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Optically Active Isoxazolidines *via* Asymmetric Cycloaddition Reactions of Nitrones with Alkenes: Applications in Organic Synthesis

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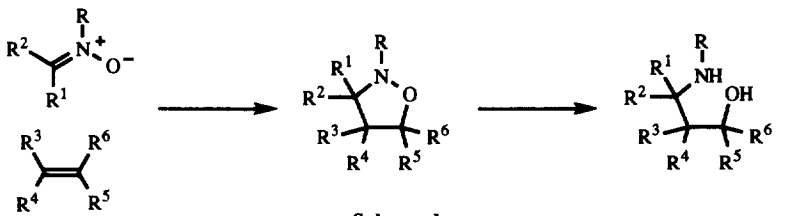
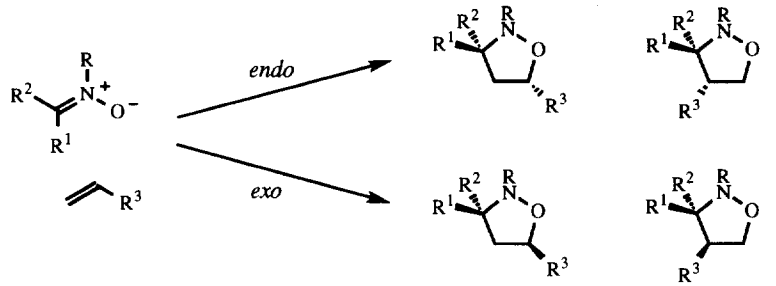
1. Introduction and scope

Isoxazolidines, the products of 1,3-dipolar cycloaddition reactions[1-8] between nitrones and alkenes, are saturated, five membered heterocycles containing adjacent nitrogen and oxygen atoms. As a result of the labile nature of the N-O bond under mildly reducing conditions, isoxazolidines have long been regarded as important synthetic intermediates and have been extensively utilized as 1,3-amino alcohol equivalents *en route* to a wide variety of natural products and related molecules, particularly alkaloids,[8] amino acids and amino-sugars.



Scheme 1

The 1,3-dipolar cycloaddition reaction between a nitrone and an alkene (*Scheme 1*) is an extremely powerful synthetic method for the creation of complex heterocyclic structures. Best regarded as a concerted but asynchronous [4π+2π] suprafacial process, the reaction allows up to three contiguous carbon stereocentres to be created in a single step. In a manner analogous to the famous [4π+2π] cycloaddition reactions first noted by Diels and Alder,[9] nitrone-alkene cycloadditions can occur with the nitrone and alkene approaching each other in either of two possible regiochemical senses and in either an *endo*- or *exo*- fashion, the four possible transition states giving rise to two pairs of regioisomeric and diastereoisomeric products (*Scheme 2*).



Scheme 2

Much has been written regarding the regioselectivity and stereoselectivity[3,4] in both intermolecular[5] and intramolecular[6] nitrone-alkene cycloadditions; copious research in this area has allowed the formulation of a set of 'rules of thumb' that, in the absence of overriding steric constraints, allow the prediction of the major products of a particular reaction based upon the electronic characteristics and substitution patterns of both the nitrone and alkene.

More recently, many researchers have switched their attention towards the development of methods for the preparation of non-racemic isoxazolidines and a growing body of literature appeared reflects these endeavours. This review represents a collation of this literature (up until the end of July 1996) concerning the use of nitrone-alkene cycloaddition reactions for the preparation of optically active isoxazolidines with particular emphasis being placed on their use in the synthesis of natural products and other biologically active molecules.

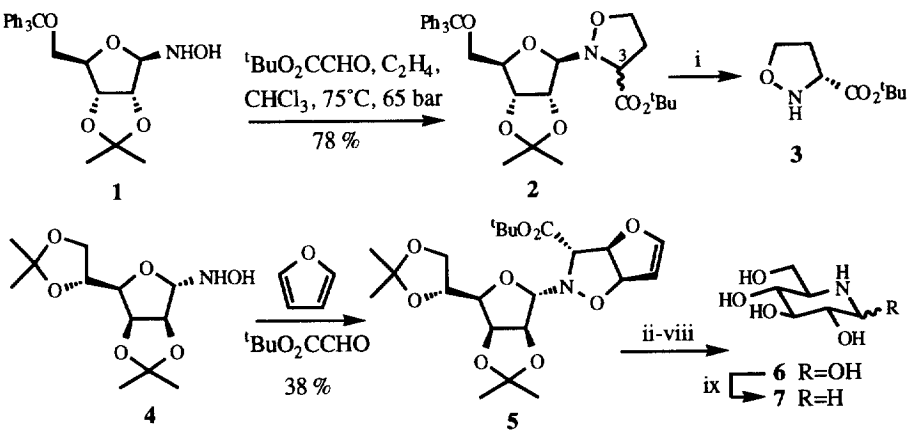
2. Intermolecular cycloadditions

2.1 Optically active nitrones[10-49]

Much has been reported on the use of chiral pool derived precursors to prepare optically active nitrones for application to the syntheses of among other things nucleoside analogues,[12] amino acids and amino sugars,[14-16,19-23] alkaloids and related compounds,[24-31] penem and carbapenem antibiotics[32-38] and vitamin D analogues.[39,40] The pioneering work in the late 1970's by Belzecki,[10,11] Vasella[12-18] and their co-workers demonstrated that relatively simple chiral substituents attached to the nitrone either through nitrogen[10-18] or carbon[11] resulted in the formation

of optically active isoxazolidines upon cycloaddition with an achiral alkene, diasteromeric excesses depending largely upon the choice of chiral substituent.

Vasella's excellent and extensive work involving the use of furanoside and pyranoside hydroxylamines as nitrone precursors proved to be particularly versatile, allowing the synthesis of several interesting biologically active molecules (or their analogues) including nucleosides,[12] proline,[14,16] nojirimycin[15] and captopril;[16] the high diastereoselectivities (up to around 90%) noted in the cycloaddition steps of these syntheses being attributed to the influence of a kinetic anomeric effect.[18] Thus, the D-ribosyl hydroxylamine **1** condensed with *tert*-butyl glyoxylate and the resulting nitrone underwent a cycloaddition reaction with ethene to afford high yields of chromatographically separable isoxazolidines **2** (d.e. 72%) from which the (3*R*)-isomer was readily converted to the D-proline analogue **3**.[14] Similarly, the corresponding nitrone derived from D-mannosyl derivative **4** reacted with furan to afford solely isoxazolidine **5** (38%), which was transformed (seven steps) to (+)-nojirimycin **6** and thence to its 1-deoxy analogue **7**.[15]

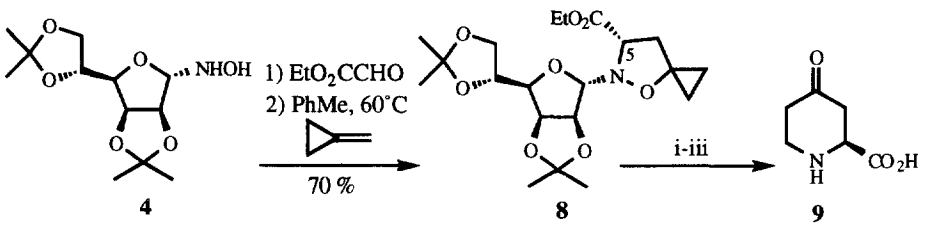


Reagents: i, HCl, MeOH, 20°C; ii, NMO, OsO_4, Me_2CO, H_2O, 60°C; iii, $FeCl_3$, SiO_2, Me_2CO, 0°C; iv, Raney Ni, H_2, 60 bar, EtOH, 60°C; v, TFA, BuCl, 20°C; vi, $LiBH_4$, THF, 20°C; vii, 10% Pd/C, H_2, EtOAc, EtOH, 20°C; viii, Dowex 1x2 (OH), H_2O, 20°C; ix, Pt, H_2, EtOH, H_2O, 20°C

Overton has described the use of nitrones containing the chiral α-methylbenzyl group attached through nitrogen in the synthesis of several amino acids and peptides including both enantiomers of β-lysine[19,20] as well as aspartame and its (*R*)-aspartyl isomer.[21] Ganem has similarly utilized this chiral substituent in the total synthesis of (+)-hypusine[22] an unusual polyamine first isolated from bovine brain extracts. The findings of these workers essentially mirrored those of Belzecki[10] who had previously observed that this cheap and readily available chiral substituent was of somewhat limited use in these reactions when attached through nitrogen giving rise to complex mixtures of products with variable levels of diastereoselectivity.

The increased stereoselectivities afforded by Vasella's chiral sugar derived auxiliaries, where restricted rotation around the C-N bond results in greater degrees of chiral discrimination have been

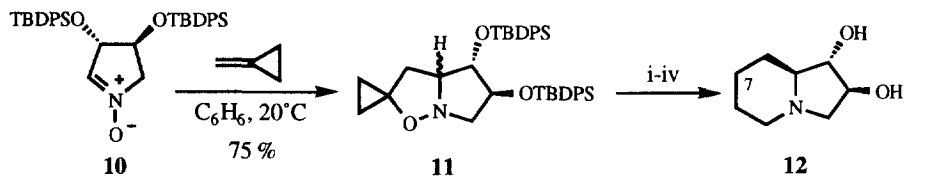
neatly utilized by Brandi and co-workers in the synthesis of the the unusual amino acid (2*S*)-4-oxopipecolic acid **9**.[23] The enantiopure nitrone derived from hydroxylamine **4** and ethyl glyoxylate reacted smoothly with methylenecyclopropane (sealed tube) to afford a separable mixture of isoxazolidine **8** and its C-5 epimer (3:1 ratio) together with traces of a regioisomeric 4-cyclopropanoisoxazolidine. Thermal rearrangement of **8** (xylene, 140°C, 4 hours) afforded the *N*-mannosyl pipecolic ester (50%), which yielded the free amino acid **9** over a further two steps.



4 **8** **9**

Reagents: i, xylene, 140°C; ii, TFA, EtOH 20°C; iii, 6M HCl, 20°C

Brandi has also utilized this 5-aza-4-oxaspiro[2.4]heptane → 4-piperidone rearrangement in the syntheses of a series of homochiral indolizidines[24-26] similar to castanospermine and swainsonine, these potent glycosidase inhibitors having been prepared in good yield from enantiopure cyclic nitrones derived from tartaric[24,25] and malic acids.[26] L-Tartrate derived nitrone **10** reacted with methylenecyclopropane in benzene to afford a separable mixture of isoxazolidines **11** (75% yield, 10:1 ratio) the appropriate isomer of which was converted *via* a similar thermal rearrangement-deprotection sequence to afford lentiginosine **12**,[24] reduction of an intermediate bicyclic ketone also affording a pair of epimeric C-7 hydroxylated indolizidines.[25] Workers in Edinburgh have utilized a similar L-tartrate derived nitrone in cycloaddition reactions with *O*-protected allyl alcohol to prepare homochiral hydroxylated pyrrolizidines.[27] Other related cycloadditions utilizing chiral cyclic nitrones[28] or Vasella's sugar derived approach[29] have allowed syntheses of (-)-allosedamine,[28] (+)-negamycin[29] and (-)-epinegamycin[29] to be realized.

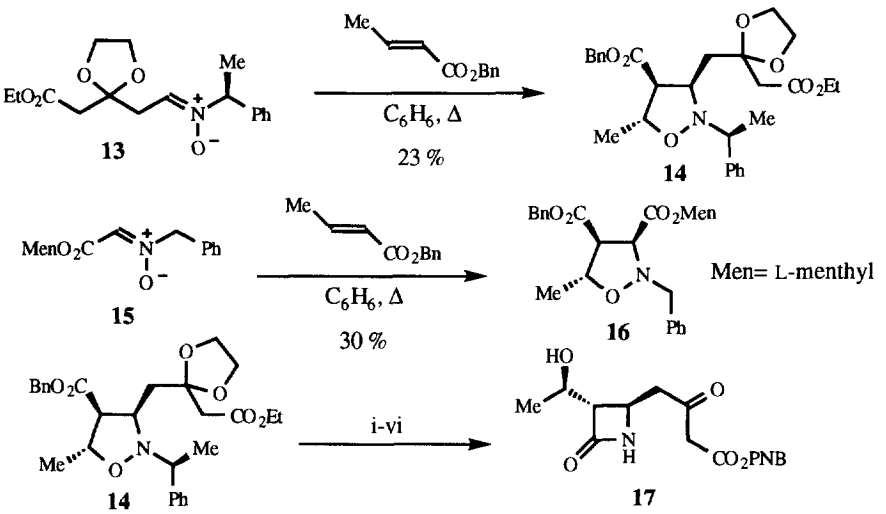


10 **11** **12**

Reagents: i, xylene, 140°C; ii, $TsNHNH_2$, MeOH, 20°C; iii, $NaBH_4$, MeOH, 65°C; iv, 40% aq. HF, MeCN, 20°C

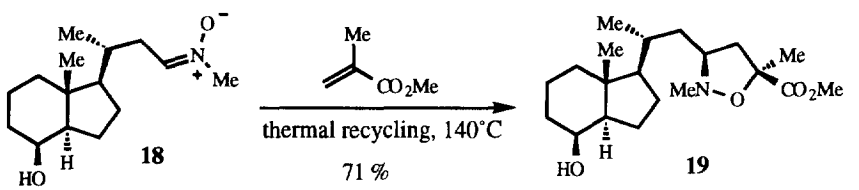
Several researchers[32-38] have utilized chiral nitrones in the syntheses of a series of specifically substituted β-lactams as precursors to naturally occuring and synthetic penems and carbapenems. In particular, Kametani's group have prepared a series of valuable penem and carbapenem precursors,[32-36] however, yields of the desired isoxazolidine cycloadducts were low due once

again[10,11] to the rather poor chiral discrimination offered by both the α-methylbenzyl and L-menthyl substituents, which resulted in the formation of complex mixtures of regio- and stereoisomeric products. Treatment of nitrones **13** and **15** with benzyl crotonate in refluxing benzene afforded low isolated yields of cycloadducts **14** and **16** (together with several stereoisomeric products); isoxazolidine **14** was subsequently converted over six steps to β-lactam **17**, a precursor to the antibiotic (+)-thienamycin.



Reagents: i, 10% Pd/C, H_2, 4·5 bar, AcOH, 20°C; ii, DCC, MeCN, 60°C; iii, TBDMSCl, Et_3N, DMF, 20°C; iv, NaOH, H_2O, THF, 20°C; v, PNBBr, DMF, 20°C; vi, HCl, MeOH, 5°C

Use of chiral nitrone precursors have been also reported for the syntheses of several cholecalciferol and ergocalciferol (vitamins D_3 and D_2) analogues,[39,40] perhaps the most interesting facet of this technique being that the required products do not contain nitrogen. Workers at Hoffman-La Roche[39] have developed an elegant strategy for the synthesis of isoxazolidine **19**. Treatment of nitrone **18** with methyl methacrylate at room temperature afforded a complex mixture of stereoisomeric isoxazolidines (36:45:7:12 ratio) from which the required (3*S*,5*S*)-isomer **19** was readily separable, thermal isomerization of the mixture of unwanted isomers in xylene at 140°C affording **19** in yields of up to 71%. Nitrogen quaternization, N-O bond cleavage and Hofmann elimination afforded the required non-nitrogenous intermediate *en route* to vitamin D_3 analogues.

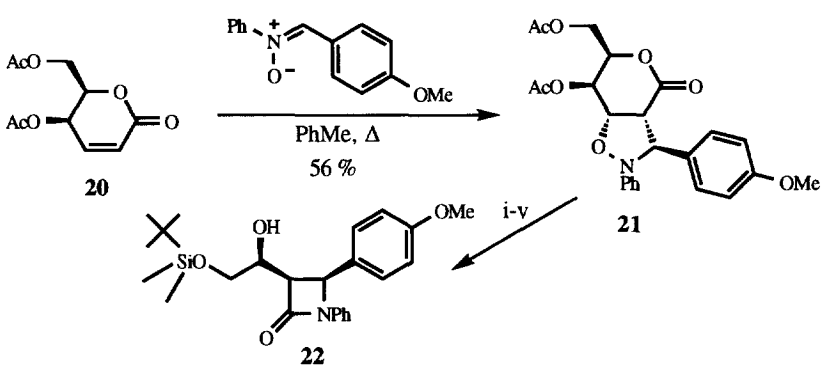


Amongst the other various uses of chiral nitrones in intermolecular cycloadditions the formation of isoxazolidines from *unprotected* sugars have been described[41,42] as has the synthesis of some novel spiro-isoxazolidines.[43] The kinetic resolution of racemic phospholes by preferential reaction of one enantoimer with L-tartrate derived nitrones has been briefly examined by Brandi and co-workers (e.e. of around 50-60% for recovered phosphole)[44] as has the use of chiral chromium(0) complexed nitrones in synthesis by Japanese workers.[45,46] More recently the use of Lewis acid (TMSOTf) to promote reaction between a chiral lactaldehyde derived nitrone and 2-trimethylsilyloxyfuran has been reported.[47]

2.2 Optically active alkenes[50-83]

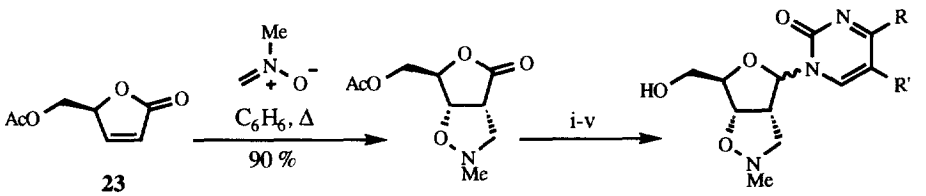
Earliest experiments in this area were concerned with the addition of 1,3-dipoles to various α,β-unsaturated natural products and related compounds including lumisantonin,[50] the steroidal skeleton[51] and elaiophylin.[52] Accordingly, later work has focused mostly on the use of chiral α,β-unsaturated carbonyl compounds chiefly lactones,[53-61] esters[62-65] and amides[66] mostly derived from sugars and related materials. The synthetic utilities of chiral allylic amines,[67-71] vinylic and allylic ethers,[72-77] vinylic sulphoxides[78-81] and vinylic phosphine oxides[82,83] as precursors to optically active isoxazolidines have also been demonstrated.

Most studies concerned with the reactions between achiral nitrones and chiral α,β-unsaturated carbonyl compounds have concentrated mainly upon the product distribution in terms of regio-, stereo- and facioselectivity in the 1,3-dipolar cycloaddition step. Extensive studies conducted by Polish and British research groups involving the use of chiral sugar derived lactones have shown that simple nitrones react with these materials both regio- and faciospecifically and with high levels of stereoselectivity.[53-58] The Polish workers demonstrated the synthetic utility of their studies by reporting the synthesis of enantiopure β-lactams.[54,56] Lactone **20** underwent a regio- stereo- and faciospecific reaction with *C*-(4-methoxyphenyl)-*N*-phenylnitrone to afford bicyclic isoxazolidine **21** in good yield, subsequent N-O bond cleavage resulted in concomitant β-lactam formation allowing the formation of **22** over a further five steps (60% yield).



Reagents: i, NaOMe, MeOH, 20°C; ii, $NaIO_4$, MeOH, H_2O, 20°C; iii, $NaCNBH_3$, 2M HCl, MeOH, 20°C; iv, TBDMSCl, imidazole, DMF, 20°C; v, 10% Pd/C, H_2, MeOH, 20°C

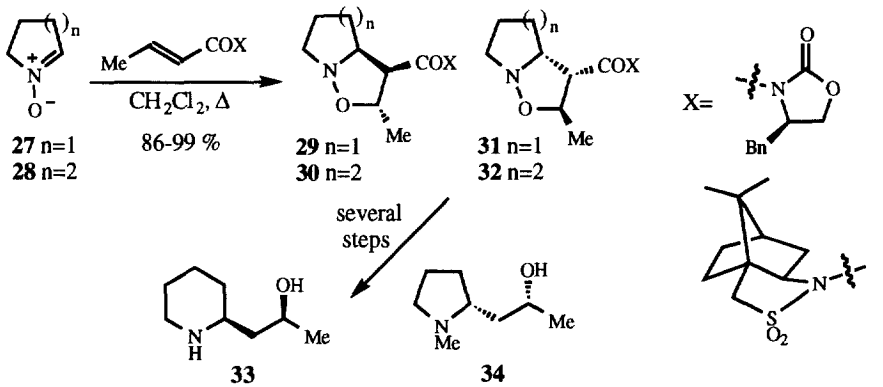
Very recent work described by researchers in New York[59] has utilized these early findings to allow the synthesis of some modified bicyclo[3.3.0] isoxazolidinyl nucleosides as part of a programme aimed at the synthesis of novel anti-HIV agents. Treatment of lactone **23** with the nitrone derived from *N*-methylhydroxylamine and paraformaldehyde in hot benzene afforded a single isoxazolidine **24** in excellent yield. Subsequent manipulation afforded the pyrimidine nucleoside analogues **25** and **26** (both anomers) in good yield over a further five steps.



23 **24** **25** R=NH_2, R'=H; **26** R=OH, R'=Me

Reagents: i, DIBAL, CH_2Cl_2, -78°C; ii, AcCl, Et_3N, CH_2Cl_2, 20°C; iii, silylated pyrimidine, CH_2Cl_2, TMSOTf, 20°C; iv, TBAF, THF, 20°C; v, NH_3, MeOH, 20°C

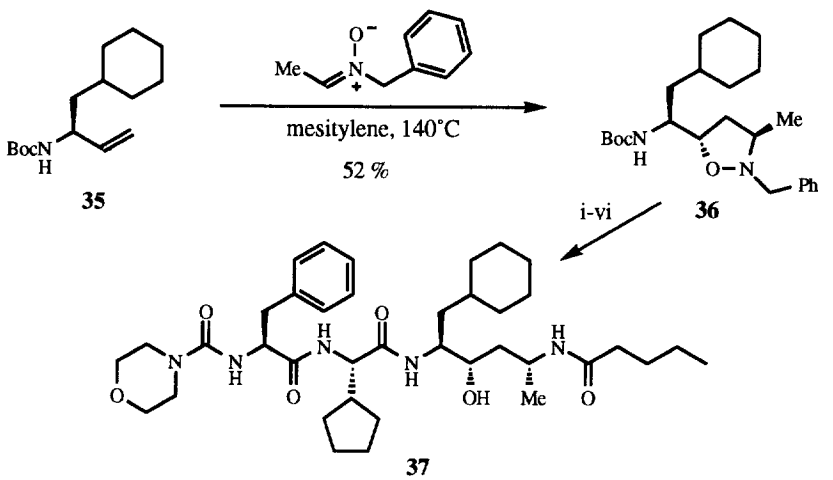
Murahashi has utilized chiral α,β-unsaturated amides[66] as isoxazolidine precursors and has elegantly exploited both *N*-crotonyl sultams and 2-oxazolidinones in the asymmetric syntheses of the β-amino alcohols (+)-sedridine **33** and (+)-hygroline **34**. Cyclic nitrones **27** and **28** reacted with chiral crotonamide to afford mixtures of *endo*-adducts **29/31** and **30/32** in excellent yield, hydrolysis, Barton decarboxylation and hydrogenolysis of **30** (X=sultam) afforded (+)-sedridine **33**; similar treatment of **31** (with *N*-methylation prior to N-O bond cleavage) yielded (+)-hygroline **34**.



27 n=1 **28** n=2 **29** n=1 **30** n=2 **31** n=1 **32** n=2 **33** **34**

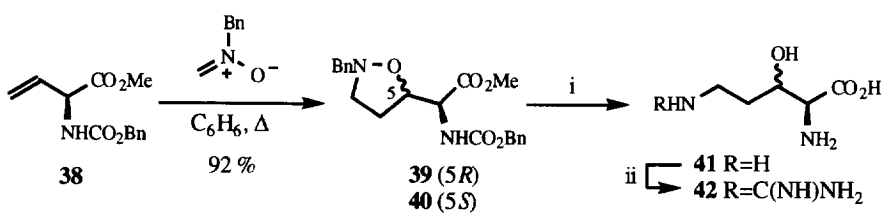
Reagents: For **30**→**33**: i, LiOH; ii, ^{i}BuOCOCl, *N*-methyl morpholine; iii, 2-thiopyridine-*N*-oxide, Et_3N; ^{t}BuSH, hν; iv, H_2, Pd/C. For **31**→**34**: i, LiOH; ii, ^{i}BuOCOCl, *N*-methyl morpholine; iii, 2-thiopyridine-*N*-oxide, Et_3N; ^{t}BuSH, hν; iv, MeI; v, H_2, Pd/C

Chiral allylic amines used in similar studies for the syntheses of a number of diverse natural products and related biologically active molecules have invariably been derived from L-α-amino acids.[67-71] The *N*-Boc protected amine **35** (from phenylalanine) has been cleverly utilized[68] in the synthesis of a novel renin inhibitor **37** which has potential utility in the treatment of hypertension. Cycloaddition between allylamine **35** and *N*-benzyl-*C*-methylnitrone afforded isoxazolidine **36**, which was converted into the required polyamidic renin inhibitor **37** over a further six steps.



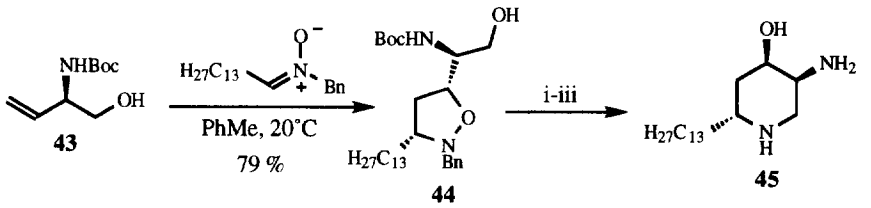
Reagents: i, HCO_2NH_4, 10% Pd/C, MeOH, 64°C; ii, $(BuCO)_2O$, Et_3N, MeOH; iii, 4M HCl, dioxane; iv, (*S*)-cyclopentylglycine, DCC, HOBT, $^iPr_2EtN$; v, 4M HCl, dioxane; vi, morpholinocarbonyl-Phe, DCC, HOBT, $^iPr_2EtN$

Independent studies by workers in Oregon and Maryland have demonstrated the synthetic utility of chiral vinylglycine derivatives in the syntheses of (3*R*)- and (3*S*)-hydroxyorthinine **41** and arginine **42**.[69,70] Thus, olefin **38** reacted smoothly with the nitrone prepared *in situ* from paraformaldehyde and *N*-benzylhydroxylamine at 80°C to afford **39** and **40** (92%, 3:2 mixture), which proved to be chromatographically separable after ester hydrolysis. Hydrogenolysis afforded the 3-hydroxyorthinines **41**[69,70] from which the 3-hydroxyarginines **42** were prepared.[69]



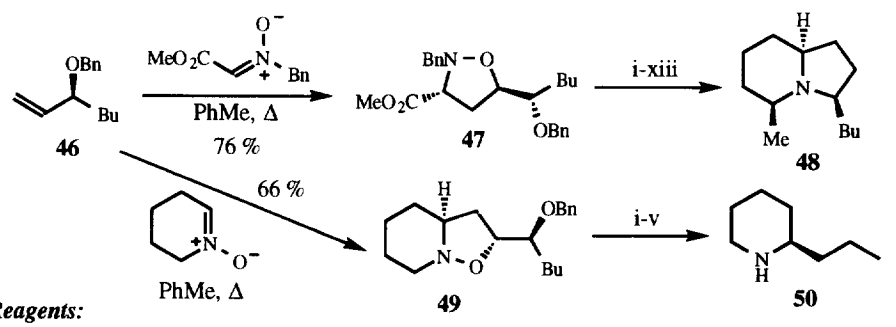
Reagents: i, $Pd(OH)_2/C$, H_2, 50 psi, 6M HCl, EtOH; ii, *S*-methyl isothiourea sulfate, basic copper carbonate, NaOH, H_2O, pH 9·7

Japanese workers have developed an extremely efficient large scale synthesis of the alkaloid (2*R*,4*R*,5*S*)-tetrahydropseudodistomin **45** by utilizing nitrone cycloaddition to a chiral vinylglycinol derivative **43**.[71] Allylamine **43** reacted readily with a tetradecanal derived nitrone to afford high yields of a four component mixture of isoxazolidines (79%) from which the requires stereoisomer **44** was readily isolated. Mesylation of **44** followed by hydrogenolysis of the resulting bicyclic mesylate salt afforded the required piperidine **45** in 67% yield. This is a remarkably attractive synthesis compared to the previously reported 24 step marathon.



Reagents: i, MsCl, C_5H_5N, 0°C; ii, 10% $Pd(OH)_2/C$, H_2, MeOH, 20°C; iii, TFA, CH_2Cl_2, 20°C

Although the use of chiral vinyl ethers in these cycloadditions has received little attention,[72] the use of chiral allylic ethers[73-77] has been championed by Kibayashi's group, who have prepared several natural products by these methods including (+)-monomorine I **48**,[73,74] (–)-coniine **50**[75] and (–)-oncinotine **54**.[76] Allylic ether **46** afforded a 3:1 mixture of isoxazolidines upon reaction with a glyoxylate derived nitrone at 110°C (76%), from which the required major isomer **47** was readily isolated; thirteen further synthetic steps yielded the bicyclic amine (+)-monomorine I **48**.[73,74] A similar reaction between **46** and 2,3,4,5-tetrahydropyridine-1-oxide afforded a mixture of cycloadducts (66%, 4:1 ratio), the major isomer **49** being utilized *en route* to (–)-coniine **50**.[75]

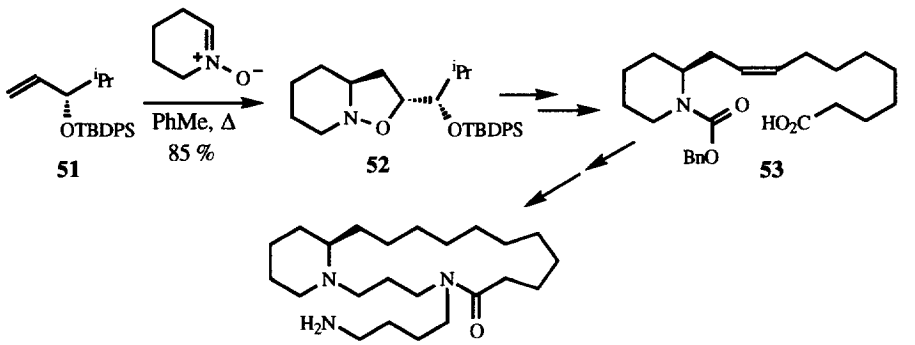


Reagents:

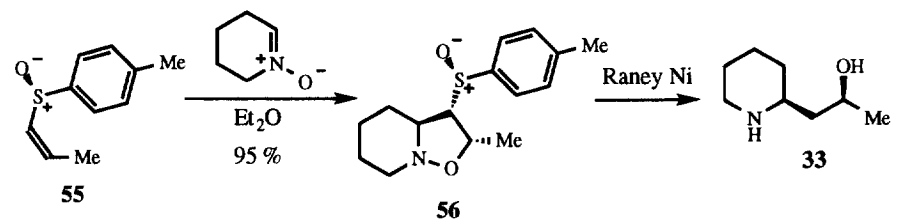
For **47**→**48**: i, $LiAlH_4$, Et_2O; ii, TsCl, DMAP, $^iPr_2EtN$, CH_2Cl_2; iii, NaI, MeCOEt; iv, $CH_2CH(CH_2)_2MgBr$, (2-thienyl)Cu(CN)Li, THF, -78°C→0°C; v, Zn, AcOH, H_2O, THF, 60°C; vi, BnOCOCl, Na_2CO_3; vii, O_2, $PdCl_2$, $CuCl_2$, DMF, H_2O, 80°C; viii, 10% Pd/C, H_2, MeOH, HCl; ix, BnBr, Na_2CO_3, DMF, 70°C; x, MsCl, Et_3N, CH_2Cl_2, -20°C; xi, 10% Pd/C, H_2, MeOH, dioxane; xii, Et_3N, CH_2Cl_2, 40°C; xiii, 10% Pd/C, H_2, Et_3N, MeOH.

For **49**→**50**: i, H_2, $PdCl_2$, MeOH; ii, BnOCOCl, Na_2CO_3, CH_2Cl_2; iii, HIO_4, THF, H_2O; iv, Ph_3PMeBr, BuLi, THF; v, Pd/C, H_2, MeOH

Extension of these ideas allowed the synthesis of (–)-oncinotine **54**.[76] Silyl ether **51** yielded isoxazolidine **52** (85%), which was converted over several steps to the advanced acid intermediate **53** serving as a precursor to the naturally occuring macrocycle **54**.



Chiral vinyl sulphoxides[78-81] have been rather surprisingly under utilized in the syntheses of natural products and related materials by nitrone cycloaddition strategies. Workers in Japan have described the syntheses of *iso*-ephedrines from (*R*)-(+)-*p*-tolyl vinyl sulphoxide[78] a strategy that has been extended to the synthesis of enantiopure fluorinated isoxazolidines.[80] Chiral sulphoxide **55** has been shown to react cleanly, if somewhat slowly (7 days), in diethyl ether with 2,3,4,5-tetrahydropyridine-1-oxide to afford excellent yields of **56**, contaminated with only traces of a stereoisomer. Reduction and desulphurization of **56** afforded the piperidine alkaloid (+)-sedridine **33**.[81] Vinylic phosphine oxides[82,83] have been even less well studied in such asymmetric cycloadditions, although Brandi has described the synthesis of selectively protected 1-phosphinyl-*seco*-dausonamine.[82]

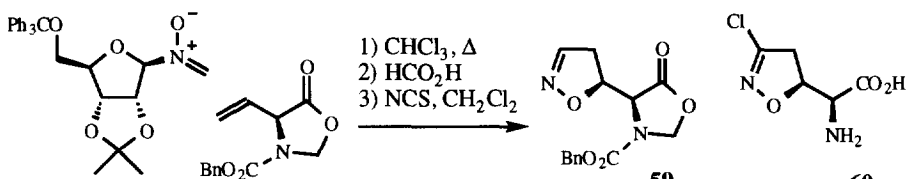


2.3 Optically active nitrones and alkenes[83-87]

Double asymmetric induction in intermolecular nitrone-alkene cycloaddition reactions has received little attention by comparison with the wealth of reports concerned with the use of chirality in just one of the two reaction components. Of the five reports to date two are concerned with the reaction between one of Vasella's sugar derived nitrones and amino acid derived allylamines[86,87] and

the others report the partial kinetic resolution of vinylic phosphine oxides with D-glyceraldyde derived nitrones.[83-85]

Whitney and co-workers have described the synthesis of the antimetabolite antibiotic Acivicin (AT-125) **60** produced by cultures of *Streptomyceus sviceus*.[86,87] Reaction between nitrone **57** and the protected vinylglycine derivative **58** afforded high yields of isoxazolidines with high levels of diasteroselectivity (80%, 19:1 isomeric ratio). The required major isoxazolidine isomer afforded **59** (after deprotection under acidic conditions and *N*-chlorosuccinimide induced isoxazoline formation), which was transformed over a further two steps (50% yield) to Acivicin (AT-125) **60**.

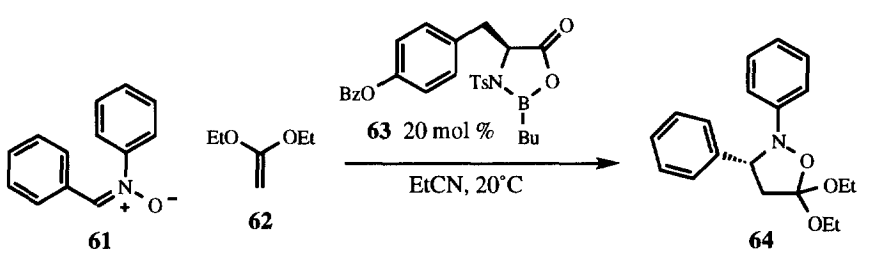


57 **58** **59** **60**

2.4 Catalytic asymmetric synthesis[88-92]

Over recent years, the induction of chirality using sub-stoichiometric amounts of optically active catalysts has been widely expounded as a valuable synthetic tool in asymmetric synthesis and has resulted in the development of methods for the synthesis of optically active products in a plethora of varied chemical processes. However, this area remains relatively unexplored in the field of intermolecular nitrone-alkene cycloadditions with the few advances having been reported only comparatively recently.

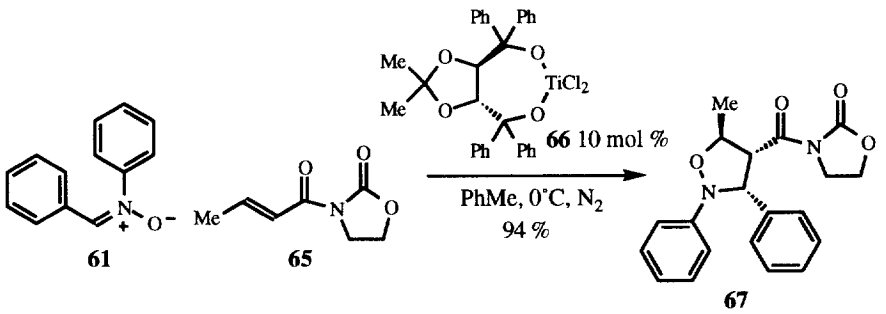
Dutch workers have described the use of Corey's oxazaborolidine technology in the synthesis of optically active isoxazolidines.[88,89] Although their results were somewhat varied both in terms of chemical yield and enantioselectivity (e.e. 0-74%) these workers did, nonetheless, successfully demonstrate the utility of this technique. Thus *C,N*-diphenyl nitrone **61** reacted with ketene acetal **62** in propionitrile in the presence of the homochiral oxazaborolidine catalyst **63** (20 mol %) to afford isoxazolidine **64** in low yield (10%) but high level of enantioselectivity (e.e. 74%).[88]



61 **62** **64**

Jørgenson and co-workers have concentrated on the use of optically active metal based catalysts to induce asymmetry, particularly those derived from a $Ti(^iOPr)_2Cl_2$-TADDOL combination.[90,91]

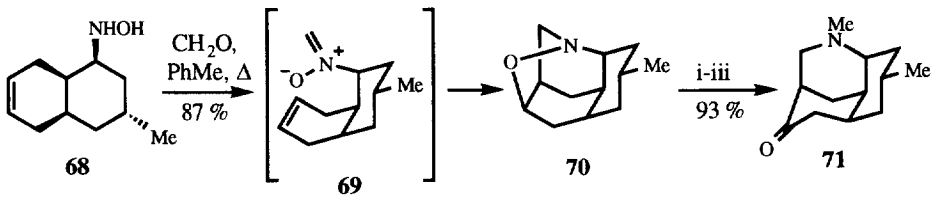
Nitrone **61** reacted with *N*-crotonyl-2-oxazolidinone **65** in the presence of catalyst **66** (10 mol %) to afford mostly the *endo*-isoxazolidine **67** in excellent yield (94%) with a reasonably good degree of enantioselectivity (e.e. 60%). Later work by the same research group demonstrated that Mg(II) and Cu(II) derived catalysts containing homochiral bis-oxazoline ligands were also useful in these transformations allowing enantioselectivities of up to of up to 82% to be realized.[92]



3. Intramolecular cycloadditions

3.1 Optically active alkenyl nitrones[93-152]

Early experiments in this area by workers in Detroit were concerned with intramolecular cycloaddition reactions of nitrones derived from (+)-citronellal and simple hydroxylamines;[93,94] later reports by a Yugoslavian group showed that unsaturated 5,10-*seco*-steroidal oximes afforded isoxazolidines by a process involving formal 1,2-prototropy and 1,3-dipolar cycloaddition.[95-97] The true synthetic potential of these methods lay dormant, however, until Oppolzer[98] reported an extremely elegant synthesis of the naturally occurring lycopodium alkaloid (+)-luciduline **71**. Treatment of hydroxylamine **68** with formaldehyde in reluxing toluene afforded the isoxazolidine **70** in high yield (87%) *via* a regiospecific intramolecular cycloaddition involving the intermediate nitrone **69**, a further three synthetic steps affording the desired dextrorotatory alkaloid **71**.

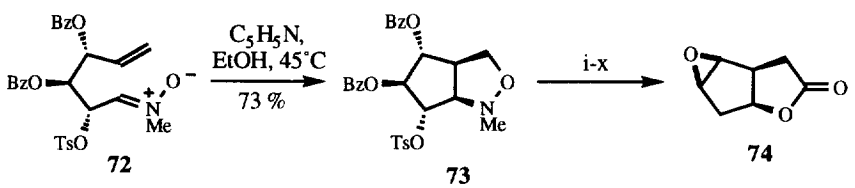


Reagents: i, $MeOSO_2F$, Et_2O, 0°C; ii, $LiAlH_4$, THF, 20°C; iii, Jones reagent, Me_2CO, 0°C

Since this landmark synthesis, research in this area has burgeoned and workers across the world have reported their findings concerning regio-, stereo- and facioselectivity in intramolecular cycloaddition reactions of alkenyl nitrones containing remote stereocentres.[99-126] Their investigations

have allowed the syntheses of a variety of natural products and related materials including alkaloids,[127-134] nucleosides,[135,136] carbapenems,[137,138] enzyme inhibitors[139-142] and vitamins.[143] The majority of published work has involved the condensation of chiral hydroxylamines or aldehydes, although the use of oximes as nitrone precursors *via* either 1,2-prototropy[141,145-147] or 1,3-azaprotio cyclotransfer[148,149] has also been reported. As in the corresponding intermolecular cases, outlined in Section 2.4, the use of sub-stoichiometric catalysts to induce enantioselectivity in intramolecular cycloadditions remains an unexplored area.

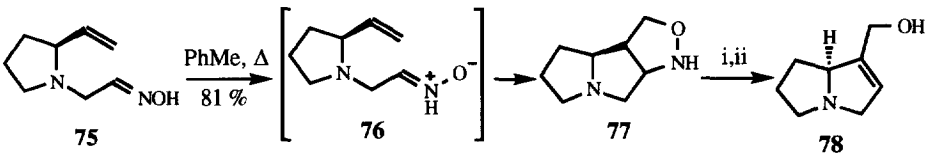
Extensive studies by Vasella's group have led to the preparation of compact, bicyclic isoxazolidines from protected 5-hexenals, derived from simple hexoses;[104-106] workers in New Zealand have subsequently used this strategy to prepare optically pure prostaglandins from D-glucose.[107] Thus, upon heating, nitrone **72** smoothly afforded cycloadduct **73** (73%) and was converted over several steps to the known lactone **74**, from which prostoglandin $F_2\alpha$ has previously been prepared. A series of recent papers presented by German workers has shown that similar nitrones derived from readily accessible α-amino and α-hydroxy acids behave almost identically in terms of their regio- and stereoselectivities in such reactions.[109-114]



Reagents: i, Raney Ni, H_2; ii, *m*-CPBA, CH_2Cl_2, 20°C; iii, TsCl, C_5H_5N; iv, NaCN, DMSO; v, Raney Ni, sodium hypophosphite, $PhNHCH_2CH_2NHPh$; vi, PDC, DMF; vii, I_2, $NaHCO_3$; viii, Bu_3SnH, C_6H_6; ix, K_2CO_3, MeOH; x, *N*-tosyl imidazole, NaH, DMF;

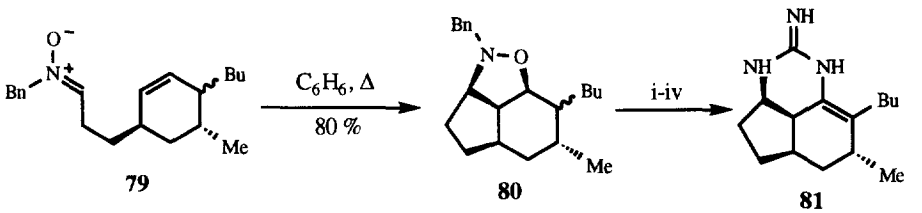
Intramolecular cycloaddition reactions of alkenyl nitrones derived from *O*-allylated sugar based aldehydes have been widely utilized in the synthesis of optically active oxepanes,[116-123] Shing's group having described[121-123] the use of furanoside derived aldonitrones and nitrile oxides in their attempts to prepare zoapatanol and its derivatives (potent diterpenoids isolated from the Mexican plant *Montanoa tomentosa*). Studies have also been reported concerning the reactivity of similar nitrones derived from simple pyranosides,[124-126] allowing the formation of highly substituted aminated cyclohexanes akin to various inositols and *pseudo*-sugars.[125]

Intramolecular nitrone-alkene cycloadditions have been utilized as key steps in the syntheses of a number of important alkaloids including (–)-supinidine **78**,[127] (–)-ptilocaulin **81**,[128,129] (–)-indolizidine 209B,[130,131] (–)-hobartine,[132] L-daunosamine **84** and L-acosamine **85**.[133,134] Hassner's simple synthesis of the necine base (–)-supinidine **78** utilized a 1,2-prototropy-cycloaddition sequence of the proline derived vinylic oxime **75**. Thermolysis of oxime **75** afforded tricycle **77** *via* the nitrone **76** (81% yield, single isomer), which was converted to the natural alkaloid **78** over a further two steps.[127]



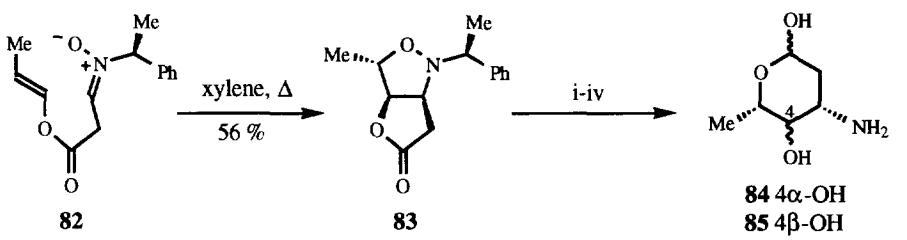
Reagents: i, $LiAlH_4$, THF, -10°C; ii, $NaNO_2$, 2M HCl, THF, H_2O, 20°C

Roush has described a synthesis of (-)-ptilocaulin **81** employing an intramolecular nitrone cycloaddition as a key step. Nitrone **79** (mixture of epimers) cyclized cleanly at 80°C to afford the tricyclic isoxazolidine **80** in high yield (80%) from which the desired alkaloid **81** followed over a further four steps.[128,129]



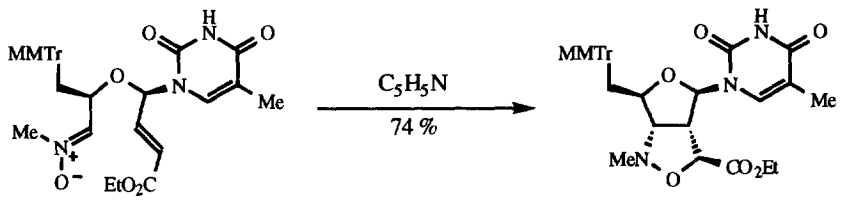
Reagents: i, Zn, AcOH, H_2O, 55°C; ii, Jones reagent, AcOH, HCl, H_2O, 0°C; iii, Pd black, HCO_2H, MeOH, 20°C; iv, 1-guanyl-3,5-dimethylpyrazole nitrate, 150°C

Workers at Hoffmann-La Roche have reported the synthesis of both L-daunosamine **84** and L-acosamine **85** from a common isoxazolidine intermediate **83**. Nitrone **82** underwent cycloaddition at 140°C to afford bicyclic isoxazolidine **83** (together with a stereoisomer) from which both alkaloids **84** and **85** could be prepared after several further synthetic transformations.[133,134]



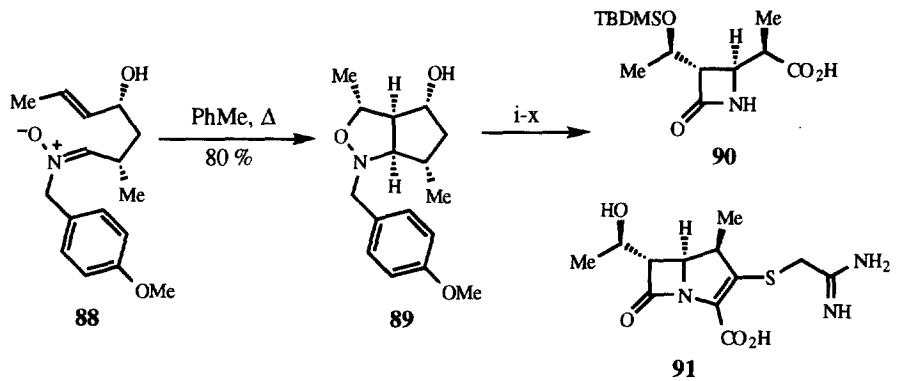
Reagents: i, Zn, AcOH, H_2O, 20°C; ii, MeOCOCl, Na_2CO_3, THF, H_2O, 0°C; iii, DIBAL, PhMe, THF, -78°C; iv, Amberlite CG 120 (H), MeOH, 20°C; iv, NaOAc, H_2O, DMF, 105°C

Intramolecular cycloaddition of alkenyl nitrones has been elegantly employed in the synthesis of a series of novel branched, fused and *spiro*-isoxazolidinyl nucleosides.[135,136] Thus, the 2',3'-*seco*-nucleoside derived nitrone **86** (prepared from D-thymidine over six steps) reacted at room temperature in pyridine to afford the 2',3'-α-fused isoxazolidinyl nucleoside **87** in good yield (74%).[136]



86 **87**

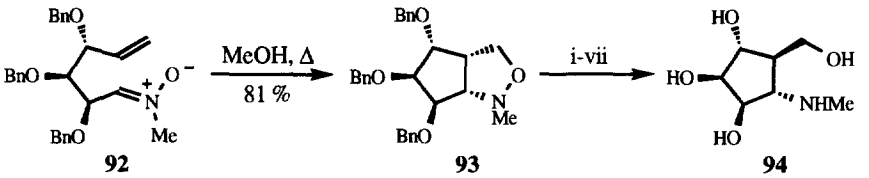
Two seperate research groups have described the syntheses of precursors to 1β-methylcarbapenem antibiotics employing an intramolecular nitrone-alkene cycloaddition as a key step in the synthesis of the core β-lactam structure.[136,137] Korean workers have shown that nitrone **88** affords a single bicyclic isoxazolidine **89** upon heating in refluxing benzene (80%). Iosxazolidine **89** cleanly yields β-lactam **90**, an intermediate in the synthesis of the antibiotic **91**, over a further nine synthetic steps.[138]



88 **89** **90** **91**

Reagents: i, Swern oxidation; ii, DIBAL, CH_2Cl_2, -78°C; iii, OsO_4, $NaIO_4$, Me_2CO, H_2O, dioxane, 20°C; iv, $(EtO)_2P(O)CH_2CO_2Et$, ^nBuLi, THF, 0°C; v, Zn, AcOH, 70°C; vi, HCl, MeOH, 0°C; vii, $(CF_3CO)_2O$, Et_3N, DMAP, CH_2Cl_2, 0°C; viii, CAN, MeCN, H_2O; ix, TBDMSCl, imidazole, DMF, 20°C; x, $KMnO_4$, $^nBu_4NBr$, C_6H_6, H_2O, 20°C

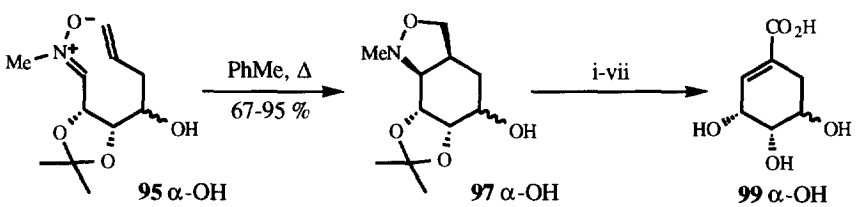
α-Glycosidase inhibitors have been highlighted as valuable targets for synthesis because of their unique biological properties, which include their use as potential immunomodulatory agents. Such compounds have been prepared by a number of methods, one of the most efficient involving intramolecular cycloaddition strategies.[139-142] Workers at the Merrell Dow Research Institute have described the synthesis of the carbocyclic amine **94**, an inhibitor of jack bean α-mannosidases from a sugar derived nitrone **92** *via* an isoxazolidine intermediate **93**.[139] A similar compound containing a pyrrolidine core (a selective inhibitor of α-glucosidase) has been described from an alkenyl oxime precursor using a 1,2-prototropy-cycloaddition approach.[141]



92 **93** **94**

Reagents: i, Zn, AcOH; ii, $(Boc)_2O$; iii, Dess-Martin periodinane; iv, DBU, -78°C; v, $NaBH_4$; vi, Pd, H_2; vii, HCl

The important vitamin (+)-biotin has been synthesized by similar methods involving an unsaturated nitrone derived from L-cysteine.[143] Similarly the synthesis of (–)-shikimic acid **100**, an important precursor to aromatic metabolites in plants, fungi and micro-organisms, and its C-5 epimer **99** have been described by such means, these syntheses being particularly worthy of note since neither product contains nitrogen.[144] Epimeric nitrones **95** and **96**, prepared from D-ribose, cleanly afforded isoxazolidines **97** (67%) and **98** (95%) which were transformed over seven steps to 5-*epi*-shikimic acid **99** and the natural laevorotatory acid **100** respectively *via* a sequence involving N-O bond cleavage, nitrogen quaternization, Hofmann elimination, oxidation and deprotection.



95 α-OH **97** α-OH **99** α-OH
96 β-OH **98** β-OH **100** β-OH

Reagents: i, Ac_2O, DMAP, C_5H_5N; ii, $Pd(OH)_2/C$, H_2, MeOH; iii, MeI, K_2CO_3, THF, 20°C; iv, DMSO, $(COCl_2)$, CH_2Cl_2, -78°C, Et_3N; v, $NaClO_2$, H_2O_2, NaH_2PO_4, MeCN, 20°C; vi, K_2CO_3, MeOH, H_2O, 20°C; vii, TFA, H_2O, 20°C

Homochiral isoxazolidine synthesis has been quite heavily investigated utilizing alkenyl oximes as precursors. In particular, Hassner has shown that such substrates act as powerful precursors to various highly functionalized pyrrolidines[145] and cyclopentanes;[146] Italian workers have made similar observations and have described an asymmetric approach to pyrrolidinone and pyrrolizidinones by such means.[147] Grigg and co-workers have noted the preference for highly conformationally flexible alkenyl nitrones (prepared from homochiral oxygenated aldoximes and divinyl sulphone using a 1,3-azaprotio cyclotransfer approach) to undergo cycloaddition with extremely high levels of π-facial selectivity, this selectivity being attributed to the influence of stereoelectronic effects which serve to stabilize and so favour one of the two possible transition states relative to the other.[148-149]

Of the few other reports of research in this area, Masamune has described the camphorsulphonic acid based resolution of racemic isoxazolidines in the preparation of novel chiral auxilliaries for use in asymmetric synthesis;[151] recently cycloaddition reactions of chiral chromium(0) complexed aromatic nitrones have also been described.[152]

4. Conclusion

Asymmetric nitrone-alkene cycloaddition reactions continue to inspire many research workers around the world. The use of these reactions in synthesis has clearly burgeoned over recent years allowing concise and flexible approaches to a growing number of important synthetic targets. The future of this fascinating area of research must surely hold many important developments, especially in the relatively unexplored areas. In particular, nitrone-alkene cycloadditions involving the use of sub-stoichiometric quantities of optically active catalysts to induce asymmetry in the isoxazolidine products are undoubtedly set to become prominent in years to come.

REFERENCES

1. Tufariello, J.J. in *1,3-Dipolar Cycloaddition Chemistry*, Padwa, A. Ed.; John Wiley and Sons: New York, **1984**; Vol. 2; Chapter 9; p. 83-168.
2. Torsell, K.B.G. *Nitrile oxides, Nitrones and Nitronates in Organic Synthesis*, VCH: New York, **1988**.
3. Confalone, P.N.; Huie, E.M. *Org. React.*, **1988**, *36*, 1-173.
4. Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Gazz. Chim. Ital.*, **1989**, *119*, 253-269.
5. Padwa, A. in *Comprehensive Organic Synthesis*, Trost, B.M.; Fleming, I. Eds., Pergamon Press: Oxford, **1991**; Vol. 4, p. 1069-1109.
6. Wade, P.A. in *Comprehensive Organic Synthesis*, Trost, B.M.; Fleming, I. Eds., Pergamon Press: Oxford, **1991**; Vol. 4, p. 1111-1168.
7. Breuer, E. in *Nitrones, Nitronates and Nitroxides*, Breuer,E.; Aurich, H.G.; Nielsen, A. Eds.; John Wiley and Sons: Chichester, **1989**; Chapters 2 and 3, p. 139-244 and 245-312.
8. Tufariello, J.J. *Acc. Chem. Res.*, **1979**, *12*, 396-403.
9. Diels, O.; Alder, K. *Liebigs Ann. Chem.*, **1928**, *460*, 98-122.
10. Belzecki, C.; Panfil, I. *J. Org. Chem.*, **1979**, *44*, 1212-1218.
11. Panfil, I.; Belzecki, C. *Pol. J. Chem.*, **1981**, *55*, 977-985.
12. Vasella, A. *Helv. Chim. Acta*, **1977**, *60*, 426-446.
13. Vasella, A. *Helv. Chim. Acta*, **1977**, *60*, 1273-1295.
14. Vasella, A.; Voeffray, R. *J. Chem. Soc., Chem. Commun.*, **1981**, 97-98.
15. Vasella, A.; Voeffray, *Helv. Chim. Acta*, **1982**, *65*, 1134-1144.
16. Vasella, A.; Voeffray, R.; Pless, J.; Huguenin, R. *Helv. Chim. Acta*, **1983**, *66*, 1241-1252.
17. Bernet, B.; Krawczyk, E.; Vasella, A. *Helv. Chim. Acta*, **1985**, *68*, 2299-2311.
18. Huber, R.; Vasella, A. *Tetrahedron*, **1990**, *46*, 33-58.
19. Kiers, D.; Moffat, D.; Overton, K. *J. Chem. Soc., Chem. Commun.*, **1988**, 654-655.
20. Kiers, D.; Moffat, D.; Overton, K.; Tomanek, R. *J. Chem. Soc., Perkin Trans 1*, **1991**, 1041-1051.
21. Kiers, D.; Overton, K. *Heterocycles*, **1989**, *28*, 841-848.
22. Tice, C.M.; Ganem, B. *J. Org. Chem.*, **1983**, *48*, 5048-5050.

23. Machetti, F.; Cordero, F.M.; De Sarlo, F.; Guarna, A.; Brandi, A. *Tetrahedron Lett.*, **1996**, *37*, 4205-4208.
24. Cordero, F.M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.*, **1994**, *35*, 949-952.
25. Goti, A.; Cardona, F.; Brandi, A.; Picasso, S.; Vogel, P. *Tetrahedron: Asymmetry*, **1996**, *7*, 1659-1674.
26. Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.*, **1995**, *60*, 4743-4748.
27. McCaig, A.E.; Wightman, R.H. *Tetrahedron Lett.*, **1993**, *34*, 3939-3942.
28. Oppolzer, W.; Deerberg, J.; Tamura, O. *Helv. Chim. Acta*, **1994**, *77*, 554-560.
29. Iida, H.; Kasahara, K.; Kibayashi, C. *J. Am. Chem. Soc.*, **1986**, *108*, 4647-4648.
30. Schiehser, G.A.; White, J.D.; Matsumoto, G.; Pezzanite, J.O.; Clardy, J. *Tetrahedron Lett.*, **1986**, *27*, 5587-5590.
31. White, J.D.; Badger, R.A.; Kezar III, H.S.; Pallenberg, A.J.; Schiehser, G.A. *Tetrahedron*, **1989**, *45*, 6631-6644.
32. Kametani, T.; Nagahara, T.; Honda, T.; *J. Org. Chem.*, **1985**, *50*, 2327-2331.
33. Kametani, T.; Chu, S.-D.; Honda, T. *Heterocycles*, **1987**, *25*, 241-244.
34. Kametani, T.; Chu, S.-D.; Honda, T. *J. Chem. Soc., Perkin Trans. 1*, **1988**, 1593-1597.
35. Ihara, M.; Takahashi, M.; Fukumoto, K.; Kametani, T. *Heterocycles*, **1988**, *27*, 327-330.
36. Ihara, M. Takahashi, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1*, **1989**, 2215-2221.
37. Ito, Y.; Kimura, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.*, **1987**, *60*, 3337-3340.
38. Martin, H.; Herrmann, R.; Ugi, I. Z. *Naturforsch., Teil B*, **1987**, *42*, 1588-1590.
39. Wovkulich, P.M.; Barcelos, F.; Batcho, A.D.; Sereno, J.F.; Baggiolini, E.G.; Hennessy, B.M.; Uskokovic, M.R. *Tetrahedron*, **1984**, *40*, 2283-2296.
40. Baggiolini, E.G.; Iacobelli, J.A.; Hennessy, B.M.; Batcho, A.D.; Sereno, J.F.; Uskokovic, M.R. *J. Org. Chem.*, **1986**, *51*, 3098-3108.
41. Borthakur, D.R.; Prajapati, D.; Sandhu, J.S. *Indian J. Chem., Sect. B*, **1988**, *27*, 724-725.
42. Fisera, L.; Al-Timari, U.A.R.; Ertl, P.; Prónayová, N. *Monatsh. Chem.*, **1993**, *124*, 1019-1029.
43. Yokoyama, M.; Sujino, K.; Irie, M.; Yamazaki, N.; Hiyama, T.; Yamada, N.; Togo, H. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2801-2809.
44. Brandi, A.; Cicchi, S.; Goti, A. *J. Org. Chem.*, **1994**, *59*, 1315-1318.
45. Mukai, C.; Cho, W.J.; Kim, I.J.; Hanaoka, M. *Tetrahedron Lett.*, **1990**, *31*, 6893-6896.
46. Mukai, C.; Kim, I.J.; Cho, W.J.; Kido, M.; Hanaoka, *J. Chem. Soc., Perkin Trans. 1*, **1993**, 2495-2503.
47. Castellari, C.; Lombardo, M.; Pietropaolo, G.; Trombibi, C. *Tetrahedron: Asymmetry*, **1996**, *7*, 1059-1068.
48. Al-Timari, U.A.R.; Fisera, L.; Ertl, P.; Goljer, I.; Prónayová, N. *Monatsh. Chem.*, **1992**, *123*, 999-1013.
49. DeShong, P.; Dicken, C.M.; Leginus, J.M.; Whittle, R.R. *J. Am. Chem. Soc.*, **1984**, *106*, 5598-5602.

50. Sasaki, T.; Eguchi, S. *J. Org. Chem.*, **1968**, *33*, 4389-4392.
51. Green, M.J.; Tiberi, R.L.; Friary, R.; Lutsky, B.N.; Berkenkoph, J.; Fernandez, X.; Monohan, M. *J. Med. Chem.*, **1982**, *25*, 1492-1495.
52. Hammann, P.; Kretzschmar, G. *Tetrahedron*, **1990**, *46*, 5603-5608.
53. Panfil, I.; Chmielewski, M. *Tetrahedron*, **1985**, *41*, 4713-4716.
54. Panfil, I.; Belzecki, C.; Chmielewski, M. *J. Carbohydr. Chem.*, **1987**, *6*, 463-470.
55. Panfil, I.; Belzecki, C.; Chmielewski, M.; Suwinska, K. *Tetrahedron*, **1989**, *45*, 233-238.
56. Panfil, I.; Belzecki, C.; Urbanczyk-Lipowska, Z.; Chmielewski, M. *Tetrahedron*, **1991**, *47*, 10087-10094.
57. Blake, A.J.; Forsyth, A.C.; Paton, R.M. *J. Chem. Soc., Chem. Commun.*, **1988**, 440-442.
58. Blake, A.J.; Cook, T.A.; Forsyth, A.C.; Gould, R.O.; Paton, R.M. *Tetrahedron*, **1992**, *48*, 8053-8064.
59. Xiang, Y.; Schinazi, R.F.; Zhao, K. *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 1475-1478.
60. de Lange, B.; Feringa, B.L. *Tetrahedron Lett.*, **1988**, *29*, 5317-5320.
61. Rispens, M.T.; Keller, E.; de Lange, B.; Zijlstra, R.W.J.; Feringa, B.L. *Tetrahedron: Asymmetry*, **1994**, *5*, 607-624.
62. Vasu, J.; Nadkarni, P.J.; Trivedi, G.K.; Steigel, A. *Magn. Reson. Chem.*, **1991**, *29*, 645-649.
63. Baskaran, S.; Trivedi, G.K. *J. Chem. Res. (S)*, **1995**, 308-309.
64. Baskaran, S.; Trivedi, G.K. *J. Chem. Res. (S)*, **1996**, 126.
65. Katagiri, N.; Watnabe, N.; Sakaki, J.-I.; Kawai, T.; Kaneko, C. *Tetrahedron Lett.*, **1990**, *31*, 4633-4636.
66. Murahashi, S.-I.; Imada, Y.; Kohno, M.; Kawakami, T. *Synlett*, **1993**, 395-396.
67. Mzengeza, S.; Whitney, R.A. *J. Chem. Soc., Chem. Commun.*, **1984**, 606-607.
68. Benz, G.; Henning, R.; Stasch, J.-P. *Angew. Chem., Intl. Ed. Engl.*, **1991**, *30*, 1702-1704.
69. Wityak, J.; Gould, S.J.; Hein, S.J.; Keszler, D.A. *J. Org. Chem.*, **1987**, *52*, 2179-2183.
70. Krol, W.J.; Mao, S.-S.; Steele, D.L.; Townsend, C.A. *J. Org. Chem.*, **1991**, *56*, 728-731.
71. Naito, T.; Ikai, M.; Shirakawa, M.; Fujimoto, K.; Ninomiya, I.; Kiguchi, T. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 773-775.
72. Carruthers, W.; Coggins, P.; Weston, J.B. *J. Chem. Soc., Chem. Commun.*, **1991**, 117-118.
73. Ito, M.; Kibayashi, C. *Tetrahedron Lett.*, **1990**, *31*, 5065-5068.
74. Ito, M.; Kibayashi, C. *Tetrahedron*, **1991**, *47*, 9329-9350.
75. Ito, M.; Maeda, M.; Kibayashi, C. *Tetrahedron Lett.*, **1992**, *33*, 3765-3768.
76. Ina, H.; Ito, M.; Kibayashi, C. *J. Org. Chem.*, **1996**, *61*, 1023-1029.
77. Al-Timari, U.A.R.; Fisera, L.; Goljer, I.; Ertl, P. *Carbohydr. Res.*, **1992**, *226*, 49-56.
78. Koizumi, T.; Hirai, H.; Yoshii, E. *J. Org. Chem.*, **1982**, *47*, 4004-4005.
79. Takahashi, T.; Fujii, A.; Sugita, J.; Hagi, T.; Kitano, K.; Arai, Y.; Koizumi, T.; Shiro, M. *Tetrahedron: Asymmetry*, **1991**, *2*, 1379-1390.

80. Bravo, P.; Bruché, L.; Farina, A.; Fronza, G.; Valdo Meille, S.; Merli, A. *Tetrahedron: Asymmetry*, **1993**, *4*, 2131-2134.
81. Louis, C.; Hootelé, C. *Tetrahedron: Asymmetry*, **1995**, *6*, 2149-2152.
82. Brandi, A.; Cicchi, S.; Goti, A.; Pietrusiewicz, K.M.; Zablocka, M.; Wisniewski, W. *J. Org. Chem.*, **1991**, *56*, 4383-4388.
83. Brandi, A.; Cicchi, S.; Goti, A.; Pietrusiewicz, K.M. *Tetrahedron: Asymmetry*, **1991**, *2*, 1063-1074.
84. Goti, A.; Cicchi, S.: Brandi, A.; Pietrusiewicz, *Tetrahedron: Asymmetry*, **1991**, *2*, 1371-1378.
85. Brandi, A.; Cicchi, S.; Goti, A.; Pietrusciewicz, K.M. *Phosphorus Sulphur*, **1993**, *75*, 155-158.
86. Mzengeza, S.; Yang, C.M.; Whitney, R.A. *J. Am. Chem. Soc.*, **1987**, *109*, 276-277.
87. Mzengeza, S.; Whitney, R.A. *J. Org. Chem.*, **1988**, *53*, 4074-4081.
88. Seerden, J.-P.G.; Scholte op Reimer, A.W.A.; Scheeren, H.W. *Tetrahedron Lett.*, **1994**, *35*, 4419-4422.
89. Seerden, J.-P.G.; Kuypers, M.M.M.; Scheeren, H.W. *Tetrahedron: Asymmetry*, **1995**, *6*, 1441-1450.
90. Gothelf, K.V.; Jørgensen, K.A. *J. Org. Chem.*, **1994**, *59*, 5687-5691.
91. Gothelf, K.V.; Thomsen, I.; Jørgensen, K.A. *J. Am. Chem. Soc.*, **1996**, *118*, 59-64.
92. Gothelf, K.V.; Hazell, R.G.; Jørgensen, K.A. *J. Org. Chem.*, **1996**, *61*, 346-355.
93. LeBel, N.A.; Post, M.E.; Whang, J.J. *J. Am. Chem. Soc.*, **1964**, *86*, 3759-3767.
94. LeBel, N.A.; Lajiness, T.A. *Tetrahedron Lett.*, **1966**, *7*, 2173-2178.
95. Mihailovic, M.L.; Lorenc, L.; Gasic, M.; Rogic, M.; Melera, A.; Stefanovic, M. *Tetrahedron*, **1966**, *22*, 2345-2358.
96. Mihailovic, M.L.; Lorenc, L.; Maksimovic, Z.; Kalvoda, J. *Tetrahedron*, **1973**, *29*, 2683-2692.
97. Mihailovic, M.L.; Lorenc, L.; Rajkovic, M.; Juranic, I.; Milovanovic, A. *Heterocycles*, **1989**, *28*, 869-878.
98. Oppolzer, W.; Petrzilka, M. *Helv. Chim. Acta*, **1978**, *61*, 2755-2762.
99. Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron*, **1987**, *43*, 4051-4056.
100. Annunziata, R.; Cinquini, M.; Cozzi, F.; Giaroni, P.; Raimondi, L. *Tetrahedron: Asymmetry*, **1990**, *1*, 251-264.
101. Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *J. Org. Chem.*, **1990**, *55*, 1901-1908.
102. Baldwin, S.W.; Gedon, S.C. *Synth. Commun.*, **1991**, *21*, 587-596.
103. Baldwin, S.W.; McFayden, R.B.; Aubé, J.; Wilson, J.D. *Tetrahedron Lett.*, **1991**, *32*, 4431-4434.
104. Bernet, B.; Vasella, A. *Helv. Chim. Acta*, **1979**, *62*, 1990-2016.
105. Bernet, B.; Vasella, A. *Helv. Chim. Acta*, **1979**, *62*, 2400-2410.
106. Bernet, B.; Vasella, A. *Helv. Chim. Acta*, **1979**, *62*, 2411-2431.
107. Ferrier, R.J.; Prasit, P. *J. Chem. Soc., Chem. Commun.*, **1981**, 983-985.

108. Ferrier, R.J.; Furneaux, R.H.; Prasit, P.; Tyler, P.C.; Brown, K.L.; Gainsford, G.J.; Diehl, J.W. *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1621-1628.
109. Aurich, H.G.; Biesemeier, F.; Boutahar, M. *Chem. Ber.*, **1991**, *124*, 2329-2334.
110. Aurich, H.G.; Frenzen, G.; Gentes, C. *Chem. Ber.*, **1993**, *126*, 787-795.
111. Aurich, H.G.; Quintero, J.-L.R. *Tetrahedron*, **1994**, *50*, 3929-3942.
112. Aurich, H.G.; Biesemeier, F. *Synthesis*, **1995**, 1171-1178.
113. Aurich, H.G.; Gentes, C.; Harms, K. *Tetrahedron*, **1995**, *51*, 10497-10512.
114. Aurich, H.G.; Geiger, M.; Gentes, C.; Köster, H. *Tetrahedron Lett.*, **1996**, *37*, 841-844.
115. Saito, S.; Ishikawa, T.; Moriwake, T. *J. Org. Chem.*, **1994**, *59*, 4375-4377.
116. Bhattacharjya, A.; Chattopadhyay, P.; McPhail, A.T.; McPhail, D.R. *J. Chem. Soc., Chem. Commun.*, **1990**, 1508-1509.
117. Bhattacharjya, A.; Chattopadhyay, P.; McPhail, A.T.; McPhail, D.R. *J. Chem. Soc., Chem. Commun.*, **1991**, 136.
118. Datta, S.; Chattopadhyay, P.; Mukhopadhyay, R.; Bhattacharjya, A. *Tetrahedron Lett.*, **1993**, *34*, 3585-3588.
119. Bhattacharjee, A.; Bhattacharjya, A.; Patra, A. *Tetrahedron Lett.*, **1995**, *36*, 4677-4680.
120. Mukhopadhyay, R.; Kundu, A.P.; Bhattacharjya, A. *Tetrahedron Lett.*, **1995**, *36*, 7729-7730.
121. Shing, T.K.M.; Fung, W.-C.; Wong, C.-H. *J. Chem. Soc., Chem. Commun.*, **1994**, 449-450.
122. Shing, T.K.M.; Fung, W.-C.; Wong, C.-H. *J. Chem. Soc., Chem. Commun.*, **1994**, 1403.
123. Shing, T.K.M.; Wong, C.-H.; Yip, T. *Tetrahedron: Asymmetry*, **1996**, *7*, 1323-1340.
124. Collins, P.M.; Ashwood, M.S.; Eder, H.; Wright, S.H.B.; Kennedy, D.J. *Tetrahedron Lett.*, **1990**, *31*, 2055-2058.
125. Shing, T.K.M.; Elsley, D.A.; Gillhouley, J.A. *J. Chem. Soc., Chem. Commun.*, **1989**, 1280-1282.
126. Hewson, A.T.; Jeffery, J.; Szczur, N. *Tetrahedron Lett.*, **1995**, *36*, 7731-7734.
127. Hassner, A.; Singh, S.; Sharma, R.; Maurya, R. *Tetrahedron*, **1993**, *49*, 2317-2324.
128. Roush, W.R.; Walts, A.E. *J. Am. Chem. Soc.*, **1984**, *106*, 721-723.
129. Walts, A.E.; Roush, W.R. *Tetrahedron*, **1985**, *41*, 3463-3478.
130. Smith, A.L.; Williams, S.F.; Holmes, A.B.; Hughes, L.R.; Lidert, Z.; Swithenbank, C. *J. Am. Chem. Soc.*, **1988**, *110*, 8696-8698.
131. Holmes, A.B.; Smith, A.L.; Williams, S.F.; Hughes, L.R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.*, **1991**, *56*, 1393-1405.
132. Gribble, G.W.; Barden, T.C. *J. Org. Chem.*, **1985**, *50*, 5900-5902.
133. Wovkulich, P.M.; Uskokovic, M.R. *J. Am. Chem. Soc.*, **1981**, *103*, 3956-3958.
134. Wovkulich, P.M.; Uskokovic, M.R. *Tetrahedron*, **1985**, *41*, 3455-3462.
135. Rong, J.; Roselt, P.; Plavec, J.; Chattopadhyaya, J. *Tetrahedron*, **1994**, *50*, 4921-4936.
136. Papchikhin, A.; Chattopadhyaya, J. *Tetrahedron*, **1994**, *50*, 5279-5286.
137. Ihara, M.; Takahashi, M.; Fukumoto, K.; Kametani, *J. Chem. Soc., Chem. Commun.*, **1988**, 9-10.

138. Kang, S.H.; Lee, H.S. *Tetrahedron Lett.*, **1995**, *36*, 6713-6716.
139. Farr. R.A.; Peet, N.P.; Kang, M.S. *Tetrahedron Lett.*, **1990**, *31*, 7109-7112.
140. Peet, N.P.; Huber, E.W.; Farr, R.A. *Tetrahedron*, **1991**, *47*, 7537-7550.
141. Hassner, A.; Falb, E.; Nudelman, A.; Albeck, A.; Gottlieb, H.E. *Tetrahedron Lett.*, **1994**, *35*, 2397-2400.
142. Rudge, A.J.; Collins, I.; Holmes, A.B.; Baker, R. *Angew. Chem., Intl. Ed. Engl.*, **1994**, *33*, 2320-2322.
143. Baggiolini, E.G.; Lee, H.L.; Pizzolato, G.; Uskokovic, M.R. *J. Am. Chem. Soc.*, **1982**, *104*, 6460-6462.
144. Jiang, S.; Mekki, B.; Singh, G.; Wightman, R.H. *Tetrahedron Lett.*, **1994**, *35*, 5505-5508.
145. Hassner, A.; Maurya, R.; Mesko, E. *Tetrahedron Lett.*, **1988**, *29*, 5313-5316.
146. Hassner, A.; Maurya, R. *Tetrahedron Lett.*, **1989**, *30*, 5803-5806.
147. Chiacchio, U.; Corsaro, A.; Pistarà, V.; Rescifina, A.; Romeo, G.; Romeo, R. *Tetrahedron*, **1996**, *52*, 7875-7884.
148. Frederickson, M.; Grigg, R.; Redpath, J.; Thornton-Pett., M. *Tetrahedron*, **1994**, *50*, 5495-5502.
149. Frederickson, M.; Grigg, R.; Rankovic, Z.; Thornton-Pett, M.; Redpath, J.; Crossley, R. *Tetrahedron*, **1995**, *51*, 6835-6852.
150. Stanssens, D.; De Keukeleire, D.; Vandewalle, M. *Tetrahedron: Asymmetry*, **1990**, *1*, 547-560.
151. Abiko, A.; Moriya, O.; Filla, S.A.; Masamune, S. *Angew, Chem., Intl. Ed. Engl.*, **1995**, *34*, 793-795.
152. Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Papagni, A.; Albinati, A. *Tetrahedron: Asymmetry*, **1995**, *6*, 1711-1717.

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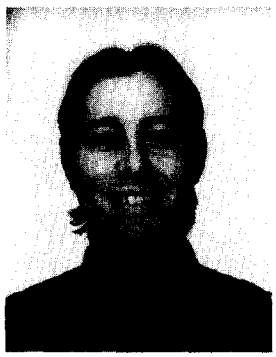
Biographical Sketch



Martyn Frederickson

Martyn Frederickson received his B.Sc. (First class) in 1988 from The University of Sheffield and remained in Sheffield to read for his Ph.D. under the supervision of Professor Edwin Haslam where he investigated the synthesis of stereospecifically substituted analogues of naturally occuring (–)-shikimic and (–)-chorismic acids as potential enzyme inhibitory based anti-microbial agents. Having successfully completed his Ph.D. in 1992 he moved to Leeds as a Postdoctoral Research Fellow to collaborate with Professor Ronald Grigg on the synthesis of optically active isoxazolidines *via* oxime-nitrone-isoxazolidine cascade reactions and on the use of palladium (0) catalysts in cascade synthesis. His interests include shikimate pathway chemistry and enzymology, asymmetry in nitrone cycloaddition chemistry, palladium (0) catalysed cascade synthesis and organofluorine chemistry.