Synthesis of Acylnitroso Intermediates and Their Synthetic Applications

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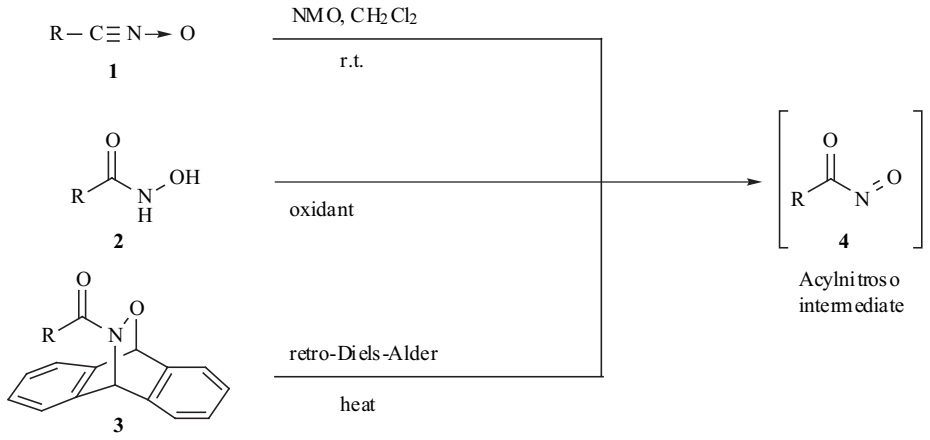
Abstract: Acylnitroso intermediates are usually known as super reactive species, always prepared *in situ* and can be readily trapped *via* hetero-Diels-Alder reactions with dienes or with olefins *via* ene reactions, which open a magnificent access to produce a variety of complicated and very demanding organic molecules. Both of these reactions of acylnitroso species have been proved as the key synthetic tool in the total synthesis of natural products. The synthetic methods used to prepare these intermediates as well as their recent synthetic applications to the total synthesis of natural products are briefly described in this minireview.

Keywords: Hydroxamic acid, acylnitroso intermediate, hetero-Diels-Alder reaction, ene reaction, asymmetric synthesis, total synthesis.

I. INTRODUCTION

Acylnitroso intermediates are of a great interest and attraction in the area of organic synthesis during the last decades. Since, highly functionalized molecules such as pyrrolidines, amino alcohols and aza sugars can be readily achieved from nitroso compounds by hetero-Diels-Alder reactions. In the utility of these intermediates, the most achievement came from the synthesis of 1,4-amino alcohols, which stands as building blocks for the total synthesis of natural products. Thus, acylnitroso intermediates show a wide range of applications in organic synthesis to achieve many multi-functionalized molecules such as natural products [1].



Scheme 1.

W. G. Kirby was the pioneering contributor to acylnitroso chemistry as he reported a review of this subject in 1977 [2]. In 1982, S. M. Weinreb and R. R. Staib also discussed this topic, emphasizing the utilization of acylnitroso compounds as hetero-dienophiles in Diels-Alder cycloadditions [3]. An excellent review has appeared in 1998 from the contribution of P. F. Vogt and M. J. Miller on the development and application of amino-acid derived chiral acylnitroso hetero-Diels-Alder reactions [4].

Although, recent studies are focused to enhance the utility of nitroso intermediates, the synthetic methods for the generation of these intermediates are still limited. In general, acylnitroso species are obtained from the oxidation of hydroxylamine derivatives, using organic and inorganic oxidants. Currently, hydrogen peroxide is successfully used as an oxidant for the generation of acylnitroso intermediates *via* its hetero-Diels-Alder reactions with transition metal complexes as catalysts [5].

II. SYNTHESIS OF ACYLNITROSO INTERMEDIATES

Since acylnitroso species are unstable and very reactive, they are traditionally prepared *in situ* as transient intermediates by oxidation of hydroxamic acids [2]. They can also be generated by oxidation of nitrile oxides [6] and by cyclo-reversion from the corresponding cycloadducts (Scheme **1**) [7]. Acylnitroso species could not be isolated

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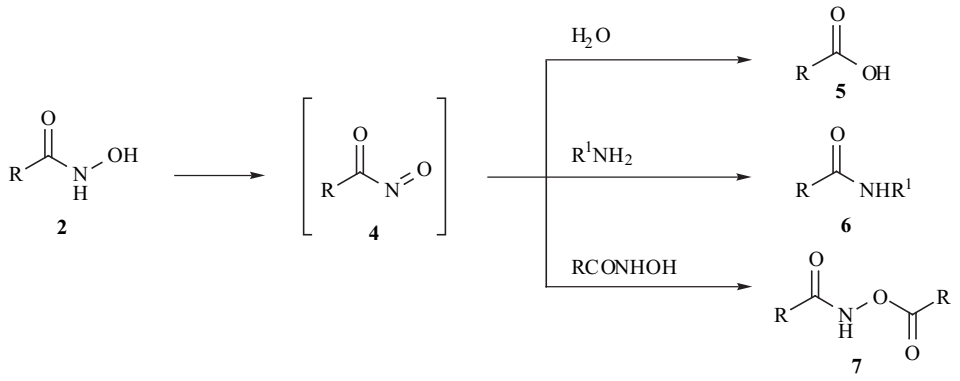


Scheme 2.

and W. G. Kirby pointed out that the only evidence for their existence were products **5**–**7** resulting from nucleophilic attack at the acylnitroso carbonyl **4** (Scheme **2**) [2]. The first direct spectroscopic evidence for acylnitroso species came from the work of H. Schwarz *et al*. as they generated these species by retro-Diels-Alder reactions of cycloadducts and were directly detected by neutralization-re-ionization mass spectrometry [8]. Very recently, these species have directly been detected in solution by time-resolved IR spectroscopy [9].

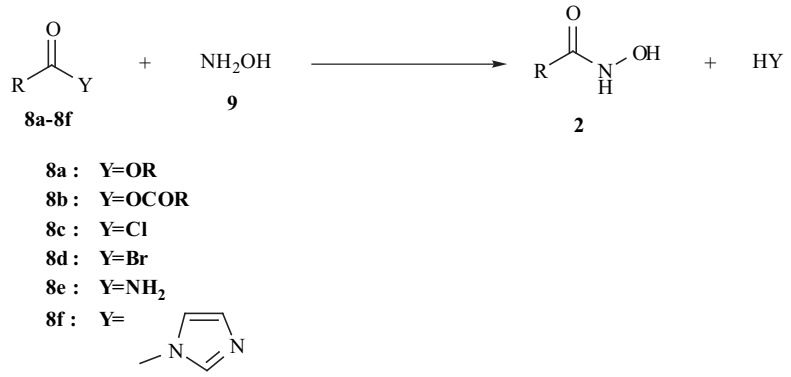
A. Synthesis of Hydroxamic Acids

Hydroxamic acids have been known for over a century and their derivatives possess a wide spectrum of biological activities [10]. Therefore, several methods have been developed for the preparation of hydroxamic acids. They have generally been synthesized in solution from nitro compounds or through the reaction of *O*/*N*-protected hydroxylamines with activated carboxylic acids [11]. The most important method for the preparation of hydroxamic acids is the acylation of hydroxylamine as shown in Scheme (**3**) [12].

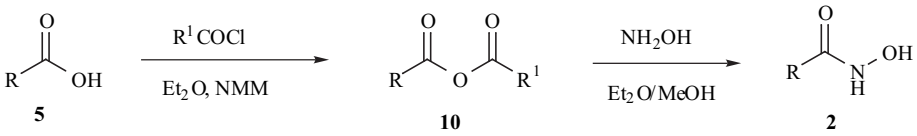
A mild and simple one-step approach for the preparation of hydroxamic acids from carboxylic acid derivatives as shown in Scheme (**4**) has been reported by G. R. Reddy *et al*. [13].

A new method for the preparation of *para*-substituted benzohydroxamic acids was described by M. M. Salunkhe *et al*. as shown in Scheme (**5**) [14].

Recently, hydroxamic acids were obtained from the reaction of *N*-acyloxazolidinones with hydroxylamines using



Scheme 3.



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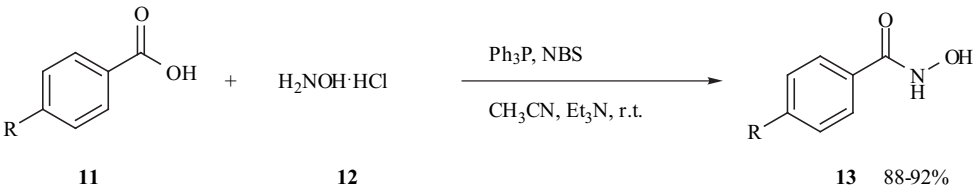
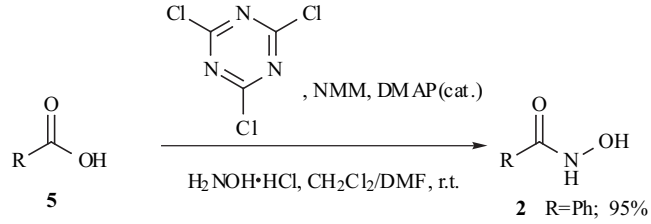


Scheme 5.

samarium triflate as a Lewis acid.[15] Solid-phase synthesis has also become an important tool, and there have been several reports describing synthesis of hydroxamic acid derivatives [16].

Very recently, G. Giacomelli *et al*. have reported a simple one-flask method for the synthesis of hydroxamic acids as shown in Scheme (**6**) [17].



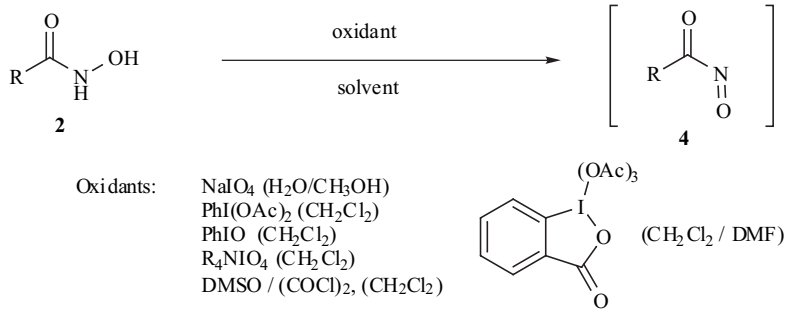
Scheme 6.

B. Oxidation of Hydroxamic Acids

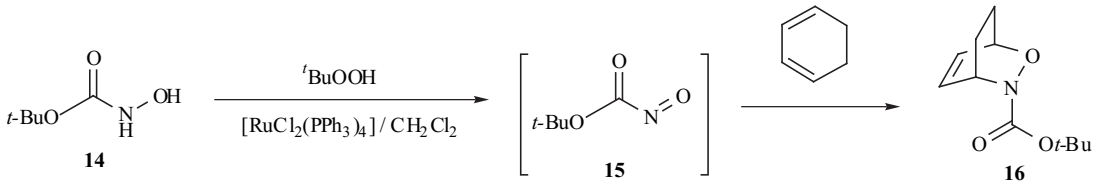
In general, the acylnitroso intermediates are obtained *in situ* from the oxidation of hydroxyl amine derivatives, such as: periodate salts [18], Dess-Martin periodinane [19], hypochlorite [20], and Swern-Moffat method (Scheme **7**) [21].

These methods have some drawback in the sense that always there was formation of inorganic or organic undesirable side products. Recently, A. Whiting *et al*. reported a new ruthenium(IV)-based method for the *in situ* generation of an acyl nitroso dienophile as shown in Scheme (**8**) [22].

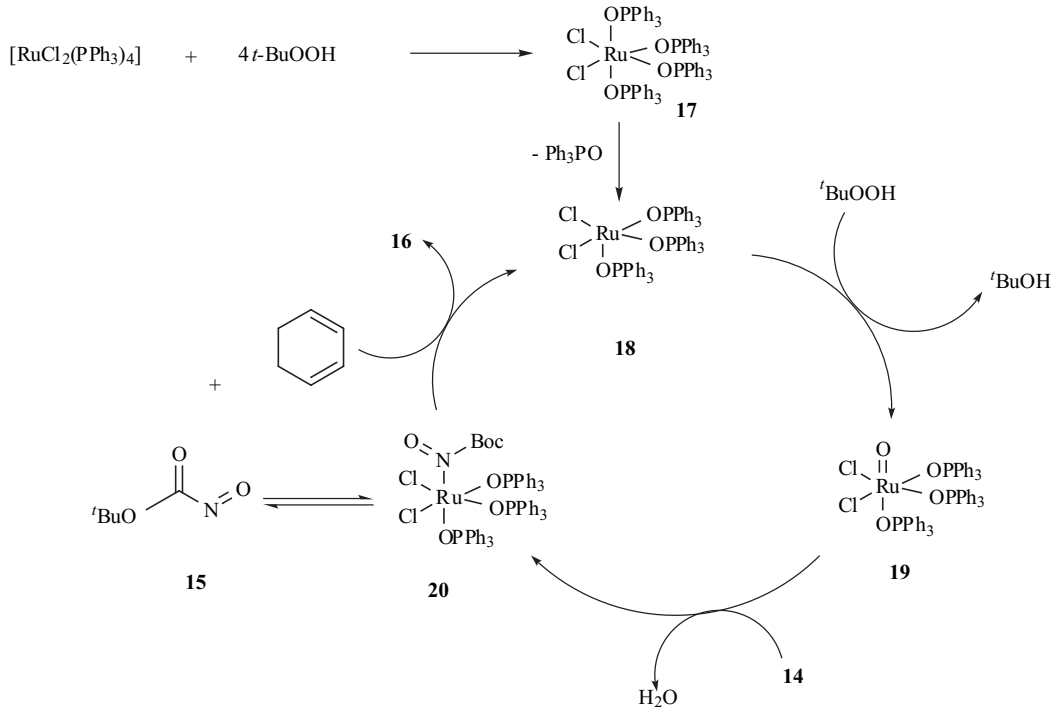
A plausible mechanism of this oxidation process was out lined as in Scheme (**9**).



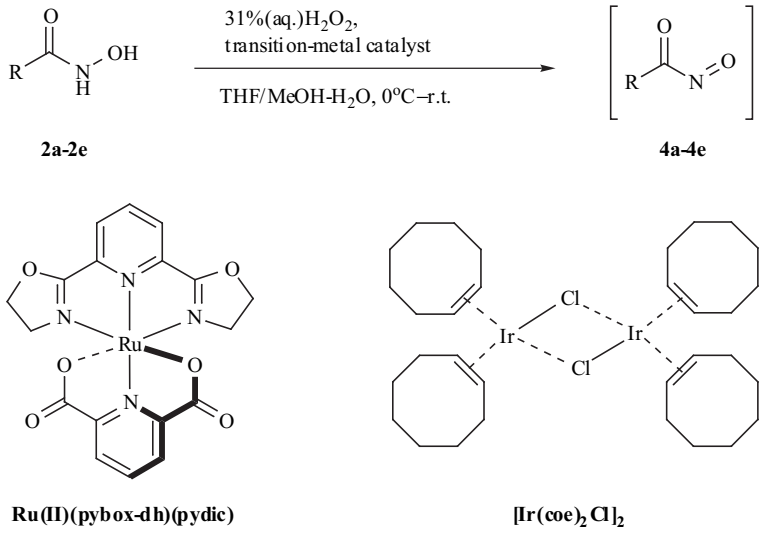
Scheme 7.



Scheme 8.



Scheme 9.



Scheme 10.

In the choice of oxidant, hydrogen peroxide attracted considerable attention and it was generally used in the presence of metal-complex catalysts. The use of it as an oxygen donor is particularly attractive, both for its high oxygen contents and the formation of water as the side product [23]. Among the tested metallic hydrogen peroxide oxidation systems. Ru(pybox-dh)(pydic), $[Ir(coe)_2Cl]_2$, $[Ir(cod)Cl]_2$ and CuI were found effective and can be successfully employed to generate acylnitroso intermediates from hydroxamic acids (Scheme **10**) [5].

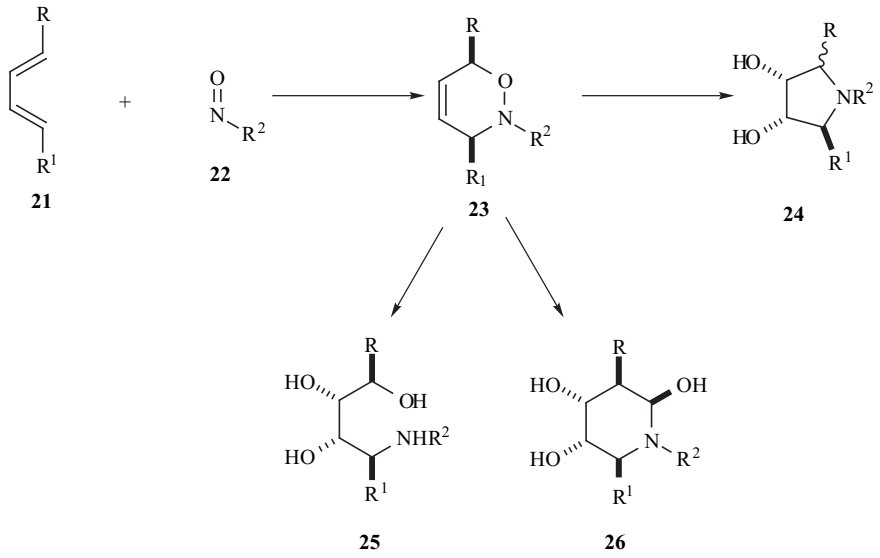
III. SYNTHETIC APPLICATION

The generation of 1,2-oxazine **23** by hetero-Diels-Alder reaction is a transformation, which discloses a resourceful array of highly functionalized acyclic and cyclic structures. Thus, pyrrolidine derivatives **24**, amino alcohols **25** and aza-sugars **26** are easily available from these cycloadducts as sketched in Scheme (**11**).

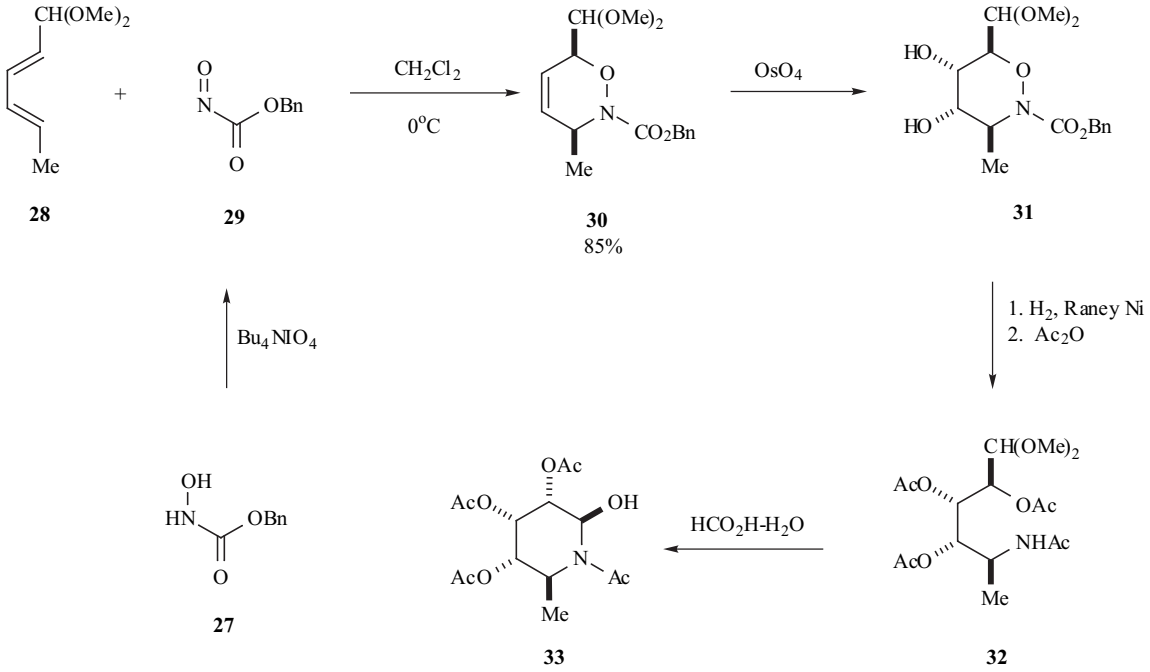
A. Hetero-Diels-Alder Reaction

The potential of nitroso carbonyls as very reactive dienophiles in hetero-Diels-Alder (HDA) cycloadditions has been explored in great detail since last three decades. The HDA cycloaddition often represents a pivotal reaction step in total syntheses of natural products, because of the high stereo- and regio-selective outcome and the convenient introduction of multifunctionality by reductive cleavage of the N-O bond of the adduct.

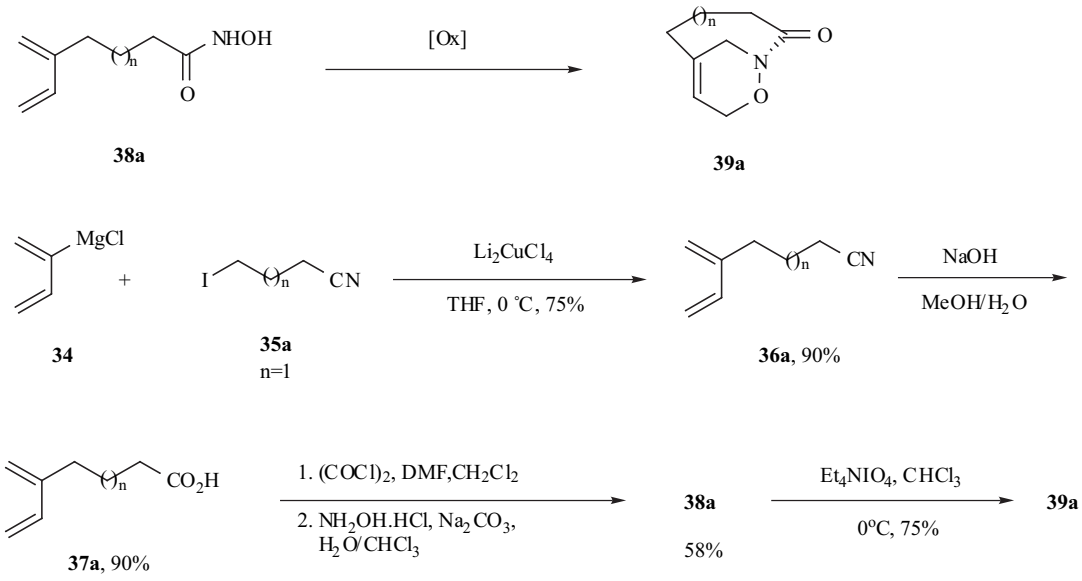
The *in situ* generated acylnitroso compounds react with 1,3-dienes to form derivatives of 1,2-oxazine, which on cleavage of the nitrogen-oxygen bond afford 4-aminoalcohols. Reactions of this kind have been used to prepare a series of polyhydroxy-piperidines and polyhydroxyamino-cyclohexanes. The synthesis of tetra-acetylated aminoallose **33** starting from dimethylacetal of hexa-2,4-dienal **28** and acylnitroso species(**29**) is an example of utilizing intermolecular hetero Diels-Alder reaction (Scheme **12**) [24].



Scheme 11.



Scheme 12.

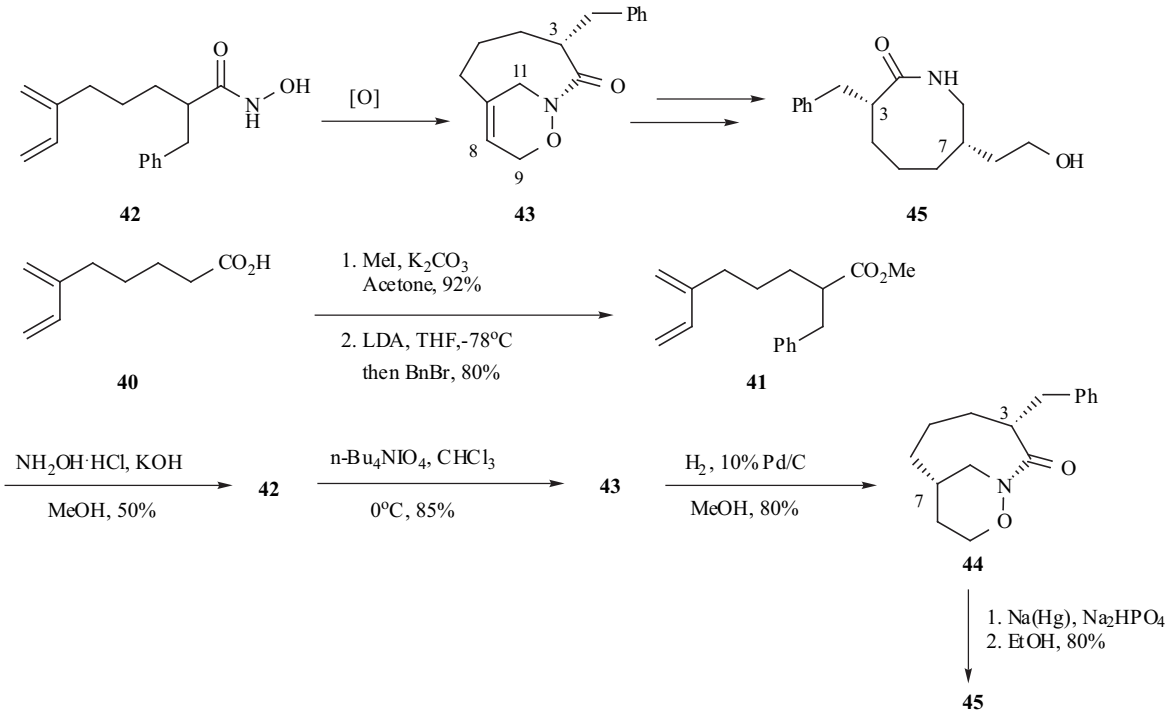


Scheme 13.

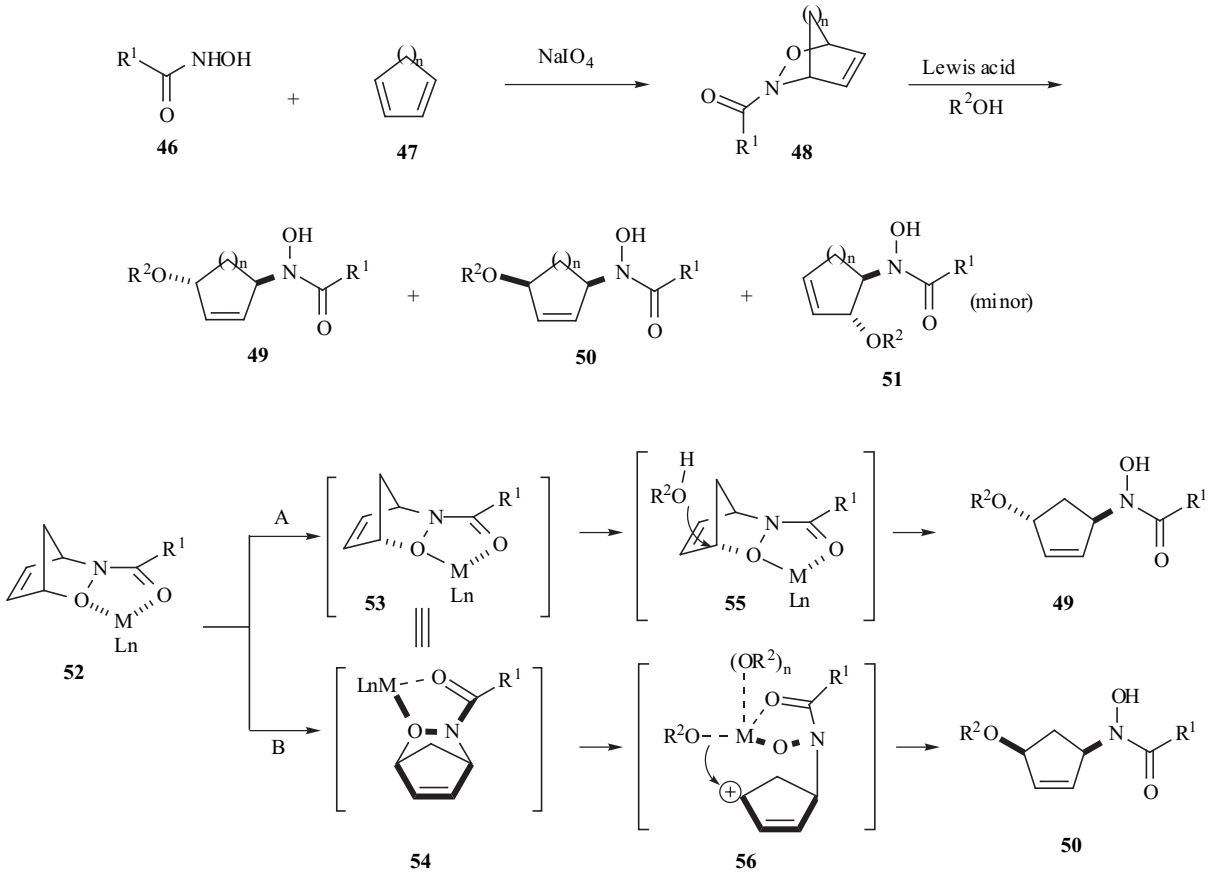
K. J. Shea *et al*. have reported the synthesis of bridgehead oxazinolactums **39** by intramolecular Diels-Alder cycloaddition utilizing *N*-acylnitroso dienophiles and pointed out that after the appropriate manipulations, these could be elaborated to medium-ring amines or lactams (Scheme **13**) [25].

In another report K. J. Shea and coworkers have employed the intramolecular *N*-acylnitroso Diels-Alder reaction (IMDA) in steroselective synthesis of bridged bicyclic oxazinolactams. Upon oxidation of hydroxamic acid **42**, a 3-benzylated oxazinolactam **43** was synthesized with complete diastereoselectivity and elaboration of cycloadduct **43** liberated a *cis*-3,7-disubstituted azocin-2-one **45** as shown in Scheme (**14**) [26].

The regio and stereochemically controlled formation of hydroxamic acid containing *anti*- or *syn*- 1,4-cycloalkenols was reported by M. J. Miller *et al*. [27]. Treatment of acylnitroso hetero-Diels-Alder cycloadducts **48** with iron(III) or copper(II) in an alcohol solvent induces ring opening to afford predominantly monocyclic *anti*-1,4-hydroxamic acids **49**. However, treatment of cycloadducts **48** with copper(II) in toluene reverses the stereoselectivity of the ring opening to afford syn-1,4-hydroxamic acids **50**. A plausible mechanism involves an initial Lewis acid mediated opening of the cycloadduct to give a tight ion pair was out lined as Scheme (**15**).

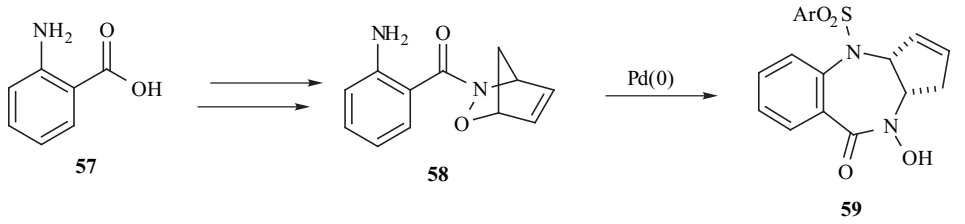


Scheme 14.

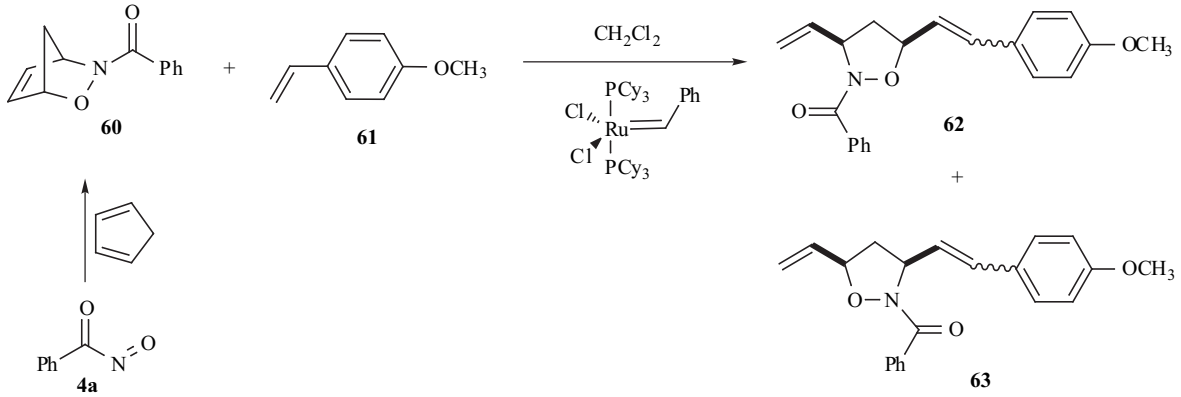


Scheme 15.

Compound **59** containing the 1,4-benzodiazepine core, which make up an important class of privileged structures with a broad spectrum of biological activities and therapeutic uses can be synthesized in a single step from synthetically versatile acylnitroso-derived hetero-Diels-Alder cycloaddition (Scheme **16**) [28]. The efficiency of this transformation was found to be dependent on the NH pK_a of the cycloadduct sulfonamide.



Scheme 16.



Scheme 17.

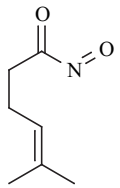
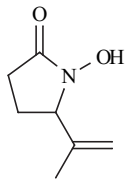
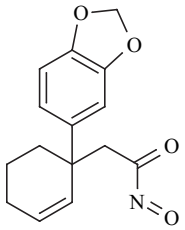
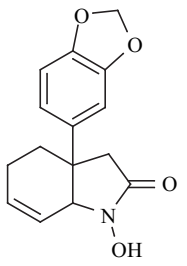
S. B. King *et al*. reported that the cycloadduct **60** of 1,3-cyclopentadiene and acylnitroso compound underwent ring-opening cross metathesis (ROCM) to give a mixture of four cyclic hydroxylamine in nearly equal amounts in 57% yield (Scheme **17**) [29]. NMR experiments indicate that the four compounds consist of the *E* and *Z* diastereomers of the two regioisomers **62** and **63**.

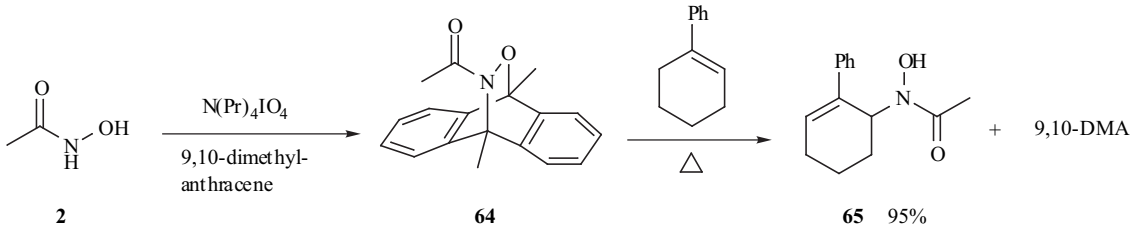
B. Ene Reaction

The acylnitroso compounds have been used relatively little for the ene reaction due to their labile nature. In this reaction although the enophile is unsymmetrical only one mode of addition is observed, reaction always leading to the formation of a C-N bond and generation of a N-OH compound.

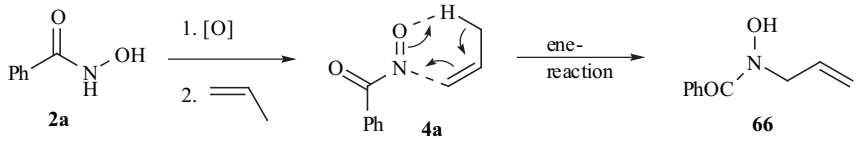
E. G. Keck *et al.* have described the use of acylnitroso compounds of the general formula RCONO as enophiles in the formation of carbon-nitrogen bonds. They have studied both inter- and intramolecular ene reactions *via* thermal transfer of nitrosocarbonylmethane from its Diels-Alder adduct with 9,10-dimethyl anthracene [30]. Nitrosocarbonylmethane liberated *in situ* from its Diels-Alder adduct **64** in the presence of phenylcyclohexene gave the adduct **65** in 95% yield is an example of bimolecular ene reaction (Scheme **18**). The regiochemistry of the intermolecular reaction is observed to be the result of kinetic control, and the direction of addition is consistent with attack by the olefin on electron-deficient nitrogen. Table **I** shows two examples of intramolecular ene reactions.

Table 1. Intramolecular ene Reactions: All Acylnitroso Compounds were Generated by Thermolysis of their Diels-Alder Adducts with 9,10-Dimethylanthracene

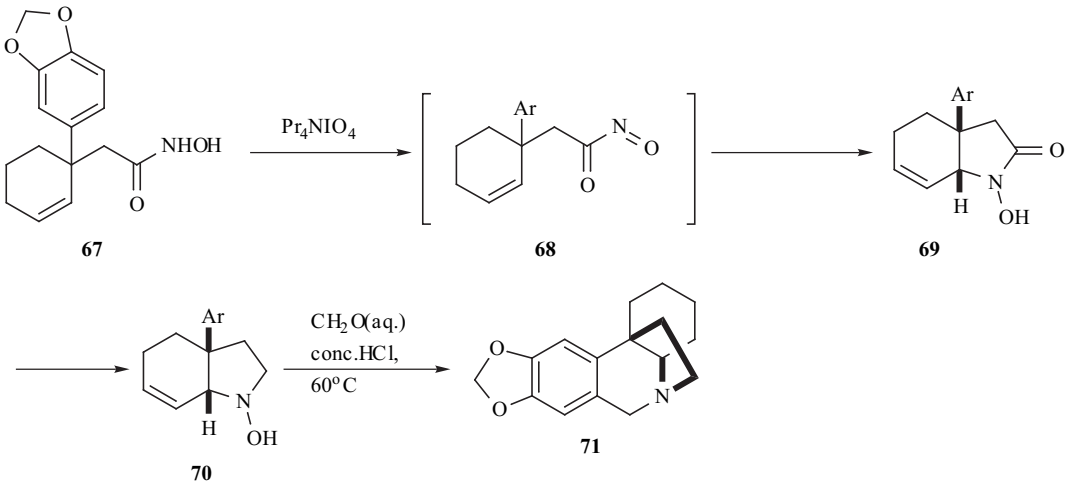
ene substrates	yield(%)	product	yield(%)
	74		100
	85		100



Scheme 18.



Scheme 19.



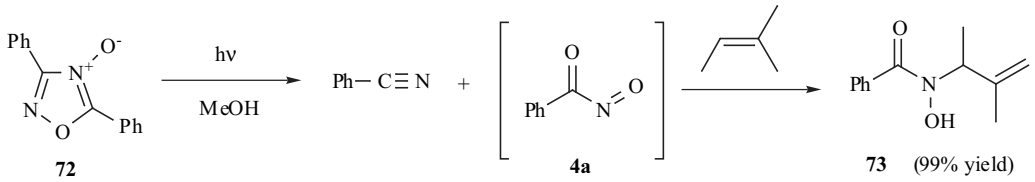
Scheme 20.

A general approach of the oxidation of hydroxamic acid **2a** and its bimolecular ene reaction with olefin may be out lined as Scheme (**19**).

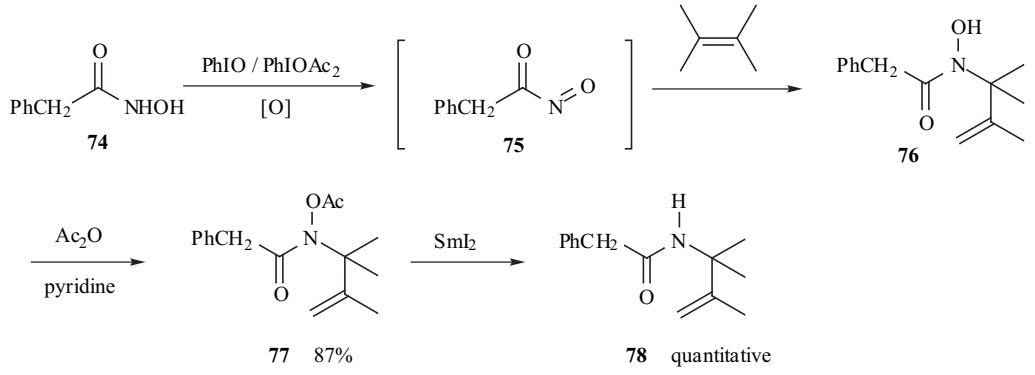
Intramolecular ene reactions take place readily. Oxidation of the hydroxamic acid **67** in the presence of 9,10-dimethylanthracene afforded the Diels-Alder adduct of the nitroso-ketone **68**, which on thermal release in boiling toluene gave the adduct **69** in quantitative yield. This was converted into the amino **70** and thence into (±)-crinane **71** (Scheme **20**) [31].

W. G. Kirby *et al*. and E. G. Keck *et al*. synthesized acylnitroso intermediates by thermal retro-cleavage of their Diels-Alder adducts with 9,10-dimethylanthracene or cyclopentadiene in the presence of various olefins and have demonstrated their propensity to undergo an ene reaction [32a-c].

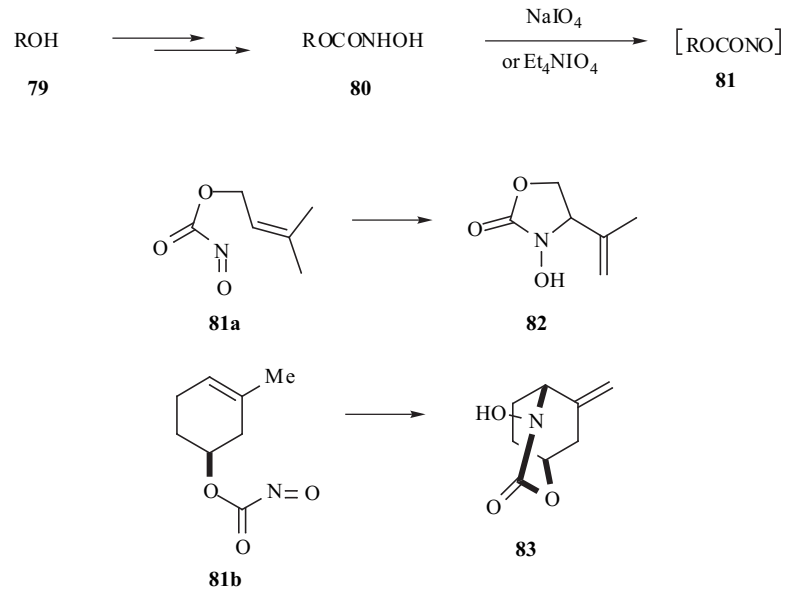
Alternatively, the *in situ* oxidation of nitrile oxides by *N*-methylmorpholine *N*-oxide has led to intermediary acylnitroso compounds, which afford ene products with olefins in high yield [33a]. This procedure fails however with less substituted ethylenes because of competing 1,3-dipolar cycloaddition of nitrile oxide to the alkene. This shortcoming can be avoided by using the photochemical generation of nitrosocarbonyls by irradiation of oxadiazole **72**, thence in the presence of differently substituted ethylenes formed the crystalline ene products **73** in excellent yield (Scheme **21**) [33b].



Scheme 21.



Scheme 22.



Scheme 23.

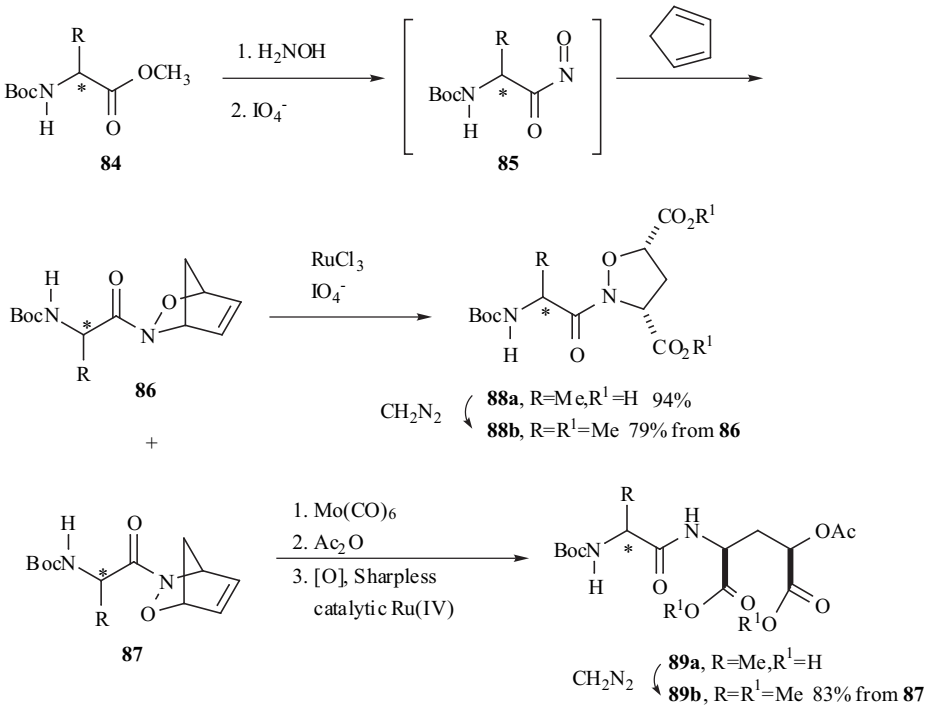
W. Adam *et al*. demonstrated that good yields of the intermediary acylnitroso compound can be achieved under mild conditions, as manifested by the ene reaction with the appropriate olefins (Scheme **22**) [34].

W. G. Kirby *et al*. have reported the first study of the intramolecular ene reactions of nitrosoformate esters, ROCONO, derived from allylic and homoallylic alcohols (Scheme **23**) [35].

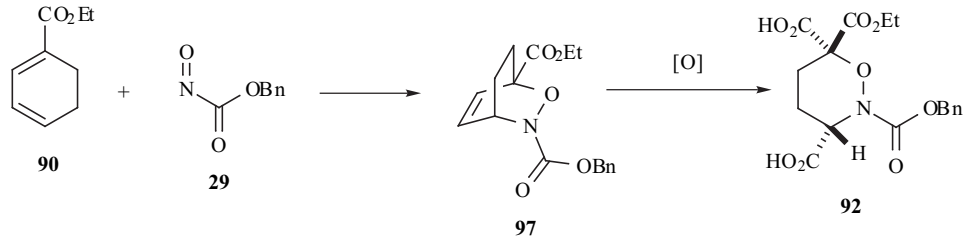
C. Asymmetric Synthesis

Asymmetric synthesis of novel amino acids and peptides from acylnitroso- derived cycloadduct was reported by M. J. Miller *et al*. Optically pure oxazines derived from Diels-Alder reaction of amino acid-based acylnitroso compounds provides effective routes to novel highly functionalized peptides in which the carbon framework of the new *C*-terminal amino acid residue originates from the diene as outlined in Scheme (**24**) [36].

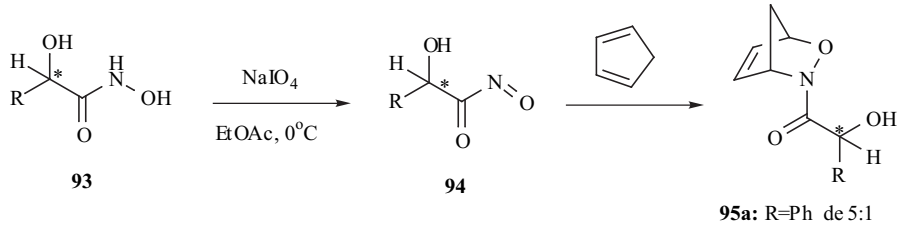
Similar methodology was utilized in Baldwin's racemic synthesis of tabtoxin precursors **92**. In that study, oxidation of acylnitroso cycloadduct **91** was accomplished by using permanganate and a phase transfer catalyst (tetrabutyl-ammonium hydrogen phosphate) in water and benzene (Scheme **25**) [37].



Scheme 24.



Scheme 25.



Scheme 26.

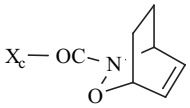
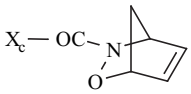
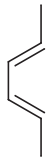
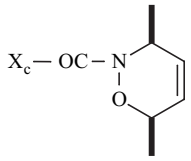
W. G. Kirby and M. Nazeer have reported cycloaddition reactions of the chiral *C*-nitroso carbonyl compounds **94** with cyclopentadiene and cyclohexa-1,3-diene and the highest ratio of diastereoisomers (ca. 5:1) has been observed for the mandelic derivatives of cyclopentadiene **95a** as shown in Scheme (**26**) [38].

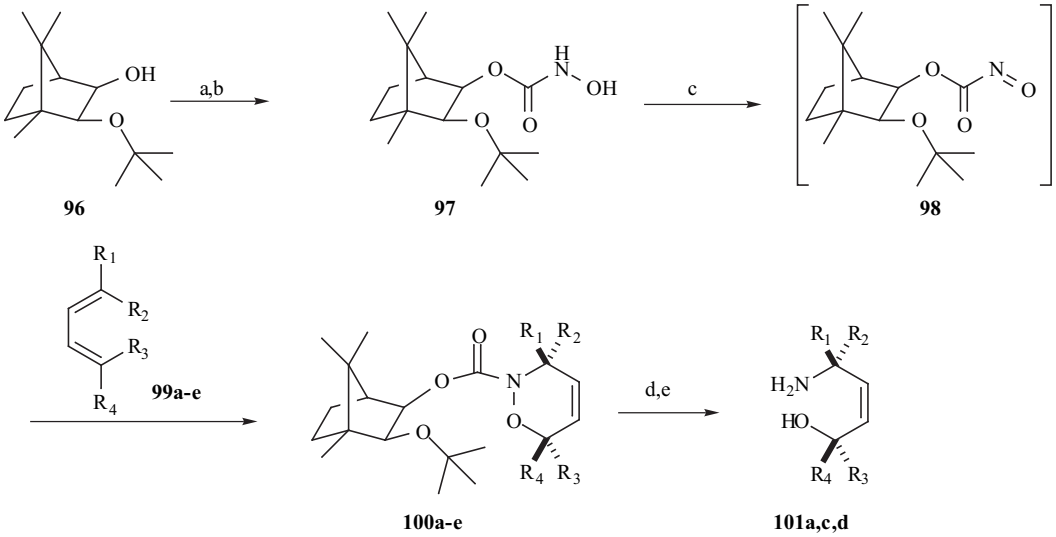
S. F. Martin *et al*. have developed a more general approach to unsaturated, enantiomerically pure 1,4-amino alcohols from alcohol **96** utilizing asymmetric Diels-Alder reaction of chiral nitroso carbamates (Scheme **27**) [39].

Table **II** shows [4+2] cycloaddition of chiral acylnitroso compounds to variety of conjugated dienes where highly diastereoselective products were formed.

A. Defoin *et al*. described three-step synthesis of the amino lyxose derivatives **107** and **108**, starting from the readily accessible 1,2-dihydropyridine derivatives **102** (Scheme **28**) [40].

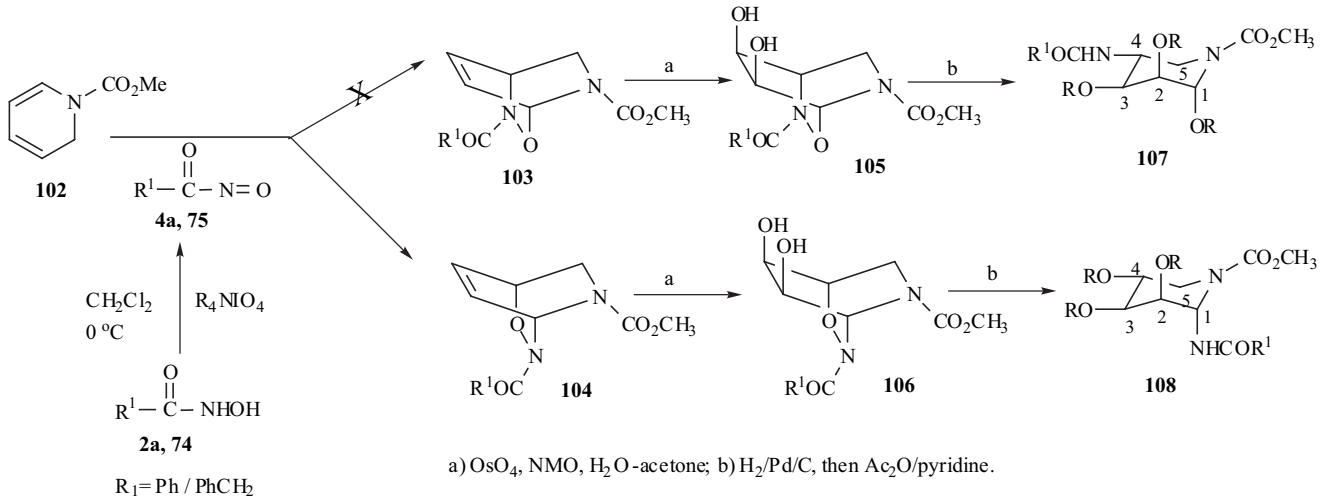
Table 2. Diels-Alder Reaction of Chiral Acylnitroso Dienophiles with Diene

Entry	Diene 6	Major product 7	Diastereo-meric excess de(%)	Total yield(%)
1			95	93
2			91	89
3			>96	94

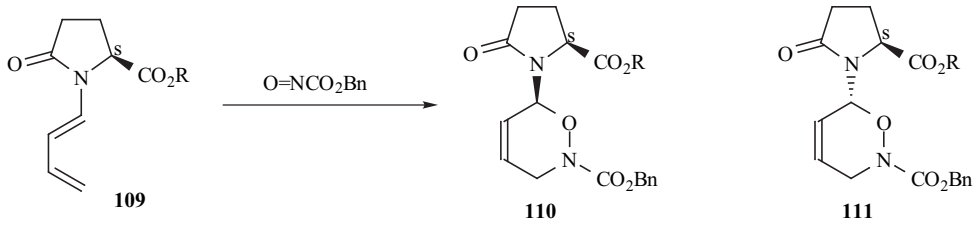


(a) Cl_3COCCl_3, quinoline, PhH, 5 °C; (b) $H_2NOH.HCl$, aq.Na_2CO_3; (c) $(COCl)_2$, CH_2Cl_2; DMSO; **99a-e**, Et_3N; (d) Na(Hg), aq.MeOH, NaH_2PO_4; (e) NaOH, aq.EtOH, aq.HCl.

Scheme 27.



Scheme 28.

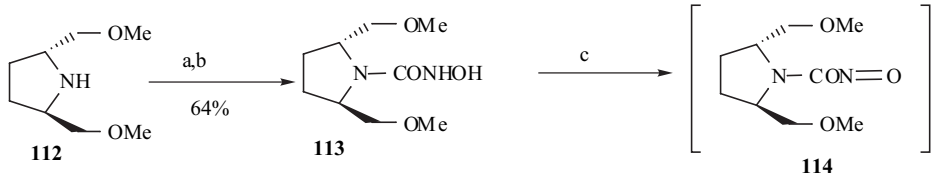


solvent/temp.				de(%)
CH_2Cl_2/0 °C	R= *t*Bu	84	16	68
MeOH/-20 °C	R= *t*Bu	88	12	76

Scheme 29.

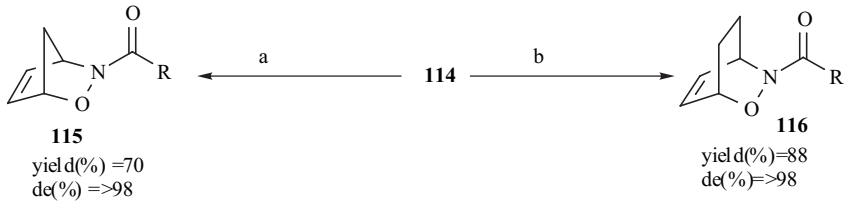
Another example of the synthesis of chiral compounds with good diastereomeric excess (de) from chiral *N*-butadienylpyroglutamate derivatives **109** has come from A. Defoin *et al*.'s work (Scheme **29**) [41].

L. Ghosez *et al*. showed that much higher level of diastero-selectivities can be obtained with a carbamoylnitroso compound **114** derived from a disubstituted pyrrolidine **112** possessing C_2 symmetry (Scheme **30**) [42].



(*2R, 5R*)-bis(methoxymethyl)-pyrrolidine

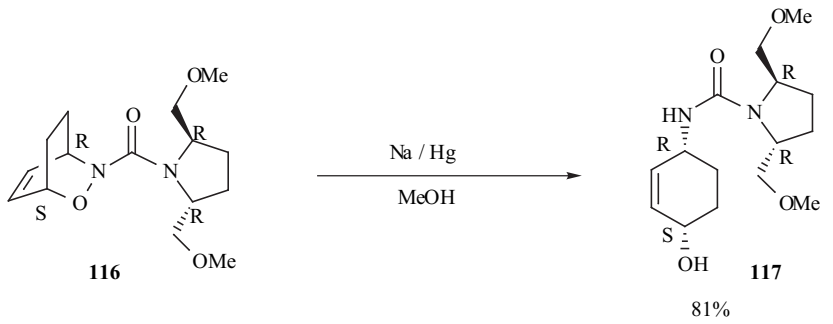
Reagents : a) $COCl_2$ at -30 °C in ether; b) $Me_3SiNHOSiMe_3$, Neat, 60 °C,MeOH; c) Et_4NIO_4, MeOH.



R= (2*R*, 5*R*) -bis(methoxymethyl)-pyrrolidine

Reagents : a) cyclopentadiene, 20 °C; b) cyclohexadiene, 20 °C.

Scheme 30.



Scheme 31.

The absolute configuration of adduct **116** has been determined by an X-ray diffraction analysis of the crystalline reduced product **117** by reference to the known absolute configuration of the asymmetric carbon atoms of the pyrrolidine ring (Scheme **31**).

IV. THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

The hetero Diels-Alder reactions and the ene reactions of acylnitroso intermediates occupy the central step in the total synthesis of natural products. Many examples are available in the literature, among them only five excellent total syntheses are described herein.

A. Total Synthesis of (±)-Lycoricidine

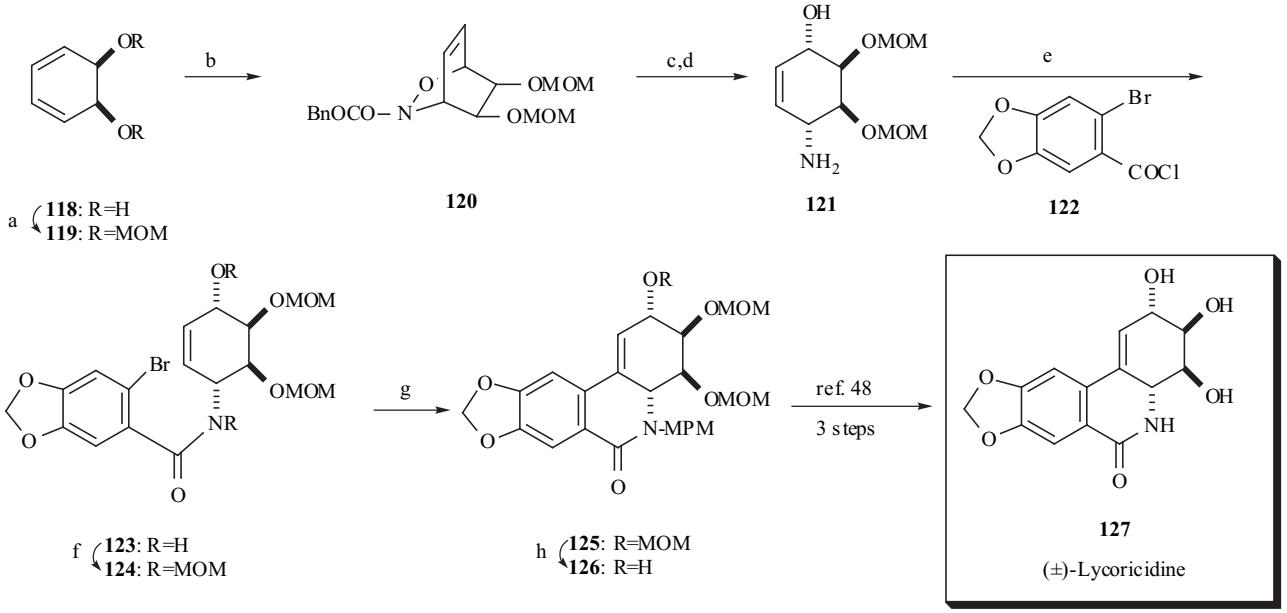
A concise synthesis of racemic lycoricidine **127**, a member of the narciclasine family of the *Amaryllidaceae* alkaloid has been demonstrated starting from the commercially available diol, *cis*-1,2-dihydrocatechol **118**. It requires a total of only eleven steps. The hetero-Diels-Alder reaction of benzylnitoso carbamate with the diene **119** and the Heck cyclization of the derived amide **124** served as the key steps in this synthesis process (Scheme **32**) [43].

B. Total Synthesis of *dl*-Cephalotaxine

A total synthesis of racemic cephalotaxine **147** was developed starting from vinyl sulfone **128** utilizing triply convergent vinyl sulfone methodology and stands as a first example of an intramolecular [4+2] cycloaddition where the dienophile has been delivered from the face opposite to the tethering moiety (Scheme **33**) [44].

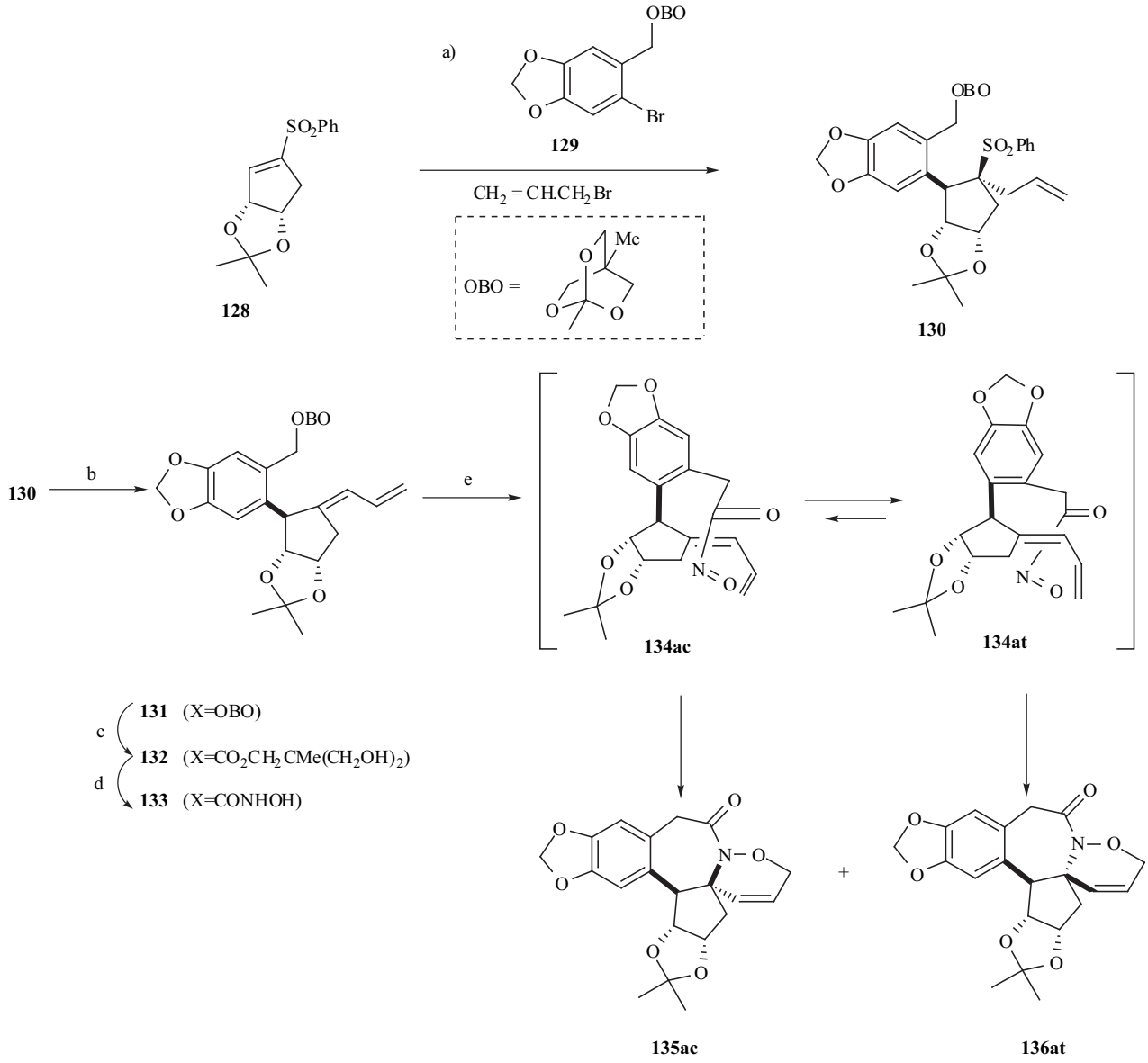
C. Total Synthesis of (-)-Kainic acid

A concise route to (-)-kainic acid **159** from enantiopure (+)-*cis*-4-carbobenzoxy amino-2-cyclopentanol **150** has been devised by employing concurrent Chugaev *syn*-elimination and intramolecular ene reaction as the key step (Scheme **34**) [45].

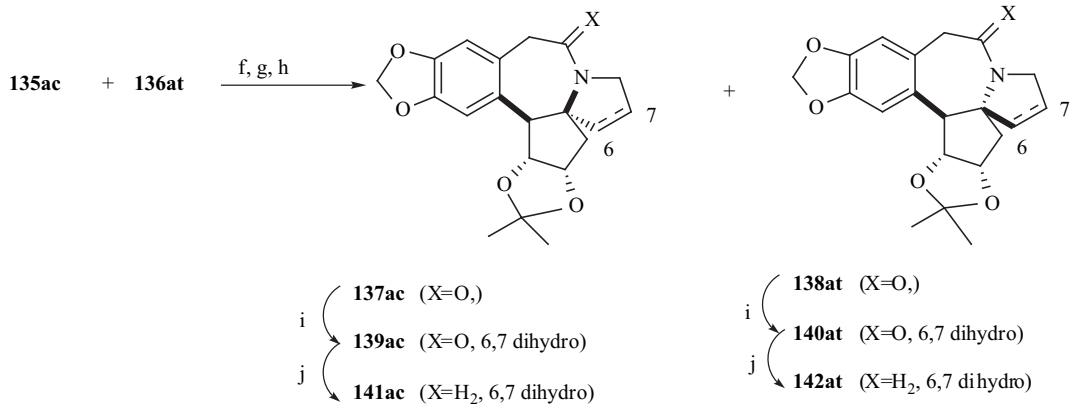


Conditions: (a) MOMCl, Et_2NPr, CH_2Cl_2; 92%; (b) BnOCONHOH, n-Bu_4NIO_4, CH_2Cl_2, -15 °C; 69%;
(c) 5% Na(Hg), Na_2HPO_4, aq. EtOH, 0 – 25 °C; 86%; (d) aq. EtOH, NaOH, heat; 98%;
(e) **122**, Et_3N, CH_2Cl_2, 25 °C; 90%; (f) NaH, MPMCl, DMF, 25 °C; 71%;
(g) $Pd(OAc)_2$, DIPHOS, TlOAc, DMF, 145 °C; 51%; (h) DDQ, CH_2Cl_2/H_2O (20:1), 25 °C; 81%.

Scheme 32.

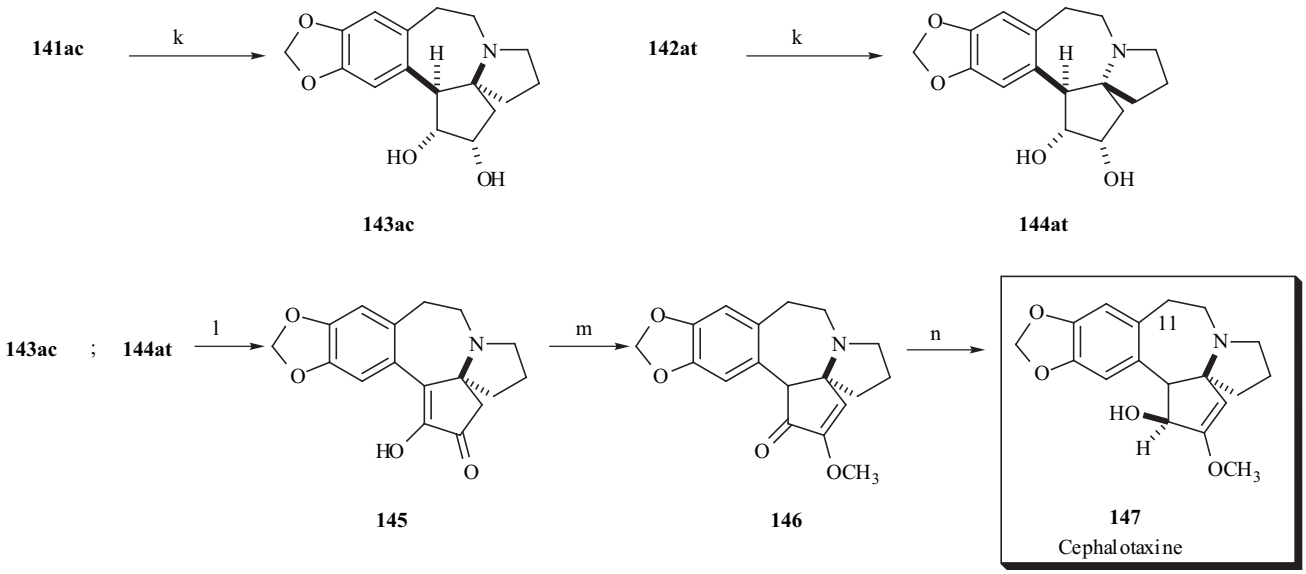


(a) **129**, *t*-BuLi (2.2 equiv), THF, -78 °C; and **128**, THF, -78 °C; THF:HMPA (1:1); (b) *t*-BuLi, THF, -78 °C–r.t.; (c) *p*-TsOH (0.2 equiv), THF, H_2O, 0 °C; (d) NH_2OH, MeOH, 0 °C; (e) n-Bu_4NIO_4, CH_2Cl_2, -78 °C–r.t.



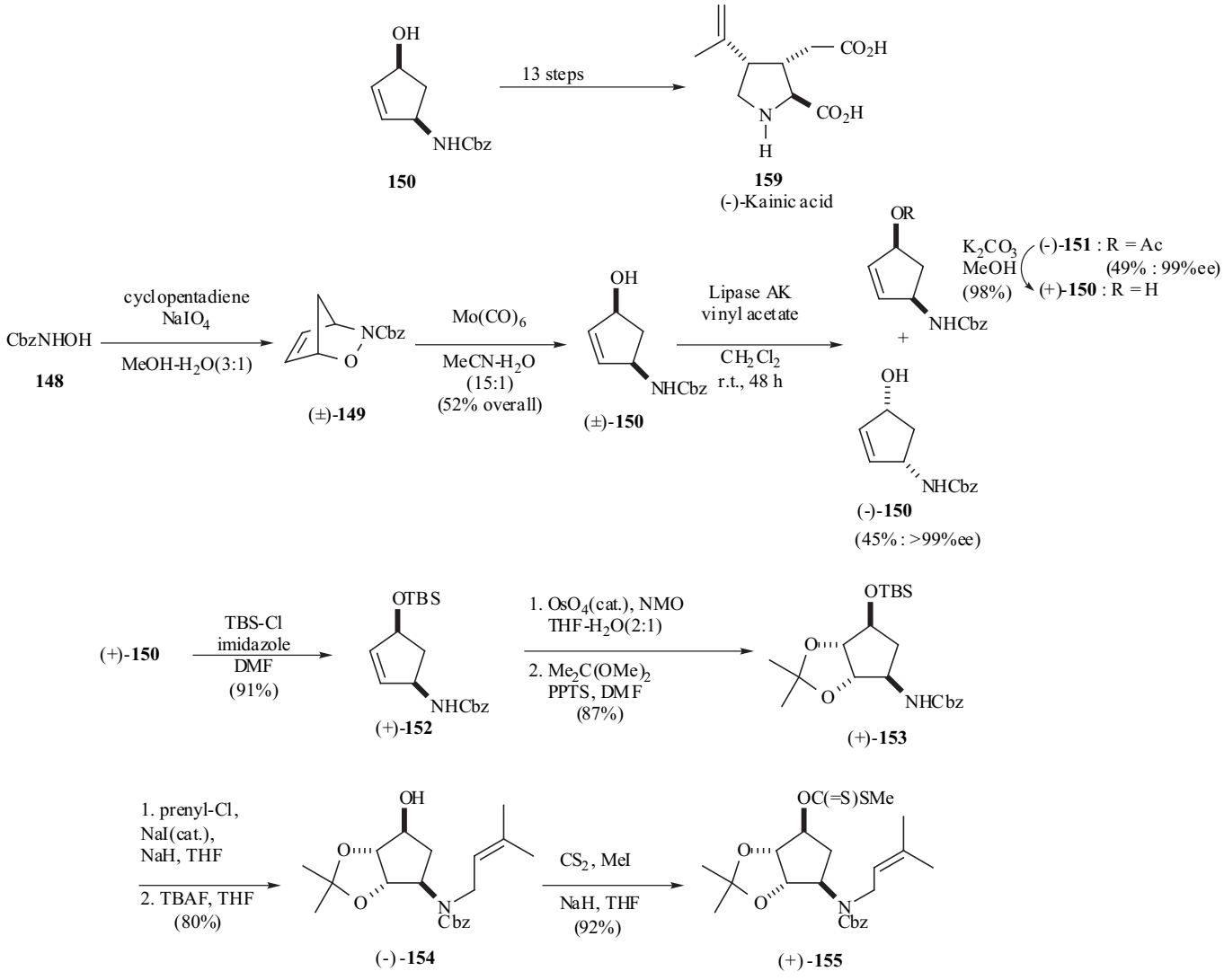
(f) 6% Na(Hg), EtOH, r.t.; (g) MsCl, Et_3N, CH_2Cl_2, 0 °C; (h) NaH, THF, r.t.; (i) H_2, 10% Pd/C, EtOH; (j) BH_3–THF, THF, reflux; MeOH, reflux.

(Scheme 33)contd.....



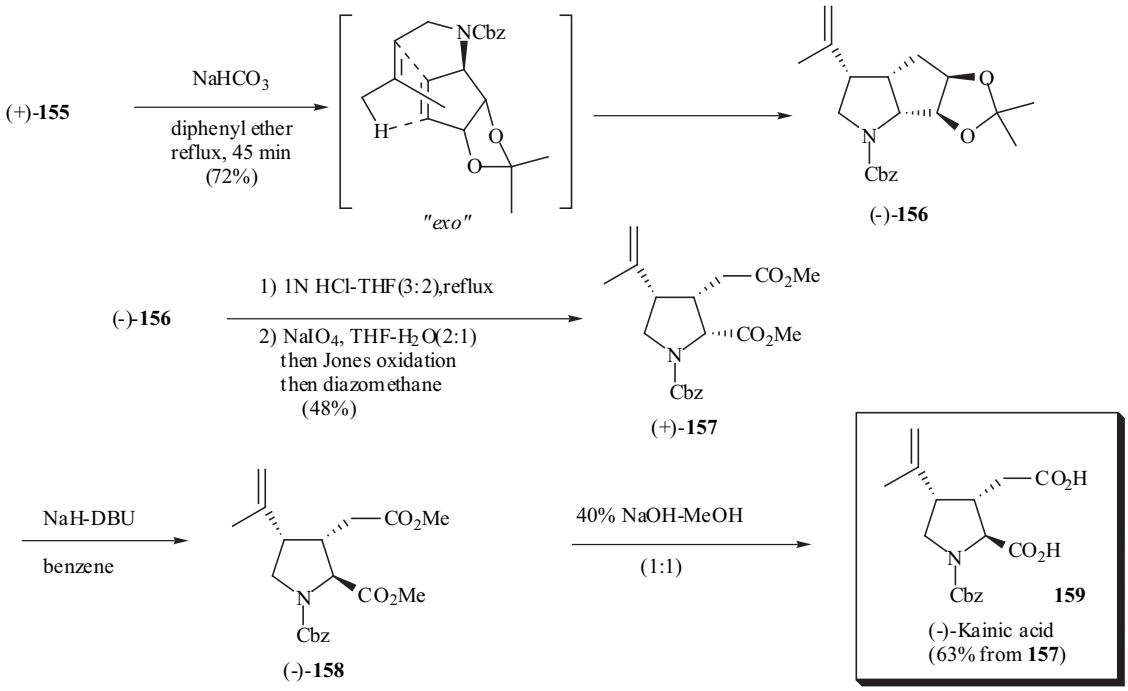
(k) 1 N HCl:THF (1:1), r.t.; (l) DMSO, TFAA, Et_3N, CH_2Cl_2, -78 °C; (m) dimethoxypropane, dioxane, *p*-TsOH,reflux; (n) $NaBH_4$, MeOH, -78 °C–r.t.

Scheme 33.

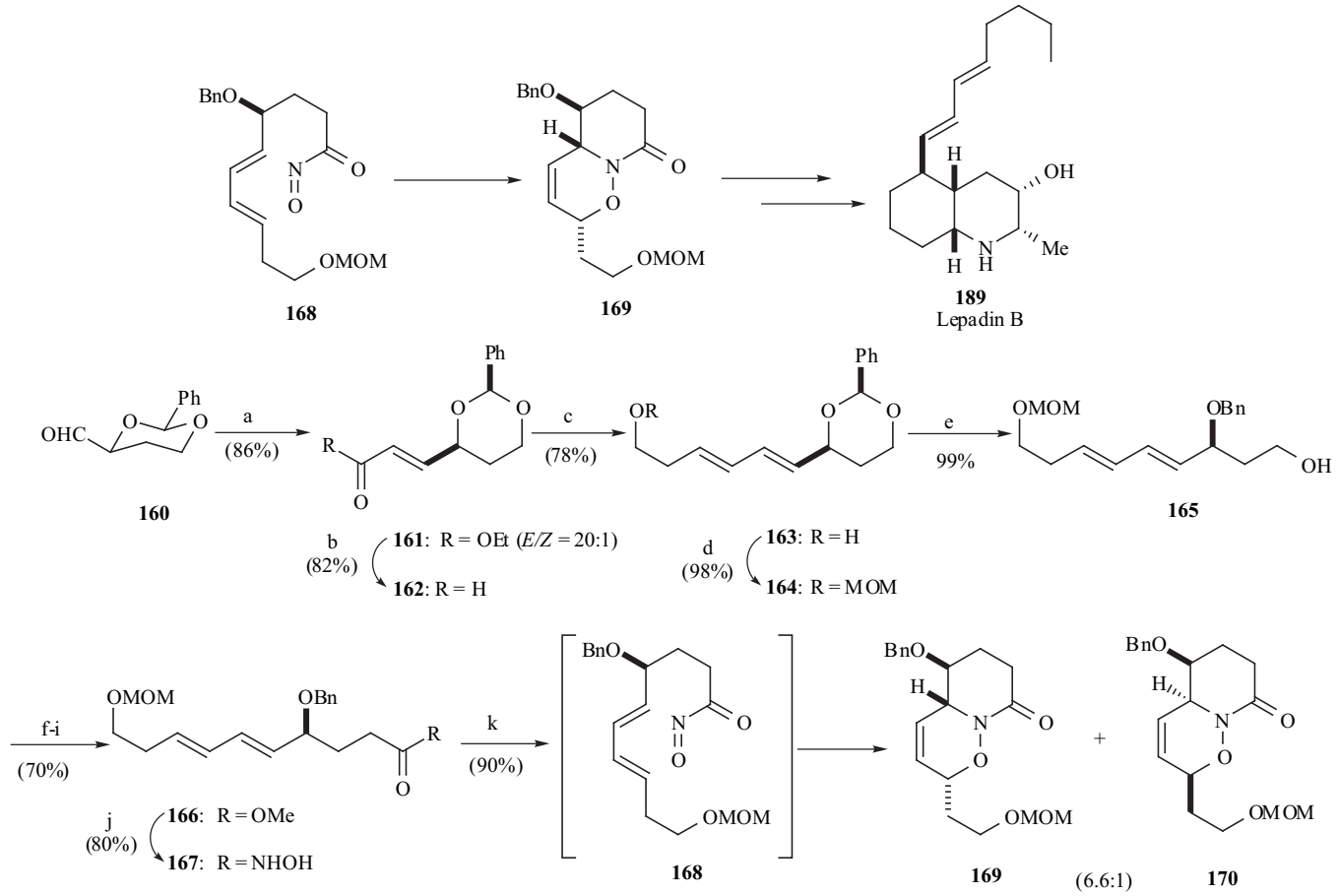


Scheme 33.

(Scheme 34)contd.....

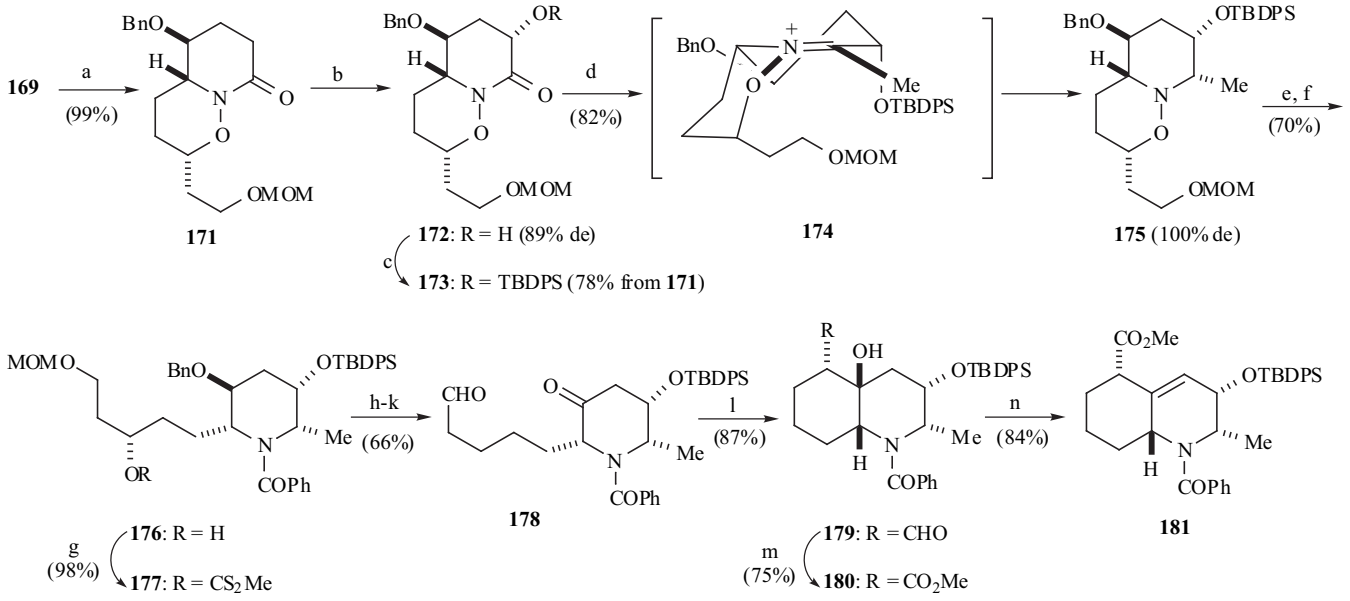


Scheme 34.

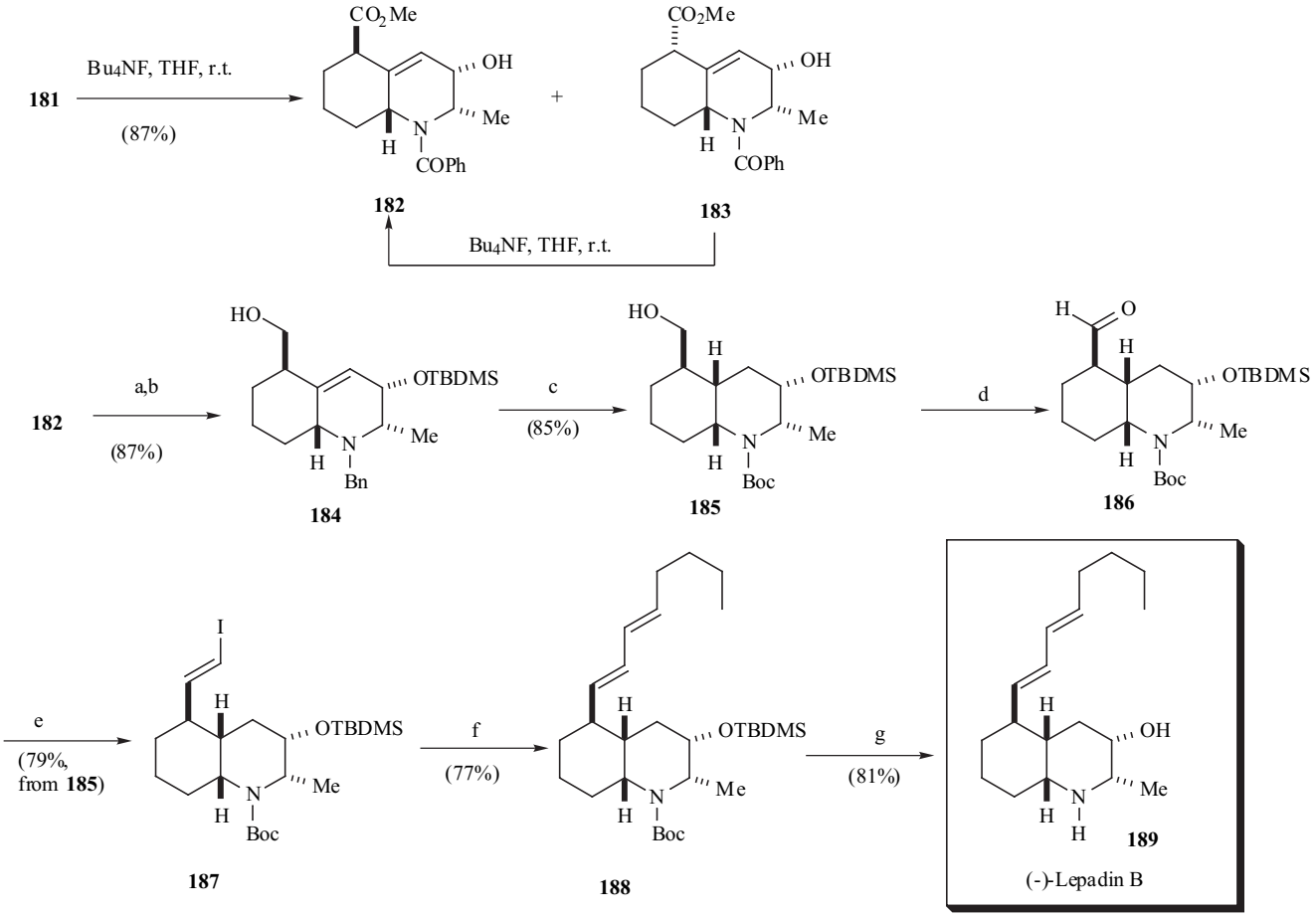


Reagents and conditions: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, -20 °C–r.t.; (b) i) DIBALH, THF, r.t.; ii) MnO_4, CH_2Cl_2; (c) $Ph_3P^+(CH_2)_3OHI^-$, LiHMDS, THF, 0 °C–r.t.; (d) MOMCl, *i*-Pr_2NEt, CH_2Cl_2; (e) DIBALH, CH_2Cl_2;
(f) TsCl, DMAP, Et_3N, CH_2Cl_2; (g) NaCN, DMSO, 50 °C; (h) NaOH, MeOH-H_2O, reflux; (i) CH_2N_2, Et_2O; (j) $NH_2OH.HCl$, KOH, MeOH, 0 °C;
(k) Pr_4NIO_4, H_2O-DMF (50:1), 0 °C.

(Scheme 35)contd.....



Reagents and conditions: (a) H_2, Pd-C, THF; (b) LiHMDS, (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine, THF, -78 °C; (c) TBDPSCl, imiazole, DMF; (d) MeMgBr, THF, 0 °C, then $NaBH_3CN$, AcOH, THF, 0 °C; (e) Zn, 90% AcOH, 60 °C; (f) PhCOCl, then 5% KOH; (g) CS_2, NaH, imidazole, then MeI, THF; (h) Bu_3SnH, AIBN, benzene, reflux; (i) PPTS, *t*-BuOH, reflux; (j) H_2, $Pd(OH)_2$, MeOH; (k) $(COCl)_2$, DMSO, Et_3N, -78 °C–r.t.; (l) piperidine(0.2 equiv), AcOH(0.2 equiv), benzene, reflux; (m) i) PDC, DMF; ii) CH_2N_2, Et_2O; (n) $SOCl_2$, Et_3N.



Reagents and conditions: (a) TBDMSCl, imidazole, DMF; (b) $LiAlH_4$, THF, reflux; (c) i) H_2(5 atm), Pd-C, THF; ii) (Boc)O, CH_2Cl_2; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78–0 °C; (e) CHI_3, $CrCl_2$, THF; (f) (*E*)-1-hexenyldihydroxy-borane, $Pd(PPh_3)_4$ (5 mol%), 2M aq. KOH, THF, 50 °C; (g) Bu_4NF, THF, then CF_3CO_2H, CH_2Cl_2.

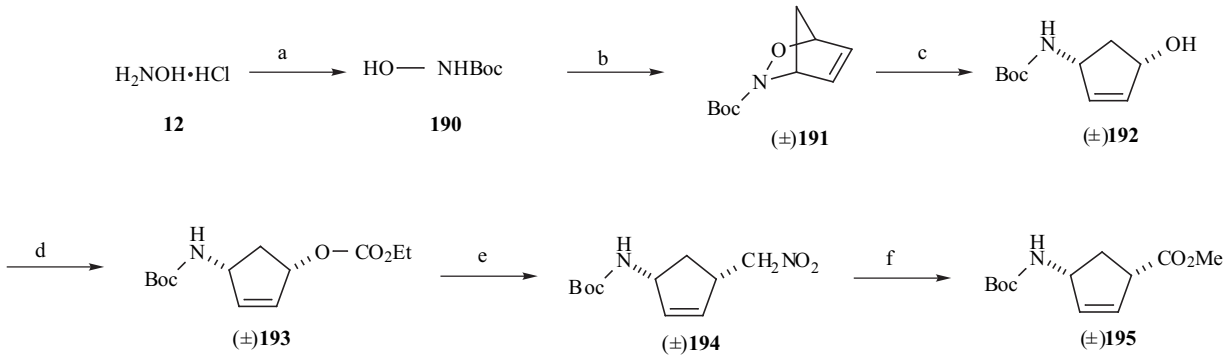
Scheme 35.

D. Total Synthesis of (-)-Lepadine B

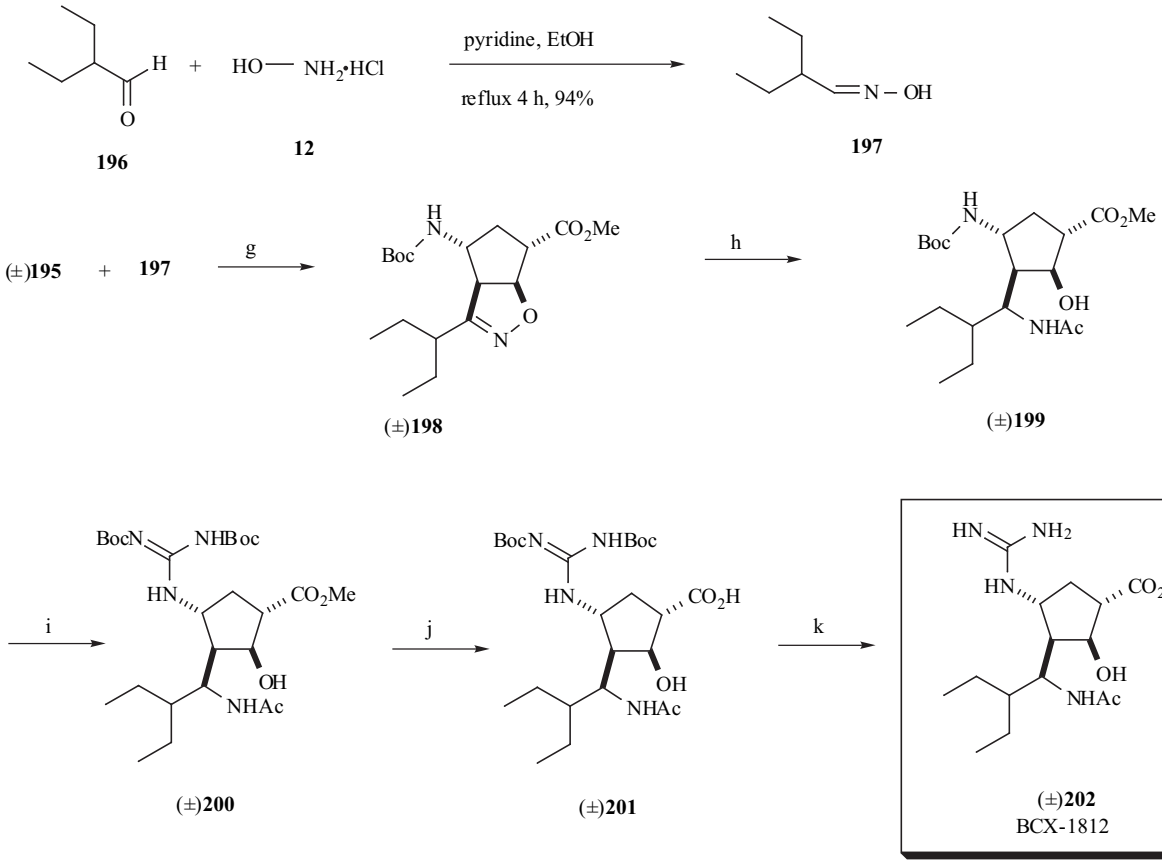
An enantioselective total synthesis of (-)-lepadine B **189** has been developed starting from (*2S,4S*)-2,4-*O*-benzylidene-2,4-dihydroxybutanal **160**. The key steps in this synthesis include the use of an aqueous intramolecular acylnitroso Diels-Alder reaction to afford the *trans*-1,2-oxazinolactam and Suzuki cross-coupling reaction to elaborate the (*E,E*)-octadienyl unit (Scheme **35**) [46].

E. Total Synthesis of racemic BCX-1812(RWJ-270201)

A convergent and versatile racemic total synthesis of the anti-influenza agent BCX-1812 **202** was accomplished on the basis of a sequence of stereo selective reactions. The size of the core ring can be varied depending on the size of the diene used for the preparation of the cycloadduct **191** using an acylnitroso-based hetero-Diels-Alder reaction. Elaboration of **191** to methyl ester **195** followed by a precedented [3+2] dipolar cycloaddition gave bicyclic isooxazoline **198** in a



Reagents: (a) Boc_2O, $NaHCO_3$, THF/H_2O (4:1), 89%; (b) $NaIO_4$, Cp, $MeOH/H_2O$ (4:1), 81%; (c) $Mo(CO)_6$, $NaBH_4$, $MeCN/H_2O$ (20:1), 66%; (d) ethyl chloroformate, pyridine/CH_2Cl_2 (1:1), 92%; (e) $MeNO_2$, Et_3N, $Pd(OAc)_2$, PPh_3, THF, 70%; (f) i) $NaNO_2$, AcOH, DMF, ii) (TMS)Cl, MeOH, 58% in two steps.



Reagents: (g) NaOCl (bleach), Et_3N, CH_2Cl_2, 61%; (h) i) H_2, PtO_2, HCl, MeOH, ii) Ac_2O, Et_3N, CH_2Cl_2, 82% in two steps; (i) i) HCl gas, ether, ii) 1,3-bis(*t*-Boc)-2-methyl-2-thiopseudourea, $HgCl_2$, Et_3N, DMF, 82% in two steps; (j) 1 N NaOH, EtOH/THF (1:1), 95%; (k) TFA, Et_3SiH, CH_2Cl_2, 78%.

Scheme 36.

region- and stereoselective fashion. Incorporation of the peripheral guanidino group and subsequent deprotection provided the target molecule **202** (Scheme **36**) [47].

V. CONCLUSION

The chemistry of acylnitroso species are very interesting. Scientists are utilizing these transient intermediates for the designing of many molecules of natural products and many complicated organic molecules and this trend is going on for the new inventions. Hetero-Diels-Alder reactions as well as ene reactions of acylnitroso intermediates occupy the central position as an essential step in the chemical transformations. Acylnitroso intermediates in hetero-Diels-Alder reactions have been studied more extensively than any other of the nitroso dienophiles. Examples of Lewis acid mediated asymmetric catalysis lack completely in the area of hetero Diels-Alder chemistry. Nevertheless, cycloadditions involving acylnitroso dienophiles have reached an advanced level concerning stereoselectivity and therefore, much attention has been paid towards the preparation and application of chiral, enantiopure dienophiles and dienes for these reactions. Consequently, acylnitroso species stand as the very reactive and useful intermediates in the total synthesis of natural products.

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