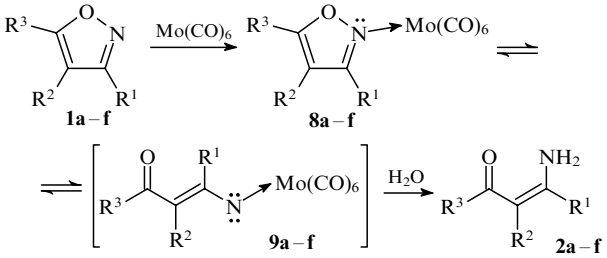
The most common procedure is the reductive scission of isoxazoles by hydrogenation over Raney nickel or platinum dioxide to afford enamino ketones **2**.[26–28]



(*a*) H_2, Ni/Ra (Pt_2O), EtOH; (*b*) Na/NH_3, 3 equiv. Bu^{t}OH, THF; (*c*) *p*-TsOH, PhMe, Δ; (*d*) PhCOCl, Py; (*e*) $NaBH_4$; (*f*) H^+; (*g*) 90% AcOH; (*h*) Ni/Ra, BCl_3, MeOH–H_2O; (*i*) Ni–Al, MeOH, KOH.

Enamino ketones **2** can also be prepared by reduction of isoxazoles with sodium in liquid ammonia in the presence of 1 equiv. of Bu^{t}OH.[29] With 3 equiv. of Bu^{t}OH, this reaction yields intermediate β-amino ketones; their acid hydrolysis results in enones **3**.[29] The regioisomeric enones of the type **4** are obtained by benzoylation of enamino ketones **2** followed by reduction of the amido ketones formed and hydrolysis of the intermediate hydroxy enamides.[30] Hydrolysis of hydroxy enamides by 90% AcOH yields β-hydroxy ketones **5**.[27,31] β-Diketones **6** are prepared by catalytic hydrogenation of isoxazoles in the presence of Lewis acids.[32] Isoxazoles are reduced to amino alcohols **7** using nickel–aluminium alloys in the presence of an alkali.[33]

However, reductive scission of isoxazoles cannot be used if the substrates contain double bonds or protective groups susceptible to hydrogenolysis. In this case, cleavage of the N–O bonds is achieved by using other methods. Thus molybdenum or iron carbonyls were recommended for use in the synthesis of enamino ketones **2a–f**.[34]

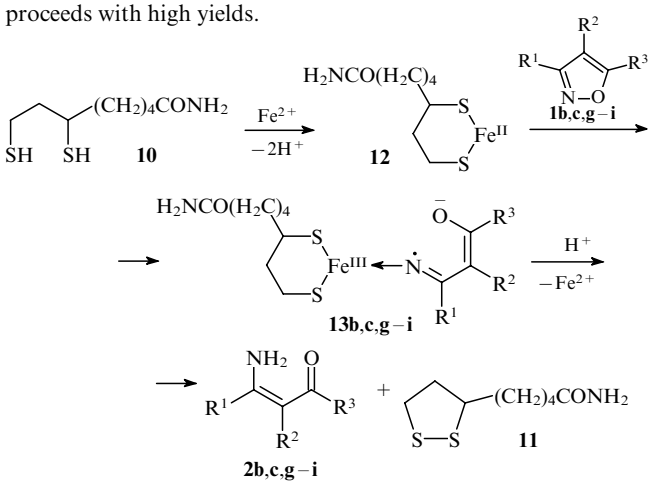


$R^1 = R^3 = Ph$, $R^2 = H$ (**a**); $R^1 = Me$, $R^2 = H$, $R^3 = Ph$ (**b**); $R^1 = R^3 = Me$, $R^2 = H$ (**c**); $R^1 = Ph$, $R^2 = R^3 = H$ (**d**); $R^1 = Ph$, $R^2 - R^3 = (CH_2)_4$ (**e**); $R^1 = Ph$, $R^2 - R^3 = (CH_2)_3$ (**f**).

The mechanism of this reaction includes the formation of the molybdenumhexacarbonyl complexes **8a–f** involving the nitrogen atom of the isoxazole with subsequent cleavage of the N–O bond and hydrolysis of the nitrene complexes **9a–f** to the enamino ketones **2a–f**.

The reductive opening of isoxazoles leading to enamino ketones is achieved with samarium iodide in tetrahydrofuran containing methanol as the proton source in 57% to 80% yields.[35]

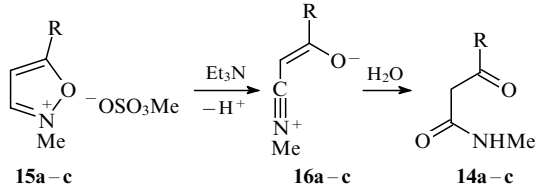
Dihydrolipoamide (**10**) was used for reductive cleavage of 4,5-dihydroisoxazoles[36] [lipoamide (**11**) is a coenzyme in redox reactions occurring in living organisms]. The reductive cleavage of N–O bonds in 3,5-disubstituted isoxazoles **1b,c,g–i** under the action of compound **10** in the presence of iron(II) salts also proceeds with high yields.



$R^1 = Me$, $R^2 = H$: $R^3 = Ph$ (**b**), Me (**c**); $R^1 = R^2 = H$, $R^3 = Me$ (**g**); $R^1 = Ph$: $R^2 = CO_2Me$, $R^3 = Me$ (**h**); $R^2 = CO_2H$, $R^3 = Me$ (**i**).

It is suggested that isoxazoles **1b,c,g–i** react with the complex (**12**) to give the intermediates **13b,c,g–i** which are further hydrolysed to enamino ketones **2b,c,g–i**. Compound **10** is converted into lipoamide **11** under these conditions.

N-Methylated β-oxo amides **14a–c** are formed in high yields upon fragmentation of *N*-methylated isoxazoles **15a–c** catalysed by Et_3N.[37]

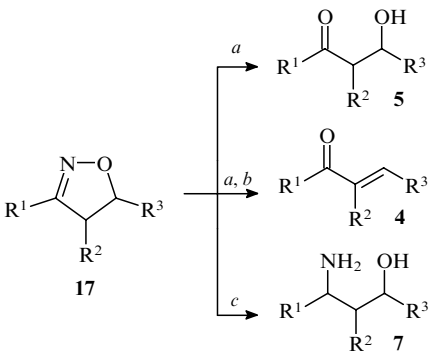


R = Me (**a**), CH=CHPh (**b**), $CH_2PO(OEt)_2$ (**c**).

The isoxazolium salts **15a–c** are deprotonated with subsequent cleavage of the N–O bond and generation of the nitrilium ions **16a–c** which are further converted into β-oxo amides **14a–c** in the presence of water.

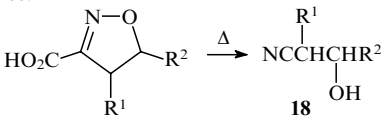
The reductive scission of 4,5-dihydroisoxazoles **17** has long been poorly understood. A method for their reduction over Raney nickel in the presence of trifluoroacetic or hydrochloric acid, which yielded a mixture of β-hydroxy ketones **5** and their dehydration products (α,β-unsaturated ketones **4**), was developed in 1979.[38] Later,[39] it was suggested to carry out this reaction in the presence of boric acid, which afforded β-hydroxy ketones **5** in high yields. The latter can further be dehydrated into enones **4**.[40] This method for the opening of 4,5-dihydroisoxazoles is widely used in the synthesis of natural compounds.[4]

The use of rhodium on Al_2O_3 and platinum dioxide as catalysts in the hydrogenation of dihydroisoxazoles **17** has been described.[41] Amino alcohols **7** are prepared by reduction of 4,5-dihydroisoxazoles by $LiAlH_4$,[42–44] the $BH_3 \cdot Me_2S$ complex (see Ref. 45) and zinc (or sodium) borohydride in the presence of nickel chloride in methanol.[46]

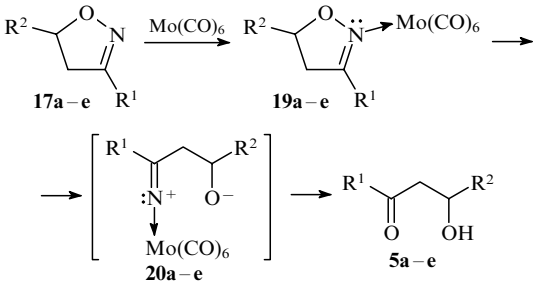


(*a*) H_2, Ni/Ra, H_3BO_3, EtOH; (*b*) p-TsOH; (*c*) $LiAlH_4$, Et_2O.

Hydroxy nitriles **18** are prepared from carboxydihydroisoxazoles.[47]

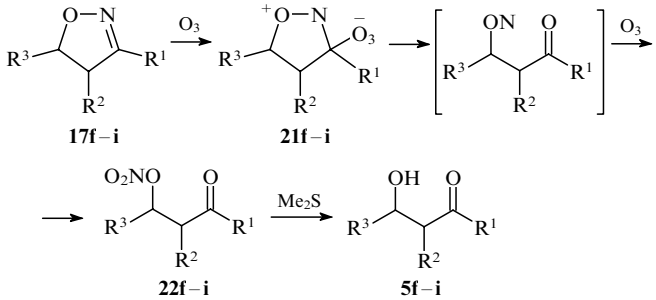


Similar to isoxazoles, 4,5-dihydroisoxazoles **17a–e** are opened under the action of molybdenum hexacarbonyl.[48] This reaction occurs *via* the complexes **19a–e** and **20a–e** which are further converted into β-hydroxy ketones **5a–e**. The complexes **19a–e** undergo retrodegradation in the absence of water.



$R^1 = Me_2C(OH)$: R^2 = n-C_8H_{17} (**a**), Bn (**b**); $R^1 = MeO_2C(CH_2)_2$, R^2 = n-$C_{10}H_{21}$ (**c**); $R^1 = HO_2C(CH_2)_2$, R^2 = n-$C_{10}H_{21}$ (**d**); $R^1 = CH_3(CH_2)_5$, R^2 = (*Z*)-MeCH=CH (**e**).

The possibility of opening of dihydroisoxazoles **17f–i** by ozonolysis resulting in β-hydroxy ketones **5f–i** has been studied.[49] It is suggested that similar to oxime ozonolysis [50] this involves the electrophilic attack of ozone at the C(3) atoms of dihydroisoxazoles resulting in the formation of the intermediates **21f–i** with subsequent cleavage of C–N bonds.



R^1 = Me, $R^2 = R^3$ = cyclo-C_5H_{11}, (**f**); R^1 = Ph, R^2 = H, R^3 = Bu^n (**g**); $R^1 = CH_2OH$, R^2 = H, R^3 = Bu^n (**h**); $R^1 = R^2 = R^3$ = Me (**i**).

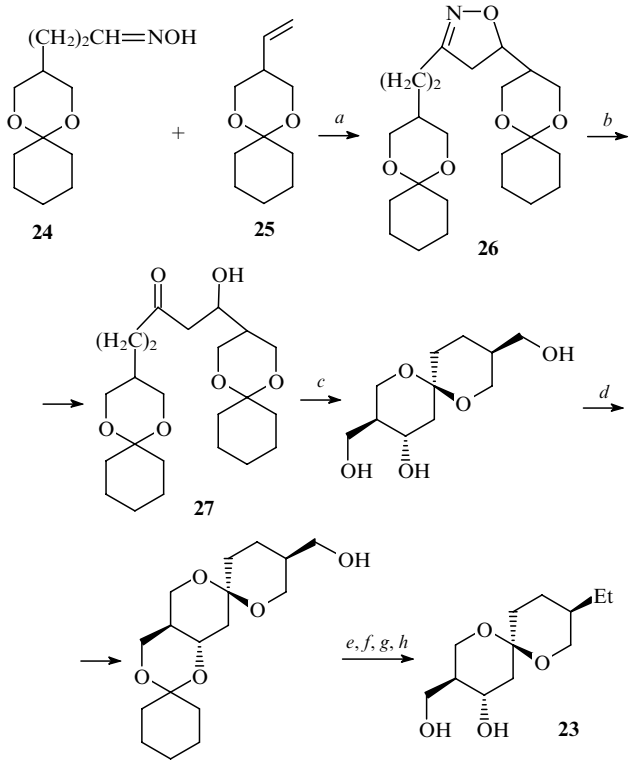
Further oxidation leads to hydroxy ketone nitrates **22f–i**; their reduction by dimethyl sulfide yield β-hydroxy ketones **5f–i**. Although the yields of the final products are lower (61%–74%) than those obtained by hydrogenolysis, the ozonolysis of 4,5-dihydroisoxazoles is effective if the substrates **17** contain functional groups susceptible to hydrogenolysis.

IV. Intermolecular 1,3-dipolar cycloaddition reactions of nitrile oxides

1,3-Dipolar cycloaddition of nitrile oxides used in the synthesis of natural compounds can be effected in two ways, *viz*., as intermolecular and as intramolecular reactions. The first approach entails convergent syntheses of complex molecules from two simpler blocks. The latter approach can be used for the generation of new C–C bonds in preformed molecules and/or for the introduction of additional functional groups.

1. Synthesis of talaromycin

The structures containing spiroketal groups were discovered in insects, microorganisms, plants and fungi in the mid-1970's.[51, 52] One of the representatives of this class, *viz*., talaromycin B (**23**), was isolated from the toxic fungus *Talaromyces stipitatus*.[53] The synthesis of talaromycin involved intermolecular 1,3-dipolar cycloaddition of a nitrile oxide to the alkene.[54]



(*a*) NaOCl, Et_3N, H_2O, CH_2Cl_2 (67%); (*b*) H_2, Ni/Ra (72%); (*c*) MeOH, Amberlyst-15 (93%); (*d*) Amberlyst-15, 1-methoxycyclohexene, THF (80%); (*e*) MsCl, Et_3N, Et_2O; (*f*) NaI, Me_2CO; (*g*) Me_2CuLi, THF; (*h*) HCl, MeOH, H_2O.

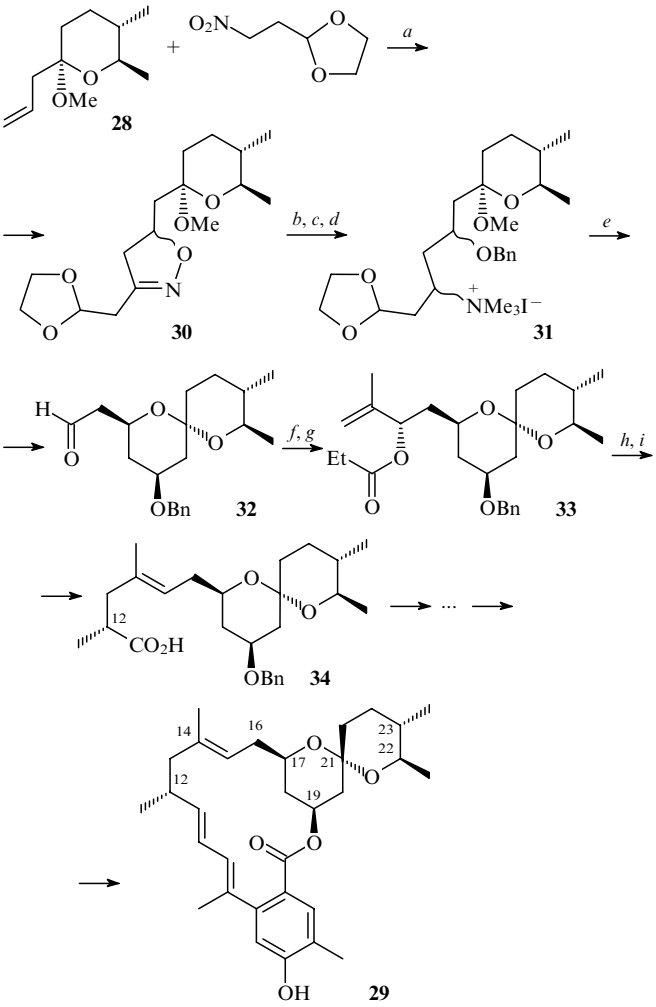
The nitrile oxide generated from the oxime **24** reacted with the alkene **25** to give 4,5-dihydroisoxazole **26**. Cleavage of the N–O bond was achieved by hydrogenation over Raney nickel. Spiroketalisation of the hydroxy ketone **27** proceeded in a weakly acidic medium in the presence of Amberlyst-15 in methanol. The resulting trihydroxy derivative **28** contained the main fragments of the talaromycin (**23**) backbone. After protection of *cis*-diol groups, racemic talaromycin (**23**) was formed in a total yield of 12%.

2. Synthesis of milbemycin β_3

Intermolecular 1,3-dipolar cycloaddition of a nitrile oxide to the alkene **28** was used in the first total synthesis of yet another compound containing a spiroketal system, *viz*., milbemycin β_3 (**29**).[55] Milbemycin β_3 was isolated in 1974 [56] and is one of more than twenty compounds of the milbemycin series. The interest in these compounds is due to their high antileukemic [57] and insecticidal [58, 59] activities and low toxicities for mammals. The synthesis

of milbemycin (**29**) faced several complicated problems including stereo-controlled formation of six asymmetric centres of the molecule, *viz*., C(12), C(17), C(19), C(21), C(22) and C(23).

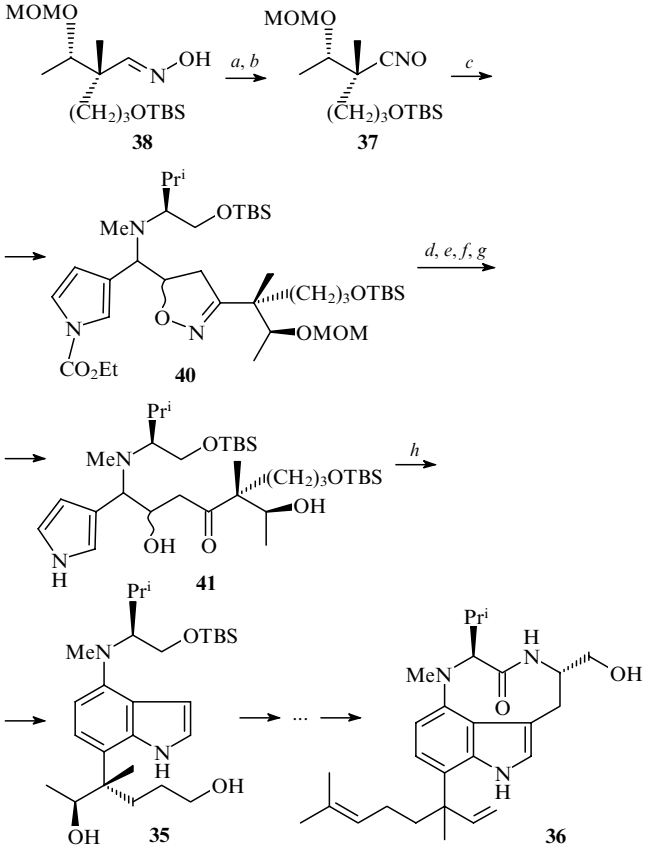
The first step of this synthesis included cycloaddition of the optically active 1,3-dipolarophile **28** and the nitrile oxide prepared by treatment of protected nitropropanal with methyl isocyanate. The resulting mixture of isomeric dihydroisoxazoles **30** was reduced by lithium aluminium hydride with subsequent protection of hydroxy and amino groups. The diastereomeric mixture of the ammonium salts **31** was treated with an aqueous solution of *p*-toluenesulfonic acid resulting in spiroketalisation and simultaneous deprotection of the aldehyde group. The addition of isopropenyllithium cuprate to aldehyde **32**, which was controlled by the chelate complex formed, yielded a mixture of allylic alcohols (7 : 1 in favour of the desired isomer). Compound **33** prepared by the reaction with propionyl chloride was selected for the Ireland–Claisen rearrangement. An attempt to use lithium diisopropylamide (LDA) in the synthesis of enolate was unsuccessful; the ester **33** could be deprotonated by potassium bis(trimethylsilyl)amide. Further treatment of the (*Z*)-enolate formed with trimethylchlorosilane and heating afforded the acid **34** with the required configuration of the C(12) centre. Total synthesis of the macrolide **29** required four additional steps.



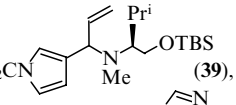
(*a*) MeNCO, Et_3N, PhH (68%); (*b*) $LiAlH_4$, Et_2O; (*c*) KH, BnI; (*d*) MeI; (*e*) TsOH, H_2O (24%–30%); (*f*) $CH_2=CH(Me)CuLi$; (*g*) EtCOCl, CH_2Cl_2, Py (63%); (*h*) $(Me_3Si)_2NK$, THF, −78 °C; (*i*) Me_3SiCl (TMSCl), 55 °C (57%).

3. Synthesis of lingbiatoxin A

The synthesis of indole **35**, the intermediate product in the synthesis of the alkaloid lingbiatoxin A (**36**), has been described.[60] It is assumed that compound **36** is a potential carcinogen and plays a key role in cell responses to some hormones and drugs. Structurally, lingbiatoxin A (**36**) represents a tricyclic compound the indole fragment in which is fused to a nine-membered ring.



MOM — $MeOCH_2$, TBS — $SiMe_2Bu^t$;



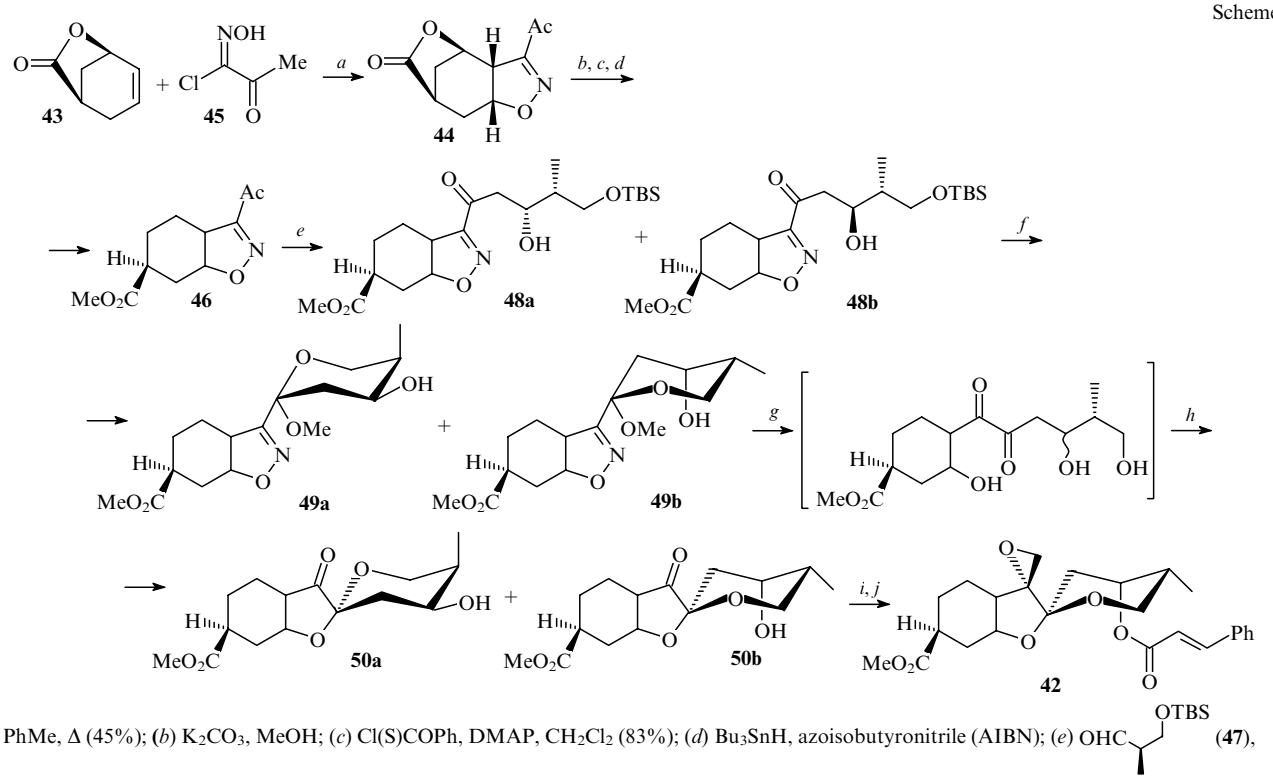
(*a*) Bu^tOCl, −78 °C; (*b*) Et_3N, 20 °C; (*c*) EtO_2CN (**39**), PhH, 80 °C, 20 h (78%); (*d*) HCl, MeOH (80 °C); (*e*) TBSCl, , DMAP, THF; (*f*) 5% KOH, MeOH; (*g*) H_2, Ra/Ni, MeOH, H_2O, AcOH; (*h*) TBSOTf, CH_2Cl_2 (68%).

The strategy of this synthesis was based on the reaction of the nitrile oxide **37**, generated from the chiral oxime **38**, with the pyrrole derivative **39** as the dipolarophile. The attempts to synthesise hydroximoyl chloride (bromide) from the oxime **38** using conventional halogenating reagents (*e.g.*, *N*-chloro- or *N*-bromosuccinimide) were without success. Positive results were attained with *tert*-butyl hypochlorite in dichloromethane at −78 °C. Dehydrochlorination of hydroximoyl chloride by triethylamine at 20 °C afforded a highly stable nitrile oxide **37**, which was isolated in a pure state and characterised. The cycloaddition of the nitrile oxide **37** to the alkene **39** in benzene with heating gave 4,5-dihydroisoxazole **40**, which represented a mixture of diastereomers (2.5 : 1). The synthesis of hydroxy ketone **41** included manipulations with protective groups, elimination of the *N*-ethoxycarbonyl group and hydrogenolysis of 4,5-dihydroisoxazole under standard conditions. *tert*-Butyldimethylsilyl triflate proved to be the best catalyst in the formation of the annelated phenyl ring[61] of the indole **35**, a convenient intermediate for lingbiatoxin A (**36**).

4. Synthesis of (+)-phyllanthocin

Phyllanthocin (**42**) (Scheme 1) is an aglycone of the glycoside phyllanthoside isolated from the roots of the South American tree *Phyllanthus acuminatus* in 1977.[62] This glycoside manifests high activity against mouse leukemia P 388 and mouse melanoma B16; therefore, it was decided to carry out its clinical trials as an

Scheme 1



(*a*) PhMe, Δ (45%); (*b*) K_2CO_3, MeOH; (*c*) Cl(S)COPh, DMAP, CH_2Cl_2 (83%); (*d*) Bu_3SnH, azoisobutyronitrile (AIBN); (*e*) OHC–CH(OTBS)–CH(Me)–CH=CH$_2$ (**47**), LDA, THF (75%); (*f*) 5% HF, MeOH, 20 °C (70%); (*g*) H_2, Ni/Ra, H_3BO_3, MeOH–H_2O (89%); (*h*) CF_3SO_3H, CH_2Cl_2; (*i*) $MeS(O)=CH_2$, DMSO, THF, 1 h (89%); (*j*) *trans*-PhCH=CHCOCl, DMAP, CH_2Cl_2 (40%).

anticancer drug for humans.[63] Several structurally related compounds were isolated and given a common name 'phyllanthostatins'.[64] Total syntheses of (+)-phyllanthocin (**42**) have been described in a number of papers.[65–68] One of them involves 1,3-dipolar cycloaddition of a nitrile oxide to the cyclohexene derivative **43**. A detailed analysis of regio- and stereochemistry of the cycloadducts has been carried out (see Scheme 1).[69]

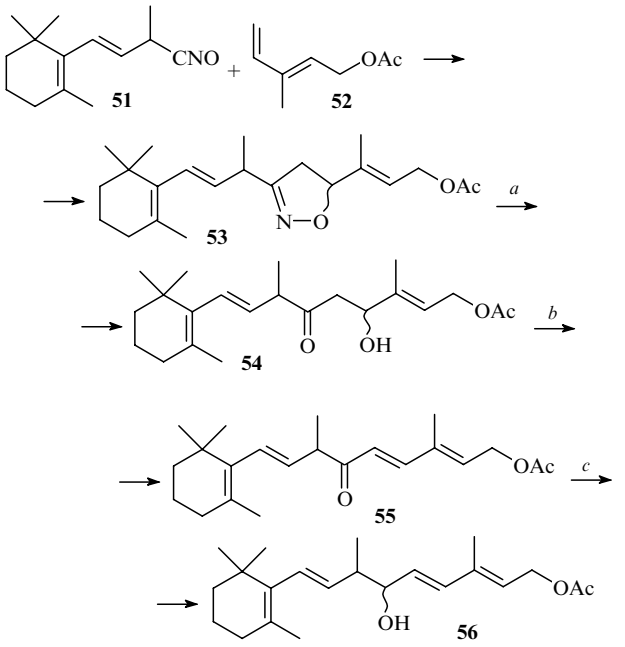
Lactone **43** was used as a starting compound for an increase in the stereo- and regioselectivity of the subsequent 1,3-dipolar cycloaddition reaction. The cycloadduct **44** of the required stereo- and regiochemistry was prepared by slow thermal generation of highly reactive nitrile oxide from the hydroximoyl chloride **45** in boiling toluene in the presence of the lactone **43** (yield 45%). 4,5-Dihydroisoxazole **46** was synthesised from compound **44** in three steps. Aldol condensation of the optically active aldehyde **47** with the ketone **46** gave a mixture of adducts **48a**,**b** in a 1 : 1.2 ratio.

It is of note that several attempts to open the heterocycle in compounds **48a**,**b** failed. Increased robustness of the 4,5-dihydroisoxazole ring is presumably due to its conjugation with the keto group. A mixture of isomers **48a**,**b** was converted into a mixture of methylglycosides **49a**,**b** followed by hydrogenolysis of the N–O bond in 4,5-dihydroisoxazole fragments and cyclisation of the intermediates which gave a mixture of spiroketals **50a**,**b** (1 : 18). The main isomer **50b** was converted to the target product, *viz*., (+)-phyllanthocin (**42**).

5. Synthesis of vitamin A

Vitamin A and its analogues remain in the focus of attention of synthetic chemists due to their prominent biological and pharmacological activities.[70,71] The Grignard reaction between compounds incorporating C_6- and C_{14}-fragments of vitamin A is one of the most general approaches to the synthesis of the vitamin A backbone.[72,73]

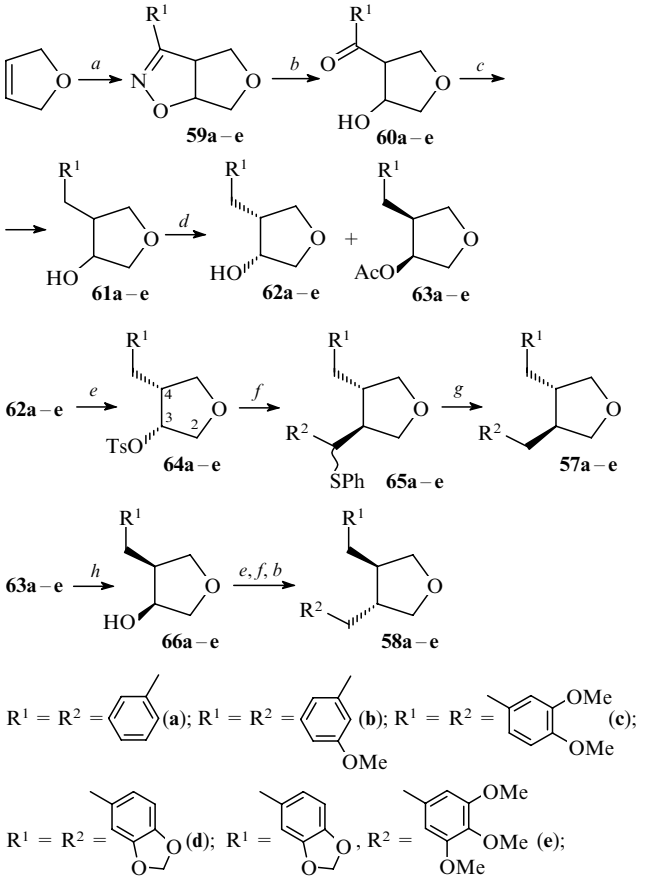
An alternative strategy for the construction of the basic backbone [74] consists in the simultaneous formation of the C–C bond and the introduction of functional groups in the interaction of the nitrile oxide **51** (the C_{14}-fragment) with the alkene **52** (the C_6-fragment) resulting in 3,5-disubstituted 4,5-dihydroisoxazole **53**. The cleavage of the N–O bond was achieved through the previously developed procedure using $Mo(CO)_6$.[48] The resulting β-hydroxy ketone **54** was dehydrated and enone **55** was reduced by $NaBH_4$ to the intermediate **56**, which is common in the synthesis of vitamin A. This scheme allows one to obtain large amounts of vitamin A and easy introduction of new functional groups in the synthesis of its analogues.



(*a*) $Mo(CO)_6$, MeCN (60%); (*b*) MsCl, Et_3N, 0 °C; (*c*) $NaBH_4$ (70%).

6. Synthesis of burseran and brassilignan

Preparations based on aloe have long been known in folk medicine.[75,76] Some aloe components are related to lignans, while certain representatives of this family possess antitumour activities and prevent metastasis.[77,78] Several approaches to the synthesis of natural lignans and their analogues manifesting biological activities have been developed.[79–82] In the majority of these syntheses, chiral compounds were used as starting materials. Achiral starting compounds were recommended for the synthesis of optically active natural lignans, *viz*., burserans **57e** and **58e** and brassilignans **57c** and **58c**, and some of their analogues.[83]



(*a*) $R^1CCl{=}NOH$, Et_3N, Et_2O, ~20 °C (58%–84%); (*b*) H_2, Ni/Ra, EtOH, H_3BO_3; (*c*) H_2, Pd/C, MeOH–H_2O; (*d*) $CH_2{=}CHOAc$, lipase PS; (*e*) MeLi, THF, −78 °C, TsCl; (*f*) R^2CH_2SPh, BuLi, THF, 0 °C; (*g*) Ni/Ra, EtOH, Δ, 20 h; (*h*) K_2CO_3, MeOH.

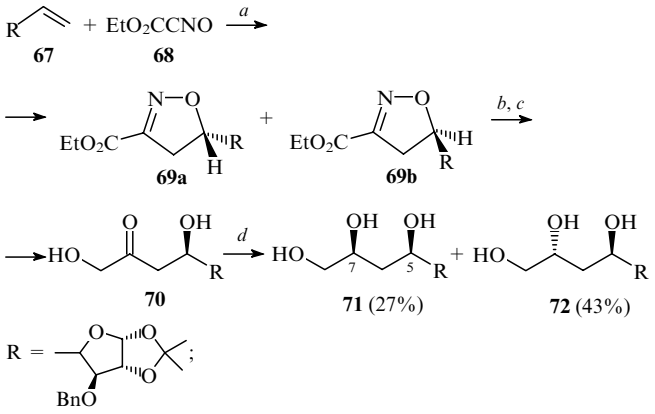
1,3-Dipolar cycloaddition of aromatic nitrile oxides to 2,5-dihydrofuran yielded furoisoxazoles **59a–e**. Hydrogenolysis of the cycloadducts **59a–e** over Raney nickel in the presence of a large excess of boric acid gave β-hydroxy ketones **60a–e** the keto group in which was reduced by hydrogen on palladium.

Lipase PS was used to separate the optical antipodes of the resulting alcohols **61a–e**. The absolute stereochemistry of alcohols **62a–e** and acetates **63a–e** was established later, following completion of the synthesis of the natural compounds **57e**, **58e**, **57c** and **58c**. Tosylation of compounds **62a–e** and **63a–e** (after preliminary hydrolysis) and subsequent nucleophilic substitution of the secondary tosyloxy group pursued two goals, *viz*., the introduction of the second aromatic substituent and the inversion of the C(3) centre so that the configurations of the substituents corresponded to those of the natural compounds. *p*-Toluenesulfonates **64a–e** gave a mixture of diastereomeric sulfides **65a–e**; their desulfurisation with Raney nickel in EtOH gave the target products **57a–e** in a total yield of 6%–16%. The same reaction sequence was applied to the isomers **66a–e** resulting in the preparation of optically active products **58a–e** (yield 6%–14%). Thus, a series of natural compounds, *viz*., burserans **57e** and **58e**, brassilignans **57c** and **58c** and artificial analogues *viz*., dehydroxycubebins **57d** and **58d**, 3,4-bis(3-methoxybenzyl)-tetrahydrofurans **57b** and **58b,** 3,4-dibenzyltetrahydrofurans **57a** and **58a**, were prepared. This method[83] gives an access to a vast variety of natural and non-natural lignans including their aza analogues owing to the high accessibility of 2,5-dihydrofuran, aromatic nitrile oxides and diverse phenyl sulfides.

7. Synthesis of higher monosaccharides

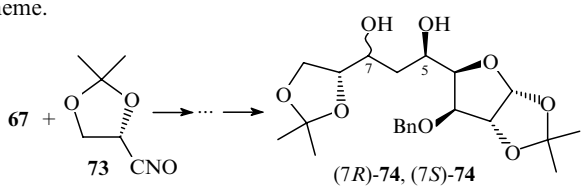
The role of monosaccharides in vital activities of animals, plants and human beings is generally acknowledged. The discovery of antibiotics[84,85] containing higher monosaccharides gave strong impetus to investigations into their synthesis.[86,87] An approach described by Poton and Young[88] is based on cycloaddition of accessible unsaturated monosaccharides to nitrile oxides with subsequent reduction of the dihydroisoxazoles formed.

Thus the reaction of the alkene **67** derived from D-glucose with the nitrile oxide **68** gave a mixture of diastereomeric 4,5-dihydroisoxazoles **69a**,**b** in a 14 : 86 ratio. Compound **69b** gave the dihydroxy ketone **70** in two steps; its reduction with sodium borohydride yielded a mixture of 6-deoxy-D- and 6-deoxy-L-*glycero*-D-*gluco*-octofuranoses **71** and **72**.

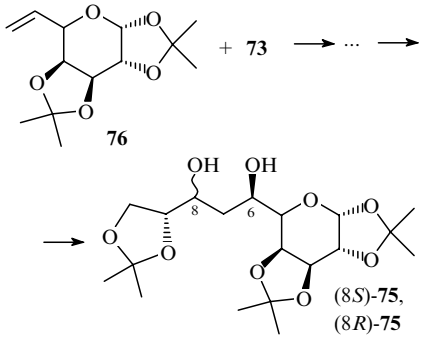


(*a*) Et_2O, Et_3N, 14 h (75%); (*b*) $NaBH_4$, THF, EtOH; (*c*) H_2, Pd/C, H_3BO_3, MeOH–H_2O, 18 h (78% **69b**); (*d*) $NaBH_4$, EtOH, H_2O.

The alkene **67** and D-glyceronitrile oxide **73** were used in the synthesis of (7*R*)- and (7*S*)-nonofuranoses **74** by the same reaction scheme.



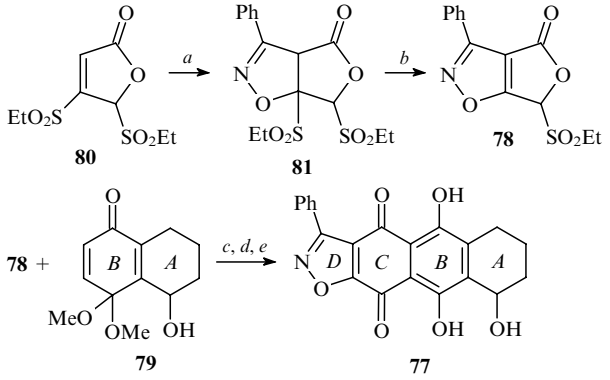
(8*S*)- And (8*R*)-7-deoxydecopyranoses **75** were prepared from the nitrile oxide **73** and the alkene **76** derived from D-galactose.



The configurations of the C(5) and C(7) centres in compounds **71**, **72** and **74** and of the C(6) and C(8) centres in compounds **75** were established on the basis of ^{1}H NMR spectroscopic data and stereochemistry of their precursors, *viz*., 4,5-dihydroisoxazoles, and confirmed by X-ray diffraction analysis. This approach enables the synthesis of diverse higher monosaccharides.

8. Synthesis of a heterocyclic analogue of daunomycin

Daunomycin is a typical representative of anthracycline antibiotics used in the chemotherapy of malignant tumours.[89,90] However, its application is restricted due to side effects including high cardiotoxicity. An attempt was made to synthesise modified anthracycline derivatives in which the benzene rings (*D*) is replaced by a heteroaromatic rings. The daunomycin analogues thus synthesised contained thiophene [91] or indole fragments [92] as rings *D* and manifested high activities comparable to that of daunomycin, but lower toxicities. The synthesis of compound **77**, an intermediate in the synthesis of the daunomycin analogue containing an isoxazole fragment as ring *D*, has been developed.[93]



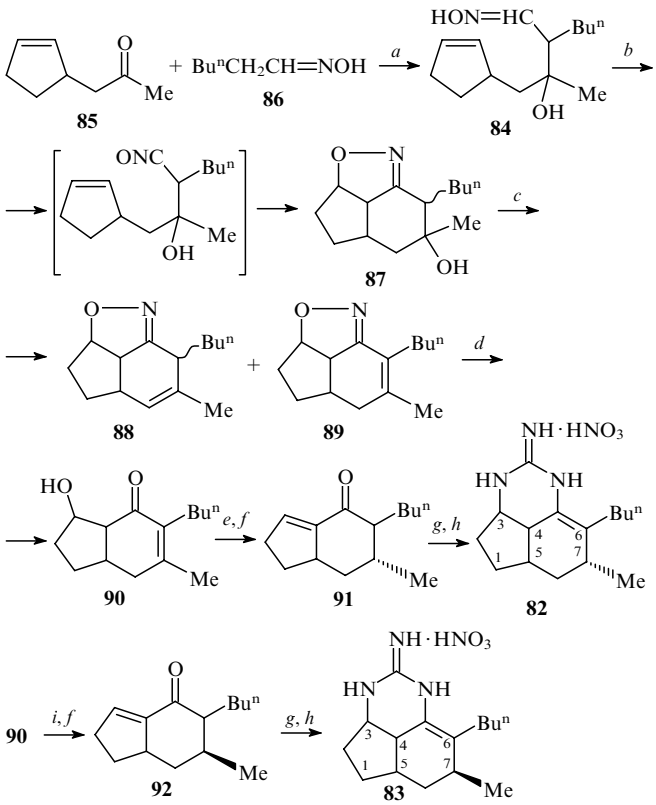
(*a*) PhCCl=NOH, molecular sieves, 20 °C, 10 h; (*b*) SiO_2 (85%); (*c*) LDA, THF, −78 °C; (*d*) −2 °C, 120 h (40%); (*e*) BCl_3, −78 °C, 45 min (50%).

The key stage in this synthesis is the annelation of furoisoxazole **78** and the bicyclic derivative **79** (the DC + BA strategy) under the action of lithium diisopropylamide. Compound **78** was synthesised by cycloaddition of benzonitrile oxide to 4,5-di(ethylsulfonyl)-2,5-dihydrofuran-2-one **80**. Numerous experiments showed [94] that this dipolarophile far exceeds other dipolarophiles as concerns reactivity. Moreover, the presence of the ethylsulfonyl group at the C(5) atom significantly affects the regio- and stereochemistry of the cycloaddition reaction, whereas the ethylsulfonyl group in position 4 enables subsequent aromatisation of compound **81** into isoxazole **78**.

V. Intramolecular 1,3-dipolar cycloaddition reactions of nitrile oxides

1. Stereoselective synthesis of ptilocaulin and its epimer

Ptilocaulin (**82**) and its epimer at the C(7) atom, *viz*., isoptilocaulin (**83**), isolated from the sea sponge *Ptilocaulis spiculfer* in 1982 [95] manifest antileukemic and antibacterial activities. These compounds have relatively simple but unusual structures in which guanidine is annelated with the hydrindan system. A seven-step stereoselective synthesis of compounds **82** and **83** has been developed,[96] which includes the formation of a six-membered carbocycle by intramolecular cycloaddition of a nitrile oxide to the double bond in the cyclopentene derivative **84**.

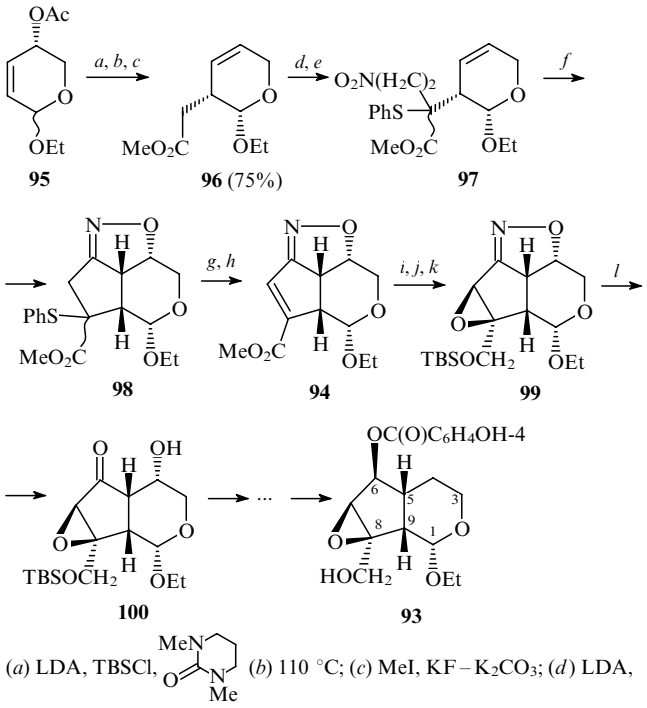


(*a*) 2 equiv. BuLi, THF, 0–20 °C, 6 h (90%); (*b*) NaOCl, CH_2Cl_2, −10 to −20 °C, 5 h (80%); (*c*) $SOCl_2$–Py, −10 °C, 40 min; (*d*) H_2, Ni/Ra, H_3BO_3, MeOH–H_2O (60%); (*e*) H_2, Pd/C (95%); (*f*) TsOH, PhH, 40 °C, 30 min; (*g*) $(H_2N)_2C$=NH, PhH, Δ, 36 h (35%); (*h*) HNO_3; (*i*) Li–$EtNH_2$, −70 °C, 30 min (85%).

Aldol condensation of the ketone **85** with the hexenal oxime (**86**) dianion yields the β-hydroxy oxime **84**. Its treatment with sodium hypochlorite gives tricyclic 4,5-dihydroisoxazole **87** as a mixture of four diastereomers. Compound **87** is dehydrated into a 1 : 1 mixture of unsaturated 4,5-dihydroisoxazoles **88** and **89** which are further subjected to reductive scission over Raney nickel. The unsaturated ketol **90** is the key intermediate in the synthesis of ptilocaulin (**83**) and its C(7) epimer (**82**).[97,98] The enone **91** prepared from the ketol **90** by hydrogenation of the double bond over palladium and subsequent dehydration reacted with guanidine to give isoptilocaulin **82**. The epimer of enone **91** with the β-configuration of the methyl group at C(7) (compound **92**) was prepared by reduction of the double bond in ketol **90** with lithium in diethylamine (in this case, the carbanion undergoes axial protonation) with subsequent dehydration. The use of lithium in liquid ammonia made it possible to achieve simultaneous reduction of the double bond and the keto group. Ptilocaulin (**83**) was prepared by heating of the enone **92** with guanidine. Compounds **82** and **83** were isolated as nitrates.

2. Synthesis of (−)-specionin

(−)-Specionin (**93**) was isolated from leaf extracts of the tree *Catalpa speciosa*.[99] This compound manifests insecticidal activity against various pests of coniferous plants which inflict severe damages to the wood-processing industry. The first synthesis of racemic specionin was carried out in 1985.[100] Synthesis of the optically active compound based on the nitrile oxide-based approach was developed by Curran *et al*.[41] The 4,5-dihydroisoxazole intermediate **94** was synthesised from the acetal **95** in eight steps.



(*a*) LDA, TBSCl, (*b*) 110 °C; (*c*) MeI, KF – K_2CO_3; (*d*) LDA, PhSSPh; (*e*) LDA, $CH_2=CHNO_2$ (85%); (*f*) *p*-ClC_6H_4NCO, Et_3N, 110 °C (89%); (*g*) *m*-chloroperbenzoic acid (*m*-CPBA); (*h*) PhH, 80 °C; (*i*) $Bu^i_2Bu^nAlHLi$ (42%); (*j*) TBSCl, DMAP, Et_3N (72%); (*k*) 3,5-dinitroperbenzoic acid, Na_2HPO_4, CH_2Cl_2 (77%); (*l*) H_2, Rh/Al_2O_3 (57%).

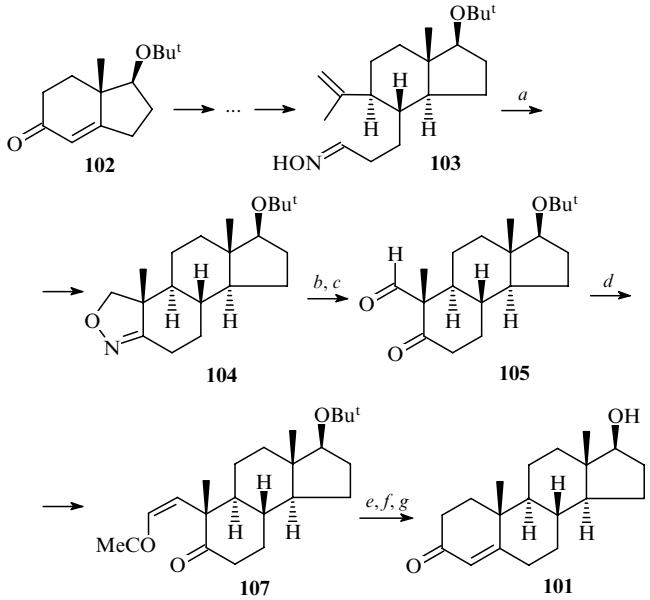
The Ireland – Claisen rearrangement yielded compound **96**; its sulfenylation and the addition of the α-sulfite formed to nitroethylene led to the derivative **97**, which was further involved in the intramolecular cycloaddition of the nitrile oxide fragment to the double bond. The sulfide group in the tricyclic 4,5-dihydroisoxazole **98** was oxidised and the sulfoxide formed was boiled in benzene, which resulted in elimination of $PhSO_2H$ and the formation of a double bond. Selective reduction of the ester group in the derivative **94** was carried out using a complex prepared from butyllithium and diisobutylaluminium hydride; the resulting alcohol was converted into the silyl ether. Its epoxidation by 3,5-dinitroperbenzoic acid could be performed due to the resistance of the dihydroisoxazole ring to oxidants; this reaction was stereoselective and yielded a single isomer (**99**). The dihydroisoxazole ring in compound **99** was opened smoothly by hydrogenolysis in the presence of 5% rhodium on Al_2O_3 in aqueous methanol resulting in β-hydroxy ketone **100**. The use of other catalysts (*e.g.,* Ni-Ra, Pd/C, Pt_2O) in this step resulted in the destruction of the molecule. (−)-Specionin (**93**) was obtained from its precursor **100** in eight steps; the total yield was 0.5% with respect to compound **95**.

3. Synthesis of testosterone

Total synthesis of steroids, which play an extremely important role in the human organism as well as in animal and plant organisms, has been the subject of numerous investigations.[101, 102]

The use of 4,5-dihydroisoxazoles in the formation of steroid backbones was described back in the 1960-70's. In some studies, 4,5-dihydroisoxazoles were used as parts of alkylating agents bearing a masked β-diketone function [103, 104] in the synthesis of D-homotestosterone, progesterone, testosterone and 13-ethyltestosterone.

The synthesis of testosterone (**101**) made use of a new approach based on intramolecular 1,3-dipolar cycloaddition.[105] This procedure enabled the construction of the ring *B* with the β-configuration of the C(19) methyl group and simultaneous introduction of functional groups for further synthesis of ring *A*. Starting from the optically active indanone **102**, the oxime **103** was prepared in eight steps (total yield 37%). The intramolecular 1,3-dipolar cycloaddition of the nitrile oxide prepared from this oxime occurred stereospecifically and resulted in the cycloadduct **104**. Although the stereochemistry of the angular methyl group of 4,5-dihydroisoxazole formed cannot be inferred from the spectroscopic data, the structure **104** was assigned to this compound [105] on the assumption [106, 107] that the chair-like conformation is more preferable in the transition state than the boat-like conformation leading to the C(10) isomer.



(*a*) NaClO, CH_2Cl_2 (87%); (*b*) H_2, Ni/Ra, $B(OMe)_3$, MeOH (97%); (*c*) SO_3 – Py, DMSO (97%); (*d*) $MeCOCH=PPh_3$ (**106**), $Me_2C_6H_3$ (89%); (*e*) H_2, 10% Pd/C; (*f*) KOH, MeOH; (*g*) CF_3CO_2H (76%).

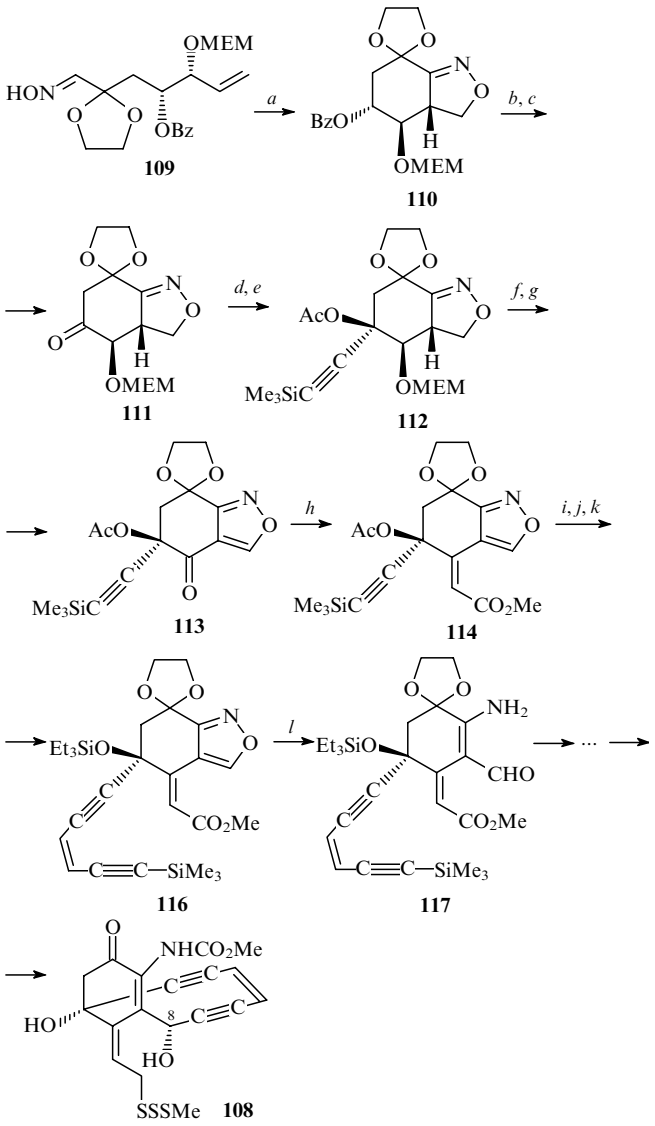
The reductive opening of 4,5-dihydroisoxazole **104** over Raney nickel in the presence of trimethyl borate in aqueous methanol gave a hydroxy ketone; its oxidation yielded the aldehyde **105**. A three-carbon fragment was introduced by the Wittig reaction with 1-triphenylphosphoranylidenepropan-2-one (**106**). The resulting enone **107** was converted into testosterone *tert*-butyl ether as a result of catalytic hydrogenation and treatment with potassium hydroxide in methanol, eventually resulting in the closure of the ring *A*. Removal of the protective group from the C(17) hydroxy group completed the synthesis of testosterone **101** in a total yield of 17%. Thus, the use of intramolecular 1,3-dipolar cycloaddition of nitrile oxide enabled effective construction of testosterone rings *A* and *B*.

4. Synthesis of calicheamicin γ_1^I

Compounds related to antitumour antibiotics of the enedyine series, *e.g.,* calicheamicin γ_1^I, esperamycin A_1, dinemycin A, were isolated from cultured bacterial cells of *Micromonospora echinospora*.[108, 109] These compounds produce strong therapeutic effects by cleaving double-stranded DNA at specific sequences.[110, 111] A number of papers published soon after their discovery [112 – 116] were devoted to the synthesis of their main backbones, *e.g.*, to the racemic calicheamicin aglycone, calicheamicinone (**108**). The syntheses of oligosaccharide fragments attached to the hydroxy group at C(8) of calicheamicinone (**108**) have also been described.[117, 118]

The first enantioselective synthesis of (−)-calicheamicinone (**108**) and a total synthesis of calicheamicin γ_1^I were carried out by Nicolaou and coworkers.[119, 120] This synthesis is based on the use of the intramolecular 1,3-cycloaddition reaction of alkenyl nitrile oxide prepared from the aldoxime **109**.

This aldoxime was treated with aqueous sodium hypochlorite under standard conditions, which resulted in intramolecular cyclisation and the formation of a 4 : 1 mixture of 4,5-dihydro-



MEM is $MeO(CH_2)_2$; (*a*) NaOCl, CH_2Cl_2, 25 °C, 2 h (65%); (*b*) NaOMe MeOH, 0 °C (100%); (*c*) CrO_3, H_2SO_4, Me_2O, 0 °C (95%); (*d*) 1.5 equiv. $Me_3SiC{\equiv}CLi$, THF, −78 °C (67%); (*e*) Ac_2O, 25 °C, 3 h; (*f*) 10 equiv. $ZnBr_2$, CH_2Cl_2, 25 °C, 2 h; (*g*) $COCl_2$, DMSO (54%); (*h*) $Ph_3P{=}CHCO_2Me$, PhMe, 90 °C, 16 h (84 %); (*i*) K_2CO_3, MeOH – CH_2Cl_2, 0 °C, 6 h (90%); (*j*) Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min (96%); (*k*) (*Z*)-$Me_3SiC{\equiv}CCH{=}CHCl$ (**115**), $Pd(PPh_3)_4$, CuI, $BuNH_2$, PhH, 0 °C, 2 h (91%); (*l*) $Mo(CO)_6$, MeCN – H_2O, 80 °C, 1.5 h (82%).

isoxazole diastereomers; the main isomer **110** was isolated in 51% yield. After removal of benzoyl protection, the secondary alcohol formed was oxidised by the Jones reagent to the ketone **111**. The nucleophilic addition of lithium (trimethylsilyl)acetylenide to the ketone **111** was fully stereoselective; the hydroxy group in the resulting acetylenic alcohol was protected by acetylation.

Removal of the methoxyethoxymethyl group in compound **112** and subsequent Swern oxidation of the alcohol formed yielded unexpectedly isoxazole **113** instead of 4,5-dihydroisoxazole. The use of other oxidants gave the same results. Therefore, the strategy of the synthesis had to be changed in favour of the Wittig reaction of the ketone **113** with methyl triphenylphosphoranylideneacetate, which resulted in selective synthesis of compound **114** having the *E*-configuration of the double bond in the enediyne fragment.

After removal of the protective trimethylsilyl group, the enyne group was introduced by high-yielding palladium-catalysed addition of (*Z*)-chloroenyne (**115**), which gave the enediyne **116**. The opening of the isoxazole ring in this molecule under the action of molybdenum hexacarbonyl in aqueous acetonitrile resulted in the enamino aldehyde **117**.

The final product of this synthesis, *i.e.*, (−)-calicheamicinone (**108**), was prepared from the aldehyde **117** in 16 steps. The total yield of compound **108** was 2.6% with respect to the starting aldoxime **109**.

5. Synthesis of zoapatanol

The intramolecular cycloaddition reaction was used to prepare compound **118**, the optically active intermediate in the synthesis of zoapatanol (**119**), one of novel diterpenoids containing an oxepane ring.[121] This is endowed with contraceptive activity [122, 123] and was isolated from the leaves of the Mexican plant *Montanoa tomentosa*.[124] Syntheses of racemic zoapatanol [125, 126] and the optically active product (Scheme 2) have been described.[127]

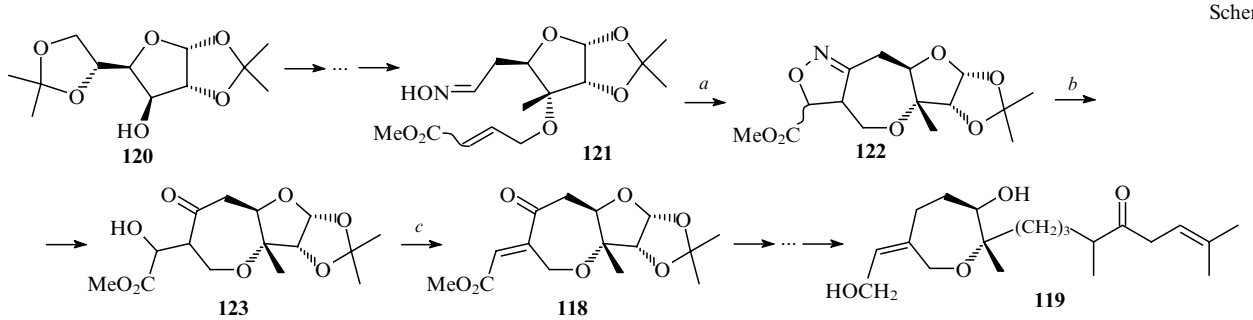
D-Glucose diacetonide (**120**) was used as the starting compound in the 13-step synthesis of the oxime **121**. The intramolecular nitrile oxide cycloaddition reaction was carried out under standard conditions. The resulting dihydroisoxazole **122** (a mixture of diastereomers) was reduced over Raney nickel to the hydroxy ketone **123**. Its dehydration gave α,β-unsaturated oxo ester **118** which is considered [121] to be a convenient intermediate in the synthesis of zoapatanol **119.**

VI. Syntheses based on enantiocontrolled 1,3-dipolar cycloaddition reactions of nitrile oxides

The optical purity of natural compounds is of crucial importance where they are used as medicinal drugs or plant protectors. In contrast to non-symmetrical Diels – Alder reactions, studies on enantiocontrolled cycloaddition reactions of nitrile oxides have a relatively short history.

The feasibility of stereocontrolled cycloaddition using optically active nitrile oxides or alkenes has been studied.[128, 129] Dipolarophiles containing bulky chiral auxiliaries have become especially popular. As a result, the nitrile oxide attack occurs in a strictly stereoselective manner; the chiral substituents are then removed. Chiral (−)-menthyl acrylates,[130] bornyl crotonates,[131] alkenes containing tricarboxylic Kemp's acid [132] or the Oppolzer

Scheme 2

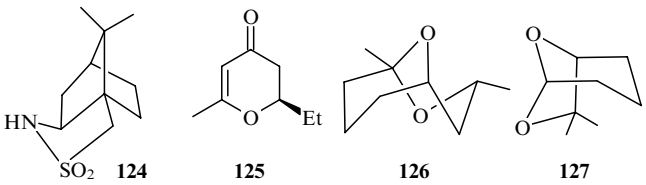


(*a*) NaOCl, CH_2Cl_2, Et_3N (61%); (*b*) Ra/Ni, H_2, MeOH – H_2O; (*c*) $MeSO_2Cl$, CH_2Cl_2, Et_3N.

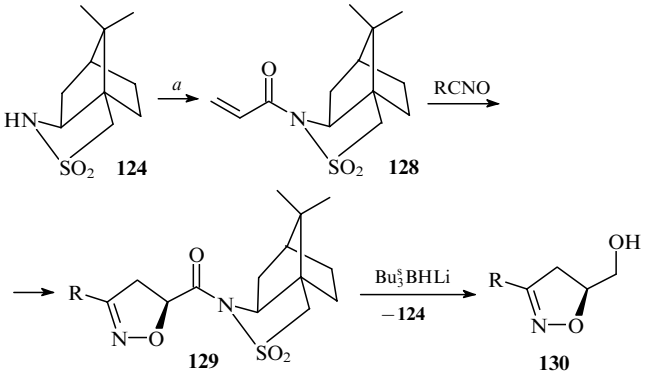
sultam [133, 134] as substituents as well as alkenes coordinated to iron [135] or cobalt [136] complexes belong to such dipolarophiles.

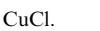
1. Syntheses using the chiral Oppolzer reagent

The chiral Oppolzer reagent, *viz*., L-camphor sultam (**124**), was used [137] in the synthesis of several natural compounds, *e.g*., the sex pheromone of the butterfly *Hepialis californicus* [(+)-hepialone **125**)[138]], (−)-(1*R*,3*R*,5*S*)-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane (**126**),[139] the constituent of the Norwegian spruce bark, and (−)-(1*S*)-7,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (**127**)[140] isolated from hop oil and confering characteristic odour to beer.

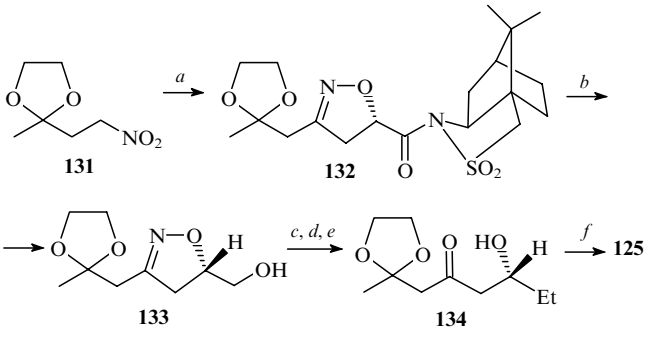


Syntheses of compounds **125**–**127** were performed according to non-sophisticated and efficient schemes the key step in which included the addition of readily accessible nitrile oxides to the amide **128** prepared by treatment of the chiral sultam **124** with acryloyl chloride in the presence of sodium hydride and CuCl. Subsequent reduction of the adducts **129** resulted in 4,5-dihydroisoxazoles **130** and regeneration of L-camphor sultam **124.**



(*a*)  , NaH, CuCl.

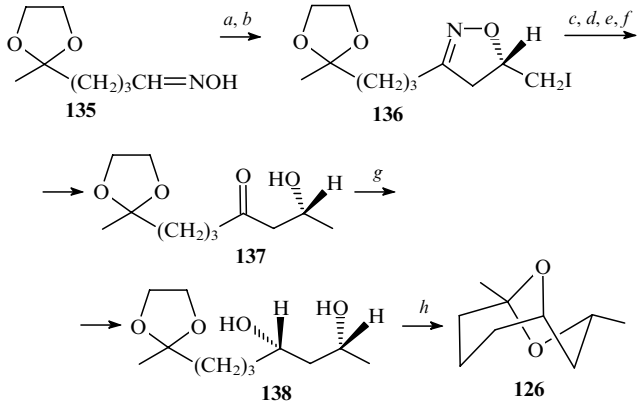
(+)-Hepialone (**125**) was synthesised from the nitro ketal **131**.[137] The cycloaddition performed under standard conditions [9] yielded a mixture of epimeric 4,5-dihydroisoxazoles (88 : 12); the main diastereomer **132** was isolated by chromatography. Its reduction by L-selectride (Bu^s_3BHLi) gave the alcohol **133** with recovery of the chiral reagent **124**. Tosylation of the alcohol **133** and subsequent treatment of the *p*-toluenesulfonate with lithium



(*a*) **128**, PhNCO, Et_3N; (*b*) Bu^s_3BHLi, THF, 25 °C, 30 min (85%); (*c*) TsCl, Et_3N, DMAP, 25 °C, 26 h (100%); (*d*) Me_2CuLi, Et_2O, −5 °C, 18 h (57%); (*e*) Ni/Ra, H_2O, MeOH, H_3BO_3 (75%); (*f*) 3 M HCl, Et_2O, 25 °C, 20 h (88%).

dimethylcuprate led to the replacement of the hydroxymethyl group by the ethyl group. Reduction of 4,5-dihydroisoxazole by hydrogen over Raney nickel occurred with the retention of the original configuration of the chiral centre and yielded the β-ketol **134** . Subsequent ring closure under conditions of acid catalysis afforded the pheromone **125**.

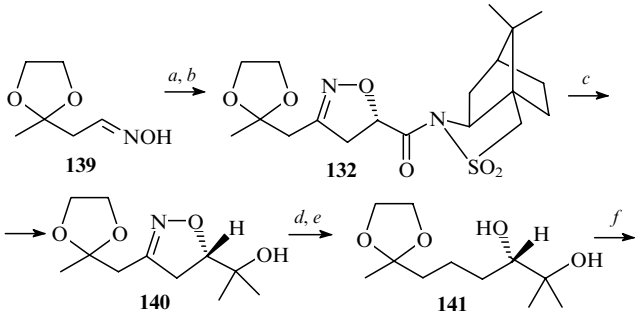
(−)-(1*R*,3*R*,5*S*)-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (**126**) was synthesised from the oxime **135** and the amide **128**.[137] Cycloaddition gave epimeric 4,5-dihydroisoxazoles (92 : 8); the main isomer was isolated in 89% yield by column chromatography. Deoxygenation of the hydroxy group had to be carried out following removal of the chiral reagent by L-selectride.

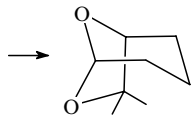


(*a*) **128**, NCS, DMF; (*b*) Et_3N, Et_2O; (*c*) Bu^s_3BHLi, THF, 25 °C, 45 min (86%); (*d*) TsCl, CH_2Cl_2, Et_3N, DMAP, 9 h (83%); (*e*) NaI, $NaHCO_3$, MeCOEt, Δ (98%); (*f*) Ni/Ra, H_2, H_3BO_3, MeOH – H_2O (15 : 1), 16 h (74%); (*g*) Et_2BOMe, −70 °C, $NaBH_4$, THF – MeOH (86%); (*h*) Et_2O, 3 M HCl, 20 °C, 16 h (57%).

Initially, this was attempted by radical reduction of the iodide **136** prepared from the corresponding *p*-toluenesulfonate, which however resulted in racemisation. Numerous experiments allowed finally elaboration of the optimum conditions for such reduction [*viz*., Bu_3SnH, diazabicycloundecene (DBU), AIBN, 50 °C]. Hydrogenation of the 4,5-dihydroisoxazole **136** over Raney nickel, which was accompanied by reductive deiodination, appeared to be the shortest way to the optically pure ketol **137**. The target product **126** was obtained by treatment of the optically active 1,3-diol **138** with HCl.

(−)-(1*S*)-7,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane (**127**) was synthesised from the oxime **139**.[137] The optically pure cycloadduct **132** was isolated in 70% yield from a mixture of epimers (85 : 15). The Grignard reaction of the 4,5-dihydroisoxazole **132** with MeMgBr gave compound **140**, the chiral reagent **124** was recovered simultaneously. Reduction of the dihydroisoxazole **140** with lithium aluminium hydride occurred stereoselectively to give the optically active amino alcohol in 97% yield. The latter was deaminated with sulfamic acid and the diol **141** obtained was treated with an acid, which resulted in the target bicyclic product **127**.



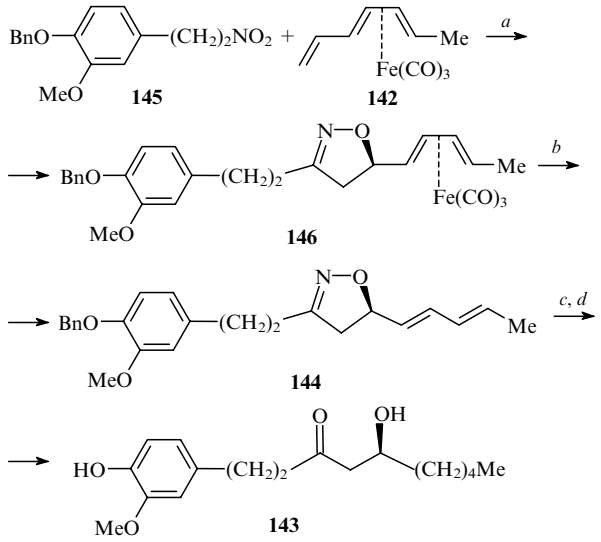


127

(*a*) **128**, NCS, CH_2Cl_2; (*b*) Et_3N, CH_2Cl_2 (70%); (*c*) MeMgBr, THF, −78 °C (72%); (*d*) $LiAlH_4$, Et_2O, −78 °C (97%); (*e*) NH_2OSO_3H, NaOH, CH_2Cl_2, 1 h, 60 °C (54%); (*f*) PhH, TsOH, 48 h, 60 °C (61%).

2. Synthesis of (+)-(*S*)-gingerol

A group of French chemists[141] studied the enantiocontrolled synthesis of dihydroisoxazoles using the chiral acyclic irontricarbonyl complex **142** as a dipolarophile. The complex **142** was prepared by olefination of optically active aldehydes coordinated to ironpentacarbonyl.[135] The method proved to be efficient in the synthesis of (+)-(*S*)-gingerol (**143**), a biologically active compound[144, 145] isolated from plants.[142–145]



(*a*) PhNCO, Et_3N, ~20 °C, 48 h (75%); (*b*) $(NH_4)_2Ce(NO_3)_6$, MeOH, −20 °C, 25 min (62%); (*c*) H_2, Ni/Ra, H_3BO_3, MeOH–H_2O, 3.5 h (80%); (*d*) H_2, 10% Pd/C, MeOH, 20 °C, 40 min (66%).

Synthesis of compound **143** has been the subject of numerous studies; two of those employ the 1,3-dipolar cycloaddition of nitrile oxides with subsequent reductive scission of the cycloadducts formed.[31, 46] The formation of the β-hydroxycarbonyl fragment in gingerol **143** was achieved by enantioselective reduction of chiral enamido ketones[31] and transformation of chiral 3-sulfenyldihydroisoxazoles.[46]

The 4,5-dihydroisoxazole **144** was synthesised by the 1,3-dipolar cycloaddition of a nitrile oxide to the chiral acyclic irontricarbonyl complex **142**.[141] The nitrile oxide precursor, *viz*., the nitrocompound **145**, was synthesised in five steps from the readily accessible 4-benzyloxy-3-methoxybenzaldehyde (total yield 33%). The cycloaddition of triene **142** to the nitrile oxide generated from the nitro compound **145** yielded a mixture of diastereomeric 4,5-dihydroisoxazoles in a 89 : 11 ratio; the main isomer **146** was isolated in 75% yield. The irontricarbonyl complex was decomposed by oxidation with cerium ammonium nitrate in methanol. The final product, *viz*., (+)-(*S*)-gingerol (**143**), was prepared from the 4,5-dihydroisoxazole **144** in two steps. First, 4,5-dihydroisoxazole was reduced into the corresponding β-hydroxy ketone over Raney nickel under standard conditions. In this step, the diene group was partly reduced. The reduction was completed by catalytic hydrogenation over palladium.

* * *

The data presented in the rewiew illustrate the efficiency of the nitrile oxide-based approach as both an alternative to classical reactions employed in organic chemistry (*e.g.*, the aldol condensation) and an independent method aimed at the solution of complicated problems in the synthesis of pheromones, alkaloids, vitamins, monosaccharides, antibiotics, steroids and other natural compounds.

References

1. A A Akhrem, F A Lakhvich, V A Khripach *Khim. Geterotsikl. Soedin*. 1155 (1981) [a]
2. B H Lipshutz *Chem. Rev*. **86** 795 (1986)
3. S Kanemasa, O Tsuge *Heterocycles (Spec. Issue)* **30** 719 (1990)
4. A P Kozikowski *Acc. Chem. Res*. **17** 410 (1984)
5. F A Lakhvich, E V Koroleva, A A Akhrem *Khim. Geterotsikl. Soedin*. 435 (1989) [a]
6. A Annunziata, M Cinquini, F Cozzi, L Rainmondi *Gazz. Chim. Ital*. **119** 253 (1989)
7. P G Baraldi, A Barco, S Benetti, G P Pollini, D Simoni *Synthesis* 857 (1987)
8. C Grundman, P Grunangeger *The Nitrile Oxides* (Berlin: Springer, 1971)
9. T Mukaiyama, T Hoshino *J. Am. Chem. Soc*. **82** 5339 (1960)
10. C Grundmann, R Richter *J. Org. Chem*. **33** 476 (1968)
11. V Jäger, I Müller *Tetrahedron* **41** 3519 (1985)
12. P Caramella, P Grunangeger, in *1,3-Dipolar Cycloaddition Chemistry* (Ed. A Padwa) (New York: Wiley, 1984) p. 291
13. R V Stevens, N Beaulieu, W H Chan, A R Daniewski, T Takeda, A Waldner, P G Williard, U Zutter *J. Am. Chem. Soc*. **108** 1039 (1986)
14. G Kumaran, G H Kulkarni *J. Org. Chem*. **62** 1516 (1997)
15. T Shimizu, Y Hayashi, K Teramura *Bull. Chem. Soc. Jpn*. **57** 2531 (1984)
16. T Shimizu, Y Hayashi, H Shibafuchi, K Teramura *Bull. Chem. Soc. Jpn*. **59** 2827 (1986)
17. Y Basel, A Hassner *Synthesis* 309 (1997)
18. A Hassner, K M L Rai *Synthesis* 57 (1989)
19. D P Curran, C J Fenk *J. Am. Chem. Soc*. **107** 6023 (1985)
20. K B G Torssell *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis. Novel Strategies in Synthesis* (Purdue: Purdue University, 1987)
21. H Irngartinger, A Werber, T Escher *Liebigs Ann*. 1845 (1996)
22. A Diaz-Ortiz, E Diez-Darra, A De la Hoz, A Moreno, M J Gomez-Escalonilla, A Loupy *Heterocycles* **43** 1021 (1996)
23. A Corsaro, U Chiacchino, V Librando, S Fisichella, V Pistara *Heterocycles* **45** 1567 (1997)
24. R F Cunico, L Bedell *J. Org. Chem*. **48** 2780 (1983)
25. J N Kim, E K Ryu *Heterocycles* **31** 1693 (1990)
26. K H Schulte-Elte, B L Müller, G Ohloff *Helv. Chim. Acta* **56** 310 (1973)
27. P G Baraldi, A Barco, S Benetti, F Moroder, G P Pollini, D Simoni *J. Org. Chem*. **48** 1297 (1983)
28. A I Kotyatkina, V N Zhabinsky, V A Khripach, A de Groot *Collect. Czech. Chem. Commun*. **65** 1173 (2000)
29. G Buchi, J C Vederas *J. Am. Chem. Soc*. **94** 9128 (1972)
30. S Kashima, Y Yamamoto, Y Tsuda *J. Org. Chem*. **40** 526 (1975)
31. P G Baraldi, F Moroder, G P Pollini, D Simoni, A Barco, S Benetti *J. Chem. Soc., Perkin Trans. 1* 2983 (1982)
32. A P Kozikowski, S Goldstein *J. Org. Chem*. **48** 1139 (1983)
33. R Plate, P H H Hermkens, J M M Smits, R J F Nivard, H C J Ottenheijm *J. Org. Chem*. **52** 1047 (1987)
34. M Nitta, T Kobayashi *J. Chem. Soc., Perkin. Trans. 1* 1401 (1985)
35. N R Natale *Tetrahedron Lett*. **23** 5009 (1982)
36. M Kijima, Y Nambu, T Endo *J. Org. Chem*. **50** 1140 (1985)
37. P DeShong, J A Cipollina, N K Lowmaster *J. Org. Chem*. **53** 1356 (1988)
38. A A Akhrem, F A Lakhvich, V A Khripach, I B Klebanovich *Dokl. Akad. Nauk SSSR* **244** 615 (1979) [b]
39. D P Curran *J. Am. Chem. Soc*. **105** 5826 (1983)

40. A P Kozikowski, C-S Li *J. Org. Chem.* **52** 3541 (1987)
41. D P Curran, P B Jacobs, R L Elliott, B H Kim *J. Am. Chem. Soc.* **109** 5280 (1987)
42. D C Lathbury, P J Parsons *J. Chem. Soc., Chem. Commun.* 291 (1982)
43. I Müller, V Jäger *Tetrahedron Lett.* **23** 4777 (1982)
44. R Annunziata, M Cinquini, F Cozzi, A Restelli *J. Chem. Soc., Perkin Trans. 1* 2293 (1985)
45. E P Schreiner, H Gstach *Synlett* 1131 (1996)
46. R Annunziata, M Cinquini, F Cozzi, A Gilardi, A Restelli *J. Chem. Soc., Perkin Trans. 1* 2289 (1985)
47. A P Kozikowski, M Adamczyk *J. Org. Chem.* **48** 366 (1983)
48. P G Baraldi, A Barco, S Benetti, S Manfredini, D Simoni *Synthesis* 276 (1987)
49. A P Kozikowski, M Adamczyk *Tetrahedron Lett.* **23** 3123 (1982)
50. R E Erickson, P J Andrulis Jr, J C Collins, M L Lungle, G D Mercer *J. Org. Chem.* **34** 2961 (1969)
51. J W Westley *Adv. Appl. Microbiol.* **22** 177 (1977)
52. R Baker, R H Herbert, A H Parton *J. Chem. Soc., Chem. Commun.* 601 (1982)
53. D G Lynn, N J Phyllips, W C Hutton, J Shabanowitz, D I Fennell, R J Cole *J. Am. Chem. Soc.* **104** 7319 (1982)
54. A P Kozikowski, J G Scripko *J. Am. Chem. Soc.* **106** 353 (1984)
55. S R Schow, J D Bloom, A S Thompson, K N Winzenberg, A B Smith III *J. Am. Chem. Soc.* **108** 2662 (1986)
56. H Maishima, M Kurabayashi, C Tamura *Tetrahedron Lett.* 711 (1975)
57. J R Egerton, D A Ostlind, L S Blair, C H Eary, D Suhayda, S Cifelli, R F Riek, W F Campbell *Antimicrob. Agents. Chemother.* **15** 372 (1979)
58. M Ono, H Mishima, Y Takiguchi, M Terao *J. Antibiot.* **36** 509 (1983)
59. H Mishima, J Ide, S Muramatsu, H Ono *J. Antibiot.* **36** 980 (1983)
60. A P Kozikowski, X-M Cheng *Tetrahedron Lett.* **28** 3189 (1987)
61. S Nakatsuka, T Masuda, O Asano *Tetrahedron Lett.* **27** 4327 (1986)
62. S M Kupchan, E J LaVoie, A R Branfman, B Y Fei, W M Bright, R F Bryan *J. Am. Chem. Soc.* **99** 3199 (1977)
63. G R Pettit, G M Cragg, D Gust, P Brown, J M Schmidt *Can. J. Chem.* **60** 939 (1982)
64. G R Pettit, G M Cragg, M I Suffness, D Gust, F E Boettner, M Williams, J A Saenz-Renauld, P Brown, J M Schmidt, P D Ellis *J. Org. Chem.* **49** 4258 (1984)
65. P R McGuirk, D B Collum *J. Org. Chem.* **49** 843 (1984)
66. A B Smith III, M Fukui *J. Am. Chem. Soc.* **109** 1269 (1987)
67. S D Burke, J E Cobb, K Takeuchi *J. Org. Chem.* **50** 3420 (1985)
68. A B Smith III, R A Rivero *J. Am. Chem. Soc.* **109** 1272 (1987)
69. S F Martin, M S Dappen, B Dupré, C J Murthy, J A Colapret *J. Org. Chem.* **54** 2209 (1989)
70. B Blumberg *Semin. Cell Dev. Biol.* **8** 417 (1997); *Chem. Abstr.* **127** 290 808 (1997)
71. D M Kochhar *Handb. Exp. Pharmacol.* **124** 3 (1997); *Chem. Abstr.* **126** 98 741 (1997)
72. R S H Liu, A E Asato *Tetrahedron* **40** 1931 (1984)
73. J Otera, H Misawa, T Onishi, S Suzuki, Y Fujita *J. Org. Chem.* **51** 3834 (1986)
74. P G Baraldi, A Barco, S Benetti, M Guarneri, S Manfredini, G P Pollini, D Simoni *Tetrahedron Lett.* **29** 1307 (1988)
75. R S Ward *Chem. Soc. Rev.* **11** 75 (1982)
76. R S Ward *Tetrahedron* **46** 5029 (1990)
77. E Bianchi, M E Caldwell, J R Cole *J. Pharm. Sci.* **57** 195 (1968)
78. Z Getahum, L Jurd, P S Chu, C M Lin, E Hamel *J. Med. Chem.* **35** 1058 (1992)
79. T Morimoto, M Chiba, K Achiwa *Heterocycles* **33** 435 (1992)
80. N Rehnberg, G Magnusson *J. Org. Chem.* **55** 4340 (1990)
81. N Rehnberg, G Magnusson *Tetrahedron Lett.* **29** 3599 (1988)
82. M P Sibi, J A Gaboury *Synlett* 83 (1992)
83. J A Gaboury, M P Sibi *J. Org. Chem.* **58** 2173 (1993)
84. N B Perry, J W Blunt, M H G Munro, L K Pannell *J. Am. Chem. Soc.* **110** 4850 (1988)
85. X Ye, Y Quiang *Weishengwu Xuebao* **27** 156 (1987); *Chem. Abstr.* **107** 112 294 (1987)
86. S J Danishefsky, M P DeNino *Angew. Chem., Int. Ed. Engl.* **26** 15 (1987)
87. S Jeganathan, P Vogel *J. Chem. Soc., Chem. Commun.* 993 (1989)
88. R M Paton, A A Young *J. Chem. Soc., Chem. Commun.* 132 (1991)
89. K Krohn *Angew. Chem., Int. Ed. Engl.* **25** 790 (1986)
90. K Krohn *Tetrahedron* **46** 291 (1990)
91. Y Kita, M Kirihara, J Sekihachi, R Okunaka, M Sasho, S Mohri, T Honda, S Akai, Y Tamura, K Shimooka *Chem. Pharm. Bull.* **38** 1836 (1990)
92. Y Kita, M Kirihara, Y Fujii, R Okunaka, S Akai, H Maeda, Y Tamura, K Shimooka, H Ohushi, T Ishida *Chem. Pharm. Bull.* **39** 857 (1991)
93. R Alguacil, F Farina, M V Martin *Tetrahedron* **52** 3457 (1996)
94. R Alguacil, F Farina, M V Martin, M C Paredes *Tetrahedron Lett.* **36** 6773 (1995)
95. G C Harbour, A A Tymiac, K L Rinehart Jr, P D Shaw, R G Hughes, Jr, S A Mizak, J H Coats, G E Zurenko, L H Li, S L Kuentzel *J. Am. Chem. Soc.* **103** 5604 (1981)
96. A Hassner, K S K Murthy *Tetrahedron Lett.* **27** 1407 (1986)
97. B B Snider, W C Faith *J. Am. Chem. Soc.* **106** 1443 (1984)
98. A E Walts, W R Roush *Tetrahedron* **41** 3623 (1985)
99. C C Chang, K Nakanishi *J. Chem. Soc., Chem. Commun.* 605 (1983)
100. E van der Eycken, J van der Eycken, M Vandewalle *J. Chem. Soc., Chem. Commun.* 1719 (1985)
101. F J Zeelen, M B Groen *Recl. Trav. Chim. Pays-Bas* **105** 465 (1986)
102. F J Zeelen *Nat. Prod. Rep.* 607 (1994)
103. G Stork, J E McMurry *J. Am. Chem. Soc.* **89** 5464 (1967)
104. J W Scott, G Sausy *J. Org. Chem.* **37** 1652 (1972)
105. M Ihara, Y Tokunaga, K Fukumoto *J. Org. Chem.* **55** 4497 (1990)
106. K S K Murthy, A Hassner *Tetrahedron Lett.* **28** 97 (1987)
107. K Shishido, Y Tokunaga, N Omachi, K Hiroya, K Fukumoto, T Kametani *J. Chem. Soc., Chem. Commun.* 1093 (1989)
108. N Zein, A M Sinha, W J McGahren, G A Ellestad *Science* **240** 1198 (1988)
109. N Zein, M Poncin, R Nilakantan, G A Ellestad *Science* **244** 697 (1988)
110. K C Nicolaou, W-M Dai *Angew. Chem., Int. Ed. Engl.* **30** 1387 (1991)
111. W -d Ding, G A Ellestad *J. Am. Chem. Soc.* **113** 6617 (1991)
112. P Magnus, P A Carter *J. Am. Chem. Soc.* **110** 1626 (1988)
113. J N Haseltine, S J Danishefsky, G Schulte *J. Am. Chem. Soc.* **111** 7638 (1989)
114. S L Schreiber, L L Kiessling *J. Am. Chem. Soc.* **110** 631 (1988)
115. P Magnus, H Annoura, J Harling *J. Org. Chem.* **55** 1709 (1990)
116. J N Haseltine, M P Cabal, N B Mantlo, N Iwasawa, D S Yamashita, R S Coleman, S J Danishefsky, G K Schulte *J. Am. Chem. Soc.* **113** 3850 (1991)
117. K C Nicolaou, D Clark *Angew. Chem., Int. Ed. Engl.* **31** 855 (1992)
118. R L Halcomb, M D Wittman, S H Olson, S J Danishefsky, J Golik, H Wong, D Vyas *J. Am. Chem. Soc.* **113** 5080 (1991)
119. A L Smith, E N Pitsinos, C-K Hwang, Y Mizuno, H Saimoto, G R Scarlato, T Suzuki, K C Nicolaou *J. Am. Chem. Soc.* **115** 7612 (1993)
120. K C Nicolaou, C W Hummel, M Nakada, K Shibayama, E N Pitsinos, H Saimoto, Y Mizuno, K-U Baldenius, A L Smith *J. Am. Chem. Soc.* **115** 7625 (1993)
121. T K M Shing, C-H Wong, T Yip *Tetrahedron Asymmetry* **7** 1323 (1996)
122. R M Konojia, E Chin, C Smith, R Chen, D Rowand, S D Levine, M P Wachter, R E Adams, D W Hahn *J. Med. Chem.* **28** 796 (1985)
123. D W Hahn, A J Tobia, H E Rosenthale, J L McGuire *Contraception* **26** 133 (1984)
124. S D Levine, R E Adams, R Chen, M L Cotter, A F Hirsch, V V Kane, R M Kanojia, C Shaw, M P Wachter, E Chin, R Huettemann, P Ostrowski, J L Mateos, L Noriega, A Guzmán, A Mijarez, L Tovar *J. Am. Chem. Soc.* **101** 3404 (1979)
125. R C Cookson, N J Liverton *J. Chem. Soc., Perkin Trans. 1* 1589 (1985)
126. K C Nicolaou, D A Claremon, W E Barnette *J. Am. Chem. Soc.* **102** 6611 (1980)
127. B M Trost, P D Greenspan, H Geissler, J H Kim, N Greeves *Angew. Chem., Int. Ed. Engl.* **33** 2182 (1994)
128. B de Lange, B L Feringa *Tetrahedron Lett.* **29** 5317 (1988)
129. S Kanemasa, T Hayashi, H Yamamoto, E Wada, T Sakurai *Bull. Chem. Soc. Jpn.* **64** 3274 (1991)

130. D P Curran, B H Kim, H P Piyasena, R J Loncharich, K N Houk *J. Org. Chem.* **52** 2137 (1987)
131. T Olsson, K Stern *J. Org. Chem.* **53** 2468 (1988)
132. D P Curran, K-S Jeong, T A Heffner, J Rebek Jr *J. Am. Chem. Soc.* **111** 9238 (1989)
133. W Oppolzer, G Poli, C Starkemann, G Bernardinelli *Tetrahedron Lett.* **29** 3559 (1988)
134. W Oppolzer *Tetrahedron* **43** 1969 (1987)
135. T Le Gall, J-P Lellouche, L Toupet, J-P Beaucourt *Tetrahedron Lett.* **30** 6517 (1989)
136. S Dare, B Ducroix, S Bernard, K M Nicholas *Tetrahedron Lett.* **37** 4341 (1996)
137. D P Curran, T A Heffner *J. Org. Chem.* **55** 4585 (1990)
138. I Kubo, T Matsumoto, D L Wagner, J N Shoolery *Tetrahedron Lett.* **26** 563 (1985)
139. J P Vita, W Franke *Naturwissenschaften* **63** 550 (1976)
140. Y Naya, M Kotake *Tetrahedron Lett.* 2459 (1967)
141. T Le Cull, J-P Lellouche, J-P Beaucourt *Tetrahedron Lett.* **30** 6521 (1989)
142. D W Connell, M D Sutherland *Austr. J. Chem.* **22** 1033 (1969)
143. T Murata, M Shinohara, M Miyamoto *Chem. Pharm. Bull.* **20** 2291 (1972)
144. M Kobayashi, N Shoji, Y Ohizumi *Biochim. Biophys. Acta* **903** 96 (1987)
145. S Gerner, G Flanz *Deutsch. Apoth. Ztg.* **137** 4260 (1997); *Chem. Abstr.* **128** 7427 (1997)

[a] — *Chem. Heterocycl. Compd. (Engl. Transl.)*
[b] — *Dokl. Chem. Technol., Dokl. Chem. (Engl. Transl.)*