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CYCLOADDITION REACTIONS

OF

C-NITROSOCARBONYL COMPOUNDS

IN

ASYMMETRIC SYNTHESIS

A thesis presented in part fulfilment

of

the requirements for the degree of

Ph.D.

By

MUHAMMAD NAZEER

Department of Chemistry

University of Glasgow

October 1989

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To

My parents, whose sacrifices

made possible this Degree

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MUHAMMAD NAZEER

CONTENTS

SUMMARY

Oxidation of (±)-mandelohydroxamic acid (328a) with periodate gave the corresponding transient C-nitrosocarbonyl compound (329a) which was trapped at 0°C in situ by the diene, thebaine (26) to give a mixture of cycloadducts (330a) in 1:1 ratio. No stereochemical control was observed, even when the racemic dienophile was generated in the presence of a deficiency of thebaine. Cycloaddition of the same transient dienophile (329a) to cyclopentadiene yielded an inseparable mixture of diastereoisomers (338a) and (339a). The corresponding O-acetyl derivatives (338b) and (339b) were shown by ^{1}H n.m.r. spectroscopy to be in a ratio of 5.1:1. Similarly cyclohexa-1,3-diene and the mandelic dienophile (329a) gave inseparable mixture of the isomers (340a) and (341a). This mixture, after acetylation, afforded the O-acetyl derivatives (340b) and (341b) and separable by t.l.c., in a ratio of 3.5:1. The cycloadducts (349) and (350) derived from (±)-hexahydromandelohydroxamic acid (345) and cyclohexa-1,3-diene were obtained in a ratio of 2.5:1. Similarly cyclopentadiene and (±)-hexahydromandelic nitroso compound (346) yielded a mixture of diastereoisomeric cycloadducts (347) and (348) in a ratio of 3.6:1. Finally oxidation of (±)-3,3-dimethyl-2-hydroxybutanohydroxamic acid (356) in the presence, separately, of cyclohexa-1,3-diene and cyclopentadiene affo-rded the corresponding mixtures of diastereoisomers (357) and (358) and (359) and (360) in the ratios of 4.6:1 and 3.4:1, respectively.

The asymmetric induction observed in all the cases was thought to have been enhanced by intramolecular hydrogen bonding in the α-hydroxy acylnitroso dienophiles. This ideas was strengthened when the racemic O-methylmandelo-hydroxamic acid (364), on oxidation with

cyclohexa-1,3-diene and cyclopentadiene, gave the diastereoisomeric products (365) and (366) , and (367) and (368) in a ratio 2.1:1 and 2.6:1, respectively, inferior to those for the mandelic nitroso compound (329a).

As hoped considerably higher asymmetric inductions were observed in all the cases when the foregoing reactions were carried out at -78°C rather than at 0°C. The highest ratio of the diastereoisomers 11:1 was obtained for the cycloadducts (357) and (358) derived from the tert-butyl derivative and cyclohexa-1,3-diene. Generally a two-fold increase in ratios were observed.

Oxidation of (S)-mandelohydroxamic acid (328c) in the presence of cyclohexa-1,3-diene at 0°C gave a mixture of cycloadducts, which were acetylated, as before. The O-acetyl derivatives were separated and the major isomer (377b) was cleaved to give the known, optically active, bicyclic oxazine hydrochloride (273). This degradation established the stereo-chemistry of the major cycloadduct as 1R, 4S.

(R)-Phenylglycine was converted into the corresponding 2-acetylamino-2-phenylacetohydroxamic acid (381), which was oxidised at -78°C, in the presence of cyclohexa-1,3-diene to give a mixture of the diastereoisomeric cycloadducts (382) and (383) in 1:1 ratio, i.e. no stereochemical control was observed.

To test whether asymmetric induction would be observed using a

known precursor of (±)-trans-2-phenylcyclohexanol (392) was prepared from cyclohexene oxide and converted into the racemic N-hydroxy carbamic ester (394) via the chloroformate (393). Oxidation of the carbamic ester (394) with periodate at - 78°C, in the presence of cyclohexa-1,3-diene gave a mixture of diastereoisomeric cycloadducts (395) and (396) in a ratio of 3.6:1. Oxidation of N-hydroxycarbamic ester (394) at 0°C, failed to give the mixture of cycloadducts (394) and (395), therefore ratio of the products could not be measured due to complexity of ^1H n.m.r. spectrum.

CHAPTER 1

INTRODUCTION

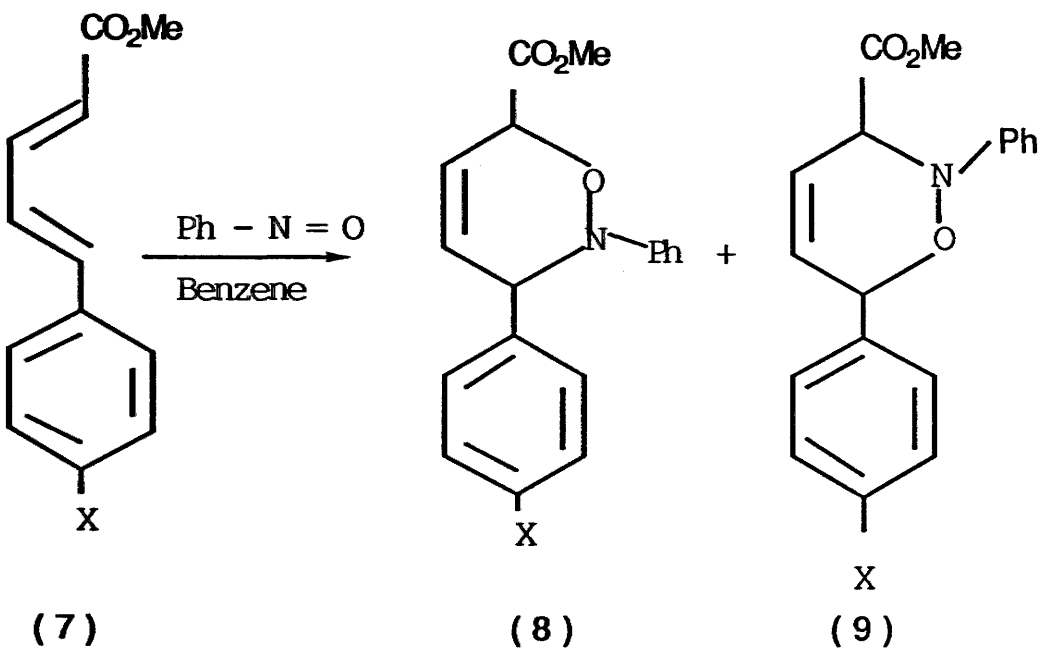
Cycloaddition Reactions of C -Nitroso Compounds

C-Nitroso compounds (1) are known to react with conjugated dienes (2) to afford 3,6-dihydro-1,2-oxazines (3) (Scheme1). In general, most types of C-nitroso compounds appear to be reactive heterodienophiles. But, on the other hand, N-nitroso and O-nitroso compounds and nitrosyl chloride do not undergo Diels-Alder cycloaddition reaction. The subject has been reviewed by Hamer et al[1]., Kresze et al[2]., Kirby[3] and Weinreb et al[4]. The present review will emphasize some of the newer aspects along with some examples from the earlier reviews.

Aryl nitroso compounds

The most thoroughly studied dienophiles of this class are the aryl nitroso compounds (nitrosoarenes). Wichterle et al[5]. and later Arbuzov et al[6]. treated nitrosobenzene (4) with buta-1,3-diene (5) and obtained the Diels-Alder cycloadduct (6) in good yield (Scheme 2).

The orientational preferences and the kinetics of the cycloadduct formation of various substituted nitrosoarenes were studied by Kresze and co-workers[7]. They therefore, treated the dienes (7) with nitrosobenzene to give the mixture of adducts (8) and (9) in different ratios depending upon the nature of the substituents (Scheme 3). These workers rationalized these results by considering dipolar and non-polar transition states and their



(7) (8) (9)

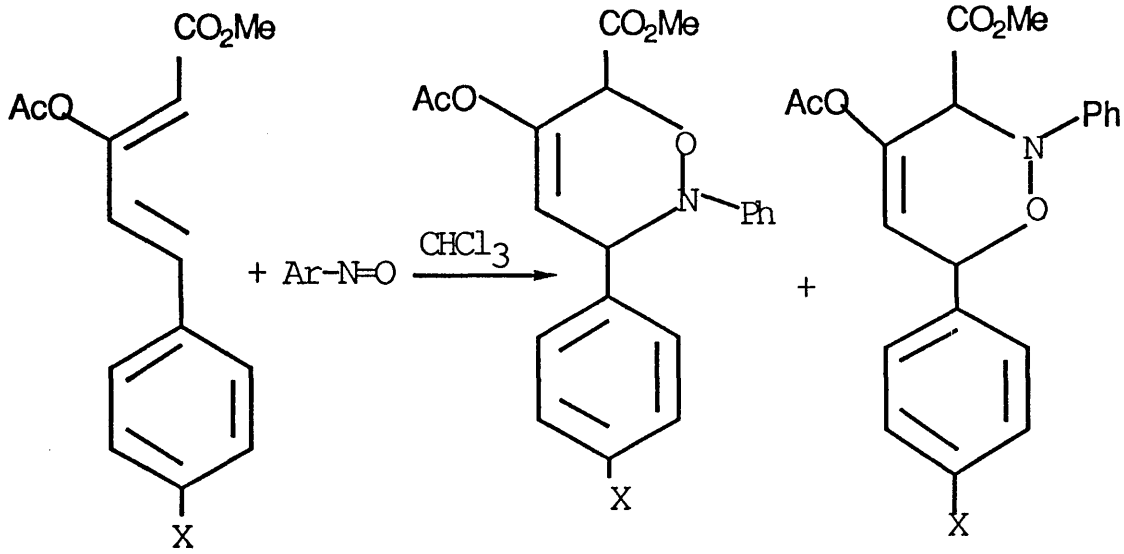
X	Ratio (8)	:	Ratio (9)
CN	61	:	39
H	80	:	20
OMe	78	:	22
Me	81	:	19
Cl	76	:	24
NMe_2	66	:	34

Scheme 3

relative stablization by aromatic electron- donating and electron-withdrawing groups. They also found that electron-withdrawing substituents *para* to to the nitroso group in substituted nitrosobenzene had a marked enhancing effect on the addition rate. Thus, *p*-nitronitrosobenzene added 3,500 times faster than did *p*-methoxynitrosobenzene. Kresze and co-workers[8] also found that the aromatic ring of the the 2π nitroso component also effects the regioisomer ratio, presumably by electronic stablization of the polar states leading to the formation of each product. Thus, they treated the dienes (10) with differently substituted nitrosobenzenes (11) and the adducts (12) and (13) were obtained in different ratios. The adduct (12; X=H,Ar=Ph) was converted into the pyrrole (14) by treatment with silica gel (Scheme 4).

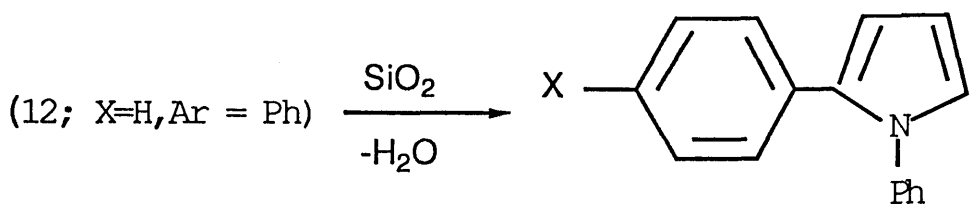
Recently, Given *et al*[9]. reported that the dihydrooxazine (16) derived from buta-1,3-diene and *p*-methoxycarbonylnitrosobenzene(15), contained a good chromophore for photochemical elimination of water. Reduction of the dehydration product (17) afforded the pyrrole (18) (Scheme 5).

The reaction of the nitrosobenzene with conjugated dienone (19) was studied by Hart and co-workers[10]. Only a single regioisomer (20) was obtained. Its formation was rationalized by FMO analysis by considering the interaction of the HOMO of the dienone and LUMO of the nitrosobenzene. The formation of the single regioisomer (25) from the dienol (24) may be due to the hydrogen bonding in the transition state of the reaction. The lack



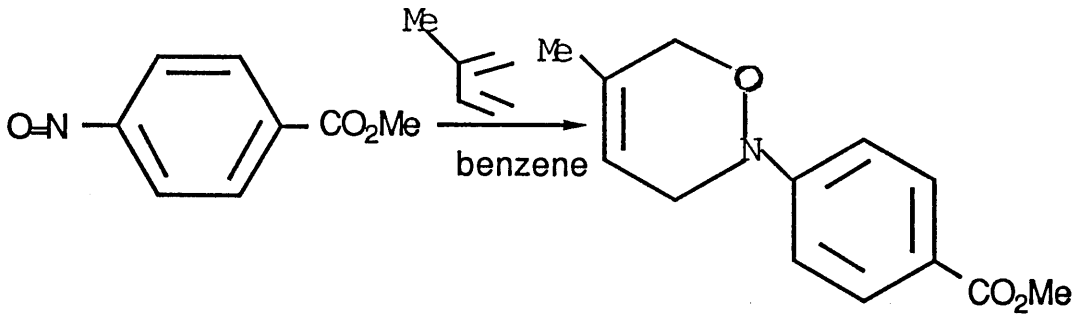
(10) (11) (12) (13)

X	Ar	Ratio (12)	:	Ratio (13)
H	Ph	76	:	24
H	4-ClC_6H_4	68	:	32
OMe	Ph	62	:	38
H	4-$NO_2C_6H_4$	54	:	46

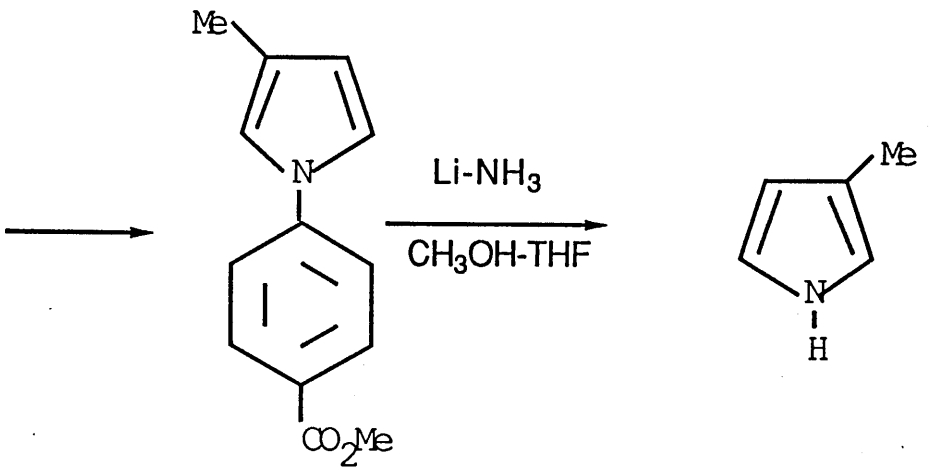


(14)

Scheme 4



(15) (16)



(17) (18)

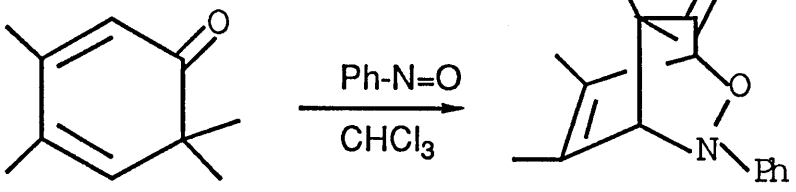
Scheme 5

of regioselectivity in the reaction of the dienone (21) to give the mixture of isomers (22) and (23) may be attributed to steric hindrance (Scheme 6).

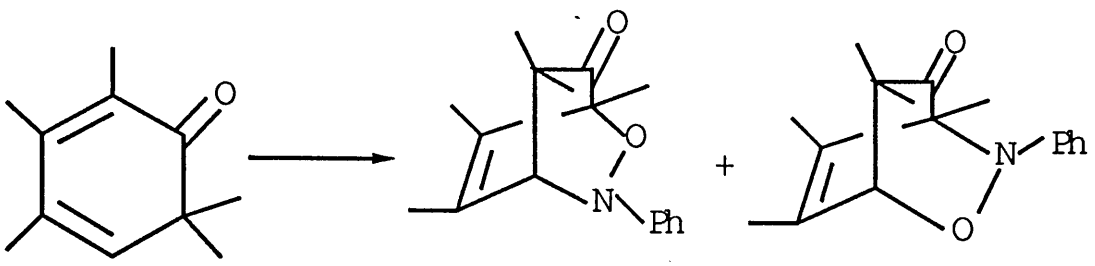
Kirby et al.[11] reported that nitrosobenzene adds to thebaine (26) both regio- and stereo-specifically to give the adduct (27) in good yield. They observed that the cycloaddition reaction was reversible at room temperature. Later it was found that, if cycloadducts of type (27) were made from nitosobenzene substituted with electron-withdrawing groups at the para position, no dissociation of the adducts was observed, and that the electron-donating groups favoured the dissociation . Further,this reaction provided the first route to the formation of 14-aminocodeinone derivatives (28) (Scheme 7).

A new methodology was developed by Taylor and co-workers[12] for the synthesis of aryl and heteroaryl nitroso compounds (31) from their parent amines (29). The adducts (32) of the expected type were obtained in reaction with 2,3-dimethylbuta-1,3-diene. They employed this method[13] for the synthesis of p-methoxycarbonylnitrosobenzene (15) and its reacton with 1-methoxy-buta-1,3-diene yielded a single regioisomer (33). This was then converted into pyrrolidinone (35) (Scheme 8).

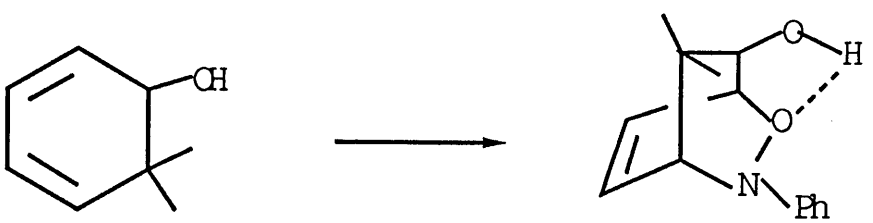
Knaus et al.[14] reported that nitrosobenzene adds regio - selectively to the N-acyl-1,2-dihydropyridines (36) to give a single adduct of type (37). They could not established the



(19) (20)

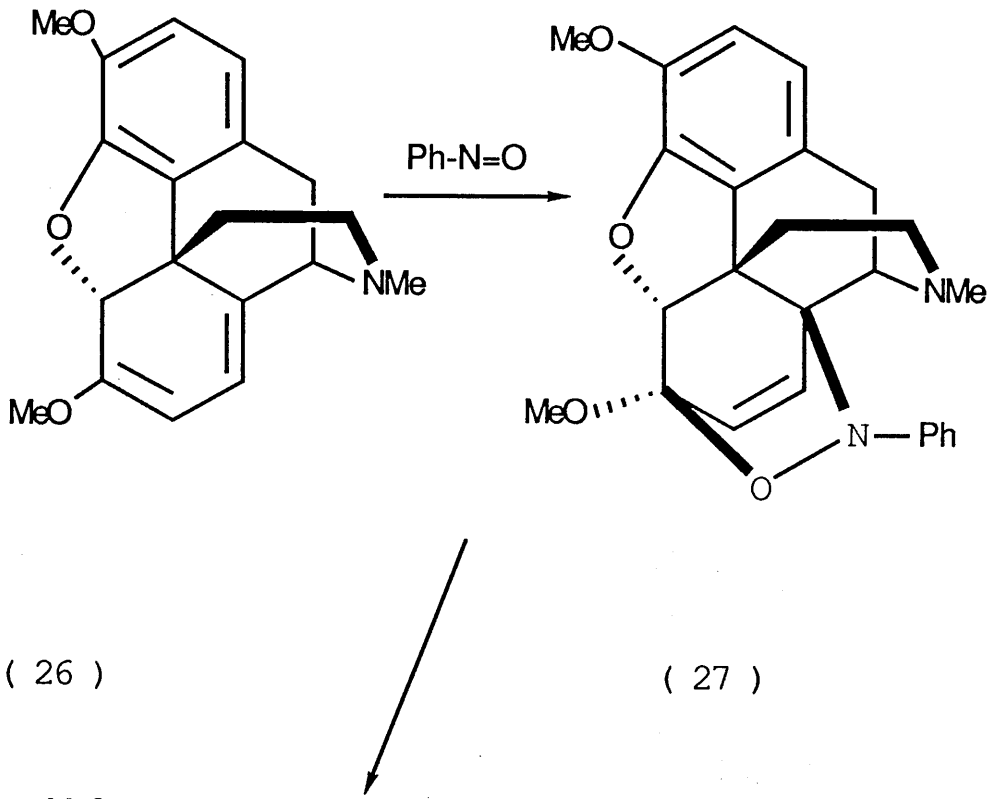


(21) (22) (23)



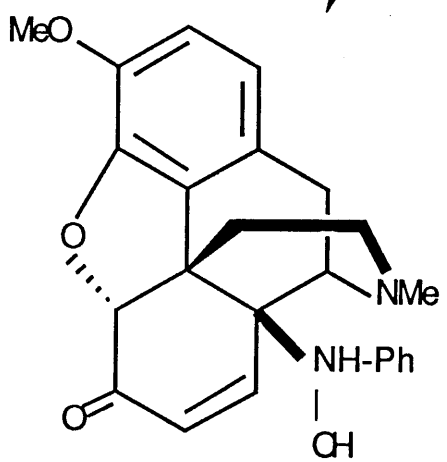
(24) (25)

Scheme 6



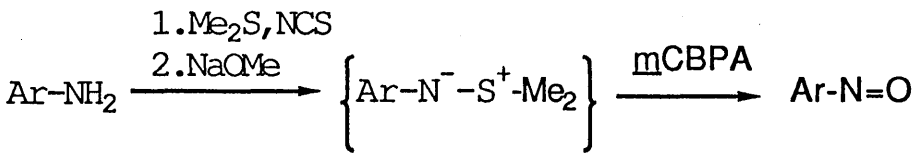
(26)

(27)

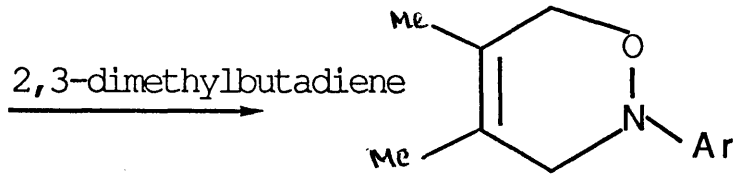


(28)

Scheme 7

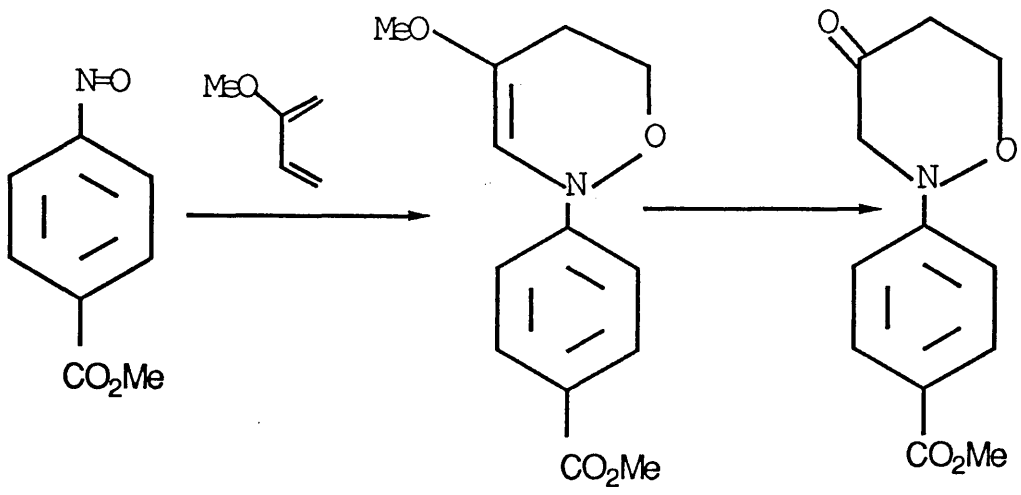


(29) (30) (31)

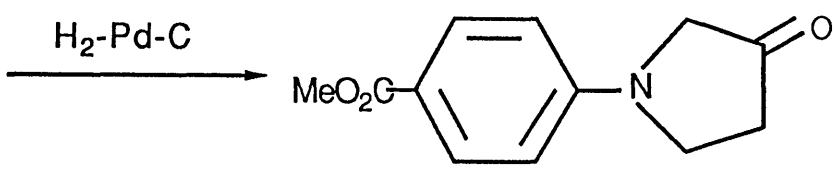


(32)

Ar= 2-pyridyl, 1-isoquinolyl and 2-pyrimidyl



(15) (33) (34)



(35)

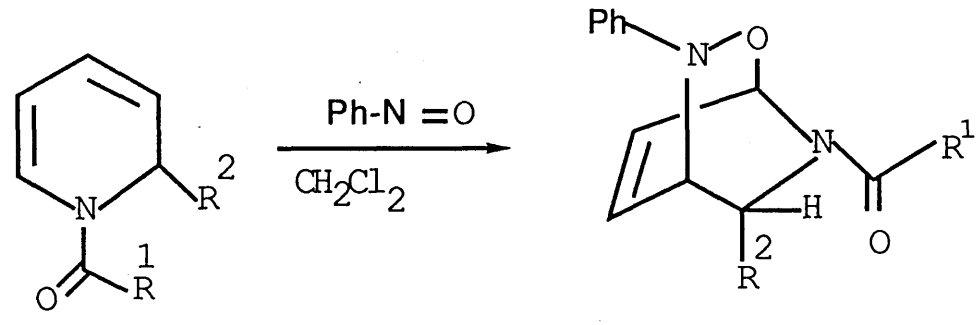
Scheme 8

orientation of the addition. The same reaction was studied by Streith and co-workers[15], who showed that the addition is governed by steric factors. They proved the structure of the adducts (37) as shown (Scheme 9).

Nitrosobenzene was treated with some 5,6-difunctionalized cyclohexa-1,3-dienes by Kresze et al.[16]. The difunctionalized diene (38) afforded the single regioisomer (39) , but the dienes (40) and (43) gave mixtures of the products (41) and (42) and (44) and (45), respectively. They were unable to rationalize these findings. However with diene (40) the adduct (41) with the hydroxyl group syn to the nitrosobenzene may be formed as the major compound because of the hydrogen bonding in the transition state (Scheme 10).

Gavalero et al.[17] treated protoporphyrin II dimethyl ester (46) with p-nitronitrosobenzene and obtained the mono Diels-Alder adduct (47) in good yield (Scheme 11).

Nitrosobenzene was treated with propellane (48) by Ashkenazi and co-workers[18] to give the mixture of anti and syn (2:1) adducts (49) and (50) (Scheme 12). When (48) was allowed to react with N-methylmaleimide, only the anti product was obtained. But N-phenyltriazolinedione produced the syn adduct exclusively

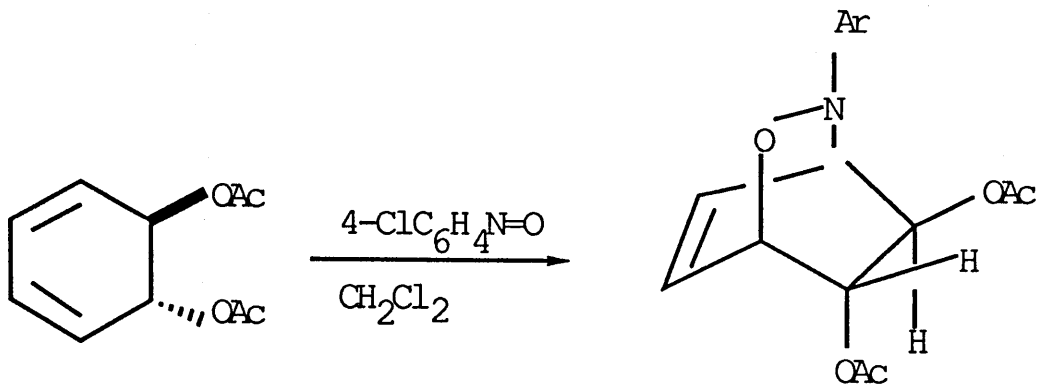


(36) (37)

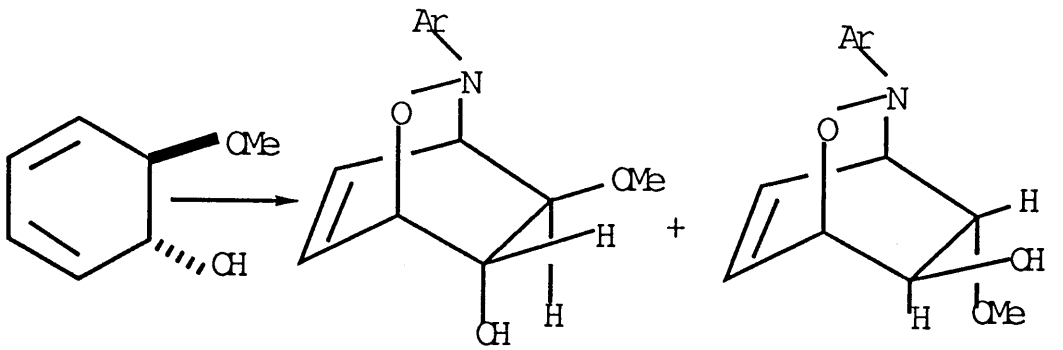
R^1 Me, OMe

R^2 Ph, H, Bu^n

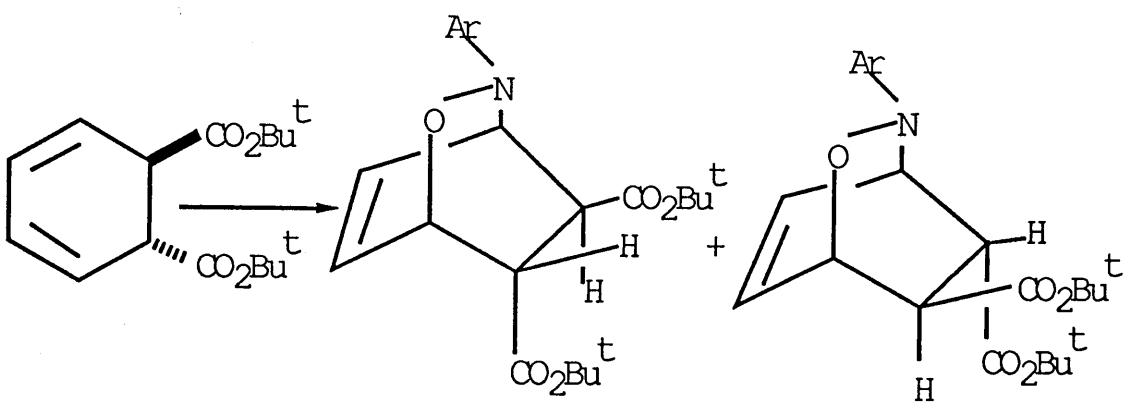
Scheme 9



(38) (39)

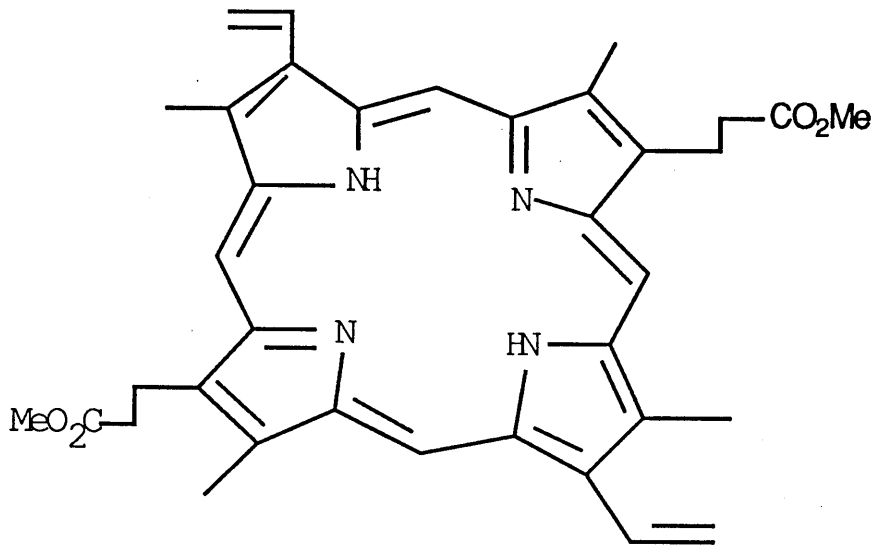


(40) (41) (42)

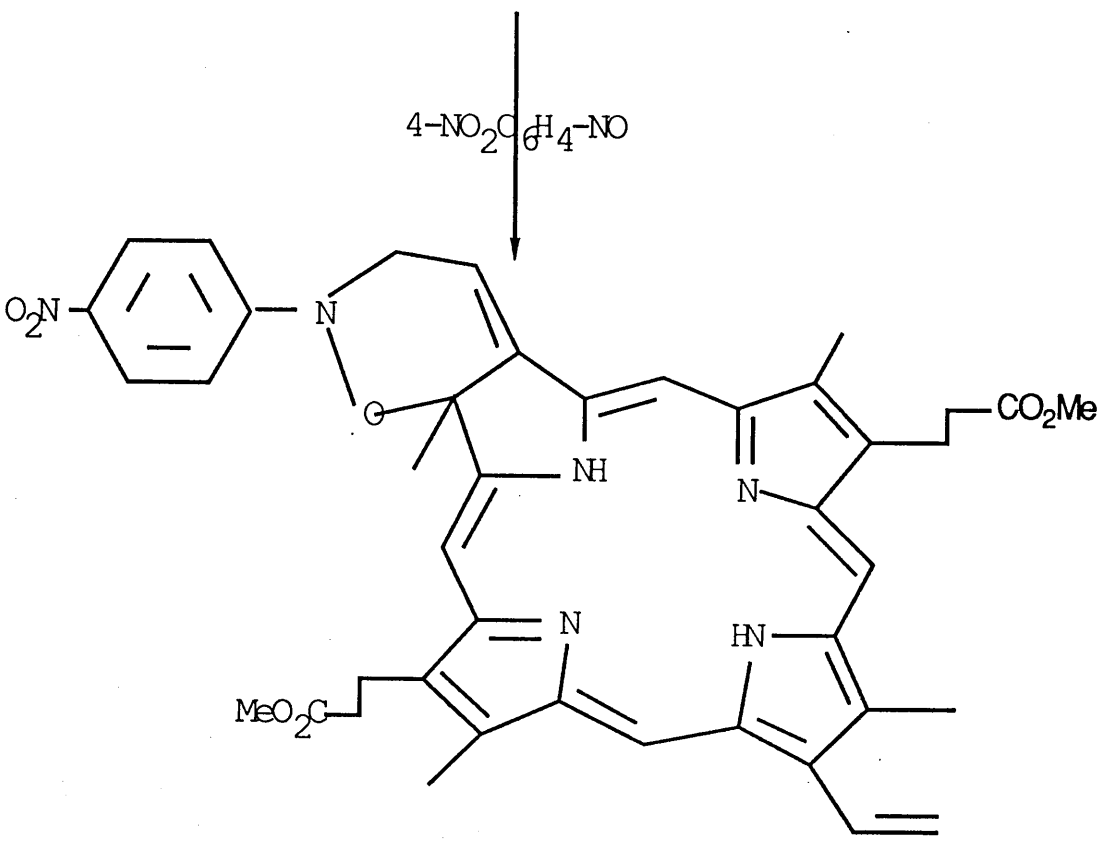


(43) (44) (45)

Scheme 10

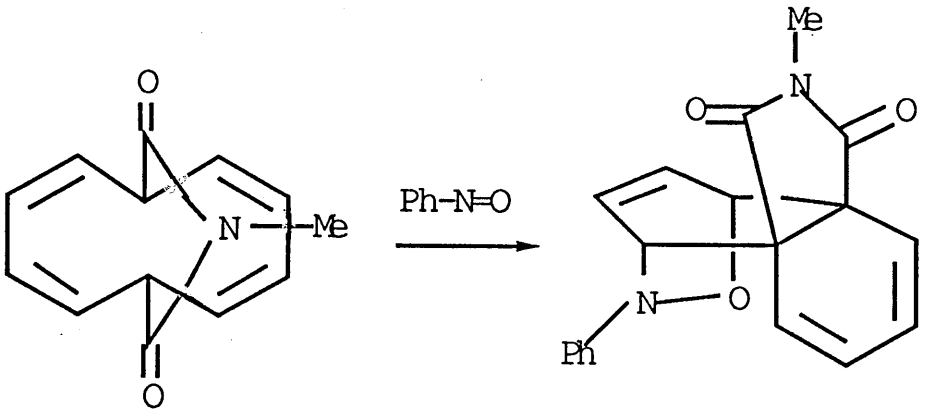


(46)

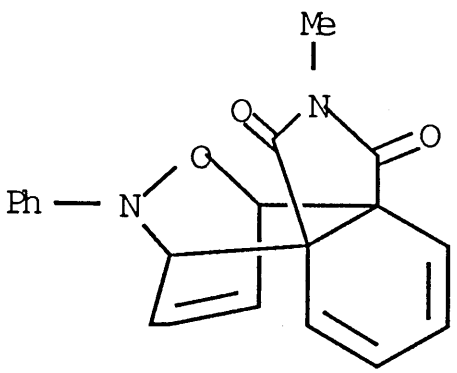


(47)

Scheme 11

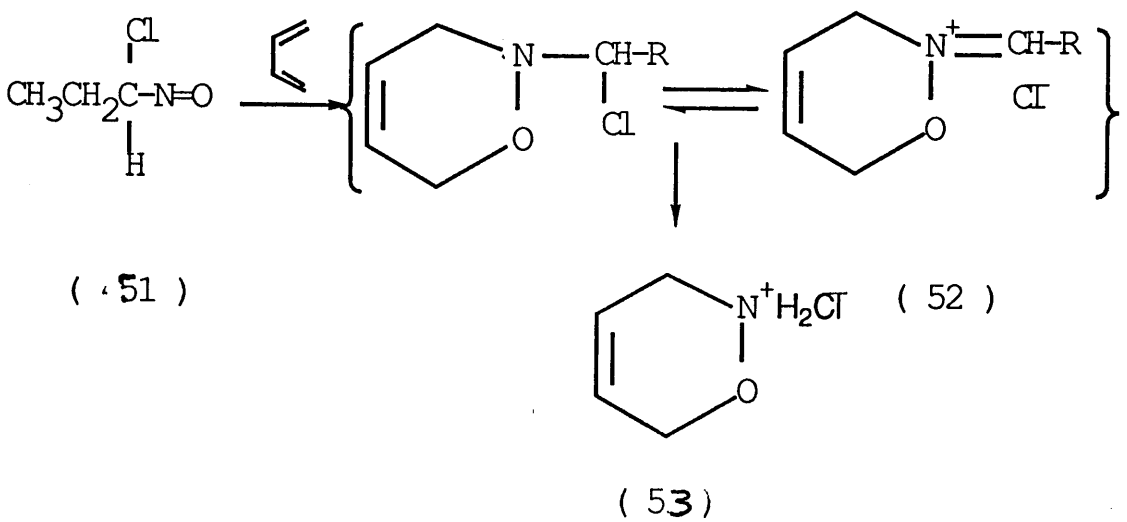


(48) (49)



(50)

Scheme 12



(51) (52)

(53)

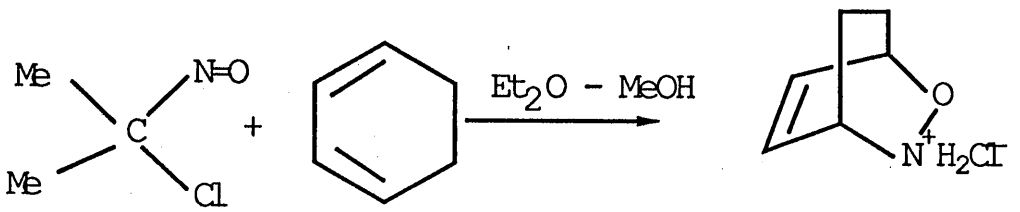
Scheme 13-a

Alpha-Halo nitroso compounds

Wichterle and co-workers[19] treated 1-chloro-1-nitroso-propane (51) with buta-1,3-diene and obtained the unstable adduct (52). Later it was found[20] that, if the reaction was conducted in an alcoholic solvent, or if the adduct (52) was heated in an alcoholic solvent, the ultimate product in both the cases was the hydrochloride of 3,6-dihydro-1,2-oxazine (53) (Scheme 13a). Similarly, Kelser[21] found that 2-chloro-2-nitrosopropane (54) when treated with cyclohexa-1,3-diene (55) to give the hydro-chloride (56) (Scheme13b). Again, Ranganathan and co-workers[22] reported the formation of an oxazine hydrochloride from cyclopentadiene in 89 % yield.

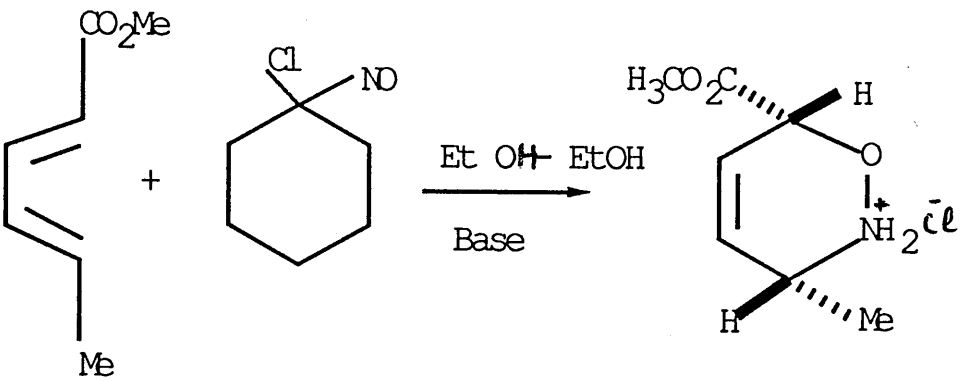
The orientational preferences of the α-chloronitroso compound were found to be similar to those of the nitrosoarenes by Belleau and co-workers[23]. Thus they synthesized stereospecifically (±)-5-amino-5,6-deoxyallonic acid (61) from methyl-trans, trans-sorbate (57) and 1-chloro-1 - nitrosocyclo-hexane (58) (Scheme 14).

The cycloaddition reaction of 1-chloro-1-nitrosocyclohexane (58) was exploited by Kresze et al.[24] with 5,6-diacetoxy-cyclohexa-1,3-diene (37) to give a single regioisomer (62), which was then converted to inosamine (63). When the same methodology was employed with nitrogen containg cyclohexa-1,3-diene (64), again a single adduct of the expected type (65) was

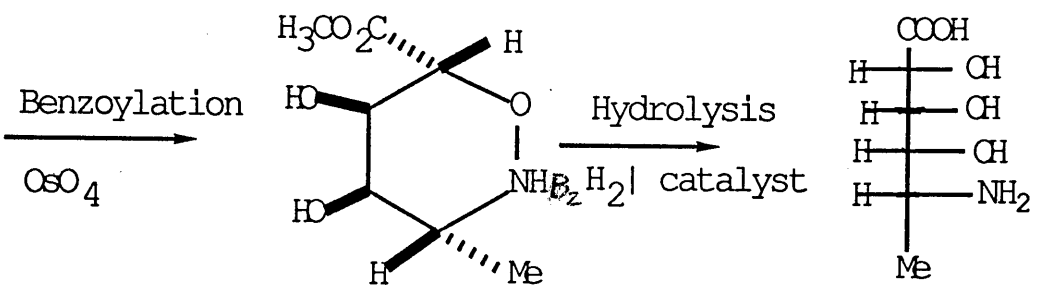


(54) (55) (56)

Scheme 13-b



(57) (58) (59)



(60) (61)

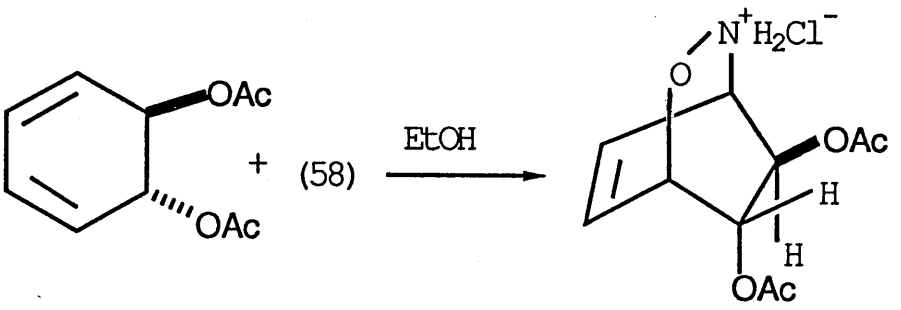
Scheme 14

obtained[25], probably due to hydrogen bonding in the transition state (Scheme 15)

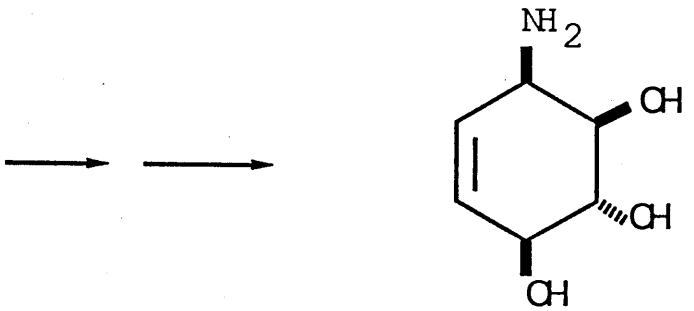
A Diels-Alder reaction of an α-chloronitroso compound was exploited by Leonard et al.[26] in the synthesis of cell division stimulant cis- zeatin (68). The major adduct from buta-1,3-diene and 1-chloro-1-nitrosocyclohexane (58) was employed for the above synthesis (Scheme 16). Kibayshi and co-workers[27] used this methodology in the synthesis of pseudotropanes (73). The benzoyloxy-cyclohepta-1,3-diene (69) and 1-chloro-1-nitroso-cyclohexane (58) gave adducts (70) and (71) in a 3 : 1 ratio. The major adduct (70) was converted into a tropane alkaloid in straightforward sequence (Scheme 17).

Nitrosyl cynide and acyl nitroso compounds

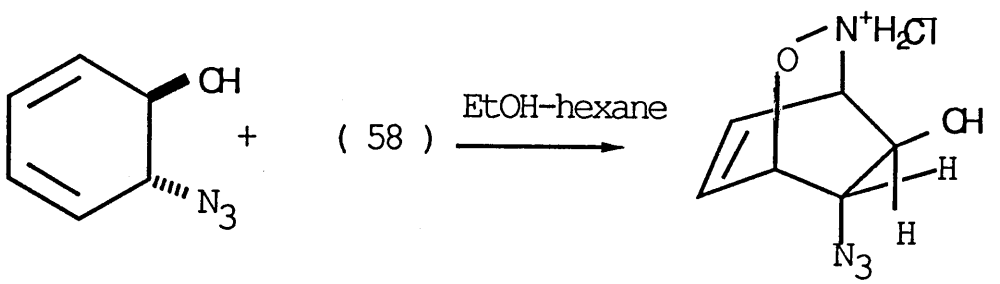
The synthetic utlity of the cycloaddition of nitrosoarenes and that of gem-chloronitroso compounds with conjugated dienes encouraged Kirby et al. to desgin a highly dienophilic species, nitrosyl cynide (74). They prepared this as a green gas from silver cynide and nitrosyl chloride. When the preparation was carried out in the presence of thebaine (26), they obtained an adduct (75) of the expected type[28]. The chemistry of nitrosyl cynide was conveniently explored by preparing its 9,10-dimethylanthracene (DMA) adduct (76). This adduct was then heated with thebaine (26) to give the thebaine adduct (75) along with a quantitative amount of DMA. This thermal transfer from DMA adduct provided a cleaner and more convenient source of nitrosyl cynide. The orientational



(35) (62)

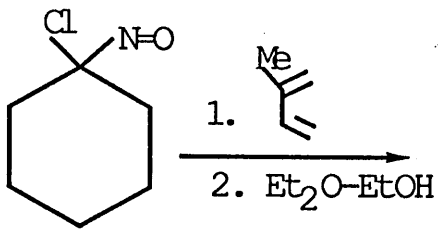


(63)

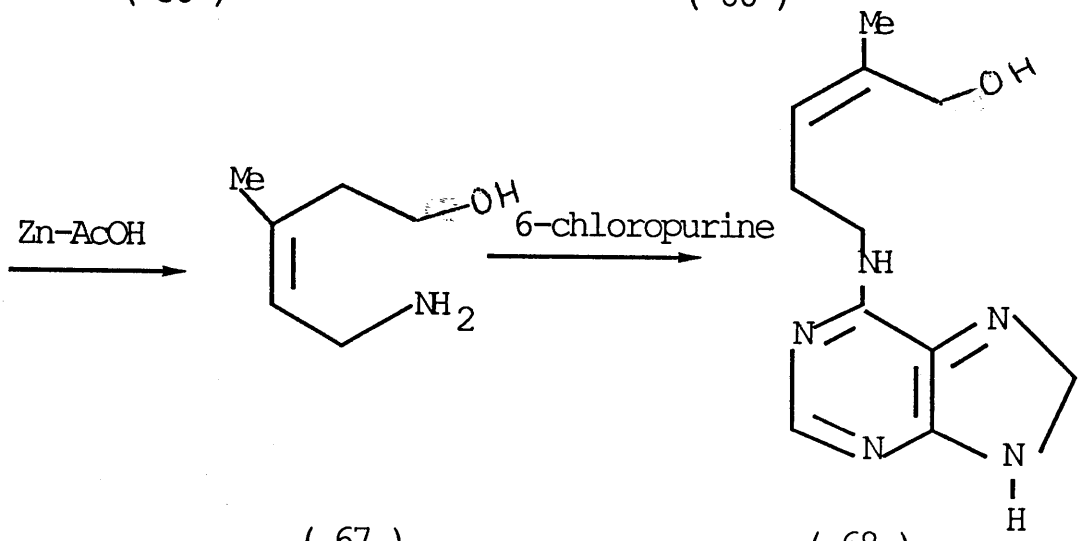


(64) (65)

Scheme 15

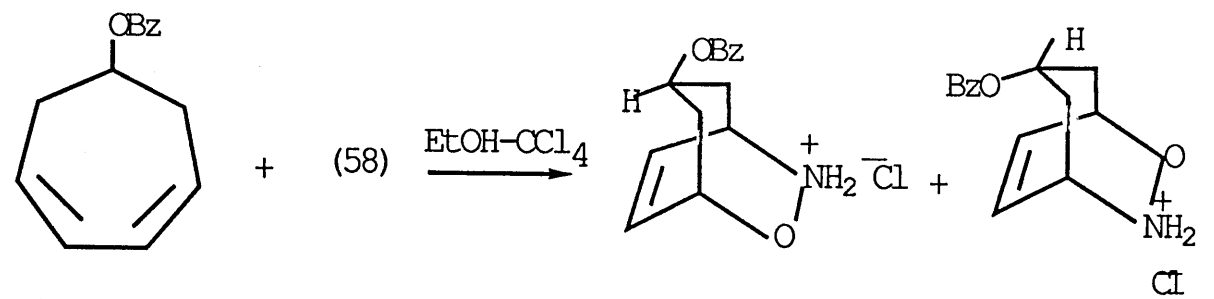


(58) (66)

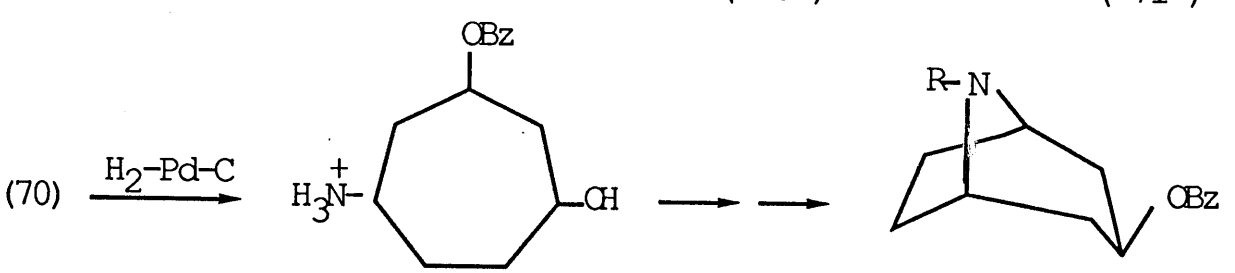


(67) (68)

Scheme 16



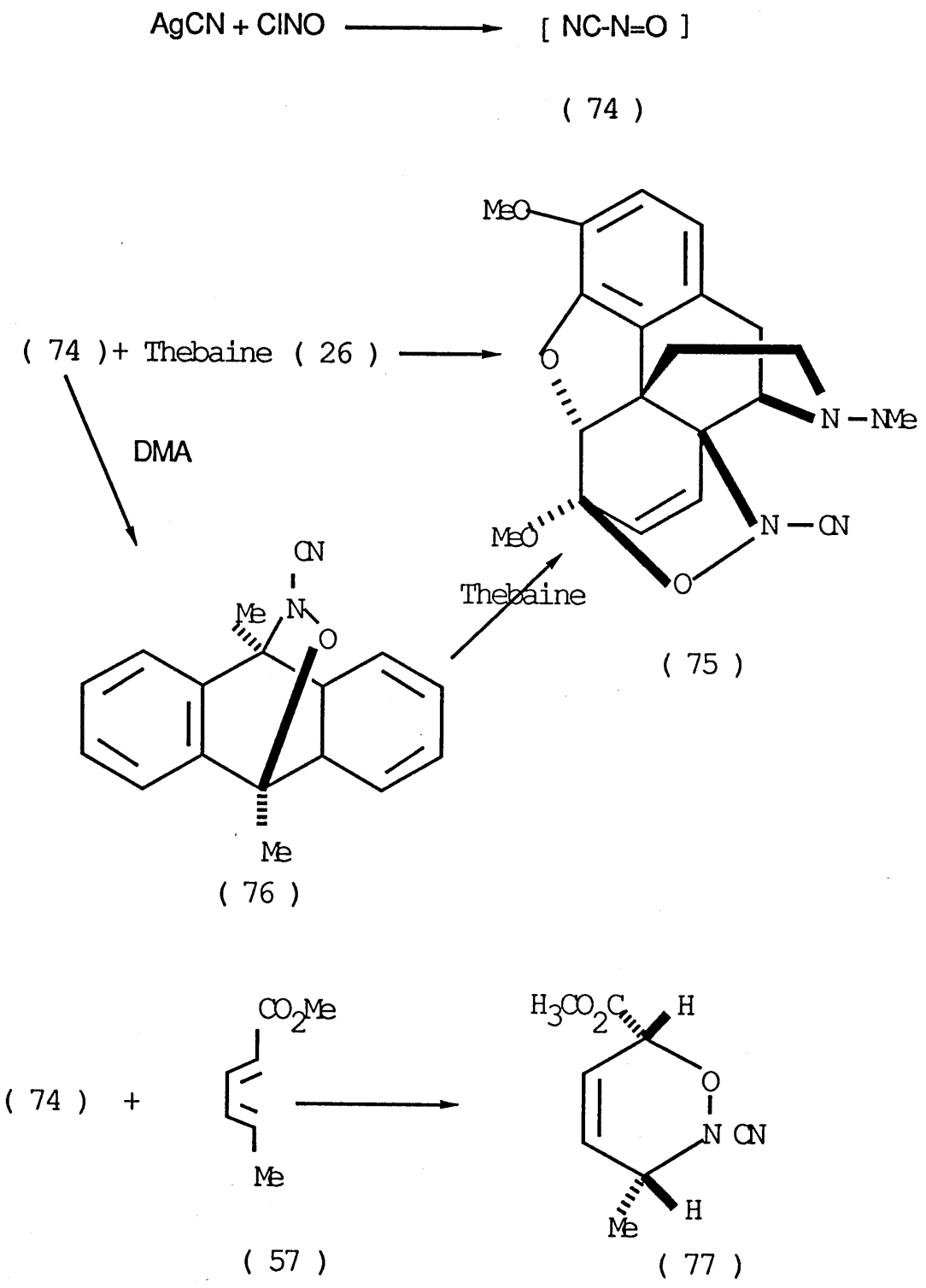
(69) (70) (71)



(72) (73)

R= H, Me

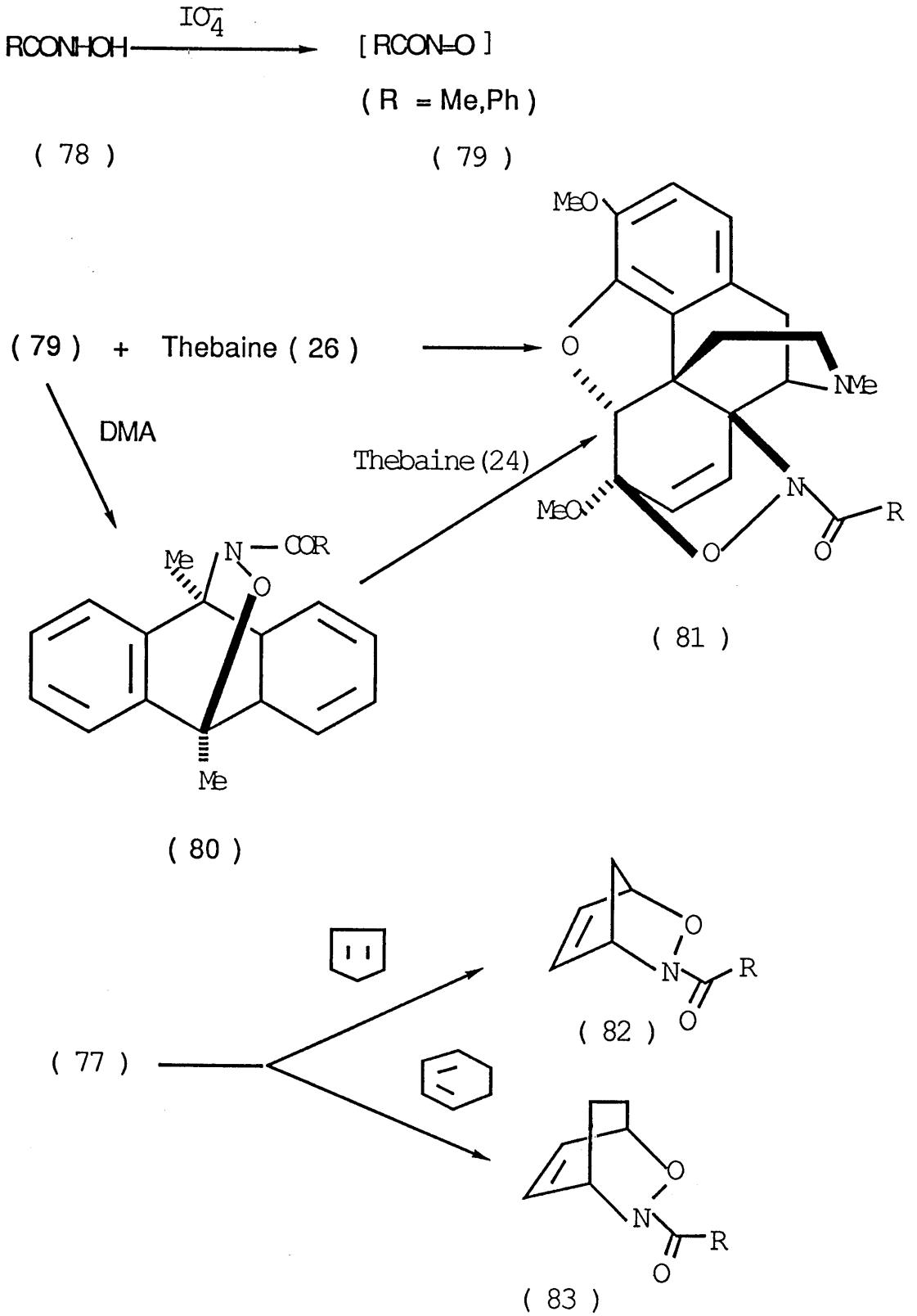
Scheme 17


AgCN + ClNO
[NC-N=O]
(74)
(74)+ Thebaine (26)
DMA
MeO
N-NMe
N-CN
MeO
Thebaine
(75)
CN
Me
N
O
Me
(76)
(74) +
CO2Me
Me
(57)
H3CO2C
H
O
N CN
Me
H
(77)

scheme 18

preference of this reaction was found to be similar as that of nitrosoarenes and gem-chloronitroso compounds. Again, when nitrosyl cyanide reacted with methyl trans, trans-sorbate (57) the stereochemistry of the resulting adduct (77) was found to be identical to that of the adduct (59) prepared by Belleau et al. (Scheme 14).

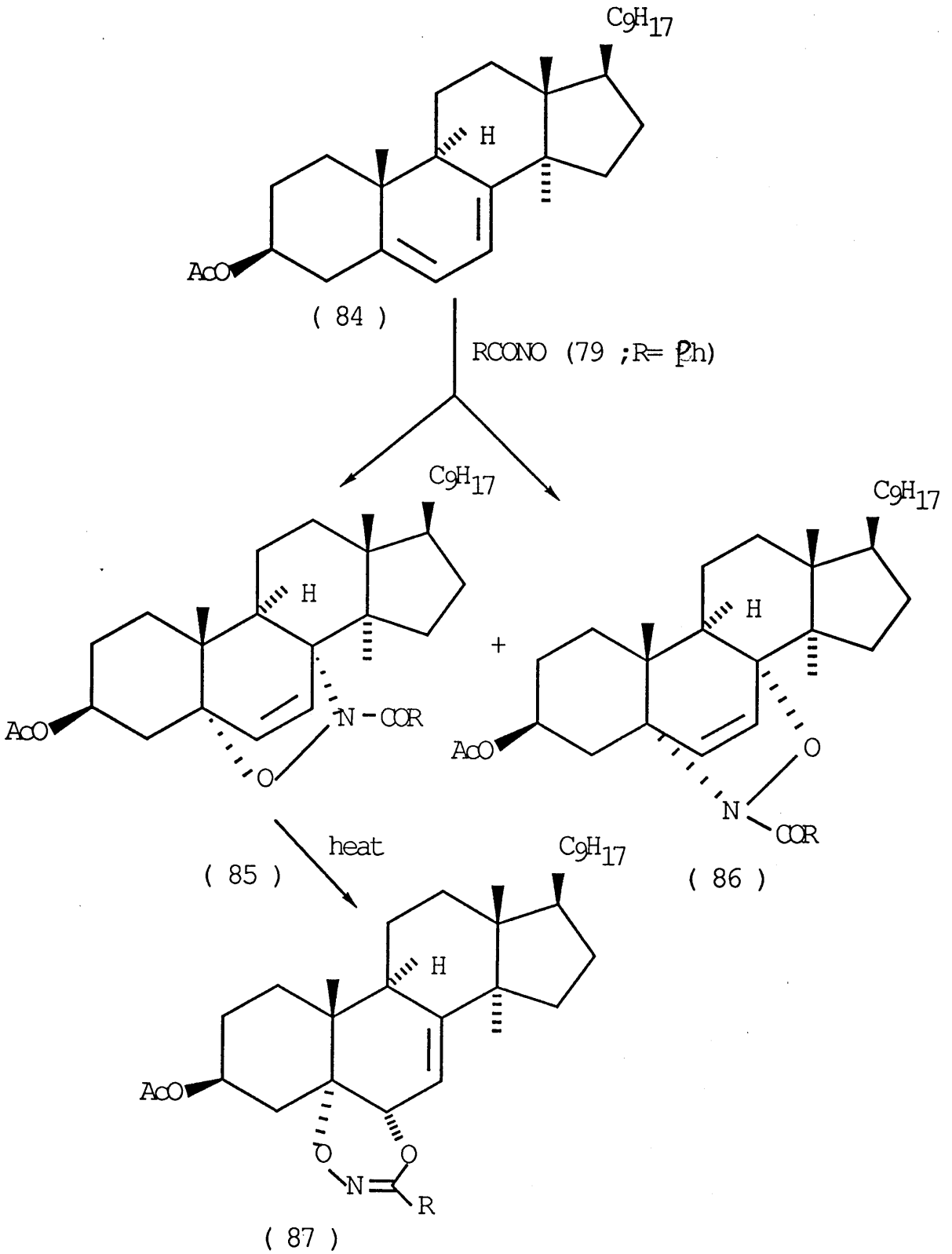
The chemistry of nitrosyl cynide cycloaddition reactions prompted Kirby and co-workers to carry out the pioneering studies of acyl nitroso compounds as synthetically useful heterodienophiles. The acyl nitroso compounds had been proposed[29] as the reactive intermediates in the reaction involving the oxidation of hydroxamic acids, RCONHOH and ROCONHOH. The transient species [RCONO] and [ROCONO] can be best generated by periodate oxidation and these highly unstable and reactive species were known to undergo rapid solvolysis[30]. Kirby et al., thought that, if such nitroso compounds really did exist, they might be trapped as their corrsponding cycloadducts if the oxidation of the hydroxamic acid was done in the presence of conjugated dienes. Indeed, oxidation of the hydroxamic (78) with periodate in the presence of thebaine (26) gave the cycloadduct (81) (96 % for R=Ph). The other adducts (80) ,(82) and (83) were also prepared likewise (Scheme 19). The formation of these adducts (31) did not necessarily indicate the involvement of the acyl nitroso compounds as discrete intermediates. The free existence of this class of heterodienophiles was confirmed by transfering the acyl nitroso compounds from the DMA adduct (80) to thebaine (26) in


RCONHOH
IO_4^-
[RCON=O]
(R = Me,Ph)
(78)
(79)
(79) + Thebaine (26)
DMA
Thebaine (24)
MeO
NMe
N
R
O
Me
N — COR
(81)
(80)
(77)
(82)
(83)

Scheme 19

refluxing benzene. The resulting mixture yielded the thebaine adduct (81) along with quantitative amount of DMA. These transfer reactions were followed kineticaly and first order kinetics was observed, consistent with the slow dissociation of DMA adducts followed by rapid trapping of the nitroso compounds by thebaine. The unsymmeterical diene, ergosteryl acetate (84), when treated with the hydroxamic acids (78) in the presence of periodate, yielded the types of adducts (85 ; R = Ph) and (86 ; R=Ph) in a 1 : 1.7 ratio. The adduct of type (85 ; R= Ph) when heated, it rearranged to form the dioxazines (87) which are thought to be due to intramolecular [3,3] sigmatropic rearrangement[32]. The formation of two adducts (85) and (86) from ergosteryl (84) and benzohydroxamic acid was further strengthened when the DMA adduct (80, R =Ph) was refluxed with ergosteryl acetate (84) to give the adduct (85) and (86) in a 1 : 1.6 ratio. This close agreement in ratio of the initially formed adducts (85) and (86) irrespective of the nature of reaction ,suggested that the common species in both the cases were the acyl nitroso compounds derived from benzohydroxamic acid (Scheme 20).

The thermal transfer of acyl nitroso compounds in some cases might lead to the formation of ^ene^ product. Therefore the ^ene^ reaction in some cases may become competitive with cyclo-addition reaction[33]. Such reactions are only possible when the olefin possesses the allylic hydrogen such as 2,3- dimethyl-butadiene. The ^ene^ reaction will occur by the shift of one of the double bond and the transfer of the allylic hydrogen to the enophile. Concurrent bonding between two unsaturated termini

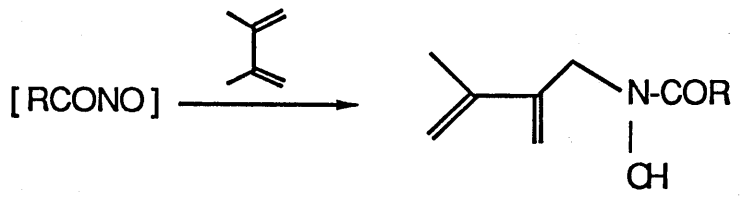

C9H17
H
AcO
(84)
RCONO (79 ; R= Ph)
C9H17
H
AcO
N - COR
O
+
C9H17
H
AcO
O
N
COR
heat
(85)
(86)
C9H17
H
AcO
O
O
N
R
(87)

Scheme 20

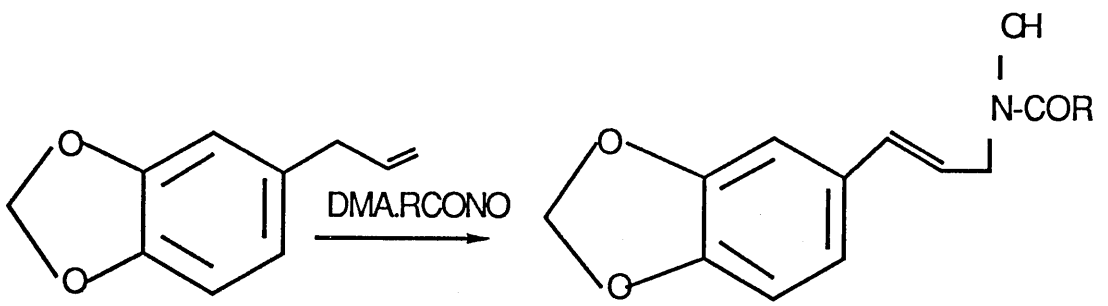
results in the formation of a hydroxamic derivative (88). Kirby and co-workers[34] refluxed safrol (89) in benzene in the presence of DMA adduct (80; R =Me) of nitrosocarbonylmethane and as a result of thermal release of acyl nitroso compound from DMA adduct, they obtained the N-allyl hydroxamic acid (90)(Scheme 21)

The chemistry of the cycloaddition of C-nitrosocarbonyl compounds, [RCONO] encouraged Kirby and co-workers to focus their attention on the C-nitrosoformate esters, [ROCONO], with the hope that they too would undergo Diels-Alder reactions. Thus the oxidation of the N-hydroxy carbamic ester (91 ; R= CH_2Ph) in the presence of DMA gave the expected adduct (93 ; R = CH_2Ph) in good yield[35]. The DMA adduct (93;R=$phCH_2$) when heated with thebaine (26) gave the corrsponding thebaine adduct (94) along with quantitative amount of DMA. This transfer reaction of benzyl-C- nitrosoformate, followed the same kinetics as had been observed for the thermal transfer of the C-nitrosocarbonyl compounds. Later Kirby and co-workers[36] converted the adduct (94;R=Cl_3CCH_2) to 14-amino-codeinone (96) by successive treatment with ethylene glycol- hydrogen chloride followed by reduction and hydrolysis (Scheme 22).

The cycloadditon reactions of the C-nitrosoformamides (98) were also reported by Kirby and co-workers[37]. The oxidation of the N-hydroxy ureas (97) with periodate yielded a new class of transient dienophiles (98) and when oxidation of the N-hydroxy ureas (97) was carried out in the presence of cyclopentadiene, the transient species (98) was trapped by cyclopentadiene to give the

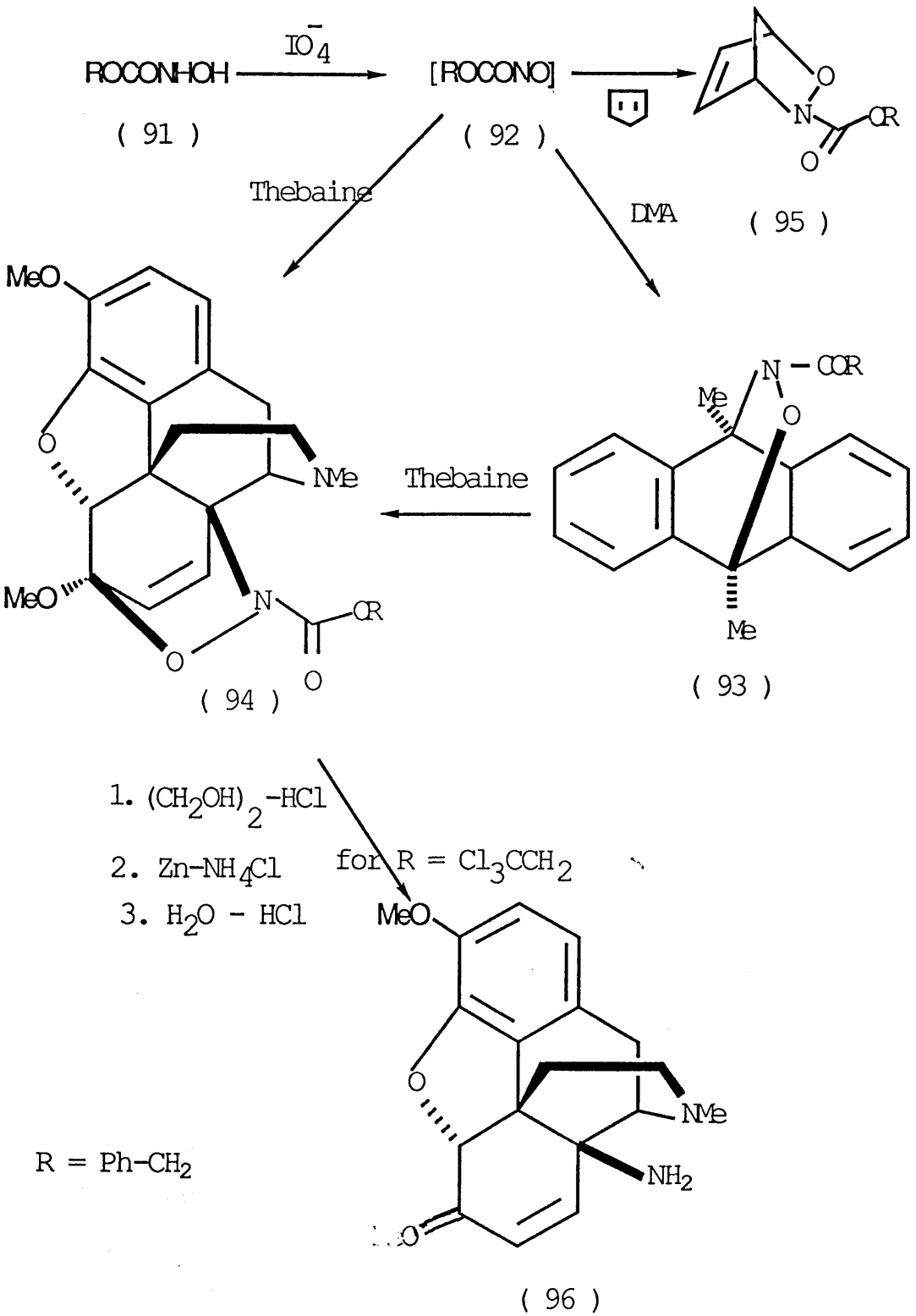


(79) (88)



(89) (90)

Scheme 21

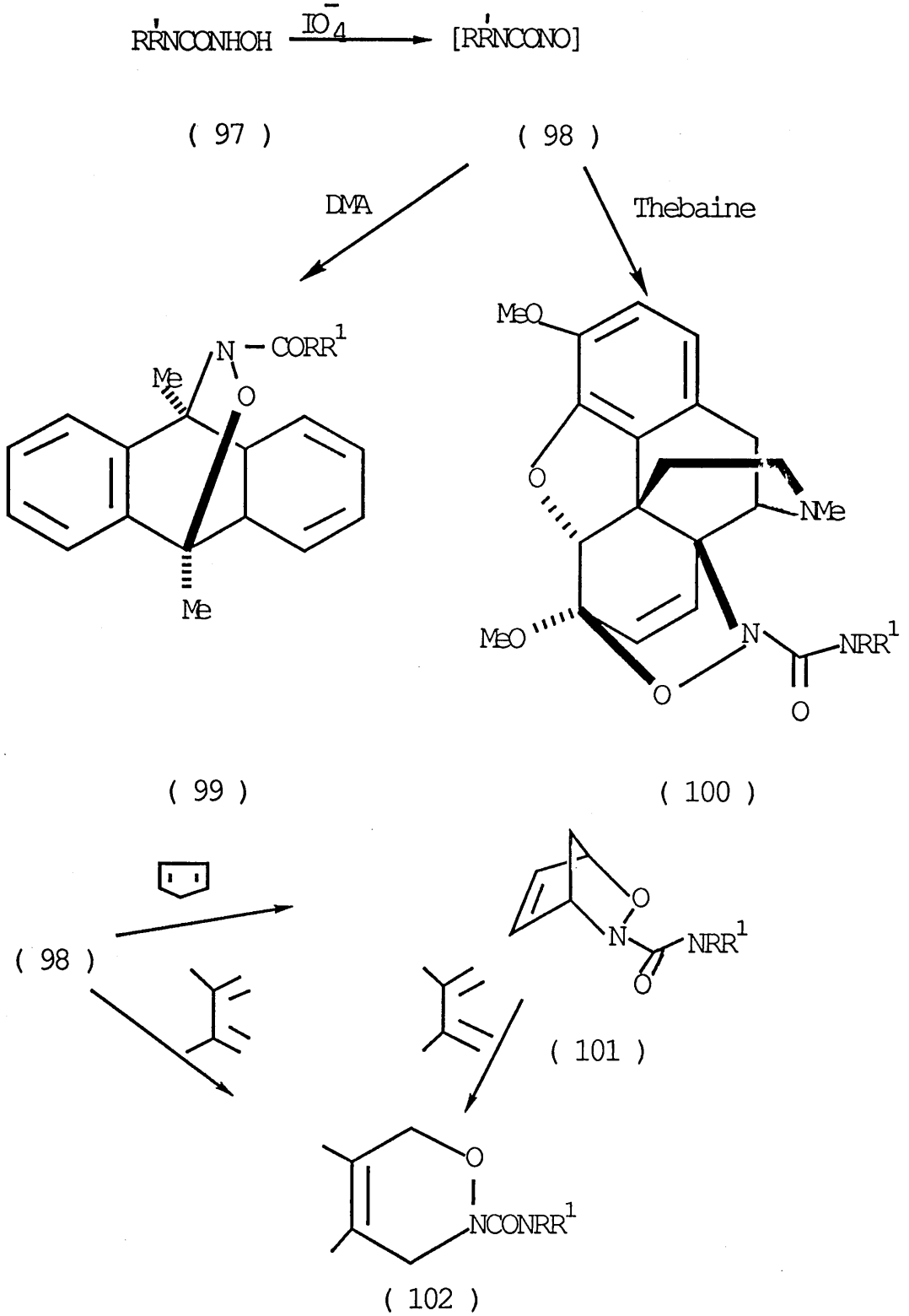

ROCONHOH
IO_4^-
[ROCONO]
(91)
(92)
(95)
Thebaine
DMA
MeO
NMe
MeO
N
CR
O
O
(94)
Thebaine
N – CCR
Me
O
Me
(93)
1. $(CH_2OH)_2$-HCl
2. Zn-NH_4Cl
3. H_2O - HCl
for R = Cl_3CCH_2
MeO
NMe
NH_2
O
R = Ph-CH_2
(96)

Scheme 22

expected adduct (101). They also prepared the adduct of 2,3-dimethylbuta-1,3-diene (102), the thebaine adduct (100) and also the DMA adduct (99 ; RR^1 = H). When the cyclopentadiene adduct (101) was heated with 2,3-dimethylbuta-1,3-diene,the 2,3-dimethylbuta-1,3-diene adduct (102) was obtained. In a similar way, when DMA adduct (99 ; RR^1= H) was heated with thebaine (26), C-nitrsoformamide was released and trapped in situ to give the thebaine adduct (100) and DMA (Scheme 23).

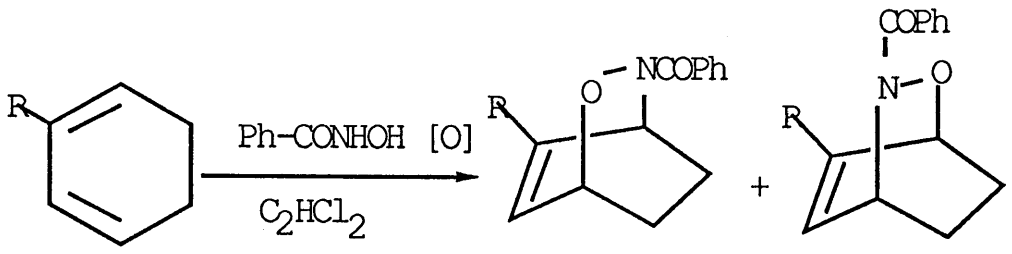
Boger et al.[38] recently studied the regioselectivity of nitrosocarbonylbenzene derived by the oxidation of benzohydroxamic acid,in Diels-Alder reaction with 2-substituted-cyclyhexa-1,3-dienes (103). They found that both the electron-donating and the electron-withdrawing groups had the same effect on the orientation of the cycloaddition. The same isomeric ratio 3 : 1 of the two adducts (104) and (105) was obtained (Scheme 24).

Diels-Alder cycloaddition reaction of acyl nitroso compounds were exploited by Defoin and co-workers[39] for the synthesis of diamino sugars. They oxidised the hydroxamic acids in the presence of N-methoxycarbonyl-1,2-dihydropyridine (106) to give the mixture of the adducts (107) and (108). The ratio of the adducts (107) and (108) depends upon the nature of the alkyl groups in the hydroxamic acids (Scheme 25). The adducts (107) and (108) were then converted into diamino sugars (109) and (110), respectively.



$RR^1 = H$

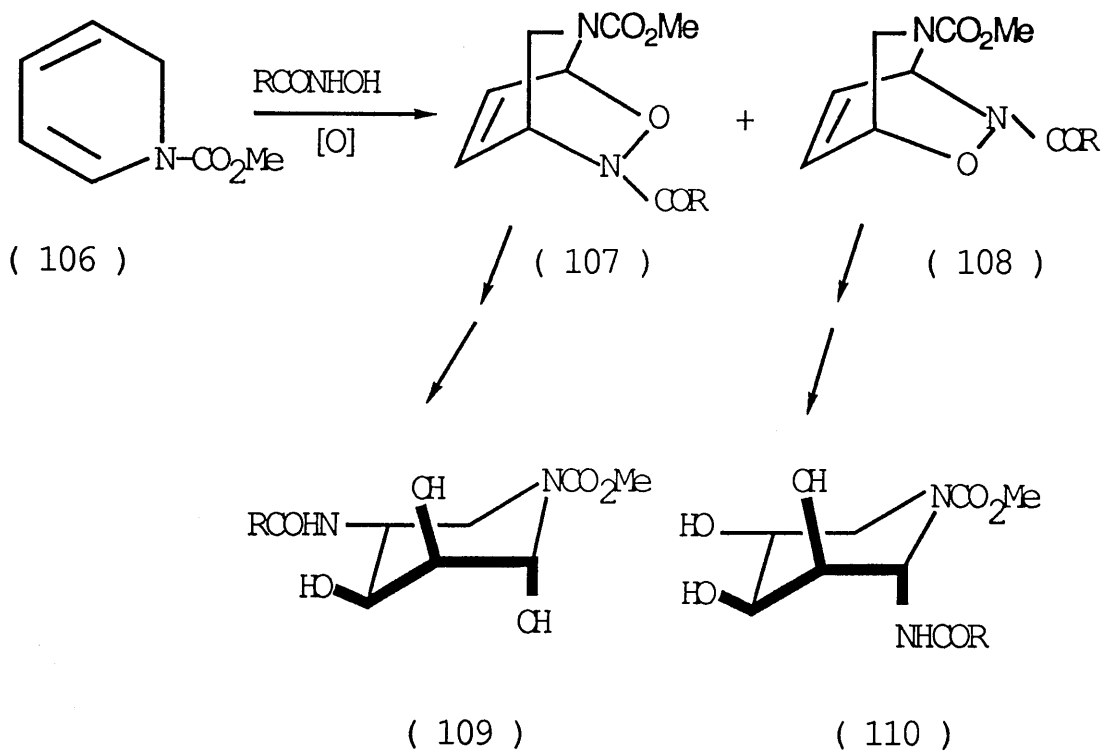
Scheme 23



(103) (104) (105)

R= $CH_2OTBOMS$
CO_2CH_3

Scheme 24



(106) (107) (108)

(109) (110)

R	Ratio (108) : (109)
Ph	0 : 100
MeOCO	50 : 50
Me_2NCO	75 : 25

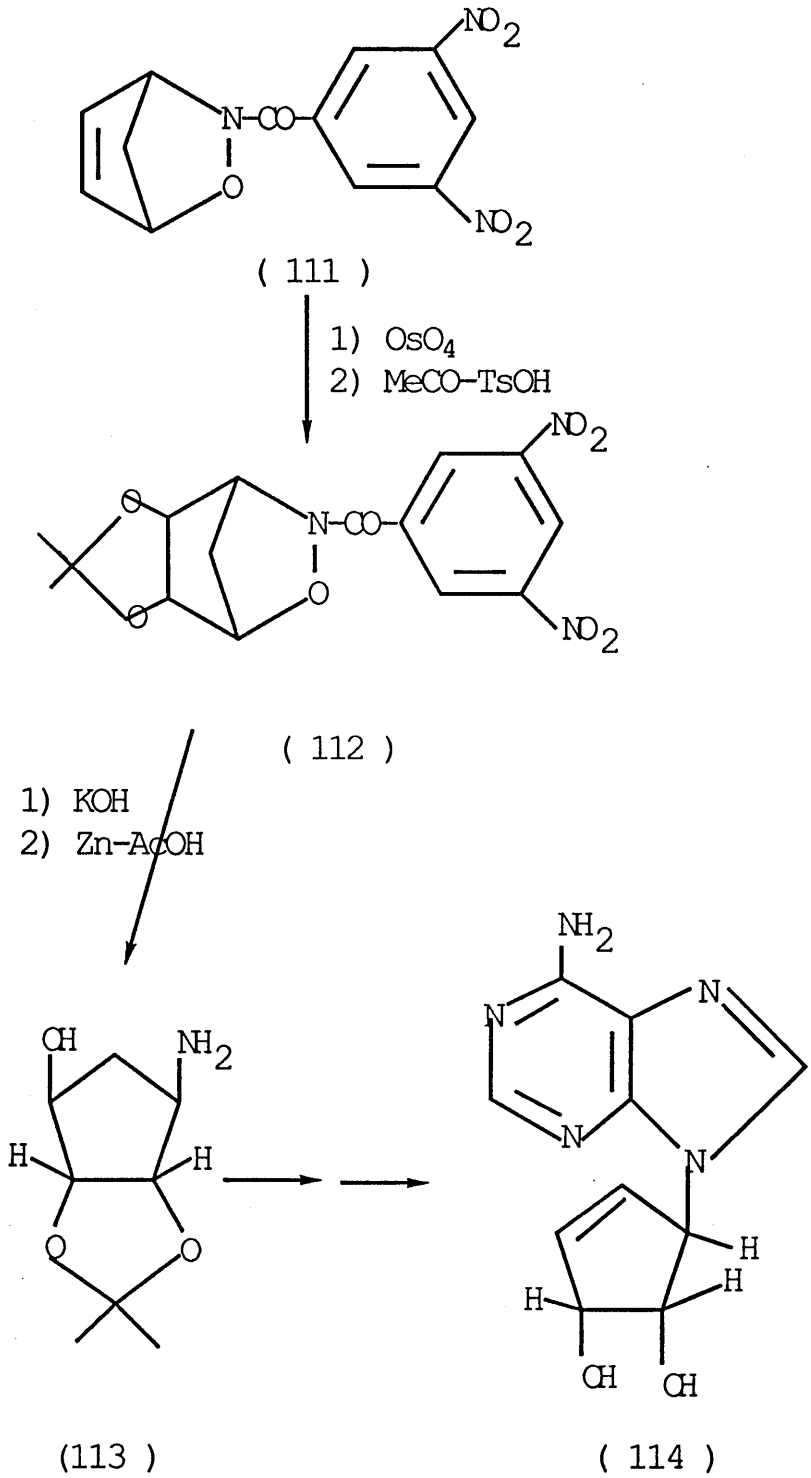
Scheme 25

The acyl nitroso compounds derived from 2,4-dinitro-benzohydroxamic acid were trapped by cyclopentadiene to give the adduct (111) . This adduct (111) was then comverted into antitumor compound naplanocin A (114) by Retey et al.[40] (Scheme 26).

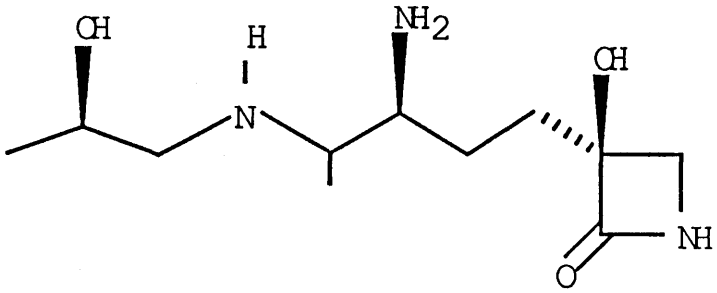
A Diels-Alder cycloaddition reaction of benzyl C-nitrosoformate was employed in the synthesis of tabotoxin (115), a metabolite causing the leaf spot disease in tabacco[41], and tabotoximine ß-lactum (116) the active principle generated in vivo by enzymatic hydrolysis[42] of (115). In both syntheses, the cycloaddition of the C-nitrosoformate to the appropriate dienes was regiospecific and provided the functionality and also the relative stereochemistry. The synthesis of (116) has been shown in (Scheme 27).

Recently Keck and co-workers[43] have synthesized heliotridine (126) and retrocine (127) by using the dimethylanthracene adduct (80;R=Me), of nitrsocarbonylmethane as precursor for the unsaturated acyl nitroso compound (124) (Scheme 28). The intramolecular Diels-Alder reaction afforded the mixture 1.3 :1, of the epimeric adducts. Which were then convertd into individual alkaloids (126) and (127).

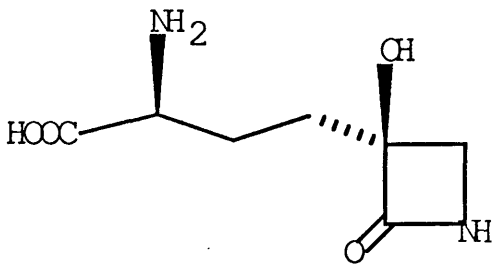
Diels-Alder reaction of acyl nitroso compound has also been exploited by Iida and co-workers[44], for the synthesis of frog neurotoxin gephyrotoxin (132) (Scheme 29).


NO2
N-CO-
O
NO2
(111)
1) OsO4
2) MeCO-TsOH
NO2
O
O
N-CO-
O
NO2
(112)
1) KOH
2) Zn-AcOH
OH
NH2
H
H
O
O
NH2
N
N
N
N
H
H
H
OH
OH
(113)
(114)

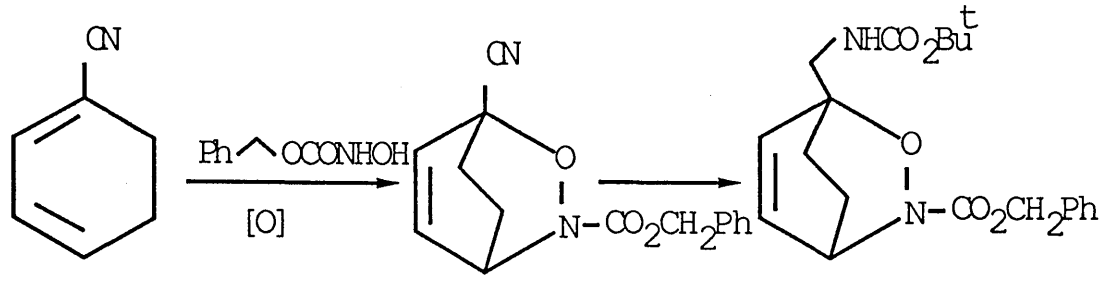
Scheme 26



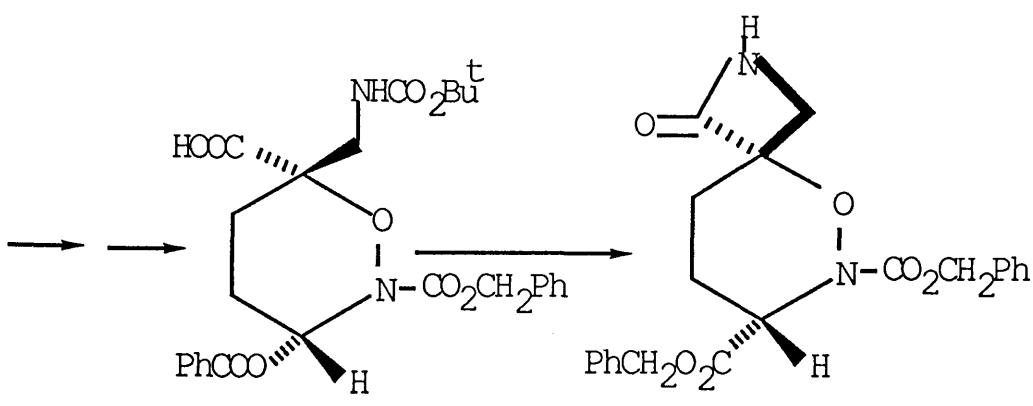
(115)



(116)



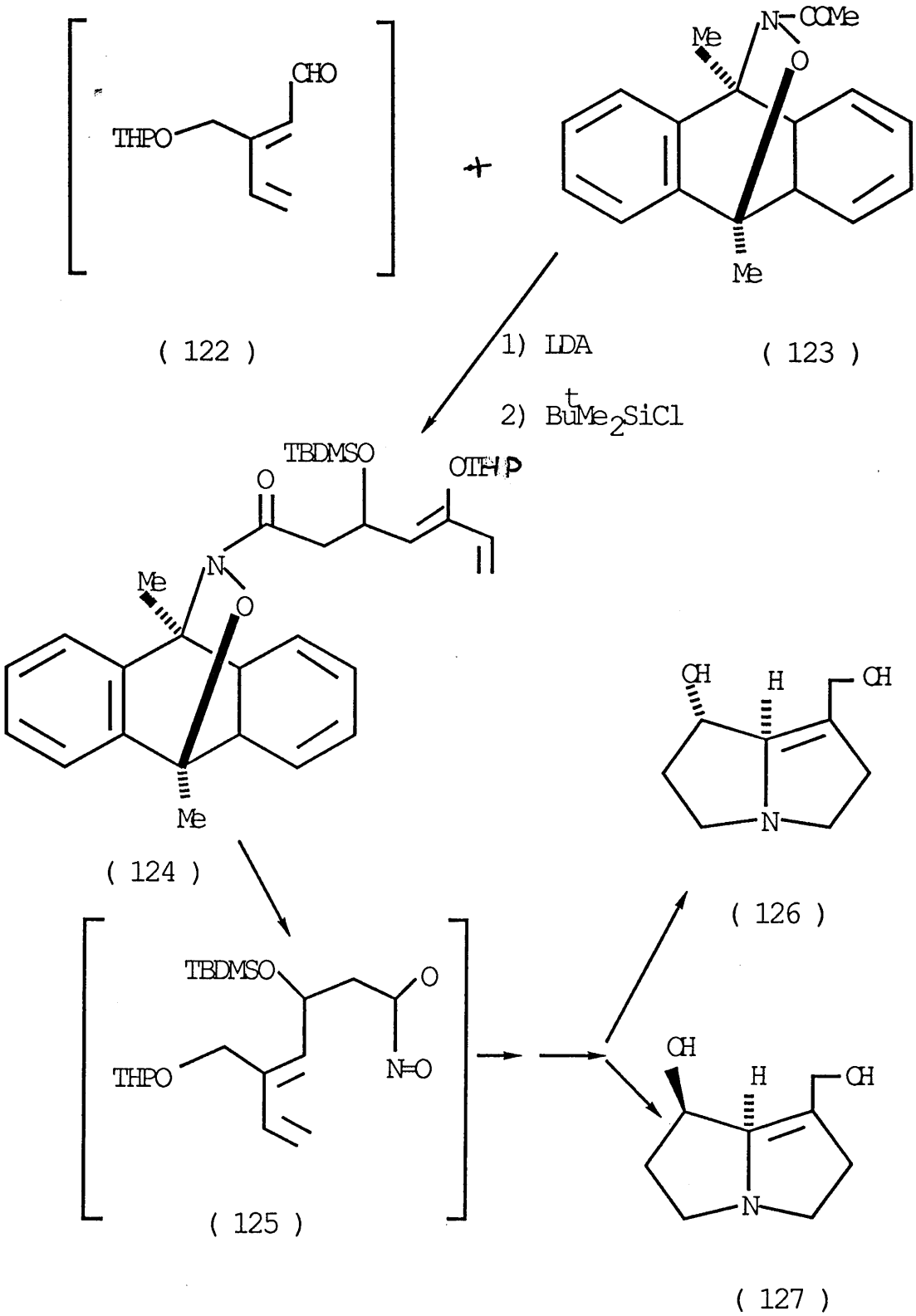
(117) (118) (119)



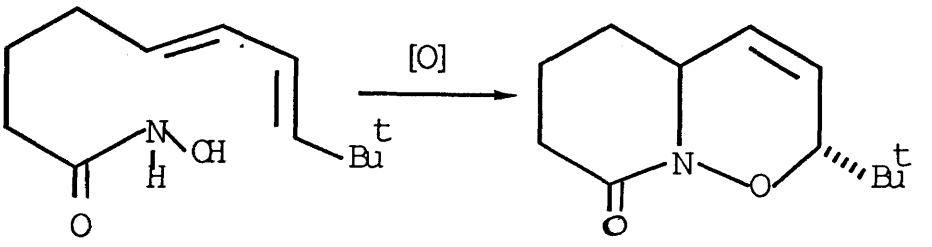
(120) H_2- Pd-C- EtOH (121)

(116)

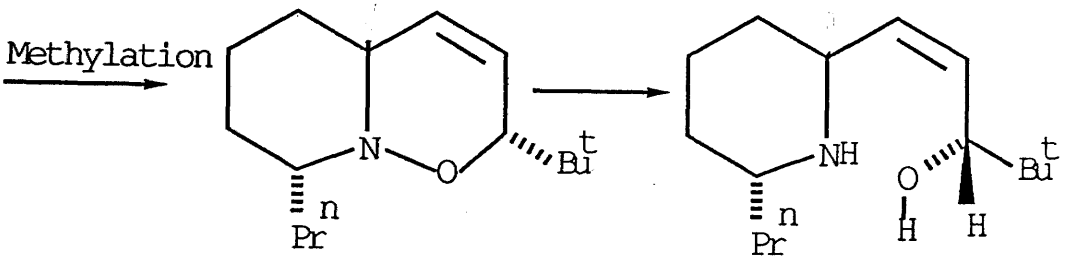
Scheme 27


CHO
THPO
+
N-COMe
Me
O
Me
(122)
1) LDA
2) $BuMe_2SiCl$
(123)
TBDMSO
OTHP
O
N
O
Me
Me
(124)
CH
H
CH
N
(126)
TBDMSO
O
THPO
N=O
(125)
CH
H
CH
N
(127)

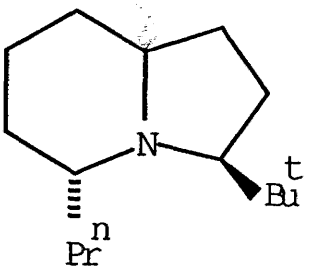
Scheme 28



(128) (129)



(130) (131)

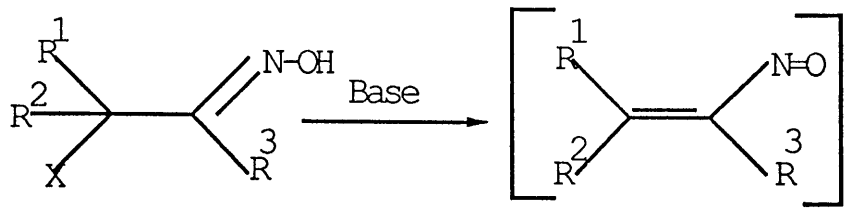


(132)

Scheme 29

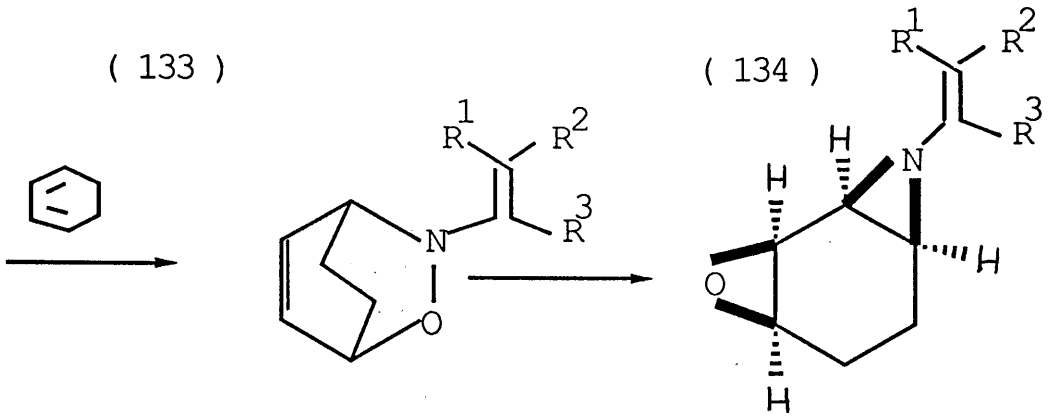
Vinyl Nitroso Compounds

Vinyl nitroso compounds (134) though highly unstable have recently been reported as components in the Diels-Alder cycloaddition reaction[45]. These compounds are capable of exhibiting dual functionality, either as heterodienophile or as the heterodiene. Which of the properties displayed depends upon the structures. If there is any ß-substituent present the system behaves like a dienophile, and if there is no ß-substituent the system behaves as a heterodiene. Vinyl nitroso compounds (134) are generally generated in situ by base promoted elimination of alpha-halooximes (133) and they are trapped by conjugated dienes to give the usual cycloaddition products, the dihydrooxazines. In some cases these adducts rearranged to epoxyaziridines. Francotte and co-workers[46] reported the formation of adducts (138) from vinyl nitroso compound (134) and oxepin (137) and the adduct (138) then rearranged into (139). They also treated[46] 2,3-dimethylbenzofuran (142) with (134) and the adduct (141) was converted into hexa-3-ene-2,5-dione (142) (Scheme 30).



(133)

(134)

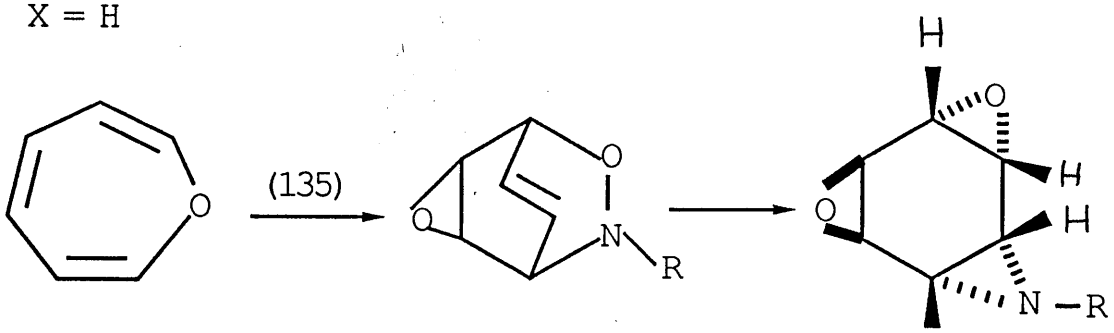


(135)

(136)

$R^1{=}R^2{=}R^3$ Cl

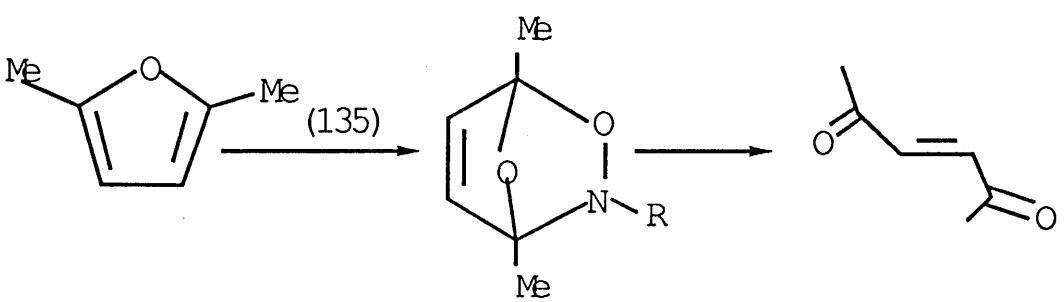
X = H



(137)

(138)

(139)



(140)

(141)

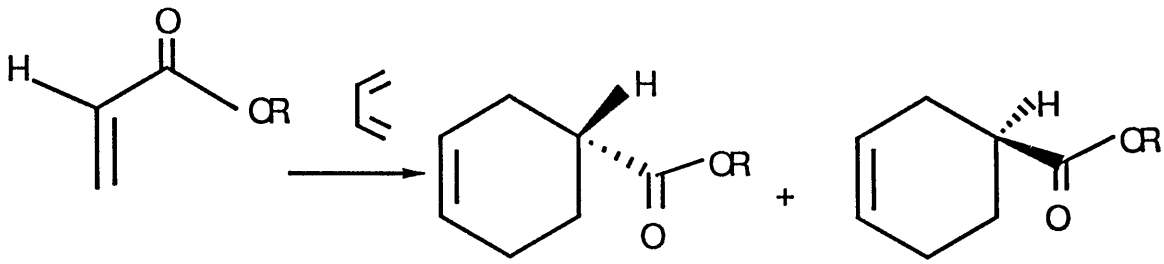
(142)

R= $CCl_2CCl(N{=}O)$

Scheme 30

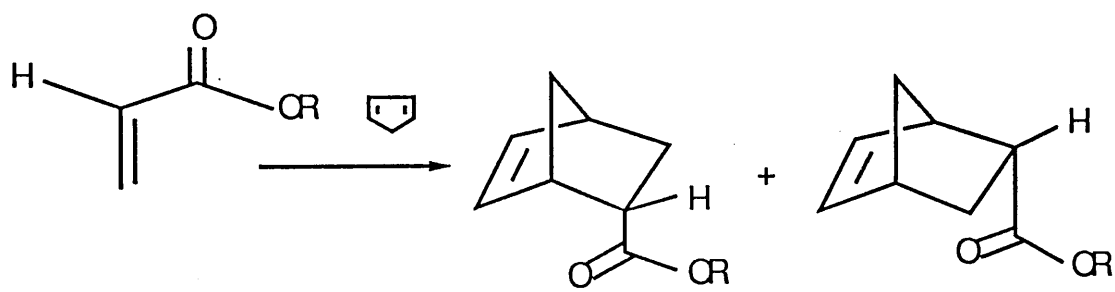
Asymmetric Diels-Alder Reactions

The various specialized stereochemical concepts and terminology that will arise repeatedly in this review, will be illustrated first with a few simple examples. The Diels-Alder reaction of butadiene with a simple acrylic ester (143) will give a pair of enantiomeric products (144), and (145) in equal amounts (Scheme 31). However, if (143) is a single enantiomer of a chiral ester then the products formed would be a pair of diastereoisomers and, in general, will be formed in unequal amounts. Hydrolysis of these esters will yield a mixture of enantiomeric acids, that is a partial racemate. The formation of unequal amounts of (144) and (145) is said to result from chiral induction. The relative amount of (144) and (145) is often expressed as the diastereoisomeric excess, d.e. If the amounts of (144) (the major product) and (145) are M_2 and M_3 respectively, then : d.e. $(M_2 - M_3) \times 100 / (M_2 + M_3)$. Also the relative amounts of the derived acids (144; R = H) and (145; R = H) may be expressed as the enantiomeric excess, e. e., in the same way. The products (144) and (145) may be thought of arising from the attack by the diene on the top face, for (145), and the bottom face for (144), of the acrylate double bond as shown. These two faces, designated re and si by the usual convention using C(1), are therefore enantiotopic for the simple esters and diastereotopic for the esters of chiral alcohols. The attack of a diene on a chiral acrylate might be described as diastereofacially selective. Similarly a chiral diene (as one enantiomer) might attack a

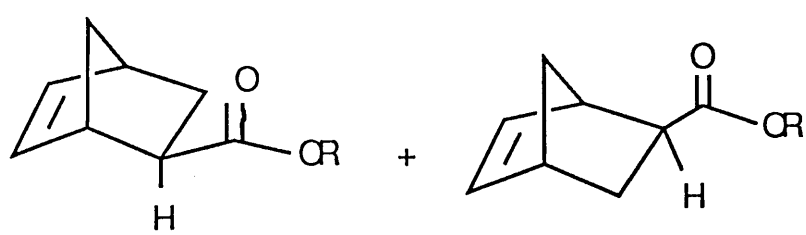


(143) (144) (145)

Scheme 31



(143) (146) (147)



(148) (149)

Scheme 32

simple acrylate selectively on either face to give diastereoisomers.

With many substituted butadienes, even achiral dienes with identical faces like cyclopentadiene, four products, two endo adducts (146) and (147), and two exo adducts (148) and (149) will be produced (Scheme 32). With a chiral acrylates an unequal mixture of racemic endo and racemic exo products will arise: M4 = M5≠M6 = M7. Most of the acrylates are predominantly endo selective. With chiral acrylates the diastereoisomeric excess for endo cycloaddition will generally differ from that of exo cycloaddition, i.e. M4 ≠ M5 M6 ≠ M7, and :$\frac{M4-M5}{M4+M5} \neq \frac{M6-M7}{M6+M7}$,

since all four products are now diastereoisomers of each other.

Since its discovery the Diels-Alder reaction[47] has been recognized as one of the most efficient organic transformations. The most attractive feature of asymmetric Diels-Alder reactions is the simultaneous creation of as many as four chiral centers, with largely predictable relative stereochemistry, when a chiral dienophile reacts with a chiral diene. Achievement of this potential stereoselection requires the advantageous and simultaneous exercise of at least four factors, namely cis addition, endo addition and diastereofacial selectivity of both the diene and the dienophile. The diastereofacial selectivity has received renewed interest in the last few years. The subject has been reviewed by Morrison and Mosher[48], Oppolzer[49], and

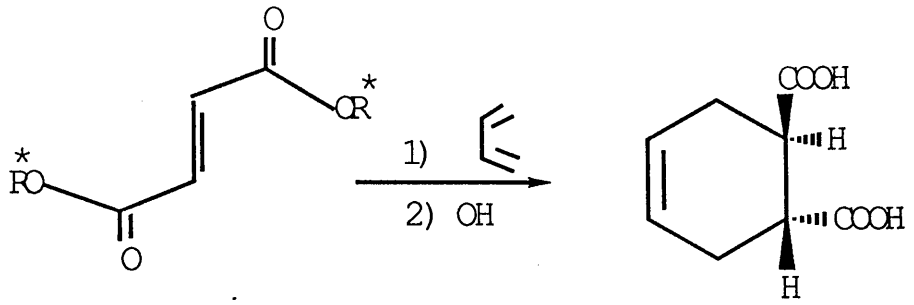
Wurziger[50]. The present review will describe some newer examples along with some examples from the earlier reviews.

Chiral C-C dienophiles

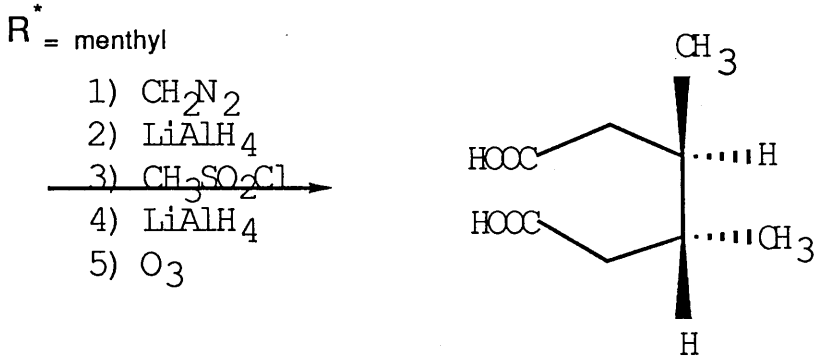
The optically active dimenthyl fumarate (150) was treated with buta-1,3-diene to give the corresponding adduct[51], which then was saponfied to give the levorotatory, 4-cyclohexene-1,2-dicarboxylic acid (151). The d.e. for the above reaction was found to be less than 4.5%.

Walbrosky et al.[52] later studied the same reaction but discovered that the diacid (151) was dextrorotatory rather than levorotatory. The diacid (151) was then converted into threo-3,4-dimethyladipic acid (152), an acid of known configuration (Scheme 33). They also treated optically active fumarate (150) with cyclopentadiene to yield predominantly the diol (153) after saponification followed by reduction with lithium aluminium hydride. The diacid (154) was converted into the lactone (155) of known configuration (Scheme 34).

The optically active acrylates (156) derived from various chiral alcohols were treated with cyclopentadiene by Kredel et al.[53]; to give the chiral endo alcohol (157) as the major product and the chiral, exo alcohol (158) as the minor product. They found that the acrylates (156d) derived from (S)-(+)-3,3-dimethylbutan-2-ol showed superior chiral induction as compared with the other alcohols (Scheme 35).

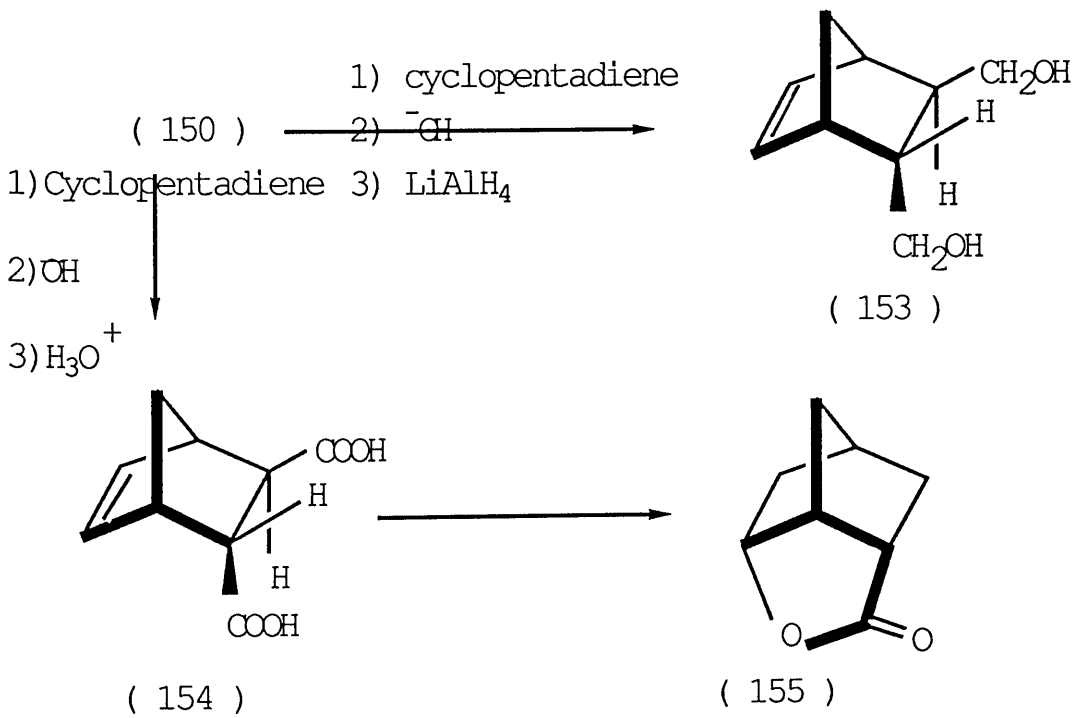


(150) (151)



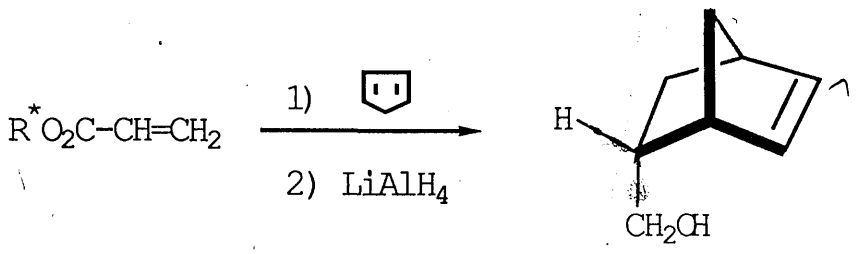
(152)

Scheme 33



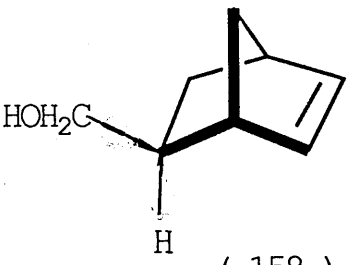
(153) (154) (155)

Scheme 34



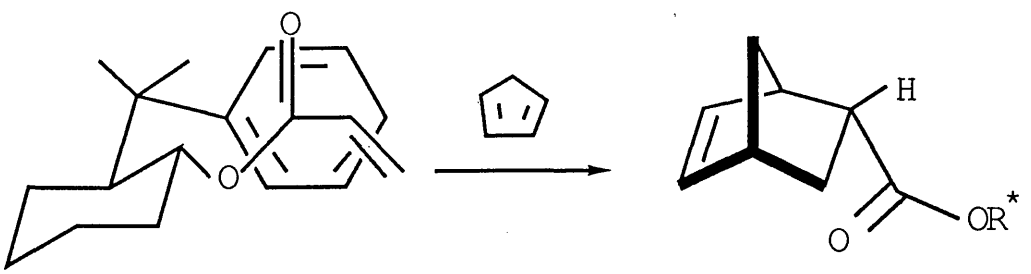
(156) (157)

R* = a) (R)-(-)-menthyl
b) (R)-(-)-2-octyl
c) (S)-(+)-2-octyl
d) (S)-(+)-2-(3,3-dimethyl)-butyl



(158)

Scheme 35



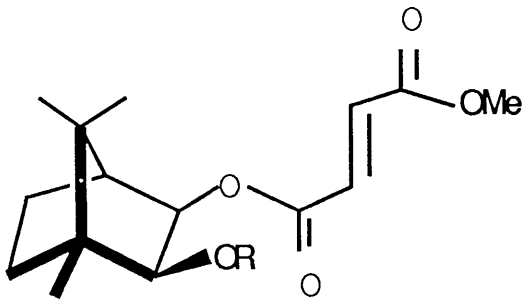
(159) (160)

R* = 8-phenylmenthyl

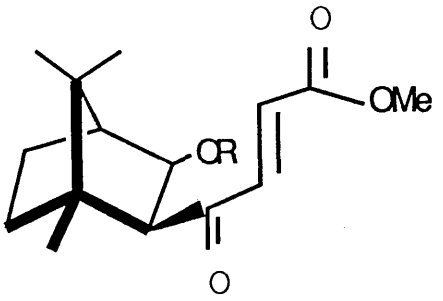
Scheme 36

These early asymmetric Diels-Alder reactions encouraged Corey et al.[54] to design a chiral alcohol, namely (R)-(-)-8-phenylmenthol (159a). Its acrylate ester showed dramatically superior chiral induction in reaction with cyclopentadiene as compared to (R)-(-)-menthol. The acrylate ester (159a) yielded predominantly endo adduct (160); endo: exo ratio ca 8:1. Also, the endo adduct (160) predominated over its exo diastereoisomer; endo diastereoselectivity ca 19:1 (Scheme 36). The use of (R)-(-)-8-phenylmenthol as a chiral unit suffers from a severe drawback because of the difficulty in its synthesis and access to its enantiomer is even more restricted. Despite this 8-phenylmenthol has been in use since its discovery in 1975. Its use in asymmetric Diels-Alder reaction helped to stimulate the design of other chiral auxiliaries which later proved to be superior.

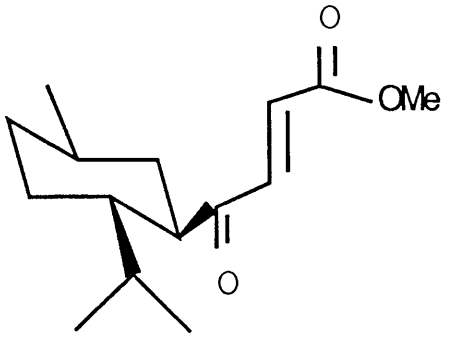
Helmchen et al.[55] elegantly designed chiral prosthetic groups from camphor, which is readily commercially available in both the enantiomeric forms. They therefore prepared optically active fumarates (161), (162) and as well as the simple methyl ester (163). They, then treated (162b) with anthracene in the presence of aluminium chloride, followed by reduction of the adducts with lithium aluminium hydride to give diols (164) and (165) with e.e. 94%. The reaction of methyl fumarate (163) with anthracene gave the corresponding diols (164) and (165). The major diol (164) had the opposite configuration to that obtained from the fumarate (162b). These authors rationalized these results on the basis of



(161)

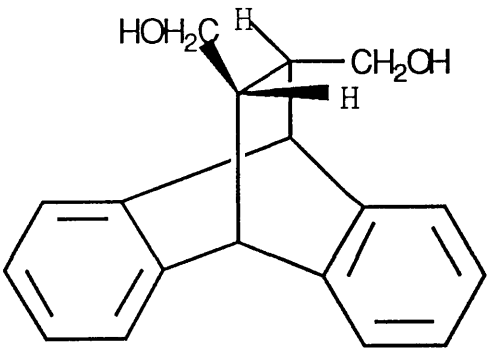


(162)

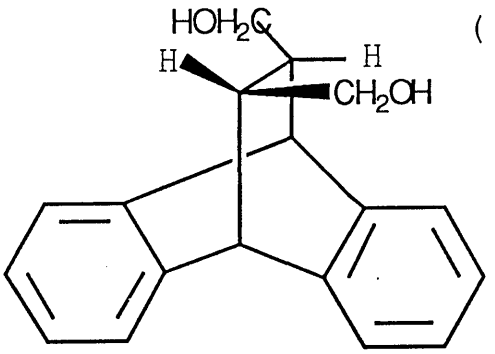


(163)

(162-b) 1) Anthracene 2) $LiAlH_4$



(164)



(165)

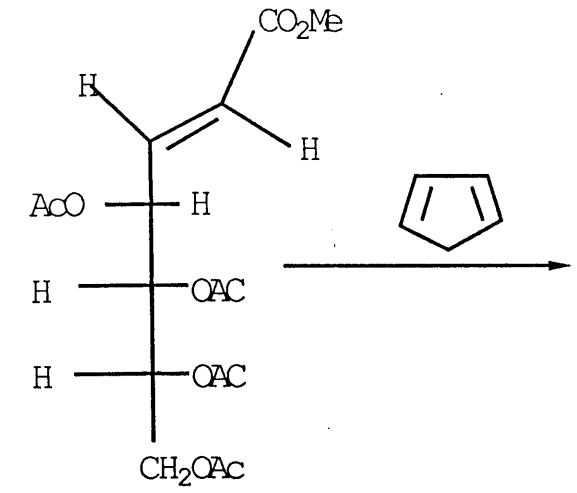
R= a;CH_2Ph
b;CONHPh
c;$CHPh_2$

Scheme 37

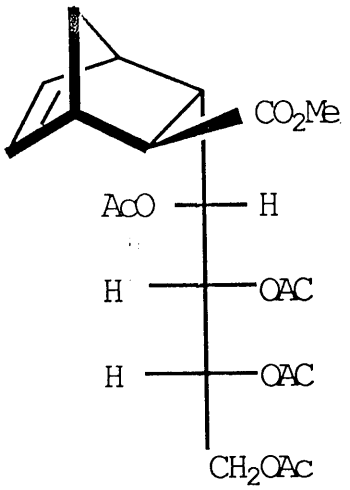
the electronic effect of the N-phenylaminocarbonyl group and its conformational influence on the neighboring unsaturated group (Scheme 37).

The early attempts by Jurczuk et al.[56] and Primeau et al.[57] to use carbohydrate templates in asymmetric Diels-Alder reactions, failed to achieve high inductions, primarily due to extensive decomposition. In contrast, Horton et al.[58] found that with the trans-α-β-unsaturated acrylic sugar derivative (166) the reaction proceeds with high stereochemical control. Thus, the adduct (167) was found to be the major product with cyclopentadiene. This adduct (167) was converted into the diol (169) of known configuration. Oxidation of the double bond in the adduct (167) yielded a tetrasubstituted cyclopentane derivative (170), an important precursor in the synthesis of some natural products, such as prostagladin (Scheme 38).

The level of induction achieved with (R)-(-)-phenylmenthol and camphor derivatives encouraged Oppolzer et al.[59] to undertake a broader study of the asymmetric Diels-Alder reaction. They, therefore prepared a series of chiral alcohols and studied the titanium chloride mediated cycloaddition reaction of their respective acrylates (171 a-g) with cyclopentadiene. The (5 R)-(172a) and (5 S)-2-norborene (172b) adducts yielded the corresponding alcohols (173a) and (173b) on reductive cleavage of the chiral units. They found that, with every chiral unit, high chiral induction was achieved. During this study Oppolzer et al. realized that the camphor derivatives showed similar induction

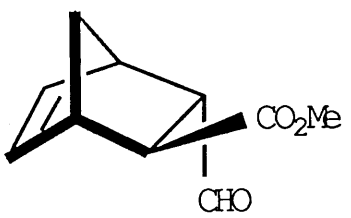


(166)



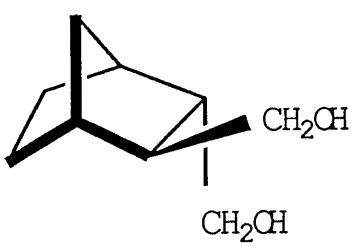
(167)

(167) 1) NaOMe 2) IO_4^-

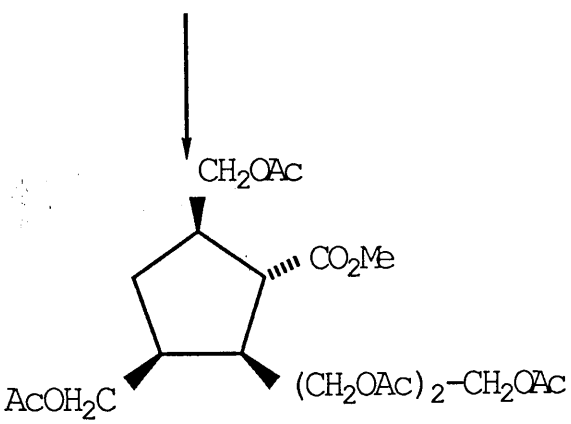


(168)

1) $LiALH_4$ 2) H_2-Pt

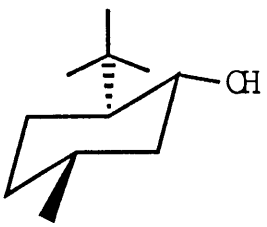


(169)

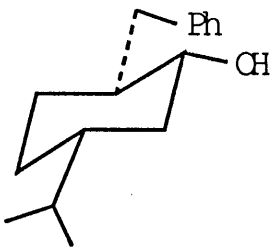


(170)

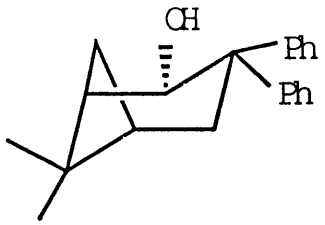
Scheme 38



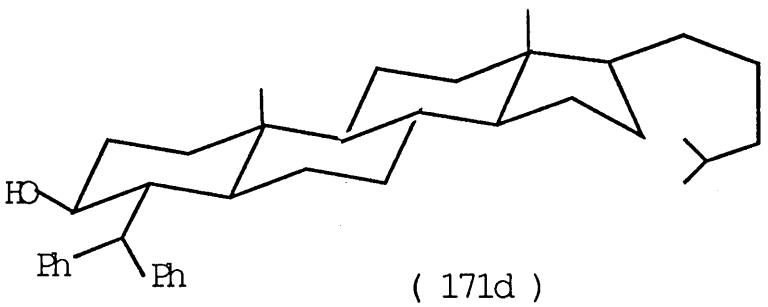
(171a)



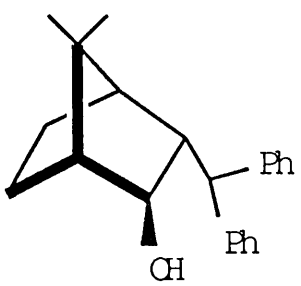
(171b)



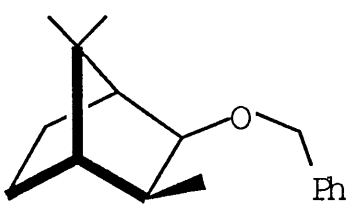
(171c)



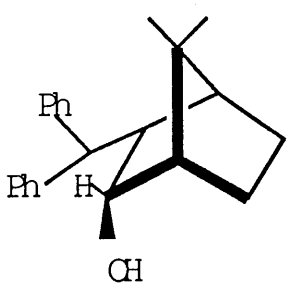
(171d)



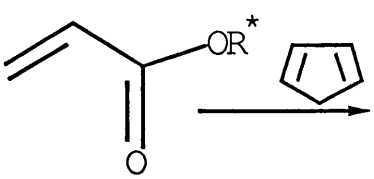
(171e)



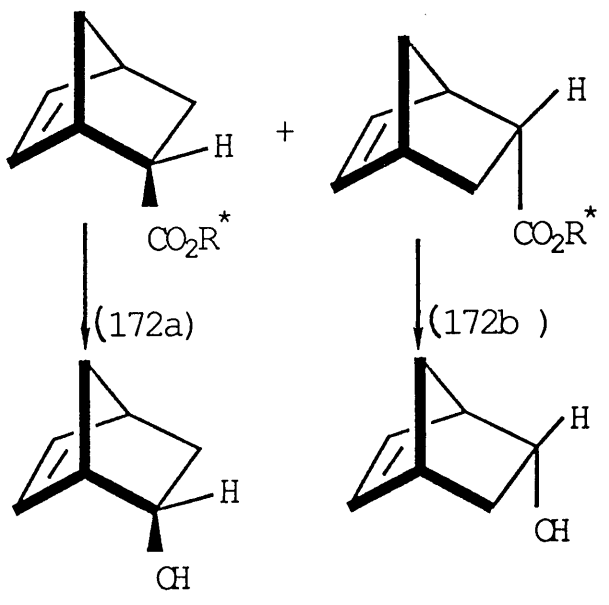
(171f)



(171g)



(171a to g)

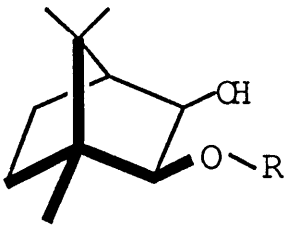


(173a)

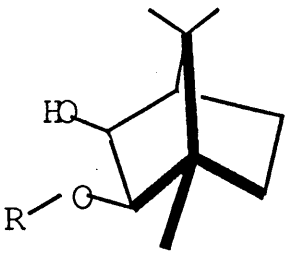
(173b)

Scheme 39

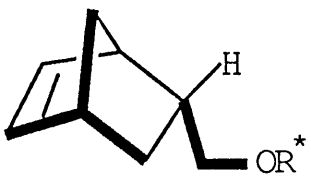
level as was obtained with the derivatives of 8-phenylmenthol. Further, they found that most of the camphor derivatives were found to be crystalline. Thus, Oppolzer et al.[60] seeking better chiral auxiliaries, prepared the cis-hydroxyisobornyl ethers (174) and (175). The corresponding acrylates esters when added to the cyclopentadiene in the presence $TiCl_2(OiPr)_2$ yielded the (5R)-2-norborborene adducts (176) in good chemical yield and d.e. 89% with (174a). These results were very encouraging and they extended this methodology by increasing the steric bulkiness on the acrylarte face. They therefore prepared a cis-hydroxyisobornyl ether having a neopentyl group shielding the acrylate (174d). Its addition to cyclopentadiene dramatically showed a superior chiral induction than did the (R)-(-)-phenylmenthyl derivatives. They proposed that the neopentyl group sterically blocked the C_α re-face of the acrylate and showed predominantly si-face attack to give largely the adduct (176d) in 99% d.e. Neopentyl ethers are readily available in both the enantiomeric forms. The oily nature of ether (174d) of cis-hydroxyisobornyl created problem for their purification. This difficulty in the purification of chiral auxiliaries was encountered by Oppolzer et al.[61] by preparing the crystalline sulfonamide (177), starting from camphor-10-sulfonyl chloride. Its crystalline acrylate (178), in the presence of $TiCl_2$ $(OiPr)_2$ underwent highly endo selective cycloaddition with cyclopentadiene to give the adducts (179, RR = cyclohexyl) with 99% d.e. Reductive cleavage of the ester (179, RR = cyclohexyl) yeilded the alcohol (180), along with 94% recovery of the sulfonamide (177; RR = cyclohexyl) (Scheme 40).



(174)

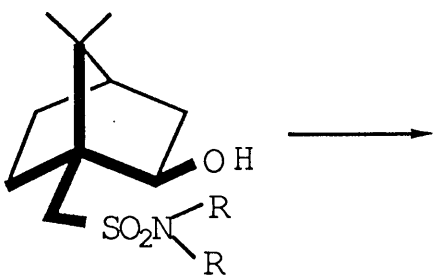


(175)

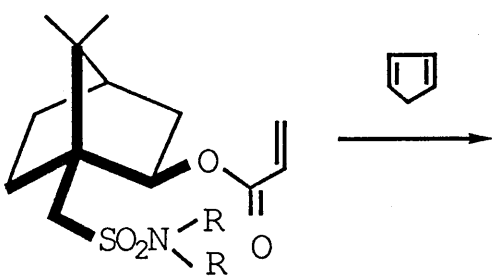


(176)

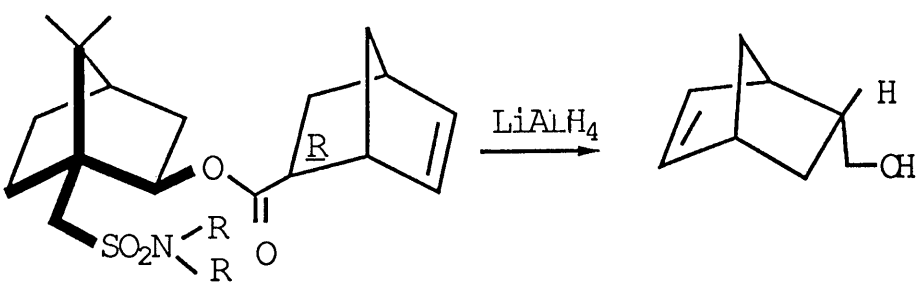
(174) R = a; $PhCH_2$
b; 2-naphthyl methyl
c; 1-naphthyl methyl
d; neopentyl
(175) R = neopentyl



(177)



(178)



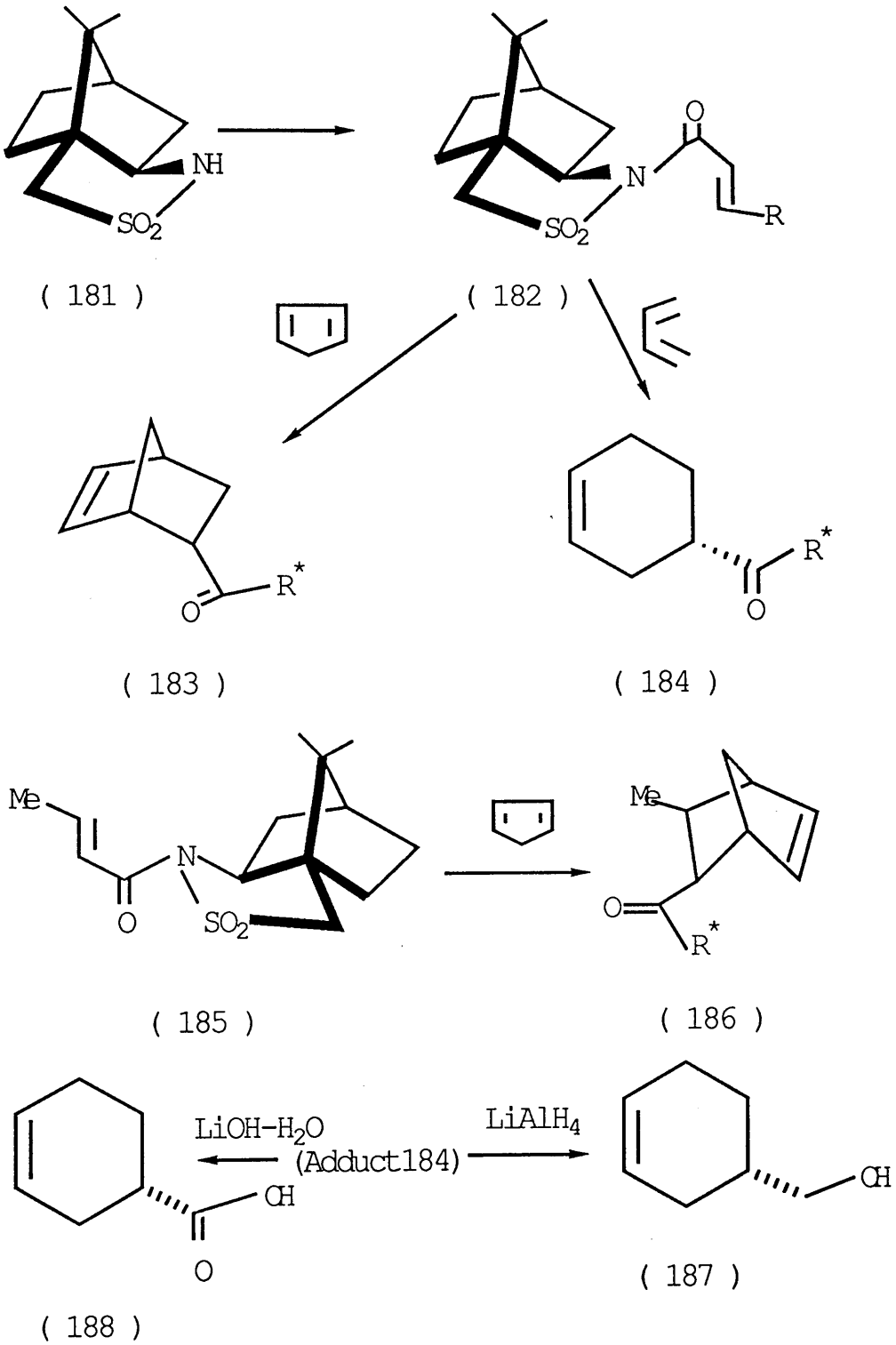
(179)

(180)

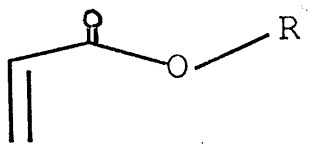
Scheme 40

Oppolzer et al.[62] also converted (+)-camphor-10-sulfonyl chloride into the crystalline sultam (181), N-acylation then gave amide (182) and the N-crotonyl derivative (185). These derivatives when reacted with cyclopentadiene and 1,3-butadiene in the presence of ethyl aluminium chloride to give the adducts (183) and (184) and (186) in 90% yields and d.e. 99%. The adduct (184) was converted into the alcohol (187) with lithium aluminium hydride. Alternatively, saponification of the adduct (184) with lithium hydroxide gave the acid (188) of known configuration (Scheme 41).

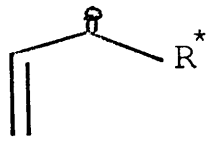
Chiral dienophiles may be grouped into two main types (189) and (190). In type (190) the chiral unit is one atom closer to the αβ-unsaturated carbonyl group than in type (189). The type (189) dienophile have been discussed before. The type (190) dienophiles (191) and (192) were prepared by Masmaune et al.[63] and their reaction with cyclopentadiene were studied at -40°C in the presence of zinc chloride, as a catalyst. The endo diastereoisomers (193) and (194) were found to be the major compounds. The diastereofacial selectivity for endo was found to be >100:1 in both cases. This high diastereofacial selectivity was attributed to the co-ordination of the Lewis acid catalyst with the α-hydroxy ketone group of the dienophile and formed a ridged five-membered chelate structure (195). This would freeze rotation about the C(α)-C=O bond making the diastereotopic faces of the enone double bond highly distinguishable. This


NH
SO2
N
O
R
(181)
(182)
R*
O
(183)
(184)
Me
N
O
SO2
(185)
(186)
LiOH-H2O
(Adduct184)
LiAlH4
OH
(187)
(188)

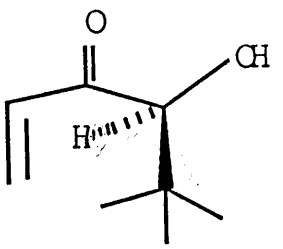
Scheme 41



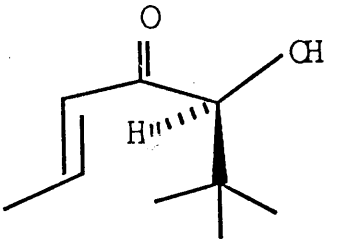
(189)



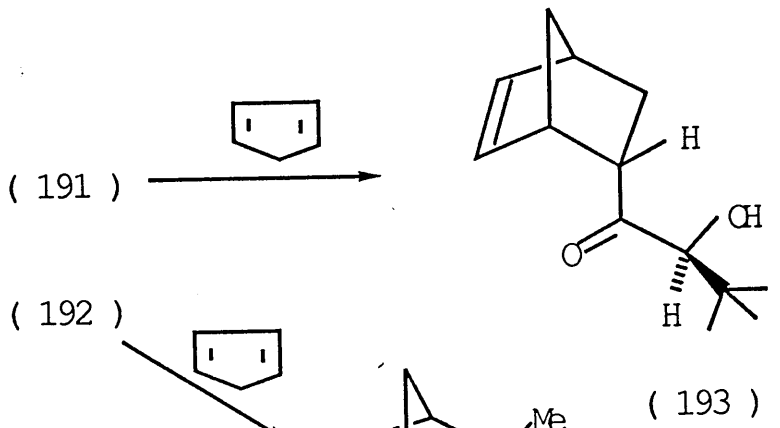
(190)



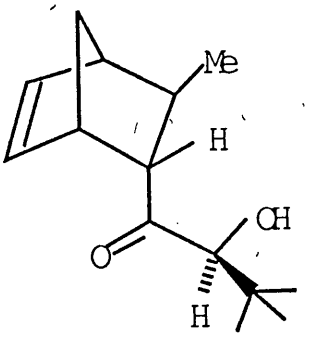
(191)



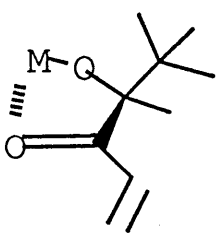
(192)



(193)



(194)



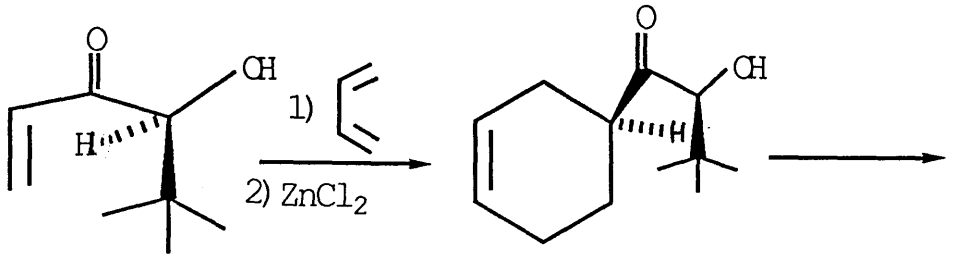
(195)

Scheme 42

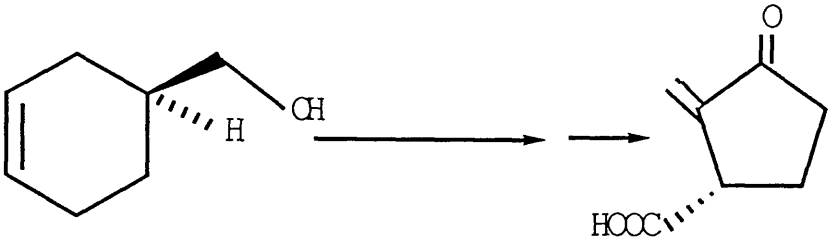
rationalisation was supported when the α-hydroxy group of the dienophile (191) was O-silylated and allowed to react with cyclopentadiene under the same conditions. The diastereoselectivity of the endo products dropped to 40:60 (Scheme 42).

Boeckman et al.[64] treated the dienophile (191) with buta-1,3-diene and the adduct (196) was converted into sarkomycin (198) (Scheme 43). In a similar way[65] 1,4-diacetoxybuta-1,3-diene (199) was treated with the dienophile (191) to give mainly the adduct (200) which was then elegantly converted into shikimic acid (201) (Scheme 43). Oppolzer et al.[66] treated the dienophile (202) with the diene (203) and the resulting adduct (204) was transformed into the hydrochloride of (+)-pumiliotoxin (205) (Scheme 43).

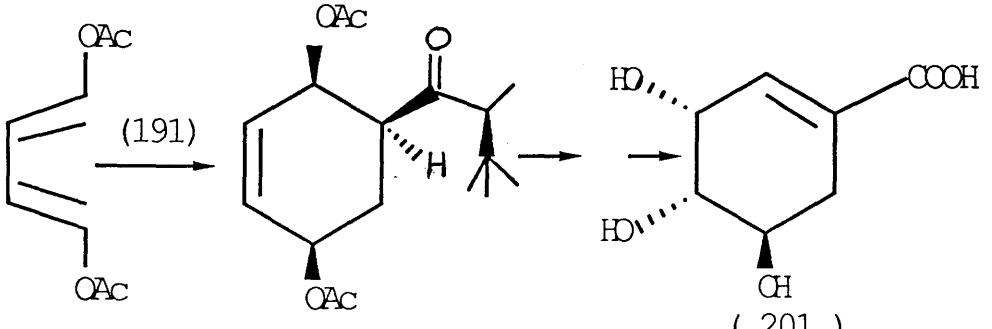
The high diastereoselectivity associated (67) with (S)-hydroxy Ketone (191) was reconfirmed when it was treated with diene (206) to give the major adduct (207) of the reaction which proceeds with >100:1 stereoselection in the presence of catalyst $BF_3.OEt_2$. They then treated the diene (S-208) which is close in structure to prochiral diene (206), with (S-191) to give the major adduct (204), in > 130:1. While the ratio of adducts (211) to its diastereoisomer obtained from diene (R-210) and (S-191) was found to be 35:1. The major adducts (209) and (211) had the same configuration at the newly created chiral centers that means that the configuration at the new centres in adducts (209) and (211) does not depend upon the chirality of the dienes (208) and (210)



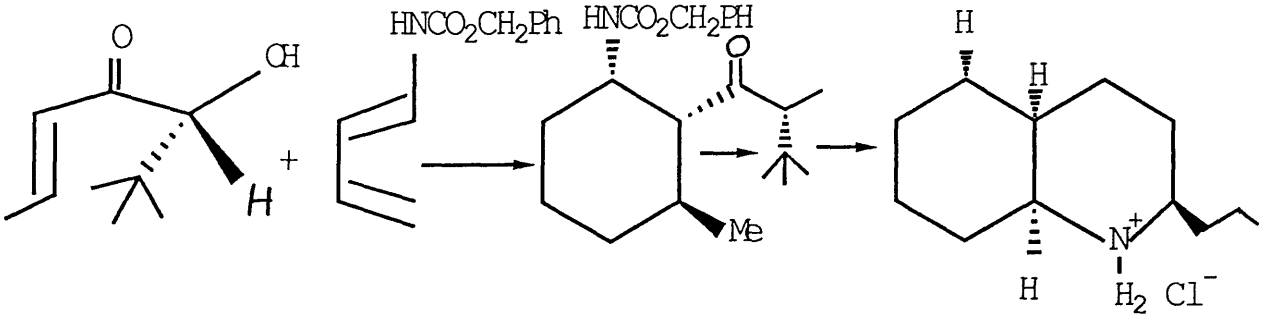
(191) (196)



(197) (198)

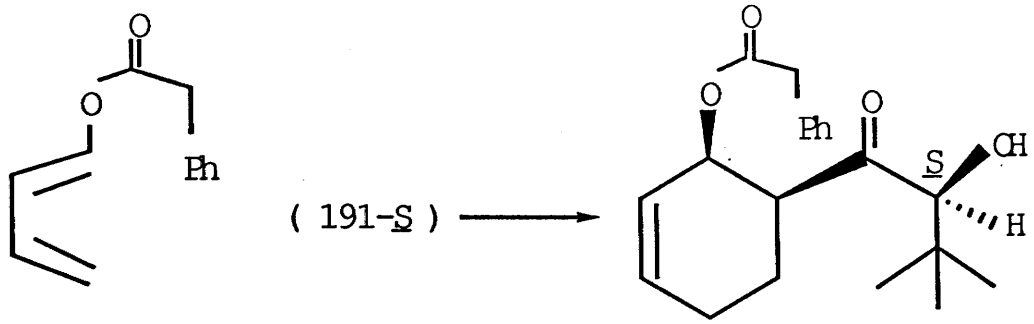


(199) (200) (201)

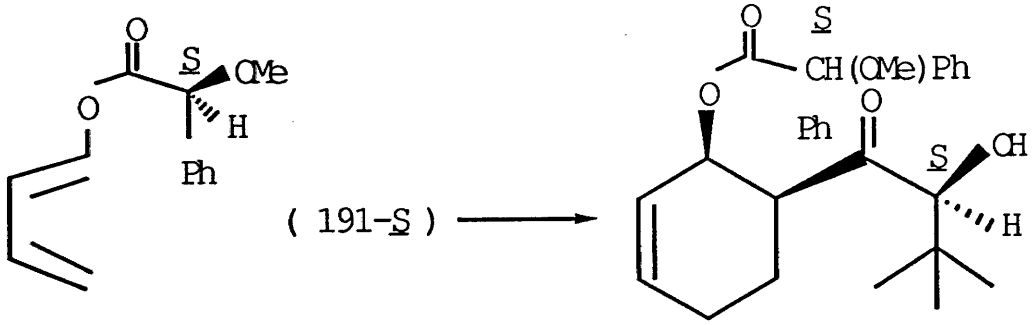


(202) (203) (204) (205)

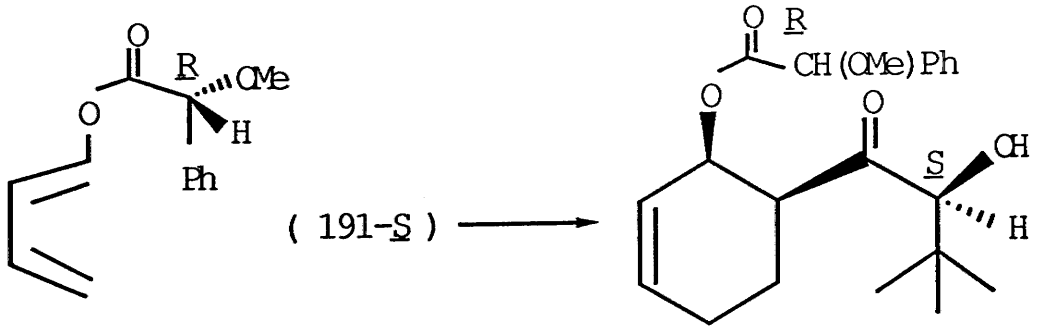
Scheme 43



(206) (207)



(208) (209)



(210) (211)

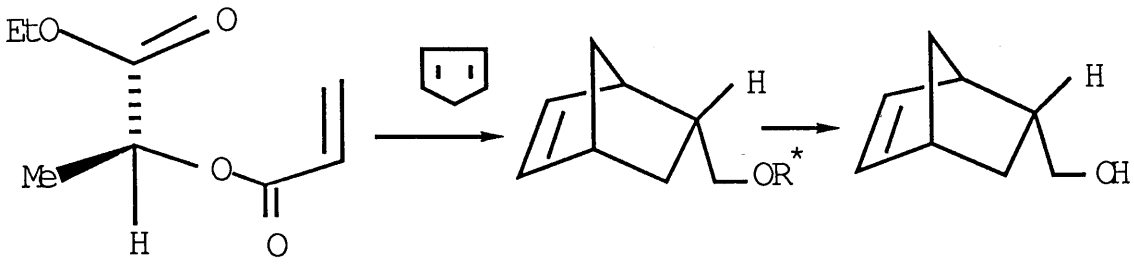
Scheme 44

but only upon that of the dienophile employed (Scheme 44).

The acrylate (212) of (S)-ethyl lactate reacted with cyclopentadiene in the presence of titanium tetrachloride to give the major (5 S)-adduct (213) in 86% d.e. This high d.e. is mainly due to Cα-re face selection. The (5 S)-adduct (213) was purified by medium pressure chromatography and was saponified to give the alcohol (180) as expected with retention of configuration[68] (Scheme 44a).

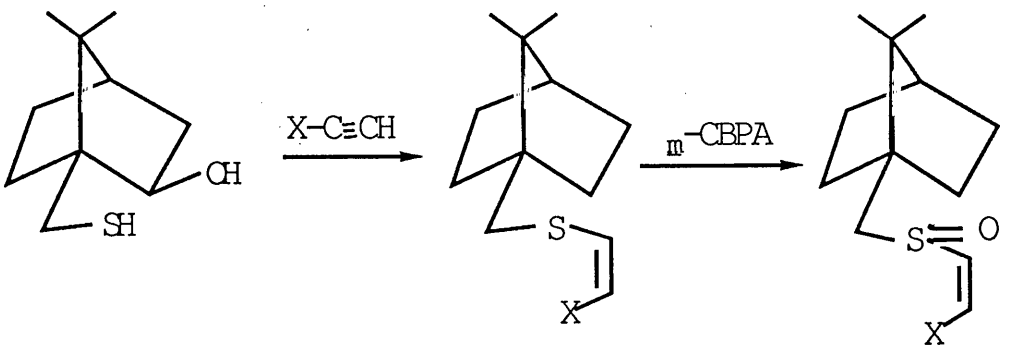
The preparation of sulfinyl activated chiral dienophile (216) was reported by Lucchi et al.[69] in 1985 by morpholine catalysed Michael addition of the hydroxythiol (214) to give benzenesulfonyl acetylene (215). Oxidation of (215) with m-choloroperbenzoic acid in dichloromethane yielded a mixture of 9:1 of the sulfoxide (216) and its minor epimer. The reaction of this mixture (216) with cyclopentadiene again afforded a 9:1 mixture of cycloadducts (217). The most abundant isomer crystallized from methanol. The removal of the chiral auxiliary yielded the pure 2-sulfonyl benzene norbornadiene (218) (Scheme 45).

Envas et al.[70] designed the chiral α, β-unsaturated cyclic carbamates. The derived acrylates (219), (221) and (223) underwent cycloaddition reactions with cyclopentadiene in the presence of diethyl aluminum chloride. The major endo adducts (220), (222), and (224) were largely obtained in good yield. The non-destructive removal of the chiral auxiliary group through lithium benzyloxide transesterification of the cycloadduct (220;

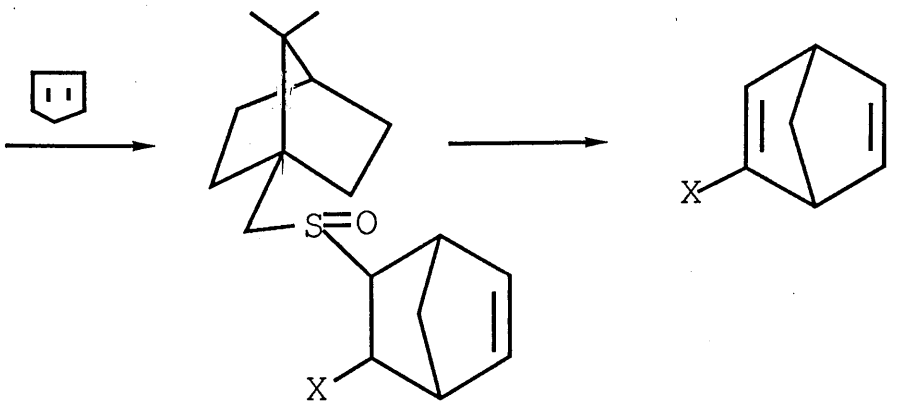


(212) (213) (180)

Scheme 44a



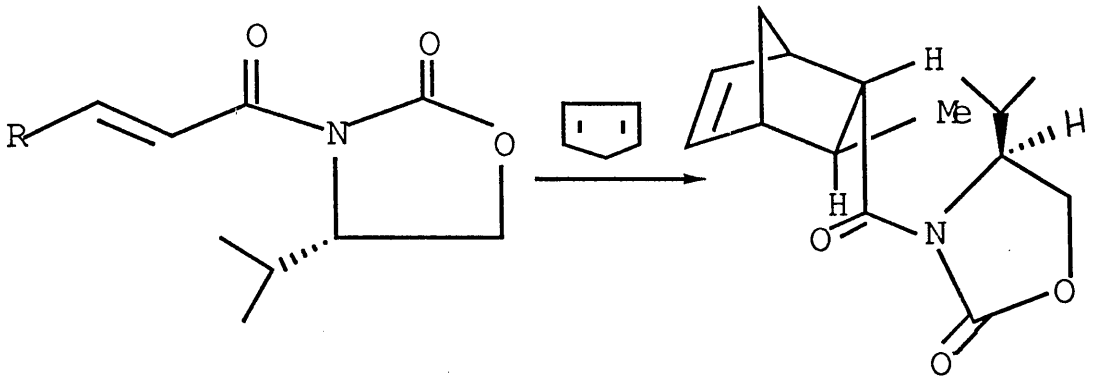
(214) (215) (216)



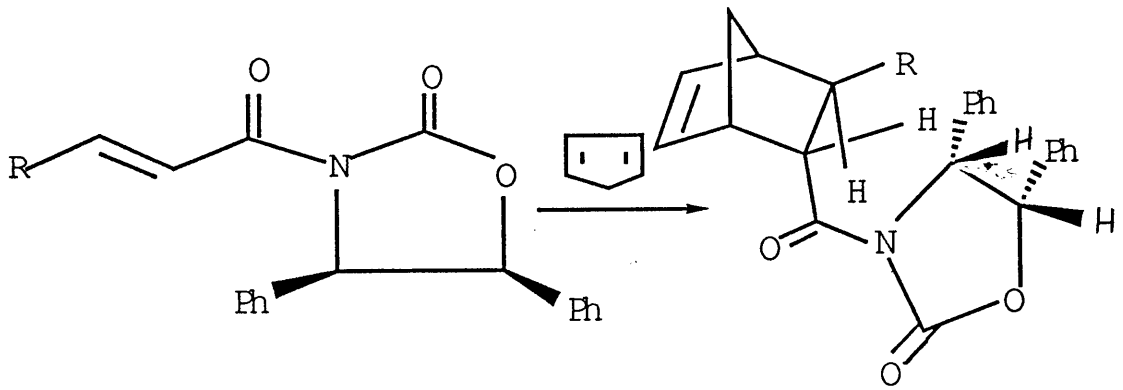
(217) (218)

X= $MeCO_2$
Benzenesulphonyl

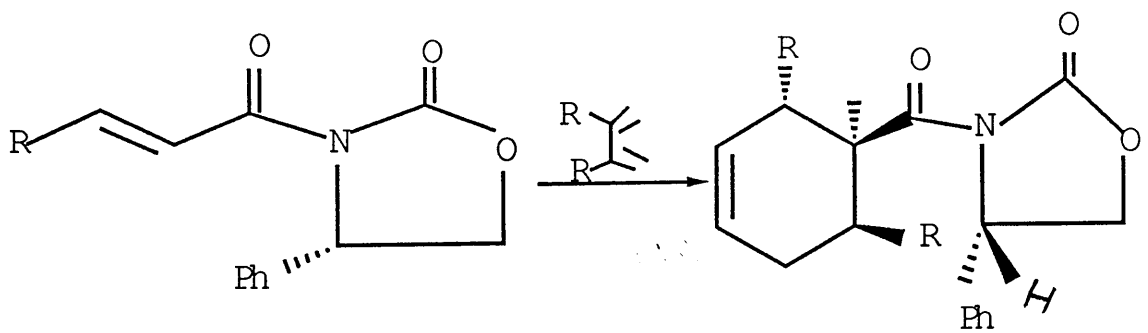
Scheme 45



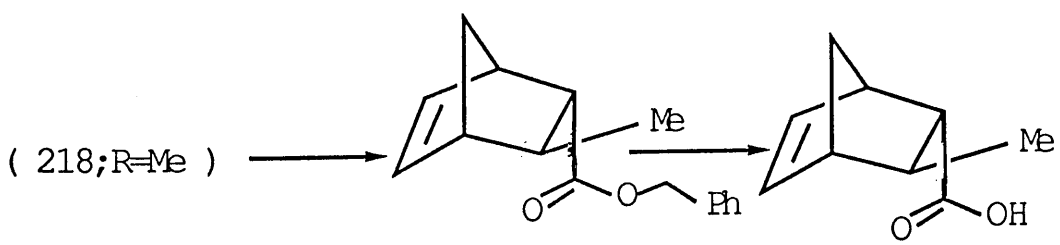
(219) (220)



(221) (222)



(223) (224)



(218;R=Me) (225) (226)

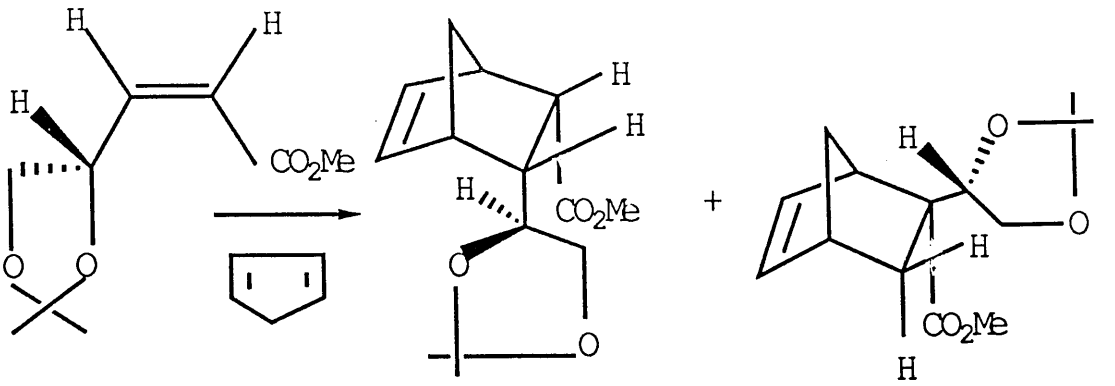
Scheme 46

R = Me) afforded the benzyl ester (225), subsequent hydrolysis yeilded the carboxylic acid (226) of known configuration (Scheme 46).

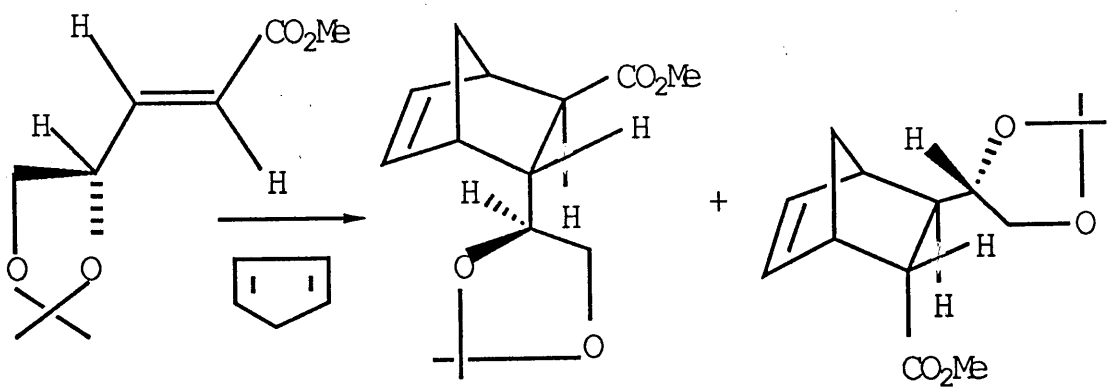
The uncatalysed reaction of cyclopentadiene with (E)-(227) and (Z)-(R)-4,5-di-O-isopropylidenepent-2-enonate (230) were reported by Mulzer et al.[71]. The dienophile (227) yeilded the adducts (228) and (229) in the ratio of 85:15. Basic hydrolysis of the adduct (228) afforded the corresponding carboxylic acid of known configuration. The adducts (231), and (232) were obtained with the dienophile (230), and cyclopentadiene. The adduct (231) with the ester group exo was the major product; hydrolysis afforded a carboxylic acid with the carbonyl configuration opposite to that from the adduct (228), (Scheme 47).

The zinc chloride mediated reaction of the (S) iron complex (234) with cyclopentadiene was reported by Stephen et al.[72]. The endo adduct (235) was found to be the major product with a d.e. of 80%. The adduct (235) was elegantly converted into (2-S)-(-)-bicyclo [2.2.1] hept-5-ene-2-endo-carboxylic acid (236). The carboxylic acid (236) was then converted into the optically active pure iodolactone (237) (Scheme 48).

The reactions[73] of menthyl (S)-(238) and (R)-3-(2- pyridyl sulfinyl)propenoate (241) with cyclopentadiene in the presence of diethyl aluminium chloride gave largely the endo diastereo-isomers (239) and (242), respectively. These adducts were then transformed into (-)-neplanocin (240) and aristeromycin (243)

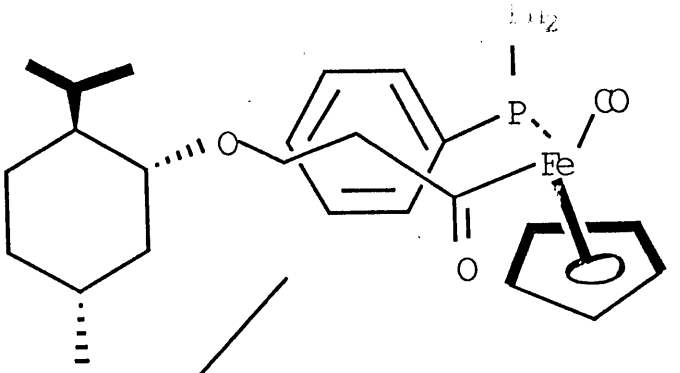


(227) (228) (229)

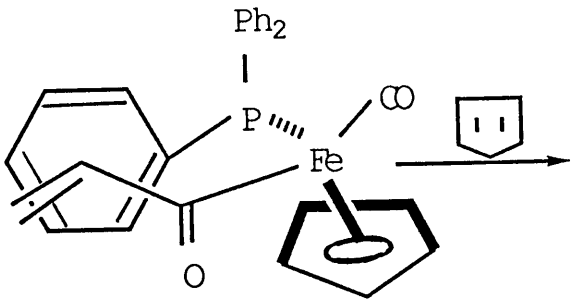


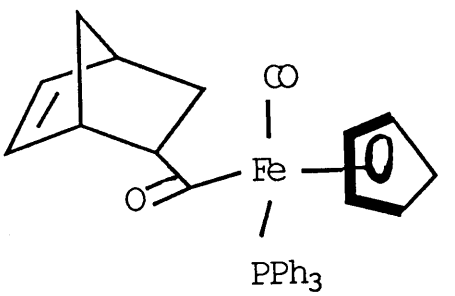
(230) (231) (232)

Scheme 47



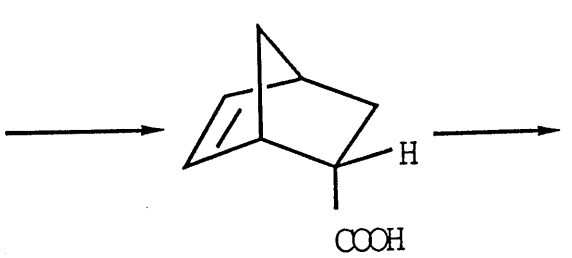
(233)

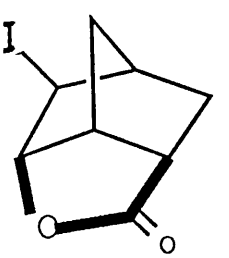




(234)

(235)

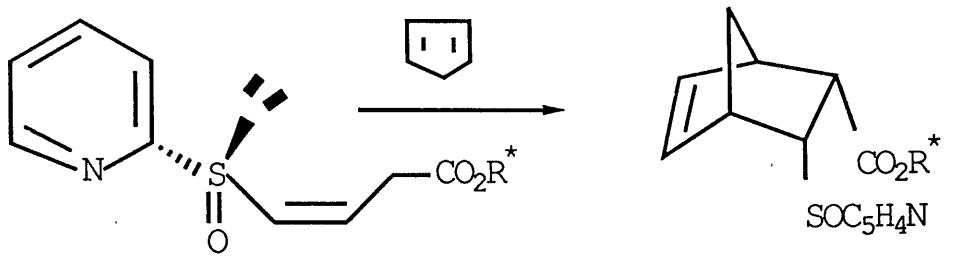




(236)

(237)

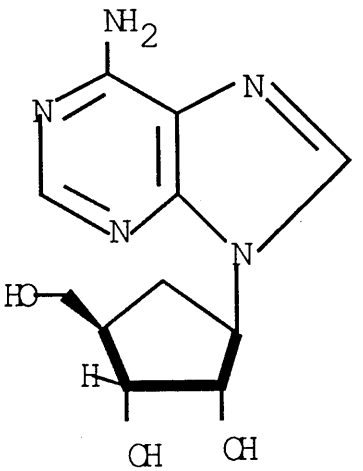
Scheme 48



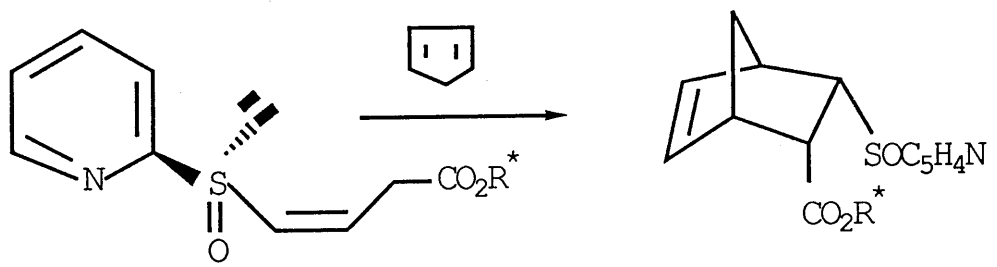
(238)

(239)

1) OsO_4
2) Me_2CO
3) 6-chloropurine



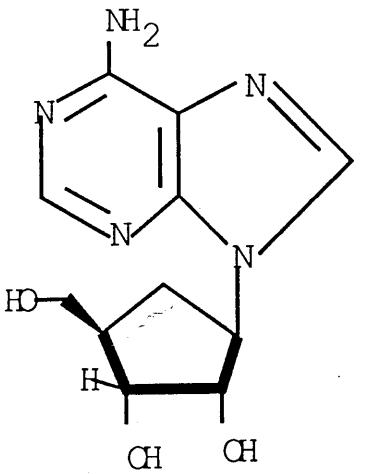
(240)



(241)

(242)

1) OsO_4
2) Me_2CO
3) 6-chloropurine



(243)

R^* = menthyl

Scheme 49

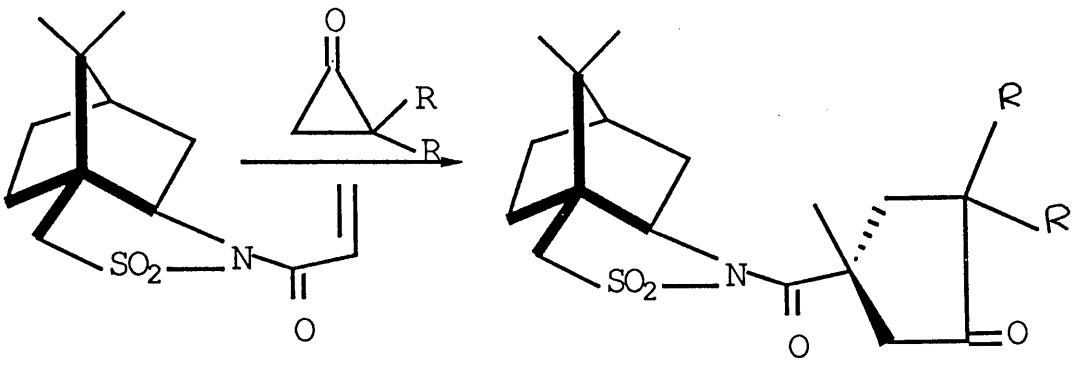
(Scheme 49).

Binger et al.[74] reported the nickel-catalysed cycloaddition reaction of the camphor sultam acrylate (244) with methylenecyclopropane (R = CH_3) to give the 3-methylene-cyclopentane carboxamide (245; R= CH_3) in the high d.e. of 96% (Scheme 50).

The new chiral dienophile di-l-menthyl-(acetoxymethylene)-malonate (246) was prepared by Katagri and co-workers[75] from Meldrum's acid and L-menthol. They treated the dienophile (246) with cyclopentadiene to give a mixture of the adducts (247) and (248). The mixture of adducts (247) and (248) was then hydrogenated where retro aldol C-C bond fission occurred under the reductive conditions to yield the product (250). Examination of the acetyl derivative of (250) by 'H n.m.r. showed it to be largely a single isomer d.e. 99%. The adduct (247) was also converted into (251), a carboxylic C-nucleoside precursor (Scheme 51).

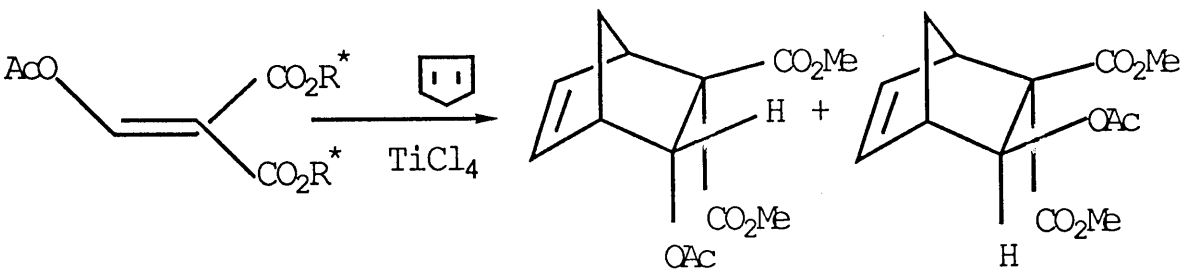
Chiral heterodienophiles

Zamojski et al.[76] reported the cycloaddition reaction of l-methoxybutadiene to the optically active ester of glyoxylic acid (252) to give the adduct (253) in good yield. The adduct (253) was then degraded into the methyl malate (254), an ester of known configuration. The adducts of type (254) are considered to be suitable for the stereoselective synthesis of various mono-

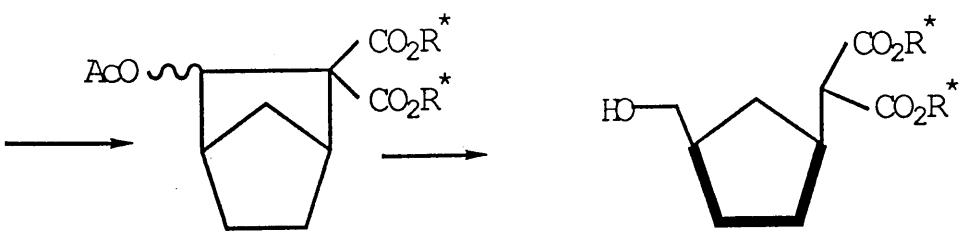


(244) (245)

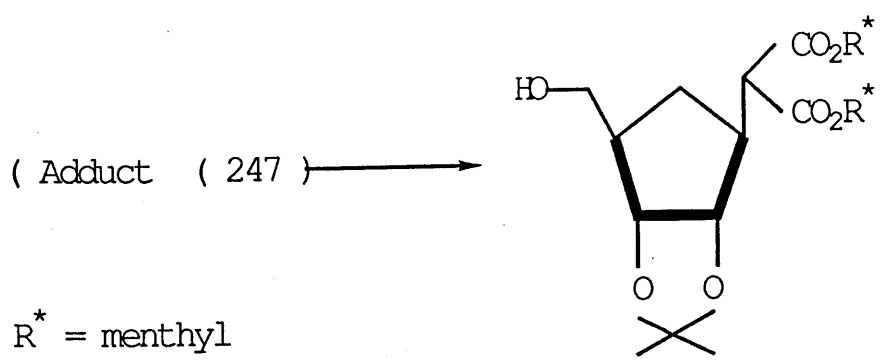
Scheme 50



(246) (247) (248)



(249) (250)



(Adduct (247)

R^* = menthyl

(251)

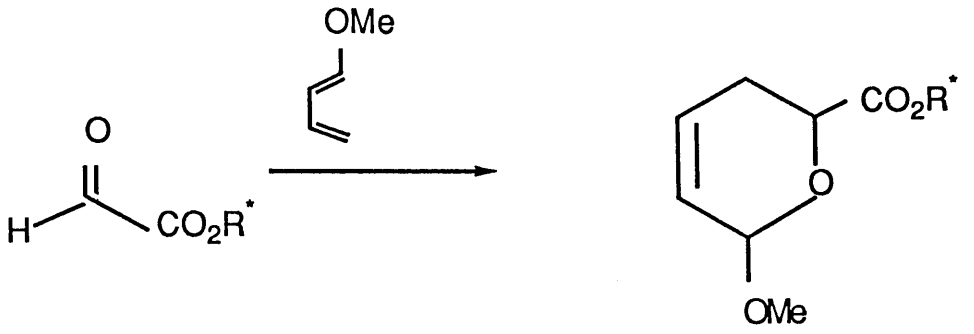
Scheme 51

saccharides (Scheme 52).

In 1976 Kresze et al.[77] reported the non-catalysed reaction of 2-chloro-2-nitroso-9-cyanodecalin (255) with some 1,3-conjugated dienes. This reaction in ethyl alcohol and ether yielded a single diastereoisomic chiral bicyclic oxazine hydrochloride (256) with d.e. 39%. The chiral oxazine hydrochloride (256 $R^1=R^2=CH_3$) was then degraded to acid of known configuration (258) (Scheme 53).

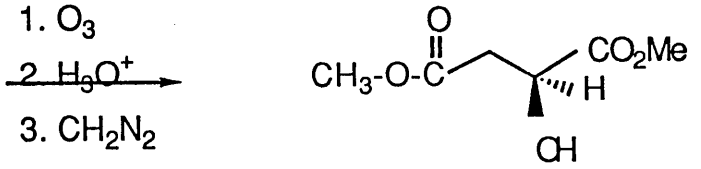
The optically active triazolinediones (259), (260), and (261) were reported by Paquette et al.[78]. The reaction of these chiral dienophiles failed to achieve any high level of asymmetric induction in Diels-Alder reaction. However, they used the triazolinediene (261) to achieve the nondestructive resolution of substances that are not obviously resolvable. The racemic methyl cyclooctatetraene (262) was treated with dienophile (261) and the adduct (263) was then converted into the optically pure (+)-methylsemibullvalene (265), the first rapidly fluxional molecule to be prepared in the optical form (Scheme 54).

The reaction of 10-chloro-10-sulfinylcamphor (266) with dimethylbuta-1,3-diene gave the dihydrothiapyran (267) as the major compound[79] with d.e. 94%. The absolute configurations of the new chiral centres in (267) were established by crystallography.. Pascal et al. also treated the sulfoximinosulfine (268) with buta-1,3-diene to give largely the diastereoisomeric adduct (269) with d.e. 94% (Scheme 55).



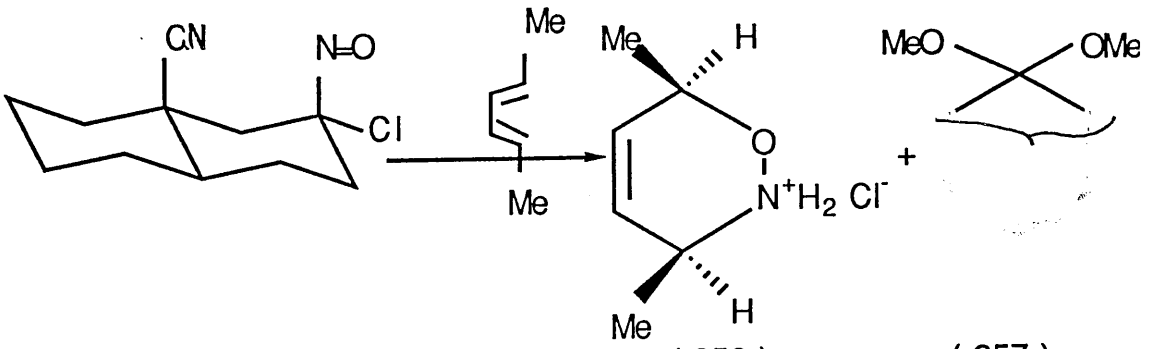
(252) (253)

R^* = menthyl

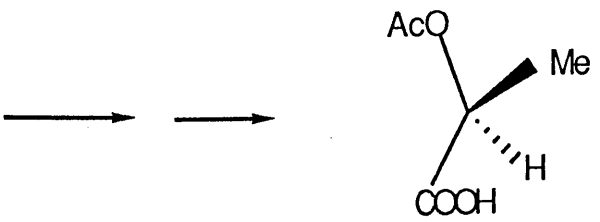


(254)

Scheme 52

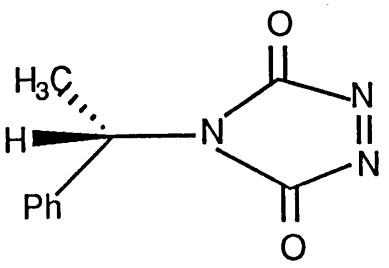


(255) (256) (257)

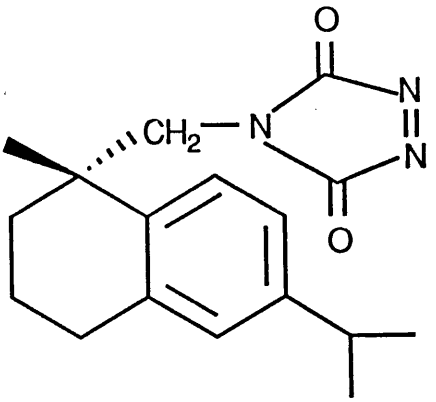


(258)

Scheme 53



(259)



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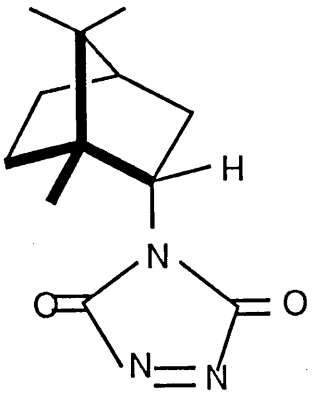
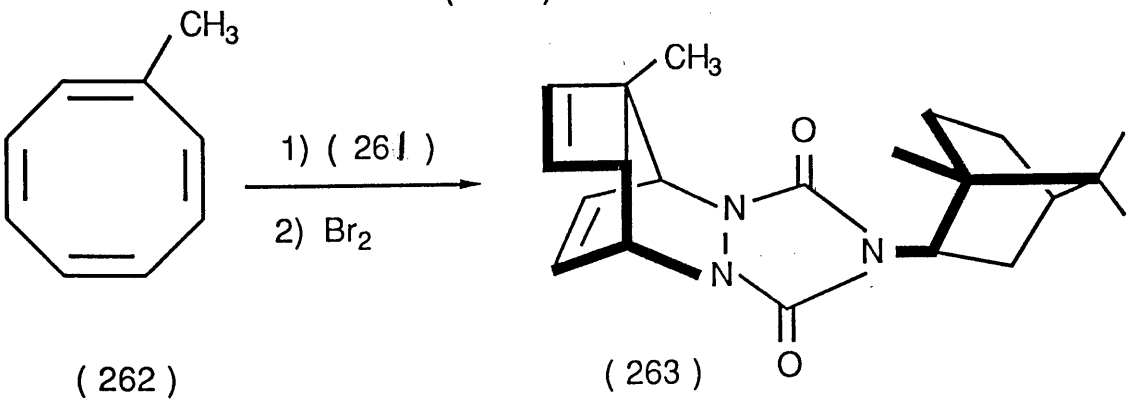
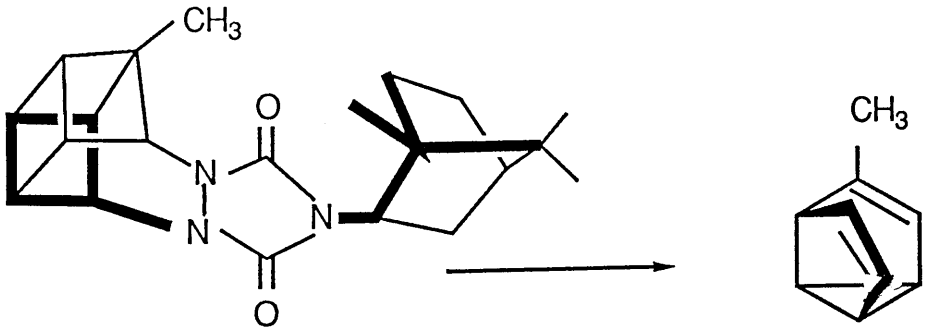


(261)



(262)

(263)



(264)

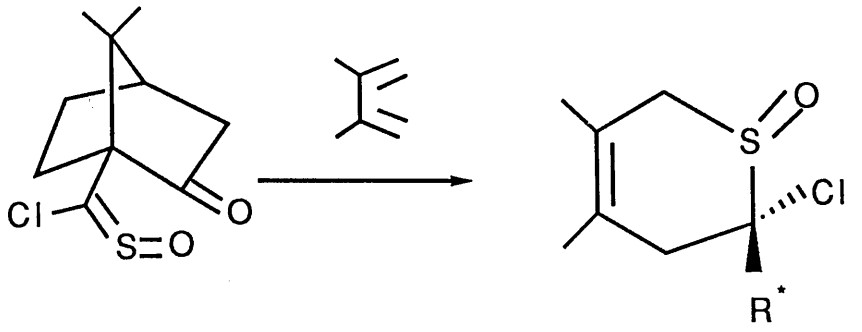
(265)

Scheme 54

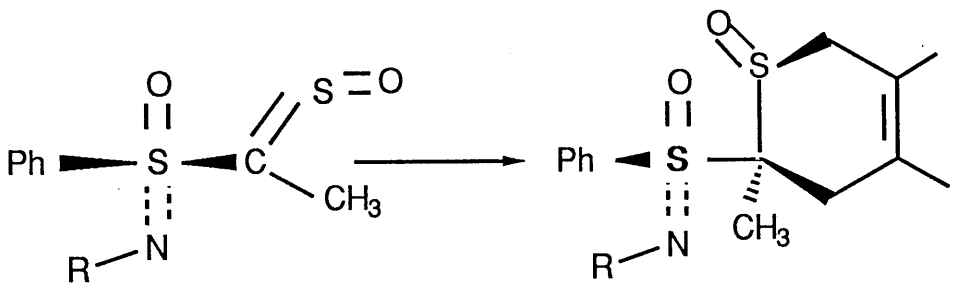
Kresze et al.[80] synthesised the α-chloronitroso compound (270) from 2,3,5-di-O-isopropylene-D-manofuranose. The dienophile (270) reacted with cyclohexa-1,3-diene to give the chiral bicyclic oxazine derivative (271) as the major compound in 69% yield and 95% e.e. The configuration of the adduct (271) was established as (1S, 4R) (Scheme 56). They also prepared 17-chloro-17-nitroso-3β-hydroxy-5-androstane (272) and reacted with cyclohexa-1,3-diene[81] to give again a bicyclic chiral oxazine derivative, but this time the major product (273) had the opposite configuration (1R, 4S) (Scheme 56b).

The iminium salt prepared from (-)-α-methylbenzylamine hydrochloride [82] reacted with cyclopentadiene to give a separable mixture of adducts (275) and (276) in a 4:1 ratio. The same workers treated the dienyl aldehyde (277) with α-methylbenzylamine hydrochloride (274) to give a mixture of adducts (278) and (279) in a 2.5:1 ratio. The adducts of types (275) and (276) can be used for the preparation of other heterocyclic compounds (Scheme 57).

Posner et al.[83] in 1986 reported that chiral alkyl vinyl ethers (281) underwent Diels-Alder cycloaddition reaction with 3-arenesulfonyl-2-pyrone (280) to form bridged bicyclic lactone adducts (282) in excellent yields with diastereoselectivities of 64-90%. They found that the alkyl vinyl ethers derived from tert-butylphenylcarbinyl formed adducts (282c), more

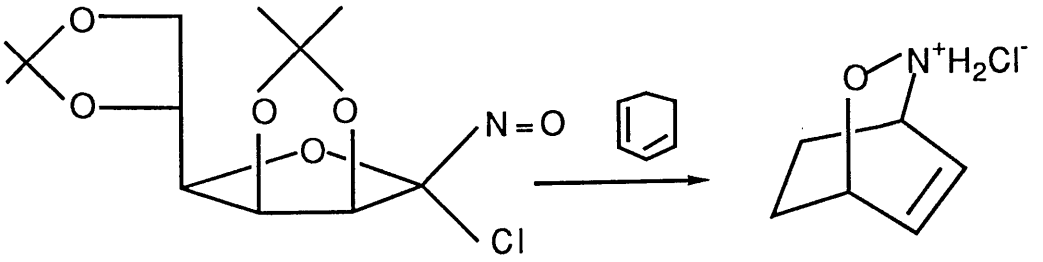


(266) (267)



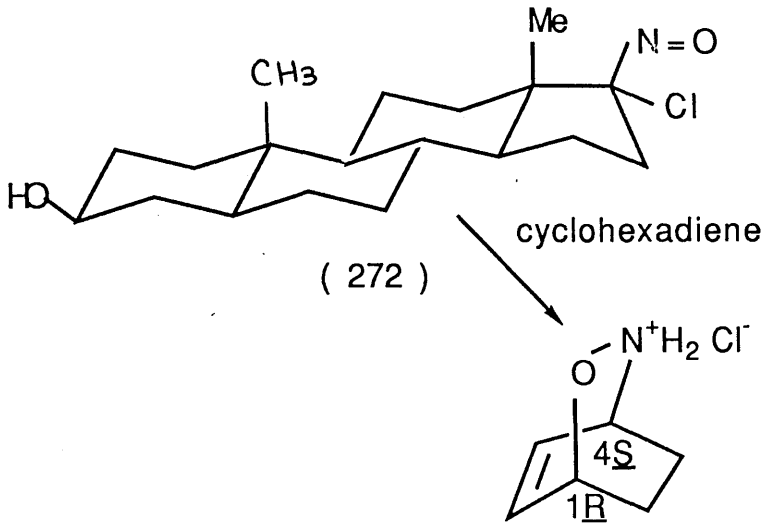
(268) (269)

Scheme 55

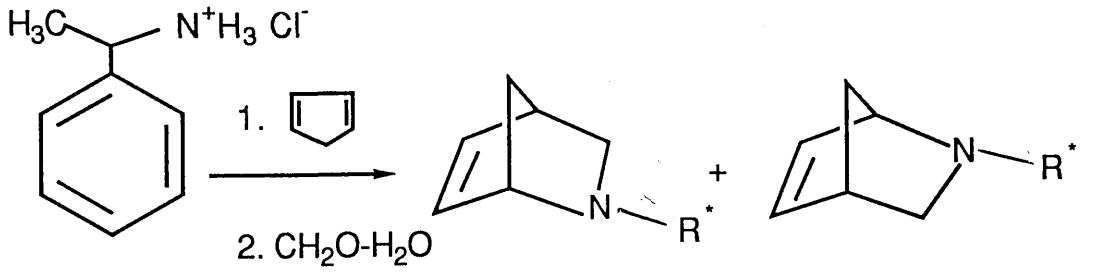


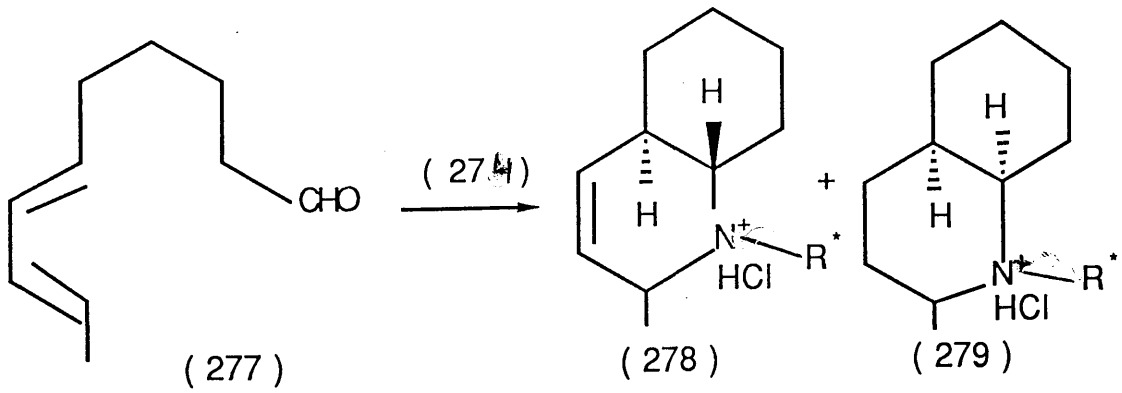
(270) (271)

Scheme 56



Scheme 56b





$R^* = C_6H_5CH(CH_3)$

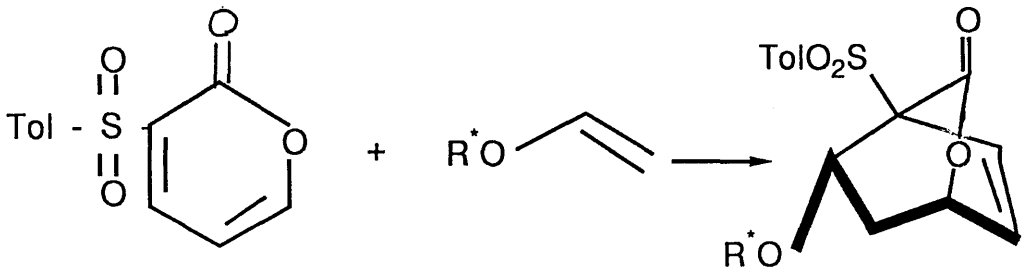
Scheme 57

diastereoselectively as compared to alkyl vinyl ethers derived from some traditionally used chiral alcohols such as 8-phenylmenthol. They could not offer any possible explanation to this anomaly (Scheme 58).

The N-sulfinylcarbamates (283) and (284) were prepared by Weinerb et al.[84]. They treated (282) with cyclohexa-1,3-diene in the presence of Lewis acid catalyst to give a mixture containing mainly 3,6-dihydrothiazine oxide (285) in 77% yield, with d.e. of 90%. They converted adduct (285) to cyclic carbamate (286) of known configuration. The reaction of the dienophile (284) with cyclohexa-1,3-diene again yielded the diastereoisomeric cycloadducts (285) with superior d.e. 99%, (scheme 59).

Whitesell and co-workers [85] treated the N-sulfinylcarbamate (283) of 8-phenymenthol with E,E-hexa-2,4-diene in the presence of the Lewis acid catalyst, stanic chloride, to give largely the diastereoisomeric cycloadduct (287), in 97% d.e. The relative and absolute configuration was established by treating with phenylmagnesium bromide, followed by 1,3-rearrangement and desulphurization with trimethyl phosphate in refluxing methanol yielded the carbamate alcohol (288), of known configuration (Scheme 60).

Chapleur et al.[86] prepared multichiral arrays from α,β-unsaturated ketone (289) from carbohydrates. Its reactions with enol ethers (290) afforded the fused dihydropyrans (291), completely stereospecifically with the creation of chiral centres



(280) (281) (282)

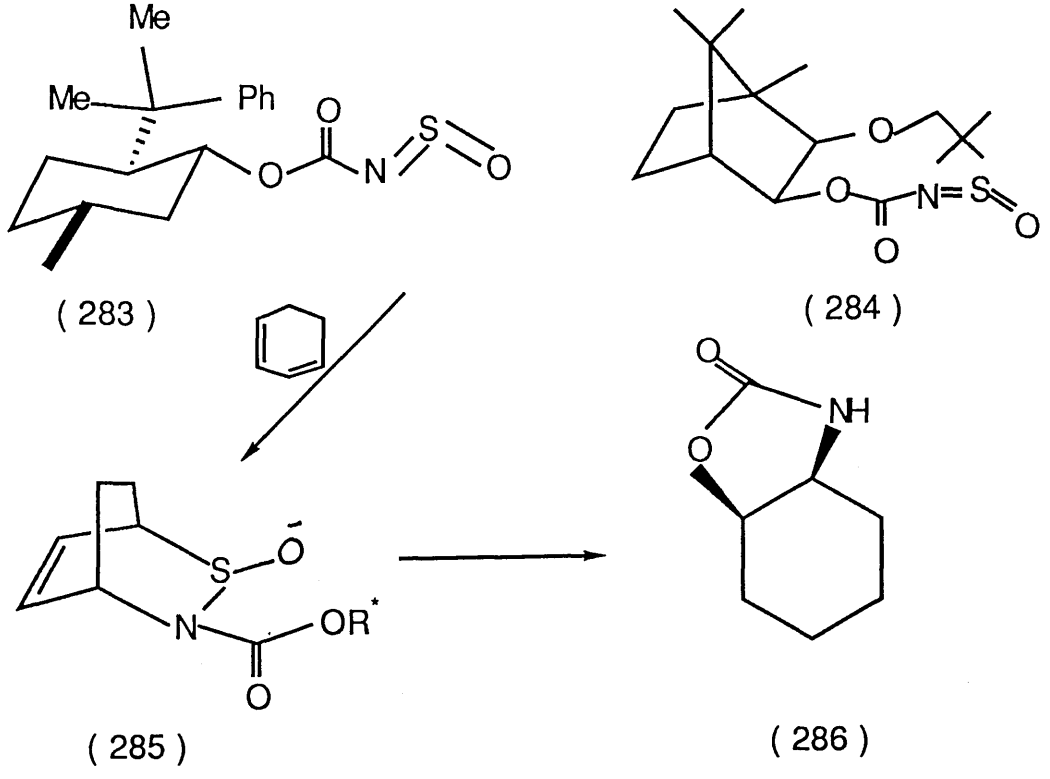
a; R^* = menthyl

b; R^* 8-phenylmenthyl

c; R^* tert. butyl-phenyl carbinyl

d; R^* isopropylmethylcarbinyl

Scheme 58



(283) (284)

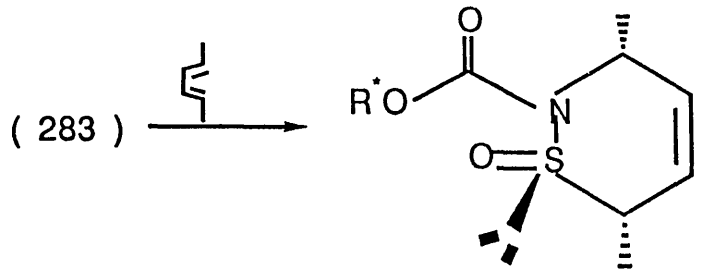
(285) (286)

Scheme 59

on the newly formed templates. This type of approach using heterodienophiles with a proper choice of substituents on the reactants should permit the synthesis of long chain multichiral arrays, which are present in a number of natural products (Scheme 61).

In 1988 the use of (R) and (S) amino acid methyl ester hydrochlorides (292) was reported by Herbert et al.[87] in aymmetric Diels-Alder reactions with cyclopentadiene and cyclohexa-1,3-diene in the presence of aqueous formaldehyde to give the diastereoisomeric bicyclic aza adducts (294) and (295). It is thought that the iminium ion (293) is the reactive intermediate. The (S)-amino acid derivatives preferentially yielded the (1R, 4S)-2-aza-bicycloheptenes (294) and amino acid esters of (R)-configuration gave preferentially the (1S, 4R)-2-aza bicycloheptenes (295). The adducts of types (294) and (295) were converted into the nitrogen heterocyclic compounds (295) (Scheme 62).

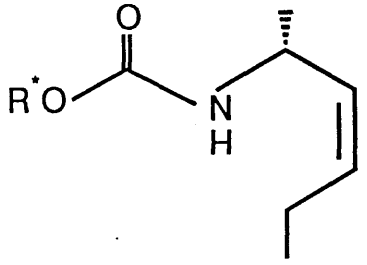
The diastereoselectivity of chiral thioaldehydes in asymmetric Diels-Alder reactions, was reported by Vedjes and co-workers [88] in 1988. They prepared a number of precursor for the chiral thioalddehydes. Photolysis of (297) in the presence of cyclopentadiene gave four diastereoisomeric cycloadducts (299) and (300) by endo addition in a ratio of 75:18, and (301) and (302) by exo mode in a ratio of 5:2. The endo facial selectivity was found to be 93:7. The three acetoxy derivatives (298a), (298b), and (298c) gave almost similar ratios of the diastereoisomeric



(283)

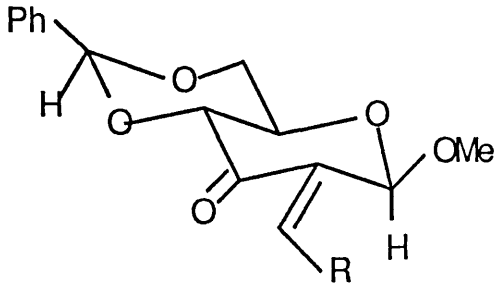
(287)

1. PhMgBr
2. heat, $(MeO)_3P$

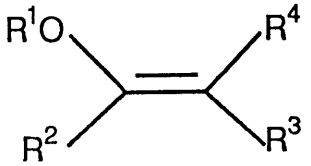


(288)

Scheme 60

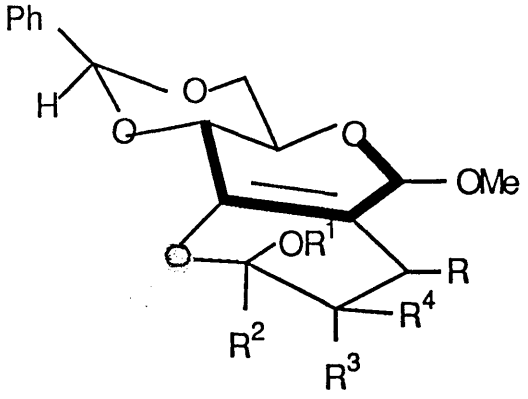


(289)



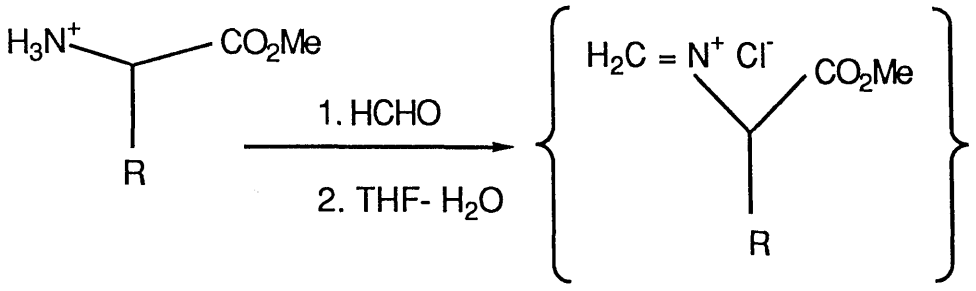
(290)

	R^1	R^2	R^3	R^4
a;	Et	H	H	H
b;	Me	Me	H	H
c;	Et	H	H	Me
d;	Et	H	Me	H

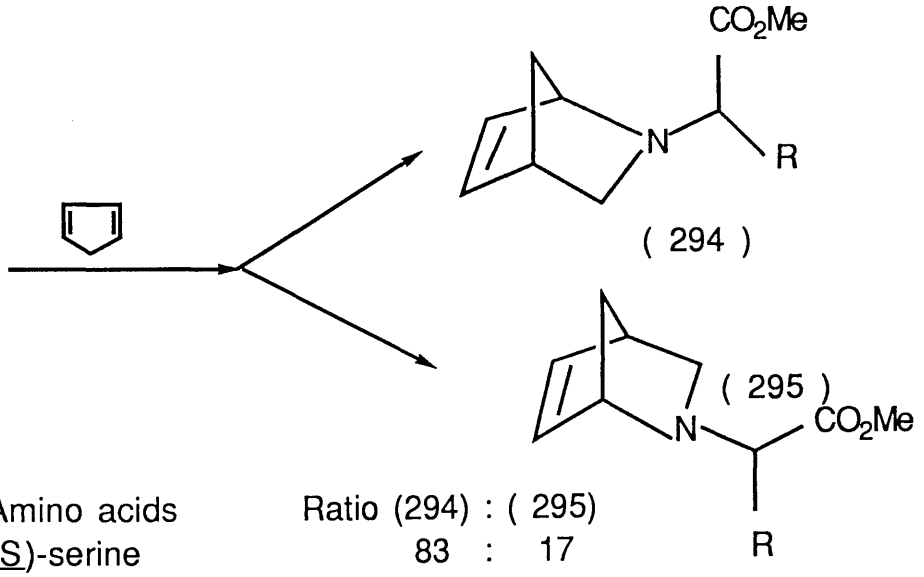


(291)

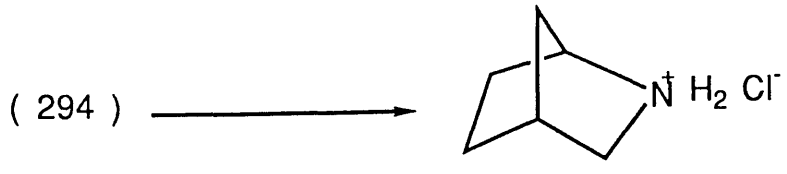
Scheme 61



(292) (293)



Amino acids	Ratio (294) : (295)
a; (S)-serine	83 : 17
b; (S)-isoleucine	93 : 7
c; (S)-valine	86 : 14
d; (S)-phenylglycine	78 : 22
e; (R)-phenylglycine	20 : 80
f ; (R)-serine	27 : 73
g; (R)-valine	17 : 83



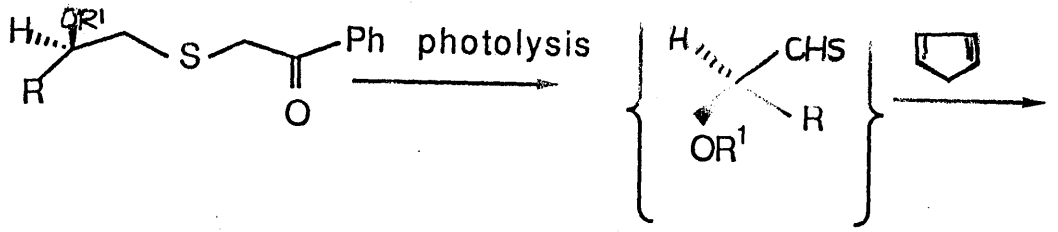
(296)

Scheme 62

products. The thioaldehyde derivative (298d) containing a free α-hydroxyl group, gave the ratio of the endo products in the opposite way, i.e. 30:56 and exo ratio 2:5. This time for the endo diastereoisomers, the thioaldehyde preference was inverted as compared with acetoxy derivatives. This was explained on the basis of hydrogen bonding in the intermediate as shown (303) (Scheme 63). They even obtained higher facial selectivity i.e. 30:1, when the thioglyceraldehyde acetamide precursor (304) was photolysed in the presence of cyclopentadiene. Photolysis of (304) in the presence of Danishefsky diene (306) yeilded the enone (307) and (308) in a 40:1 ratio, after hydrolysis of the products (Scheme 64). They found that the diastereoselectivity associated with thioaldehydes mainly depend upon the bulkiness at the α-carbon atom and best ratios were obtained with α-alkoxy thioaldehydes.

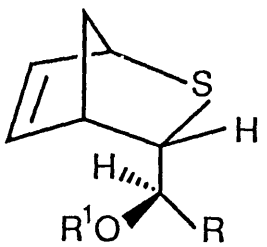
Chiral dienes

The addition of chiral dienes to achiral dienophiles is the least explored aspect of the asymmetric Diels-Alder. This may be perhaps due to the non-availability of the suitable chiral dienes. David et al.[89] found that thermal addition of the 1,3-dienol ester (309), derived from a carbohydrate, to n-butylglyoxylate yielded a complex mixture of four diastereoisomeric cycloadducts in a very low d.e. Trost et al.[90], later found that Lewis acid catalysed cycloaddition of the dienol ether (310) to acrolein yeilded the cycloadduct, the major product (311; R = Et) with a d.e. 20%. The diene (310; R = H) reacted similarly with acrolein to give the

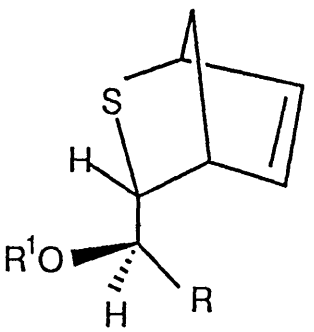


(297)

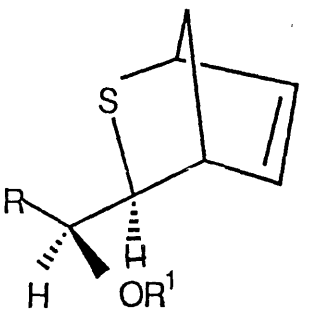
(298)



(299)



(300)



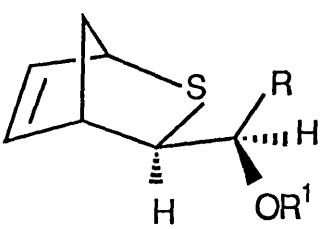
(301)

a; R^1 = Ac, R = Et

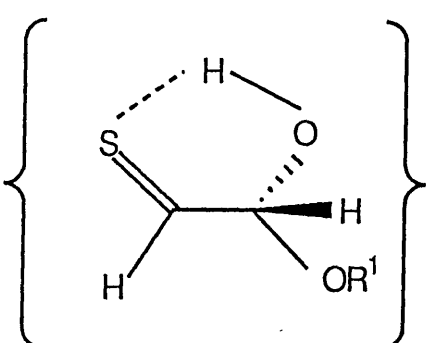
b; R^1 = Ac, R = Ph

c; R^1 = Ac, R = Bu^t

d; R^1 = H , R = Et

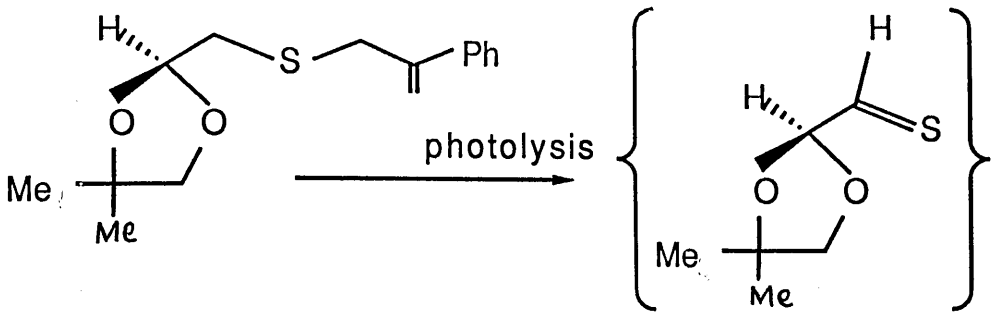


(302)



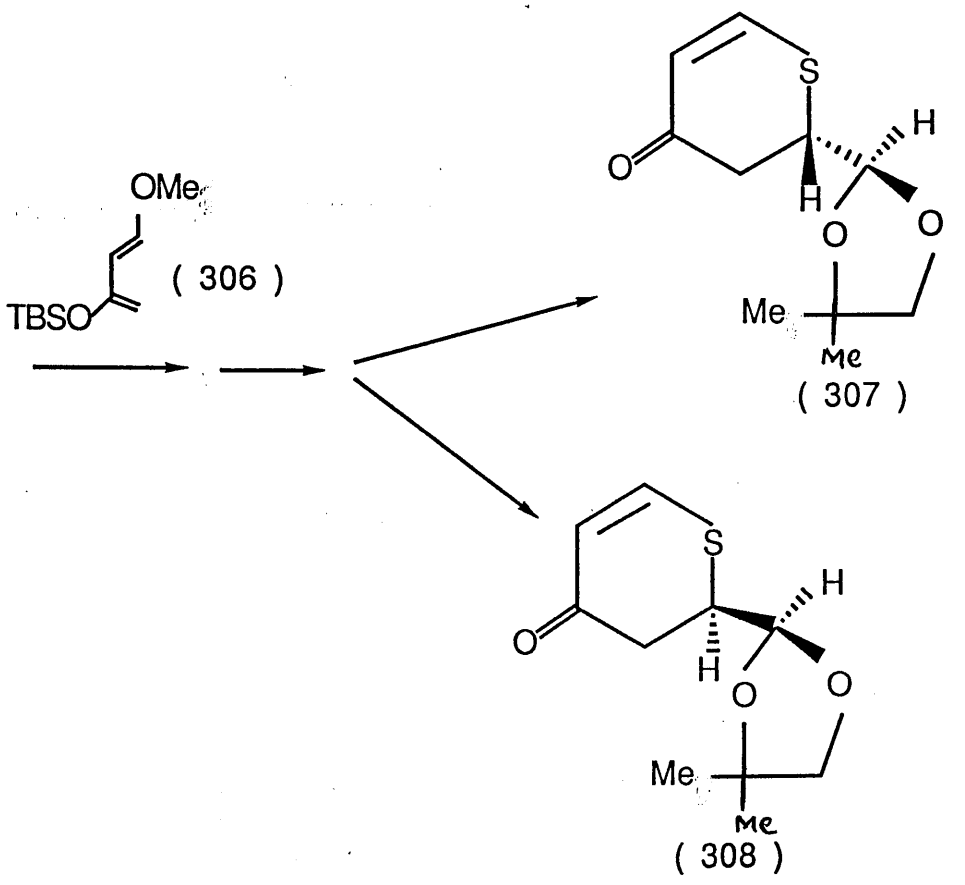
(303)

Scheme 63

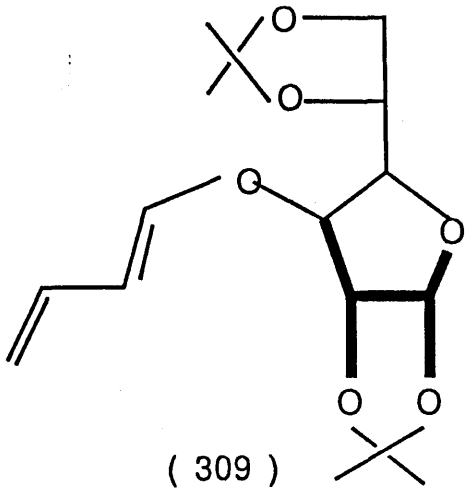


(304)

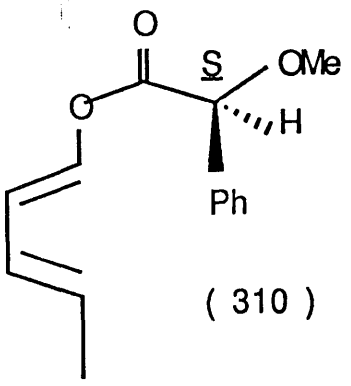
(305)



Scheme 64

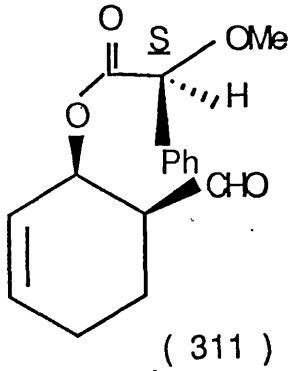


(309)



(310)

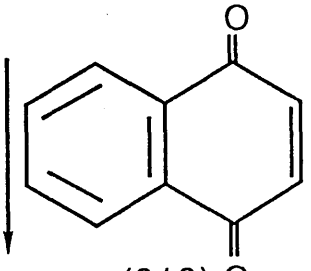
(309) $H_2C=CH-CHO$



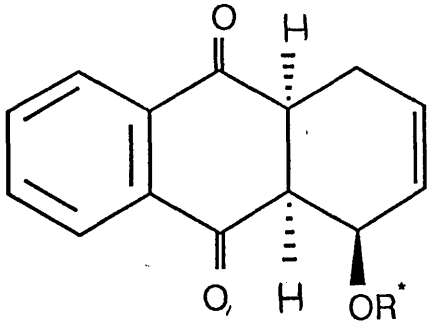
(311)

1. $NaBH_4$

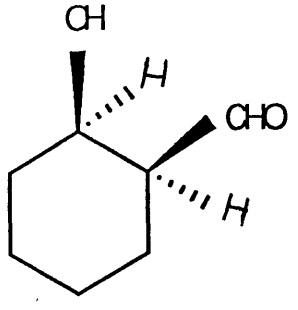
2. H_2-Pd-C



(313)



(314)



(312)

Scheme 65

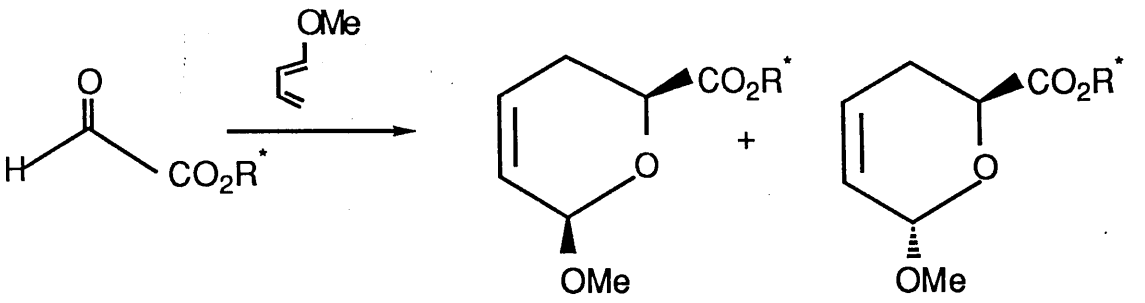
major adduct (311; R = H) with a d.e. 64%. A single diastereoisomer (314; R = H) was obtained exclusively when the diene (310; R = H) was added to juglone (313) (Scheme 65).

The effect of high pressure on the asymmetric Diels-Alder reaction

Jurczak and co-workers [91] were the first to study the effect of high pressure on the asymmetric Diels-Alder reactions.These workers found that the configuration of the diacid (151) (Scheme 33) was reversed when high pressure was applied to the reaction mixture. In a similar fashion, they discovered that when 1-methoxy-1,3-butadiene was treated with (R)-methylglyoxylate (252) it gave a mixture of products (315) and (316) in different ratios [92] depending upon the combination of reaction solvent and pressure applied (Scheme 66). They found that at a pressure of 15.5 kbar in ether, the dominating product was that with R configuration at C-6. However at 11.1 kbar in n-hexane the major product had the S configuration at C-6. When (252) was treated under pressure with 2,3-dimethylbutadiene[93], the d.e. was raised to 21%.

Jurczak and co-workers[94] treated the dienophile (317) with 2,3-dimethybutadiene to give the major diastereoisomeric cycloadduct (318), 80% and the minor adduct (319), 20%, under purely thermal conditions. When the reaction was performed at higher pressure, only the major diastereoisomer (318) was obtained (Scheme 67).

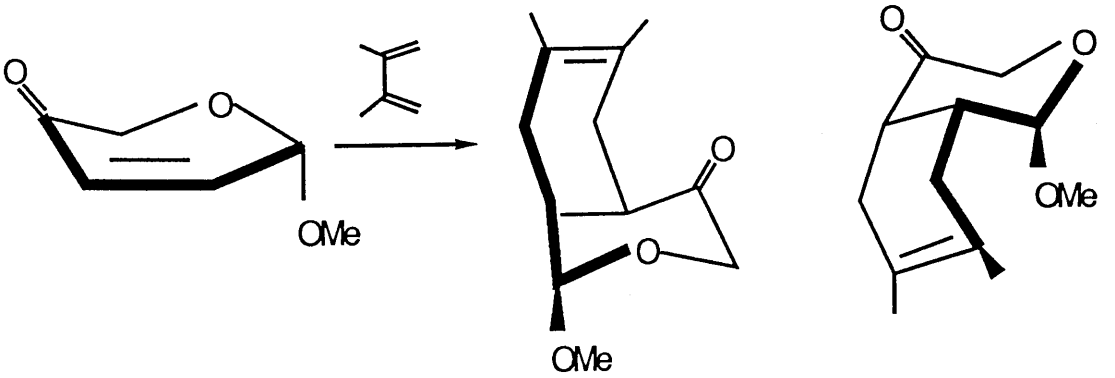
Dauben et al.[95], treated the menthyl ester of 2,4-pentadienoate



(252) (315) (316)

R^* = mentyl

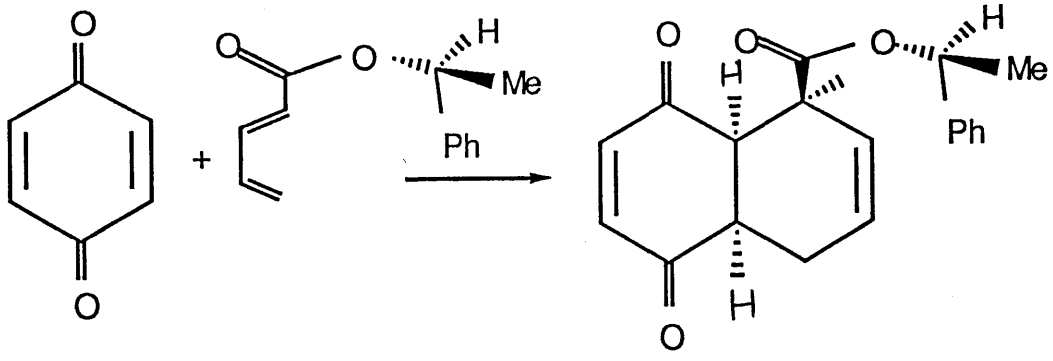
Scheme 66



(317) (318) (319)

Scheme 67

(321) with benzoquinone (320) to give the single adduct (322) in 99% d.e. (Scheme 68).



(320) (321) (322)

Scheme 68

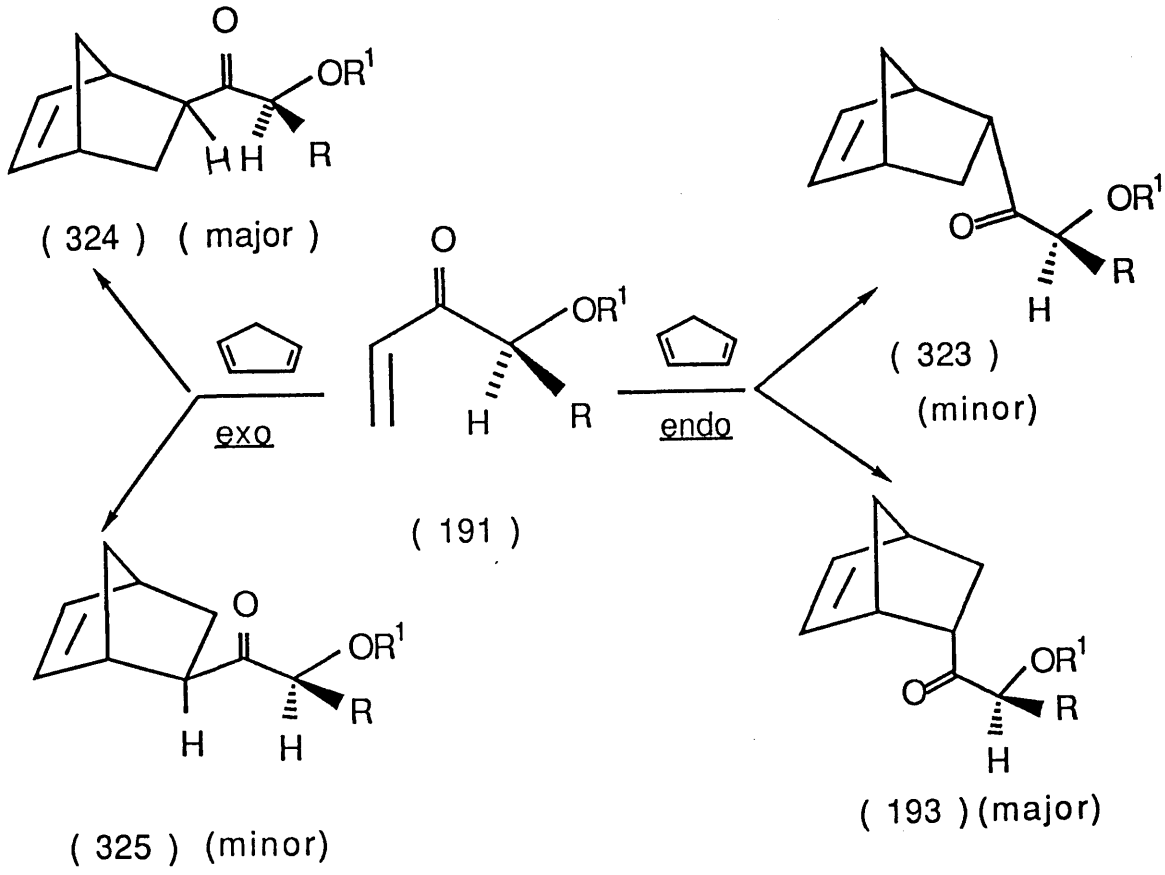
CHAPTER 2

RESULTS AND DISCUSSION

SECTION I

Cycloaddition reactions of (±)-mandelic acid derivatives and thebaine

In 1983 Choy et al.[96] explored the influence of intramolecular hydrogen bonding in asymmetric Diels-Alder reactions. These workers prepared the chiral dienophile (191a) by treating (S)-hexahydromandelic acid with vinyl-lithium in tetrahydrofuran (THF) at -78°C (Scheme 69). Similarly, the enone (191d) was prepared from (S)-2-hydroxy-3,3-dimethylbutanoic acid. The enone (191a) was treated with either trimethylsilyl chloride and N,N-di-isopropylethylamine, or tert-butyldimethylsilyl triflate and 2,6-di-tert-butylpyridine to give the silylated enone (191b) and (197c), respectively. Similarly, treatment of enone (191d) with trimethylsilyl chloride gave the enone (191e). The reaction of the enone (191a) with cyclopentadiene, studied at various temperatures, yielded four diastereoisomeric cycloadducts (193a), (323a), (324a), and (325a). At -55°C, the ratio of the two endo cycloadducts (193a) and (323a) was found to be 28:1, and for the exo products (324a) and (325a) the ratio was 7:1. The reaction of the tert-butyl derivative (191d) with cyclopentadiene yielded only the endo diastereoisomers (193d) and (323d) with a diastereofacial selectivity >100:1 in favour of (193d); no exo products were detected. These workers rationalized this high diastereofacial selectivity on the basis of intramolecular hydrogen bonding between the hydroxyl and carbonyl groups in the dienophiles (191a) and (191d), to form a five membered chelate ring [see (326)], would prevent rotation about the C(=O)-C bond,



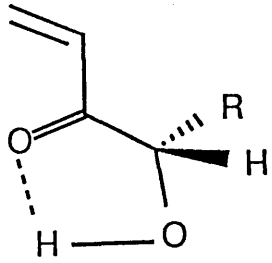
a; R = cyclohexyl, R^1 = H

b; R = cyclohexyl, R^1 = Me_2Si

c; R = cyclohexyl, R^1 = Bu^tMe_2Si

d; R = tert-butyl, R^1 = H

e; R = tert-butyl, R^1 = H



(326)

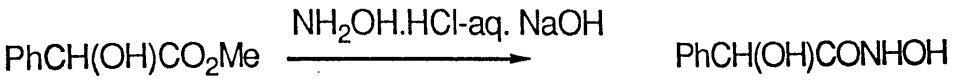
Scheme 69

thereby making the two diastereotropic faces of the dienophiles more distinguishable. To account for (193) and (323) being the major products, they postulated that the dienophile must adopt the 'cisoid' conformation (326). The idea of intramolecular hydrogen bonding was strengthend when the O-silylated cyclohexyl derivatives (191b) and (191c) reacted with cyclopentadiene at -20°C, to give the endo cycloadducts (193b) and (323b), and (193c) and (323c), in ratios of 36:64, and 60:40 respectively. The exo products (324b) and (325b), and (324c) and (325c), were found in ratios of 50:50 and 64:34 respectively. A similar reaction of the tert-butyl enone (191e) yielded the endo diastereoisomers (193e) and (323e) in a ratio of 40:60 and the exo diastereoisomers (324e) and (325e) in a ratio of 38:62. These inferior diastereofacial selectivities for the O-silylated dienophiles support the idea of intramolecular hyrogen bonding. However, they might also be due to the increase in size of the siloxy groups relative to the hydroxy group, thereby reducing the difference in size relative to the cyclohexyl or tert-butyl groups.

Kirby et al.[37] in 1985 suggested that intramolecular hydrogen bonding in chiral α-amino and α-hydroxy C-nitrosocarbonyl derivatives might also enhanced the asymmetric induction in their Diels-Alder reaction with achiral dienes. One possible hydrogen bonded conformation (329c) is shown in Scheme 70 for the nitroso compound derived from (S)-mandelohydroxamic acid. The aim of the present study, therefore, was to explore the stereochemistry of the cycloaddition reactions of certain chiral C-nitrosocarbonyl compounds of this type with some conjugated

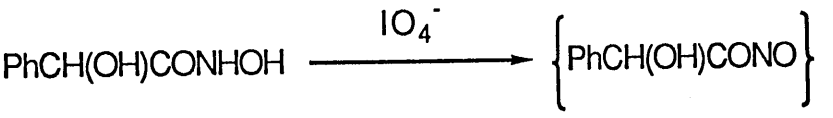
1,3-dienes. The use of nitrosocarbonyl compounds, XCONO (X=Ar, R, RO, or RR'N) for the synthesis of dihydro-oxazines and derived amino-alcohols has been discussed in Chapter I.

Mandelic acid, a typical α-hydroxy acid readily available in all 3 forms, (R)-(-), (S)-(+), and (±), was selected for the first experiments. The racemic mandelic acid was converted into methyl (±)-mandelate (327) by refluxing in dry methanolic hydrogen chloride. The ester was obtained as a viscous liquid. Methyl (±)-mandelate (327) was treated with hydroxylamine hydrocloride in ethanol-water in the presence of 10M sodium hydroxide, at 0°C, then at room temperature, in the usual way[97]. (±)-Mandelohydroxamic acid (328a) m.p. 144-145°C was obtained in good yield. The m.p. was in good agreement with that 146-147°C, reported for material obtained from the ethyl ester [98]. The ^{1}H n.m.r spectrum (CD_3OD) showed signals similar to the ester (327a) with replacement of O-methoxyl signal with broad signal at δ4.95 for NH and OH, and singlet for HO-CH, δ5.15. The corresponding enantiomers (328b) and (328c) were obtained similarly from the corresponding methyl mandelates, (R)-(-)-mandelohydroxamic acid (328b) had m.p. 138-139°C (from ethyl acetate- light petroleum). The composition was confirmed, mass spectrometrically by accurate mass measurement, and by microanalysis. The i.r. spectrum showed bands for a hydroxyl group at 3350 cm^{-1} and carbonyl group at 1655 cm^{-1}. The ^{1}H n.m.r spectrum (CD_3OD) was identical to that of the known racemate. (S)-mandelohydroxamic acid (328c) was prepared and characterised like its enantiomer (328b) (Scheme 70).

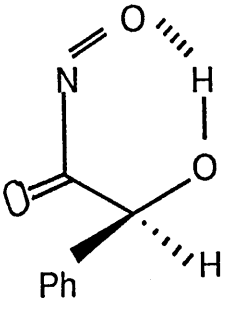


(327) (328)

a; (±)
b; (R)-(-)
c; (S)-(+)



(328) (329)



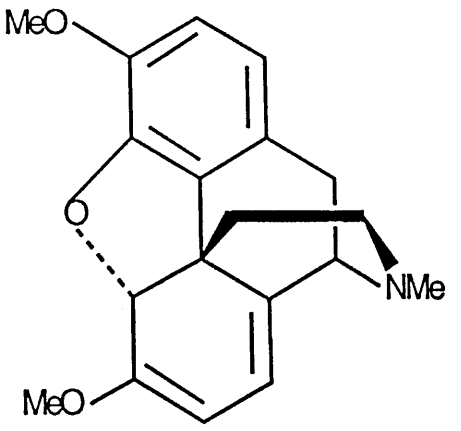
(329c)

Scheme 70

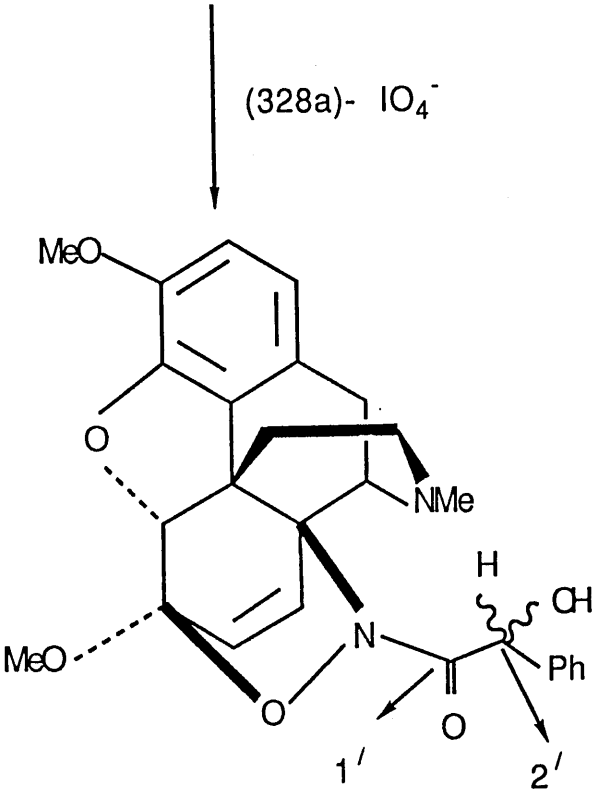
The chiral diene thebaine (26) was chosen for the first experiment so that experience could be gained with crystalline products and, it was hoped, separable diastereoisomeric cycloadducts would be obtained. As described before (Chapter I, Section I), simple nitrosocarbonyl compounds add to thebaine solely from the ß-face of the diene system to give regioisomers with formation of C(14)-N bonds.

Thus, when (±) mandelohydroxamic acid (328a) was oxidized with sodium periodate, in aqueous sodium acetate-ethyl acetate at 0°C, in the presence of an equimolecular amount of thebaine (26), a mixture of diastereoisomeric cycloadducts (330a) was obtained in 82% yield (Scheme 71). The ratio of the diastereoisomers (330a) was found to be ca 1:1 from the integrals for the signals for 2′-H and 7- and 8-H in the ^{1}H m.m.r spectrum. Some striking differences in the ^{1}H n.m.r. spectra of the pair of cycloadducts (330a) were observed; these will be discussed later. As hoped, the mixture of the cycloadducts (330a) was easily separated chromotographically. It was not possible to identify the diastereoisomers spectroscopically, so it was decided to prepare each of them separately from the corresponding enantiomer of mandelohydroxamic acid.

(R)-(-)-Mandelohydroxamic acid (328b) was oxidized, as before, in the presence of thebaine (26) to give the cycloadduct (331b), m.p. 115-116°C, in 79% yield (Scheme 72). This was the more polar (t.l.c.) component of the initial mixture (330a). The

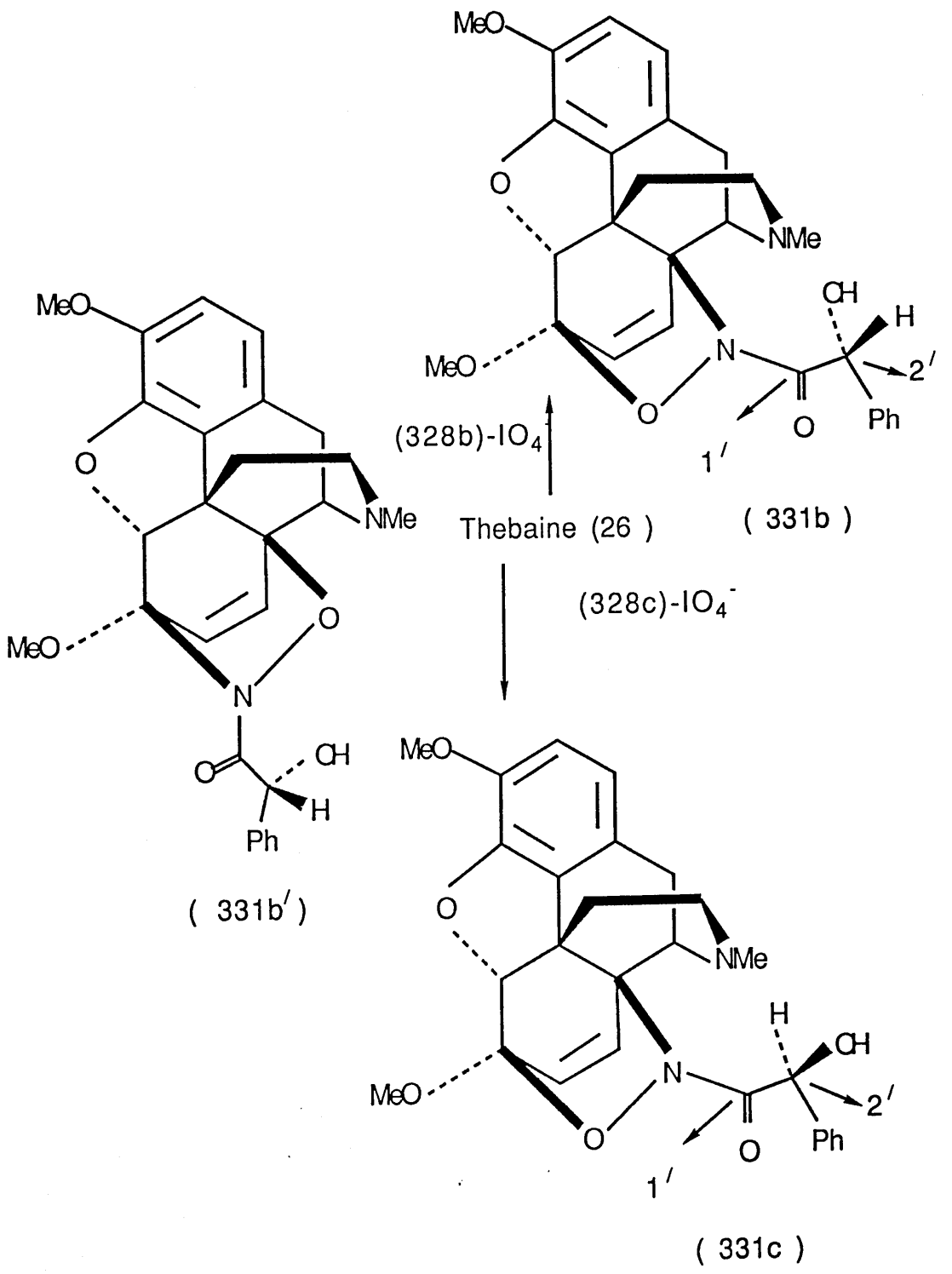


(26)



(330a)

Scheme 71


MeO
O
NMe
CH
H
2′
MeO
N
O
O
Ph
1′
(328b)-IO4
Thebaine (26)
(331b)
(328c)-IO4-
MeO
O
NMe
MeO
N
O
CH
H
Ph
(331b′)
MeO
O
NMe
H
CH
MeO
N
2′
O
O
Ph
1′
(331c)

Scheme 72

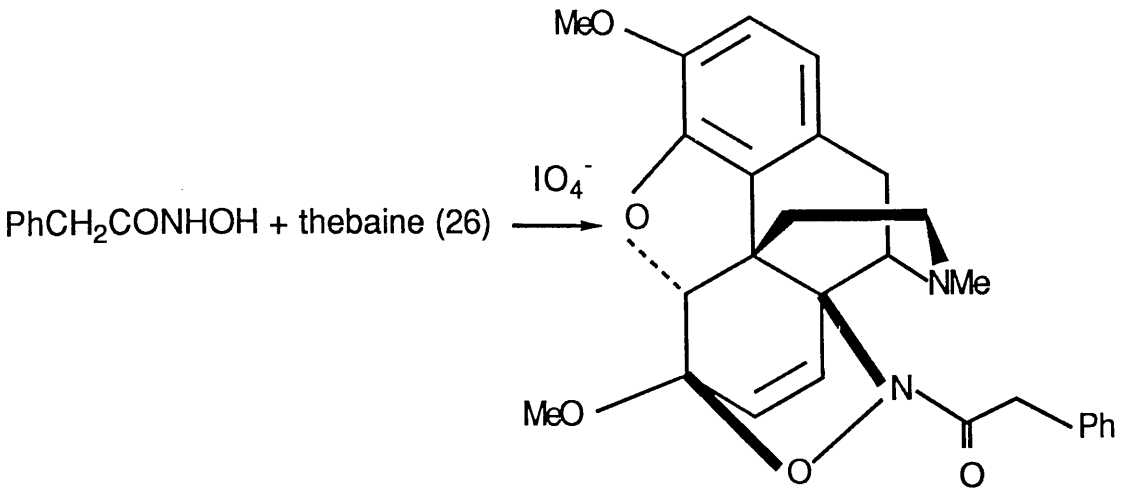
molecular formula was determined by accurate mass measurement and microanalysis supported the composition, $C_{27}H_{28}N_2O_6$. The i.r. spectrum (KBr) showed bands for a hydroxyl group, ν_{max} 3580 cm^{-1} and a carbonyl group, 1658 cm^{-1}. Similarly, oxidation of (S)-mandelohydroxamic acid (328c) in the presence of thebaine (26) gave the cycloadduct (331c), m.p. 159-160°C (78%) (Scheme 72). The composition was again confirmed by accurate mass measurement, and i.r. spectrum showed hydroxyl group ν_{max} 3400 cm^{-1} and carbonyl group, ν_{max}1658 cm^{-1} bands. The ^1H n.m.r. spectra of the cycloadducts (331b) and (331c) along with a standard compound[100] are listed in Table I

Table I: ^1H n.m.r. spectra $\delta(CDCl_3)$ of cycloadducts of thebaine (26)

Cycloadducts	Protons						
	7-H and 8-H		9-H	5-H	3.0Me	6.0Me	NMe
(331b)	5.48 (d,J,10Hz)	5.95 (d,J,10Hz)	4.85 (d,J,8Hz)	4.55 (s)	3.70 (s)	2.80 (s)	2.48 (s)
(331c)	6.00 a 6.10 (ABq)		4.68 (d,J,8Hz)	4.49 (s)	3.80 (s)	3.60 (s)	2.40 (s)
(337)	6.02 (s)		4.51 (d,J,8Hz)	4.57 (s)	3.80 (s)	3.49 (s)	2.44 (s)

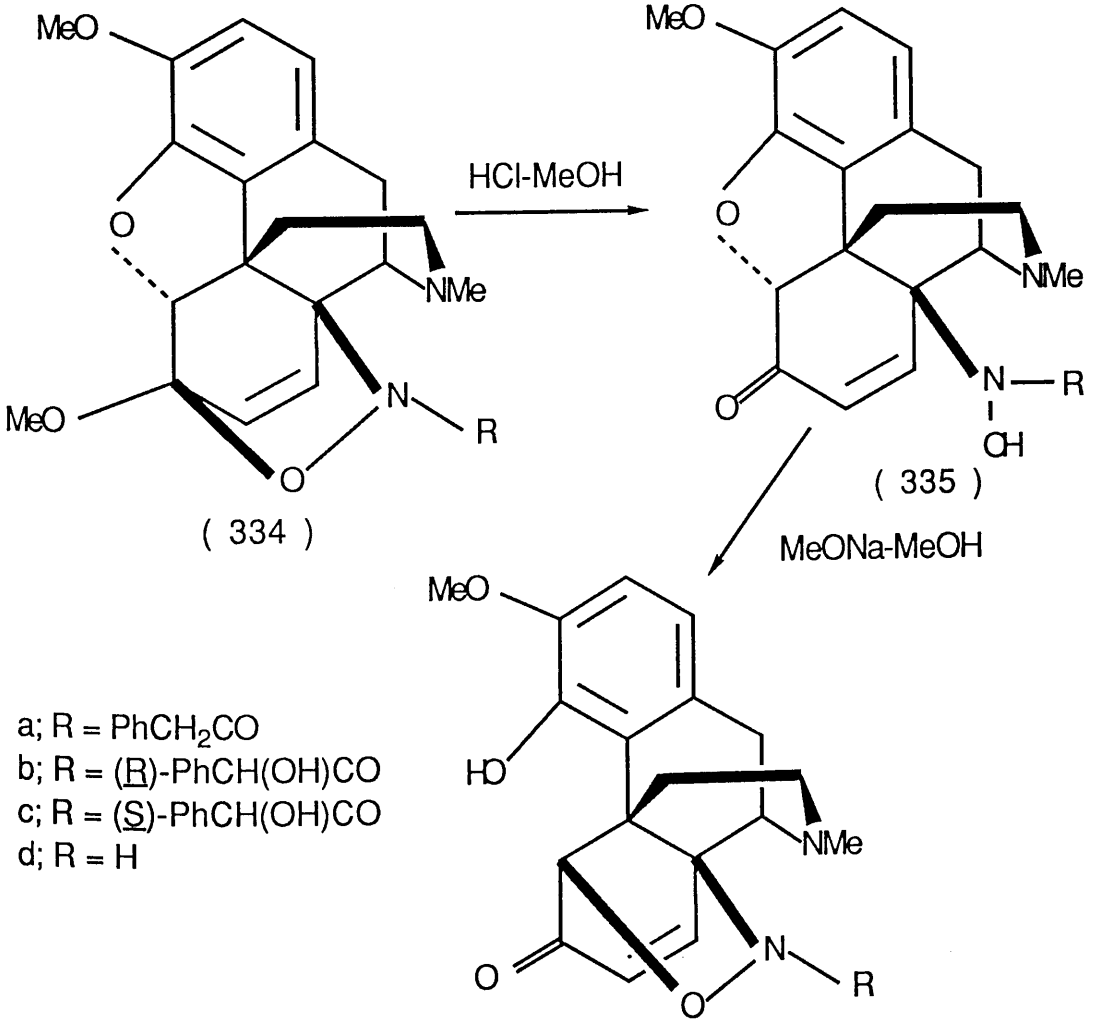
The abnormally low chemical shift, δ2.80, for the 6-methoxyl group of adduct (331b), compared with those for its diastereoisomer (331c), δ3.60, and the phenylacetyl derivative (333), δ3.49, was unexpected. Also the olefinic protons 7- and 8-H in cycloadduct (331b) gave doublets, δ5.48 and δ5.95, but in the diastereoisomeric cycloadduct (331c) both 7- and 8-H showed, ABq, δ6.00-6.10 and same was the ease with phenylacetyl derivative (333), δ6.02 (AB_q). These spectroscopic data, taken with the ease of chromatographic separation of the diastereoisomers meant that the isomer (331b) was in fact the corresponding regioisomer (331b′), had to be taken seriously. However, all previously prepared adducts of thebaine (26) and nitrosocarbonyl compounds are of the type (331b), i.e. having C(14)-N bonds. This is to be expected from the following, simple electronic argument. In thebaine (26) C-(14) is thought to be electron rich end of the diene on account of electron donation from the 6-methoxyl group. The nitrogen of the nitroso group is electron deficient, therefore nitroso group will attack the diene with formation of C(14)-N and C(6)-O bonds. Nevertheless, it was decided to degrade the cycloadducts (331b) and (331c) using the literature methods, to confirm their structure unambiguously.

To provide a model compound, the known derivative (333) was prepared (Scheme 73) by oxidizing phenylacetohydroxamic acid (332) with aqueous sodium periodate in the presence of thebaine (26). The cycloadduct (334a) was then hydrolyzed with 6M



(332) (333)

Scheme 73



(334) (335)

(336)

a; R = $PhCH_2CO$
b; R = (R)-PhCH(OH)CO
c; R = (S)-PhCH(OH)CO
d; R = H

Scheme 74

hydrochloric acid in hot methanol (1:1) to give the thebainone (335a) (Scheme 74). When the thebainone (335a) was treated with 1M sodium methoxide at room temperature, it yielded the bridged ketone (336a) as a crystalline solid, m.p. 112-113°C. This compound (336a) was previously reported[99] as an oil. The molecular formula was determined by accurate mass measurement, microanalysis supported the elemental composition, $C_{26}H_{26}N_2O_5$. 0.5 H_2O. The same procedure was then used for the cycloadducts (334b) and (334c). The adduct (334b), from (R)-(-)-mandelohydroxamic acid and thebaine, was selected first, because it showed the unusual chemical shifts in its ^1H n.m.r. spectrum. Thus, the adduct (334b) was heated in methanolic hydrochloric acid (1:1) to yield the crude thebainone (335b), which was then treated with sodium methoxide at room temperature. The rearranged, bridged ketone (336b) was obtained, which crystallized as a hemihydrate, m.p. 125-126°C (Scheme 74). The molecular formula was determined by accurate mass measurement and microanalysis supported the composition, $C_{26}H_{26}N_2O_6$. 0.5 H_2O. The i.r. spectrum showed the presence of a hydroxyl group, ν_{max} 3580 cm^{-1}, and a carbonyl group, ν_{max} 1658 cm^{-1}. The ^1H n.m.r. spectrum ($CDCl_3$) showed a signal, δ4.25 (d, J 8Hz), typical for 9-H and doublets (J 8Hz), δ5.45 and 6.95, for 7- and 8-H, respectively. The 5-H signal (δ 5.02,S) had a chemical shift usual for 5,14-epoxyimino derivatives. This degradation unambiguously showed that the nitroso group in the adduct (334b) was attached in the usual sense, i.e. with C(14)-N and C(6)-O rather than C(14)-O and C(6)-N bonds. By way of confirmation the other diastereoisomer (334c), from (S)-(+)-mandelohydroxamic

acid (328c) and thebaine (26), was also subjected to the same sequence. However, when the cycloadduct (334c) was heated as before with a mixture of hydrochloric acid and methanol, 14-β-hydroxylaminocodeinone (335d) was obtained instead of the usual expected product (335c). This product reacted in 1M sodium methoxide to yield the known rearranged product (336d). This experiment suggested that less concentrated acid should be employed and perhaps would not remove the mandelo group. Therefore, the cycloadduct (334c) was heated with 1M hydrochloric acid in methanol. The codenione (335c) was obtained as the major product, along with (335d). This mixture of codeinones was treated with 1M sodium methoxide, but the codenione (336d) was again obtained. In a last attempt, the mixture of codeinones (335c) and (335d) was treated with 0.1M sodium methoxide at room temperature for 5 min. The major product (336c) (60%) was obtained along with (336d). The former was obtained pure by chromatographic separation. The molecular formula was determined by accurate mass measurement and microanalysis confirmed the composition as a hemihydrate, $C_{26}H_{26}N_2O_6$ 0.5 H_2O. The i.r. spectrum showed hydroxyl and carbonyl bands, ν_{max} 3540 and 1690 cm^{-1}. The ^1H n.m.r. spectrum resembled that of its diastereoisomer (336b), showing signals at σ4.27(d, J,8Hz, 9-H), 5.98 (d, J,8Hz, 7-H), 7.00 (d, J,8Hz, 8-H), and 5.02(s, 5-H).

In a model of the cycloadduct (331b) the 6-methoxyl group (δ2.80) can be brought into the shielding zone of the mandelic phenyl group. However, it is not clear why the large (ca. 0.8 p.p.m.)

shielding is shown by this particular stereoisomer. The same difficulty arises in explaining the differences in chemical shift for the olefinic proton signals in the diastereoisomer (331b). The different behaviour of the cycloadducts (331b) and (331c) in the degradation again showed an unexpected effect of the mandelic chiral centre. The codeinone derived from the adduct (331c) was more labile to acid hydrolysis and therefore less vigorous conditions were needed to give the desired product.

As the present study is mainly concerned with the diastereoselectivity of cycloadditions of chiral C-nitrosocarbonyl compounds with dienes, experiments were carried out in an attempt to detect differences in the rates of reaction of thebaine (26) with the (R)- and (S)-nitroso compounds (329b) and (329c). When the reaction was carried out in the usual way (Scheme 71), with one or more equivalents of the racemic hydroxamic and (328a), the cycloadducts (331b) and (331c) were obtained in a ca. 1:1 ratio. Next, 2 molecular equivalents of the racemic hydroxamic acid (328a) were added to 2 equivalents of sodium periodate in aqueous sodium acetate stirred with 1 equivalent of thebaine (26) in ethyl acetate. However, the diastereoisomeric cycloadducts (331b) and (331c) were again formed (^{1}H n.m.r. spectrum of the crude product) in ca. 1:1 ratio. Presumably, both enantiomeric nitroso compounds reacted with thebaine as soon as they were formed. That is, there was effectively no competition for the deficient quantity of thebaine. In another experiment, sodium periodate (2equivalent) was stirred at 0°C in the 2-phase mixture of aqueous sodium acetate

and ethyl acetate. The racemic hydroxamic acid (328a) (2 equivalents) and thebaine (1 equivalent) were dissolved in ethyl acetate-methanol (1:1). This mixture was then added slowly to the stirred sodium periodate solution. The idea behind the experiment was that there should not be an excess of thebaine in the solution at any time. It was hoped that the chiral dienophiles from the (R)-(-) (328b) and (S)-(+) (328c) hydroxamic acid would be in excess of thebaine throughout the experiment and might compete with each other to give unequal amount of the diastereoisomeric adducts (331b) and (331c). Surprisingly, this time again the crude product showed (^{1}H n.m.r.) a 1:1 ratio of the cycloadducts (331b) and (331c). This experiment was repeated but sodium periodate was replaced with tetraethylammonium periodate so that the oxidation could be carried out in a homogenous solution. Again, 1:1 ratio of the cycloadducts (331b) and (331c) was obtained. Most asymmetric reactions have been studied at low temperature; it is thought that low temperature generally enhance asymmetric induction. We therefore decided to study the reaction of thebaine and the mandelic nitroso compounds at a lower temperature. Initially, a single solvent, ethyl acetate was used. This solvent proved unsuitable because even at -20°C, both the hydroxamic acid (328a) and tetraethylammonium periodate began to crystallise out. The main problem was the solubility of the racemic hydroxamic acid. It was partially soluble in ethyl acetate but was completely soluble in methanol. As we were hoping for a beneficial effect of hydrogen bonding on the asymmetric induction, methanol was undesirable. However, no alternate was left for studies on the

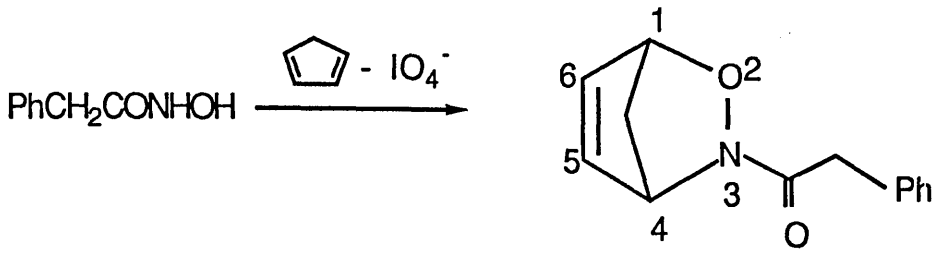
reaction at low temperatures. Therefore, a minimum amount of methanol was used in combination with dichloromethane. Tetraethylammonium periodate was dissolved in dichloromethane and the solution was cooled to -78°C. To this was added the racemic hydroxamic acid (328a) (2 equivalent) and thebaine (26) (1 equivalent) in dichloromethane and methanol (1:1). The temperature was maintained at -78°C for 30 min, then raised to room temperature. The reaction mixture (^{1}H n.m.r.) once more showed a 1:1 mixture of the diastereoisomers (331b) and (331c). It appears therefore that, either cycloaddition of the enantiomeric nitroso compounds (329b) and (329c) occurs at the same rate, or, more likely, the rates of cycloaddition exceeded those of oxidation of the hydroxamic acids. In the later case, each enantiomeric nitroso compound will react completely with thebaine soon after it is formed, i.e. the thebaine will effectively be in excess until it all has reacted. The foregoing studies with thebaine provided experience with the formation and trapping of the mandelo nitroso dienophiles, and also showed that cyclo-addition was still be rapid at low temperature. Attention was then turned to achiral dienes, that is to asymmetric synthesis rather than, attempted, kinetic resolution.

SECTION II

Cycloadducts from (±)-mandelohydroxamic acid and cyclopentadiene and Cyclohexa-1,3-diene

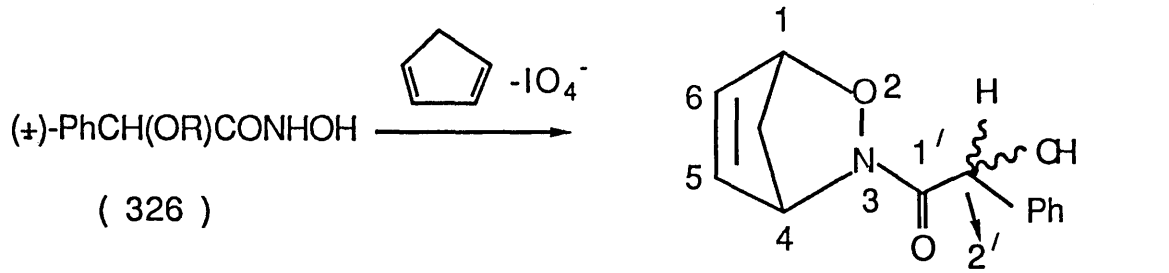
Cyclopentadiene was selected as the first achiral diene. In a model experiment, phenylacetohydroxamic acid (332) was oxidised with aqueous sodium periodate (1 mol equivalent) in the presence of cyclopentadiene (1 equivalent) in ethyl acetate at 0°C (Scheme 75). The racemic cycloadduct (337) of the expected type was obtained as a gum. The molecular formula, $C_{13}H_{13}NO_2$, was determined mass spectrometrically by accurate mass measurement. The i.r. spectrum showed a band for the carbonyl group, ν_{max} 1650 cm^{-1}. The ^1H n.m.r. spectrum ($CDCl_3$) showed typical signals for the 7-methylene protons, δ1.63 - 1.93 (m). The olefinic protons, 5- and 6-H gave a broad singlet, δ6.23 - 6.42 and bridgehead protons, 1- and 4-H, a broad singlet, δ5.25. Signals for the phenylacetyl group appeared as expected, δ5.11(s,ph,C$\underline{H}_2$) and 7.30(s,ph).

Attention was then turned to asymmetric synthesis, and the study of diastereoselectivity of chiral α-hydroxy C-nitroso-carbonyl compounds. To this end, racemic mandelohydroxamic acid (328a) was selected as the precursor for the transient, chiral α-hydroxy compounds (329a) (Scheme 76). In these early experiments there was no advantage in employing single enantiomers of the chiral dienophiles. Thus (±)-mandelohydroxamic acid (328a) was oxidised in the usual way with aqueous sodium periodate (1 mol equivalent) in the presence



(332) (337)

Scheme 75



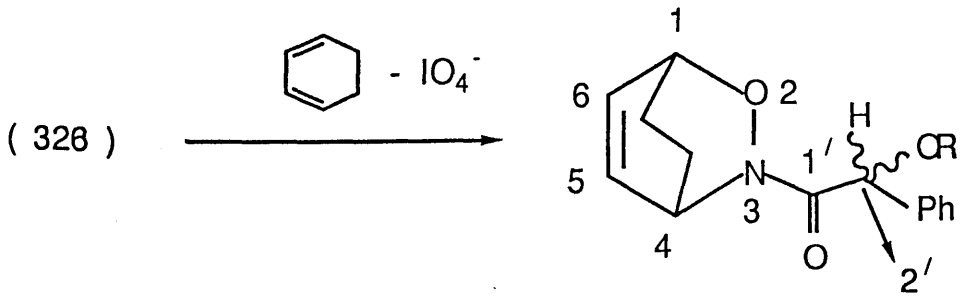
(326)

a; R = H
b; R = Ac
c; R = Bz

(338) Major diastereoisomeric racemate

(339) Minor diastereoismeric racemate

Scheme 76



(326)

a; R = H
b; R = Ac

(340) Major diastereoisomeric racemate

(341) Minor diastereoisomeric racemate

Scheme 77

of cyclopentadiene (1 equivalent) in ethyl acetate at 0°C. A mixture of diastereoisomeric racemates, consisting of a major component (338a) and a minor component (339a) was obtained as a gum (68%). No separation of the isomers (338a) and (339a) was achieved on t.l.c. The molecular formula of this mixture of cycloadducts was determined by accurate mass measurement. The i.r. spectrum ($CHCl_3$) showed the bands expected for the hydroxyl and carbonyl groups, ν_{max} 3450 and 1650 cm^{-1}, respectively. The ^1H spectrum ($COCl_3$) of the mixture showed a typical signal for the 7-methylene group, δ1.60 - 193 (m). Signals for the olefinic protons 5- and 6-H appeared with the usual chemical shift, δ5.60 and 6.35 (2 x t, J, 6Hz). It was hoped that the singlets expected for 2′-H in each diastereoisomer might be separate, so that integration could give the ratio of the products. However, the complexity and integration of the signals centred at δ5.25, strongly suggested that they arose from bridgehead protons, 1- and 4-H and 2′-H of both the diastereoisomers (338a) and (339a). In the model cycloadduct (337) 1- and 4-H proton gave signals at δ5.25 and the side chain methine of (±)-mandelohydroxamic acid (328a) also gave a signal with a similar chemical shift, δ5.15. These chemical shifts strongly suggested that the 1- and 4-H protons and side chain methine were overlapping at δ5.25 in isomers (338a) and (339a). Owing to this overlap of the signals, δ5.25 in the spectrum of the mixture of cycloadducts, their ratio could not be calculated, since no other pair of signals were separate and available for integration. As the products (338a) and (339a) were alcohols, it was decided to make derivatives in the hope that their n.m.r. spectrum might be distinguishable in

mixtures or derivatisation might lead to the chromatographic separation of the products. Thus, the mixture of the diastereoisomers (338a) and (339a) was treated with acetic anhydride in pyridine. The O-acetyl derivatives (338b) and (339b) were obtained, as like alcohols, a gum (84%). Unfortunately no separation of these O-acetyl derivatives was achieved on t.l.c. The molecular formula of the mixture of the products was determined by accurate mass measurement, $C_{15}H_{15}NO_4$. The i.r. spectrum showed bands for 2 carbonyl groups ν_{max} 1675 and 1740 cm^{-1}, and there was no hydroxyl band. Gratefyingly, the ^1H n.m.r. spectrum of the mixture of O-acetyl derivatives (338b) and (339b) showed signals for some of the protons in the two diastereoisomeric products (Table II).

Table II: ^1H n.m.r. spectra, δ (200MHz; $CDCl_3$), of cycloadduct derivatives from cyclopentadiene and racemic mandelohydroxamic acid

cycloadducts	Protons		
	1- or 4-H	5- or 6-H	2′- H
(338a) and (339a)	ca. 5.25 (br s)	5.60 and 6.35 (2 x t J Hz 6Hz)	ca. 5.25 (br s)
(337)	5.25 (br s)	6.23-6.42 (br s)	

(338b) (major isomer)	5.15 and 5.35 (2 x br s)	5.75 and 6.25 (2 x br s)	6.10 (s)
(339b) (minor isomer)	5.30 (br s)	6.45 (br s)	5.95 (s)
(328a)			5.15 (s)
(338c) and (339c)	5.20	ca. 6.20-6.95 (2 x br s)	ca. 6.20-6.95 (2 x br s)

The ratio, 5.1:1 for the two O-acetyl derivatives (338b) and (339b) was measured, after averaging, from the signals integrals for 2′-H, δ6.10 and 5.95, and for 5- and 6-H, δ5.75 and 6.25 and 6.45, respectively. The relative stereochemistry of the cycloadducts (338b) and (339b), however remains unsettled. In an attempt to establish the stereochemistry, the mixture of cycloadducts was benzoylated with benzoyl chloride in pyridine to give the O-benzoyl derivatives (338c) and (339c). It was hoped that these derivatives might be separable and crystalline. The stereochemistry might then be determined by X-ray analysis. But again the O-benzoyl derivatives were obtained as gum, inseparable by t.l.c. The molecular formula of the diastereoisomeric mixture was determined by accurate mass

measurement, $C_{20}H_{17}NO_4$. The i.r. spectrum showed bands for the carbonyl groups ν_{max} 1675 and 1790 cm^{-1}. The ^1H n.m.r spectrum (Table II) showed overlapping signals, especially in the olefinic region. Signals for the bridgehead protons 1- and 4-H had a chemical shift, δ5.20, similar for the cycloadduct (337) and (338a) and (339a). Unfortunately, the signals for 2'-H overlapped with those for 5- and 6-H, δ 6.20 - 6.95, consequently the ratio of the diastereoisomers (338c) and (339c) could not be measured, as to confirm the ratio obtained for the O-acetyl derivatives. In an attempt to establish the stereochemistry of alcohols (338a) and (339a) we therefore decided to prepare their epoxides, in the hope they might be crystalline and suitable for X-ray analysis. Thus the mixture of cycloadducts (338a) and (339a) was treated at room temperature with m-chloroperbenzoic acid (2 mol equivalent). Examination of the product by ^1H n.m.r. spectroscopy showed the presence only of the starting material, although generally bicyclo [2.2.1] hept-2-ene derivatives are epoxidised quite easily. This experiment suggested that the cycloadduct might be less reactive towards m-chloroperbenzoic acid due to presence of the electronegative oxygen and nitrogen atoms. Therefore the mixture of cycloadducts was heated in acetic acid with sodium perborate[100]. This experiment yielded a product and its ^1H n.m.r. spectrum could not be interpreted fully due to its complexity, and no signals for the expected products nor for the starting material were identified. Further attempts to form crystalline derivatives of the cycloadducts (338a) and (339a) were not made. Attention was instead turned to another achiral diene, cyclohexa-1,3-diene, in the hope that products might be

separated and their stereochemistry determined.

(±)-Mandelohydroxamic acid (328a) was oxidised as usual with aqueous sodium periodate (1 mol equivalent) in the presence of cyclohexa-1,3-diene (1 equivalent) in ethyl acetate at 0°C (Scheme 77). A mixture of diastereoisomeric racemates, the major isomer (340a) and the minor isomer (341a) was obtained (55%) as a gum. This mixture of adducts could not be separated on t.l.c. plates. The molecular formula, $C_{14}H_{15}NO_3$, was determined by accurate mass measurement. The i.r. spectrum showed bands for hydroxyl groups, ν_{max} 3490 and 1635 cm^{-1}, respectively. The ^1H n.m.r. spectrum ($CDCl_3$) showed signals for the 7- and 8-methylene protons, δ1.30 - 1.50 and 2.20 (2xs). The hydroxyl proton gave a broad singlet, δ4.55, and was exchanged with D_2O. A complex multiplet was centred at δ5.10 - 5.30 (Table III) again suggested that one of the signals for the bridgehead protons 1- or 4-H was overlapping those for 2′-H in the two diastereoisomeric racemates, because the other signal for 1- or 4-H appeared separately, δ4.55 (br s). The olefinic protons, 5 or 6-H gave triplets, δ5.90 - 6.10 and 6.30 - 6.50. The overlapping of signals, especially those for 2′-H meant that ratio of the two diastereoisomeric products could not be measured.

Following the success with the O-acetyl derivatives of the cyclopentadiene adducts, it was therefore decided to apply the same method to the diastereoisomers from cyclohexa1,3-diene. Thus, the mixture of cycloadducts (340a) and (341a) was treated with acetic anhydride in pyridine to give the O-acetyl derivatives

(340b) and (341b) as a gum. This mixture showed two spots on silica t.l.c. plates developed in light petroleum-ether (1:1) after multiple elution. The molecular formula, $C_{16}H_{17}NO_4$ was confirmed by accurate mass measurment. The i.r. spectrum gave bands for the carbonyl groups, ν_{max} 1653 and 1738 cm^{-1}.

The ^1H n.m.r. spectrum (200 MHz; $CDCl_3$) showed sets of signals for the 2 diastereisomeric racemates (340b) and (341b) (Table III)

Table III: ^1H n.m.r. spectra, δ(200MHz; $CDCl_3$) of cycloadducts from cyclohexa-1,3-diene and (±)-mandelic acid.

cycloadducts or derivatives	Protons		
	1- or 4-H	5- or 6-H	2′-H
(340a) and (341a)	4.55 and ca. 5.10 -5.30 (br s)	5.90-6.10 6.30-6.50 (br m)	ca. 5.10-5.30 (br m)
(340b) (major isomer)	4.55 and 5.10 (2 x br s)	ca. 6.00-6.10 (2 x m) 6.30-6.40 (br m)	ca. 6.00-6.10 (2 x m)

(341b) (minor isomer)	4.55 and 5.20 (2 x br s)	6.60 (2 x m)	6.15

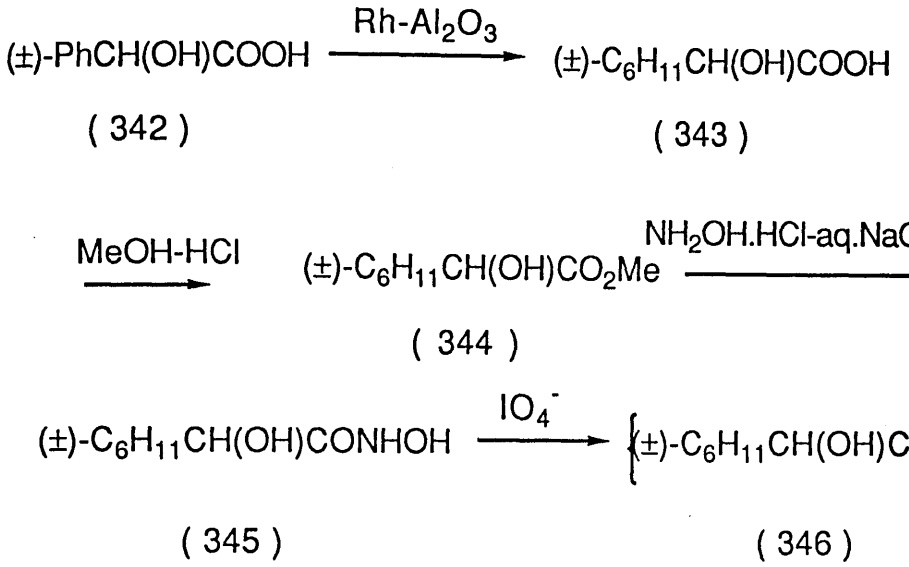
In addition to tabulated values, the 7- and 8-methylene groups in the minor diastereoisomer (341b) gave a multiplet, δ1.15 - 1.90 and a typical singlet, δ2.10, was observed for the acetyl group. In the major isomer (340b) the methylene groups gave separate signals, δ1.45 and 2.15, the later overlapping the acetyl signal. The ratio, 3.5:1, for the isomers (340b) and (341b) was measured from the integrals for 5- and 6-H and from those for 2′-H, making allowances by subtraction for overlapping signals. Determination of the stereochemistry of the cycloadducts (340b) and (341b) will be discussed later.

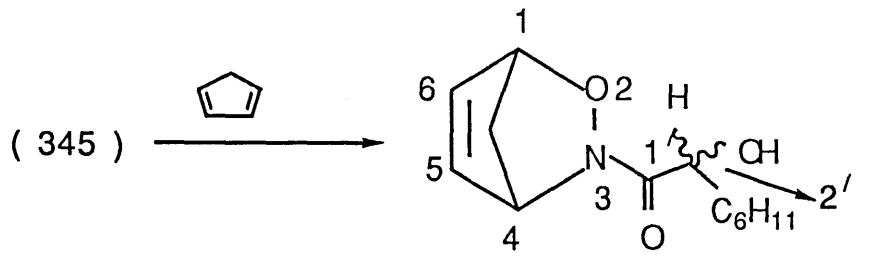
Cycloadducts from (±)-hexahydromandelic acid and cyclopentadiene and cyclohexa-1,3-diene

Choy et al. in their study, described before, with chiral enone as dienophiles, used (S)-hexahydromandelic acid rather than mandelic acid itself. They achieved high diastereoselectivity with this cyclohexyl derivative (191a) and also with tert-butyl derivatives (191d). We therefore decided to hydrogenate the (±)-mandelic acid to its hexahydro derivative[101] using 5% rhodium-on-alumina in absolute methanol in an autoclave at room temperature at a pressure of hydrogen of 1000 p.s.i. (Scheme 78).

In this way (±)-hexahydromandelic acid (343), m.p. 135-136°C (lit m.p. 135 - 136°C) was obtained in 88% yield. The racemic hexahydromandelic acid was then converted into the methyl ester (344) heating under reflux in dry methanolic hydrogenchloride. The methyl ester (344) was treated with hydroxylamine hydrochloride in the presence of aqueous sodium hydroxide to give the (±)-hexahydromandelohyboxamic acid (345) (72%), m.p. 181 - 182°C. The molecular formula, $C_8H_{15}NO_3$, was confirmed mass spectrometerically and microanalysis. The i.r. spectrum (KBr) showed bands for hydroxyl group ν_{max} 3458 cm^{-1} and carbonyl group ν_{max} 1600 cm^{-1}. The ^1H n.m.r spectrum (CD_3OD - $CDCl_3$) showed signals similar to those of its methyl ester except that the methoxyl signal was replaced by a broad singlet, δ4.90 for NH and OH, and were exchanged with D_2O.

(±)-Hexahydromandelohydroxamic acid (345) was oxidised with aqueous sodium periodate (1 mol equivalent) in the presence of cyclopentadiene (1 equivalent) in ethyl acetate at 0°C to give a mixture of a major diastereoisomer (347) and a minor diastereoisomer (348) as gum (80%). This mixture showed two spots on t.l.c. plates developed with light petroleum-ether (1:1). The fast running component (348) was the minor and the slowing running component (347) was the major. The molecular formula $C_{13}H_{19}NO_3$, was determined separately by accurate mass measurement. The i.r. spectrum of the mixture showed bands for hydroxyl and carbonyl groups ν_{max} 3495 and 1640 cm^{-1}, respectively. The ^1H n.m.r. spectrum ($CDCl_3$) gave a broad multiplet for the cyclohexyl protons overlapping for those 7-

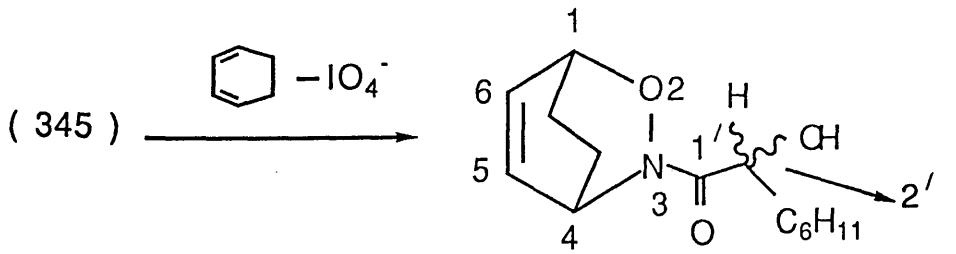




(347) Major diastereoisomeric racemate

(348) Minor diastereoisomeric racemate

Scheme 78



(349) Major diastereoisomeric racemate

(350) Minor diastereoisomeric racemate

Scheme 79

methylene groups, δ0.5 - 2.10. The side chain methine protons for (347) and (348) gave rise to 2 doublets 4.10 and 3.90, respectively. Signals for bridgehead protons 1- and 4-H, and for 5- and 6-H overlapped at δ5.40 (br s) and 6.50(m) respectively. It was possible to determine the ratio, 3.5:1, of (347) and (348) from the integrals of the side chain methine. The hydroxyl proton gave a broad signal, δ3.35(s) and was exchanged with D_2O. The formation of (347) and (348) in an inferior ratio, 3.5:5, as compared with that of the mandelic derivatives (338) and (339) 5.1:1, was unexpected; increased steric bulkiness of a group at the chiral centre in dienophiles is usually associated with an increase in the ratio of the diastereoisomeric products (Chapter I Section II). It is difficult to rationalise this anomaly at this stage (see later in Table VIII for a summary of diastereoisomer ratio).

In the next experiment, (±)-hexahydromandelohydroxamic acid (345) was oxidised in the presence of cyclohexa-1,3-diene at 0°C in the usual way to give a mixture of major (349) and minor (350) diastereoisomeric racemates as a gum (55%) (Scheme 79). This mixture of cycloadducts (349) and (350) could not be separated on t.l.c. plates. The molecular formula $C_{14}H_{21}NO_3$, was determined by accurate mass measurement. The i.r. spectrum showed band, ν_{max} 3490 and 1635 cm^{-1}, respectively for hydroxyl and carbonyl groups. The ^1H n.m.r. spectrum ($CDCl_3$) gave a broad multiplet, δ1.00-2.30 for the cyclohexyl and 7- and 8-methylene protons. The hydroxyl proton gave a broad signal, δ3.55 (s) and was exchanged with D_2O. Signals from (349) and (350) for 5- and 6-H,

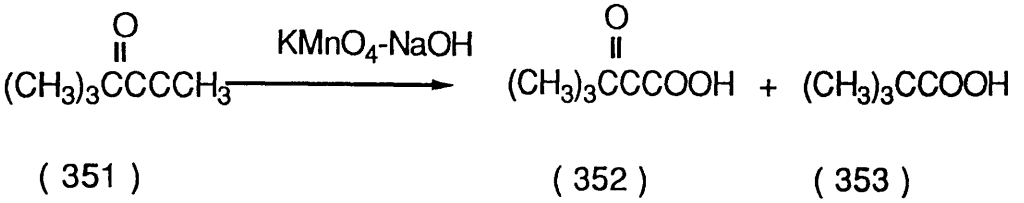
1-H and 4-H overlapped at δ6.50 - 6.80 and 4.80 and 5.25, respectively. However, the 2 side chain methine protons gave separate doublets, δ 4.05 and 4.20. Therefore, the ratio, 2.5:1 for the diastereoisomeric racemates (349) and (350) was measured from the integrals for these doublets, δ4.20 and 4.05. Again, the ratio, 2.5:1, was inferior to that 3.5:1 for the corresponding mandelic derivative (340a) and (341a). It appears once more, as if the cyclohexyl group has a smaller steric effect than the phenyl group.

Cycloadducts from (±)-2-hydroxy-3,3-dimethyl-butanoic acid and cyclopentadiene and cyclohexa-1,3-diene

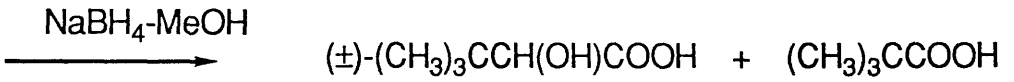
In an attempt to increase the steric bulkiness, it was decided to introduce the tert-butyl group at the chiral centre (Scheme 80). Following a literature method[102], pinacolone (351) was suspended in water and oxidised with alkaline potassium permanganate at room temperature to give a mixture of the desired keto acid (352) and trimethylacetic acid (353), in a ratio of 3:1 (^{1}H n.m.r.). The keto acid (352) was also reported a major compound and mixture could not be separated. This time again the mixture of acids (352) and (353) failed to separate by any conventional methods. Therefore, the mixture of the acids (352) and (353) was treated with sodium borohydride in methanol while it was reduced with Raney nickel by Tanabe et al.[103]. The resulting reduction product gave ^{1}H n.m.r. signals for the hydroxy acid (354), δ(s,4.00(s,CH)) along with those for terimethylacetic

acid (353). Crystallisation from light petroleum-ethyl acetate yielded the pure (±)-2-hydroxy-3,3-dimethylbutanoic acid (354), m.p. 86 - 87 °C (lit m.p. 86 - 87°C). The mother liquors afforded trimethylacetic acid (353). The hydroxy acid (354) was not recovered as its methylester (355) after refluxing in dry methanolic hydrogen chloride, perhaps due to evaporation of the voltaile ester alongwith methanol under reduced pressure. Therefore, diazomethane (from 'nitrosan', ethyleneglycol, and sodium hydroxide, in ether) was passed into a solution of the acid (354) in ether; evaporation of the ether at room temperature yielded the pure ester (355) identified by ^1H n.m.r. spectroscopy. It was pure enough for further use. The methyl ester (355) was treated with aqueous hydroxylamine hydrochloride to afford the desired product, (±)-2-hydroxy-3,3-dimethylbutanohydroxamic acid (356), m.p. 134 - 135°C (from ethyl acetate and petroleum ether). The molecular formula, $C_6H_{13}NO_3$, was confirmed mass spectrometerically and microanalysis. The i.r. spectrum showed bands for hydroxyl and carbonyl groups, ν_{max} 3235 and 1630 cm^{-1}. The ^1H n.m.r. spectrum (CD_3OD - $CDCl_3$) showed the replacement of ester methoxyl signal with that for hydroxyl proton, δ4.75. The tert-butyl signal showed similar chemical shift, δ0.95, as was for the methylester (355).

The hydroxamic acid (356) was oxidised in the presence of cyclopentadiene, in the usual way at 0°C. The mixture of major (359) and minor (360) diastereoisomeric racemates was obtained as gum (75%) (Scheme 81). This mixture of cycloadducts showed two spots on t.l.c. plates. The molecular formula, $C_{11}H_{17}NO_3$ for

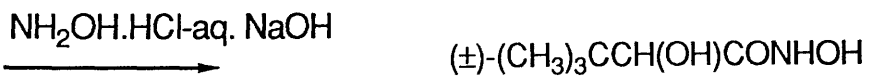


(351) (352) (353)

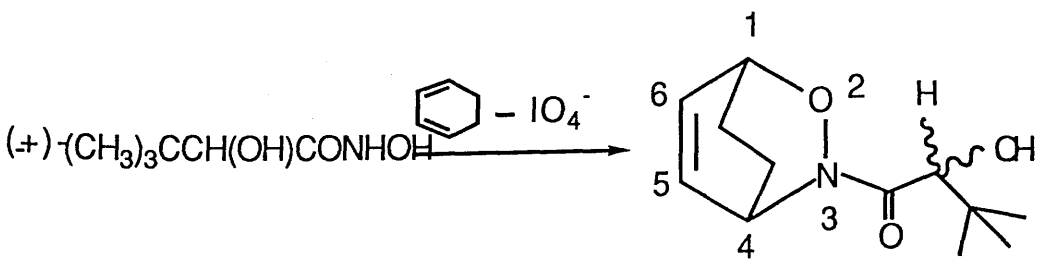


(354) (353)

(355)



(356)



(356)

(357) Major diastereoisomeric racemate

(358) Minor diastereoisomeric racemate

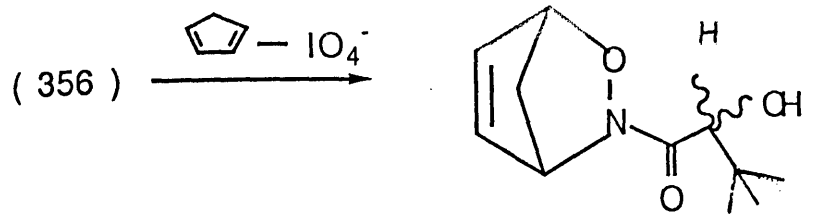
Scheme 80

the adducts (359) and (360) were determined separately from accurate mass measurements, after chromatographic separation. The i.r. spectra showed the usual bands, ν_{max} 3500 and 1625 cm^{-1} for hydroxyl and carbonyl groups, respectively. The ^1H n.m.r. spectrum of the mixture of adducts (359) and (360) showed sets of signals for 2 diastereoisomeric products. It was found, after t.l.c. separation that the component with the lower R_F value gave signals for the major component (359). Significant ^1H n.m.r. signals for (359) and (360) are given in Table IV.

Table IV: ^1H n.m.r. spectra, $\delta(CDCl_3)$ for the tert-butyl derivative and cyclopentadiene

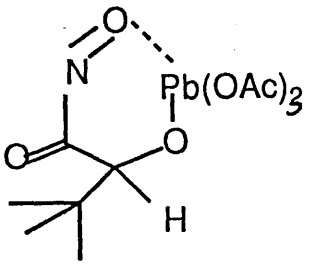
Cycloadducts	Protons			
(359) (major isomer)	Bu^t	2'-H	1- and 4-H	5- and 6-H
	0.90 (s)	4.05 (s)	5.35 (br s)	6.25-6.40 (m)
(360) (minor isomer)	0.95 (s)	3.90 (br s)	5.35 (br s)	6.20-6.40 (m)

The ^1H n.m.r. spectra of the separated adducts (359) and (360) agreed to that of the mixture. The ratio, 3.3:1, for (359) and (360)



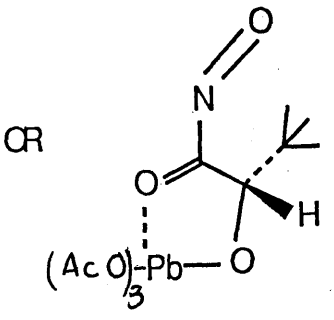
(359) Major diastereoisomeric racemate

(360) Minor diastereoisomeric racemate



(361)

OR



(361)

Scheme 81

was measured from the integrals for the 2′-H signals. Surprisingly again, this ratio, 3.3:1 was less than that, 5.1:1, for the mandelic cycloadducts (338a) and (339a).

Next the tert-butyl derivative (356) was oxidised at 0°C with aqueous sodium periodate (1 mol equivalent) in the presence of cyclohexa-1,3-diene (1 mol equivalent) in ethyl acetate to give a mixture of major (357) and minor (358) diastereoisomeric racemates as gum (58%) (Scheme 80). No chromographic separation of the (357) and (358) was achieved on t.l.c. The molecular formula, $C_{12}H_{19}NO_3$, was determined by accurate mass measurement. The i.r. spectrum of the mixture showed the expected bands, ν_{max} 3500 and 1622 cm^{-1}, for hydroxyl and carbonyl groups, respectively. The ^1H n.m.r. spectrum ($CDCl_3$) of the mixture showed a set of signals for the 2 diastereoisomeric products (Table V).

Table V: ^1H N.m.r. spectra, $\delta(CDCl_3)$, of tert-butyl cyclohexa-1,3-diene adducts (357) and (358).

Cycloadducts	Protons			
(354)	Bu^t	2′-H	1- and 4-H	5- and 6-H
(major isomer)	0.87 (s)	4.15 (s)	4.75 and 5.30 (br s)	6.40-6.60 (2 x m)
(355)	0.92 (s)	4.05	4.75 and	6.40-6.60

The ratio 4.6:1, for the diastereoisomeric racemates (357) and (358) in the total reaction product was measured from the integrals for 2′-H. This time the ratio, 4.6:1 for adducts (357) and (358) was higher than those for the corresponding mandelic (3.5:1) and hexahydromandelic (2.5:1) derivatives.

All the cycloaddition reactions described above were carried out as usual without any Lewis acid. It was reasoned that if lead tetraacetate were employed as an alternative to sodium periodate, or its reaction product lead diacetate might enhance the asymmetric induction by complexation between hydroxyl and the nitroso group or lead and carbonyl group in the transient species as shown (361). Therefore, tert-butyl hydroxamic acid (356) was oxidised at 0°C with lead tetraacetate (1 mol equivalent) in ethyl acetate in the presence of cyclohexa-1,3-diene to give the mixture of cycloadducts (357) and (358). However, the ^{1}H n.m.r. spectrum of the mixture revealed that the cycloadducts (357) and (358) were present in a ratio of 1.4:1, as compared with ratio, 4.6:1, when periodate was employed as an oxidant. This low ratio, i.e. 1.4:1, meant that perhaps lead tetraacetate eliminated the hydrogen bonding effect and no complexation occurred in return.

The highest ratios, up to this time, for the diastereoisomeric cycloadducts were observed with mandelic derivatives of cyclopentadiene (5.1:1) and the tert-butyl derivatives of cyclohexa-1,3-diene (4.6:1). To test the idea that hydrogen bonding might be important, it was decided to O-methylate the free hydroxyl group of one nitroso precursor. (±)-Mandelic acid was selected for this purpose because of its commercial availability.

Cycloadducts from (±)-O-methylmandelic acid derivatives and cyclopentadiene and cyclohexa-1,3-diene

(±)-Mandelic acid was methylated[104] in sodium hydroxide with dimethyl sulphate to yield the O-methyl derivative (362), m.p. 70-71 (lit. m.p. 69 - 70°C). The O-methyl derivative (362) was then heated under reflux in dry methanol-hydrogen chloride to yield methyl (±)-O-methylmandelate (363) (92%) as an oil. The ester (363) was converted into (±)-O-methylmandelohydroxamic acid (364), m.p. 139-140°C, by usual method. The molecular formula, $C_9H_{11}NO_3$, was determined by accurate mass measurement and microanalysis. The ^1H n.m.r. spectrum (CD_3OD) was similar to that of the methyl ester (363). (Scheme 82).

O-Methyl(±)-mandelohydroxamic acid (364) was oxidised in aqueous sodium periodate (1 mol equivalent) at 0°C in the presence of cyclopentadiene in ethyl acetate to give a mixture of major (367) and minor (368) diastereoisomeric racemates as gum

(±)-PhCH(OH)COOH $\xrightarrow{Me_2SO_4\text{-aq. NaOH}}$ (±)-PhCH(OMe)COOH

(342) (362)

$\xrightarrow{MeOH\text{-}HCl}$ (±)-PhCH(OMe)CO_2Me $\xrightarrow{NH_2OH.HCl\text{ - aq. NaOH}}$

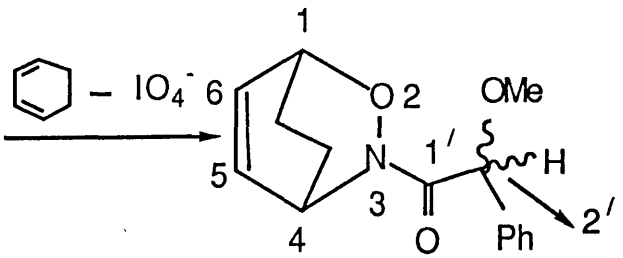
(363)

(±)-PhCH(OMe)C)CONHOH

(364)

(±)-PhCH(OMe)CONHOH

(364)



(365) Major diastereoisomeric racemate

(366) Minor diastereoisomeric racemate

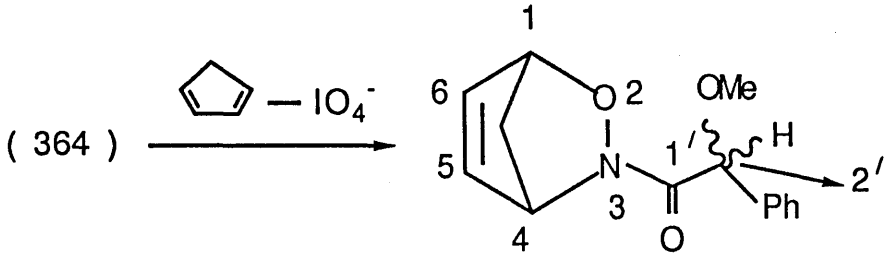
Scheme 82

(65%) (Scheme 82). The mixture failed to separate on t.l.c. plates. The molecular formula, was determined mass spectrometrically by accurate mass measurement. The i.r. spectrum of the mixture showed a bands ν_{max} 1637 cm^{-1}, for the carbonyl group. The ^1H n.m.r. spectrum showed sets of signals for the 2 diastereoisomeric products. The ^1H n.m.r. (200MHz; $CDCl_3$) showed 2 methoxyl signals, δ 3.40 and 3.35 for (365) and (366), respectively. The other significant signals are given in Table VI.

Table VI: ^1H n.m.r. spectra, δ(200MHz; $CDCl_3$) for the O-methyl derivative and cyclopentadiene.

Cycloadducts	Protons			
(367) (major isomer)	OMe	2′-H	1- or 4-H	5- or 6-H
	3.40 (s)	5.00 (s)	5.10-5.30 (m)	6.2-6.50 (m)
(368) (minor isomer)	3.35 (s)	4.90 (s)	5.10-5.30 (m)	6.20-6.50

The ratio, 2.6:1 for (367) and (368) was measured from the integrals for 2′-H and also for the methoxyl signals. The ratio, 2.6:1, for O-methyl derivatives was, as expected lower than the ratio, 5.1:1, found with the corresponding hydroxy derivatives.

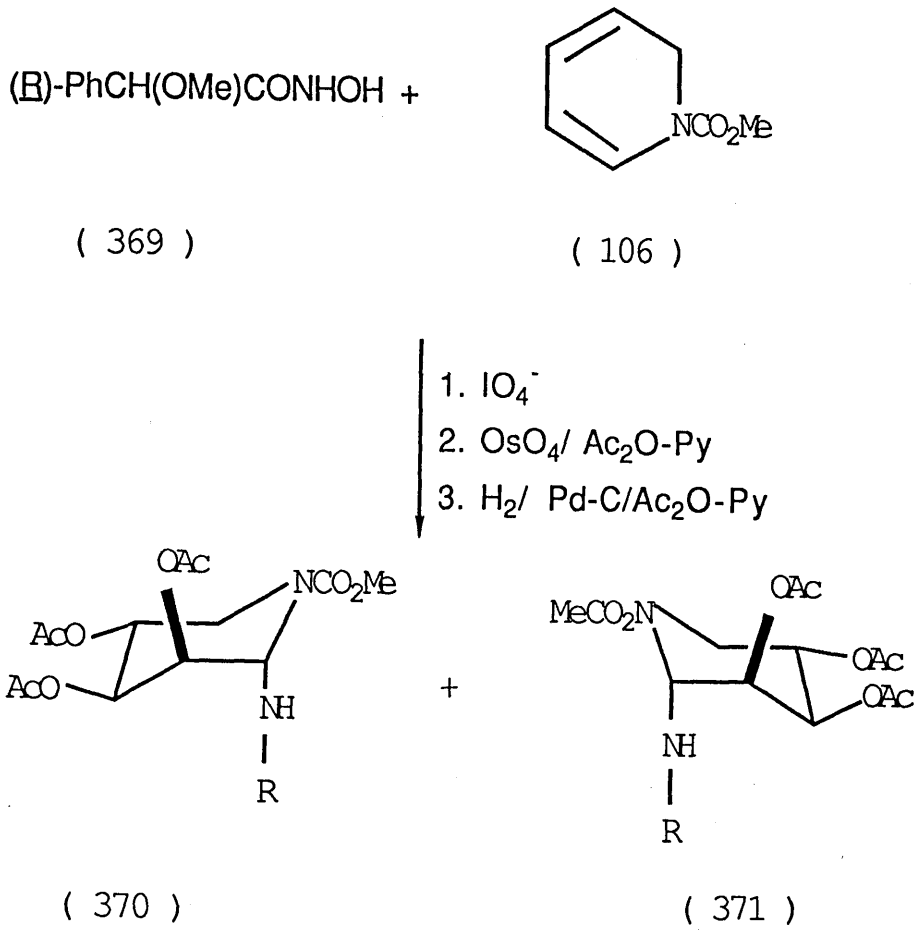


(367) Major diastereoisomeric racemate

(368) Minor diastereoisomeric racemate

Scheme 83

In the next experiment (±)-O-methylmandelohydroxamic acid (364) was oxidised in the presence of cyclohexa-1,3-diene at 0°C in ethyl acetate to give the cycloadducts (365) and (366) (59%) as gum (Scheme 83). The molecular formula, $C_{15}H_{17}NO_3$, was determined by accurate mass measurement. The i.r. spectrum showed a band for the carbonyl group, ν_{max} 1632 cm^{-1}. The ^1H n.m.r. spectrum (200MHz; $CDCl_3$) showed separate signals for the side chain methine protons, δ5.05 for (365) and 5.0 for (366). The signals for methoxyl group were overlapping, δ3.30. The olefinic protons, 5- and 6-H and also the bridgehead protons, 1- and 4-H also overlapped at δ5.90 - 6.70 and 4.60 and 5.20, respectively. The ratio, 2.1:1, was measured from the integrals for the side chain methine, δ5.05 and 5.00, respectively. This ratio, 2.1:1 like for that (367) and (368), supports the idea that hydrogen bonding in the transient α-hydroxy C-nitrosocarbonyl compound (329); plays some role in increasing the diastereoselectivity of cycloaddition. However, since a methoxy group is larger in size than hydroxy group and increase in size might alone decrease the diastereoselectivity. Defoin and co-workers[39b] reported the synthesis of diamino sugar derivatives (369) and (370) from the reaction of 1,2-dihydropyridine (106) and acyl nitroso compounds derived from (R)-O-methylmandelic acid (Scheme 84). The diastereoisomic mixture of optically active amino sugars were obtained in 6:4 ratio. They could not assign the absolute configurations of the products. These workers did not use α-hydroxy acyl nitroso derivatives in their studies.



R = (R)-PhCH(OMe)CO

Scheme 84

Cycloadducts from α-hydroxy C-nitrosocarbonyl compounds and cyclopentadiene and cyclohexa-1,3-diene at -78°C

The foregoing cycloaddition reaction with α-hydroxy C-nitroso compounds showed moderate asymmetric induction. As Choy et al.[96] studied the reaction of the dienophiles (191) with cyclopentadiene. They obtained different ratios for the two endo products (193) and (323) at different temperatures (Scheme 69). Their findings are given in Table VII.

Table VII: Ratios for the endo diastereoisomers from dienophile (191d) and cyclopentadiene at different temperatures

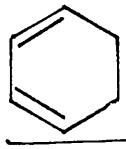
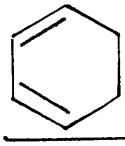
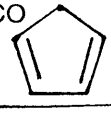
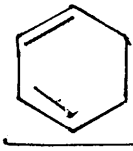
Cycloadducts	Temperature	Ratios
(193:321)	room temp. 24°C	23:1
	0°C-10°C	60:1
	-20°C-24°C	>100:1

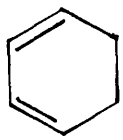
Similar to Choy et al. reactions, many other Diels-Alder reactions reported in literature had been studied, whenever the rate was adequate at low temperature. We decided to study our

cycloaddition reaction likewise at low temperature. The mixture of diastereoisomeric racemates (357) and (358) from cyclohexa-1,3-diene and racemic 2-hydroxy-3,3-dimethylbutanohydroxamic acid was selected as the first preparation (Scheme 80), because separate ^{1}H n.m.r. signals for 2′-H and Bu^t were available to measure the ratio of the products. Further, no formation of derivatives was needed to establish the ratio of (357) and (358). It had been discussed before (thehaine section) that the solubility of the hydroxamic acids and tetraethylammonium periodate was a problem at -78°C. We therefore, decided to use the same combination of solvent as was used for thebaine (26) and racemic mandelohydroxamic acid (328a). Thus, tetraethylammonium periodate (1 mol equivalent) was dissolved in dicholomethane and solution was cooled to -78°C. The (±)-racemic hydroxamic acid (356) (1 equivalent) and cyclohexa-1,3-diene (1 equivalent) were dissolved in methanol-dichloromethane (1:1). This solution was added slowly and the temperature, -78°C, was maintained for 0.5 h. The reaction mixture was then warmed up to room temperature and kept at this temperature for 1 h. A mixture of diastereoisomeric racemates (357) and (358) was obtained in a ratio of ca.11:1, as measured from the ^{1}H n.m.r. integrals (200MHz) of the 2′-H and Bu^t signals. This was a remarkable improvement as compared to our ratio, 4.6:1, that was obtained at 0°C. This successful experiment encouraged us to study the entire series at low temperature. All the cycloadducts discussed previously were made at -78°C, the product ratios along with their yields are given in Table VIII. In all cases an improvement in diastereoselectivity was observed when the reaction temperature

was lowered from 0°C to -78°C. The best results (d.e. > 80) were obtained with the mandelic derivative (328a) and cyclopentadiene and with the tert-butylglycolic derivative (356) and cyclohexa-1,3-diene. Interestingly, there was little improvement in ratios with the O-methylmandelic derivative (364), perhaps because hydrogen bonding was no longer involved.

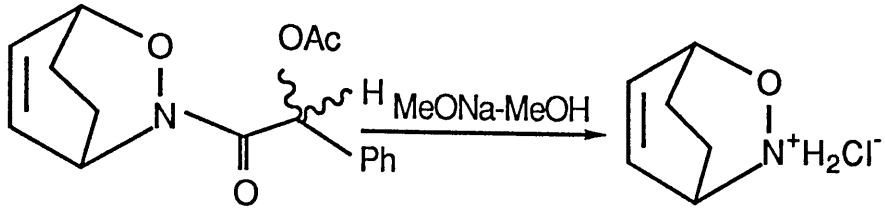
Table VIII: Cycloadducts of chiral α-hydroxy C-nitrosocarbonyl compounds with cyclopentadiene and cyclohexa-1,3-diene.

Dienophiles	Dienes	Cycloadducts	Yield	Ratios 0°C	Ratios -78°C	Yield
1. (±)-ph CH(OH)CO		(338b):(339b)	68%	5.1:1	9:1	71%
		(340b):(341b)	55%	3.5:1	6.1:1	53%
2. (±)-$C_6H_{11}CH(OH)CO$		(347):(348)	80%	3.6:1	6.3:1	83%
		(349):(350)	55%	2.5:1	5:1	56%
3. (±)-$(CH_3)_3CCH(OH)CO$		(359):(360)	75%	3.4:1	9:1	70%
		(357):(358)	58%	4.6:1	11:1	60%

4. (±)-phCH(OMe)CO 	(367):(368)	65%	2.6:1	3.5:1	63%
	(365):(366)	59%	2.1:1	3.4:1	54%

Degradation of major cycloadducts from (±)-mandelic acid derivatives and cyclohexa-1,3-diene to racemic oxazine hydrochloride

After successful study of the diastereoselectivity of the transient chiral α-hydroxy C-nitrosocarbonyl compound, attention was then turned to the absolute stereochemistry of various cycloadducts discussed before. Knowledge of the absolute stereochemistry would further test the idea of intramolecular hydrogen bonding. Also an experiment with an optically active precursor would enable a formal asymmetric synthesis to be accomplished. To establish the absolute stereochemistry, the major separable O-acetyl derivative (340b) was heated under reflux in 0.1 M sodium methoxide (1 mol equivalent) in methanol for 1.5 h (Scheme 85). The reaction mixture was acidified with 0.1M methanolic hydrogen chloride and evaporated to dryness. The brown gum–like residue was dissolved in water and extracted with chloroform. The chloroform extract yielded racemic methyl mandelate (^{1}H n.m.r. spectrum) one of the methanolysis products of the cycloadduct (340b). The aqueous layer, which was expected to contain the salt (56) was evaporated to dryness, however, the ^{1}H n.m.r. spectrum (CD_3OD) of the residue showed no signals for

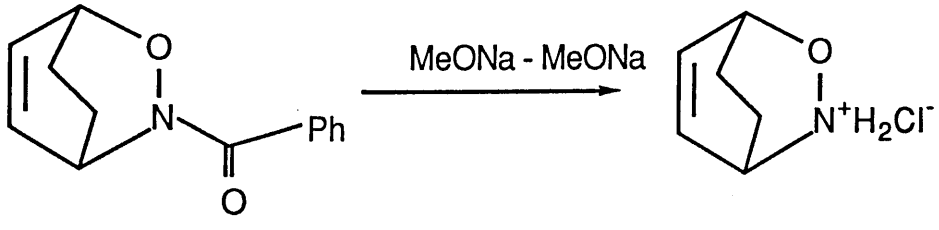


(340b)

(56)

(±)-PhCH(OH)CO_2Me

(327)



(372)

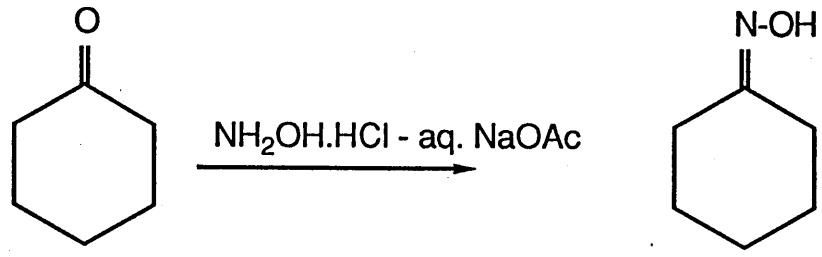
(56)

$PhCO_2Me$

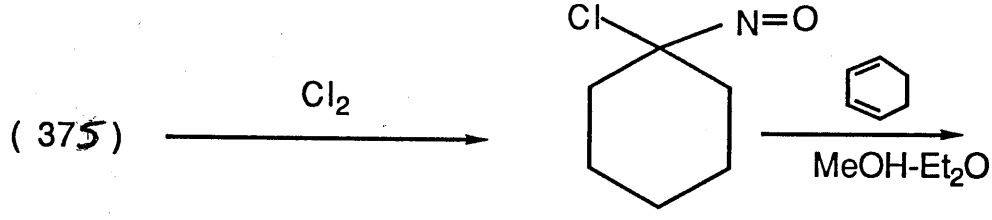
(373)

Scheme 85

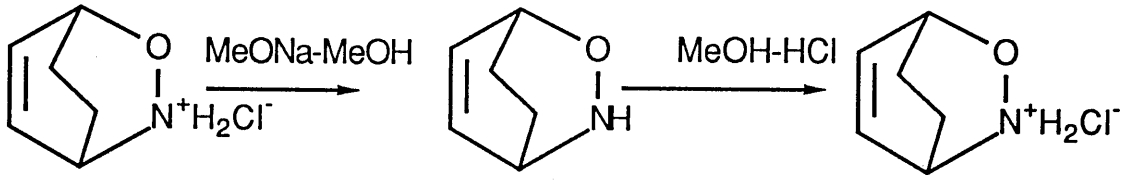
the expected product. The above methanolysis was repeated several times under different conditions but only methyl (±)-mandelate (327) was obtained. Maclean et al.[36a] also reported similar results, when they heated the cycloadduct (372) from benzohydroxamic acid and cyclohexa-1,3-diene with sodium methoxide under reflux in methanol. They reported that only methyl benzoate (373) and no oxazine hydrochloride was obtained. These experiments showed that either cycloadduct (340b) or (372) decomposed prior to methanolysis or the free oxazine formed after methanolysis had decomposed. To establish which of the possibility is true, it was decided to prepare the racemic oxazine hydrochloride (56) by a literature method (Scheme 85). Cyclohexanone oxime (375) was dissolved in dry ether and chlorine gas was passed through. The ether was evaporated off. The residue was distilled under reduced pressure to give 1-chloro-1-nitroso cyclohexane (58) as a blue liquid of unpleasant smell.[105] Cyclohexa-1,3-diene was then treated with 1-chloro-1-nitrosocyclohexane (58) in methanol-ether, first at 0°C for 30 min, then at room temperature to allow the crystalline oxazine hydrochloride (56). The oxazine hydrochloride (56) was heated under reflux with 0.1M sodium methoxide (2 mol equivalent) in methanol for 1.5 h. The reaction mixture was acidified with methanolic hydrogen chloride and evaporated to dryness. The solid residue was dissolved in water and basified with aqueous saturated sodium hydrogen carbonate as to liberate the free oxazine base (376), which was extracted with chloroform. The chloroform extracts yielded free base (376). This was dissolved in methanolic hydrogen chloride and again evaporated to dryness



(374) (375)



(58)



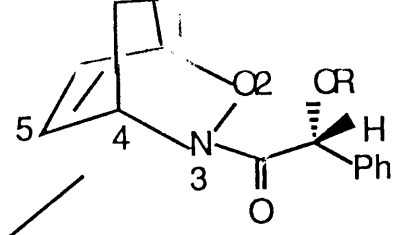
(56) (376) (56)

Scheme 86

to yield the crystalline oxazine hydrochloride (56) (87%) (Scheme 86). The recovery of oxazine hydrochloride (56) after heating with sodium methoxide proved that the free base (376) formed from methanolysis of (340b) or (372) would withstand the conditions of methanolysis. Thus we deduced that the cycloadduct (340b) had decomposed prior to cleavage of the mandeloyl group. This was largely prevented by using a higher concentration of sodium methoxide at a lower temperature. Thus, O-acetyl derivative (340b) from cyclohexa-1,3-diene and racemic mandelohydroxamic acid, was treated with 2M sodium methoxide (2 mol equivalent) at room temperature overnight. The reaction mixture was acidified with methanolic hydrogen chloride and evaporated to dryness as usual. The residue was dissolved in water and extracted with chloroform, the ^1H n.m.r. spectrum ($CDCl_3$) of the chloroform soluble extract showed the presence of methyl (±)-mandelate (327). The aqueous solution was basified with aqueous sodium hydrogen carbonate and extracted with chloroform. The chloroform extract was evaporated and the resulting residue was dissolved in methanolic hydrogen chloride and again evaporated to yield the racemic oxazine hydrochloride (56) (30%). This low yield is thought to be associated with decomposition of the cycloadduct (340b) prior to methanolysis.

The successful conversion of the racemic cycloadduct (340b) into the racemic oxazine (56) encouraged us to undertake preparation of the optically active oxazine hydrochloride from a single enantiomer of the cycloadduct (340b). To achieve this, (S)-mandelohydroxamic acid (328c) was oxidized with aqueous

(S)-(+)-PhCH(OR)CONHOH

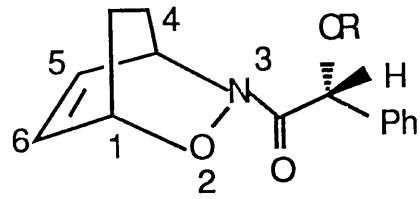


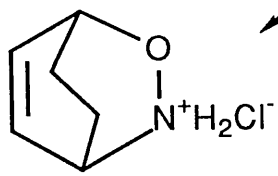
(328c)

(377)

MeONa-MeOH

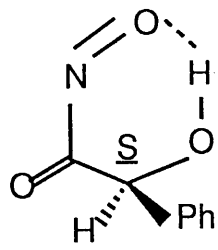
a;R H
b;R=Ac

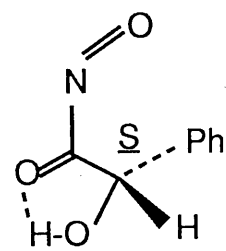


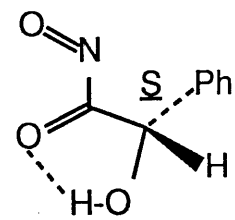


(378)

(273)



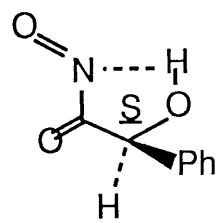




(327cI)

(327c II)

(327c III)



(327cIV)

Scheme 87

sodium periodate (1 mol equivalent) in the presence of cyclohexa-1,3-diene at 0°C as usual to give a mixture of 2 diastereoisomeric cycloadducts (377a) and (378a) (Scheme 87). This mixture showed similar spectroscopic properties to its counter part of racemic cycloadduct (340) and (341a). In addition this mixture showed an optical rotation, $[\alpha]_D$ -15° (c 2.00 in $CHCl_3$). This mixture of optically active cycloadducts was then acetylated to give a mixture of the O-acetyl derivatives (377b) and (378b), $[\alpha]_D$ -40° (c 1.5 in $CHCl_3$). The same ratio, 3.5, was obtained (^1H n.m.r. spectroscopy) for these acetate as was obtained for the racemic derivatives. The major isomer (377b), 1R, 4S, $[\alpha]_D$ +32° (c 0.75 $CHCl_3$), was then methanolysed[106] to give the optically pure oxazine hydrochloride (273), m.p. 161 - 162°C (lit m.p. 163°C), $[\alpha]_D$ -40° (c 1.00 in MeOH) (lit -40°)[81] and methyl (S)-mandelate (327b).Formation of the optically pure oxazine hydrochloride (272), of known absolute configuration from the major O-acetyl derivative (377b) clearly showed that the configuration of the cycloadduct (377b) was 1R, 4S.

The ratio of cycloadducts observed in various mixtures can now be interpreted on the basis of intramolecular hydrogen bonding in the transient nitroso compounds (329c) derived from (S)-mandelohydroxamic acid (328c). the dienophile (329c) can exist in 4 different hydrogen-bonded forms as shown in scheme 87. Three factors will control the relative stability of the 4 different forms (329cI), (329cII), (329cIII), and (329cIV), the hydrogen bond strength dipole-dipole repulsion between the C=O and N=O groups (favouring the anti conformers I and II), and steric

repulsion. Usually 6-membered hydrogen-bonded rings are energetically preferred as in form I which also has anti carbonyl and nitroso groups. Forms II and III have 5-membered rings believed to be important in the a-hydroxyenone dienophiles discussed earlier. Of these, the anti form II will be favoured on electronic gounds (less dipole repulsion), although III may be less sterically hindered.

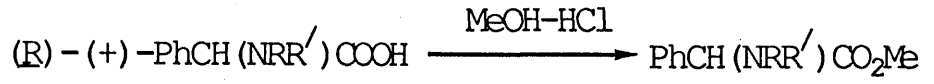
Finally, form IV appears to be least stable; it has a 5-membered ring hydrogen bond to the relatively positive nitrogen of the nitroso group, and the syn nitroso and carbonyl groups will repel each other.

It is likely that nitrosocarbonyl compounds will approach the dienes preferentially in the usual endo, with carbonyl group having secondary orbital interaction with the diene, although the amide product cannot exist as endo and exo isomers. This mode of attack will be assumed in the following discussion. Diene will approach the 4 forms from the side of hydrogen atom rather than the phenyl group. Thus, form I will be approached preferentially from the a-face, i.e. from the si face of the nitroso group, to give, with endo addition, the cycloadduct (377c) observed as the major product. Form III will behave similarly, giving (377c) as the major product, by being approached from the b-face, again the si face of the nitroso group. The forms II and III will conversely give (370c), observed as the minor product, preferentially by attack at the re face of the nitroso group. Form I seems likely to be the

preferred conformation of the dienophile and the observed stereochemistry is consistent with this idea.

SECTION III

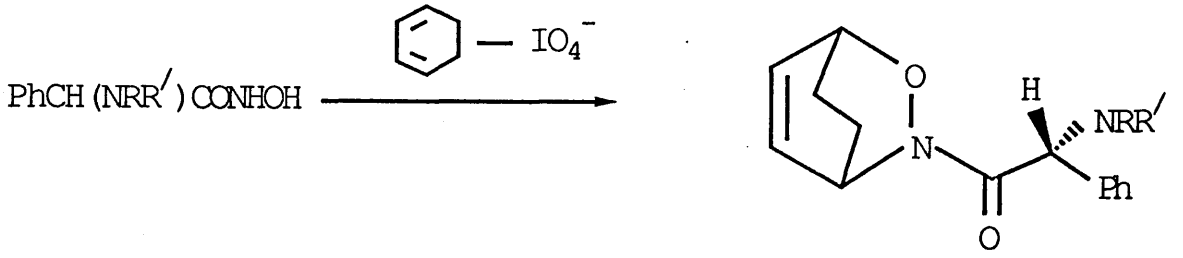
The successful study of diastereoselectivity for the cycloaddition reactions of chiral α-hydroxy C-nitrosocarbonyl compounds with achiral dienes, encouraged us to extend this work to some chiral α-amino derivatives. The use of chiral auxiliaries derived from α-amino acid has already been documented by Herbert and co-workers. They treated the amino acid methyl ester hydrochloride with cyclopentadiene in the presence of aqueous formaldehyde and obtained the mixture of diastereoisomeric products in a 93:7 ratio (Scheme 62). In a similar way, α-methylbenzylamine hydrochloride reacted with formaldehyde and cyclopentadiene to give the mixture of cycloadducts in a ratio of 4:1 (Scheme 57). These early findings encouraged us to focus attention on the study of α-amino acid derivatives. We selected (R)-phenylglycine for our studies. Since it was analogous to the α-hydroxy acid, mandelic acid. In the first experiment (R)-phenyglycine (379; R = R = H) was converted into the corresponding methylester hydrochloride (380a) by heating in dry methanolic hydrogen chloride under reflux. This ester was then treated with hydroxylamine hydrochloride in the presence of aqueous sodium hydroxide in the usual way. 2-Amino-2-phenylacetohydroxamic acid hydrochloride (381a) was obtained as a highly hygroscopic solid (Scheme 88). The ^1H n.m.r. spectrum (CD_3OD) resembled to the corresponding methyl ester hydrochloride. Oxidation of this hydroxamic acid in the presence



(379) (380)

PhCH(NRR′)CONHOH

(381)



(381) (382) (383)

a; R = H, R′ = H.HCl
b; R = H, R′ = Ac

Scheme 88

of cyclohexa-1,3-diene (1 mol equiv.) with aqueous sodium periodate (1 mol equiv.) in aqueous sodium acetate-ethyl acetate, failed to give the expected cycloadducts. The ^1H n.m.r. spectrum of the crude product could not be interpreted due to its complexity. As cyclopentadiene is thought to be more reactive diene than cyclohexa-1,3-diene in Diels-Alder reaction it was thought it might be better able to trap nitroso compound. However, the usual oxidation of the hydroxamic acid (381a) in the presence of cyclopentadiene again failed to give any identifiable product. Again, oxidation of the hydroxamic acid (381a) in homogenous methanolic solution with tetraethylammonium periodate, in the presence of cyclohexa-1,3,-diene failed to yield any of the expected adducts.

It was therefore decided next to use the N-acetyl derivative (381a). (R)-N-Acetylphenylglycine (379b), prepared by acetylation of the amino acid with acetyl chloride, was heated with dry methanolic hydrogen chloride to give the corresponding methyl ester (Scheme 88). This was then converted, as usual into (R)-2-acetylamino-2-phenylacetohydroxamic acid (381b), obtained as highly hygroscopic solid. The molecular formula, $C_{10}H_{12}N_2O_3$, was determined by accurate mass measurement. The i.r. spectrum showed bands for the hydroxyl and carbonyl groups, ν_{max} 3425 and 1625 cm^{-1}. The ^1H n.m.r. spectrum (CD_3OD-$CDCl_3$) showed in addition to signals common to the corresponding ester, a broad signal for OH and NH δ 4.90 and no signals for the methoxyl group. The N-acetyl hydroxamic acid (381b) was oxidised at 0°C with tetramethylammonium periodate (1 mol

equiv.) in the presence of cyclohexa-1,3-diene (1 mol equiv.) in ethyl acetate to give the diastereoisomeric cycloadducts (382b) and (383b) as a gum (77%) (Scheme 88). No separation of the cycloadducts was achieved on t.l.c. However 2 sets of ^1H n.m.r. signals were seen for each component of the mixture of the cycloadducts (382b) and (383b). The molecular formula, $C_{16}H_{18}N_2O_3$, of the cycloadducts was determined, for the mixture by accurate measurement. The i.r. spectrum showed bands for NH and carbonyl groups, ν_{max} 3420 and 1622 cm^{-1}, respectively. Significant signals in the ^1H n.m.r. spectrum ($CDCl_3$; 200 MHz) for the 2 diastereoisomeric products (382b) and (383b) are listed in Table IX.

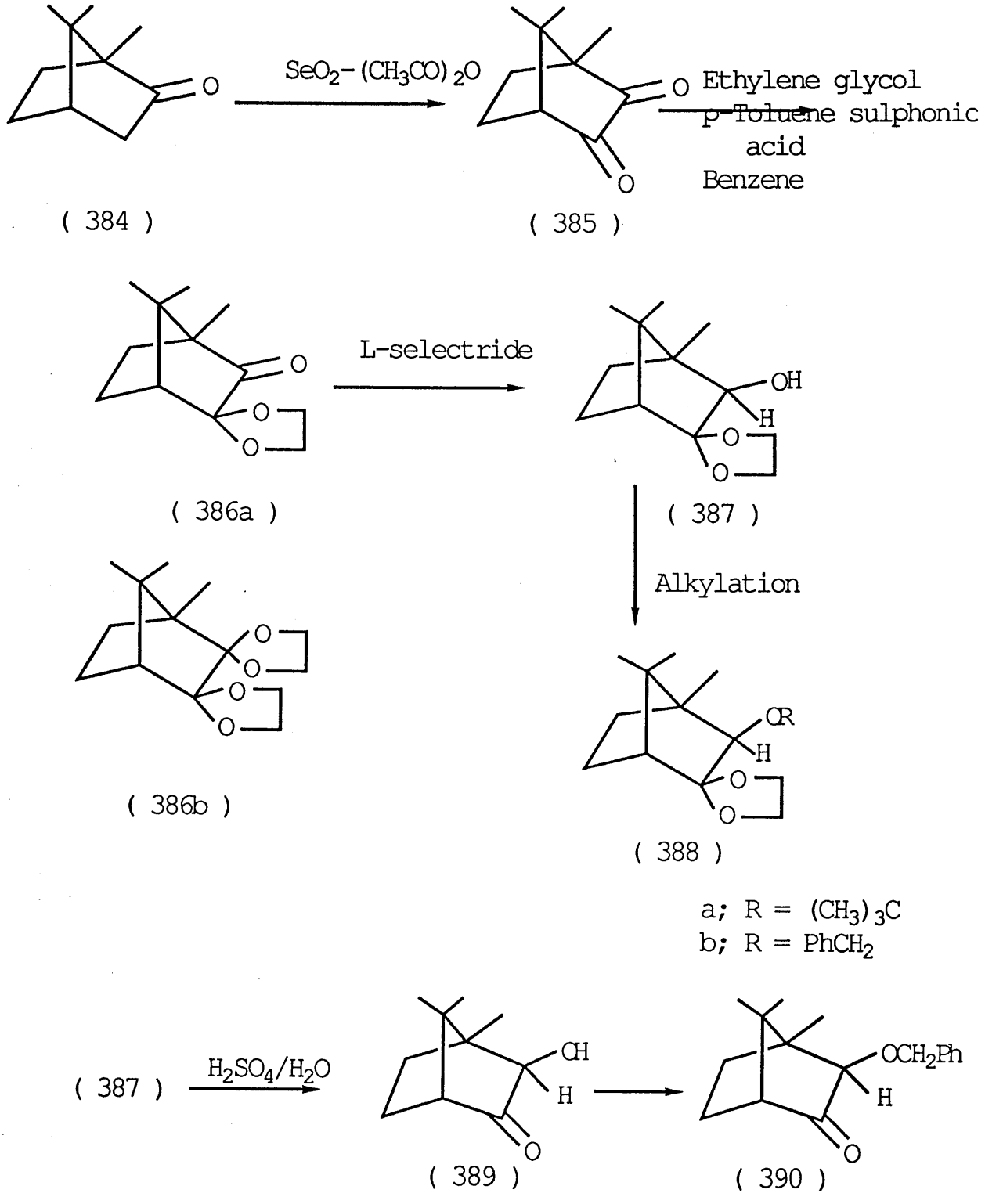
Table IX. H. N.m.r. spectrum, δ (200 MHz; $CDCl_3$) of the cycloadducts (382b) and (383b)

cycloadducts	protons			
	1- or 4-H	2′-H	5- or 6-H	NH
(382b)	4.25 and 5.25 (2 x br s)	5.75 (d, J 5Hz)	6.2 and (2 x m)	6.95 (t)
(383b)	4.25 and 5.25 (2 x br s)	5.90 (d, J 5Hz)	6.70 (2 x m)	6.95 (t)

The doublet from the NH groups overlapped with each other (as apparent triplets). The ratio, 1:1, of the cycloadducts (382b) and (383b) was measured from the integrals for the 2′-H signal, δ 5.75 and 5.90, and also from the olefinic protons signals, δ 6.02 and 6.45 and 6.70. The lack of stereoselectivity in this cycloaddition reaction might be due to the intramolecular hydrogen bonding between the α-amino and nitroso groups in the dienophile being relatively weak.

Cycloadducts from chiral N-hydroxycarbamic ester and cyclohexa-1,3-diene

Attention was next turned to another class of chiral nitrosocarbonyl dienophiles, the nitrosoformates, ROCONO prepared from chiral alchols. We wished to compare the efficiency of dienophiles based on known chiral alcohols but without the benefit of intramolecular hydrogen bonding. The proper choice and easy access to the chiral alcohol was the primary consideration. Oppolzer et al. prepared many auxiliaries starting from (R)- and (S)-camphor. The corresponding acrylates added to cyclopentadiene with high levels of asymmetric induction, in combination with some Lewis acid catalyst. We therefore decided to prepare the chiral auxiliaries (174a) and (174d) starting from (S)-camphor (384) (Scheme 89). The litreature route reported successfully to give 2-exo-hydroxy-3,3-ethylenedioxy-(1S)-7,7-trimethylbicyclo [2.2.2] heptane (387) as oil. In an attempt to alkylate this alcohol, it was heated under reflux in N-methylpyrrolidione (NMP) with sodium hydride and



(384) (385) (386a) (386b) (387) (388) (389) (390)

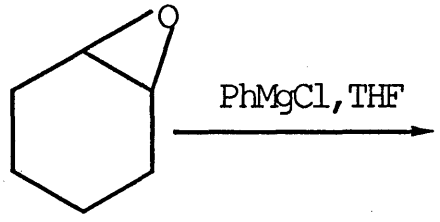
a; R = $(CH_3)_3C$
b; R = $PhCH_2$

Scheme 89

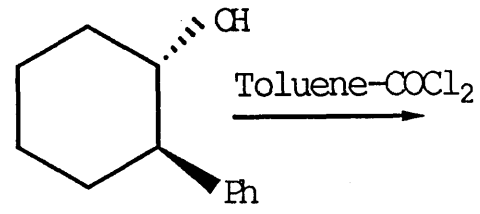
neopentyl bromide. However, only starting material was recovered. When the more reactive alkly halide, benzyl chloride, was employed in place of neopentyl bromide, the ^1H n.m.r. spectrum of the reaction mixture again showed no signal for the expected alkylated product (388b). In another experiment, N,N-dimethylformamide (DMF) was used as a solvent for the attempted benzylation, the ^1H n.m.r. spectrum of the reaction mixture again showed signals only for the starting material. The same experiment when repeated with benzyl bromide, but again only the starting material (387) was obtained (^1H n.m.r. spectrum). Finally attempted benzylation with benzyl bromide and potassium hydride in DMF gave a complex mixture containing some starting material.

Oppolzer et al. also used the hydroxy ketone (389) for the preparation of the chiral alkylated ketones (390) which were then converted into the hydroxy ethers, after reduction with sodium borohydride. We therefore decided to hydrolyse (387) to give (389) using aqueous sulphuric acid. The oily hydroxy ketone (389) was treated with benzyl bromide and sodium hydride in NMP. Again, it yielded the starting material (389), and no signal for the expected alkylated product was observed in the ^1H n.m.r. spectrum of the reaction mixture. The failure to reproduce the litreature alkylation was not understood but it was decided to abandon attempts and change to an alternative chiral auxiliary.

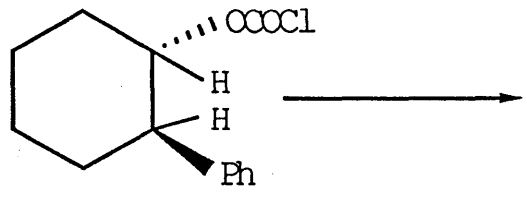
We considered initially using (R)-(-)-8-phenylmenthol, but were a little hesitant because of its high cost. At about the same time, Professor Baldwin (Oxford) reported the use of the 8-



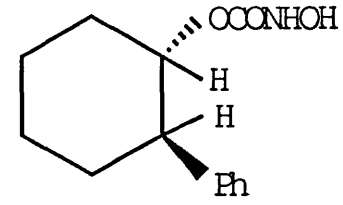
(391)



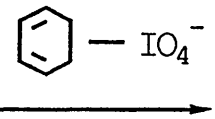
(392)

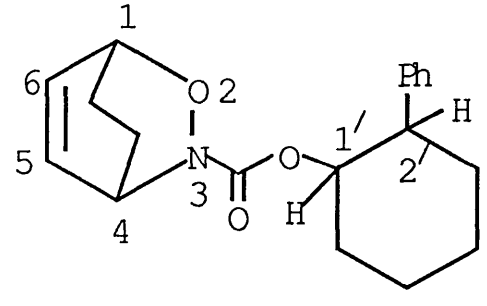


(393)



(394)

(394) 



1′,2′-trans

(395) Major diastereoisomeric racemate

(396) Minor diastereoisomeric racemate

Scheme 90

phenylmenthyl C-nitrosoformate ester[107] in a cycloaddition reaction with cyclopentadiene. He obtained a 3:2 ratio of cycloadducts. However, derivatives of the racemic trans-2-phenylcyclohexanol (392) have been reported to show similar diastereoselectivity[108] as the derivatives of 8-phenylmenthol. We therefore decided to use this chiral auxiliary. The alcohol (392) was prepared, according to litreature, from cyclohexene oxide (391) and phenylmagnesium chloride using cuprous iodide as a catalyst (Scheme 90). The oily trans-2-phenylcyclohexanol (392) was then treated with phosgene in toluene at 0°C and then at room temperature. Thin layer chromatography of the reaction mixture showed it to be a ca 1:1 mixture of the alcohol (392) and its chloroformate ester (393). Further stirring at room temperature did not alter the ratio of the two products, (392) and (393). A part of the reaction mixture was evaporated to dryness; the ^1H n.m.r. spectrum ($CDCl_3$) of the residue showed the presence of alcohol (392), δ 3.60 (m, HOCH) and the chloroformate (393), δ 4.80-5.20 (m, $ClCO_2$ CH). Integration of these signals showed the ratio for 2 compounds (392) and (393) to be ca 1:1. This mixture in toluene, was shaken with hydroxylamine hydrochloride and sodium hydroxide in water. Work up gave the alcohol (392) and the N-hydroxycarbamic ester (394). This mixture showed two spots on t.l.c., the lower spot giving a purple colour with feric chloride, thus confirming the formation of the hydroxamic acid (394). Chromatography on silica column and elution with chloroform yielded the pure trans-2-phenylcyclohexanol (392). Elution with chloroform-methanol yielded the required N-hydroxycarbamic ester (394) as a gum. The molecular formula,

$C_{13}H_{17}NO_3$ was confirmed by accurate mass measurement. The i.r. spectrum showed bands for the hydroxyl and carbonyl groups ν_{max} 3400 and 1655 cm^{-1}. The ^1H n.m.r. spectrum gave a broad signal for 1′-H, δ 4.80-5.20, similar to that of the chloroformate (393). In addition, a broad singlet δ 7.80-8.00, was observed for NH and OH and this was exchanged with D_2O. The N-hydroxycarbamic ester (394) was oxidised with tetraethylammonium periodate (1 mol equiv.) in the presence of cyclohexa-1,3-diene (1 mol equiv.) in methanol-chloroform at -78°C. The product was chromatographed on preparative silica t.l.c. plates to give a mixture (61%) of a major diastereoisomer (395) and a minor diastereoisomer (396) as a gum (Scheme 90). This mixture of cycloadducts failed to spearate on t.l.c. The molecular formula, $C_{19}H_{23}NO_3$, was determined by accurate mass measurement. The i.r. spectrum showed bands for carbonyl group, ν_{max} 1660 cm^{-1}. Significant signal from the ^1H n.m.r. spectra for the cycloadducts (395) and (396) are given in Table X.

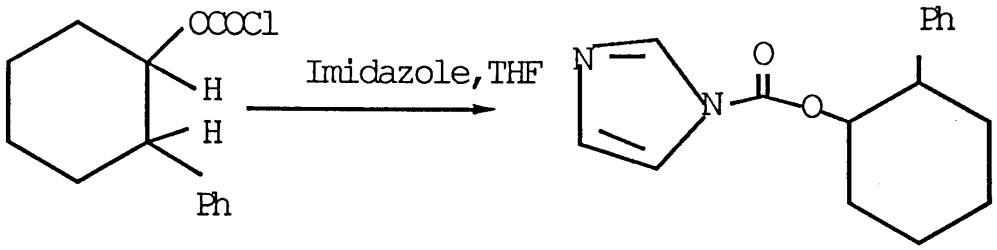
Table X. ^1H n.m.r. spectra, δ ($CDCl_3$; 200 MHz) of the cycloadducts (395) and (396)

cycloadducts	protons		
	1- or 4-H	5- or 6-H	2′-H
(395) major isomer	4.25 and 4.50	5.25 and 6.15	4.80

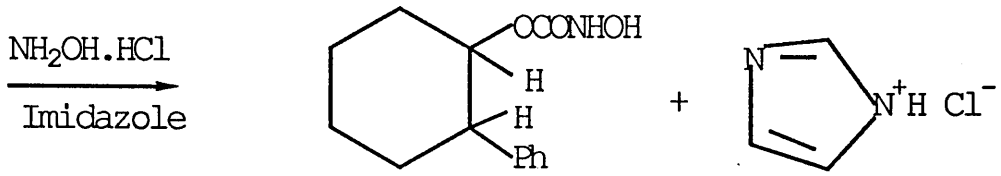
	(2 x br s)	(2 x t)	(br m)
(396) minor isomer	4.25 and 4.50 (2 x br s)	6.15 and 6.50 (2 x m)	4.80 (br m)

The ratio 3.6:1, of the racemic diastereoisomeric cycloadducts (395) and (396), was measured from the integrals for the olefinic protons signals, 5- and 6-H, at δ 5.25, 6.15 and 6.50. An attempt to carry out the same reaction at 0°C, for comparison with the experiment with α-hydroxy nitrosocarbonyl compounds, unexpectedly gave complex mixture containing insufficient amount of adducts (395) and (396) for measurement of their ratio. In contrast repetition of experiment at -78°C, gave the original compounds successfully in the same ratio, 3.6:1, of the cycloadducts (395) and (396). It was difficult to explain this anomoly at this stage.

The low yield obtained in the formation of N-hydroxycarbamic ester (394) from the mixture of the chloroformate (393) and trans-2-phenylcyclohexanol (392), forced us to explore other methods for the preparation N-hydroxycarbamic esters, especially the hindered ones like (394). In the first stage of this investigation (Scheme 91), the pure chloroformate (393) (1 mol equiv.) was treated with imidazole (3 equiv.) at room temperature. Then the solution was stirred with powdered



(393) (397)



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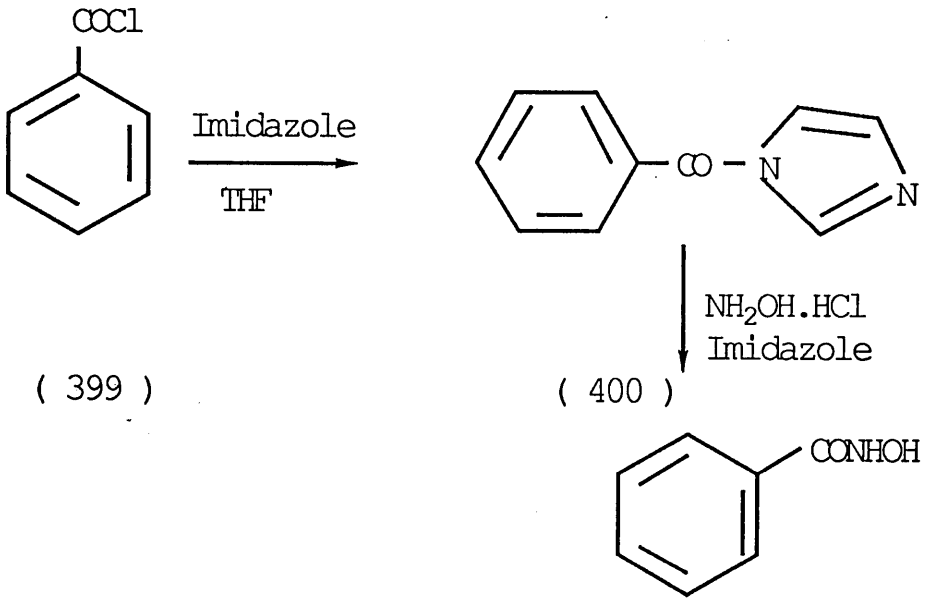


(399) (400)

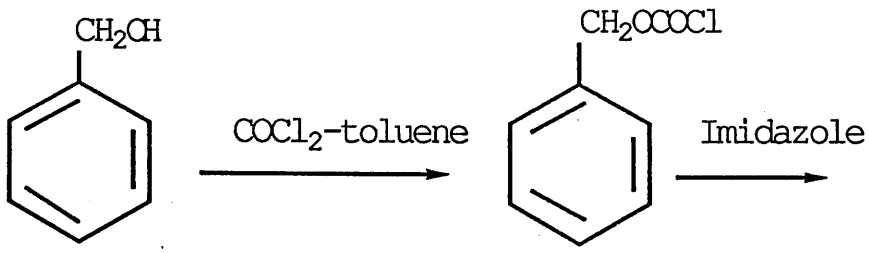
(401)

Scheme 91

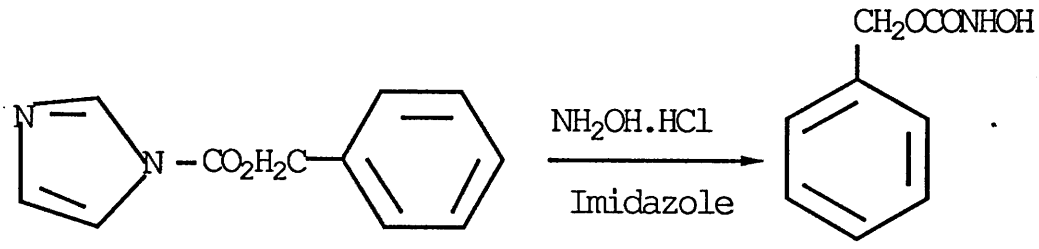
hydroxylamine hydrochloride. The idea was that after the intermediate N-acylimidazole (397) had formed, free hydroxylamine would be liberated slowly from its hydrochloride by the imidazole, and would attack the N-acyl group to give the desired product (394). These conditions would avoid hydrolysis of the chloroformate (393), a possible reason for the low yield obtained earlier. The mixture was shaken overnight then worked up. The ^1H n.m.r. spectrum of the mixture showed signals attributable to an N-acylimidazole derivative, e.g. (397) and none for the desired product, the N-hydroxycarbamic ester, (394). This experiment suggested that, either imidazole failed to liberate free hydroxylamine from hydroxylamine hydrochloride (which is contrary to previous experiment in these laboratories) or the free hydroxylamine did not cleave the N-acylimidazole (397). To test the former possibility, benzoyl chloride (399) (1 mol equiv.) in THF was added slowly to imidazole (3.5 equiv.) in THF at room temperature. Powdered hydroxylamine hydrochloride (1.5 equiv.) was then added and the mixture was shaken vigorously for 16 h. The usual work up gave pure benzohydroxamic acid (401) (70%) (Scheme 91). Therefore, free hydroxylamine was indeed liberated by imidazole from the hydrochloride and the hydroxylamine in turn displaced imidazole from the acylimidazole derivative (400). It appeared then that N-benzolyimidazole (400) is more reactive towards hydroxylamine than the alkoxycarbonyl derivative (397). To test this idea simple chloroformate (403) was prepared from benzylalcohol (402). Benzyl chloroformate (403) was treated first with imidazole, then powdered hydroxylamine hydrochloride was added as discussed above. However the same work up yielded

no phenylacetohydroxamic acid (405). Instead, the ^1H n.m.r. spectrum ($CDCl_3$) showed signal for the N-acylimidazole derivative (404) (Scheme 92). N-alkoxycarbonylimidazole derivatives unlike N-benzolimidazole are not sufficiently reactive towards hydroxylamine under these conditions, perhaps due to electronic stabilisation.

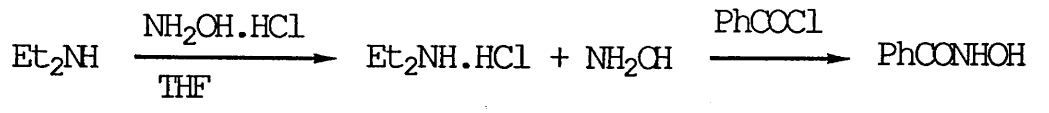
King et al.[109] prepared N,O-bis (trisilyl) hydroxylamine from chlorotrimethylsilane and hydroxylamine hydrochloride using diethylamine as a base. We decided to follow the litreature method for the preparation of benzohydroxamic acid (401). Thus, hydroxylamine hydrochloride (1 equiv.) was suspended in dry THF and diethylamine (2 mol equiv.) (406) in THF was added slowly to the stirred suspension. The small prisms like hydroxylamine hydrochloride were replaced by needle shaped tiny crystals, presumably of diethylamine hydrochloride (407) (Scheme 92). Benzoyl chloride (1 equiv.) in THF was added slowly to this mixture. The reaction mixture was evaporated and the residue was washed with water so as to remove the salt of diethylamine. The ^1H n.m.r. spectrum of the residue showed no signals for the expected product, benzohydroxamic acid (401), indeed signals for diethylbenzamide (409), δ 1.15 (br m, Me), 3.35 (br s, CH_2) and 7.35 (s, ph), identified with those of a sample prepared separately from benzoyl chloride and diethylamine. To avoid the presence of an excess of diethylamine, equivalent amounts of both diethylamine and hydroxylamine hydrochloride were next used. Thus hydroxylamine (2 mol equiv.) and diethylamine (2 mol equiv.) were mixed, as stated above. Benzyl chloride (1 equiv.)



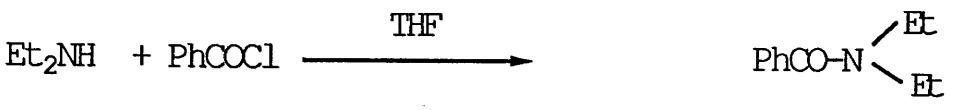
(402) (403)



(404) (405)



(406) (407) (408) (401)



(406) (399) (409)

Scheme 92

was then added. However, the ^{1}H n.m.r. spectrum of the product again showed the presence of signals for diethylbenzamide (409) and no signals for the benzohydroxamic acid (401) were observed.

These investigations ended in failure and no further attempts were made to improve the yield of the N-hydroxycarbamic esters.

CHAPTER 3

EXPERIMENTAL

Instrumentation and General Notes

M.p.s. were determined on Kofler hot-stage apparatus. Microanalyses were obtained by Mrs. Harkness and her staff. Low resolution mass spectra were recorded at 70 eV on an A.E.I. M.S.12 instrument and high resolution spectra on an A.E.I. M.S.9 instrument coupled to GEC-905 computer for data collection and processing. I.r. spectra were recorded on either a Perkin-Elmer 580 or 257 Spectrometer by Mrs. F. Lawrie and her staff. ^1H N.m.r. spectra were recorded at 90 MHz on Perkin-Elmer R-32 instrument and at 200 MHz spectra on a Bruker WP 200 SY spectrometer in the pulsed Fourier transform mode by Dr. D. S. Rycroft and his colleagues; chemical shifts are quoted as p.p.m. down field from tetramethylsilane.

Analytical t.l.c. was carried out on precoated Merck Kieselgel GF_{254} plates of thickness 0.25 mm. Spots were viewed under an u.v. (254 nm) and developed by iodine vapour. Column chromatography was carried out on Merck silica HF_{254} under reduced pressure.Preparative thin layer chromatography was carried out on Merck GF_{254} silica with detection of compounds by u.v. light.

All solvents and reagents used were of analytical grade unless otherwise stated.'Light petroleum' refers to the fraction b.p. 60-80°C and 'ether' refers to diethyl ether.

Stirring of the reaction mixtures was carried out using magnetic stirrer bars.

Organic solutions were dried over anhydrous magnesium sulphate and evaporated on a Buchi rotary evaporator under water-pump vacuum.

The following abbreviations and symbols have been used in this thesis:-

br,	broad
d,	doublet
m,	multiplet
q,	quartet
s,	singlet
t,	triplet
i.r.,	infra-red
n.m.r.,	nuclear magnetic resonance
t.l.c.,	thin layer chromatography
h,	hour
min,	minute
Hz,	Hertz
THF,	tetrahydrofuran
NMP,	N-methyl pyrrolidone
DMF,	N,N-dimethylformamide
DMA,	dimethylanthracene

Preparation of (±)-mandelohydroxamic acid (328a)

Hydroxylamine hydrochloride (10.0 g, 0.14 mol) in water (5 ml) and ethanol (6 ml) was stirred at 0°C. 10 M Sodium hydroxide (10 ml) was added to it dropwise over a period of 10 min. The ice bath was then removed and the solution was stirred at room temperature. Methyl (±)-mandelate (14.0 g, 0.084 mol) in ethanol (5 ml) was added over a period of 10 min. The reaction mixture was stirred for a further period of 2h. The reaction mixture was then acidified to pH 6 with hydrochloric acid at 0°C. The solution was evaporated to dryness under reduced pressure at 50°C. Ethanol (50 ml) was added and the mixture evaporated again to dryness. This procedure was repeated and the solid residue so obtained was

extracted with boiling ethyl acetate (2 x 50 ml). The ethyl acetate extracts were dried ($MgSO_4$) and evaporated to dryness. The solid residue yielded (±)-mandelohydroxamic acid (8.0 g, 67%), m.p. 146-147°C (from Light petroleum-ethyl acetate).

Preparation of the cycloadducts (330a) from (±)-mandelohydroxamic acid and thebaine

Thebaine (311 mg, 1 mmol) in ethyl acetate (25 ml) and sodium periodate (215 mg, 1 mmol) in aqueous 0.5 M sodium acetate (25 ml), adjusted to pH 6 with hydrochloric acid, were stirred at 0°C, and (±)-mandelohydroxamic acid (167 mg, 1 mmol) was added in small portions over a period of 10 min. The reaction mixture was stirred for a further period of 0.5 h. The ethyl acetate layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 25 ml). The combined ethyl acetate extracts were washed successively with 5% aqueous sodium thiosulphate, saturated aqueous sodium hydrogen carbonate and water, and were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield a crude reaction product (435 mg). This was chromatographed on a short silica (HF_{254}) column, and eluted with Analar ethyl acetate. Evaporation of the eluate yielded a mixture of diastereoisomeric cycloadducts (330a) (380 mg, 80%). The t.l.c. of this mixture in ethyl acetate showed two spots and ^1H n.m.r. spectrum ($CDCl_3$) showed sets of signals for 2 diastereosomeric products. The ^1H n.m.r. signals for the components with R_f 0.40 and R_f 0.38 are given in this order as follows: δ ($CDCl_3$) 2.48 (3H,s,NMe), 2.80 (3H,s, 6-0Me), 3.70 (3H,s, 3-0Me), 3.95 (1H,br s,0H, exch. with D_20), 4.55 (1H,s, 5-H), 4.85 (1H, d, J,8Hz,9H), 5.35 (1H,s, side chain-CH), 5.49 (1H,d,J, 10Hz, 7-H or 8-H), 5.95 (1H,d,J 10 Hz, 7 or 8-H), 6.25 (2H,br s,1- and 2-H), and 7.25 (5H,m,

ph), and δ 2.40 (3H,s,NMe), 3.60 (3H,s,6-0Me), 3.80 (3H,s,3-0Me), 4.49 (1H,s,5-H), 4.68 (1H,d,J 8Hz, 9-H), 5.15 (1H,s, side chain-CH), 6.10 (2H,AB_q, J 10Hz, 7- and 8-H), 6.60 (2H,AB_q, J, 10Hz, 1- and 2-H), and 7.35 (5H,m,pH). The ratio of the diastereoisomers, measured from the integration of the olefinic signals and those of the side chain-CH, was found to be 1:1.

Chromatographic separation of the cycloadducts (331b) and (331c)

The mixture of cycloadducts (330a) (150 mg, 0.31 mmol) was chromatographed on preparative t.l.c. silica GF_{254} commercial plates in Analar ethyl acetate. The 2 diastereoisomeric cycloadducts (331b) and (331c) were obtained approximately in equal weights. The ^1H n.m.r. spectra ($CDCl_3$) of the separated diastereoisomers agreed with that of the mixture.

Preparation of (S)-(+)-mandelohydroxamic acid (328c)

Hydroxylamine hydrochloride (3.5 g, 0.05 mol) and methyl (S)-mandelate (7.0 g, 0.42 mol) were allowed to react in the presence of 10 M sodium hydroxide according to Sandlar and Karo's method[97]. The usual work up of the reaction mixture afforded (S)-(+)-mandelohydroxamic acid (5.0 g, 71%), m.p. 138-139°C (from light petroleum-ethyl acetate) (Found: C, 57.57; H, 5.39; N, 8.38, m/z 151.0630 and 149.0471. $C_8H_9NO_3$ requires C, 57.48; H, 5.38; N, 8.38%; M, 151.0591; $[\alpha]_D$ + 162° (c 2.5 in H_20); ν_{max} (kBr) 3350 and 1650 cm^{-1}; δ (CD_30D) 4.95-5.05 (2H,br s,NH and 0H, exch. with methanol), 5.10 (1H,s, side chain-CH), and 7.50 (5H,m,ph).

Preparation of (R)-(-)-mandelohydroxamic acid (328b)

Hydroxlamine hydrochloride (3.5 g, 0.05 mol) and methyl (R)-mandelate (7.0 g, 0.024 mol) reacted in the presence of 10 M sodium hydroxide, as above, to afford (R)-(-)-mandelohydroxamic acid (328b) (4.5 g, 64%), m.p. 138-139°C (from light petroleum-ethyl acetate) (Found: C, 57.55; H, 5.39; N, 8.39; m/z 151.0639 and 149.0471. $C_8H_9NO_3$ requires C, 57.57; H, 5.38; N, 3.38%; M, 151.0591; $[\alpha]_D$ (c 2.5 in H_2O; ν_{max} (kBr) 3350 and 1655 cm^{-1}; δ (CD_3OD) 4.95-5.15 (2H,br s,NH and OH, exch. with methanol), 5.10 (1H,s, side chain-CH), and 7.50 (5H,m,Ph).

Preparation of the cycloadduct (331b) from (R)-(-)-mandelohydroxamic acid and thebaine

Thebaine (1.87 g, 6 mmol) in ethyl acetate (100 ml) and sodium periodate (1.30 g, 6 mmol) in 0.5 M aqueous sodium acetate (100 ml), adjusted to pH 6 with hydrochloric acid, were stirred at 0°C, and (R)-(-)-mandelohydroxamic acid (0.99 g, 6 mmol) was added in small portions over a period of 10 min. The reaction mixture was stirred for a further 0.5 h. The ethyl acetate layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 50 ml). The combined ethyl acetate extracts were washed successively with 5% aqueous sodium thiosulphate (150 ml), saturated aqueous sodium hydrogen carbonate (150 ml), and water, and were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford the Crude cycloadduct. This was chromatographed on a short silica HF_{254} column. It was eluted with Analar chloroform. The eluate was evaporated to yield 6β, 14β- [N-(R)-(2-hydroxy-2-phenyl)acetylepoxyimino]-6,14-dihydro-thebaine (331b) (2.35 g, 79%) as a hydrate, m.p. 115-116°C (from light petroleum-benzene) (Found: C, 68.10; H, 5.76; N, 5.70; m/z 476.1964. $C_{27}H_{28}N_2O_6$. H_2O requires C, 68.06; H, 5.67; N, 5.80%; M, 476.1980); ν_{max} ($CHCl_3$) 3580 and 1658 cm^{-1};

δ ($CDCl_3$) 2.48 (3H,s,NMe), 2.80 (3H,s,6-0Me), 3.70 (3H,s,3.0Me), 3.90 (1H,br s,0H, exch. with D_20), 4.55 (1H,s,5-H), 4.85 (1H,d, J 8Hz, 9-H), 5.35 (1H,s, side chain-CH), 5.49 (1H,d,J, 10Hz, 7-H), 5.95 (1H,d,J 10Hz, 8-H), 6.25 (2H, AB_q, J 10Hz, 1- and 2-H), and 7.25 (5H,m,ph).

Preparation of the cycloadduct (331c) from (S)-(+)-mandelohydroxamic acid and thebaine

The foregoing preparation of the diastereoisomer was repeated but this time with (S)-(+)-mandelohydroxamic acid. The cycloadduct (331c) 6β, 14β [N-(S)- (2-hydroxy-2-phenyl)-acetyleproxyimino]-6,14-dihydrothebaine (2.25 g, 78%) was obtained as a hydrate, m.p. 159-160°C (from light petroleum-benzene) (Found: C, 68.80; H, 6.00; N, 5.77; m/z 476.1964. $C_{27}H_{28}N_20_6$. H_20 requires C, 68.05; H, 5.67; N, 5.88%; M, 476.1980); ν_{max} ($CHCl_3$) 3460 and 1655 cm^{-1}; δ ($CDCl_3$) 2.40 (3H,s,NMe), 23.60 (3H,s,6-0Me), 3.80 (3H,s,3-0Me), 4.25 (1H,br s,0H, exch. with D_20), 4.49 (1H,s,5-H), 4.60 (1H,d, J 8Hz, 9-H), 5.15 (1H,s, side chain-CH), 6.10 (2H,AB_q,J 10Hz, 7- and 8-H), 6.60 (2H,AB_q,J 10Hz, 1- and 2-H), and 7.35 (5H,m,ph).

Hydrolysis and rearrangement of the cycloadduct (334b)

The cycloadduct (334b) (523 mg, 1.09 mmol) in methanol (30 ml) and 6 M hydrochloric acid (30 ml) was heated up to 60°C for 20 min. The reaction mixture was allowed to cool down to room temperature and made alkaline with saturated aqueous sodium hydrogen carbonate. The methanol was evaporated off under reduced pressure and the aqueous solution was extracted with chloroform (3 x 100 ml). The chloroform extracts were washed with water, dried ($MgSO_4$) and evaporated to yield the crude codeinone (335b) (357 mg, 0.75 mmol).

This was stirred with 0.1 M sodium meihoxide (7.5 ml, 0.75 mmol) at room temperature for 50 min. The reaction mixture was acidified with dilute hydrochloric acid and made alkaline with saturated aqueous sodium hydrogen carbonate. The methanol was evaporated off and the remaining aqueous solution was extracted with chloroform (3 x 25 ml). The chloroform extracts were washed with water, dried ($MgSO_4$), and filtered. The filtrate evaporated to yield a crude product. Column chromatography failed to purify the product. Preparative chromatography on commercial silica GF_{254} t.l.c. plates in Analar ethyl acetate yielded the thebainone, 5β, 14β [N-(R)-(2-hydroxy-2-phenyl) acetylepoxyimino] thebainone (336b) as a hemihydrate (254 mg), m.p. 135-136°C (from light petroleum -CH_2Cl_2) (Found: C, 66.62; H, 5.78; N, 5.60; m/z 462.1784. $C_{26}H_{26}N_2O_6$. 0.5 H_2O requires C, 66.62; H, 5.78; N, 5.68%; M, 462.1782); ν_{max} ($CHCl_3$) 3580 and 1658 cm^{-1}; δ ($CDCl_3$) 2.45 (3H,s,NMe), 23.73 (3H,s,3-0Me), 4.25 (1H,d, J 8Hz, 9-H), 5.06 (1H,br s,5H), 5.25 (1H,d,J 8Hz,7-H), 5.40 (1H,s, side chain-CH), 6.60 (2H,s,1- and 2-H), 6.75 (1H,d,J 8Hz, 8-H), and 7.20 (5H,s,ph).

Hydrolysis and rearrangement of the cycloadduct (334c)

The cycloadduct (334c) (500 mg, 1.05 mmol) was treated successively with methanolic hydrochloric acid and sodium methoxide, as described for in diastereoisomer (334b) in the foregoing experiment, but with 1 M hydrochloric in methanol. Preparative chromatography on commercial silica GF_{254} t.l.c. plates in Analar ethyl acetate yielded the pure thebainone, 5β,14β[N-(S)-(2-hydroxy-2-phenyl) acetylepoxyimino] theb-ainone (336b) as a hemihydrate (240 mg), m.p. 125-126°C (from light petroleum -CH_2Cl_2) (Found: C, 66.70; H, 5.66; N, 5.84; m/z

462.1806. $C_{26}H_{26}N_2O_6$. 0.5 H_2O requires C, 66.62; H, 5.78; N, 5.68%; M, 462.1782); ν_{max} ($CHCl_3$) 3585 and 1680 cm^{-1}; δ ($CDCl_3$) 2.38 (3H,s,NMe), 3.79 (3H,s,3-OMe), 4.29 (1H,d, J 8Hz, 9-H), 5.02 (1H,br s,5-H), 5.30 (1H,br s,side chain-CH), 5.95 (1H,d,J 8Hz, 7-H), 5-H), 6.62 (2H,s,1- and 2-H), 7.00 (1H,d,J 8Hz, 8-H), and 7.50 (5H,m,ph).

Preparation of the cycloadduct (333) from phenylacetohydroxamic acid and thebaine

Thebaine (1.56 g, 5 mmol) in ethyl acetate (100 ml) and sodium periodate (1.08 g, 5 mmol) in 0.5 M aqueous sodium acetate (100 ml), adjusted to pH 6 with hydrochloric acid, were stirred at 0°C, and phenylacetohydroxamic acid (0.73 g, 5 mmol) was added in small portions over a period of 10 min. The reaction mixture was stirred for a further period of 0.5 h. The ethyl acetate layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 75 ml). The combined ethyl acetate extracts were washed successively with 5% aqueous sodium thiosulphate (100 ml), saturated aqueous sodium hydrogen carbonate (100 ml), and water, and were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield the crude product. This was chromatographed on a short silica HF_{254} Column Elution with Analar chloroform and evaporation of the eluate yielded the cycloadduct (333) (1.75 g), m.p. 146-148°C (from petroleum-benzene) (lit.[99], m-p 146-147°C).

Hydrolysis and rearrangement of the cycloadduct (334a)

The cycloadduct (334a) (500 mg, 1.12 mmol) was treated successively with methanolic hydrochloric acid and sodium methoxide, as described earlier for the cycloadducts (334b) and (334c) of (R) and (S)-

mandelohydroxamic acids. Preparative chromatography on commercial silica GF_{254} t.l.c. plates in Analar ethyl acetate yielded pure thebainone, 5b, 14β(N-phenylacetylepoxyimino) thebainone as a hemihydrate (336a) (260 mg) 112-113°C (from light petroleum-benzene). (Found: C, 68.48; H, 5.88; N, 5.72; m/z 446.1836. $C_{26}H_{26}N_2O_5$. 0.5 H_2O requires C, 68.57; H, 5.83; N, 6.25%; M, 446.1838); ν_{max} ($CHCl_3$) 3540 and 1690 cm^{-1}; δ ($CDCl_3$) 2.45 (3H,s,NMe), 3.80 (5H,s,3-OMe and ph-CH2), 4.27 (2H,d, J 8Hz, 9-H), 5.17 (1H,br s,5-H), 5.78 (1H,d, J 8Hz, 7-H), 6.32 (2H,s,1- and 2-H), 7.00 (1H,d,J 8Hz, 8-H) and 7.50 (5H,s,ph).

Competition reactions between thebaine and nitroso compounds derived from (±)-mandelohydroxamic (328a) acid (1): Thebaine (311 mg, 1 mmol) in ethyl acetate and sodium periodate (432 mg, 2 mmol) in 0.5 M aqueous sodium acetate (25 ml), adjusted to pH 6 with hydrochloric acid, were stirred at 0°C, and (±)-mandelohydroxamic acid (334 mg, 2 mmol) was added in small portions over a period of 10 min. The reaction mixture was stirred for a further 0.5 h then was worked up as described earlier. The ^1H n.m.r. spectrum ($CDCl_3$) of the total reaction product showed the presence of diastereoisomeric cycloadducts (331b) and (331c) in a ratio of ca. 1:1. Chromatographic separation of the mixture gave samples of each adduct approximately in equal amounts by weight, thus the ratio by weights also agreed with the ^1H n.m.r. ratio.

(2): Sodium periodate (432 mg, 2 mmol) in 0.5 M aqueous sodium acetate (25 ml) was stirred at 0°C and a mixture of thebaine (311 mg, 1 mmol) and (±)-mandelohydroxamic acid (334 mg, 2 mmol) in methanol-ethyl acetate was then added in small portions over a period of 10 min.

The reaction mixture was stirred for a further 0.5 h. The usual work of the reaction mixture followed by examination of the crude product by ^1H n.m.r. spectroscopy again revealed the presence of the diastereoisomeric cycloadducts (331b) and (331c) in a 1:1 ratio.

(3): Tetraethylammonium periodate (646 g, 2 mmol) in ethyl acetate (25 ml) was stirred at 0°C and a solution of thebaine (311 mg, 1 mmol) and (±)-mandelohydroxamic acid (334 mg, 2 mol) in methanol-ethyl acetate (5 ml) (1:1) was added in small portions over a period of 10 min. The reaction mixture was stirred for a further 1 h. The usual work, yielded the diastereoisomeric products (331b) and (331c) and the ^1H n.m.r. ($CDCl_3$) spectrum indicated their ratio to be ca. 1:1.

(4): (±)-Mandelohydroxamic acid (334 mg, 2 mmol) and thebaine (311 mg, 1 mmol) were dissolved in methanol (1 ml) and the mixture was diluted with dichloromethane (10 ml). This solution was added dropwise to a stirred solution of tetraethylammonium periodate (646 mg, 2 mmol) in dichloromethane (10 ml) at -78°C. The reaction mixture was stirred at this temperature for a further period of 0.5 h. It was then allowed to warm up to room temperature and stirring continued for 1 h at this temperature. The usual work up followed by examination of the total reaction product in ^1H n.m.r. spectrum ($CDCl_3$) showed the presence of the cycloadducts (331b) and (331c) again in a ca. 1:1 ratio.

Preparation of the cycloadduct (337) from cyclo-pentadiene and phenylacetohydroxamic acid

Freshly distilled cyclopentadiene (198 mg, 3 mmol) in ethyl acetate (50 ml) and sodium periodate (645 mg, 3 mmol) in 0.5 M aqueous sodium

acetate (50 ml), adjusted to pH 6 with hydrochloric acid, were stirred at 0°C, and phenylacetohydroxamic acid (453 mg, 3 mmol) was added to the mixture in small portions over a period of 10 min. The reaction mixture was stirred for a further 0.5 h and the usual work up afforded a crude product. This was chromatographed on a short silica HF_{254} column. It was eluted with Analar chloroform and evaporation of the elutate under reduced pressure yielded 3-phenylacetyl-2-oxa-3-azabiccyclo [2.2.1]hept-5-ene (337) (375 mg, 60%) as a yellowish gum. (Found: m/z 215.0945. $C_{13}H_{13}NO_3$ requires M, 215.1062); ν_{max} ($CHCl_3$) 1650 cm^{-1}; δ ($CDCl_3$) 1.63-1.93 (2H,m,7-CH_2), 3.60 (2H,s,PhCH_2), 5.25 (2H,br s,1- and 4-H), 6.23-6.42 (2H,br s,5- and 6-H), and 7.25 (5H,s,ph).

Preparation of the cycloadducts (338a) and (339a) from cyclopentadiene and (±)-mandelohydroxamic acid

The foregoing experiment was repeated but this time with (±)-mandelohydroxamic acid (500 mg, 3 mmol). The usual work up afforded the mixture of diastereoisomers (338a) and (339a) (468 mg, 68%) as a gum. (Found: m/z 231.0905. $C_{13}H_{13}NO_3$ requires M, 231.0891); ν_{max} ($CHCl_3$) 3450 and 1650 cm^{-1}; δ ($CDCl_3$) 1.60-1.93 (2H,m,7-CH_2), 4.25 (1H,br s,0H exch. with D_20), 5.25 (3H,t, side chain-CH overlapping with signals from 1- and 4-H), 5.60 (1H,br s,5- and 6-H), 6.35 (1H,br s,5- and 6-H), and 7.30 (5H,m,ph). Owing to the overlapping of the signals, the ratio of the diastereoisomers could not be ascertained and separation of the diastereoisomers could not be achieved by t.l.c.

Acetylation of the cycloadducts (338a) and (339a)

The foregoing mixture of the cycloadducts (338a) and (339a) (250 mg, 1.17 mmol) and acetic anhydride (300 mg, 2.97 mmol) in pyridine (5

ml) were stirred at room temperature overnight. The reaction mixture was diluted with water (10 ml), to decompose the excess of acetic anhydride, and extracted with chloroform (3 x 20 ml). The chloroform extracts were washed successively with dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water, and were dried ($MgSO_4$) and filtered. The filtrate was evaporated under reduced pressure to yield a crude product. This was chromatographed on a short silica HF_{254} column. It was eluted with Analar chloroform. Evaporation of the eluate yielded the O-acetyl derivatives (338b) and (339b) (300 mg) (84%) as a gum. (Found: m/z 273.0996. $C_{15}H_{15}NO_4$ requires M 273.0993)); ν_{max} ($CHCl_3$) 1675 and 1740 cm^{-1}; δ ($CDCl_3$) 1.65-2.00 (2H,m,7-CH_2), 2.15 (3H,s,Ac), 5.15 (1H,br s, 1- and 4-H), 5.30 (2H,br s, 1- and 4-H), 5.35 (1H,br s,1- and 4-H), 5.75 (1H,br s, 5- and 6-H), 5.95 1H,s, side chain-CH), 6.10 (1H,s, side chain-CH), 6.25 (1H,br s,5- and 6-H), 6.45 (1H,br s, 5- and 6-H), 6.60 (1H-br s,5- and 6-H), and 7.50 (5H,m,ph). Separation of the diastereoisomers could not be achieved by t.l.c. However, the integration of the olefinic and side chain signal in the ^1H n.m.r. spectrum ($CDCl_3$) of the total reaction mixture indicated the ratio of the O-acetyl derivatives to be 5.1:1.

Benzoylation of the cycloadducts (338a) and (339a)

The foregoing experiment for the formation of O-acetyl derivatives (338b) and (339b) was repeated but with benzoyl chloride (180 mg, 1.28 mmol) instead of acetic anhydride. The usual work up afforded the O-benzoyl derivatives (338c) and (339c) (270 mg, 80%) as a yellowish gum. (Found: m/z 335.1132. $C_{20}H_{17}NO_4$ requires M, 335.1152); ν_{max} ($CHCl_3$) 1675 and 1740 cm^{-1}; δ ($CDCl_3$) 1.70-2.20 (4H,m,7-CH_2), 5.20 (2H,br s,1- or 4-H), 5.40 (2H,br s,1- or 4-H), 5.85 (2H,br s,5- or 6-H), 6.20 (4H,m,side

chain-CH overlapping with 5- or 6-H), and 7.50 (5H,m,ph). The separation of the diastereoisomeric cycloadducts was not achieved on t.l.c. and owing to overlapping of the ^1H n.m.r. signals, the ratio could not be measured.

Preparation of the cycloadducts (340a) and (341a) from cyclohexa-1,3-diene and (±)-mandelohydroxamic acid

(±)-Mandelohydroxamic acid (501 mg, 3 mmol) was oxidised with aqueous sodium periodate (1 mol equiv.) in a usual way, in the presence of cyclohexa-1,3-diene (240 mg, 3 mmol).Usual work up yielded a mixture of the diastereoisomers (340) and (341) (393 mg, 55%) as a gum. (Found: m/z 245.1514. $C_{14}H_{15}NO_3$ requires M, 245.1515); ν_{max} ($CHCl_3$) 3490 and 1635 cm^{-1}; δ ($CDCl_3$) 1.30 (br s,7- or 8-CH_2) and 1.50 (br,s,7- or 8-CH_2), 2.10 (br s,7- or 8-CH_2), 2.20 (br s,7- or 8-CH), 4.15 (2H,br s,OH, exch. with D_20), 4.55 (2H,br s,1- or 4-H), 5.10 (br s,1- or 4-H overlapping with side chain CH), 5.30 (br s,1- or 4-H overlapping with side chain-CH), 5.90-6.10 (2H,t,J 6Hz, 5- or 6-H), 6.30-6.50 (1H,t,J 6Hz, 5- or 6-H), and 7.35 (m,ph). No separation of the stereoisomers was achieved on t.l.c. Owing to the overlapping of the signals, in the ^1H n.m.r. spectrum, the ratio of the diastereoisomeric cycloadducts could not be measured.

Acetylation of the cycloadducts (340) and (341)

The mixture of the cycloadducts (150 mg, 0.61 mmol) in pyridine (5 ml) and acetic anhydride (200 mg, 1.97 mmol), were stirred at room temperature overnight. The reaction mixture was diluted with water (10 ml) to decompose the excess of acetic anhydride, then was extracted with chloroform (2 x 20 ml). The chloroform extract was washed successively

with dilute hydrochloric acid (25 ml), saturated aqueous sodium hydrogen carbonate (25 ml), and water (25 ml), and was dried ($MgSO_4$). The chloroform solution was filtered and evaporated under reduced pressure to yield the crude product which was chromatographed on a short silica column. Elution with Analar chloroform and evaporation of the eluate afforded a mixture of the 0-acetyl derivatives (340b) and (341b) (200 mg, 88%) as a gum. The t.l.c. of the product in light petroleum-ether (1:1) showed two spots and the ^1H n.m.r. spectrum ($CDCl_3$) of the total reaction product showed a set of signals for the 2 diastereoisomeric cycloadducts. The acetate with higher R_f value was the major product. δ ($CDCl_3$, 200 MHz) 1.4-2.25 (7H,m,7- and 8-CH_2 and AC), 4.50 (1H,br s,1- or 4-H), 5.15 (1H,br s,1- or 4-H), 6.10 (2H,t,5- or 6-H,J,6Hz for the major and side chain-CH for the minor isomer), 6.25 (1H,s,side chain-CH for the major isomer), 6.40 (1H,t,J 6Hz, 5- or 6-H for the major isomer), 6.60 (2H,m,5- and 6-H for the minor isomer), and 7.35-7.45 (5H,m,ph). The ratio, ca. 3.5:1, was measured from the integration of the signals for the olefinic protons and those of the side chain-CH for the two diastereoisomeric cycloadducts in the total reaction product.

Chromatographic separation of the cycloadducts

The mixture of the 0-acetyl cycloadducts (340b) and (341b) (144 mg) was chromatographed on commercial silica GF_{254} t.l.c. preparative plates in light petroleum-ether (1:1). Multiple developments in Analar light petroleum-ether led to the separation of the diastereoisomers (340b) and (341b). These diastereoisomers were obtained approximately in the same ratio by weight as was determined from the ^1H n.m.r. spectrum ($CDCl_3$) of the total reaction product. The acetate with higher R_F was the major component, 3,(2-phenyl-2-acetoxy acetyl)-2-oxa-3-azabicyclo

[2.2.2] oct-5-ene [racemate of (341b)], was obtained as a gum (Found: m/z 287.1149. $C_{16}H_{17}NO_4$ requires M, 287.1152); ν_{max} ($CHCl_3$) 1635 and 1738 cm^{-1}; δ ($CDCl_3$) 1.45 (2H,br d,7- and 8-CH_2), 2.00 (3H,s,AC), 2.25 (2H,br d,7- and 8-CH_2), 4.50 (1H,br s,1- or 4-H), 5.15 (1H,br s,1- or 4-H), 6.10 (1H,t,J 6Hz 5- or 6-H), 6.25 (1H,s,side chain-CH), 6.40 (1H,t,J 6Hz5- or 6-H), and 7.35 (5H,m,Ph). The acetate with lower R_F was the minor component, 3-(2-Phenyl-2-acetoxy acetyl)-2-oxa-3- azabicyclo [2.2.2] oct-5-ene [racemate of (340)], was also obtained as a gum (Found: 287.1149. $C_{16}H_{17}NO_4$ requires M, 287.1152); ν_{max} ($CHCl_3$) 1635 and 1738 cm^{-1}; ($CDCl_3$) 1.40-2.85 (7H,br m,7- and 8-CH_2 and Ac), 4.50 (1H,br s,1- or 4-H), 5.15 (1H,br s,1- or 4-H), 6.15 (1H,s,side chain-CH), 6.60 (2H,m,5- and 6-H), and 7.35 (5H,m,Ph).

Preparation of (±)-hexahydromandelic acid[101] (343)

(±)-Mandelic acid (15.0 mg, 0.09 mmol) and 5% rhodium-on-alumina (3.0 g) in absolute methanol (80 ml) and acetic acid (1 ml) was hydrogenated in an autoclave at room temperature and a pressure of 1000 p.s.i., for 16 h. The reaction mixture was then filtered and concentration of the filtrate under reduced pressure yielded (±)-hexahydromandelic acid (13.0 g, 88%), m.p. 135-136°C (from ethylacetate-light petroleum), (lit. m.p. 135-136°C).

Preparation of methyl (±)-hexahydromandelate (344)

Acetyl chloride (6.43 g, 0.022 mmol) was added to an ice-cooled solution of (±)-hexahydromandelic acid (10.0 g, 0.06 mmol) in methanol (50 ml) and the mixture was refluxed overnight. Methanol was evaporated off and the residue was dissolved in chloroform. The chloroform solution was washed successively with saturated aqueous sodium hydrogen

carbonate and water, and dried ($MgSO_4$). Evaporation of the chloroform yielded methyl (±)-hexahydromandelate (9.0 g, 87%) as an oil.

Preparation of (±)-hexahydromandelohydroxamic acid (345)

Hydroxylamine hydrochloride (4.0 g, 0.057 mol) and methyl (±)-hexahydromandelate (7.0 g, 0.04 mol) were allowed to react in the presence of 10 M sodium hydroxide, according to Sandlar and Karo's method. The usual work up afforded (±)-hexahydromandelohydroxamic acid (345) (5.0 g, 72%), m.p. 181-182°C (from light petroleum-ethyl acetate). (Found: C, 55.43; H, 8.77; N, 9.97; m/z 173.1054. $C_8H_{15}NO_3$ requires C, 55.49; H, 8.67; N, 8.09%; M, 173.1052); ν_{max} (kBr) 3458 and 1600 cm^{-1}; δ (CD_3OD) 0.0-1.20 (11H,m,cyclohexyl-H), 3.85 (1H,d,side chain-CH), 4.90 (2H,br s,NH and 0H, exch. with CD_3OD).

Preparation of the cycloadducts (347) and (348) from cyclopentadiene and (±)-hexahydromandelohydroxamic acid

Cyclopentadiene (122 mg, 2 mmol) in ethyl acetate (50 ml) and sodium periodate (432 mg, 2 mmol) in 0.5 M aqueous sodium acetate (50 ml), adjusted to pH 6 with hydrochloric acid, were stirred at 0°C, and (±)-hexahydromandelohydroxamic acid (346 mg, 2 mmol) was added in small portions over a period of 10 min. The reaction mixture was stirred for a further 0.5 h. The ethyl acetate layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 40 ml). The combined ethyl acetate extracts were washed successively with 5% aqueous sodium thiosulphate (100 ml), saturated aqueous sodium hydrogen carbonate (100 ml), and water, and were dried ($MgSO_4$) and filtered. The filtrate was evaporated under reduced pressure to yield a crude cycloadduct mixture. This was chromatographed on a short silica HF_{254} column. It was eluted

with Analar chloroform, and evaporation of the eluate yielded the pure mixture of diastereoisomers (400 mg, 80%) as a gum. T.l.c. in light petroleum- ether (1:1) showed two spots and the ^1H n.m.r. spectrum ($CDCl_3$) of the total reaction product also showed sets of signals for 2 diastereoisomeric products. The fast running component was the minor isomer (348) and the slow running component was the major isomer (347). δ ($CDCl_3$) 0.5-2.10 (26H,br,m,cyclohexyl-H and 7-CH_2), 3.35 (2H,br s,0H, exch. with D_20), 3.90 (1H,d,side chain-CH for the minor isomer), 4.15 (1H,d,side chain-CH for the major isomer), 5.40 (4H,br s,1- and 4-H), and 6.40-6.55 (4H,m,5- and 6-H). The ratio of the two diastereoisomeric cycloadducts was ca. 3.5:1 as measured from the integration of the side chain-CH signals in the ^1H n.m.r. spectrum ($CDCl_3$).

Chromatographic separation of the cycloadducts (347) and (348)

The foregoing mixture of cycloadducts (347) and (348) (240 mg, 1.02 mmol) was chromatographed on commercial silica GF_{254} preparative t.l.c. plates using Analar ether light petroleum (1:1). Multiple elutions in ether and light petroleum led to the separation of the cycloadducts (347) and (348), approximately in the same ratio by weight as was determined from the ^1H n.m.r. spectrum ($CDCl_3$) of the total reaction product.The minor cycloadduct, 3-(-2-cyclohexyl-2-hydroxy)-acetyl-2-oxa-3-aza-bicyclo[2.2.1]hept-5-ene (348), having the higher R_F value, was obtained as a gum. (Found: m/z 237.1365. $C_{13}H_{19}NO_3$ requires M, 237.1359); ν_{max} ($CHCl_3$) 3495 and 1640 cm^{-1}; δ ($CDCl_3$) 0.75-2.00 (13H,m,cyclohexyl-H and 7-CH_2), 3.40 (1H,br s,0H exch. with D_20), 3.90 (1H,d,side chain-CH), 5.40 (2H,br s,1- and 4-H), and 6.45-6.50 (2H,m,5- and 6-H). The slow running, major component 3-(2- cyclohexyl-

2-hydroxyl)-acetyl-2-oxa-3-aza bicyclo [2.2.1]hep.5-ene (347) was also obtained as a gum. (Found: m/z 237.1355. $C_{13}H_{19}NO_3$ requires M, 237.1359); ν_{max} ($CHCl_3$) 3495 and 1640 cm^{-1}; δ ($CDCl_3$) 0.5-2.00 (13H,m,cyclohexyl-H and 7-CH_2), 3.0 (1H,br s,0H exch. with D_20), 4.15 (1H,d,side chain-CH), 5.40 (2H,br s,1- and 4-H), and 6.40-6.55 (2H,m,5- and 6-H).

Preparation of the cycloadducts (349) and (350) from cyclohexa-1,3-dieneand (±)-hexahydromandelohydroxamic acid

The foregoing experiment was repeated with cyclohexa-1,3-diene (80 mg, 1 mmol) and (±)-hexahydromandelohydroxamic acid (173 mg, 1 mmol). The usual work up afforded a mixture of the diastereoisomers (349) and (350) (136 mg, 55%) as a gum. Separation of the diastereoisomeric products could not be achieved on t.l.c. (Found: m/z 251.1514. $C_{14}H_{21}NO_3$ requires M, 251.1520); ν_{max} ($CHCl_3$) 3490 and 1635 cm^{-1}; δ ($CDCl_3$) 1.00-2.30 (30H,m,cyclohexyl-H and 7- and 8-CH_2), 3.35 (2H,br s,0H exch. with D_20), 4.05 (1H,d,side chain-CH for the minor diastereoisomer), 4.20 (1H,d,side chain-CH for the major diastereoisomer), 4.80 (2H,br s,1- and 4-H), 5.25 (2H,br s,1- and 4-H), and 6.50-6.80 (4H,m,5- and 6-H). A ratio of ca. 2.5:1 for the two diastereoisomeric products was measured from the integration of the side chain-CH signals at δ 4.20 and 4.05, respectively.

Oxidation of pinacolone to 3,3-dimethyl-2-oxobutanoicacid[103](352)

A solution of potassium permanganate (160.0 g) and sodium hydroxide (50.0 g) in water (1500 ml) was added dropwise over a period of 3 h to a stirred suspension of pinacolone (50.0 g) in water (150 ml) at room temperature. The reaction mixture was stirred for a further period of 4 h and the solution was examined from time to time until the permanganate colour had disappeared. Manganese dioxide was allowed to settle out of the colourless solution so obtained for 2 h. The clear, colourless supernatant solution was decanted off. The solid residue was washed several times with water and the combined supernatant and washings were acidified with sulphuric acid. The acidified solution was then concentrated under reduced pressure. The aqueous concentrate was extracted with ether (3 x 400 ml). The ether extracts were washed with water, and were dried ($MgSO_4$), filtered, and evaporated to yield a viscous liquid. The ^1H n.m.r. spectrum of this liquid showed the presence of the desired keto acid (352), along with a by-product, trimethylacetic acid (353), in a 3:1 ratio. This mixture of acids (352) and (353) failed to separate either by t.l.c. or by vacuum distillation. It was used as such in the following experiment.

Reduction of 3,3-dimethyl-2-oxo-butanoic acid (352)

Sodium borohydride (3.0 g) was added slowly with stirring at room temperature to the mixture of acids (13.00 g). After the addition of sodium borohydride, the reaction mixture was stirred for 1 h. Then methanol was evaporated off and the solid residue was dissolved in water. The aqueous solution was acidified with methanolic hydrochloric acid and extracted with ether (3 x 50 ml). The combined ether extracts were washed with water, dried ($MgSO_4$) and filtered. The filtrate was

evaporated to dryness to yield a semi-solid residue. Examination of the residue by ^1H n.m.r. spectroscopy showed the presence of the hydroxy acid (354), along with trimethylacetic acid. Crystallisation of the mixture from light petroleum-ethyl acetate yielded the pure (±)-3,3-dimethyl-2-hydroxybutanoic acid (354) (5.0 g), m.p. 86-87°C, (lit. m.p. 88°C). Evaporation of the mother liquors yielded trimethylacetic acid (353) (1.5 g) as a liquid.

Esterification of (±)-3,3-dimethyl-2-hydroxybutanoic acid (354)

Diazomethane (prepared from Nitrosan, ethylene glycol and sodium hydroxide in ether) was passed through a solution of (±)-3,3-dimethyl-2-hydroxybutanoic acid (3.0 g) in dry ether (10 ml) until the solution became yellow. The solution was stirred at room temperature for a period of 1 h. Ether was then distilled off at room temperature. Examination of the residue by ^1H n.m.r. ($CDCl_3$) spectroscopy revealed that the desired ester, methyl 3,3-dimethyl-2-hydroxy butanate (355) was pure enough for further use.

Preparation of (±)-3,3-dimethyl-2-hydroxybutano-hydroxamic acid (356)

Hydroxylamine hydrochloride (2.5 g, 0.037 mol) and methyl (±)-3,3-dimethyl-2-hydroxybutanoate (4.0 g, 0.027 mol) were allowed to react according to Sandlar and Karo's method[97]. The usual work up afforded (±)-3,3-dimethyl-2-hydroxybutanohydroxamic acid (356) (2.00 g, 50%), m.p. 134-135°C (from light petroleum-ethyl acetate). (Found: C, 48.97; H, 8.69; N, 9.49; m/z 147.0889. $C_6H_{13}N0_3$ requires C, 48.97; H, 8.84; N, 9.52%; M, 147.0891);

ν_{max} (kBr) 3235 and 1630 cm^{-1}; δ ($CDCl_3$) 0.95 (9H,s,But), 3.69 (1H,s,CH), and 4.75 (2H,br s,0H and NH, exch. with CD_3OD).

Preparation of the cycloadducts (357) and (358) from (±)-3,3-dimethyl-2-hydroxybutanohydroxamic acid and cyclohexa-1,3-diene

Cyclohexa-1,3-diene (240 mg, 3 mmol) in ethylacetate (50 ml) and sodium periodate (656 mg, 3 mmol) in 0.5 M aqueous sodium acetate (50 ml), adjusted to pH 6 with hydrochloric acid, were stirred at 0°C, and (±)-3,3-dimethyl-2-hydroxybutanohydroxamic acid (441 mg, 3 mmol) was added in small portions over a period of 10 min. The reaction mixture was stirred for a further 0.5 h. The ethyl acetate layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 40 ml). The combined ethyl acetate extracts were washed successively with 5% aqueous sodium thiosulphate (50 ml), aqueous saturated sodium hydrogen carbonate (50 ml), and water, and were dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford a crude product. It was purified by elution through a short silica HF_{254} column with Analar chloroform. The eluate was evaporated to yield a mixture of the diastereoisomers (357) and (358) (393 mg, 58%) as a gum. (Found: m/z 225.1350. $C_{12}H_{19}N0_3$ requires M, 225.1359); ν_{max} 3500 and 1622 cm^{-1}; δ ($CDCl_3$) 0.87 (9H,s,But for the major component), 0.92 (S,But for the minor component), 1.25-1.65 (4H,m,7- or 8-CH_2), 2.00-2.4 (4H,m,7- or 8-CH_2), 4.05 (1H,s,HOCH for the minor component), 4.15 (1H,s,HOCH for the major component), 4.25 (2H,br s, OH, exch. with D_20), 4.75 (2H, br s, 1- or 4-H), 5.30 (2H, br s, 1- or 4-H) 6.40-6.60 (4H,m,5- and 6-H). Separation of the diastereoisomers could not be achieved on t.l.c. The ratio, ca. 4.6:1, was measured from the integration of the HOCH signals for

minor and major isomers in the ^1H n.m.r. spectrum ($CDCl_3$) of the total reaction product.

Preparation of the cycloadducts (357) and (358) using lead tetra acetate as an oxidising agent

(1) The foregoing experiment for the formation of the cycloadducts (357) and (358) from cyclohexa-1,3-diene and (±)-3,3-dimethyl-2-hydroxybutanohydroxamic acid was repeated but with equivalent amount of lead tetra acetate as an alternative to the tetraethylammonium periodate as oxidising agent. The usual work up yielded a mixture of diastereoisomers (357) and (358). Examination of this mixture by ^1H n.m.r. spectroscopy showed a ratio of ca. 1.40:1, (cf. 4.6:1 when tetraethylammonium periodate was used as an oxidising agent).

(2) A solution of cyclohexa-1,3-diene (80 mg, 1 mmol) and (±)-3,3-dimethyl-2- hydroxybutanohydroxamic acid (147 mg, 1 mmol) in methanol (1 ml) was diluted with dichloromethane (10 ml). This solution was added dropwise to a stirred solution of lead tetra acetate (443 mg, 1 mmol) in dichloromethane (10 ml) at 0°C. The usual work up afforded a mixture of diastereoisomers (357) and (358), which on examination by ^1H n.m.r. spectroscopy showed the same ratio, i.e. 1.40:1, for the two isomers.

Preparation of the cycloadducts (359) and (360) from cyclopentadiene and (±)-3,3-dimethyl-2-hydroxy-butanoic acid

(±)-3,3-Dimethyl-2-hydroxybutanohydroxamic acid (294 mg, 2 mmol) was oxidised by usual way in the presence of cyclopentadiene (122 mg, 2 mmol) to give the mixture of diastereoisomeric products (359) and (360) (320 mg, 75%) as gum. T.l.c. of this mixture in light petroleum-ether

showed two spots and the ^1H n.m.r. spectrum ($CDCl_3$) showed a set of signals for the diastereoisomeric cycloadducts. The component with lower R_F value was the major product: δ ($CDCl_3$) 0.90 (9H,s,But for the minor component), 0.95 (9H,s,But for the major component), 1.80-1.90 (4H,m,7-CH_2), 3.90 (1H,s,HO-CH for the minor component), 4.05 (1H,s,HO-CH for the major component), 4.25 (br,s,OH, exch. with D_2O), 5.35 (4H,br s,1- and 4-H), and 6.30-6.60 (4H,m,5- and 6-H). The ratio ca. 3.30:1 was measured, from the integration of HO-CH and But signals for the two diastereoisomeric cycloadducts.

Chromatographic separation of the cycloadducts (359) and (360)

The foregoing mixture of cycloadducts (150 mg) was chromatographed on commercial preparative silica GF_{254} t.l.c. plates in Analar ether-light petroleum (1:1). Multiple elutions led to the separation of the cycloadducts (359) and (360) approximately in same ratio (3.30:1) by weight as was determined from the integration in the ^1H n.m.r. spectrum of the mixture. The component with higher R_F value was the minor product.,3-(2-tert-butyl- 2- hydroxyacetyl)- 2-oxa-3-aza-bicyclo [2.2.1]hept-5-ene (360) was obtained as a gum. (Found: m/z 211.1195. $C_{11}H_{17}NO_3$ requires M, 211.1203); ν_{max} ($CHCl_3$) 3500 and 1626 cm^{-1}; δ ($CDCl_3$) 0.90 (3H,s,But), 1.92 (2H,m,7-CH_2), 8.15 (1H,br s,OH, exch. with D_20), 3.90 (1H,s,HOCH), 5.35 (2H,br s,1- and 4-H), and 6.25-6.40 (2H,m,5- and 6-H). The component with lower R_F value was the major compound. 3-(-2- tert.- butyl- 2- hydroxyacetyl)-2-oxa-3-aza - bicyclo[2.2.1]

hept-5-ene (359) was obtained as a gum. (Found: m/z 211.1207. $C_{11}H_{17}NO_3$ requires M, 211.1203); ν_{max} 3500 and 1625 cm^{-1}; δ ($CDCl_3$) 0.95 (3H,s,But), 1.92 (2H,m,7-CH_2), 3.25 (1H,br s,OH, exch. with D_20),

5.35 (2H,br s,1- and 4-H), and 6.20-6.40 (2H,m,5- and 6-H).

Preparation of (±)-O-methylmandelic acid[104] (362)

A solution of sodium hydroxide (43.0 g) in distilled water (150 ml) was heated to 45°C and (±)-mandelic acid (12.0 g) was added to it to give a clear solution. Dimethyl sulphate (21 ml) was added dropwise over a period of 2 h. During the addition of dimethyl sulphate, the temperature of the reaction mixture was maintained between 45 and 50°C, 20 min after the addition of dimethyl sulphate, the O-methyl derivative of (±)-mandelic acid started precipitating out as its sodium salt. Complete precipitation was achieved in 2 h. The precipitate was filtered off and was dissolved in hot water (30 ml). The clear solution so obtained was acidified with hydrochloric acid to pH 3, and cooled. The resulting precipitate was collected to yield (±)-O-methylmandelic acid (362), m.p. 70-71°C (from light petroleum) (lit. m.p. 71-72°C).

Preparation of methyl (±)-O-methylmandelate (363)

(±)-O-Methylmandelic acid (13.0g, 0.078 mol) in methanol (50 ml) was treated with acetyl chloride (6.43 g, 0.082 mol) with cooling at 0°C. The reaction mixture was then refluxed overnight. The methanol was evaporated off and the residue was dissolved in chloroform and the chloroform solution was washed successively with saturated aqueous hydrogen carbonate and water, and was dried ($MgSO_4$). The solution was filtered and evaporated. The residue was passed through a short silica HF_{254} column and eluted with Analar chloroform. The evaporation of the eluate yielded methyl (±)-O-methyl mandelate (363) (13 g, 92%) as an oil.

Preparation of O-methyl-(±)-mandelohydroxamic acid (364)

Methyl O-methyl-(±)-mandelate (8.5 g, 0.047 mol) and hydroxylamine hydrochloride (4.0 g, 0.057 mol) were allowed to react in the presence of 10 M sodium hydroxide according to Sandlar and Karo's method[98]. The usual work up yielded O-methyl-(±)- mandelohydroxamic acid (364) (4.75 g, 56%), m.p. 139-140°C (from light petroleum-ethyl acetate) (Found: C, 59.85; H, 6.05; N, 7.69; m/z 181.1188. $C_9H_{11}NO_3$ requires C, 59.66; H, 6.12; N, 7.77%; M, 181.1900); ν_{max} (kBr) 1635 cm^{-1}; δ (CD_3OD) 3.35 (3H,s,OMe), 4.60 (1H,s,side chain-CH), 4.80 (2H,br s,NH and OH, exch. with CD_3OD), and 7.40 (5H,m,ph).

Preparation of the cycloadducts (365) and (366) from O-methyl-(±) mandelohydroxamic acid and cyclohexa-1,3-diene

Cyclohexa-1,3-diene (240 mg, 3 mmol) in ethyl acetate and sodium periodate (656 mg, 3 mmol) in 0.5 M aqueous sodium acetate (50 ml), adjusted to pH 6 with hydrochloric acid, were stirred at 0°C and O-methyl-(±)-mandelohydro-
xamic acid (643 mg, 3 mmol) was added in small portions over a period of 10 min. The reaction mixture was stirred for a further 0.5 h. The ethyl acetate layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 40 ml). The combined ethyl acetate layers were successively washed with 5% aqueous sodium thiosulphate (125 ml), saturated aqueous sodium hydrogen carbonate (150 ml), and water, and were dried ($MgSO_4$). The solution was filtered and evaporated under reduced pressure to afford the curde cycloadduct mixture. This was chromatographed on a short, silica HF_{254} column. It was eluted with Analar chloroform. Evaporation of the eluate yielded the mixture of diastereoisomers (365) and (366) (450 mg, 59%) as a gum. (Found: m/z

259.1650. $C_{15}H_{17}NO_3$ requires M, 259.1655); ν_{max} ($CHCl_3$) 1632 cm^{-1}; δ ($CDCl_3$, 200 MHz) 1.30 (4H,m,7- and 8-CH_2), 2.00-2.30 (4H,m,7- and 8-CH_2), 3.30 (6H,s,OMe), 4.60 (2H,s,1- and 4-H), 5.00 (1H,s,side chain-CH for the minor component), 5.05 (1H,s,side chain-CH for the major component), 5.20 (2H,br s,1- and 4-H), 5.90-6.70 (4H,5- and 6-H), and 7.30 (5H,m,ph). The diastereoisomers could not be separated by t.l.c. However the ratio, ca, 2.1:1, was measured from the integration of the side chain-CH signals of the two diastereoisomers at δ 5.05 and 5.00, respectively.

Preparation of the cycloadducts (367) and (368) from cyclopentadiene and O-methyl- (±)-mandelohydroxamic acid

The foregoing experiment for the preparation of cyclo-adducts (365) and (366) was repeated but with cyclopentadiene (122 mg, 2 mmol) and O-methyl-(±)-mandelohydroxamic acid (363 mg, 2 mmol). The usual work up yielded a mixture of the diastereoisomers (367) and (368) (322 mg, 65%) as a gum (Found: m/z 245.1488. $C_{14}H_{15}NO_3$ requires M, 245.1474); ν_{max} ($CHCl_3$) 1637 cm^{-1}; δ ($CDCl_3$, 200 MHz) 1.70-2.10 (4H,m,7-CH_2), 3.35 (3H,s,OMe for the minor component), 3.40 (3H,s,OMe for the major component), 4.90 (1H,s,side chain-CH for the minor component), 5.00 (1H,s,side chain-CH for the major component), 5.10-5.30 (4H,br d,1- and 4-H), 5.70-6.20 (4H,m,5- and 6-H), and 7.35 (5H,m,ph). The separation of the diastereoisomeric products could not be realised on t.l.c. However, it was possible to measure the ratio, ca.2.6:1, from the integration of O-methyl and side chain-CH signals for the two

products at δ 3.40 and 3.35 and 5.00 and 4.90, respectively.

Preparation of the cycloadducts (357) and (358) from (±)-3,3-dimethyl-2- hydroxybutanohydroxamic acid and 1,3-cyclohexadiene at -78°C

(±)-3,3-Dimethyl-2-hydroxybutanohydroxamic acid (294 mg, 2 mmol) in methanol (1 ml) and dichloromethane (10 ml) was added dropwise to cyclohexa-1,3-diene (160 mg, 2 mmol) and tetraethylammonmium periodate (646 mg, 2 mmol) in dichloromethane (40 ml) with stirring at -78°C (acetone-CO_2 bath). The reaction mixture was stirred for a further 0.5 h at -78°C. It was then allowed to warm up to room temperature and stirred at this temperature for a period of 1 hr. The solution was evaporated to dryness and the residue dissolved in dichloromethane (20 ml). The solution was washed successively with 5% aqueous sodium thiosulphate and water, and dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The yellowish gum was chromatographed on a short silica HF_{254} column. It was eluted with Analar chloroform and evaporation of the eluate yielded a pure mixture of the diastereoisomers (357) and (358) (270 mg, 60%). Integration of the HOC<u>H</u> and tert-butyl signals in the ^1H n.m.r. spectrum ($CDCl_3$, 200 MHz) gave a ratio of <u>ca</u>. 11:1 for the diastereoisomeric cycloadducts (357) and (358).

Preparation of the cycloadducts (359) and (360) from (±)-3,3-dimethyl-2-hydroxybutanohydroxamic acid and cyclopentadiene at -78°C

The foregoing experiment for the preparation of cycloadducts (357) and (358) at -78°C was repeated but the nitroso compound derived from

(±)-3,3-dimethyl-2-hydroxy butanohydroxamic acid (294 mg, 2 mmol) were allowed to react this time with cyclopentadiene (122 mg, 2 mmol). The usual work up afforded a mixture of the diastereoisomers (359) and (360) (295 mg, 70%). Integration of the ^1H n.m.r. spectrum ($CDCl_3$) gave a ratio ca. 9.6:1 for the two diastereoisomeric products as judged from the intensity of the HOCH signals.

Preparation of the cycloadducts (349) and (350) from cyclohexa-1,3-diene and (±)-hexahydromandelo-hydroxamic acid at -78°C

The nitroso compounds derived from (±)-hexahydro-mandelohydroxamic acid (173 mg, 1 mmol) was allowed to react with cyclohexa-1,3-diene (80 mg, 1 mmol) by the foregoing procedure described for the corresponding cyclo-pentadiene cycloadducts (359) and (360). The usual work up yielded the mixture of diastereoisomers (349) and (350) (140 mg, 56%). Examination of the mixture by ^1H n.m.r. spectroscopy ($CDCl_3$) gave a ratio ca. 5:1 from the integration of the signals for HOCH at δ 4.20 and 4.05, respectively.

Preparation of the cycloadducts (347) and (348) from cyclopentadiene and (±)-hexahydromandelohydroxamic acid at -78°C

Cyclopentadiene (122 mg, 2 mmol) was allowed to react with the nitroso compounds derived from (±)-hexahydro-mandelohydroxamic acid (546 mg, 2 mol). The products (347) and (348) (393 mg, 83%) obtained after the usual work up were in the ratio ca. 6.3:1, as was judged from the integration of the HOCH signals for the 2 diastereoisomers in the ^1H n.m.r.

spectrum ($CDCl_3$) of the product.

Preparation of the cycloadducts (367) and (368) from (±)-O-methylmandelohydroxamic acid and cyclopentadiene at -78°C

Cyclopentadiene (122 mg, 2 mmol) was allowed to react with the nitroso compound derived from (±)-O-methylmandelo-hydroxamic acid (362 mg, 2 mmol) at -78°C. The usual work up afforded a mixture of diastereoisomers (367) and (368) (308 mg, 63%). The isomer ratio ca. 3.5:1 was measured, as before, from the ^1H n.m.r. spectrum ($CDCl_3$) of the total reaction product.

Preparation of the cycloadducts (365) and (366) from (±)-O-methylmandelohydroxamic acid and cyclohexa-1,3-diene at -78°C

The above experiment for the formation of cycloadducts was repeated but this time with cyclohexa-1,3-diene (160 mg, 2 mmol). The examination of the product by ^1H n.m.r. spectro-scopy indicated, as before, the ratio of the diastereoisomeric products (259 mg, 54%) to be ca. 3.3:1.

Preparation of the cycloadducts (340a) and (341a) from (±)-mandelohydroxamic acid and cyclohexa-1,3-diene at -78°C

The cycloadducts (340a) and (341a) were prepared from cyclohexa-1,3-diene (80 mg, 1 mmol) and (±)-mandelo-hydroxamic acid (167 mg, 1 mmol) as described before but at -78°C. The mixture of diastereoisomeric products (340a) and (341a) (129 mg, 53%) was then acetylated to give

the O-acetyl derivatives (340b) and (341b) as a gum. The ^1H n.m.r. spectrum ($CDCl_3$, 200 MHz) gave the ratio ca. 6.12:1, as judged from integration of the signals for the HOCH and olefinic protons.

Preparation of the cycloadducts (338a) and (339a) from cyclopentadiene and (±)-mandelohydroxamic acid at -78°C

The cycloadducts of cyclopentadiene and (±)-mandelohydroxamic acid were prepared but this time at -78°C. The adducts (338a) and (339a) (164 mg, 71%) were then acetylated in a usual manner to give the O-acetyl derivatives (338b) and (339b). The ratio of isomers, this time ca. 9.6:1, was measured, as before, from the integration of the signals for the HOCH and the olefinic protons in the ^1H n.m.r. spectrum of the total product mixture.

Attempted preparation of the oxazine hydrochlorides (56) from the cycloadducts (340b)

The cycloadducts (340b) (241 mg, 0.98 mmol) were refluxed in 0.1 M sodium methoxide (10 ml, 1 mmol) for 40 min. The reaction mixture was acidified with 0.1 M methanolic hydrogen chloride and evaporated to dryness. The crude, yellowish residue was dissolved in water (10 ml) and extracted with chloroform (3 x 10 ml). The chloroform extract was successively washed with saturated aqueous sodium hydrogen carbonate and water, and dried ($MgSO_4$). The chloroform solution was filtered and evaporated. Examination of the residue by ^1H n.m.r. spectroscopy ($CDCl_3$) showed the presence of methyl (±)-mandelate (327), one of the degradation products of the cycloadduct (340b). When the aqueous solution was evaporated, the ^1H n.m.r. spectrum (CD_3OD) of the residue

showed no signals for the expected product, the oxazaine hydrochloride (56).

Preparation of cyclohexanone oxime[110] (375)

Hydroxylamine hydrochloride (20.0 g) and sodium acetate (32.0 g) were heated to 40°C in water (80 ml). Cyclohexanone (20.0 g) was added. The reaction mixture was shaken vigorously for 5 min then was cooled in ice-cold water to precipitate the crystalline cyclohexanone oxime. The crystals were filtered off and washed with water to yield pure cyclohexanone oxime (357) (9.0 g), m.p. 89-90°C (from light petroleum) (lit m.p. 88).

Preparation of 1-chloro-1-nitrosocyclohexane[105] (58)

Chlorine gas was passed through a solution of cyclohexanone oxime (15.0 g) in dry ether (150 ml) until the precipitate that formed initially had redissolved. The clear solution became greenish blue. The solution was washed with 2 M sodium hydroxide (80 ml) and water, and dried ($MgSO_4$). The ether was evaporated and the blue liquid residue, of unpleasant smell, was then distilled at low pressure (water pump) to give 1-chloro-1-nitrosocyclohexane (58).

Preparation of the racemic oxazine hydrochloride (56)

Cyclohexa-1,3-diene (700 mg, 8.75 mmol) and 1-chloro-1-nitrosocyclohexane (1.5 g, 10.16 mmol) in dry ether (50 ml) and methanol (50 ml) were stirred at 0°C for 15 min. The mixture was then allowed to warm up to room temperature, and was stirred at this temperature overnight. The mixture was evaporated to dryness to yield the crude product. Crystallisation from ethanol-ether yielded the pure, racemic

oxazine hydrochloride (56) (925 mg, 69%), m.p. 149-150°C (from ethanol-ether) (lit., m.p. 147-148°C).

Reaction of the racemic oxazine hydrochloride (56) with sodium methoxide

The racemic oxazine hydrochloride (165 mg, 0.67 mmol) was refluxed in 0.1 M sodium methoxide (24 ml, 2.4 mmol) for 1.5 h. The reaction mixture was acidified with methanolic hydrogen chloride and evaporated to dryness. The solid residue was dissolved in water (10 ml) and made alkaline with saturated aqueous sodium hydrogen carbonate. It was extracted with chloroform (3 x 20 ml). The chloroform extracts were washed with water (50 ml), and dried ($MgSO_4$), filtered and evaporated. The residue was dissolved in methanolic hydrochloric acid and the solution was evaporated to dryness to yield the oxazine hydrochloride (56) (300 mg, 87%).

Preparation of the racemic oxazine hydrochloride (56) from the racemic cycloadducts (340b)

The diastereoisomeric mixture of racemic cycloadduct (340b) (166 mg, 0.67 mmol) in 2 M sodium methoxide (1.34 mmol) was stirred at room temperature overnight. The reaction mixture was acidified with methanolic hydrogen chloride and evaporated to dryness. The residue was dissolved in water. The aqueous solution was extracted with chloroform (3 x 25 ml). The chloroform extract was washed with water, dried ($MgSO_4$), filtered and evaporated. The ^1H n.m.r. spectrum ($CDCl_3$) of the residue showed the presence of methyl (±)-mandelate (327), one

product of the degradation of the cycloadducts (340b). The aqueous layer was made alkaline with saturated aqueous sodium hydrogen carbonate and extracted with chloroform (3 x 60 ml). The chloroform extracts were washed with water and dried ($MgSO_4$), filtered and evaporated. The resulting residue was dissolved in methanolic hydrogen chloride and evaporated to dryness to yield the racemic oxazine hydrochloride (56) (28 mg, 30%), m.p. 147-148°C (from ether-ethanol).

Preparation of the cycloadducts (377a) and (378a) from (S)-(+)-mandelohydroxamic acid and 1,3-cyclohexadiene

Cyclohexa-1,3-diene (240 mg, 3 mmol) in ethyl acetate (50 ml) and sodium periodate (656 mg, 3 mmol) in 0.5M aqueous sodium acetate (50 ml), adjusted to pH 6 with hydrochloric acid, were stirred at 0°C, and (S)-(+)-mandelohydroxamic acid (501 mg, 3 mmol) was added over a period of 10 min. The reaction mixture was stirred for a further 0.5 h. The usual work up afforded the mixture of diastereoisomers (377a) and (378a) (392 mg, 55%) as a gum (Fond: m/z 245.1513. $C_{14}H_{15}NO_3$ requires M, 245.1515), $[\alpha]_D$-15° (c 2.00 in $CHCl_3$); ν_{max} ($CHCl_3$)3490 and 1635 cm^{-1}; δ ($CDCl_3$) 1.30-1.50 (4H,br d, 7- and 8-CH_2), 2.20 (4H,br d,7- and 8-CH_2), 4.25 (2H,br s,0H, exch. with D_20), 4.55 (2H,br s,1- or 4-H), 5.10-5.30 (3H,br d,1- or 4-H overlapping with side chain-CH), 5.90-6.10 (1H,t,J 6Hz, 5- or 6-H), 6.30-6.50 (1H,t,J 6Hz, 5- or 6-H), and 7.35 (5H,m,Ph). The stereoisomers could not be separated on t.l.c., and no separate signals in the ^1H n.m.r. spectrum ($CDCl_3$) were observed for the two diastereoisomeric products. Therefore, the ratio of the diastereoisomers was not measured.

Acetylation of the cycloadducts (377a) and (378a)

The foregoing mixture of the cycloadducts (377a) and (378a) (150 mg, 0.61 mmol) in pyridine (5 ml) containing acetic anhydride (200 mg, 1.97 mmol) were stirred at room temperature. The usual work up afforded the 0-acetyl derivatives (377b) and (378b) (195 mg, 88%) as a gum, which showed two spots on t.l.c. in light petroleum-ether (1:1); $[\alpha]_D$ + 40° (c 1.5 in $CHCl_3$). Its ^1H n.m.r. spectrum ($CDCl_3$) showed 2 sets of signals for the diastereoisomeric cycloadducts; δ ($CDCl_3$) 1.45-2.25 (14H,m,7- and 8-CH_2 and Ac), 4.50 (2H,br s,1- or 4-H), 5.15 (2H,br s,1- or 4-H), 6.10 (2H,t,5- and 6-H for the major isomer, and side chain-CH for the minor isomer), 6.25 (1H,s,side chain-CH for the major isomer), 6.40 (1H,t,5- and 6-H for the major isomer), 6.60 (2H,m,5- and 6-H for the minor isomer), and 7.35-7.45 (5H,m,ph). The ratio, 3.5:1 was measured from the integration of side chain and olefinic proton signals.

Chromatographic separation of the cycloadducts (377b) and (378b)

The mixture of cycloadduct-acetates (160 mg) was chromatographed on commercial preparative silica GF_{254} t.l.c. plates in Analar light petroleum-ether (1:1). Multiple develo-pments led to the separation of the cycloadducts (377b) and (378b). The fast running acetate was found to be the major compound, (1R, 4S)-3-[(2S)-2- phenyl-2-acetoxyacetyl]-2-oxa-3-azabicyclo [2.2.2] oct-5-ene (377b), obtained as a gum (Found: m/z 287.1148. $C_{16}H_{17}NO_4$ requires M, 287.1152); $[\alpha]_D$ + 32° (c 0.75 in $CHCl_3$); ν_{max} ($CHCl_3$) 1653 and 1738 cm^{-1}; δ ($CDCl_3$) 1.45 (2H,br d,J 12Hz, 7- and 8-CH_2), 2.00 (3H,s,Ac), 2.25 (2H,br d, 7- and 8-CH_2), 4.50 (1H,br s, 1- or 4-H), 5.15 (1H,br s, 1- or 4-H), 6.05 (1H,t,J 6Hz, 5- or 6-H), 6.25 (1H,s,side chain-CH), 6.40 (1H,t,J 6Hz, 5- or 6-H), and 7.50 (5H,m,ph). The slow running acetate was the minor compound, (1S, 4R)-3-[2S)-phenyl-2-acetoxy acetyl)-2-oxa-3-aza-bicyclo [2.2.2] oct-5-ene (378b), was also

obtained as a gum. (Found: m/z 287.1155. $C_{16}H_{17}NO_4$ requires M, 287.1152); $[\alpha]_D$ + 62° (C 0.15 in $CHCl_3$); ν_{max} ($CHCl_3$) 1653 and 1738 cm^{-1}; δ ($CDCl_3$) 1.15-1.90 (4H,m, 7- and 8-CH_2), 2.10 (3H,s,Ac), 4.50 (1H,br s,1- or 4-H), 5.20 (1H,br s, 1- or 4-H), 6.15 (1H,s,side chain-CH), 6.60 (2H,m, 5- or 6-H), and 7.55 (5H,m,ph).

The oxazine hydrochloride from the O-acetyl cycloadduct[106] (377b)

The foregoing major O-acetyl cycloadduct (377b) (230 mg, 1.24 mmol) in 2 M sodium methoxide (1.15 ml, 2.28 mmol) was stirred at room temperature overnight. The reaction mixture was acidified with methanolic hydrogen chloride and evaporated to dryness. The residue was dissolved in water and the aqueous solution was extracted with chloroform (3 x 20 ml). The chloroform extracts were washed with water, dried ($MgSO_4$), filtered and evaporated to yield the methyl(S)-mandelate. The aqueous layer was made alkaline with saturated sodium hydrogen carbonate and extracted chloroform (3 x 40 ml). The chloroform extracts were washed with water, dried ($MgSO_4$), filtered and evaporated. The resulting residue was dissolved in 0.1 M methanolic hydrogen chloride (5 ml) and the solution was evaporated to yield (1R, 4S) oxazine hydrochloride (271) (31 mg, 30%), m.p. 161-162°C (lit.[81] m.p. 163°C), $[\alpha]_D$ - 24° (C 1.00 in CH_3OH) (lit. $[\alpha]_D$ -24° (C 1.00 in CH_3OH) (lit. $[\alpha]_D$ - 24°).

Preparation of the methyl ester hydrochloride of (R)-(+)-phenylglycine[111] (380a)

A suspension of (R)-(+)-phenylglycine (5.0 g, 33 mmol) in methanol (50 ml) was stirred at 0°C. Acetyl chloride (3.92 g, 5 mmol) was added dropwise over a period of 10 min. The reaction mixture was stirred at 0°C

for 30 min. and then refluxed overnight. The methanol was evaporated off and the residue was dissolved in methanol and the solution was evaporated to dryness again. Recrystallisation of the solid residue from methanol-ethyl acetate afforded the methyl ester hydrochloride of (R)-phenylglycine (380a) (5.7 g, 87%), m.p. 195-196°C (lit. m.p. 196-197°C).

Preparation of the hydroxamic acid derived from (R)-phenylglycine

Hydroxylamine hydrochloride (2.0 g, 29 mol) and the methyl ester hydrochloride of (R)-phenylglycine (3.0 g, 14.9 mmol) were allowed to react in the presence of 10 M sodium hydroxide according to Sandlar and Karo's method[97]. The usual work up afforded the hydroxamic acid hydrochloride of (R)-phenylglycine (381a) (1.25 g) as a highly hygroscopic solid.

Attempted preparation of the cycloadduct (382a) and (383a) from cyclohexa-1,3,-diene and 2-amino-2-phenylacetohydroxamic acid hydrochloride (381a)

Cyclohexa-1,3-diene (160 mg, 2 mmol) in ethyl acetate (50 ml) and sodium periodate (432 mg, 2 mmol) in aqueous 0.5 M sodium acetate (25 ml), adjusted to pH 6 with hydrochloric acid, were stirred at 0°C, 2-amino-2-phenylacetohydroxamic acid hydrochloride (381a) (405 mg, 2 mmol) in methanol (2 ml) diluted with ethyl acetate (5 ml), was added over a period of 10 min. The reaction mixture was stirred for a further period of 0.5 h. The ethyl acetate layer was separated and the aqueous layer was basified with saturated aqueous sodium hydrogen carbonate. It was then extracted with ethyl acetate (3 x 40 ml). The combined ethyl acetate extracts were worked up in the usual fashion. The ^1H n.m.r. spectrum of the residue showed no signals for the expected cycloadduct. The

spectrum was not fully interpreted because of its complexity.

Attempted preparation of the cycloadducts and from cyclopentadiene and 2-amino-2-phenylacetohydroxamic acid hydrochloride (381a)

The foregoing experiment was repeated but with cyclopentadiene. The usual work up again afforded none of the expected cycloadduct (382a) and (383a).

Attempted preparation of the cycloadduct (382a) and (383a) from cyclohexa1-3-diene and 2-amino-2-phenylacetohydroxamic acid of hydrochloride (381a) using tetraethylammonium periodate

Cyclohexa1-3-diene (160 mg, 2 mmol) and tetraethylammonium periodate (642 mg, 2 mmol) in ethyl acetate (30 ml) were stirred at 0°C, and 2-amino-2-phenyl-
acetohydroxamic acid (405 mg, 2 mmol) in methanol (2 ml) diluted with ethyl acetate (2 ml) was added over a period of 10 min. The reaction mixture was stirred for a further period of 0.5 h. Ethyl acetate was evaporated off and the residue was dissolved in water (10 ml). The aqueous, oily suspension was basified with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate (3 x 30 ml). The ethyl acetate extracts were washed with 5% aqueous sodium thiosulphate and water, dried ($MgSO_4$), and evaporated. The ^1H n.m.r. spectrum ($CDCl_3$) of the residue again showed no signals for the expected cycloadducts (382a) and (383a).

Preparation of N-acetyl-(R)-(+)-phenylglycine[112] (379b)

A suspension of (R)-(+)-phenylglycine (5.0 g, 0.033 mol) in glacial

acetic acid (20 ml) was brought to boiling. It was then removed from the oil bath and acetic anhydride (5.0 g, 0.049 mmol) was added slowly. The mixture was refluxed for 15 min and allowed to cool down to room temperature. Glacial acetic acid was evaporated off under reduced pressure. Water (5 ml) was added to the residue and the mixture was evaporated to dryness. This procedure was repeated. The solid residue was crystallised (methanol-ethyl acetate) to give N-acetyl-(R)-phenylglycine (5.5g, 84%), m.p. 140-141°C (lit. m.p. 139-140°C).

Preparation of the methyl ester of N-acetyl-(R)-(+)-phenylglycine (381b)

N-Acetyl-(R)-phenylglycine (4.00 g, 0.020 mol) in methanol (30 ml) was stirred at 0°C under N_2 and acetyl chloride (2.36 g, 0.030 mol) was added dropwise. The reaction mixture was stirred at 0°C for 15 min. The temperature was then raised to room temperature and stirring was continued for a further 4 h. Methanol was evaporated off. Methanol (10 ml) was added and evaporated off to yield, a viscous liquid, the methyl ester of N-acetyl-(R)-phenylglycine (380b).

Preparation of 2-acetylamino-2-phenylaceto-hydroxamic acid (381b)

Hydroxamine hydrochloride (2.0 g, 0.03 mmol) was allowed to react with the methyl ester of N-acetyl-(R)-phenylglycine (3.0 g, 0.014 mol) in the presence of 10 M sodium hydroxide in the usual way. The usual work up afforded 2-acetylamino-2- phenylacetohydroxamic acid (381b) (1.5 g) as a highly hygroscopic solid (Found: m/z 208.1550. $C_{10}H_{12}N_2O_3$ requires M, 208.1548); ν_{max} ($CHCl_3$) 3425 and 1625 cm^{-1}; δ (CD_3OD-$CDCl_3$) 3.00 (3H,s,Ac), 4.90 (2H,br s,NH and OH, exch. with D_2O), 5.45 (1H,d,J

8Hz,side chain-CH), and 7.35 (5H,m,ph).

Preparation of the cycloadducts (382) and (383) from cyclohexa-1,3-diene and 2-acetylamino-2-phenyl-acetohydroxamic acid (381b)

Cyclohexa-1,3-diene (160 mg, 2 mmol) and tetraethyl-ammonium periodate (642 mg, 2 mmol) in ethyl acetate (25 ml) were stirred at 0°C and 2-acetylamino-2- phenylaceto-hydroxamic acid (381b) (416 mg, 2 mmol) in methanol (2 ml) diluted with ethyl acetate (5 ml), was added dropwise. The usual work yielded a mixture of the diastereoisomers (382b) and (383b) (705 mg, 77%) as a gum (Found: m/z 286.2033. $C_{16}H_{18}N_2O_3$ requires M, 286.2030); ν_{max} ($CHCl_3$) 3420 and 1622 cm^{-1}; δ ($CDCl_3$, 200 MHz) 1.30-1.45 (4H,m,7- or 8-CH_2), 1.90 (3H,s,Ac), 2.10-2.30 (4H,m,7- or 8-CH_2), 4.50 (1H,br s,1- or 4-H), 5.25 (1H,br s,1- or 4-H), 5.75 (1H,d,J 5Hz,side chain-CH), 5.90 (1H,d,J 5Hz,side chain-CH), 6.05 (1H,m,5- or 6-H), 6.45 (1H,m,5- or 6-H), 6.55-6.70 (2H,m,5- and 6-H), 6.95 (1H,br,t,NH), and 7.25-7.50 (5H,m,ph). The diastereoisomeric cycloadducts were not separated on t.l.c. However, the ratio ca. 1:1 was measured by integration of the side chain CH signals in the ^1H n.m.r. spectrum ($CDCl_3$) of the total reaction product (382b) and (383b).

Preparation of (+)-camphorquinone[113] (385)

(+)-Camphor (384) (70.0 g, 0.46 mol) in acetic anhydride (50 ml) containing S_eO_2 (30.0 g) was refluxed under N_2. After 1 h, another portion of S_eO_2 (30.0 g) was added and finally, after a further h, a third portion of S_eO_2 (30.0 g) was added. Thus a total amount of S_cO_2 (90.0 g, 0.81 mol) was used. The solution was refluxed overnight, cooled down to room

temperature, and then filtered. The filtrate was evaporated under reduced pressure. The crystalline residue was dissolved in ether and treated with 7 N aqueous sodium hydroxide at 0°C until basic. The ether layer was separated and the aqueous layer was extracted with ether (3 x 100 ml). The combined ether solutions were washed successively with 1 N sodium hydroxide (250 ml) and water, and were dried ($MgSO_4$), filtered, and evaporated to yield a crude product (69.0 g). Crystallisation from hexane gave camphorquinone (385) (56 g, 74%), m.p. 197-198°C (from hexane) (lit., m.p. 195-196°C)

Preparation of 3,3-ethylenedioxyepicamphor[114] (386a)

Camphorquinone (70.2 g, 429.8 mmol) and ethylene glycol (8.5 g, 137 mmol) were heated to reflux in benzene (100 ml) with toluene sulphonic acid monohydrate (1.1 g, 5.8 mmol) using a Dean and Stark head. The reaction was followed by t.l.c. [hexane-ethyl acetate (3:1)] and stopped when all the starting material had reacted (24 h). The solution was washed with dilute aqueous sodium hydroxide (50 ml) and water (3 x 80 ml) and was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield the crude product (13.64 g). It afforded pure 3,3-ethylenedioxyepicamphor (21.6 g), (from ethanol-water). The mother liquors were evaporated to dryness and the solid was chromatographed on a silica HF_{254} column and eluted with hexane-ethyl acetate (9:1). Evaporation of the eluate yielded a second batch of 3,3-ethylenedioxyepicamphor (37.23 g). Thus the total amount of the product was raised to (58.8 g). In addition to monoacetal, the corresponding diacetal (14.49) was obtained. The pure monoacetal (386a) (35.5 g, 52%), had m.p. 87-88°C (from ethanol-water).

Preparation of 2-exo-hydroxy-3,3-ethylenedioxy-1(S),7,7-trimethylbicyclo [2.2.1.] heptane[60] (387)

The solution of 3,3-ethylenedioxyepicamphor (22.3 g, 0.106 mol) in THF (140 mol) was cooled to -78°C under N_2. After 20 min L-selectride (1M in THF, 127 ml, 127 mmol, 1.2 equivalent) was added dropwise at -78°C with stirring to this solution. The resulting mixture was stirred for 1 h at -78°C. Then the reaction mixture was allowed to warm up to room temperature and was stirred at this temperature overnight. The disappearance of the starting material was followed by t.l.c. It was found that after 21 h all the starting had been consumed. Then saturated aqueous sodium hydrogen carbonate (240 ml) was added at such a rate that the temperature stayed below 10°C. The reaction mixture was then poured into precooled methanol (50 ml) and hydrogen perioxide (120 ml) was then added keeping the temperature below 10°C. The reaction mixture was evaporated and the residue was extracted with dichloromethane (3 x 100 ml). The dichloromethane extract was washed with brine and then with water, and was dried ($MgSO_4$) filtered, and evaporated under reduced pressure to yield an oil. This was passed through a silica HF_{254} column and eluted with n-hexane-ethyl acetate (3:1). The eluate was evaporated to yield pure, 2-exo-hydroxy-3,3-ethylenedioxy-1(S),7,7-trimethylbicyclo[2.2.1]heptane (387) (22.0 g, 99%) as an oil (387).

Attempted preparation of 2-exo(2,2-dimethylprop-oxy)-3,3-ethylenedioxy- 1(S), 7,7-trimethylbicyclo [2.2.1]heptane[60] (388a)

Sodium hydride (55% in oil, 2.18 g, 0.05 mol) was washed three times with pentane under nitrogen and was dried under vacuum. The sodium hydride was suspended in dry distilled N-methylpyrrolidone (20

ml) and was cooled to -15°C. A solution of alcohol (387) (7.1 g, 0.033 mol) in N-methylpyrrolidione (NMP) (20 ml) was added at -15°C, over a period of 15 min. The reaction mixture was allowed to warm up to 0°C, and was stirred at this temperature for 1 h. Then the temperature was raised to room temperature and stirring was continued for a period of 2 h at this temperature. The reaction mixture was then heated to 110°C, and neopentyl bromide (12.7 ml, 11.7 g, 0.1 mol) in NMP (15 ml) was added at 110°C, over a period of 4 h. The temperature was maintained at 110°C for 12 h then was raised to 130°C and the mixture stirred at this temperature for a further period of 18 h. The reaction mixture was allowed to cool to room temperature and then was poured onto ice. The resulting mixture was extracted with ether (3 x 100 ml). The ether extract was washed with saturated aqueous sodium hydrogen carbonate solution and water, and was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The NMP was distilled off at 40°C and 0.1 mmHg. Examination of the residue in the ^1H n.m.r. spectrum ($CDCl_3$) showed the presence of the starting material (387). No signals for the expected alkylated product (388a) were observed.

Attempted preparation of 2-exo-benzyloxy-3,3-ethylenedioxy-1(S), 7,7- trimethylbicyclo[2.2.1]

heptane (388b)

(1): The foregoing experiment for the preparation of the neopentyl derivative of the alcohol (387) was repeated but with benzyl chloride in place of neopentyl bromide. The usual work up again yeilded the starting material.

(2): The foregoing experiment was repeated with benzyl bromide in place of benzyl chloride. The usual work up again afforded the starting material

A suspension of cuprous iodide (1.61 g, 9.2 mmol) in dry distilled tetrahydrofuran (THF) (40 ml) was stirred at -30°C and 1 M phenylmagnesium chloride in THF (40 ml, 80 ml) was added dropwise at -30°C. After 5 min, cyclohexene oxide (5.92 g, 60 mmol) was added to the mixture at -30°C. This temperature was maintained for further 2 h. The reaction mixture was then warmed to room temperature and was stirred for further 2 h. The mixture was then hydrolysed with saturated aqueous ammonium chloride solution and extracted with ether (3 x 100 ml). The ether extract was washed with water, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford the crude product. Distillation at 103°C and 1 mmHg yielded pure trans-2-phenylcyclohexanol (392) (7.56 g, 80%).

Preparation of the chloroformate (393) of trans-2-phenylcyclohexanol

trans-2-Phenylcyclohexanol (6.55 g, 37.47 mmol) was stirred with phosgene (80 mmol) in toluene (70.5 ml) at 0°C for 0.5 h. The mixture was warmed to room temperature and stirred for 3 h. T.l.c. of the reaction mixture in hexane-ethyl acetate (3:1) then showed the presence of trans-2-phenylcyclohexanol along with its chloroformate (393) in a 1:1 ratio. The reaction mixture was stirred for a further 4 h. T.l.c. showed the same composition. The reaction mixture (5 ml) was evaporated under reduced pressure. The ^1H n.m.r. spectrum of the residue showed that trans-2-phenylcyclohexanol (392) and its corresponding chloroformate (393) were in a ca. 1:1 ratio. This ratio was measured from the integrals for HO-CH δ 3.65 and CH-0-COCl, δ 4.80-5.10, respectively.

Preparation of the N-hydroxycarbamic ester (394) of trans-2-

phenylcyclohexanol (392)

The mixture of trans-2-phenylcyclohexanol (392) and its chloroformate (393) was shaken with hydroxylamine hydro-chloride (2.03 g, 30 mmol) and sodium hydroxide (2.4 g, 60 mmol) in water (50 ml), for 6 h at room temperature. The reaction mixture was acidified with dilute hydrochloric acid and extracted with ethyl acetate (3 x 150 ml). The ethyl acetate extracts were washed with water, dried ($MgSO_4$), filtered, and evaporated. T.l.c. of the residue in ethyl acetate showed two spots. The t.l.c. plate was then sprayed with ethanolic ferric chloride solution. The lower spot gave a pink colour. The residue was applied to a silica HF_{254} column and eluted with chloroform. Evaporation of the chloroform eluate yielded pure trans-2-phenylcyclohexanol (392). Elution with chloroform-methanol (3:1) and evaporation of the eluate yielded the N-hydroxycarbamic ester (394) (161 mg) as a gum (Found: m/z 235.1655. $C_{13}H_{17}NO_3$ requires M, 235.1648); ν_{max} ($CHCl_3$) 3400 and 1625 cm^{-1}; δ ($CDCl_3$) 1.3-3.3 (9H,br m,cyclohexyl-H), 4.80-5.20 (1H,br m,^{1}H), 7.10-7.40 (5H,m,ph), and 7.20-8.00 (2H,br s,NH and OH, exch. with D_20).

Preparation of the cycloadduct (395) and (396) from cyclohexa-1,3-diene and the N- hydroxycarbamic ester (394) of trans-2-phenylcyclohexanol at -78°C

Cyclohexa-1,3-diene (80 mg, 1 mmol) and tetraethylammonium periodate (323 mg, 1 mmol) in dichloromethane (10 ml) were stirred at -78°C and the N-hydroxy carbamic ester (394) (160 mg, 0.68 mmol) in methanol (1 ml) and dichloromethane (10 ml) was added dropwise over a period of 10 min. The reaction mixture was stirred at -78°C for a period of 0.5 h. The mixture was warmed to room temperature and stirred at this temperature for 1 h. The usual work up yielded the crude product.

Column chromatography failed to purify the product, therefore it was chromatographed on commercial, preparative t.l.c., silica GF_{254} plates to yield the pure diastereoisomers (395) and (396) (191 mg, 61%) as a gum (Found: m/z 281.1860. $C_{19}H_{23}NO_3$ requires M, 281.1866); ($CDCl_3$, 200 MHz) 1.00-2.70 (28H,br m,cyclohexyl-H and 7- and 8-CH_2) 4.25 (2H,br s,1- or 4-H), 4.50 (2H,br s,1- or 4-H), 4.80 (1H,br m,^{1}H), 5.25 (1H,t,5- or 6-H), 6.15 (m,5- and 6-H), 6.50 (br m,5- or 6-H), and 7.25 (5H,m,ph). No separation of the diastereoisomeric cycloadducts was achieved by t.l.c. However, the ratio ca. 3.56:1, was measured from the integration of signals at δ 5.25, 6.15 and 6.50. The integral for 6.50 showed a single proton for minor product and δ 5.25 for major. The signal at d 6.15, showed overlapping of 5- and 6-H for major and minor both.

Preparation of the cycloadduct (395) and (396) from cyclohexa-1,3-diene and the N- hydroxycarbamic ester (394) at 0°C

Cyclohexa-1,3-diene (80 mg, 1 mmol) in ethyl acetate (20 ml) and sodium periodate (216 mg, 1 mmol) in 0.5 M aqueous sodium acetate (20 ml), adjusted to pH 6 with hydrochloric acid, were stirred at 0°C, and the N-hydroxy carbamic ester (394) (235 mg, 1 mmol) in ethyl acetate (5 ml) was added slowly over a period of 10 min. The reaction mixture was stirred at this temperature for a further 0.5 h. The usual work up afforded a deep brown gum. Its ^{1}H n.m.r. spectrum ($CDCl_3$) showed some additional signals along with the signals expected for the cycloadducts. The residue was then chromatographed on commercial, silica GF_{254} preparative t.l.c. plates. The ^{1}H n.m.r. spectrum ($CDCl_3$) of the purified product again showed those additional signals. The ratio of the diastereoisomeric cycloadducts could not be measured owing to the complexity of the ^{1}H

n.m.r. spectrum.

Preparation of the cycloadducts (395) and (396) from cyclohex-1,3-diene and the N-hydroxycarbamic ester (394) at 0°C

The foregoing experiment for the formation of the cycloadduct was repeated but with tetraethylammonium periodate (323 mg, 1 mmol) as an oxidising agent instead of sodium periodate. The usual work up afforded an impure mixture of the diastereoisomeric cycloadducts (395) and (396). The usual purification method again failed to remove the impurity. Therefore the ratio of the diastereoisomeric products could not be measured.

Attempted preparation of the N-hydroxycarbamic ester (394) of trans-2- phenylcyclohexanol via an N-acrylimidazole intermediate

The chloroformate of trans-2-phenylcyclohexanol (393) (2.5 g, 10.40 mmol), was slowly added to a stirred suspension of imidazole (2.32 g, 34 mmol) and hydroxylamine hydrochloride (1.04 g, 14.76 mmol). The mixture was shaken vigorously at room temperature for 16 h. The mixture was then evaporated to dryness. The solid residue was dissolved in water and acidified with dilute hydrochloric acid. It was then extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The ^1H n.m.r. spectrum of the residue showed signals for the acyl imidazole derivative (397) at δ 4.80-5.25 (br m), 6.90 (1m-H) and 7.90 (1m-H), and no signals for the expected N-hydroxy carbamic ester (394).

Preparation of benzohydroxamic acid (401) from benzoyl chloride using imidazole

Benzoyl chloride (399) (703 mg, 5 mmol) was added slowly with stirring to a solution of imidazole (1.0 g, 15 mol) in dry THF (10 ml). Powdered hydroxylamine hydrochloride (345 mg, 5 mmol) was added and the mixture was shaken vigorously at room temperature for 16 h, then was evaporated to dryness. The resulting solid was dissolved in 1 M sodium hydroxide (40 ml) and extracted with ethylacetate (3 x 50 ml). The aqueous solution was acidified with dilute hydrochloric acid and extracted with ethyl acetate (3 x 60 ml). The ethyl acetate extracts were washed with water, dried ($MgSO_4$), filtered, and evaporated to give a crude product. The crude product after crystallisation (ethyl acetate-light petroleum) yielded benzohydroxamic acid (401) (70%), m.p. 120-121°C (lit. m.p. 122-123°C).

Preparation of benzyl chloroformate (403)

Benzyl alcohol (108 g, 0.092 mmol) was allowed to react with phosgene (1.25 mol) in toluene. The reaction mixture was stirred at room temperature for 3 h then was evaporated to yield benzyl chloroformate (405) (12.0 g, 76%); δ ($CDCl_3$) 5.30 (2H,s,C$\underline{H}_2$-0) and 7.40 (5H,s,ph).

Attempted preparation of phenylacetohydroxamic acid (405) using imidazole

The foregoing preparation of benzohydroxamic acid (401) was repeated but with benzyl chloroformate (850 mg, 5 mmol), imidazole (1.2 g, 18 mmol) and hydroxylamine hydrochloride (450 mg, 6.5 mmol).

However, the same work up yielded no 2-phenylacetohydroxamic acid. Instead the ethyl acetate extract contained signals for the imidazole-N-acyl derivative (404) at δ 5.25 (CH_2), 7.10 (1m-H) and 7.80 (1m-H).

Attempted preparation of benzohydroxamic acid (401) from benzoyl chloride using diethylamine

Hydroxylamine hydrochloride (2.80 g, 40.2 mmol) was suspended in dry distilled THF (5 ml). Diethylamine (2.92 g, 40.6 mmol) in THF (5 ml) was added slowly to the stirred suspension. The reaction mixture was stirred for 15 min by which time all the hydroxylamine hydrochloride had dissolved. Benzoyl chloride (2.40 g, 17.08 mmol) in THF (10 mol) was then added slowly to the reaction mixture, which was stirred for 2 h. The mixture was evaporated to dryness and the residue was dissolved in water. The solution was extracted with ethyl acetate (3 x 30 ml). The ethyl acetate solution was washed with water, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The ^1H n.m.r. spectrum showed the product N,N-diethylbenzamide (403) δ ($CDCl_3$) 1.5 (6H,br t,Me), 3.40 (4H,br s,CH_2) and 7.35 (5H,s,ph) rather than the benzohydroxamic acid (402).

The above experiment was repeated but, before the addition of benzoyl chloride, the precipitate (400), presumably of diethylamine hydrochloride, was filtered off. The usual work up of the reaction mixture again yielded the diethyl benzamide as the sole product.

Preparation of diethylbenzamide (403) from diethylamine and benzoyl chloride

Benzoyl chloride (140 mg) in dry THF (5 ml) was added slowly to a stirred solution of diethylamine (292 mg, 2 mmol) in dry THF (5 ml). The mixture was stirred for 2 h at room temperature and was then evaporated to dryness. The residue was taken in water. The aqueous suspension

washed with water, dried ($MgSO_4$), filtered and evaporated to give an oil (403) (160 mg) (Found: m/z 177.0151. $C_{11}H_{15}NO$ requires M, 177.); √ ($CHCl_3$)1740 cm^{-1}; δ ($CDCl_3$) 1.15 (6H,br t, $(CH_3)_2$), 3.40 (4H,br s, $(CH_2)_2$) and 7.35 (5H,s,ph). The n.m.r. spectrum of the sample showed similar chemical shifts as was recorded in Aldrich Catalogue (δ 1.15 (6H,br s), 3.40 (4H,br s), and 7.35 for ph).

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