SYNTHETIC STUDIES OF SWAZINECIC ACID DILACTONE

THESIS

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by

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ABSTRACT.

The occurrence and syntheses of the pyrrolizidine alkaloids from 1976 to March 1988 is reviewed, and a stereoselective total synthesis of swazinecic acid dilactone was attempted.

One approach involved an asymmetric synthesis of the allylic α-hydroxy acid 2-hydroxy-2,3-dimethyl-3-butenoic acid employing oxazolines as chiral auxilaries. The oxazoline, (4S,5S)-2-(1-bromoethyl)-4-methoxymethyl-5-phenyl-2-oxazoline, was obtained by direct halogenation of the 2-ethyl oxazoline analogue. This was condensed with acetone in a Darzens type reaction and the resultant epoxy oxazoline rearranged to an allylic α-hydroxy oxazoline which was then hydrolysed to the chiral hydroxy acid in low enantiomeric excess.

The hydroxy acid, as the O-silylated ethyl ester, was elaborated by allylic bromination and condensation with diethyl malonate to diethyl 5-carboethoxy-2-methyl-3-methylene-2-O-tert-butyldimethylsilylhexanedioate. Removal of the silyl protecting group and epoxidation provided an epoxy triester, which on hydrolysis provided a mixture of acids of uncertain structures.

1. REVIEW OF THE PYRROLIZIDINE ALKALOIDS 1976 to March 1988

1.1 Occurrence and distribution

The pyrrolizidine alkaloids are a group of compounds of which over three hundred are known to date. The majority of them occur naturally, though an increasing number are derived synthetically or semisynthetically.

The naturally occurring ones are predominantly of plant origin, having been isolated from over four hundred species distributed among seventy-four genera from thirteen plant families.[1-18] The first pyrrolizidine alkaloid isolated was from the genus Senecio.[19] Some one hundred and fifty-three species of this genus and sixty species of the genus Crotalaria are known to contain these alkaloids. The distribution of species within the other pyrrolizidine-containing genera is shown (Table 1).

As could be expected from such species, plants containing pyrrolizidine alkaloids have been found in most parts of the world. This fact, along with the hepatotoxicity of many of the alkaloids, has resulted in considerable losses of live-stock. Human poisoning has also occurred through the ingestion of these alkaloids, from contaminated foodstuffs, and/or traditional herbal remedies and teas.[1,20]

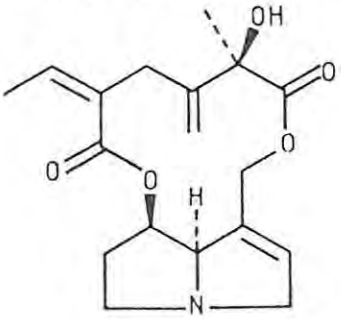
Apart from their occurrence in plants, these alkaloids have been isolated from the hair pencils of Danaid butterflies which have fed on plants rich in these alkaloids.[21-25]

TABLE 1 - Pyrrolizidine containing genera*

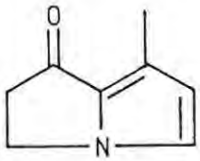
Family	Genera (with number of species investigated)
Apocynaceae	Alafia (1), Anodendron (1), Parsonsia (4), Urechtites (1).
Boraginaceae	Alkanna (1), Amsinckia (4), Anchusa (2), Asperugo (1), Borago (1), Caccinia (1), Cynoglossum (9), Echium (5), Ehretia (1), Hackelia (1), Heliotropium (40), Lappula (2), Lindelofia (8), Lithosperum (1), Macrotomia (1), Messerschmidia (1), Myosotis (2), Paracaryum (1), Paracynoglossum (1), Rindera (4), Solenanthus (4), Symphytum (7), Tournefortia (2), Trachelanthus (2), Trichodesmia (2), Ulugbekia (1).
Celastraceae	Bhesa (1).
Compositae	Adenostyles (3), Brachyglottis (1), Cacalia (5), Conoclinium (1), Crassocephalum (1), Doronicum (2), Echinaceae (2), Emilia (1), Erechtites (1), Eupatorium (6), Farfugium (1), Gynura (2), Jacmaia (1), Kleinia (1), Ligularia (5), Notonia (1), Odontocline (1), Petasites (4), Senecio (153), Syneilesis (1), Tussilago (1).
Euphorbiaceae	Phyllanthus (1), Securinega (1).
Graminae	Festuca (1), Lolium (2), Thelopogon (1).
Leguminosae	Adenocarpus (4), Crotalaria (60), Cytisus (1)
Orchidaceae	Chrysis (1), Doritis (1), Hammarbya (1), Kingiella (1), Liparis (7), Malaxis (2), Phalaenopsis (14), Vanda (4), Vandopsis (2).
Ranunculaceae	Caltha (2).
Rhizophoraceae	Cassipourea (2).
Santalaceae	Thesium (1).
Sapotaceae	Mimusops (1), Planchonella (2).
Scrophulariaceae	Castilleja (3).

* From ref.1 and updated.

Some of the alkaloids ingested are stored unaltered,[22] for example seneciphylline (1), while some are modified to danaidone (2), danaidal (3) and hydroxydanaidal (4).



(1)



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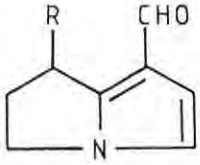
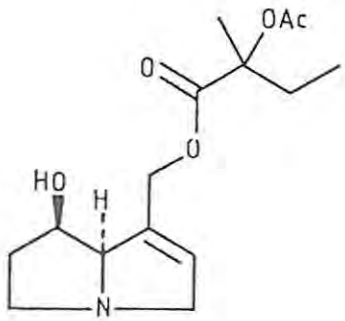


(3) R = H

(4) R = OH

The modified alkaloids are utilised as pheromones while the stored, unaltered alkaloids have now been shown conclusively to be used as a defence mechanism against predators.[26]

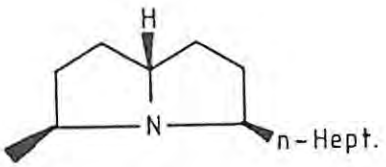
Hydroxydanaidal (4) has also been found in male moths of the genus Creatonotos,[27] from which it has been identified as the major volatile component from the scent organs. As with the Danaid butterflies, the alkaloids originate in plant material ingested by the moths. A different alkaloid, callimorphine (5), has been identified as a "metabolite" of the cinnabar moth Tyria jacobeaea.[28] This also is presumed to arise from ingested material.



(5)

Of interest is a very recent report of grasshoppers being attracted to, and feeding on, supplies of pure pyrrolizidine alkaloids (which had been laid out to attract butterflies) in preference to their normal plant foods.[29] Although no studies have yet been published, it is reasonable to suppose that, like the Danaid butterflies, these grasshoppers are using the alkaloids as a defence.

There appear to be only two naturally occurring pyrrolizidine alkaloids isolated to date which do not originate from plants. These are the (3R,5S,8R)-3-heptyl-5-methyl-pyrrolizidine (6), which was isolated from "thief"-ants of the genus Solenopsis,[30] and (3S,5R,8S)-3-(1-non-8-enyl)-5-(E-1-prop-1-enyl)pyrrolizidine (7), isolated from ants of the genus Chelaner.[31] These compounds are thought to be ant venom components, as many ant species use other nitrogen heterocycles in this capacity. (Note: the numbering follows the traditional pyrrolizidine numbering which is discussed in section 1.2.)



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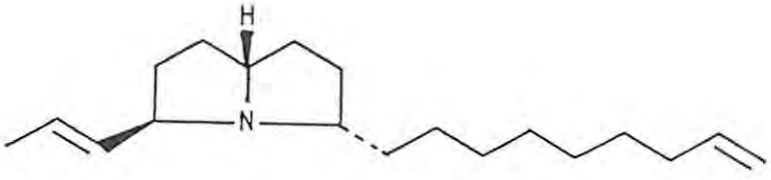
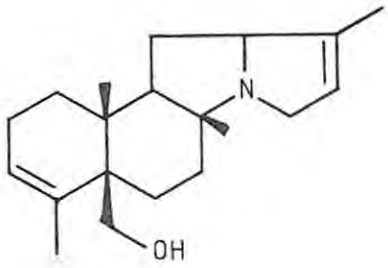


(7)

The pyrrolizidine ring structure has also been found in a number of other compounds as part of larger fused ring systems. Thus thelepogine (**8**) was isolated from Thelepogan elegans,[32] and α-cyclopiazonic acid (**9**) was isolated from a strain of Penicillum cyclopium Westling.[33] Finally ibophyllidine (**10**), is one of a growing number of recently discovered alkaloids possessing the norpandolane ring structure, and which are present in species of the genera Tabernanthe, Tabernaemontana and Daturicarpa.[34-36] Because of the presence of the indole ring, these compounds are usually included within the indole alkaloids.



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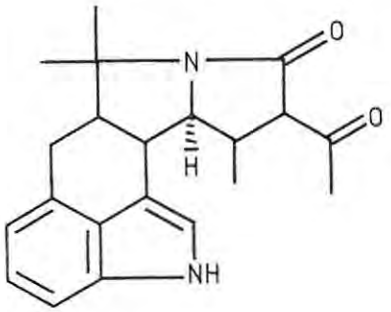

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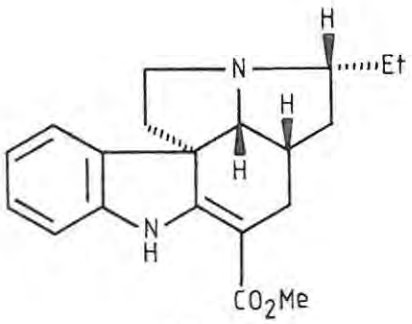
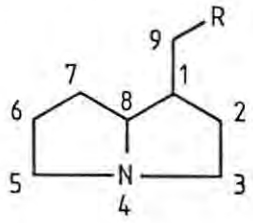


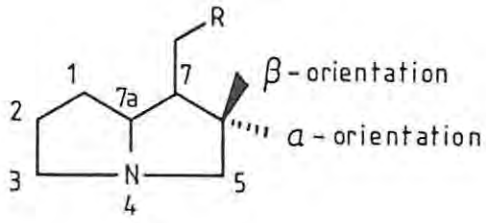
(10)

1.2 Structural considerations

As their name suggests all these alkaloids have the pyrrolizidine ring system (11) present in one form or another. Traditionally numbering of the ring is as shown in (11), and this system will be used throughout this work. The IUPAC method of numbering is given in (12) and the most recent publications concerning these alkaloids are beginning to incorporate this nomenclature in addition to the traditional one. The orientation of substituents is labeled as shown.



(11)



(12)

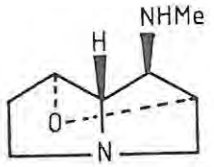
The fully saturated ring structure is non-planar and adopts an open 'V' shaped configuration, analogous to a part-open book. Whether the 'V' opens towards or away from the viewer is obviously dependent on the orientation of the substituents on C_8.

Nearly all of the pyrrolizidines identified so far have a hydroxymethyl group attached at C_1, with the new carbon atom being referred to as C_9. A small number of alkaloids have substituents which are derived from the hydroxymethyl group. These groups are the methyl, methylene, carboxaldehyde and carboxylic acid functionalities. However in the loline subgroup (cf. (13)), the substituent at C_1 is a N-group.

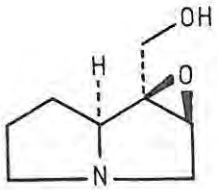
In addition to substitution at C_1 a great many of these compounds possess an oxygen functionality at C_7 which is usually a hydroxyl group. Either or both of the hydroxyl groups (at C_7 and C_9) may be esterified with a variety of acids. Hydrolysis of the alkaloids affords the individual acid (or acids) and the free base. The base portion is frequently referred to as a "necine" and the acids as the "necic" acids.[37] The simplest pyrrolizidines are not esterified, and consist of a necine base only.

1.3 The Necine Bases

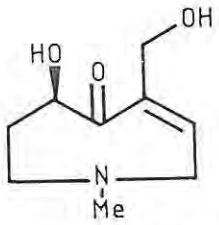
The structures and stereochemistry of the known necines are given in Tables 2, 3 and 4. Those structures which do not conveniently fit within the tables are shown below.



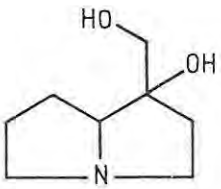
loline (13)



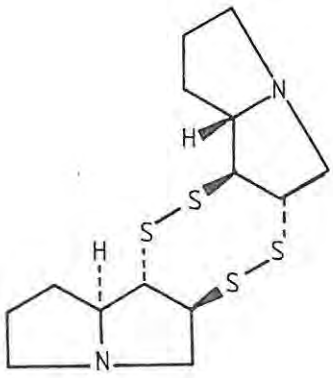
(14)



otonecine (15)

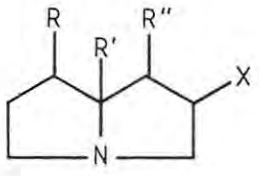


curassanecine (16)



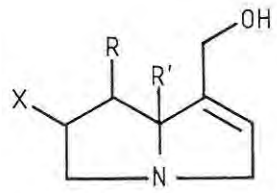
cassipourine (17)

Table 2 - Ring-saturated Pyrrolizidines.



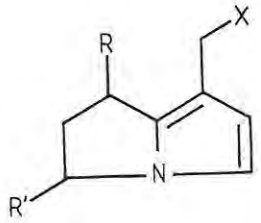
Name	R	R'	R"	X
1-methylenepyrrolizidine	H	α-H	$=CH_2$	H
heliotridane	H	α-H	β-CH_3	H
pseudoheliotridane	H	α-H	α-CH_3	H
chysine	H	β-H	α-CO_2Me	H
(-)isoretronecanol	H	α-H	β-CH_2OH	H
(+)isoretronecanol	H	β-H	α-CH_2OH	H
(-)trachelanthamidine	H	α-H	α-CH_2OH	H
(+)trachelanthamidine (laburnine)	H	β-H	β-CH_2OH	H
macronecine	H	β-H	β-CH_2OH	β-OH
petasinecine	H	α-H	β-CH_2OH	β-OH
7β-hydroxy-1-methylene-8α-pyrrolizidine	β-OH	α-H	$=CH_2$	H
7β-hydroxy-1-methylene-8β-pyrrolizidine	β-OH	β-H	$=CH_2$	H
retronecanol	β-OH	α-H	β-CH_3	H
dihydroheliotridane	α-OH	α-H	β-CH_2OH	H
(-)hastanecine	β-OH	β-H	β-CH_2OH	H
(+)hastanecine	α-OH	α-H	α-CH_2OH	H
platynecine	β-OH	α-H	β-CH_2OH	H
(-)turneforcedine	β-OH	α-H	α-CH_2OH	H
(+)turneforcedine	α-OH	β-H	β-CH_2OH	H
platynamine	α/β-OH	H	CH_2NH_2	H
croalbinecine	β-OH	α-H	α-CH_2OH	β-OH
(-)rosmarinecine	β-OH	α-H	β-CH_2OH	α-OH

Table 3 - Dehydropyrrolizidines.



Name	R	R'	X
(-)supinidine	H	α-H	H
(+)supinidine	H	β-H	H
(+)heliotridine	α-OH	α-H	H
retronecine	β-OH	α-H	H
crotanecine	β-OH	α-H	β-OH
uspallatinecine	β-OH	α-H	α-OH

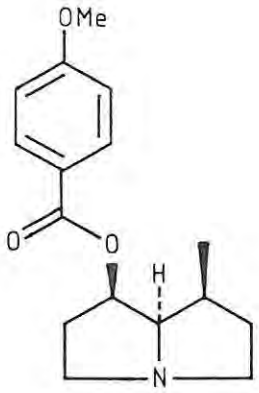
Table 4 - Didehydropyrrolizidines.



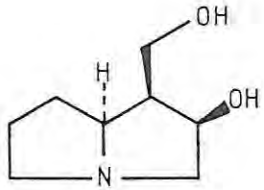
Name	R	R'	X
loroquine	=O	H	OH
senampeline	OH	OAc	OH
5,7 -didehydroheliotridin-3-one	α-OH	=O	OH
	β-OH	=O	OH
	β-OH	H	NMe
	β-OH	H	OH

Retronecanol, previously known from synthetic studies,[38] has now been identified as the base portion of ehretinine (18), isolated from Ehretia aspera (Boraginaceae) by Suri and coworkers.[39] This is the only pyrrolizidine alkaloid that has been found so far in this genus. Recently several new

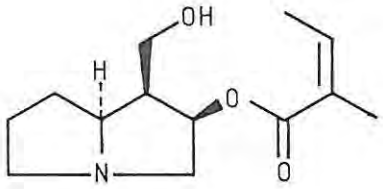
saturated pyrrolizidine bases have been reported. Petasinecine (19) is the base portion of the minor alkaloids petasinine (20) and petasinoside (21), both isolated from Petasites japonicus Maxim.[40]



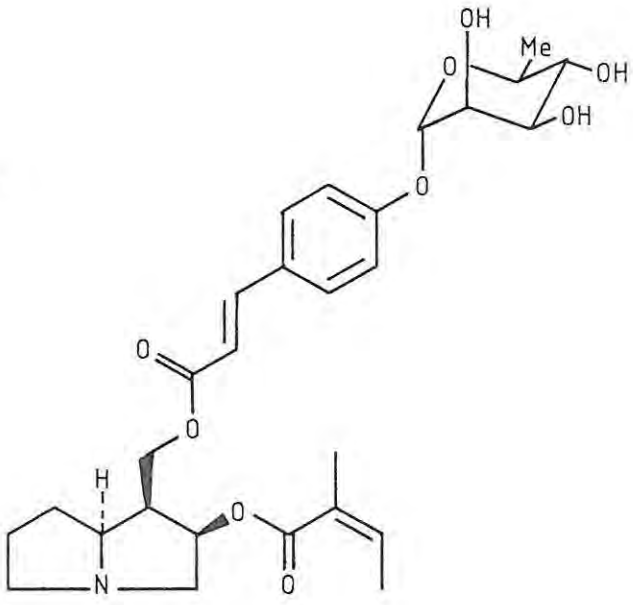
(18)



(19)



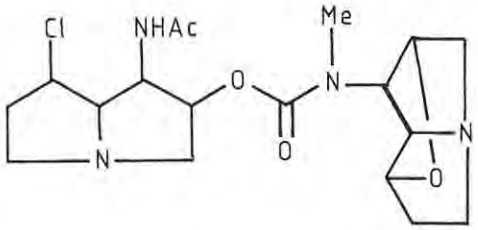
(20)



(21)

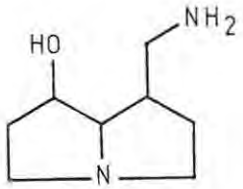
Lolidine (22), isolated by Russian workers from seeds of Lolium cuneatum,[41] contains a novel 7-chloro-pyrrolizidine base. This base appears to have been biogenetically formed by halogen induced opening of one of the ether bridges which

exists in all other members of the loline subgroup (cf. 13). Compound (22) is also unique in that it contains a carbamate unit which links the two pyrrolizidine units together.



(22)

Another new saturated pyrrolizidine, platynamine (23), is a semisynthetic product made by Suri and coworkers.[42] Reaction of platynamine with the appropriate acids led to the pyrrolizidine amides (24), (25) and (26). These amides are being used in biological studies.[42]



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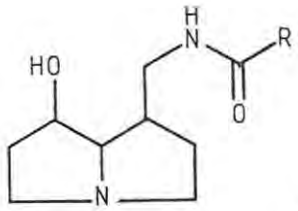
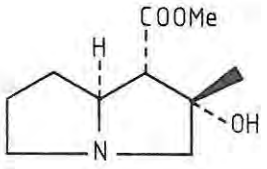


	R
(24)	-phenyl
(25)	$-CH_2-CH\begin{smallmatrix}Me\\Me\end{smallmatrix}$
(26)	$-CH{=}CH\begin{smallmatrix}Me\\Me\end{smallmatrix}$

During 1980 Roeder and coworkers isolated the simple alkaloid tussilagine (27) from Tussilago farfara.[43] The absolute configuration of (27) has recently been determined,[44] and very recently both (27) and its isomer isotussilagine (28) have been synthesised by the same group.[45]



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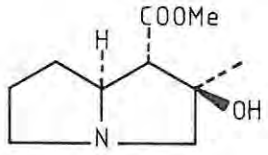
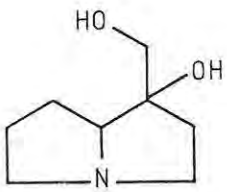
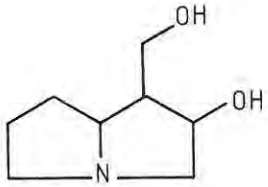


(28)

Investigations into the alkaloid content of Heliotropium Curassavicum L. by Subramanian and coworkers[46] resulted in the identification of a new type of necine (16), of uncertain stereochemistry, which was named curassanecine. Originally the structure (29) had been proposed,[47] but was revised to (16) on the basis of the 270 MHz ^{1}H NMR spectrum.

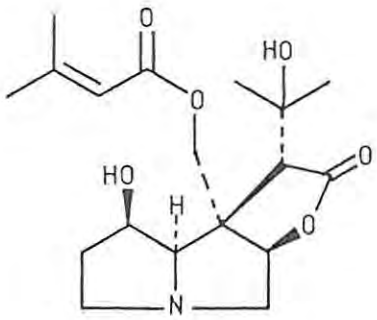


(16)



(29)

Three new saturated necines have been identified amongst the alkaloids from Senecio caudatus DC.[14] The first of these, senecicaudatine, is esterified at C_9 with senecioic acid giving structure (30), while esterification with isovaleric acid gives structure (31). Very similar in structure to (30) is 9-senecioylnorsenecicaudatine (32), which is the only example of this base. The third base found is present in the isomeric senecicaudatinal semiacetals (33) and (34).



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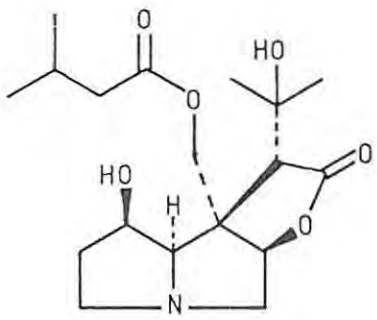

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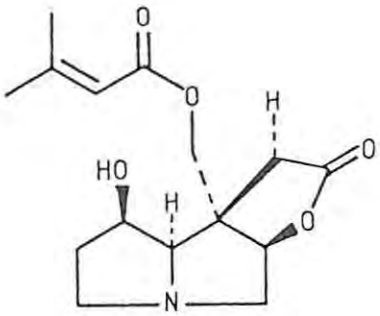

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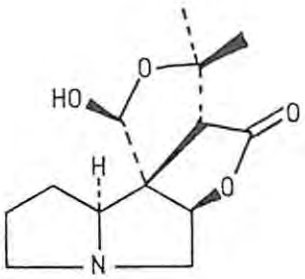

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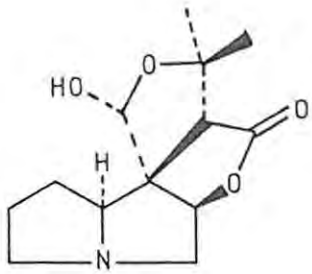

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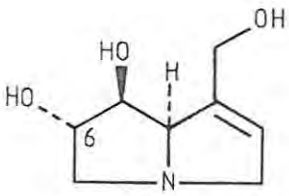

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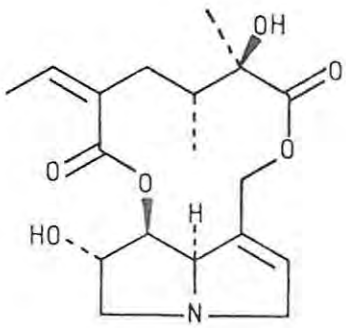
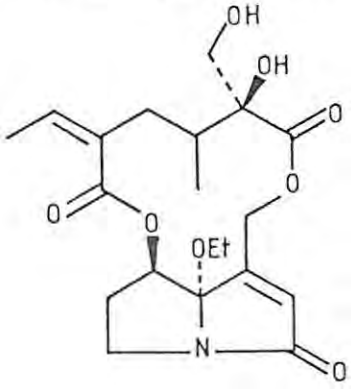


(36)

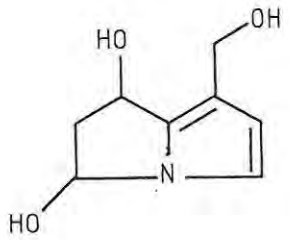
Two new dehydropyrrolizidine necines have been reported since 1976. Uspallatinecine (35), which differs from crotanecine only in the configuration at C_6, is the base portion of uspallatine (36). This was first isolated from Senecio uspallatensis Hook et Arn[48] and has since been found in other South American senecio species.[49,50]

Isolation of 8-ethoxy-3-oxoretrosine (37) from Senecio grisebachii Baker var. grisebachii [51] has provided the first example of a necine with an alkoxy group attached at C_8. It is also the only necine with a carbonyl group at C_3.



(37)

Several new didehydropyrrolizidines have been found by Bohlmann and coworkers.[52,53] In all, seven new alkaloids, senampelines A to G, were reported which contained the trihydroxy structure (38), of unknown stereochemistry. A second group of eight alkaloids containing the dihydropyrrolizinones (39) and (40) have also been reported by the same group.[54-56] In some species the senampelines and the dihydropyrrolizinones co-exist as would be expected from the close similarity of the rings.



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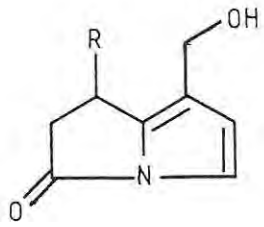
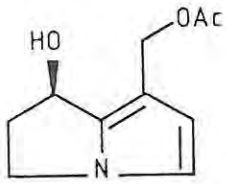


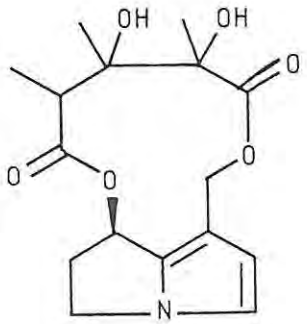
(39) R = α-OH

(40) R = β-OH

Finally a number of semisynthetic dihydropyrrolizines such as (41) and (42) have been prepared and used in studies on the kinetics of the alkylation reactions of pyrrolizidine alkaloid metabolites.[57]



(41)



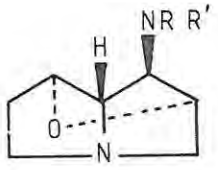
(42)

1.4 Structures of the alkaloids

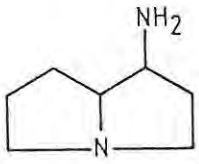
A complete listing of the known pyrrolizidine alkaloids is given in Appendix 2. Details of the alkaloids identified since 1976[58] are given below.

1.4.1 The simple alkaloids

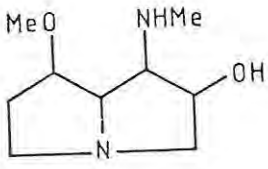
Five new alkaloids, N-methylloline (**43**), N-formylloline (**44**), N-formylnorloline (**45**), N-acetylnorloline (**46**) and lolidine (**22**), have been isolated from Lolium cuneateum by Batirov and coworkers.[41,59,60] Strictly speaking lolidine (**22**) is not a simple pyrrolizidine, consisting as it does of two pyrrolizidine units joined by a carbamate linkage. It is however convenient to include it with the other loline type alkaloids.



	R	R'
(43)	Me	Me
(44)	Me	CHO
(45)	H	CHO
(46)	H	Ac

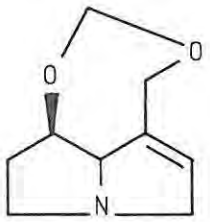


(47)

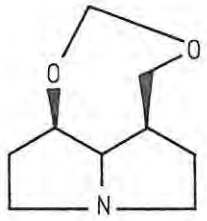


(48)

Very recently investigation of another lolium species, L. temulentum L. resulted in the identification of a further two loline related alkaloids, compounds (**47**) and (**48**).[10]



(49)



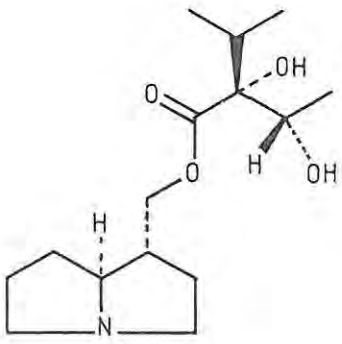
(50)

The compounds (49) and (50) were obtained by Suri and coworkers[61] as a result of attempting to chloromethylate retronecine and platynecine respectively.

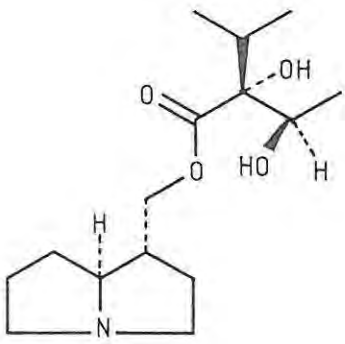
Other new simple pyrrolizidines, described earlier, are tussilagine (27) and it's synthetic isomer isotussilagine (28) (p11), and the butterfly pheromone hydroxydanaidal (4) (p3).

1.4.2 Monoester alkaloids

There are a number of new alkaloids of this type. Heliovicine (51) has (-)trachelanthic acid esterified to (-)trachelanthamidine, while in coromandaline (52) the necine is esterified with the diastereomer (+)viridifloric acid.[62]

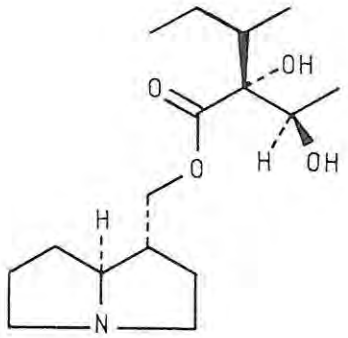


(51)



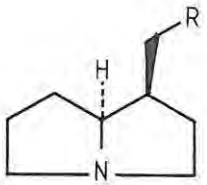
(52)

Curassavine (53) contains the novel (-)curassavic acid, which is esterified to (-)trachelanthamidine. This is the first C_8-monocarboxylic acid discovered in the pyrrolizidine alkaloids and the stereochemistry of the acid has not yet been fully defined.[62] However the relative stereochemistry is suspected to be the same as that in viridifloric acid on the basis of electrophoretic mobility data.[47]

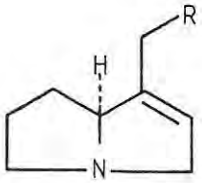


(53)

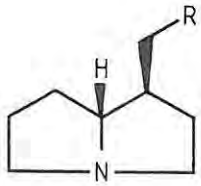
Further investigations of H. curassavicum L. by Subramanian et al, resulted in the identification of an additional seven monoester alkaloids.[46] All of the new alkaloids were found to be combinations of the three previously identified acids with the known necine bases (-)isoretronecanol, (-)supinidine and (+)trachelanthamidine (also called laburnine). Thus heliocurassavicine (54, R = 57), heliocoromandaline (54, R = 58) and heliocurassavine (54, R = 59) consist of (-)isoretronecanol (54, R = OH) esterified with (-)trachelanthic, (+)viridifloric and (-)curassavic acids respectively. Heliovinine (55, R = 57), coromandalinine (55, R = 58) and curassavinine (55, R = 59) are the equivalent (-)supinidine (55, R = OH) esters, and heliocurassavinine (56, R = 57) has (+)trachelanthamidine (56, R = OH) esterified with (-)trachelanthic acid.



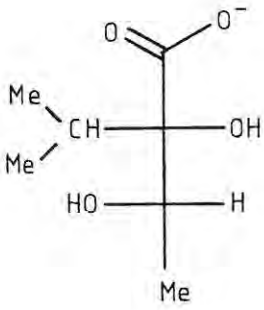
(54)



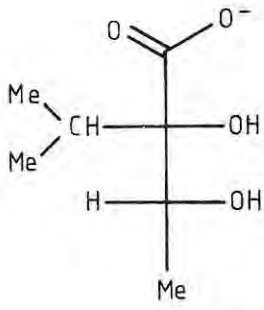
(55)



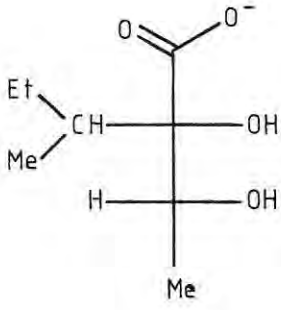
(56)



(57)

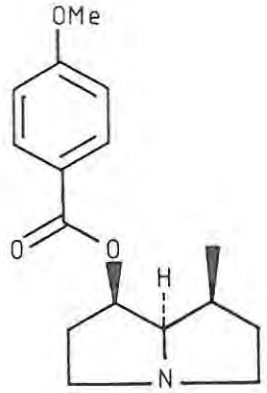


(58)

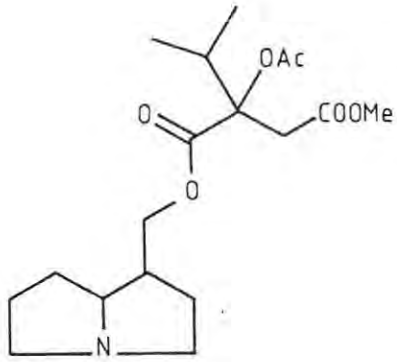


(59)

Of interest is that all three acids possess the abnormal R-configuration at the α-carbon and hence all of the alkaloids of H. curassavicum L. show this feature. It is also the first occurrence of (-)supinidine and (-)isoretronecanol esterified with C_8-acids, and of (-)isoretronecanol and (+)trachelanthamidine esterified with C_7-acids. Other new esters of monohydroxynecines are the previously mentioned ehretinine (18), which has retronecanol esterified with 4-methoxybenzoic acid, and an unnamed alkaloid (60) of undefined stereochemistry. This was isolated from Parsonsia heterophylla [63] and has a methyl succinate derivative as the acid moiety.

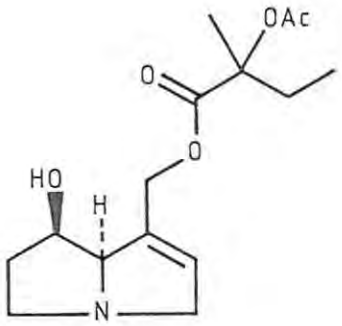


(18)

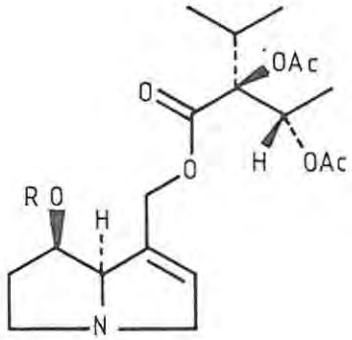


(60)

Sixteen new monoesters of pyrrolizidine diols have been found or synthesised, the majority having retronecine as the base. The previously discussed moth metabolite callimorphine[28] (5) has retronecine esterified with 2-acetoxy-2-methylbutanoic acid at C_9. The stereochemistry of the acid is not known.

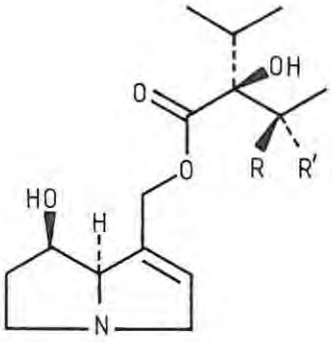


(5)

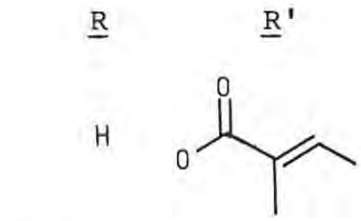


(61)

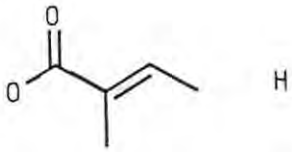
Recently 3'-acetyllycopsamine (61, R = H) was isolated from Amsinckia menziesii (Lehm.) Nels and Macbr. by Roitman,[64] along with several known alkaloids, as well as the acylic diester 3',7-diacetyllycopsamine (61, R = Ac). The acid present in these alkaloids is 3-acetyl-(-)viridifloric acid.



(62)



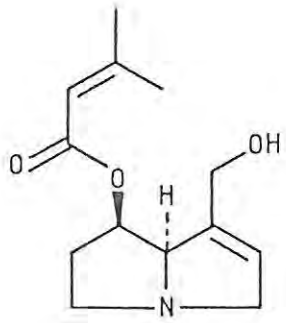
(63)



Scorpioidine (62) isolated from Myosotis scorpioides L.,[4] has the same (-)viridifloric acid but with the acetyl group replaced by a E-2-methylbutenoate (tiglyl) group. As such Scorpioidine is epimeric with the previously known anadoline (63).[65]

7-O-Senecioylretronecine (64) has been isolated from two Senecio species, S. cacaliaster (Lam.)[66] and S. triangularis Hook.[67] The isomeric 9-senecioylretronecine (65) and its N-oxide have been identified more recently,[14] along with two monoesters of macronecine, 9-senecioylmacronecine (66) and 2-senecioylmacronecine (67). Previously senecioic acid had rarely been found in pyrrolizidine alkaloids, one of the earliest reported occurrences being in 1977 with the isolation of fuchsisenecionine[68] (68) from Senecio fuchsii. The base portion of fuchsisenecionine is either platynecine (as shown in (68)) or its isomer.

Three other new esters of platynecine are the 7-angelyl- and 9-angelylplatynecines, (69) and (70), and the N-oxide of (70), which were isolated from Castilleja rhexifolia aff. miniata by Stermitz and Roby.[69]



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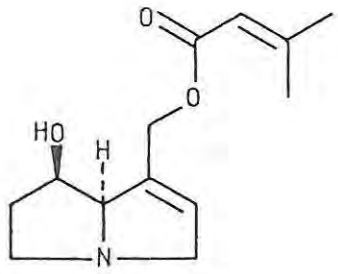

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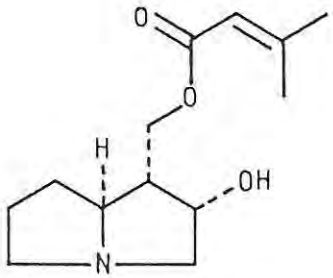

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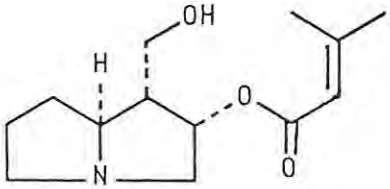

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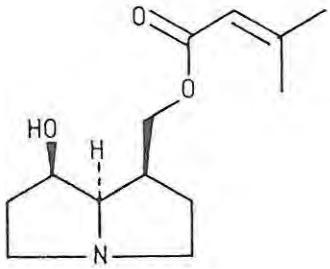

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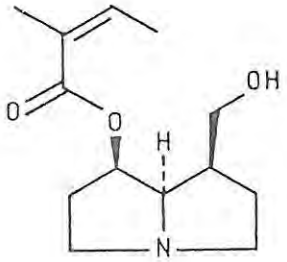
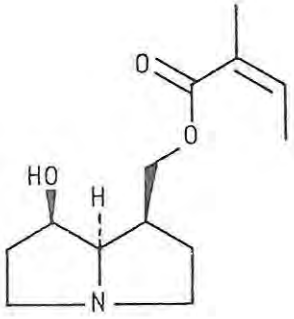
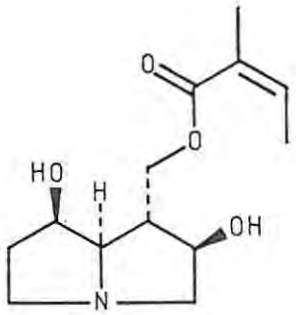


(69)

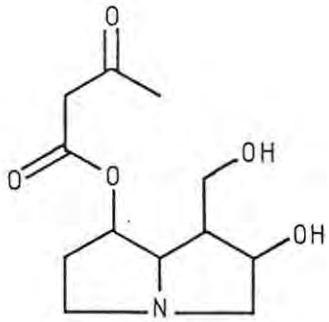


(70)

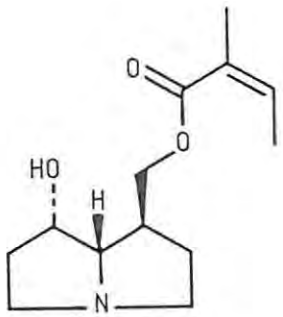
Helifoline (71) isolated from Heliotropium ovalifolium Forsk[70] possesses the base croalbinecine esterified at C_9 with Z-2-methylbutenoic (angelic) acid. This is the second reported alkaloid to contain croalbinecine, and is also the second monoester of a trihydroxynecine. The first was the incompletely characterised procerine (72), reported by Klasek et al.,[71] and which was isolated from Senecio procerus L. var. procerus Stoj, Stef et Kit..



(71)



(72)



(73)

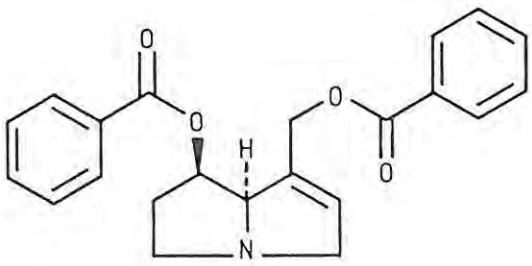
Farfugine (73), recently isolated from Farfugium japonicum Kitam[72] by Yamada and coworkers, is another example of an angelic acid ester. The base is (+)turneforcidine and was previously known only from synthetic studies. Proof of the identity of the base was obtained by synthesis of

esterification of the C_9 hydroxyl group to give the enantiomer of farfugine.

Other new monoester pyrrolizidines (discussed previously) are petasinine[40] (20) (p10), and 9-O-acetyldehydroheliotridine[57] (41) (p15). Petasinine consists of the new necine base petasinecine esterified at C_9 by tiglic acid, a geometric isomer of angelic acid.

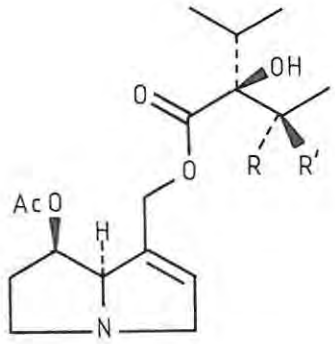
1.4.3 Acylic Diester Alkaloids

The majority of the new alkaloids of this class have retronecine as the base portion. The simplest new diester isolated is retronecine 7,9-dibenzoate (74) which was isolated from Caccinia glauca Savi.[73]

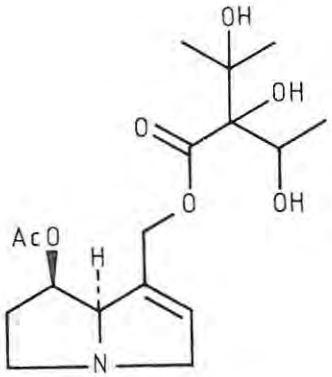


(74)

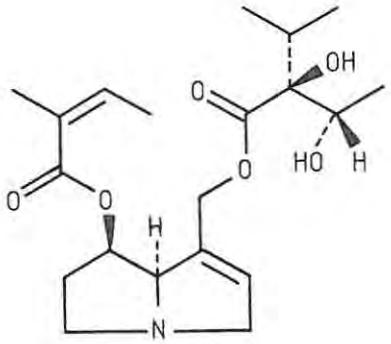
An investigation of the alkaloids of Symphytum X uplandicum Nyman (Russian Comfrey) by Culvenor and coworkers[74] resulted in the isolation of eight pyrrolizidine alkaloids, four of which were new. These are 7-acetyllycopsamine (75), 7-acetylintermedine (76), uplandicine (77) and symlandine (78). The acid attached at C_9 in uplandicine is echimidinic acid, while symlandine is esterified at C_7 with angelic acid and at C_9 with (-)viridifloric acid.



	R	R'
(75)	OH	H
(76)	H	OH

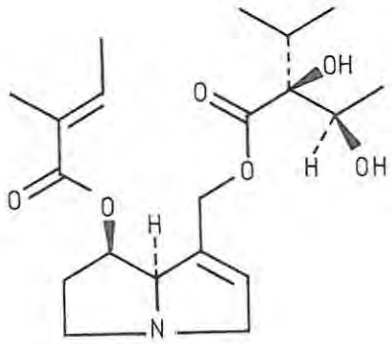


(77)

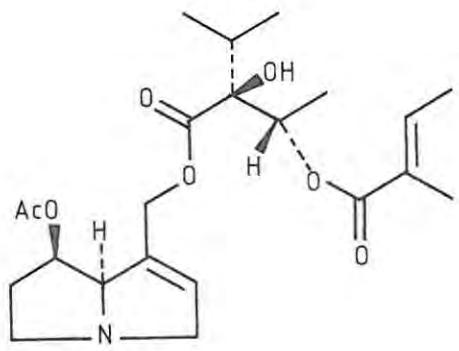


(78)

Myoscorpine (79), one of the alkaloids isolated from Myosotis scorpioides L. by Meinwald and coworkers,[4] differs from symlandine only in the stereochemistry of the esterifying acids; C_7 is esterified with tiglic acid and C_9 is esterified with (+)trachelanthic acid. Other new alkaloids from M. scorpioides are the monoester scorpioidine (62), discussed earlier (p21), and it's derivative 7-acetylscorpioidine (80).

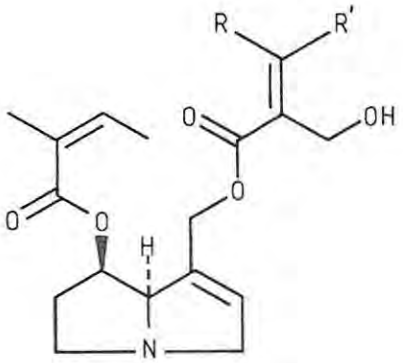


(79)

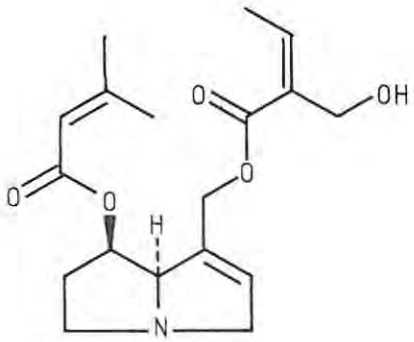


(80)

Recently Roitman[75] carried out a reinvestigation of Senecio triangularis Hook and succeeded in isolating small amounts of six alkaloids apart from the major one, senecionine. Two of the minor alkaloids are new and are named triangularine (**81**, R = Me, R' = H) and neotriangularine (**81**, R = H, R' = Me). Both have retronecine esterified at C_7 with angelic acid. Triangularine is esterified at C_9 with sarracinic acid, while neotriangularine is esterified by the geometric isomer, isosarracinic acid. This is the first time that isosarracinic acid has been reported in the pyrrolizidine alkaloids.



(**81**)

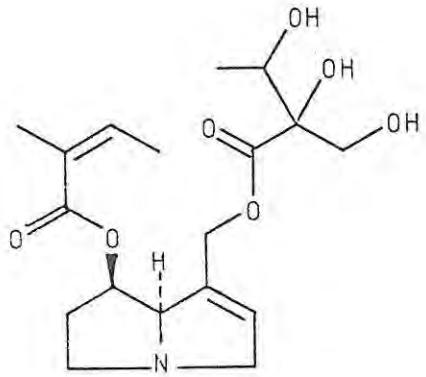


(**82**)

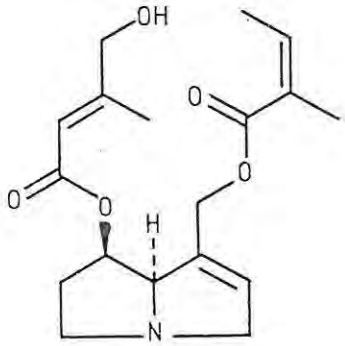
Almost identical in structure is 7-senecioyl-9-sarracinyl-retronecine (**82**), which was similarly isolated from S. triangularis.[67] Subsequently, (**82**) and its N-oxide were isolated by Bohlmann and coworkers from Senecio caudatus DC.[14]

Recently dihydroxytriangularine (**83**) was isolated by Roeder and coworkers from Alkanna tinctoria Taush[9] along with triangularine (**81**, R = H, R' = Me) and the known 7-angelyl-retronecine. The esterifying acid at C_9 in dihydroxy-

triangularine (83) is new and can be considered to be derived by hydroxylation of the C=C bond of sarracinic acid present in triangularine. This is also the first time that pyrrolizidine alkaloids have been identified in the genus Alkanna.



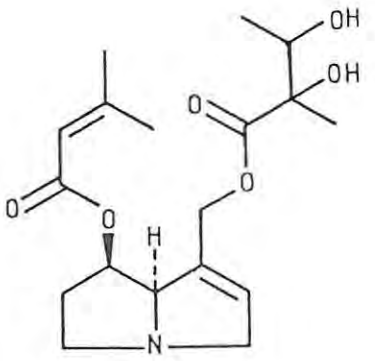
(83)



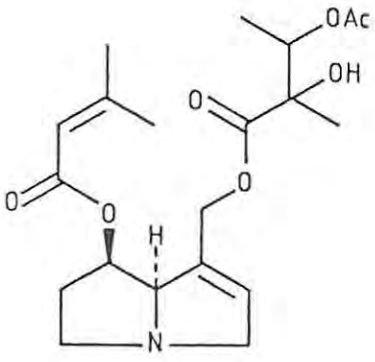
(84)

More recently sencalenine (84) was isolated from Senecio cacaliaster (Lam.).[66] This too contains a new acid moiety, being esterified at C_9 with angelic acid and at C_7 with the previously unknown hydroxysenecioic acid.

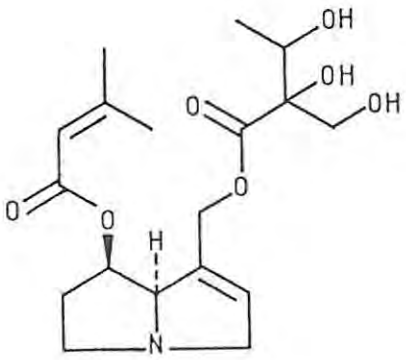
The most recently discovered acyclic diester alkaloids with retronecine as base are the ones reported by Bohlmann and coworkers.[14] In addition to (82) and its N-oxide discussed above, they also reported the isolation of three other alkaloids, (85)-(87), along with the N-oxides of (85) and (86). All are esterified at C_7 with senecioic acid. In (85) the esterifying acid at C_9 is a new necic acid, and is obviously a dihydroxy derivative of either tiglic or angelic acid, while structure (86) is the 3'-acetyl derivative of (85). The esterifying acid at C_9 in (87) is the same as that found in dihydroxytriangularine.



(85)

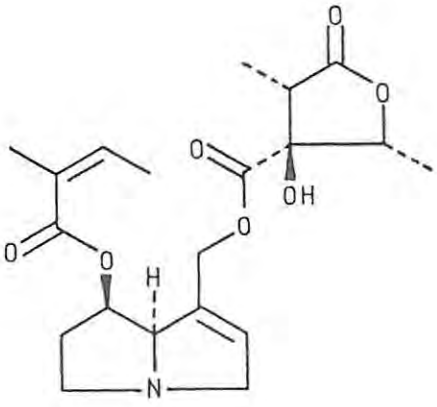


(86)



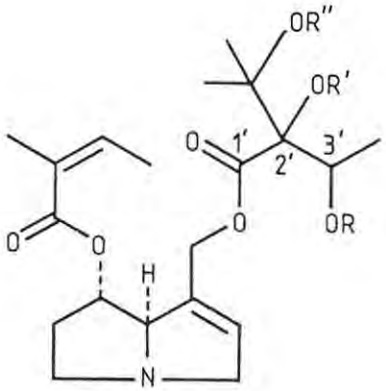
(87)

Stermitz and coworkers have reported the isolation of the rare alkaloid latifoline (88) and its previously unknown N-oxide from Hackelia floribunda (Lehm.) Johnston.[18] This is the first report of pyrrolizidine alkaloids from the genus Hackelia.



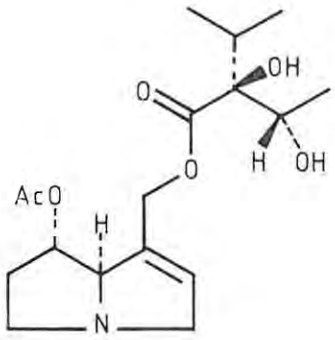
(88)

Several new acyclic diesters with heliotridine as the base have been isolated, and acetylheliosupine, originally (89), has, on the basis of NMR data,[76] been revised as (90). The stereochemistry of echimidinic acid, the esterifing acid at C_9, is still undefined.

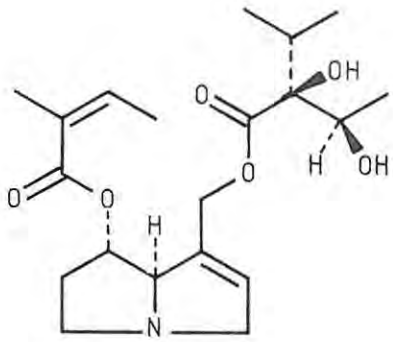


	R	R'	R''
(89)	Ac	H	H
(90)	H	Ac	H
(91)	H	Me	Ac

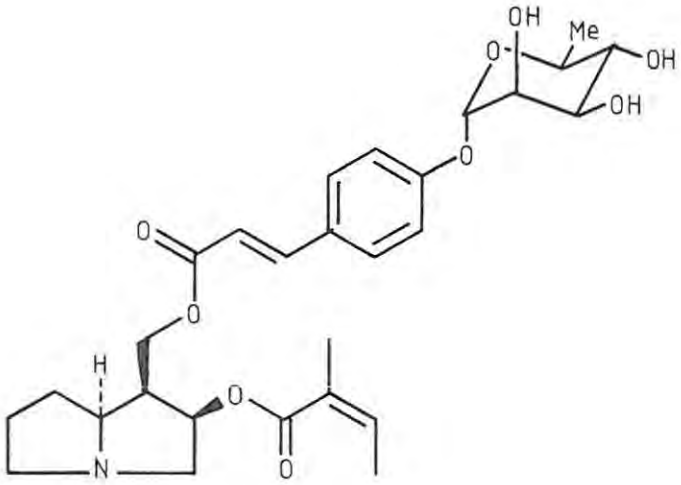
Closely related in structure is acetyllasiocarpine (91) which was found in Heliotropium europaeum.[77] Although the complete stereochemistry of the acid at C_9, lasiocarpic acid, remained unknown for a long time, the 3'-carbon was shown to have the R-configuration.[78] This has recently been confirmed by X-ray crystallography,[79] which showed that both asymmetric centres have the R-configuration. Suri and coworkers[80] have isolated 7-acetylechinatine (92) and 7-angelylheliotrine (93) from Lindelofolia spectabilis and Heliotropium eichwaldii respectively, along with several other known alkaloids. Of interest is the presence of both cyclic and acyclic diester alkaloids in L. spectabilis. This is the first such co-occurrence in Lindelofolia species.



(92)



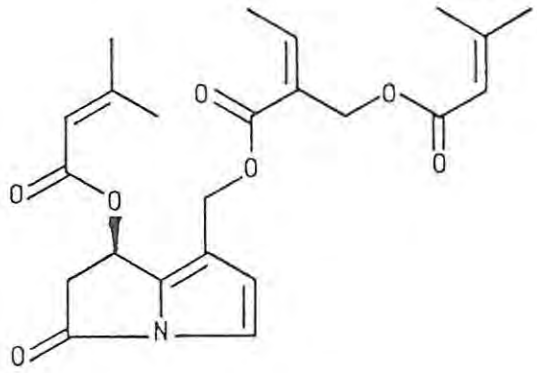
(93)



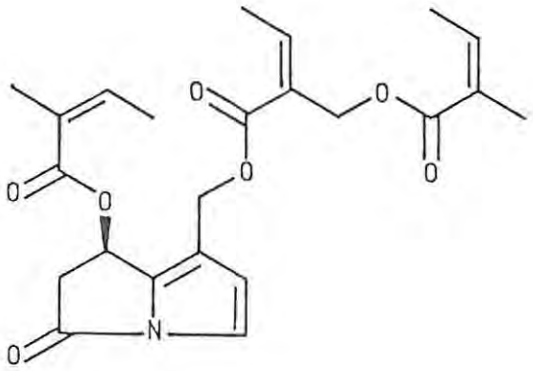
(21)

To date the only diester alkaloid containing the base petasinecine is petasinoside[40] (21) (p10). The acid portions are angelic and 4-α-L-rhamnopyranosylcinnamic acids. This is the first occurrence of a rhamnose residue in pyrrolizidine alkaloids. Five other pyrrolizidine alkaloids with either (+)isoretronecanol or (+)trachelanthamidine as the base portion are known to have glucose, or a glucosylarabinose disaccharide as the sugar residue. In all cases the sugar residue is attached at the <u>para</u> position of a benzene nucleus.

Investigation of Jacmaia incana (SW.) B.Nord. by Bohlmann and coworkers[12] has resulted in the isolation of a new type of pyrrolizidine for which structure (94) has been proposed. Spectroscopy showed the acids present to be sarracinic acid and senecioic acid. Replacement of senecioic acid by angelic acid results in structure (95), which was recently isolated from Senecio stapeliaeformis.[14]



(94)

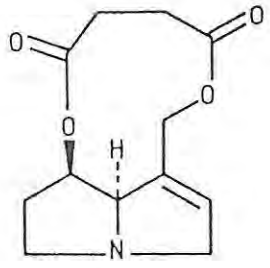


(95)

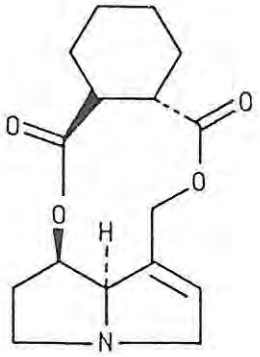
1.4.4 Cyclic Diester Alkaloids

This constitutes the largest group of pyrrolizidine alkaloids and, as could be expected, many new structures have been identified. In addition a number of known alkaloids have had their stereochemistry defined. The cyclic diesters result from the esterification of an aliphatic diacid with a necine diol. The size of the macrocyclic ring formed varies from ten to fourteen atoms, with the commonest sizes being eleven and twelve membered rings. The parent acids for the ten, eleven, twelve and thirteen membered rings are succinic (4 carbons), glutaric (5 carbons), adipic (6 carbons) and

pimelic (7 carbons) acids. Additional substituent carbons give rise to acids with from six to eleven atoms in the carbon skeleton. Hence the acids are commonly grouped both by total skeletal carbons and by parent acid, leading to groupings such as C_7-glutaric, C_8-glutaric, C_{10}-glutaric and C_{10}-adipic acids.



(96)



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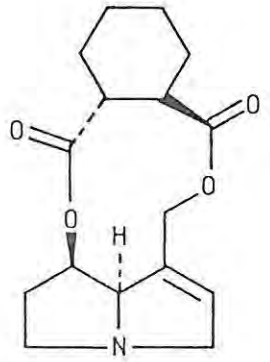
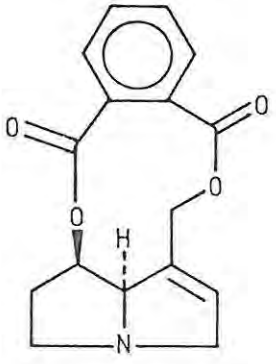


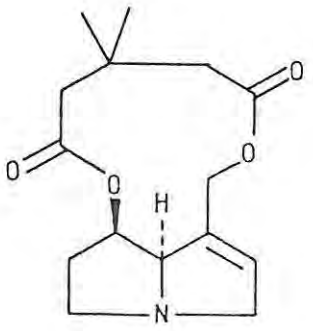
(98)



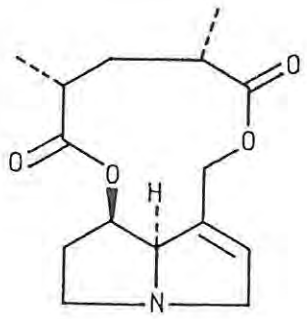
(99)

Four compounds, (96)-(99), containing a ten membered ring are known, and all are semisynthetic.[81] Of the new eleven membered rings, three are C_7-glutaric acid types. All are semi-synthetic and were produced by Robins and coworkers using naturally occurring retronecine as the base.[82,83] 13,13-Dimethyl-1,2-didehydrocrotalanine (100) was obtained from 3,3-dimethylglutaric acid anhydride, and the two

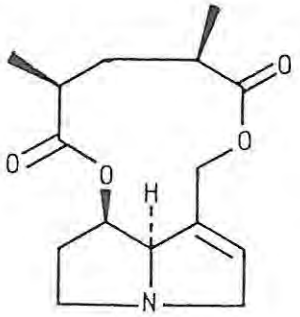
12,14-disubstituted structures, (101) and (102), were obtained from meso-2,4-dimethylglutaric anhydride.



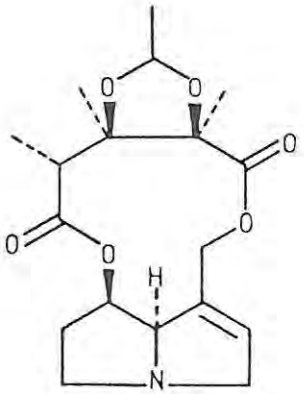
(100)



(101)



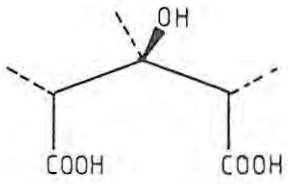
(102)



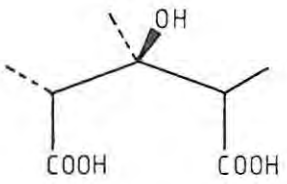
(103)

Four C_8-glutaric acid diesters have been isolated. Monocrotalinine (103), which was isolated from Crotalaria grahamiana R. Wight et Walk. Arn., is an acetal derivative of Monocrotaline.[84] [There is a possibility that this compound is an artifact.] Crocandine, isocrocandine and cropodine, isolated from Crotalaria candicans, are all esters of turneforcidine.[85,86] Hydrolysis of crocandine yielded the optically inactive fulvinic acid (104), while isocrocandine yielded the isomeric but optically active cromanduric acid, (105 or 106). Hence crocandine and isocrocandine have the same gross structure (107). Hydrolysis of cropodine yielded

monocrotalic acid, and this coupled with spectroscopic data suggests that cropodine has the structure (108).



(104)



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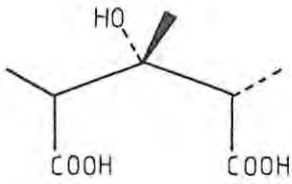

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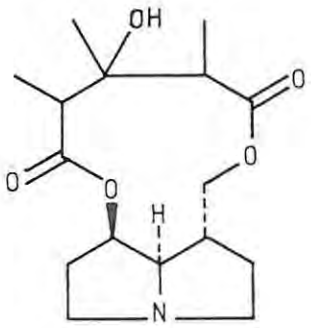

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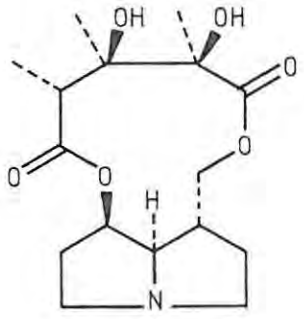
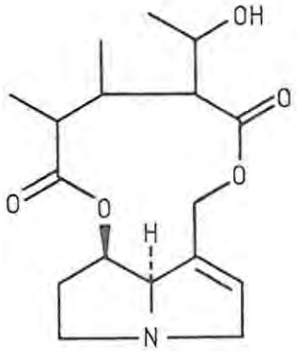
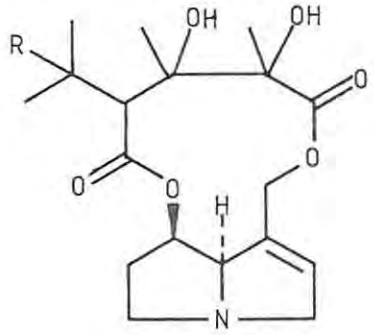


(108)

Cronaburmine (109), from Crotalaria nana Burm.,[87] consists of retronecine esterified with cronaburmic acid. This is the only C_9-glutaric acid found to date in pyrrolizidine alkaloids, and its stereochemistry is still undefined.

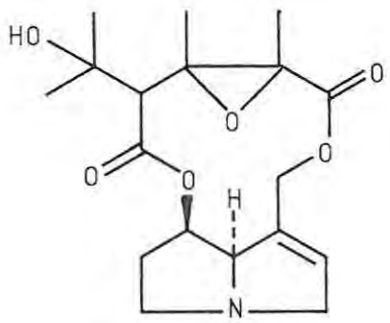


(109)

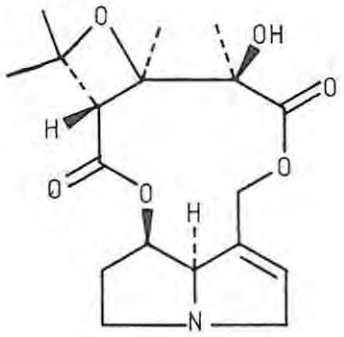


(110)

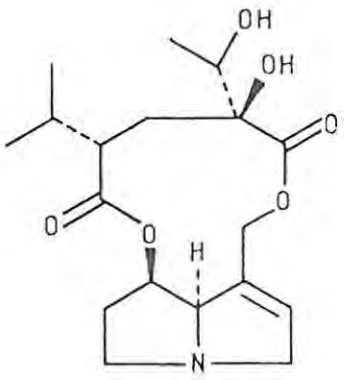
A re-examination of the alkaloids of Crotalaria globifera E. Mey. has resulted in the isolation of globiferine (110, R = OH) along with the known alkaloids grantianine and grantaline.[8] All three have retronecine doubly esterified with C_{10}-glutaric acids. Globiferine is structurally similar to trichodesmine (110, R = H). Originally[88] grantaline was assigned the structure (111), but this has recently been revised to (112) on the basis of NMR studies[89] and X-ray crystallography.[90] The oxetane ring is most uncommon in natural products.



(111)



(112)



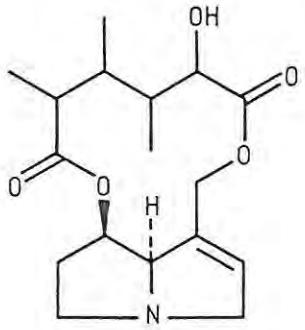
(113)

Desoxyaxillarine, (113), has been isolated as a minor alkaloid from the seeds of Crotalaria scassellati,[91] along with the known alkaloids axillarine and axillaridine.

Desoxyaxillarine differs from axillarine by the absence of a hydroxyl group on C_{13}.

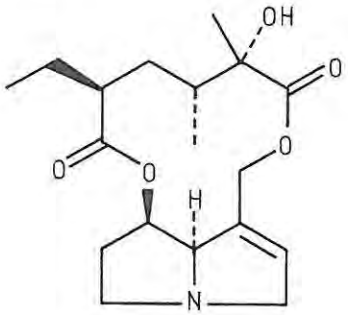
A number of known eleven membered macrocyclic pyrrolizidine alkaloids have had their absolute stereochemistry confirmed or defined by X-ray crystallographic studies. These include monocrotaline,[92] incanine,[93] retusine,[94] junceine,[95] spectabiline,[96] crispatine[97] and recently grantianine.[98] The structures of these compounds are given in Appendix 2.

Within the twelve membered macrocyclic pyrrolizidines the majority of alkaloids are based on C_{10}-adipic acids. However one new structure based on the much rarer C_9-adipic acid type has been found. Crotananine (114) was isolated from Crotalaria nana Burm.[99] which on (basic) hydrolysis gave retronecine and a new acid, crotananic acid of undefined stereochemistry.

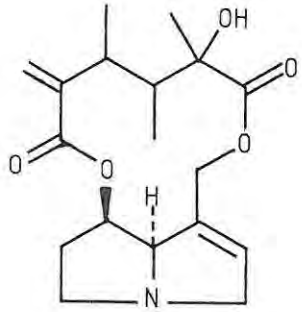


(114)

Considering the C_{10}-adipic acid diesters, yamataimine, (115), was isolated from the roots of Cacalia yatabei Maxim.[100] Spectroscopic and chemical methods showed the base to be retronecine and the acid to be new. X-Ray crystallography was used to determine the absolute configuration.[100]

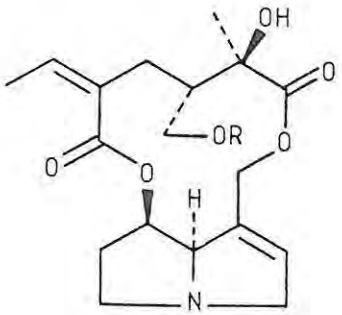


(115)

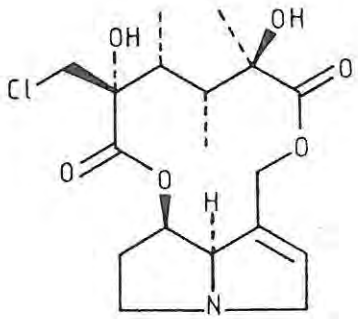


(116)

Senecivernine (116), reported by Roeder and coworkers[101] has retronecine esterified with another new acid, senecivernic acid. This acid has now been synthesised.[102] Retronecine is also the base present in gynuramine (117, R = H) and acetylgynuramine (117, R = Ac), which were isolated from Gynura scandens O.Hoffm.[103,104]



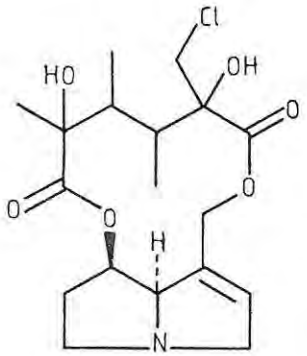
(117)



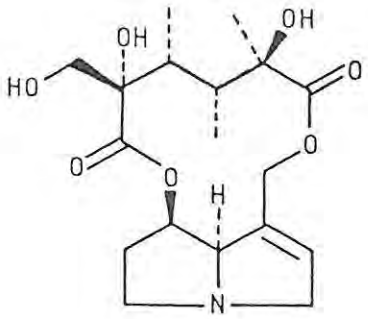
(118)

Reinvestigation of Senecio latifolius DC by Wiechers and coworkers[105] has resulted in the isolation of merenskine N-oxide, which was subsequently reduced to the free alkaloid (118). Although the physical data for merenskine matched that reported earlier for chlorodeoxysceleratine (119),[106] detailed NMR studies and X-ray crystallography of (118)

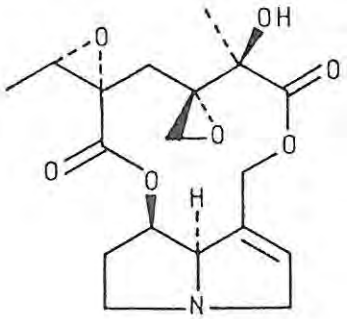
showed the mode of esterification to be the reverse of that originally proposed for (119). Thus chlorodeoxysceleratine has been reassigned as (118). The related alkaloid sceleratine, isolated from the same source, along with its N-oxide,[107] has similarly had its structure revised as (120).



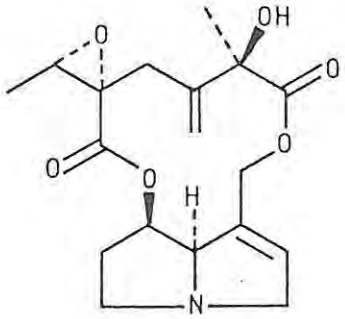
(119)



(120)

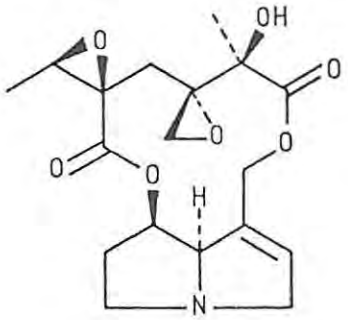


(121)

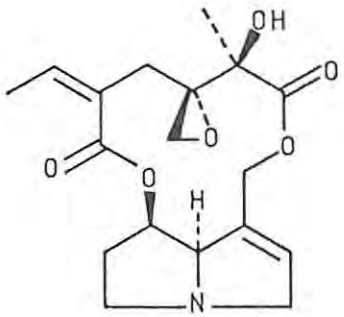


(122)

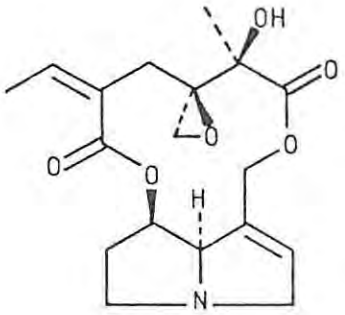
Although a number of pyrrolizidines have been reported containing an epoxide ring, senecicannabine, (121), is the first to have two such rings present.[108] More recently the stereochemistry of senecicannabine and jacozine (122) has been determined by synthesis from seneciphylline.[109] In so doing (123), the isomer of senecicannabine, and the two monoepoxides (124), (125) were produced.



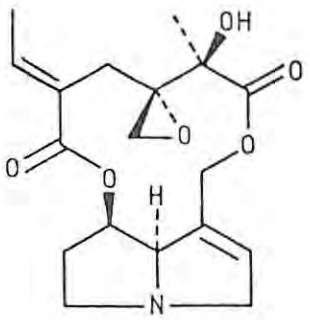
(123)



(124)

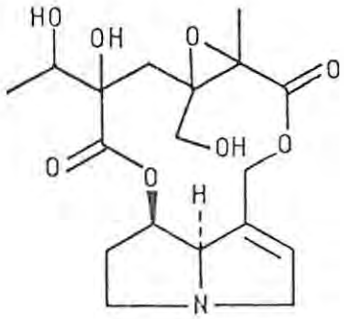


(125)



(126)

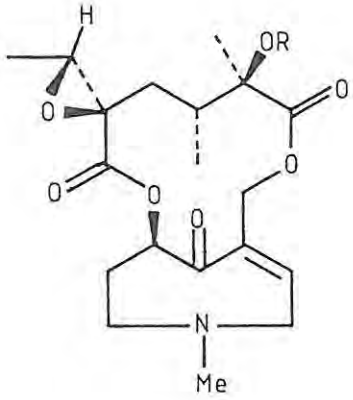
Structure (124) has since been isolated by Bohlmann and coworkers,[14] along with the geometric isomer (126), and structure (127).



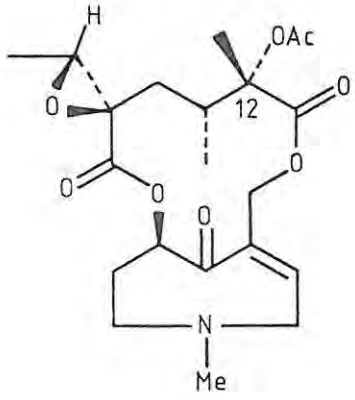
(127)

Epoxide rings are also present in petasitenine (128, R = H) and neopetasitenine (128, R = Ac) and in ligularizine (129),

the C_{12}-epimer of neopetasitenine. Both petasitenine and neopetasitenine were isolated by Yamada and coworkers[110] from Petasites japonicus Maxim. At the same time Furuya and coworkers reported fukinotoxin from the same species.[111] Subsequently Yamada's group showed that these two compounds had identical stereochemistry and hence the names are synonymous.[112] Recently petasitenine has also been found in a second genus, Farfugium, during a reinvestigation of Farfugium japonicum Kitam.[113]



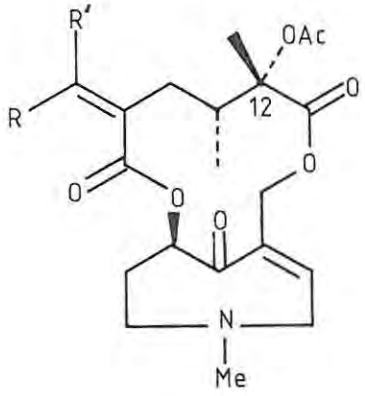
(128)



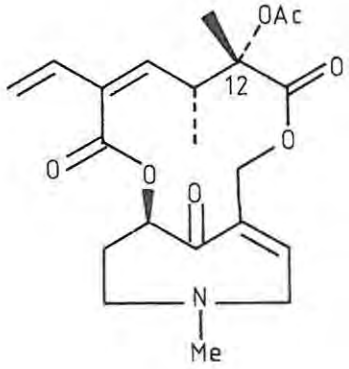
(129)

Ligularizine, (129), is one of four new alkaloids from Ligularia dentata Hara.[114,115] Ligularidine (130, R = H, R' = Me) and its geometric isomer, neoligularidine (130, R = Me, R' = H), are also otonecine diesters, and all are structurally similar to the previously known and co-occurring clivorine (131). The remaining alkaloid of this group, ligularinine (132) has the same acid as neoligularidine, but it is unacetylated at C_{12}, and has platynecine as the base. Thus it is a C_{12}-epimer of the known alkaloid platyphylline. The Ligularia dentata alkaloids are unusual in that all have

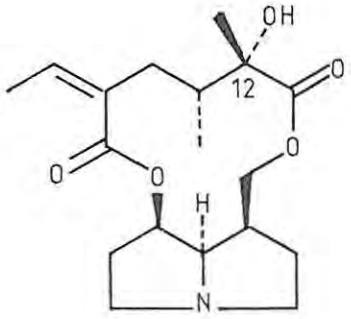
the 12-S-configuration and are suspected to be carcinogenic and mutagenic, in common with clivorine.



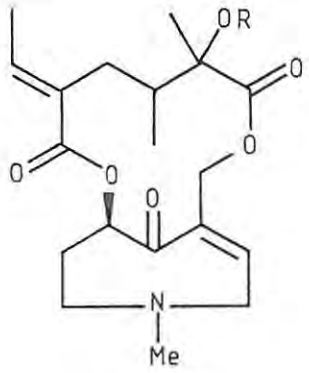
(130)



(131)

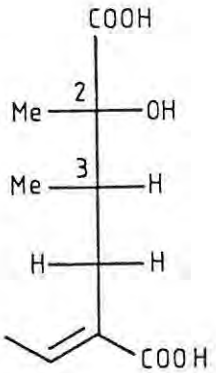


(132)



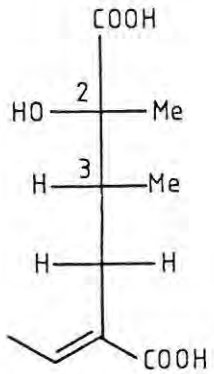
(133)

Closely related structurally to the alkaloids from Ligularia dentata are crotaverrine (133, R = H) and acetylcrotaverrine (133, R = Ac) from Crotalaria verrucosa L.[116] and C. walkeri Arnott[117] reported by Suri and coworkers. On the basis of spectroscopic and chemical evidence they were able to deduce the gross structure of crotaverrine, and show that the acid obtained on alkaline hydrolysis was a diastereoisomer of integerrinecic acid. As such, the absolute configuration of the acid was either [2R, 3S] or [2S, 3R] as in structures (134) and (135) respectively.



[2R, 3S]

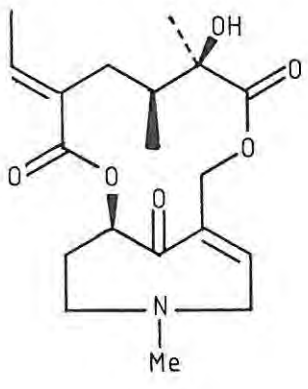
134)



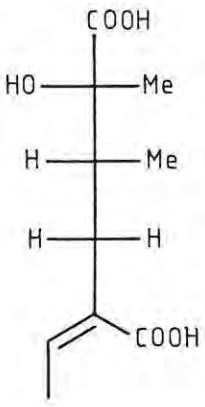
[2S, 3R]

(135)

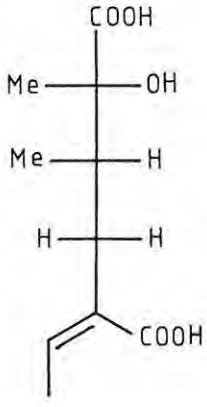
Earlier, Edwards et al. had synthesised all eight stereomers of these 5-ethylidene-2-hydroxy-2,3-dimethyladipic acids and reported their physical data.[118,119] However they only correlated absolute configuration with the physical data for senecic and integerrinecic acids. Complete correlation for all isomers follows from the absolute configurations of ligularidine and neoligularidine. Since ligularidine has been shown to have the same [2S, 3R] absolute configuration as acid (135), it follows that crotaverrine must have the [2R, 3S] absolute configuration of acid (134), and hence has the structure (136).



(136)

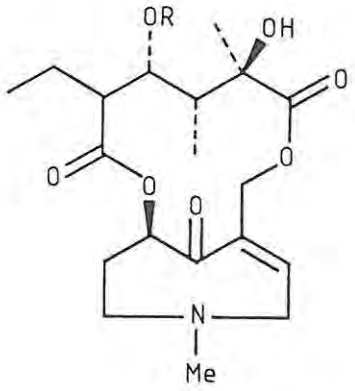


(137)



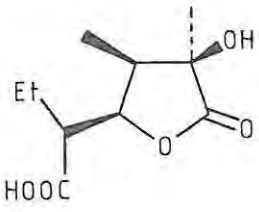
(138)

Further, the correlation of optical rotation and absolute configuration for the diastereoisomers (137) and (138) of senecic acid similarly follows from the establishment of (137) as the acid moiety of neoligularidine (130, R = Me, R = H) (p41). Acid (138) has not yet been found naturally.

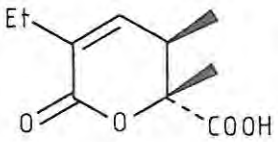


(139)

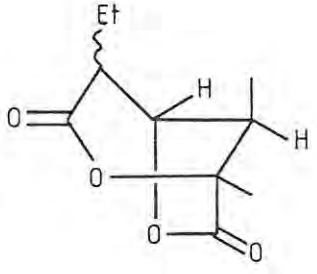
Other new otonecine based alkaloids are syneilesine, acetylsyneilesine, doronine, 18-hydroxysenkirkine and 18-acetoxysenkirkine, all of which have C_{10}-adipic acid moieties. Syneilesine (139, R = H), and acetylsyneilesine (139, R = Ac) were isolated from Syneilesis palmata Maxim.[120,121] These are the first pyrrolizidine alkaloids to be reported from this genus. Alkaline hydrolysis of syneilesine gave three lactones, (140) - (142), whose structures and stereochemistry were deduced from spectroscopic data.



(140)

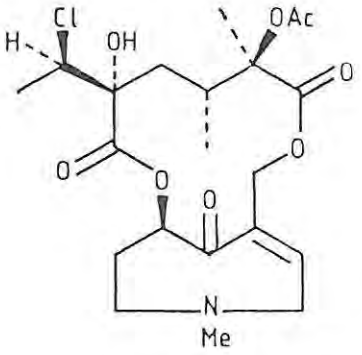


(141)

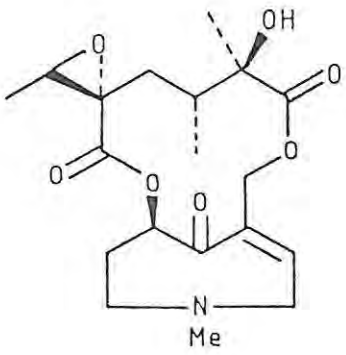


(142)

Doronine (143) was isolated from Doronicum macrophyllum,[122] and this too is the first pyrrolizidine reported from this genus. The absolute stereochemistry of this alkaloid has been determined by X-ray crystallography,[123] and shown to be related to otosenine (144). Recently otosenine has been isolated from the roots of a second Doronicum species, D. pardalianches Linn.[17]

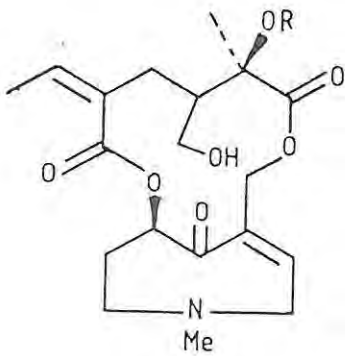


(143)

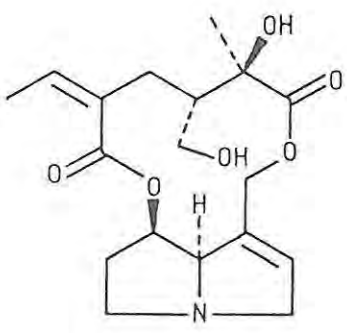


(144)

18-Hydroxysenkirkine (145, R = H) and 18-acetoxysenkirkine (145, R = Ac) were isolated from Senecio laricifolius, as were senkirkine and two other known alkaloids. It has been suggested that the two new alkaloids are derived from the equivalent retronecine-based alkaloid gynuramine (117),[14] (p37).

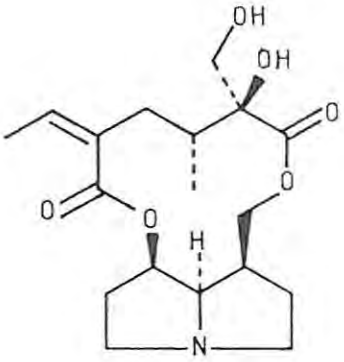


(145)

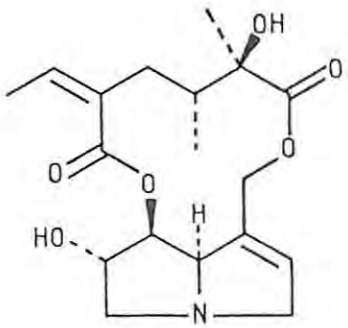


(117)

Dihydroretrorsine (146) has been isolated from the roots of Senecio subulatus Don ex Hook et Arn var. erectus together with senecionine and retrorsine.[124] Alkaline hydrolysis of (146) gave isatinecic acid, identical to that found in retrorsine, and the base portion proved to be platynecine.



(146)



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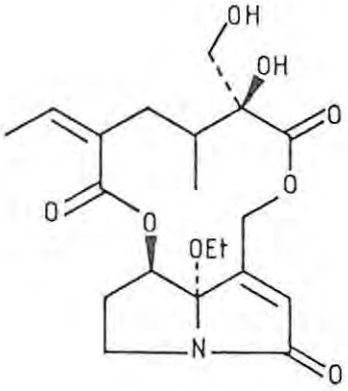
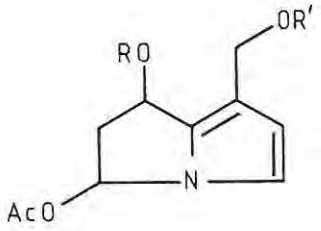


(37)

Other new cyclic diester alkaloids are the previously discussed uspallatine (36),[48] (p14), which has the novel base uspallatinecine esterified with senecic acid, and 8-ethoxy-3-oxoretrorsine (37),[51] (p14). The structure of (37) was determined by NMR and mass spectroscopy.

Two totally new sub-groups of pyrrolizidine alkaloids have been discovered by Bohlmann and coworkers during their extensive studies on the chemotaxonomy of the genus Senecio.[52-56,125,126] One, the senampeline group, are acyclic triesters of general structure (147). The other is the related, and often co-occurring, macrocyclic dihydropyrrolizinone group of general structure (148).



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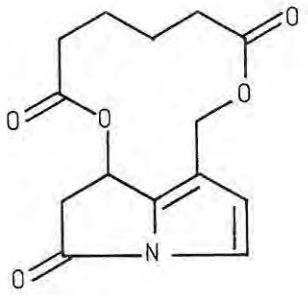
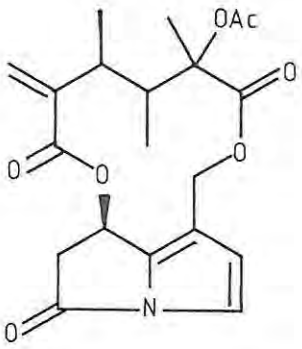


(148)

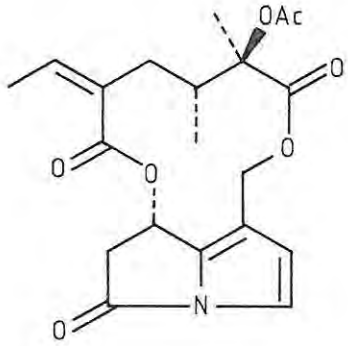


(149)

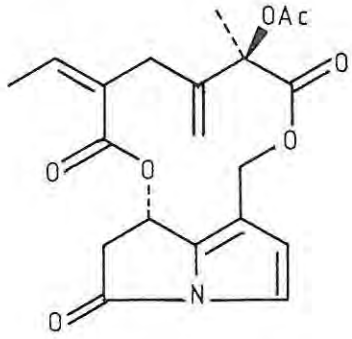
To date, eight macrocyclic dihydropyrrolizinones have been identified. Seven are C_{10}-adipic acid diesters, and the other is a C_{13}-adipic diester. The first of this subgroup to be identified,[52] pterophorine (149), was isolated as a minor alkaloid of Senecio pterophorus DC. Later it was also found in a number of other senecio species. In one of

these, namely S. pulviniformis Heiron., the C_7-epimer isopterophorine, was also isolated.[55] The stereochemistry of the acid moiety of these alkaloids has not been determined. However the gross structure is identical to that of senecivernic acid.

Senaetnine (150) from Senecio aetnensis Jan[56] has (+)senecic acid esterified to the base while isosenaetnine is the C_7-epimeric alkaloid, and this has been found in Kleinia kleinioides (Sch. Bip.) M.R.F. Taylor.[54] A geometric isomer of senaetnine has also been reported.[53]



(150)

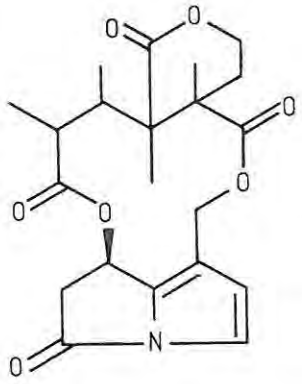


(151)

Closely related to the senaetnine type of alkaloids are dehydrosenaetnine (151), and dehydroisosenaetnine, its C_7-epimer. Both of these have been isolated from Senecio barbertonicus Klatt.[125] and Kleinia kleiniodes (Sch. Bip.) M.R.F. Taylor.[54] The esterifed acid in these alkaloids is the acetyl derivative of seneciphyllic acid.

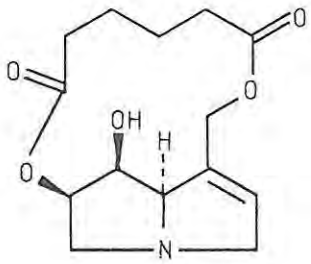
Inaequidenine (152) was isolated from Senecio inaequidens DC.,[56] and has a novel C_{13}-adipic acid esterified to the necine. Embedded within the adipic acid structure is a glutaric acid structure, the additional acid unit forming a

δ-lactone with the hydroxyethyl unit attached at C_{11}. This is the first example of a δ-lactone incorporated into the acid moiety in pyrrolizidine alkaloids, although γ-lactones have been identified in grantianine and retusamine.

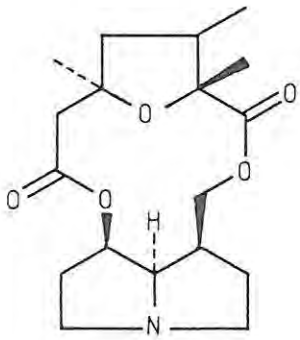


(152)

The absolute stereochemistry of the known twelve-membered macrocyclic alkaloids retrorsine,[127] platyphylline[128] and rosmarinine[129] have been confirmed by X-ray crystallography.



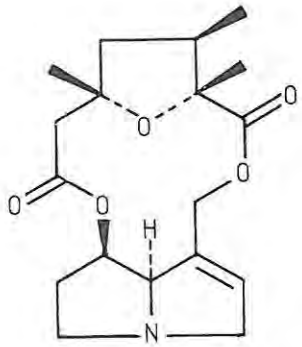
(153)



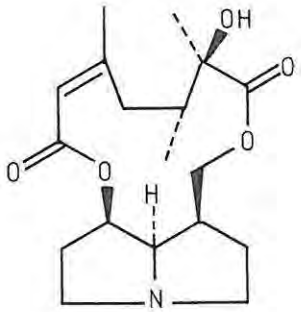
(154)

Thirteen-membered macrocyclic pyrrolizidine alkaloids are uncommon. Only five have been reported prior to this survey, and of these, four have the general structure (153) resulting from esterification by C_{10}-adipic acids at C_6 and C_9 of the necine, rather than at C_7 and C_9 as is usual. The remaining previously known thirteen-membered macrocyclic pyrrolizidine

is nemorensine (154). This has platynecine esterified by nemorensic acid, which is a C_{10}-pimelic acid. This is the first such acid found in these alkaloids.[130] Recently this alkaloid has been isolated as it's N-oxide, oxynemorensine, and the stereochemistry of the acid portion elucidated further.[131]



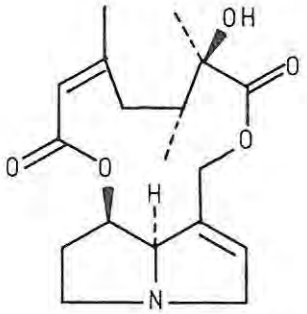
(155)



(156)

Closely related to nemorensine (154), are retroisosenine, (155), and bulgarsenine, (156), which were isolated from Senecio nemorensis L., var. bulgaricus (Vel.) Stoj. et Stef.[132] On alkaline hydrolysis retroisosenine, (155), gave retronecine as the base, while the acid portion was shown to be the cis-isomer of nemorensic acid. Spectroscopic data indicated that bulgarsenine (156) contained an αβ-unsaturated acid and a free hydroxyl group, while hydrolysis gave the same products as nemorensine, namely platynecine and trans-nemorensic acid.The presence of unsaturation in the alkaloid, but not in the hydrolysis products, therefore fixed the relative positions of the olefin and the hydroxyl group within the acid moiety. This behavior of bulgarsenine parallels that observed in erucifoline.[133] The absolute stereochemistry of bulgarsenine has now been confirmed by X-ray crystallography.[134]

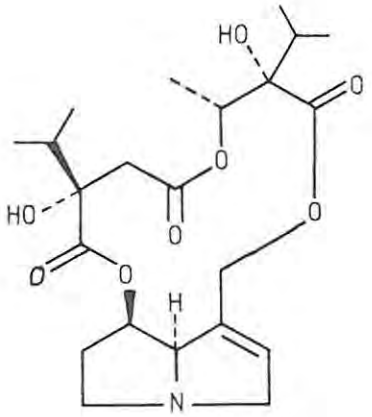
A third new alkaloid in this group is doronenine (157) which was isolated from Senecio doronicum L. along with bulgarsenine.[135] Structurally these two alkaloids are very similar. They have the same acid moiety but doronenine has retronecine as the base in place of the saturated platynecine of bulgarsenine.



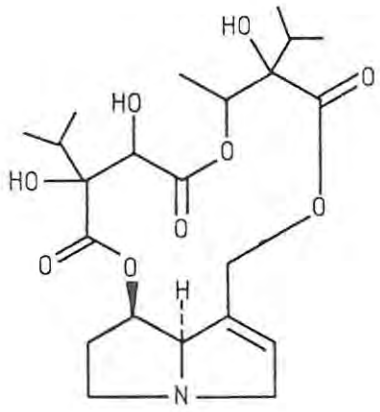
(157)

The fourteen-membered macrocyclic pyrrolizidine alkaloids are a new sub-group which to date (1987) have only been found in two species of the genus Parsonsia, namely P. heterophylla A.Cunn. and P. spiralis Wall.[63] Their fourteen-membered ring structure arises from esterification of retronecine with an acid moiety. This acid consists of a diacid, itself esterified at one acid unit to a hydroxyacid. The macrocyclic ring is therefore, more correctly, a triester ring. However since only two ester linkages are to the necine, the structure as a whole is grouped with the diester alkaloids.

Only one of the five known examples, parsonsine (158), has had its stereochemistry defined by crystallographic studies.[136,137] The other four vary only in the structure of the diacid which forms the 'northwest' quadrant of the structure.

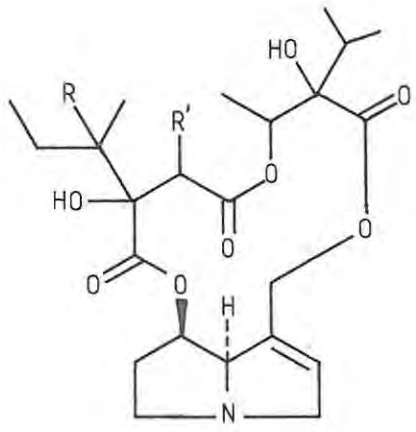


(158)



(159)

Closest in structure to parsonsine is spiraline (159) which has an additional hydroxyl group attached to the macrocyclic ring. The remaining three alkaloids have an additional carbon atom, as shown in heterophylline (160, R = R' = H). Spiranine (160, R = H, R' = OH) is analogous to spiraline, while spiracine (160, R = R' = OH) has four free hydroxyl groups.

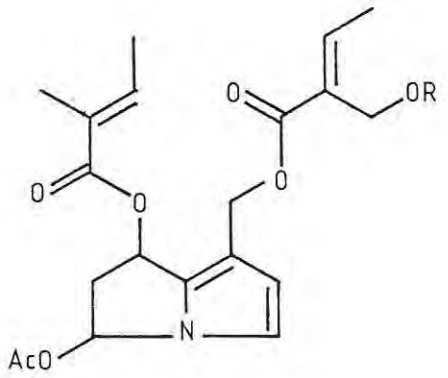


(160)

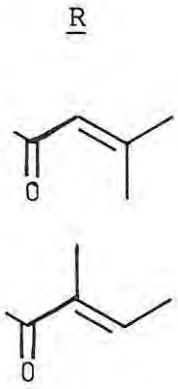
1.4.5. Acyclic triester alkaloids

Seven structures of this type are known and have been named senampeline A to G.[52,53] Because of their close similarities

in structure, these compounds have proved difficult to separate completely, and hence some uncertainty exists regarding their precise structures. All the senamplines have an O-acetyl group at C_5. Senampeline A and B have the general structure (161), which has C_7 esterified by tiglic acid, and C_9 esterified by an acylated sarracinic acid, the acylating group being either a senecioyl or a second tiglyl group.



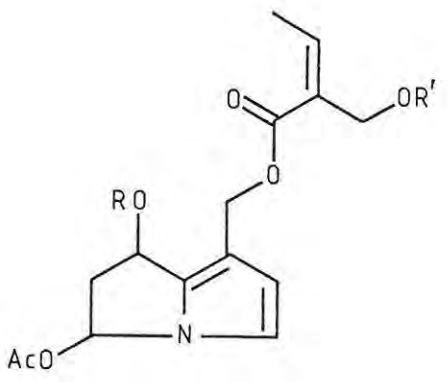
(161)



(senecioyl)

(tiglyl)

The senampelines C and D, (162, 163), are isomeric with senampelines A and B, differing only in the geometry of the C_9-esterifing acid, which is isosarracinic acid.



	R	R'
(162)	tiglyl	tiglyl
(163)	tiglyl	senecioyl
(164)	angelyl	tiglyl
(165)	angelyl	senecioyl
(166)	angelyl	angelyl

Finally senampelines E, F and G all have C_7 esterified with angelic acid while C_9 is esterified with isosarricinic acid acylated with tiglic, angelic or senecioic acids, as in structures (164)-(166).

2. SYNTHESES OF THE NECINES, NECIC ACIDS AND ALKALOIDS.

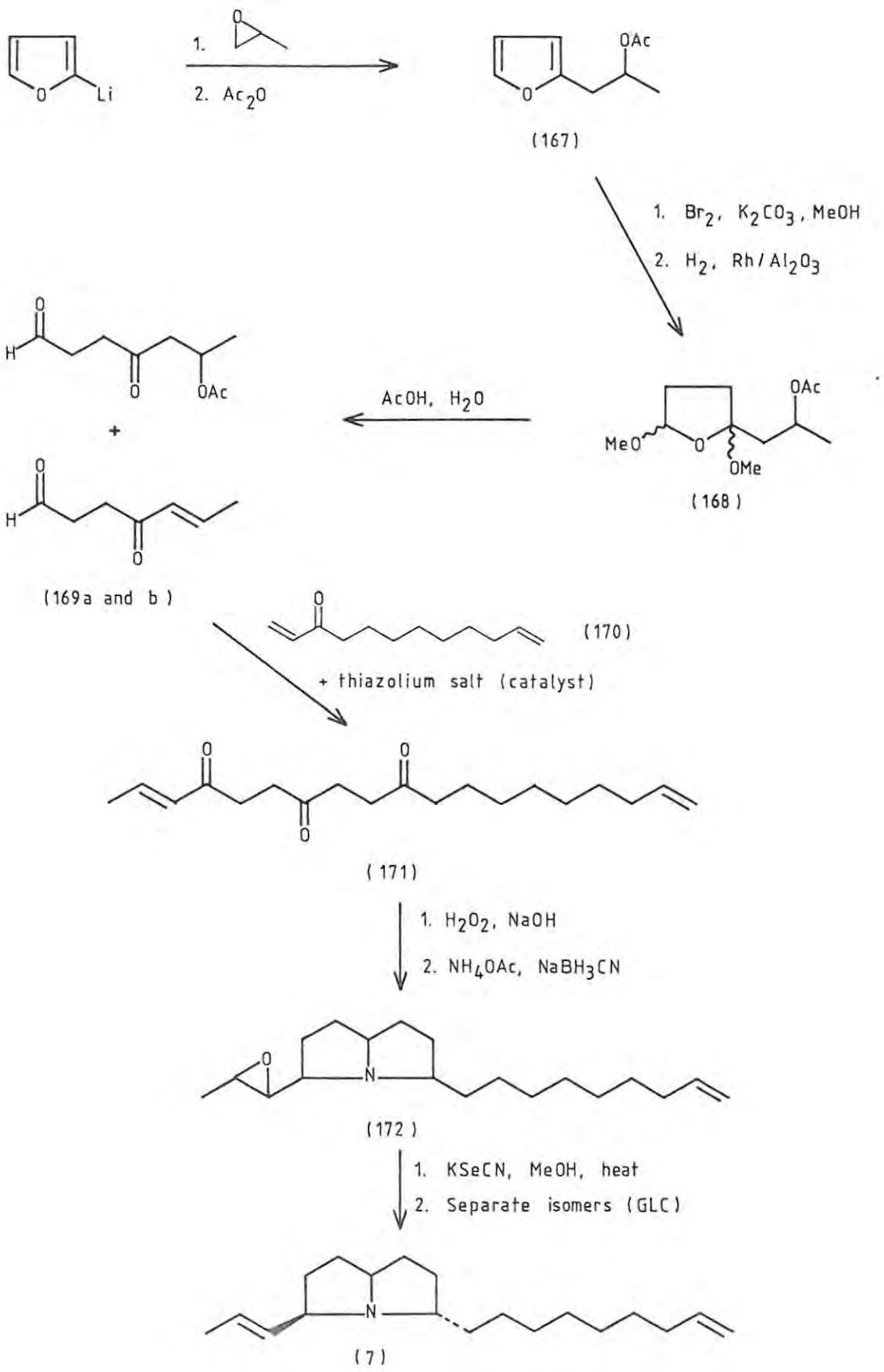
In recent years there has been an increase in the number of syntheses of both the necine bases and necic acids. Syntheses of these compounds had been reviewed earlier by Whiteley,[138,58] therefore only syntheses reported since 1976 will be discussed in this work.

2.1. Necine bases

Of the more than fifty reported syntheses of necines since 1976 most have concentrated on the simpler necines, principally isoretronecanol, trachelanthamidine, supinidine and retronecine. The synthetic approaches used are diverse yet fall into one of three types:- 1) synthesis of both rings from acyclic precursors; 2) formation of the second ring onto a heterocyclic precursor; and 3) modification of the existing pyrrolizidine system.

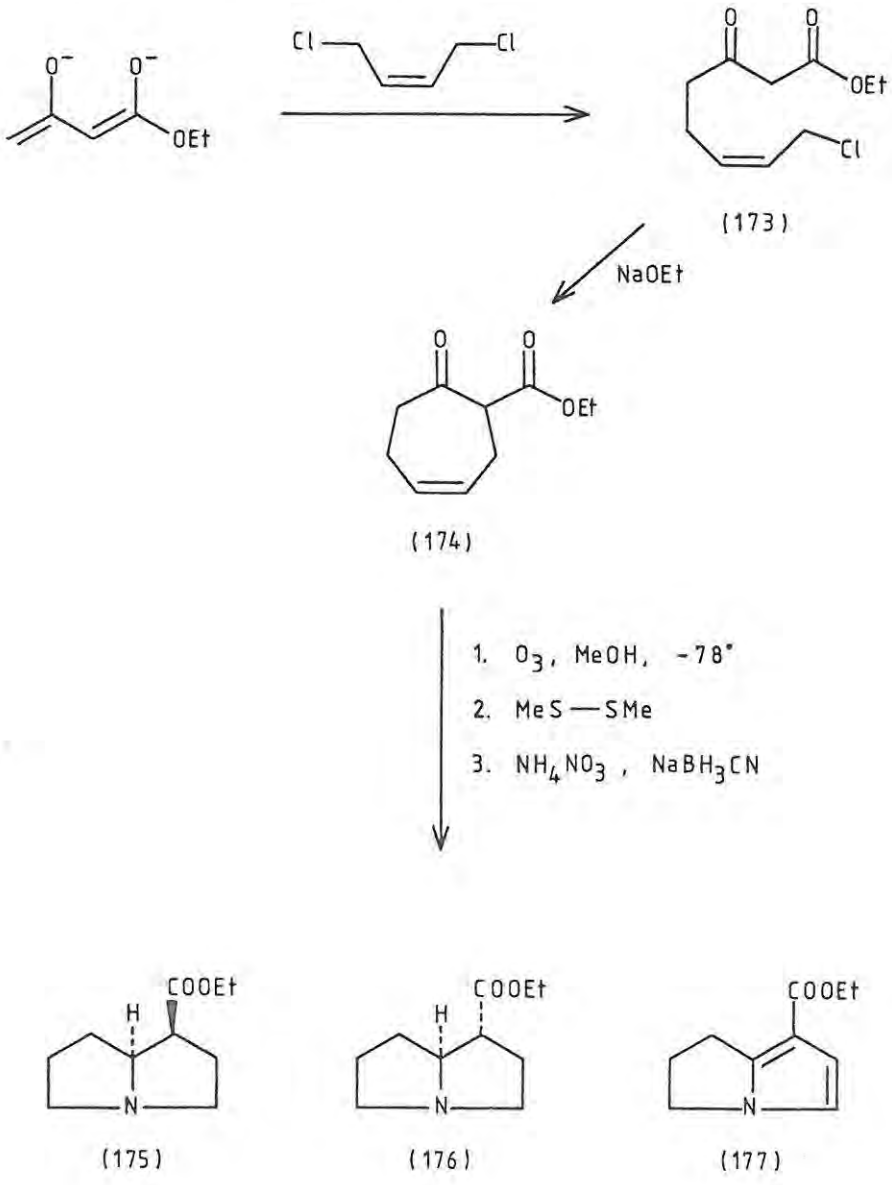
2.1.1. Syntheses from acyclic precursors

Conceptually the simplest route to the pyrrolizidine nucleus from acyclic precursors is the reductive amination of a suitable tricarbonyl compound with ammonia. This approach was used by Jones and coworkers[31] in their synthesis of the alkaloid (7). The ketoaldehyde mixture (169) was synthesised by treatment of 2-furyllithium with propylene oxide and acetic anhydride to give (167), [Scheme 1]. This, on oxidative methoxylation and selective hydrogenation gave (168), from which the unstable ketoaldehyde mixture (169a) and (169b) was obtained on acid hydrolysis.


1.
2. Ac2O
OAc
(167)
1. Br2, K2CO3, MeOH
2. H2, Rh/Al2O3
OAc
MeO
OMe
(168)
AcOH, H2O
OAc
(169a and b)
(170)
+ thiazolium salt (catalyst)
(171)
1. H2O2, NaOH
2. NH4OAc, NaBH3CN
(172)
1. KSeCN, MeOH, heat
2. Separate isomers (GLC)
(7)

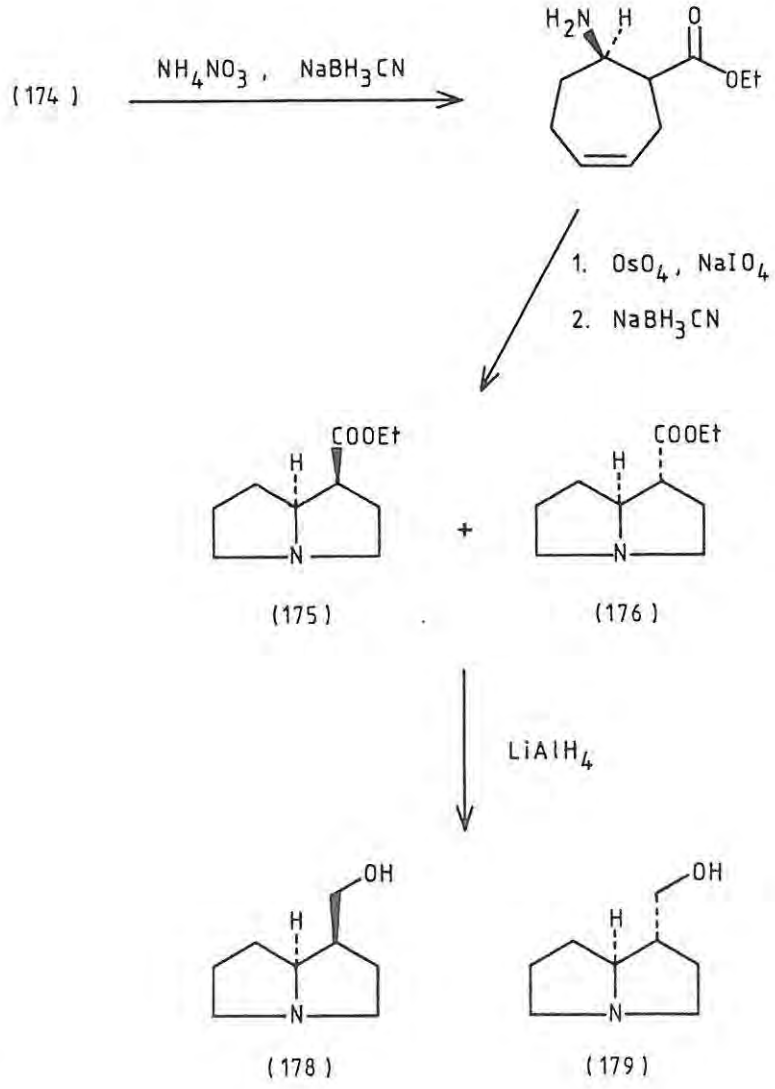
Scheme 1.

Condensation of the ketoaldehyde mixture (169a) and (169b) with freshly prepared vinyl ketone (170) provided the key tricarbonyl compound (171). The vinylic C=C bond of (171) was protected as the epoxide prior to the reductive amination step which gave the unstable epoxypyrrolizidine (172) as a mixture of isomers. Regeneration of the double bond was achieved using potassium selenocyanate, and the required isomer (7) isolated from the mixture of isomers by GLC.



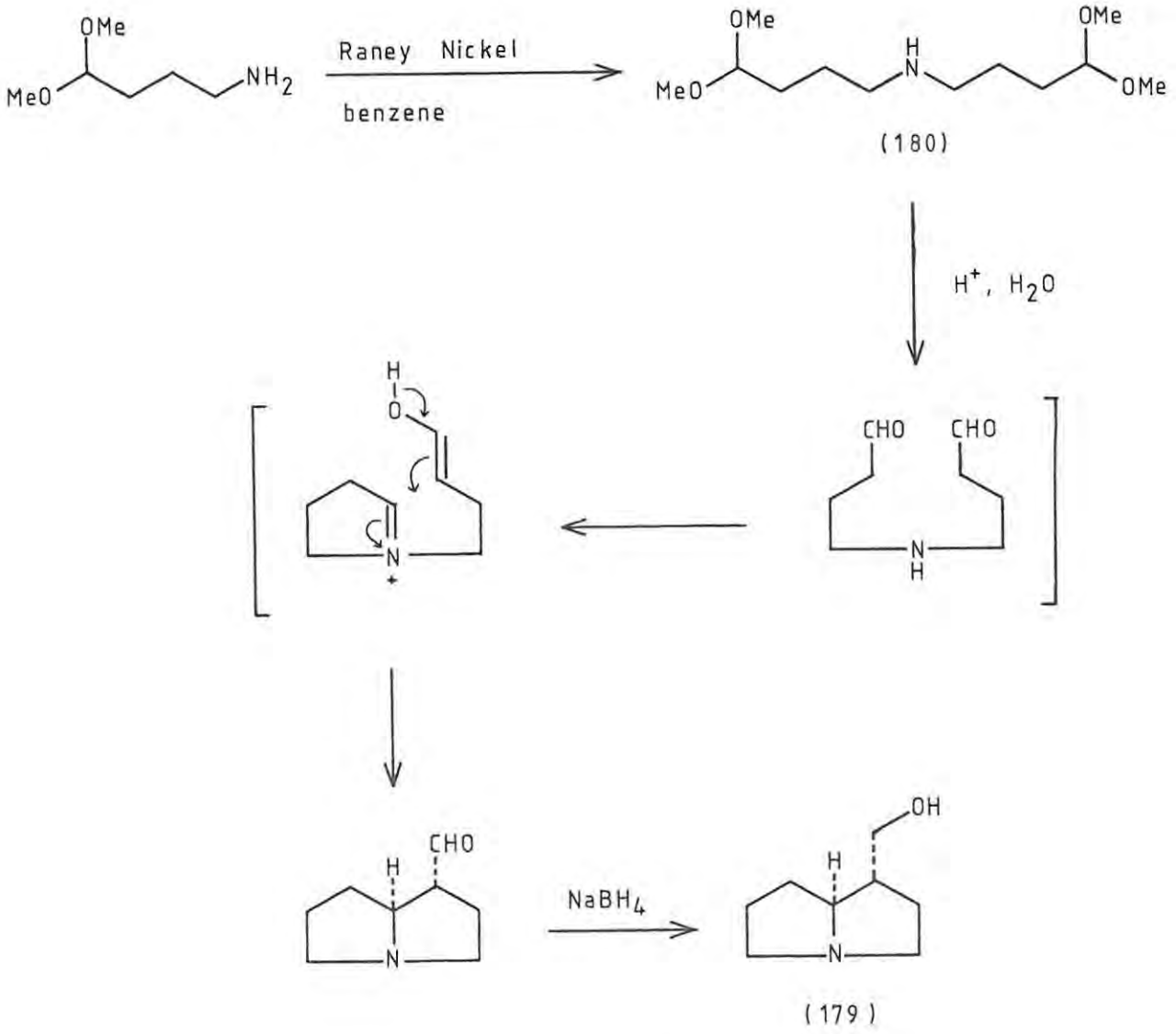
Scheme 2.

The approach used by Borch and Ho[139] is also essentially the reaction of a tricarbonyl compound (generated in situ) with ammonia, [Scheme 2]. Reaction of ethyl acetoacetate dianion with cis-1,4-dichloro-2-butene gave, in low yield, the chloro-octenoate (**173**), which was cyclised to (**174**), the precursor of the required tricarbonyl compound. This, on ozonolysis, reduction of the ozonide and immediate reaction with ammonium nitrate-sodium cyanoborohydride gave the pyrrolizidine esters (**175, 176**) and some pyrrole (**177**).



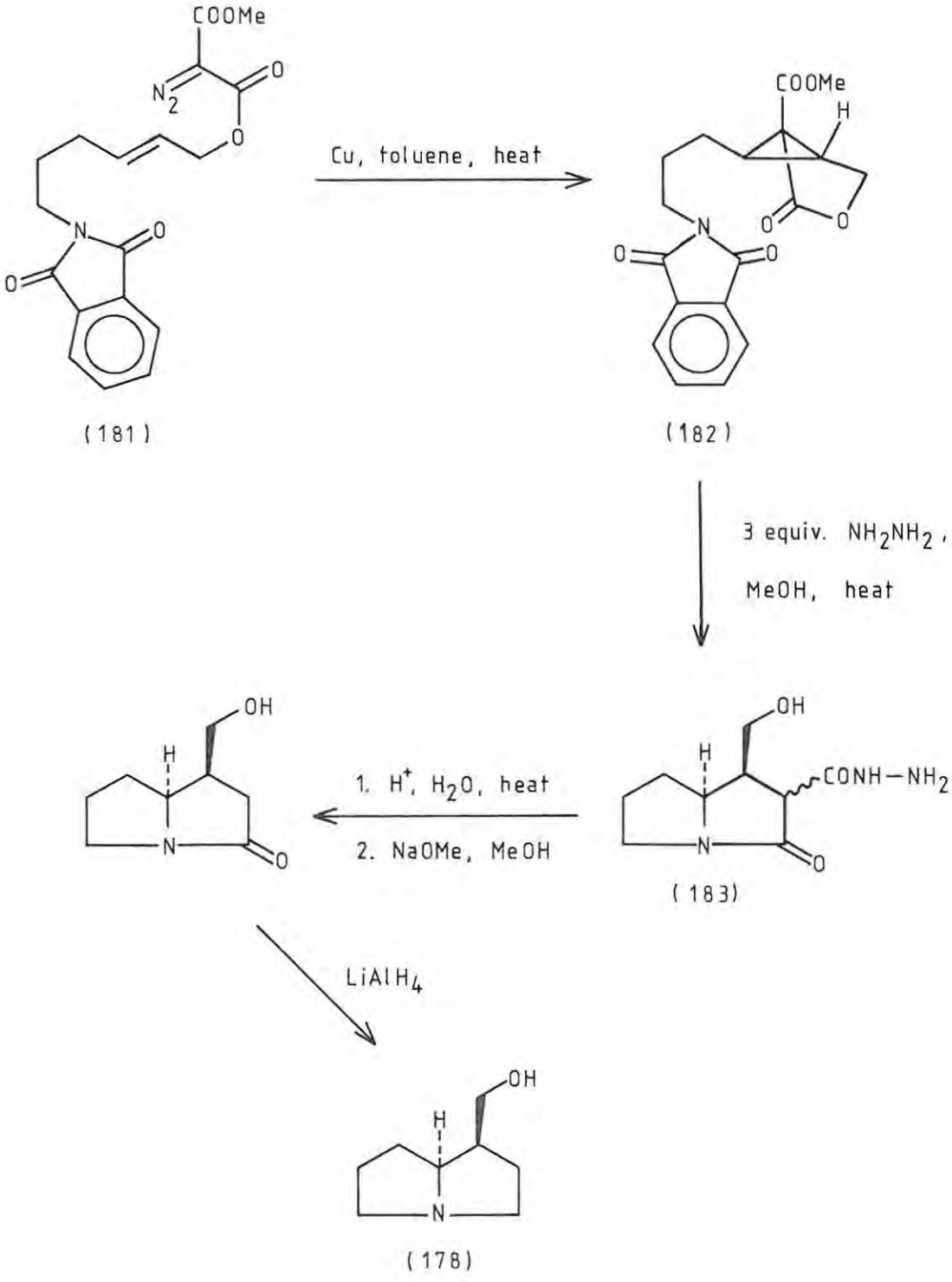
Scheme 3.

Because of the low overall yields achieved, a second route, involving prior introduction of the nitrogen atom, was developed at the same time, [Scheme 3]. Yields improved by aminating (**174**) first, then carrying out the oxidation-reduction step to obtain the esters (**175**, **176**) as before. A final reduction of the esters gave racemic isoretronecanol (**178**) and racemic trachelanthamidine (**179**).



Scheme 4.

A related approach is that of Takano and coworkers,[140] [Scheme 4]. Hydrolysis of the aminoacetal (**180**) in the

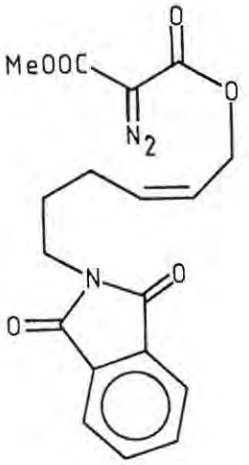

COOMe
N2
O
O
O
N
O
O
(181)
Cu, toluene, heat
COOMe
H
O
O
N
O
O
(182)
3 equiv. NH2NH2,
MeOH, heat
OH
H
CONH—NH2
N
O
(183)
1. H+, H2O, heat
2. NaOMe, MeOH
OH
H
N
O
LiAlH4
OH
H
N
(178)

Scheme 5.

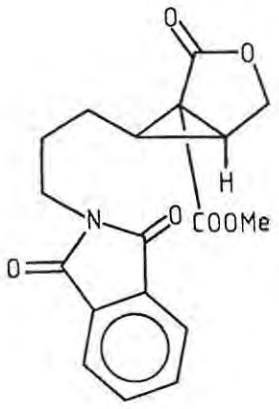
presence of pyridinium (+)camphor-10-sulphonate led to spontaneous cyclisation to the pyrrolizidine aldehyde, which gave racemic trachelanthamidine (179) on reduction.

Danishefsky and coworkers made use of the reactivity of doubly activated cyclopropanes in their syntheses of isoretronecanol and trachelanthamidine.[141] The required cyclopropane intermediate (182), [Scheme 5], for the isoretronecanol synthesis was obtained via a highly stereospecific intramolecular carbene insertion reaction, the carbene being generated by the copper catalysed thermolysis of the E-diazomalonate (181). Deprotection of the amine induced the stereospecific intramolecular attack on the cyclopropane with concommitent ring opening and formation of the lactam hydrazide (183). Deacylation and reduction of the pyrrolizidinone gave the desired product.

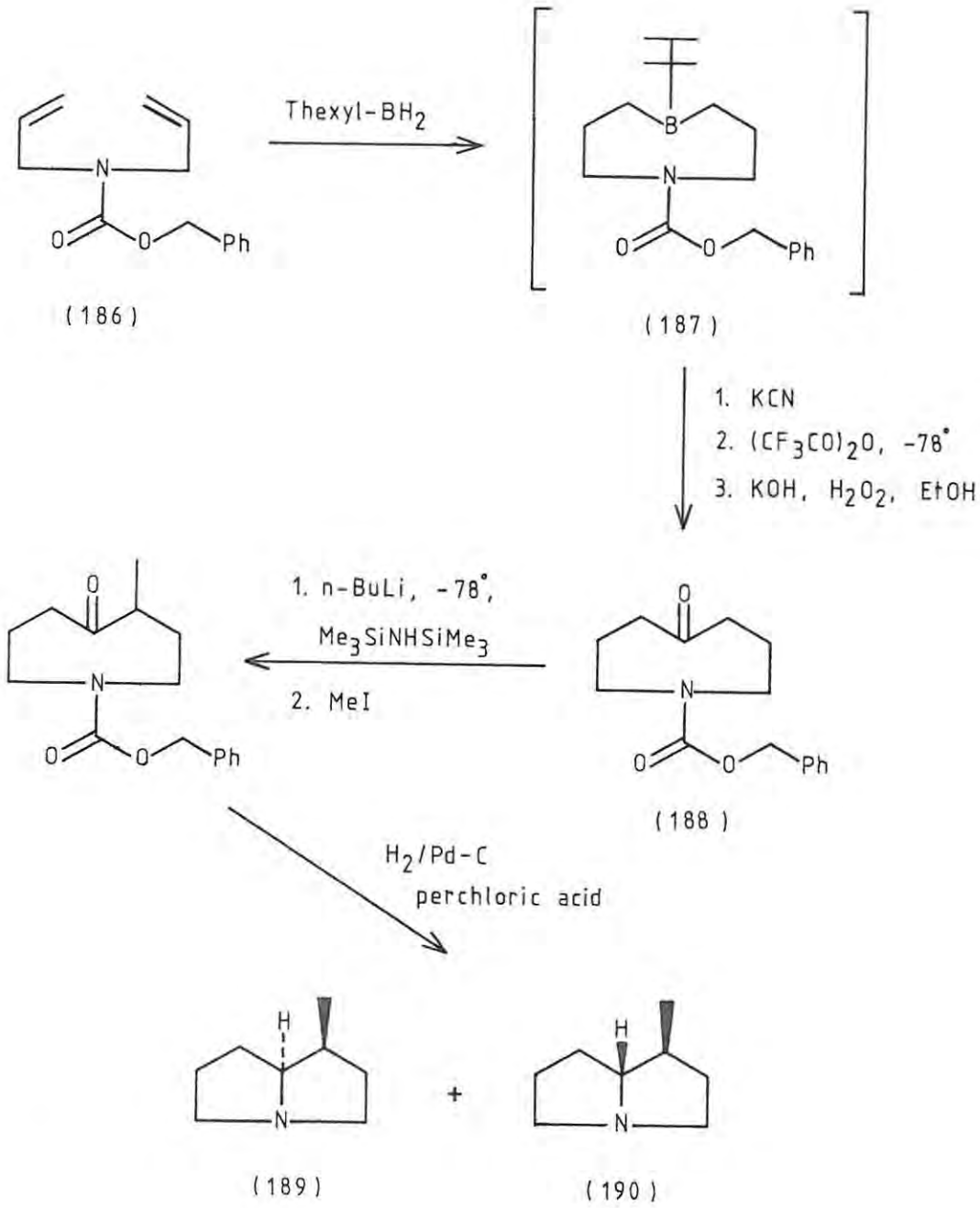
The synthesis of trachelanthamidine was similarly effected from the Z-diazomalonate (184), the precursor of cyclopropane (185).



(184)



(185)

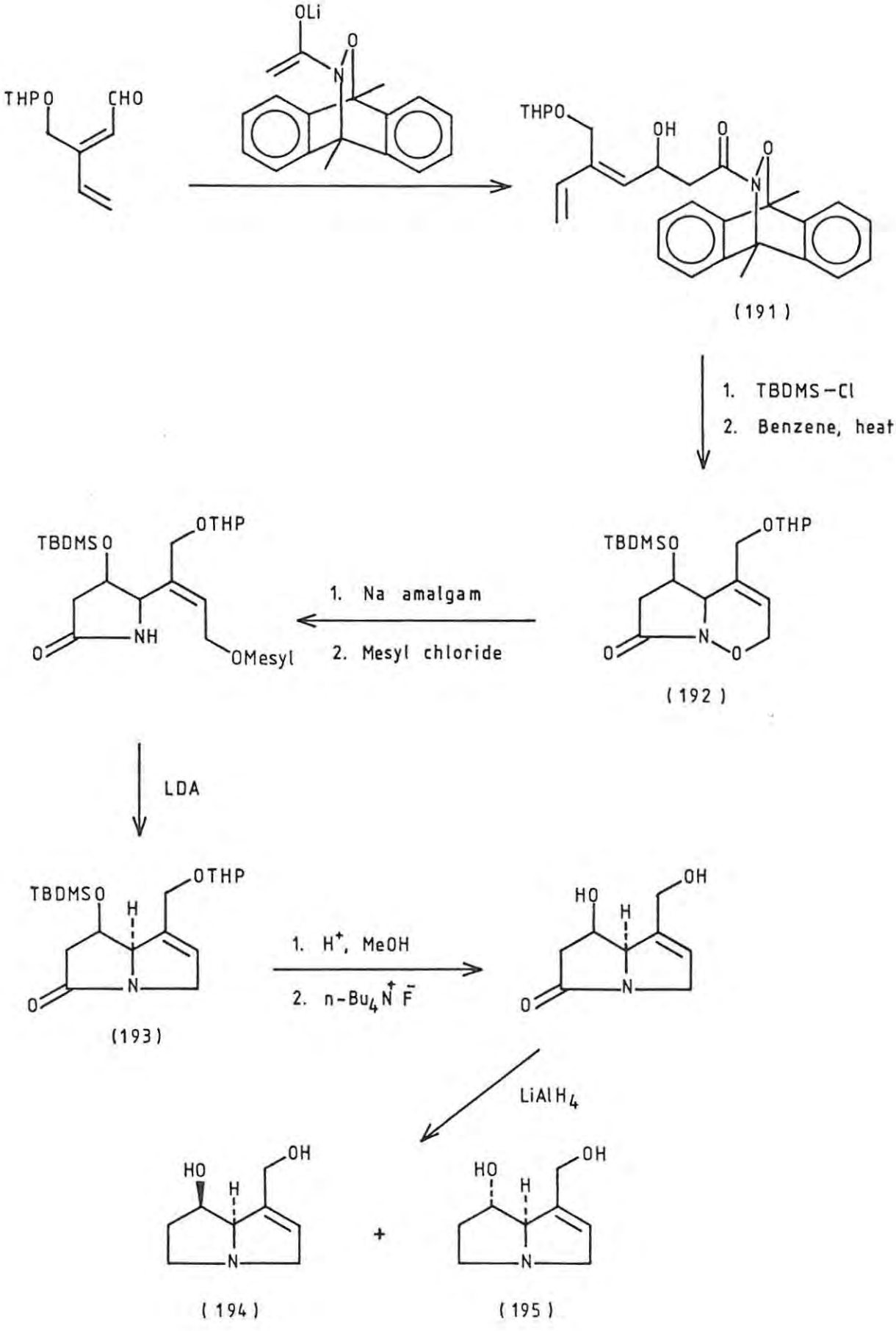


Scheme 6.

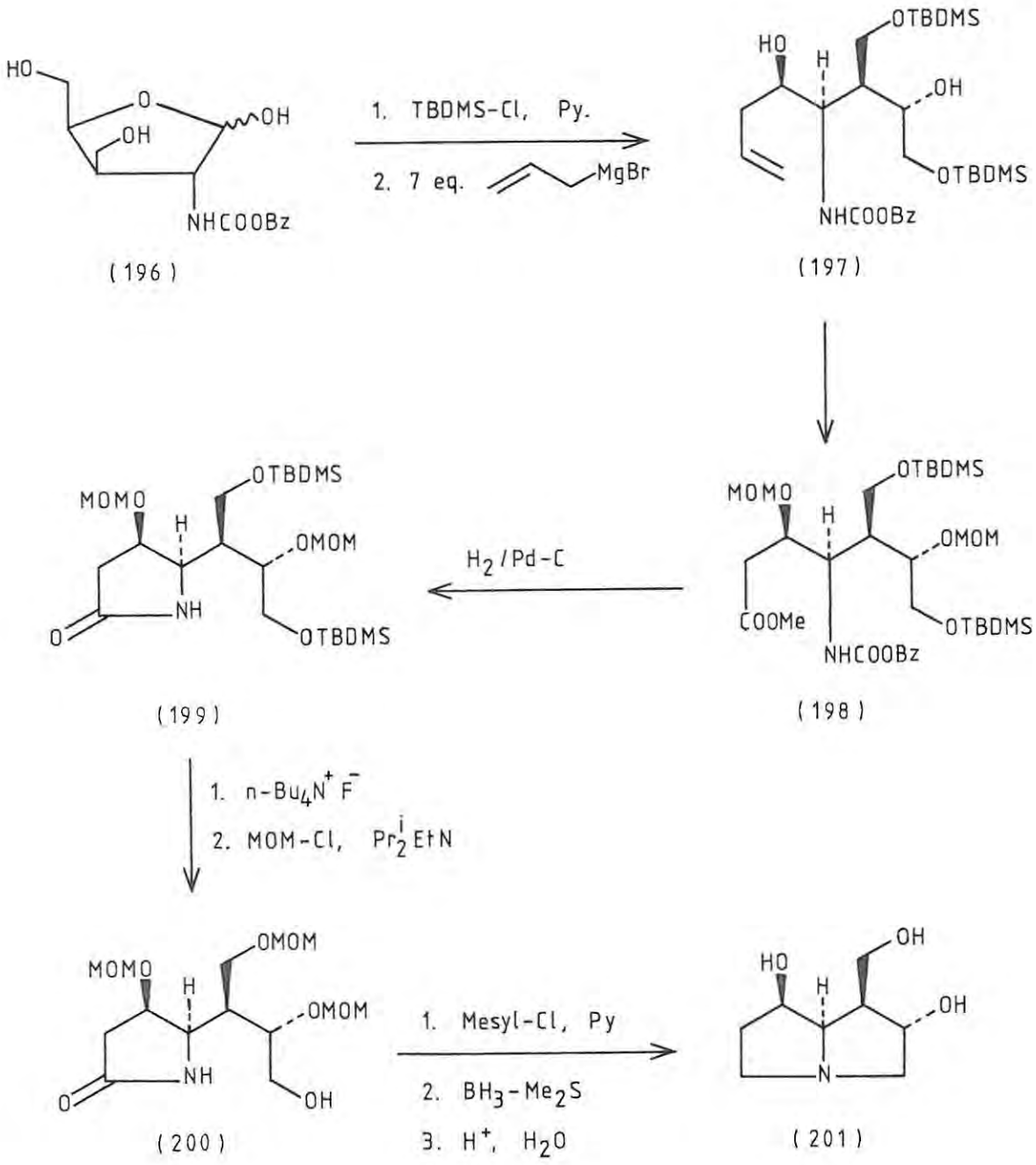
Recently a hydroboration-carbon monoxide insertion pathway has been developed by Garst et al,[142] [Scheme 6]. Hydroboration of the diallylamine (186) using thexylborane, and cyanidation of the resultant borane intermediate (187) gave azacyclooctanone (188). Methylation of the enolate anion of (188) followed by catalytic reduction gave a mixture of heliotridane (189) and pseudoheliotridane (190).

All the preceding approaches have generated the two rings of the pyrrolizidine nucleus in a single step of the reaction sequence. Other approaches have synthesised the nucleus in two separate steps. Thus Keck and Nickell[143] in their synthesis of the diastereomers retronecine and heliotridine first assembled the acylnitroso derivative (191), [Scheme 7]. This structure already possesses all the carbon, nitrogen and oxygen atoms of the target necines. Ring formation was accomplished by intramolecular transfer of the acylnitroso portion to form the cycloaddition product (192). Cleavage of the N-O bond, production of the mesylate followed by treatment with lithium diisopropylamide gave the pyrrolizidinone (193) as a mixture of diastereomers. These were separated, the protection groups removed and the lactam groups reduced to give either racemic retronecine (194) or its diastereomer heliotridine (195), depending on the diastereoisomer (193) used.

In the last few years there has been increasing interest in the use of sugars as starting materials in organic syntheses. This can be attributed to their cost, availability and precise stereochemistry. These facts along with the advances in protective group chemistry has led to their use in a variety of applications. In the synthesis of necines this approach has been used by Tatsuta and coworkers in their stereoselective synthesis of (-)isoretronecanol and (-)rosmarinecine.[144] Based on earlier work[145] D-glucosamine was converted into the furanoside (196), [Scheme 8]. Protection of the primary hydroxyls and reaction with allyl magnesium bromide gave the amidoalcohol (197).


OLi
THPO
CHO
O
N
THPO
OH
(191)
1. TBDMS-Cl
2. Benzene, heat
TBDMSO
OTHP
1. Na amalgam
2. Mesyl chloride
NH
OMesyl
(192)
LDA
H
(193)
1. H+, MeOH
2. n-Bu4N+ F-
HO
OH
LiAlH4
+
(194)
(195)

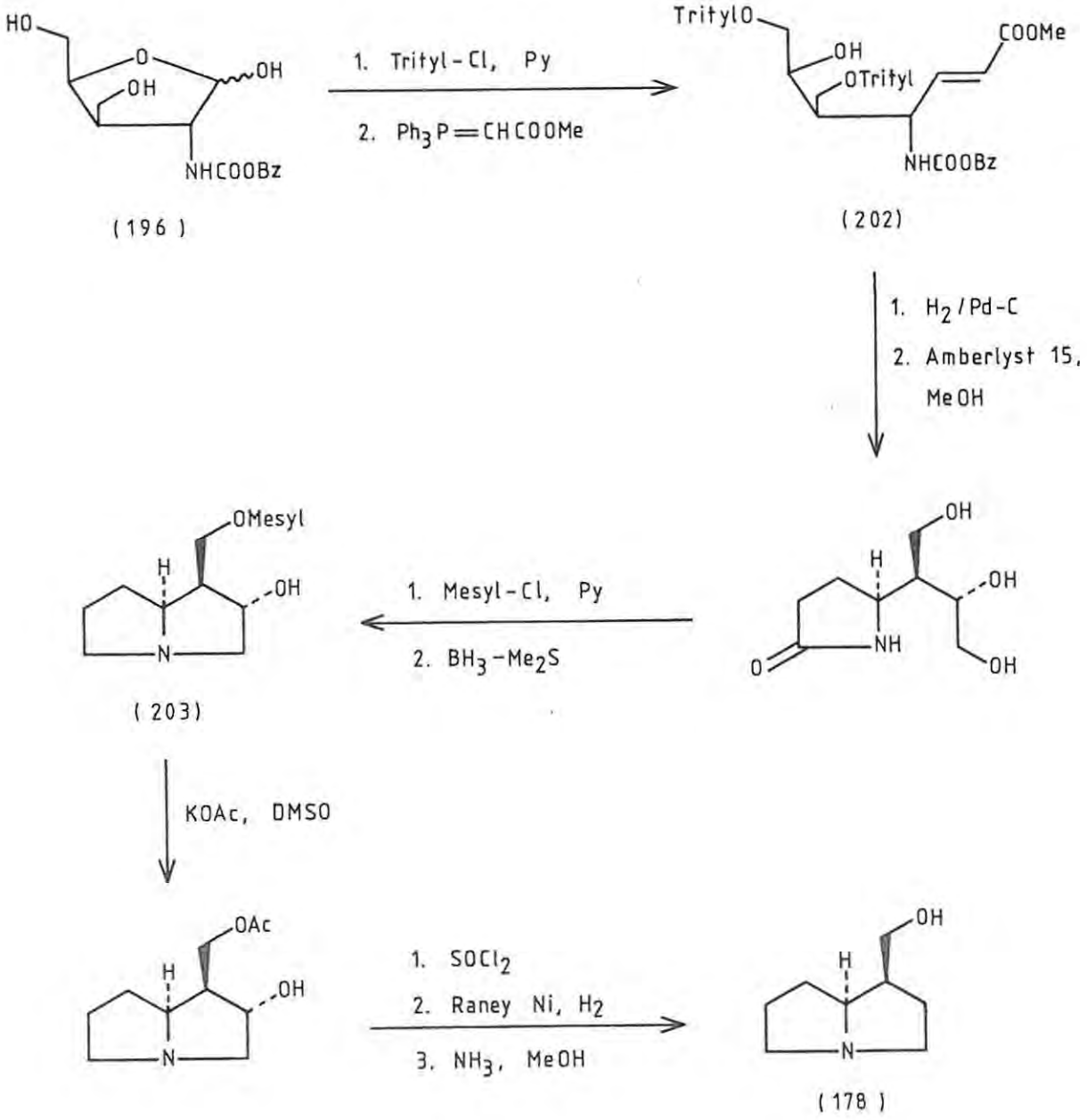
Scheme 7.



Scheme 8.

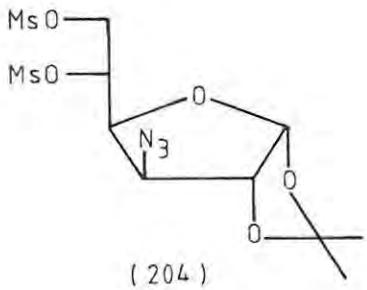
The very high stereoselectivity of the reaction is presumed to arise by a chelation controlled approach of the Grignard reagent to the anomeric carbon of the furanoside. The alkenyl side chain of (197) was then oxidised and esterified, and the hydroxyls protected as their MOM ethers giving (198).

Selective reductive removal of the N-protecting group and subsequent cyclisation gave (199). Removal of the silane protecting groups and selective methoxymethylation gave (200) as the major product. Mesylation of the remaining hydroxy group followed by reductive cyclisation using borane-methyl sulphide, and a final deprotection gave (-)rosmarinecine (201) as the final product.

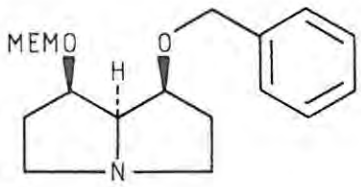


Scheme 9.

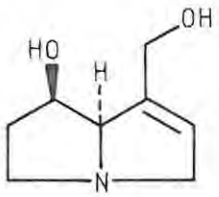
Synthesis of (-)isoretronecanol from (196) required the removal of the oxygen functionality at the anomeric carbon, [Scheme 9]. This was effected prior to the sequential cyclisation procedure of Scheme 8 by protection of the primary hydroxyl groups of (196), followed by a Wittig reaction which gave (202). Reduction and successive cyclisation as before gave the pyrrolizidine (203). This was converted to the monoacetate and then subjected to dehydrochlorination, reduction and hydrolysis, to yield (-)isoretronecanol (178).



(204)



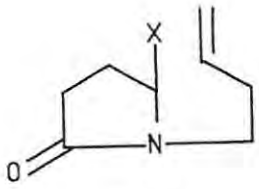
(205)



(194)

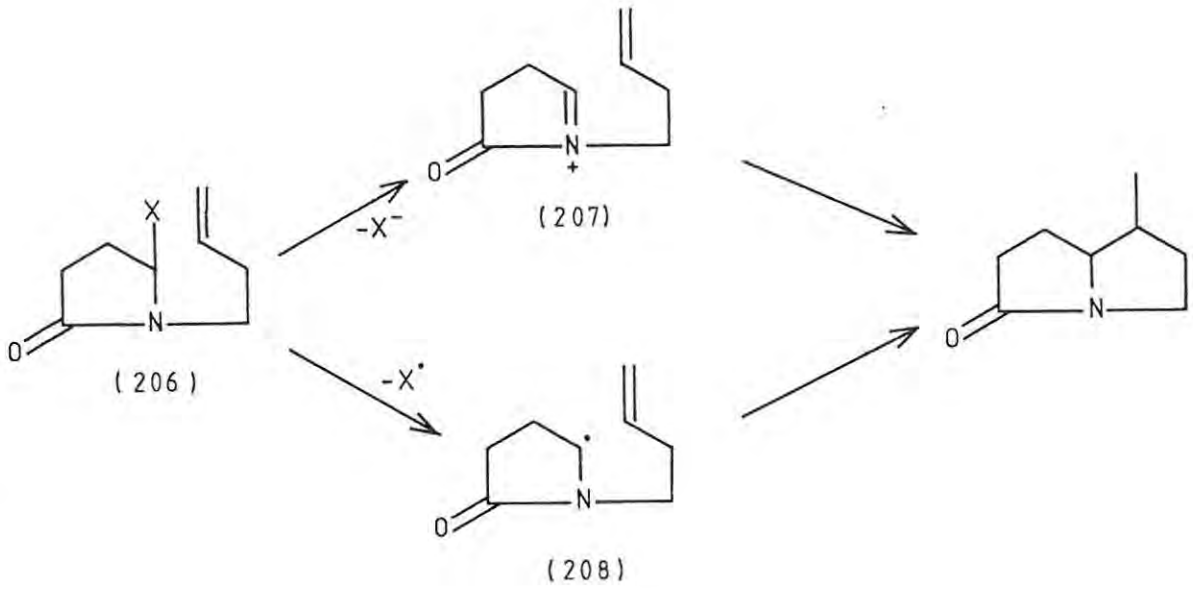
More recently Nishimura et al[146] have synthesised both isomers of retronecine from the modified glucofuranose (204). A lengthy series of manipulations converted (204) into the differentially protected pyrrolizidine diol (205). Selective removal of one or the other of the protecting groups, followed by a parallel series of reactions, produced the required isomers of retronecine (194).

Two other groups, Hart and Yang,[147] and Chamberlin and Chung,[148] have synthesised necines from acyclic precursors. Although their approaches differ in detail, the key intermediate required, for the formation of the second ring in both approaches, resembled structure (**206**, X = various leaving groups).



(**206**)

Compounds containing structure (**206**) are readily available from succinimides, either via N-alkylation using homoallylic halides, or via Mitsunobu coupling using homoallylic alcohols.[149]

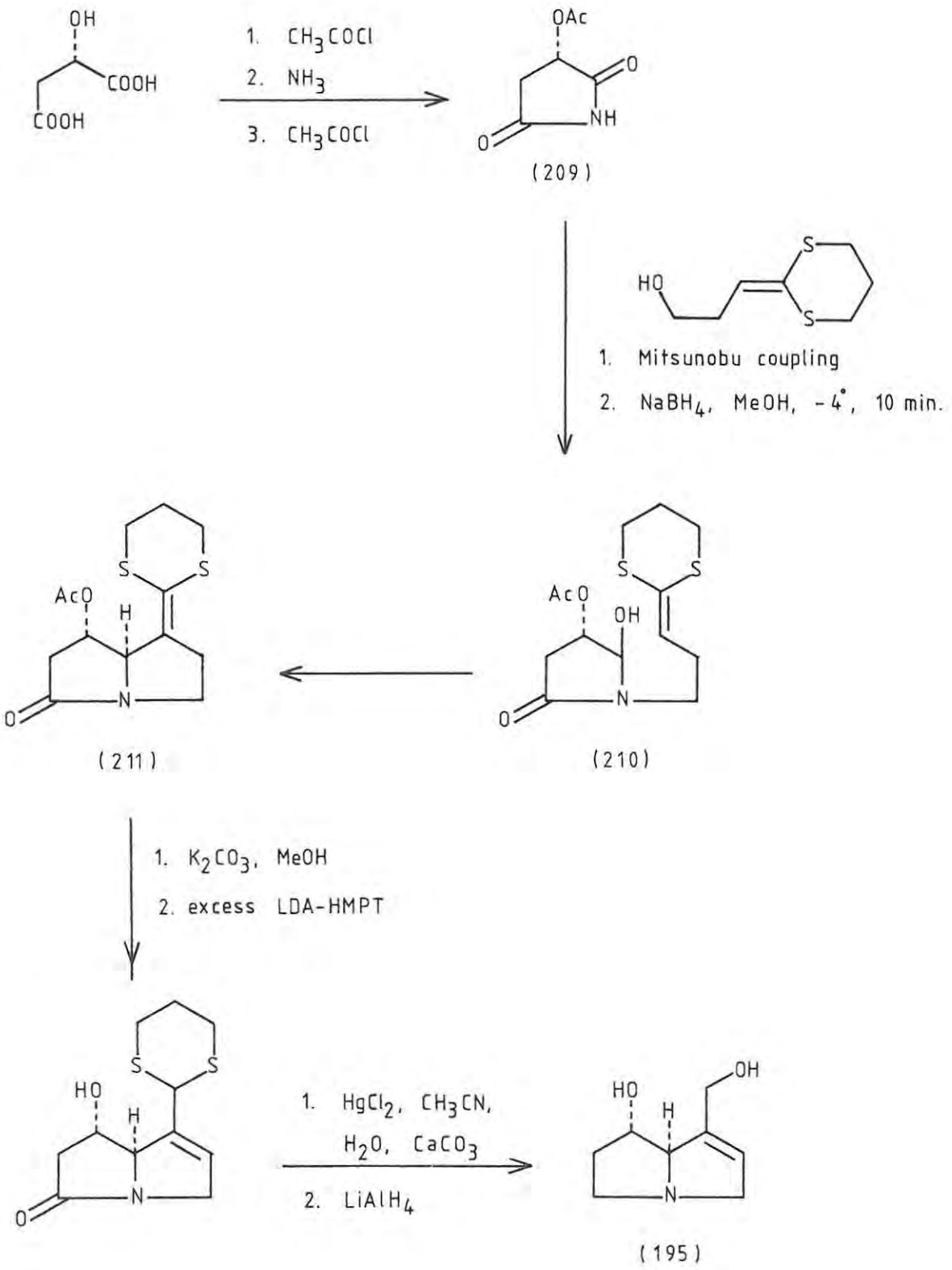


Scheme 10.

Conversion of structure (**206**) into a pyrrolizidine ring system can be effected by two routes, either via formation of the -acyliminium ion (**207**), or via the -acylamino radical (**208**), [Scheme 10].

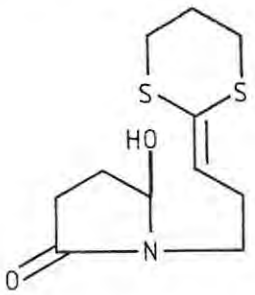
Illustrative of the α-acyliminium ion approach to pyrrolizidines is the enantioselective synthesis of (+)heliotridine by Chamberlin and Chung.[148] Treatment of S-malic acid with acetyl chloride, then gaseous ammonia and again with acetyl chloride completed the synthesis of the first ring as the succinimide (209), [Scheme 11]. Mitsunobu coupling of (209) with 2-(3-hydroxypropylidene)-1,3-dithiane followed by a regioselective controlled sodium borohydride reduction then gave the acyliminium ion precursor (210) as a mixture of isomers. Generation of the iminium ion and cyclisation to pyrrolizidine (211) was accomplished by reaction with mesyl chloride and triethylamine at -20° followed by warming to room temperature. The high stereoselectivity of the cyclisation is due in large part to the steric hindrance by the acetoxy group at the α-face of the acyliminium ion. Conversion of (211) to (+)heliotridine (195) was effected by hydrolysis of the acetoxy group, migration of the carbon-carbon double bond into the endocyclic position using excess lithium diisopropylamide-hexamethylphosphoramide, removal of the dithiane by mercuric chloride hydrolysis, and finally, hydride reduction of the resultant aldehyde and lactam.

In a subsequent paper,[150] Chamberlin and Chung also reported the transformation of (211) into (-)dihydroxyheliotridane, (+)hastanecine, (+)dehydroheliotridine, (-)turneforcidine, (-)platynecine and (+)retronecine by suitable adjustment of the oxidation levels and stereochemistry of the substituents.

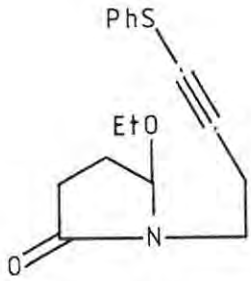

OH
COOH
COOH
1. CH_3COCl
2. NH_3
3. CH_3COCl
OAc
O
NH
O
(209)
HO
S
S
1. Mitsunobu coupling
2. $NaBH_4$, MeOH, -4°, 10 min.
AcO
H
S
S
O
N
(211)
AcO
OH
S
S
O
N
(210)
1. K_2CO_3, MeOH
2. excess LDA-HMPT
HO
H
S
S
O
N
1. $HgCl_2$, CH_3CN, H_2O, $CaCO_3$
2. $LiAlH_4$
HO
OH
H
N
(195)

Scheme 11.

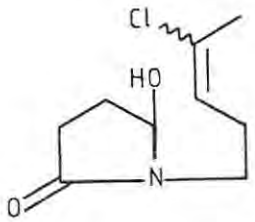
Other syntheses using the acyliminium ion route include dl-supinidine[151] via (212), dl-trachelanthamidine and dl-isoretronecanol[152] via (213), (the acetylenic equivalent of (206)), some synthetic pyrrolizidines[153] via (214) or substituted variants thereof, and of (-)heliotridine and (-)hastanecine[147,154] via (215).



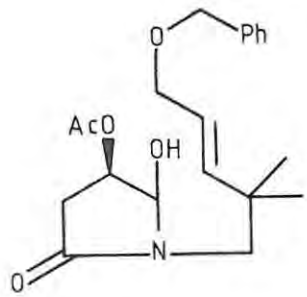
(212)



(213)

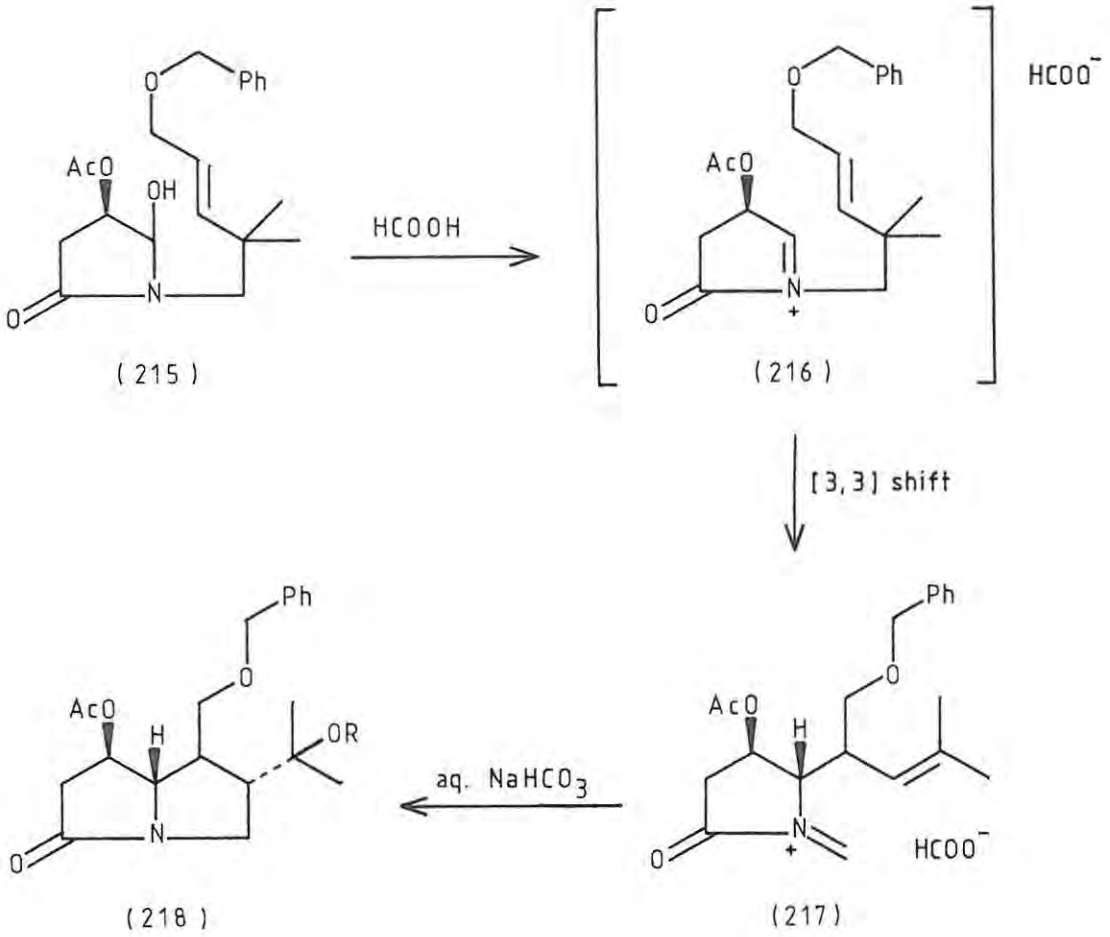


(214)



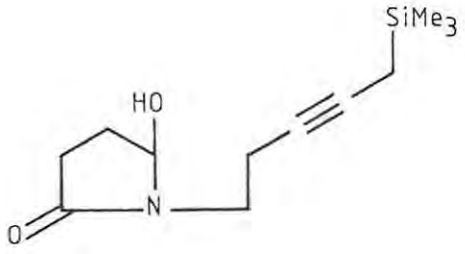
(215)

Interestingly, the cyclisation of (215) is more complex than in other cases, and has been explained by a rearrangement cyclisation pathway, [Scheme 12]. Thus generation of the expected endocyclic acyliminium ion (216) is followed by a rapid rearrangement to the exocyclic acyliminium ion (217). Cyclisation of this ion leads to the observed product (218), predominantly as the formate (R=CHO), but with some free alcohol (R=H).

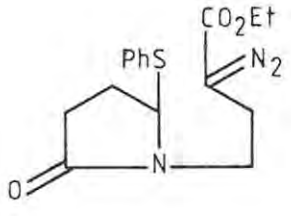


Scheme 12.

More recently isoretronecanol has been synthesised via (219) by Speckamp and coworkers,[155] and very recently supinidine, trachelanthamidine and isoretronecanol have been synthesised via (220) by Kametani's group.[156]



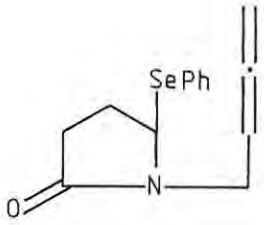
(219)



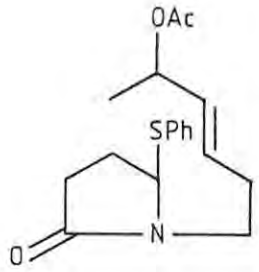
(220)

An alternate route via α-acylamino radicals has been explored by Hart's group[157] and has resulted in the synthesis of

supinidine[158] via the radical precursor (221), and isoretronecanol[159] via (222).



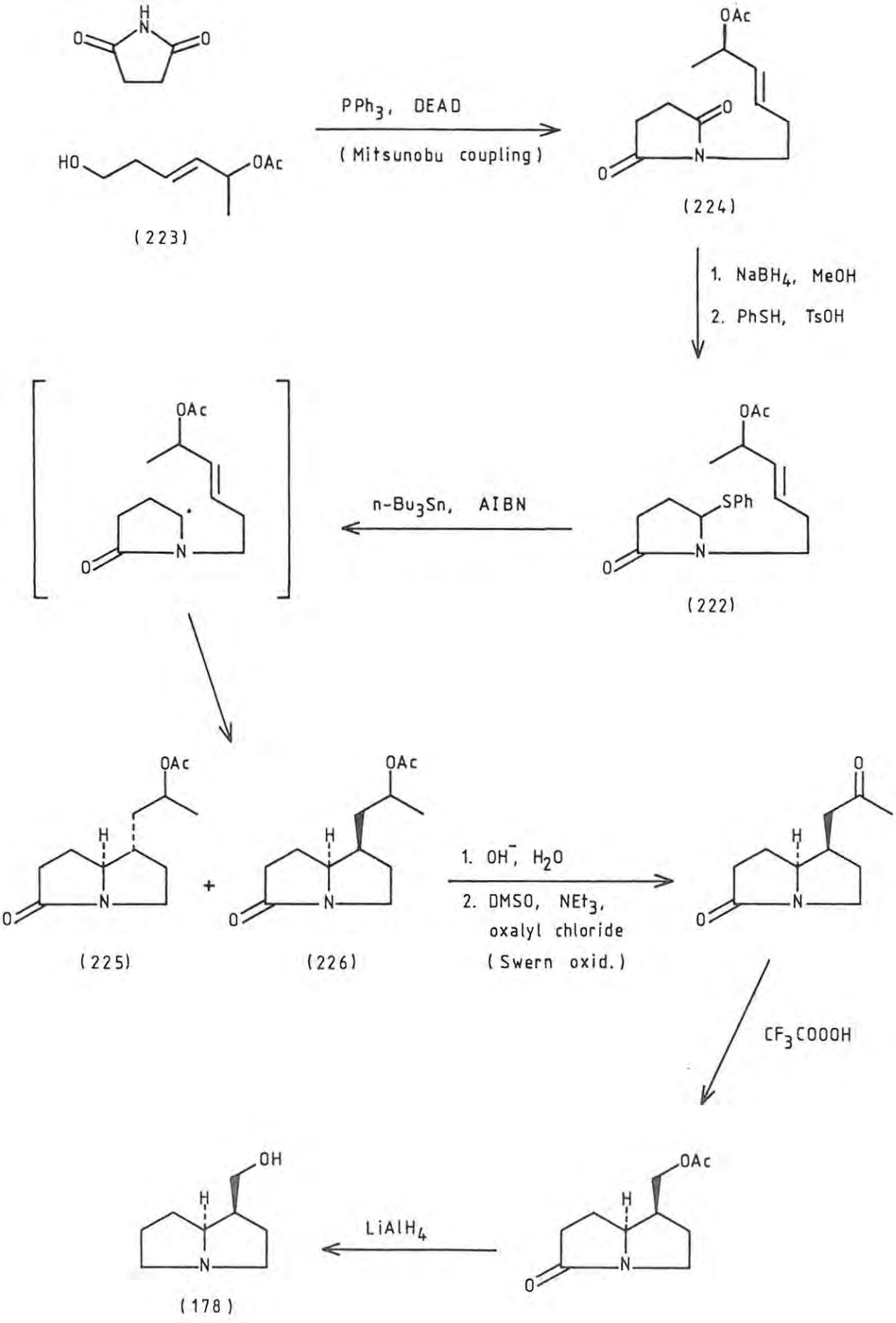
(221)



(222)

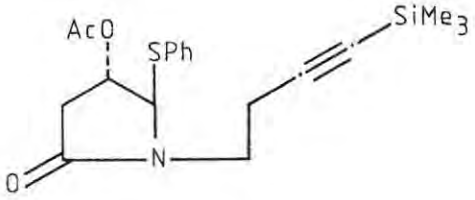
The synthetic approach employed in these syntheses is very similar to the approach used in the acyliminium ion route. Thus Mitsunobu coupling of succinimide with the alkenol (223) gave the succinimide (224), [Scheme 13]. This was converted into the radical precursor (222) by controlled reduction and hydroxy-thiophenoxy exchange. Generation of the free radical by treatment with tributyltin hydride and azobis-isobutyronitrile, (AIBN), and subsequent exocyclisation gave a 1:9 mixture of the pyrrolizidinones (225) and (226) along with small amounts of a 5,6-fused indolizidinone arising from an endocyclisation reaction. The high stereoselectivity has been shown to be largely due to steric effects, in addition to possible stabilisation by the acetoxy group of the transition state intermediate in the exocyclisation reaction. The major isomer (226) was converted to racemic isoretronecanol (178) by hydrolysis, Swern oxidation, Baeyer-Villager oxidation and finally hydride reduction.[159]

More recently Hart and Choi[160] have used (227) as the free radical precursor in the enantioselective synthesis of the three bases (+)heliotridine, (+)hastanecine and (-)dehydro-

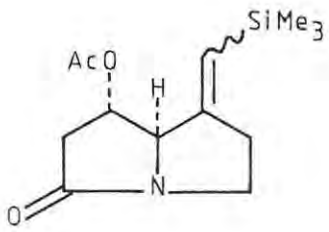

PPh3, DEAD
(Mitsunobu coupling)
(223)
(224)
1. NaBH4, MeOH
2. PhSH, TsOH
n-Bu3Sn, AIBN
(222)
(225)
(226)
1. OH⁻, H2O
2. DMSO, NEt3,
oxalyl chloride
(Swern oxid.)
CF3COOOH
LiAlH4
(178)

Scheme 13.

hastanecine. Cyclisation of (227) gave (228), from which the three bases were obtained by subsequent oxidation and reduction steps.

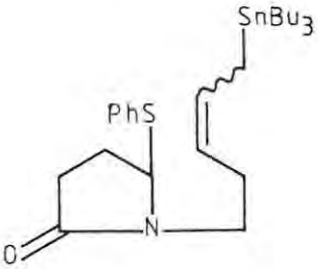


(227)

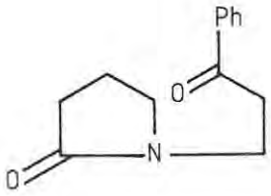


(228)

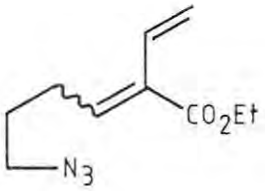
Two other syntheses, both of isoretronecanol, have made use of the α-acylamino free radical route. Keck and Enholm[161] used the alkylstannane (229) as the radical precursor, and (230) was the precursor used by Gramain and coworkers.[162]



(229)



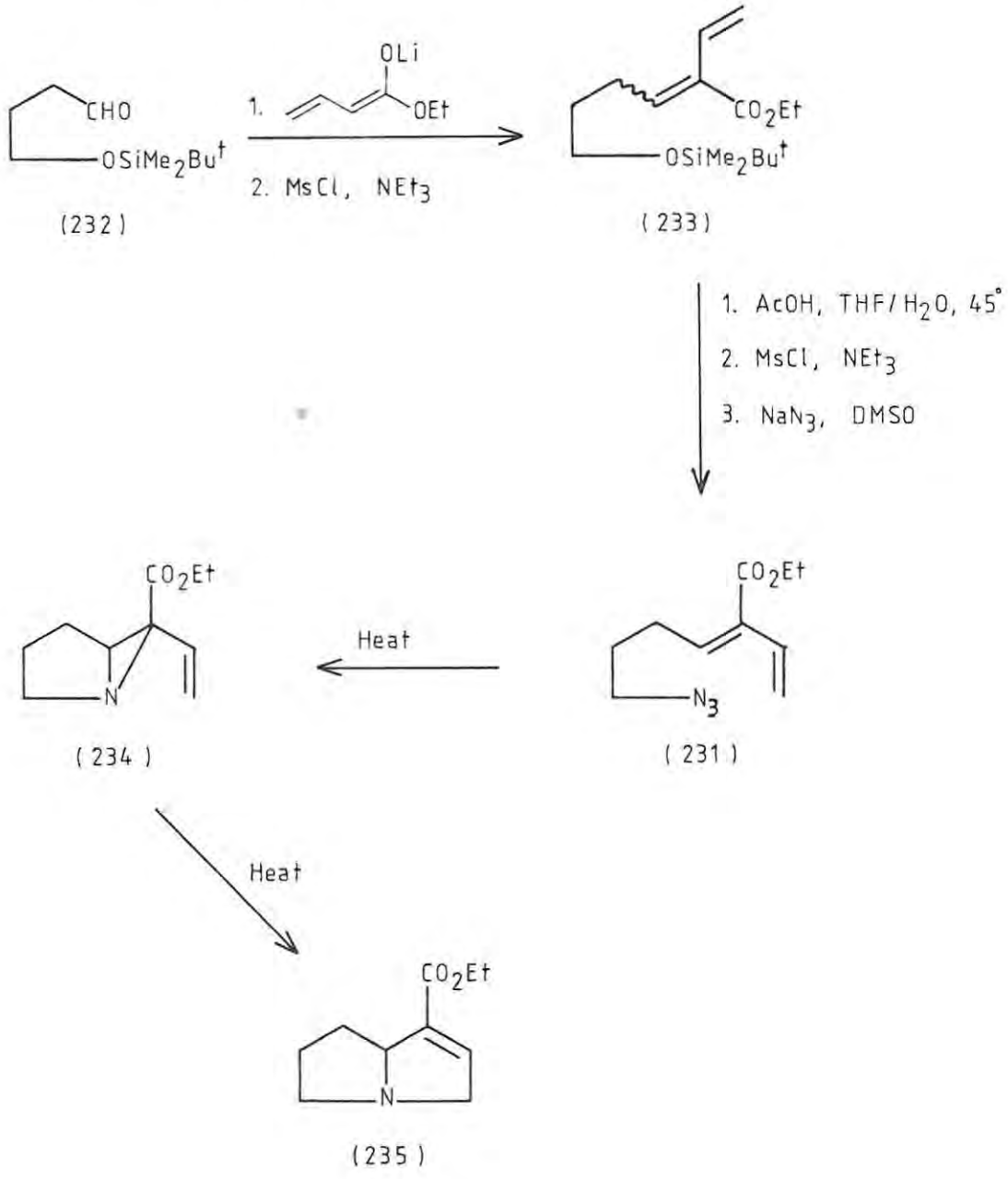
(230)



(231)

The most recently devised route to pyrrolizidines from acyclic precursors is that of intramolecular cycloaddition of azides developed independently by Pearson,[163] and by Hudlicky and coworkers.[164,165] The key intermediate required is the azidodiene (231). Pearson synthesised this compound from

the known aldehyde (232) by reaction with the lithium enolate of ethyl crotonate, followed by elimination to give the diene (233), [Scheme 14]. Deprotection, mesylation and azide displacement led to the required (231). Hudlicky's group generated the same intermediate by a similar route, differing only in the sequence of events.[164,165]

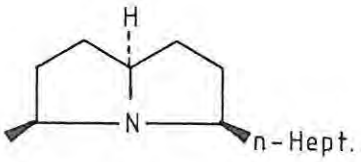


Scheme 14.

Thermolysis of (231) under a variety of conditions led, via (234), to a number of products. One of these was (235) from which supinidine, trachelanthamidine and isoretronecanol were obtained by reduction.

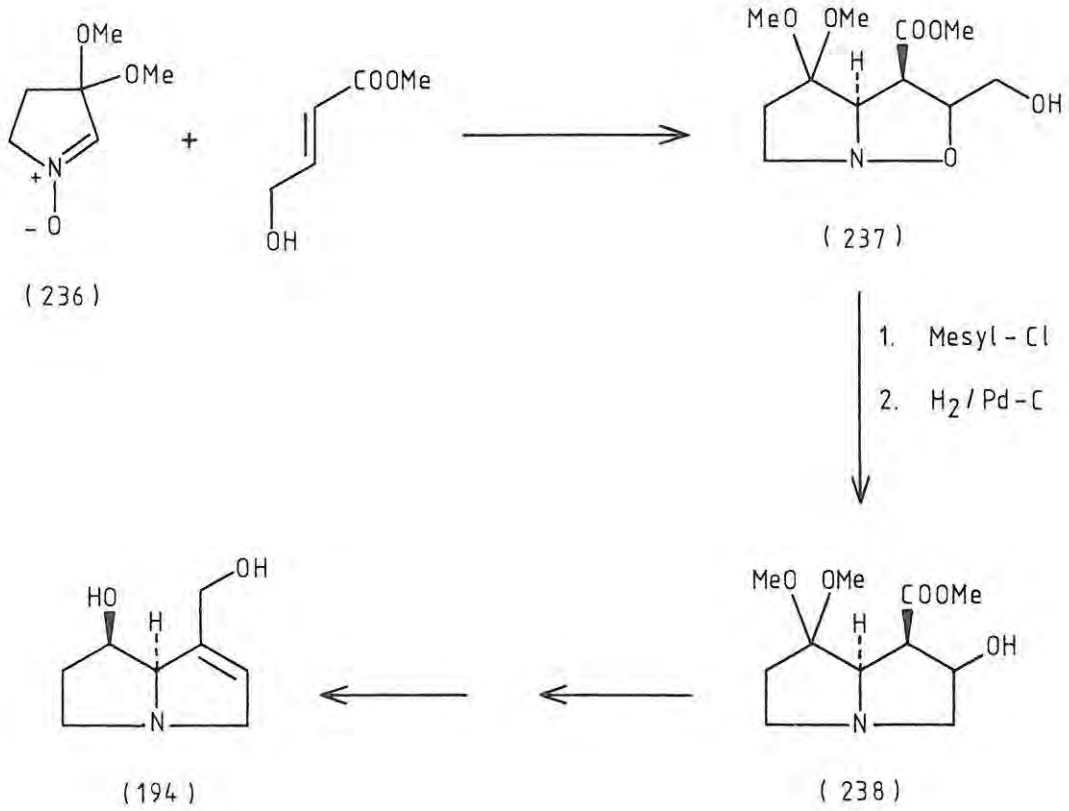
2.1.2. Synthesis from an N-heterocyclic precursor.

Elaboration of an existing heterocycle by 1,3-dipolar cycloaddition has been used previously as a route to necines.[166,167] This has now been extended by the synthesis of dl-retronecine,[168,169] dl-isoretronecanol,[170] and croalbinecine.[171] Isoretronecanol has also been synthesised in both optically active forms, as has supinidine and trachelanthamidine.[172,173] The lolium alkaloids loline and norloline, and the ant 'alkaloid' (6) have also been synthesised.[174,175]

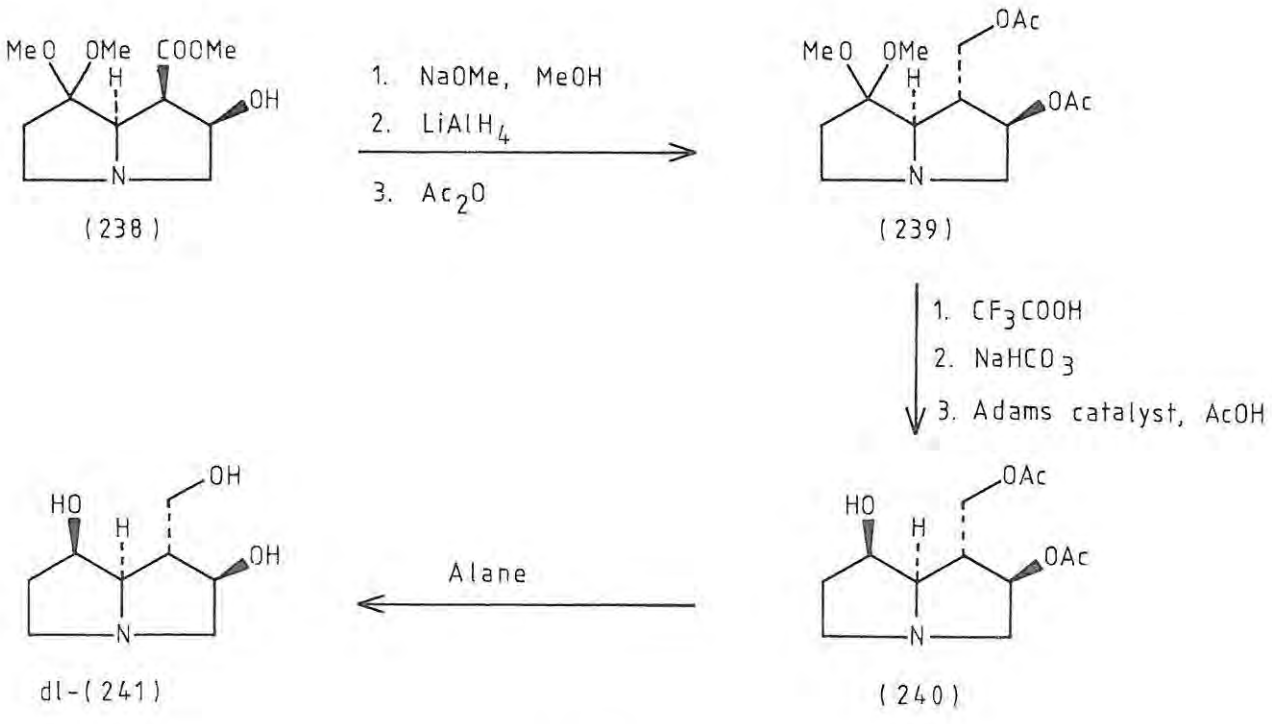


(6)

The synthesis of retronecine[168,169] is an extension of Tufariello's earlier synthesis of supinidine,[167] and the key step is the 1,3-dipolar addition of the substituted pyrroline N-oxide or nitrone (236), [Scheme 15], to methyl 4-hydroxy-crotonate to form the isoxazolidine (237). Mesylation of the hydroxyl followed by hydrogenolysis of the N-O bond gave pyrrolizidine ester (238), from which retronecine (194) was obtained by a second mesylation, an elimination, a hydrolysis and finally a reduction.

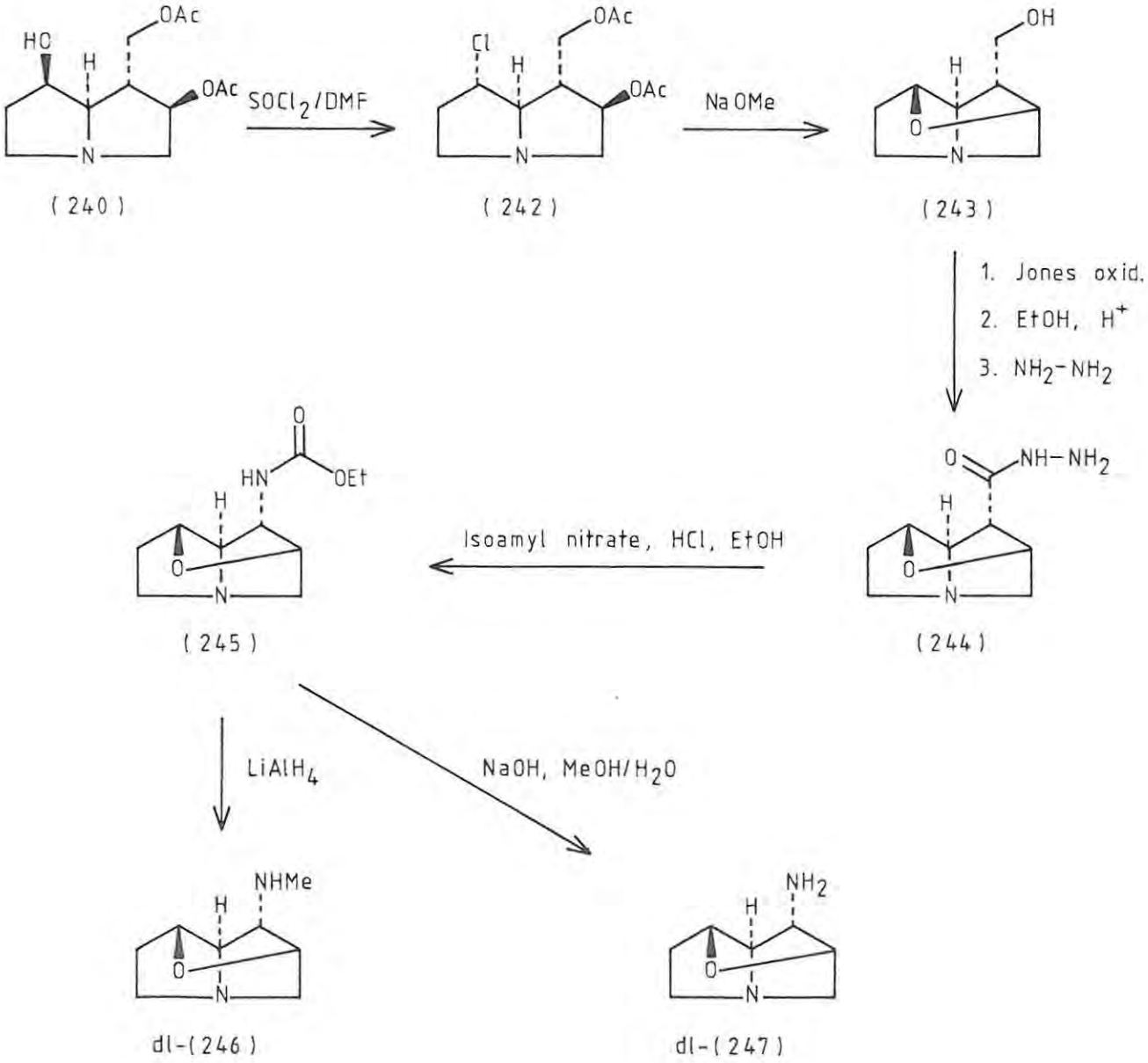


Scheme 15.



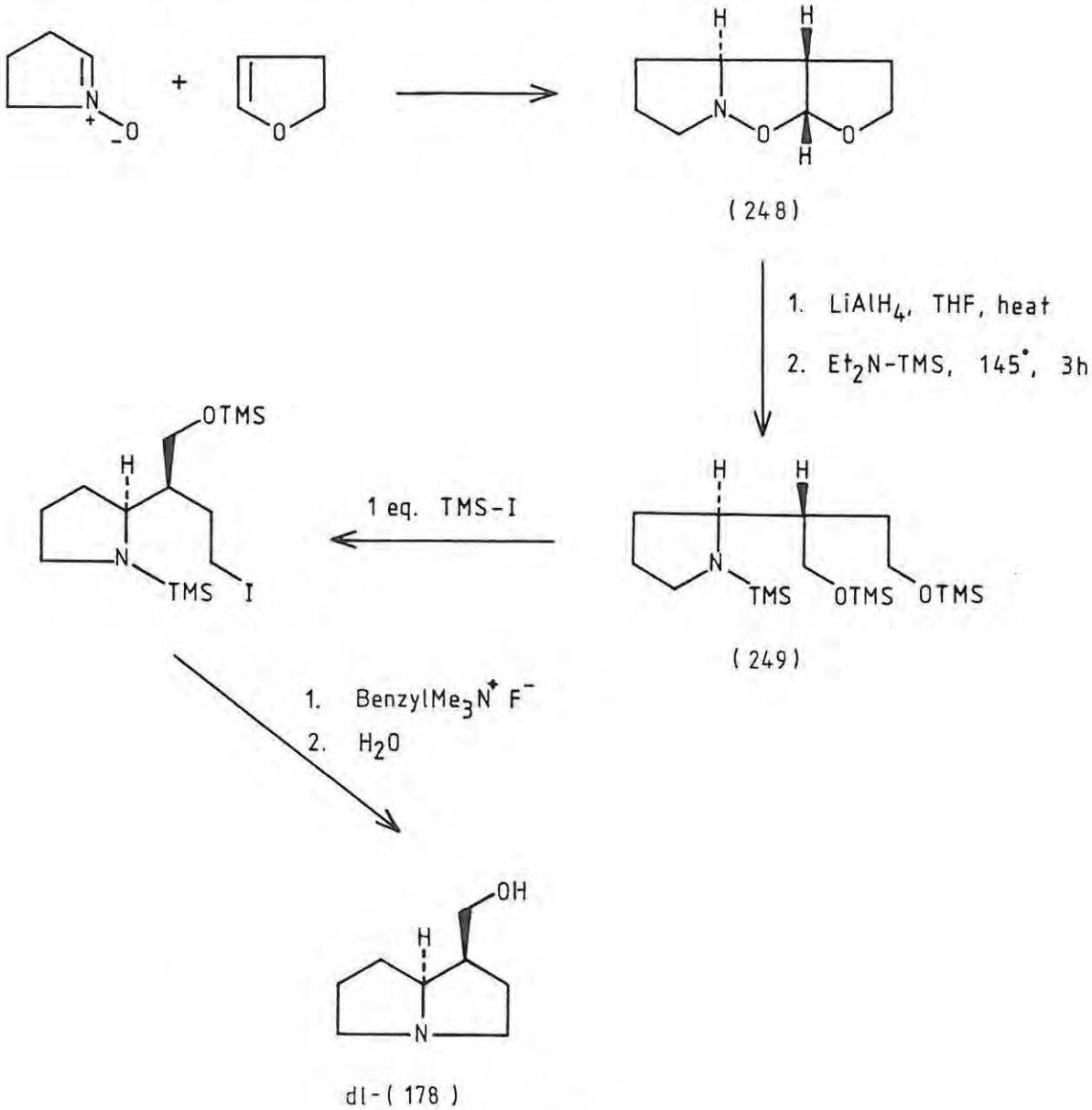
Scheme 16.

Pyrrolizidine (**238**) was also utilised in the synthesis of croalbinecine.[171] Inversion of the stereochemistry at C_1 of (**238**) followed by reduction and acetylation gave (**239**), [Scheme 16]. Removal of the ketal using trifluoroacetic acid, followed by Adams catalyst hydrogenation gave (**240**), from which racemic croalbinecine (**241**) was obtained by deprotection.



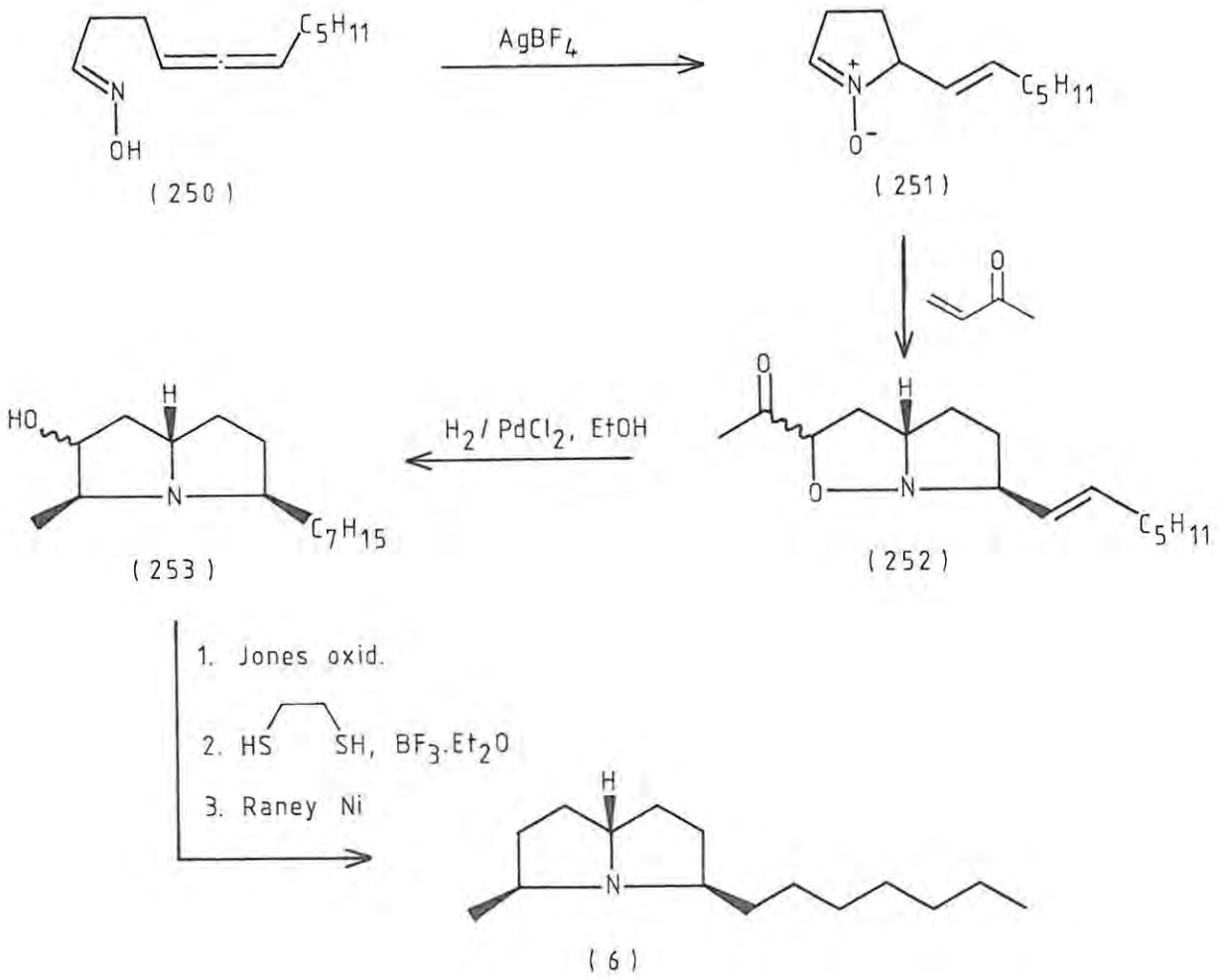
Scheme 17.

Synthesis of the lolium alkaloids, loline and norloline, was identical to that of croalbinecine as far as structure (**240**) [Cf. Scheme 16].[174] However treatment of (**240**) with Vilsmeier's reagent gave the chloride (**242**) which was deprotected and cyclised to (**243**), [Scheme 17]. Oxidation, esterification and reaction with hydrazine hydrate gave hydrazide (**244**). This was rearranged to the carbamate (**245**), which on reduction gave racemic loline (**246**). Alternatively, hydrolysis of (**245**) gave racemic norloline (**247**).



Scheme 18.

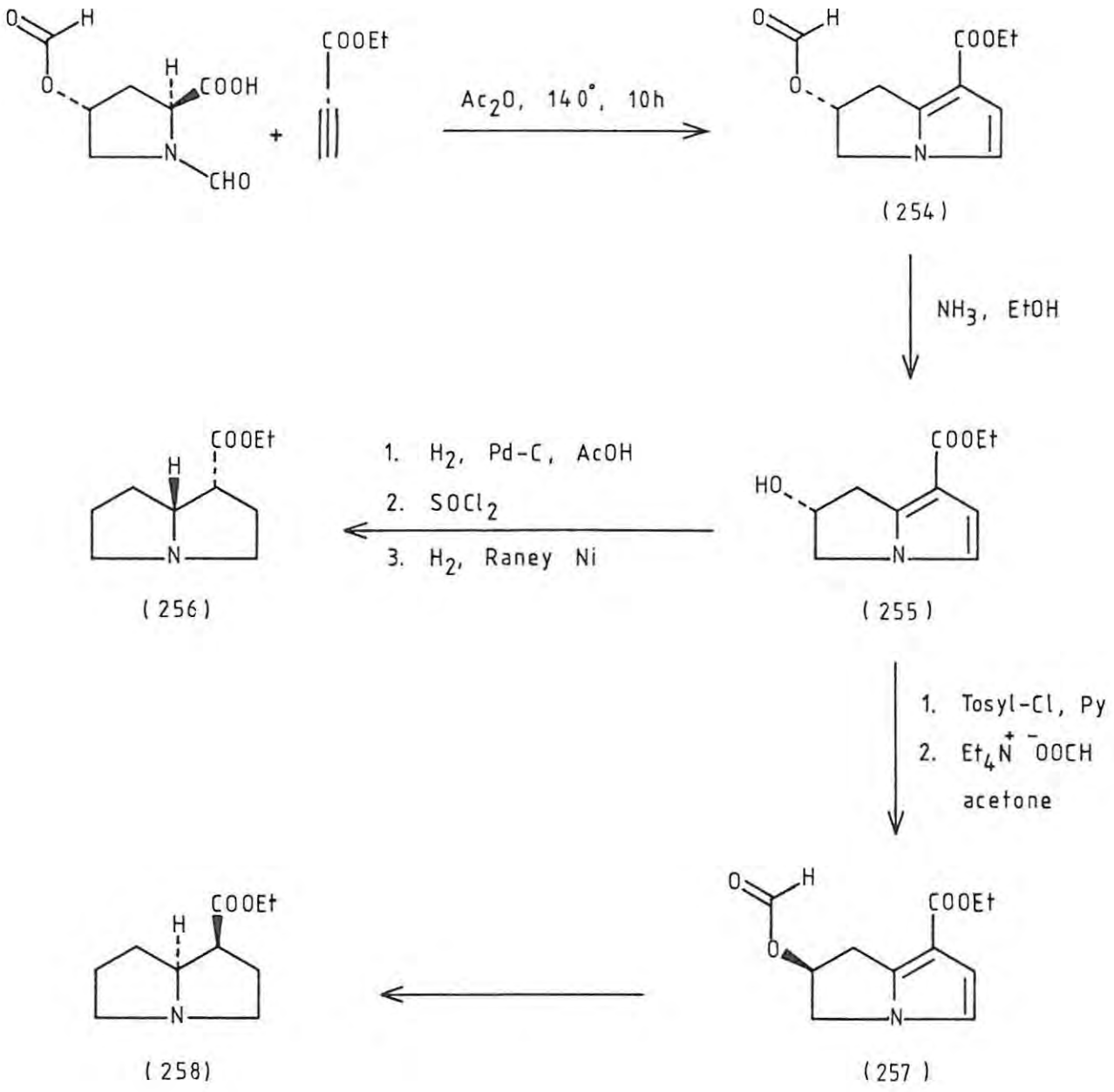
Iwashita's group,[170] in their synthesis of isoretronecanol generated the tricyclic intermediate (**248**), [Scheme 18], by a 1,3-dipolar addition of pyrroline N-oxide to dihydrofuran. This addition led almost exclusively to the exo-addition product as a result of the absence of secondary orbital interactions which are possible with conjugated reactants. Reduction of (**248**) to the aminodiol and total silylation gave (**249**). Selective iodination of the least hindered silyl ether followed by treatment with benzyltrimethylammonium fluoride gave the required necine (**178**).



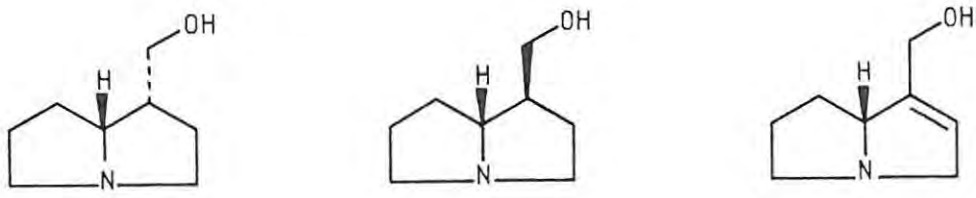
Scheme 19.

Nitrones have also been used in the synthesis of (6), an ant venom component.[175] The allenic oxime (250), derived from 1-octyn-3-ol, was cyclised to the nitrone (251) using silver tetrafluoroborate as catalyst, and the nitrone trapped with butenone, which gave (252) as a mixture of isomers, [Scheme 19]. Hydrogenation of (252) reduced the C=C bond, cleaved the N-O bond and effected reductive amination resulting in (253). Finally removal of the unwanted hydroxyl group was achieved by Jones oxidation, thioketal formation and desulphurisation generated the desired alkaloid (6), which was separated from its stereoisomers by gas chromatography.

The synthesis of the optically active forms of supinidine, isoretronecanol and trachelanthamidine by Robins and Sakdarat[172,173] is based on the earlier work of Pizzorno and Albonico.[176] Use of L(-)-N-formyl-4-formyloxy-proline and ethyl propynoate, [Scheme 20], resulted in a stereospecific 1,3-dipolar cycloaddition reaction to give the dihydro-pyrrolizine ester (254). Removal of the formyl protecting group gave (255) as a key intermediate. Hydrogenation of this ester followed by removal of the hydroxyl group gave the saturated ester (256). The hydrogenation step proceeded stereospecifically due to the steric hindrance of the hydroxyl group. Conversion of (256) into (+)isoretronecanol (259), (+)trachelanthamidine (260) and (+)supinidine (261) was readily effected by standard methods.



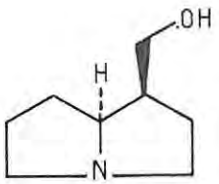
Scheme 20.



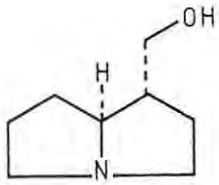
(259) (260) (261)

The (-)isomers were obtained by epimerisation of the hydroxyl group of (255) into the formyl derivative (257), which could

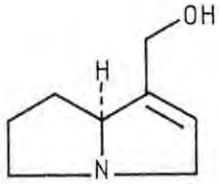
be converted into (258) and then into (-)isoretronecanol (178), (-)trachelanthamidine (179), and (-)supinidine (262).



(178)

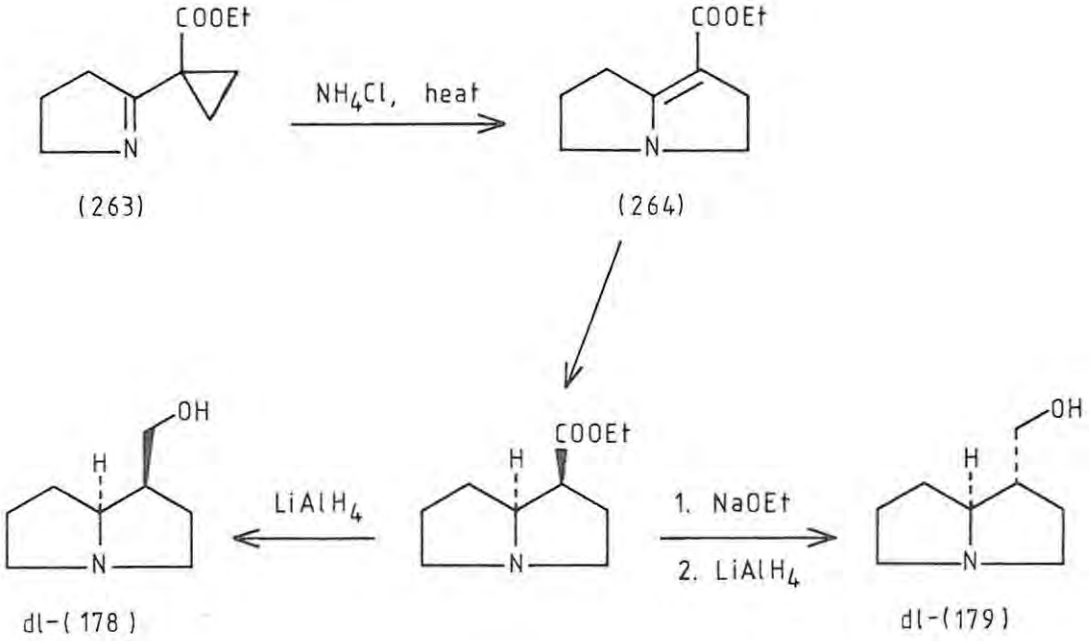


(179)

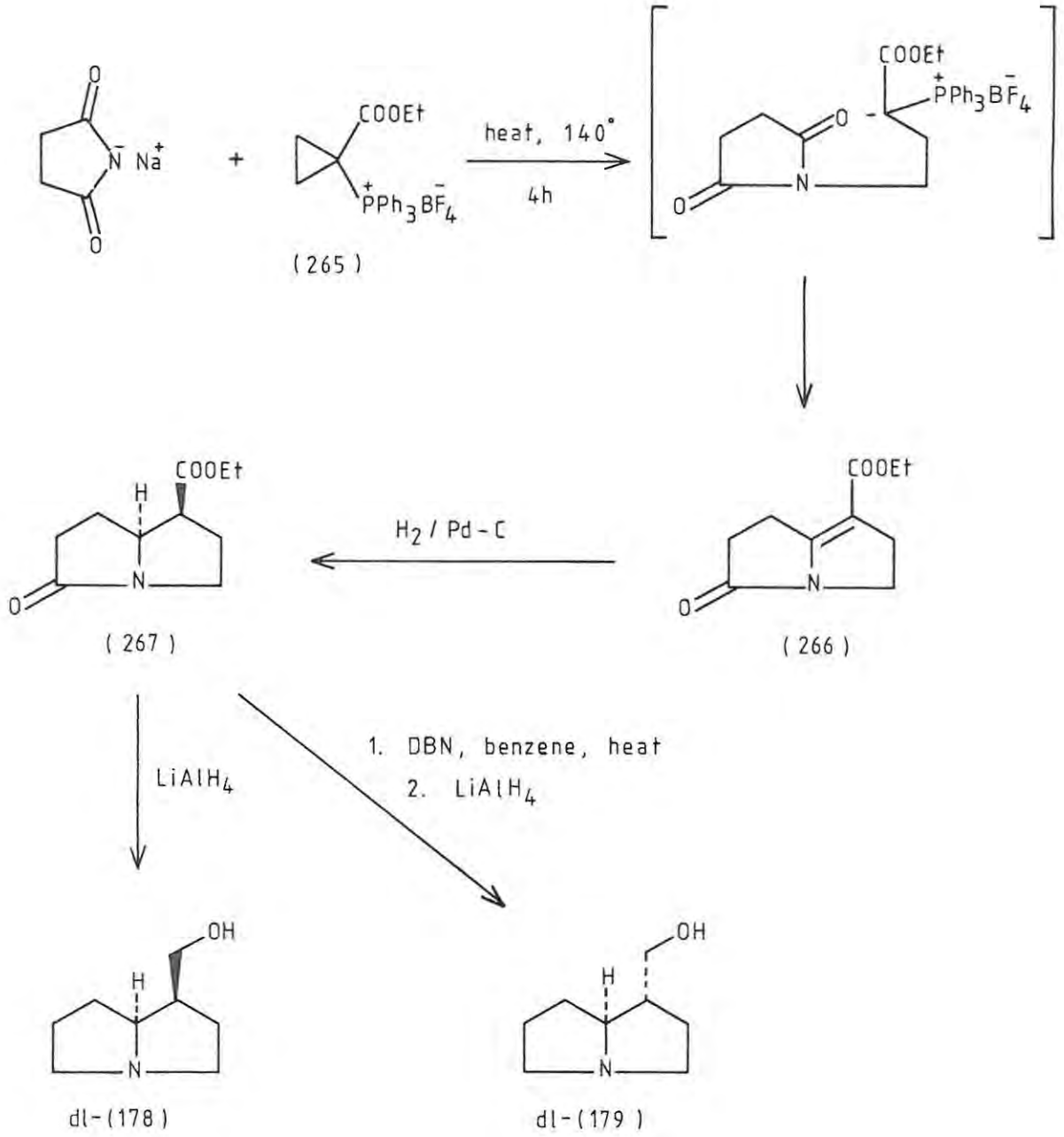


(262)

Three groups have synthesised necines by reaction of cyclopropanes. The earliest approach is that of Pinnick and Chang[177] who rearranged the cyclopropyl imine (263), [Scheme 21], into the unsaturated pyrrolizidine ester (264) by heating (263) in the presence of a catalytic amount of ammonium chloride. Catalytic hydrogenation followed by lithium aluminium hydride reduction gave racemic isoretronecanol (178). Alternatively, epimerisation then hydride reduction gave racemic trachelanthamidine (179).



Scheme 21.



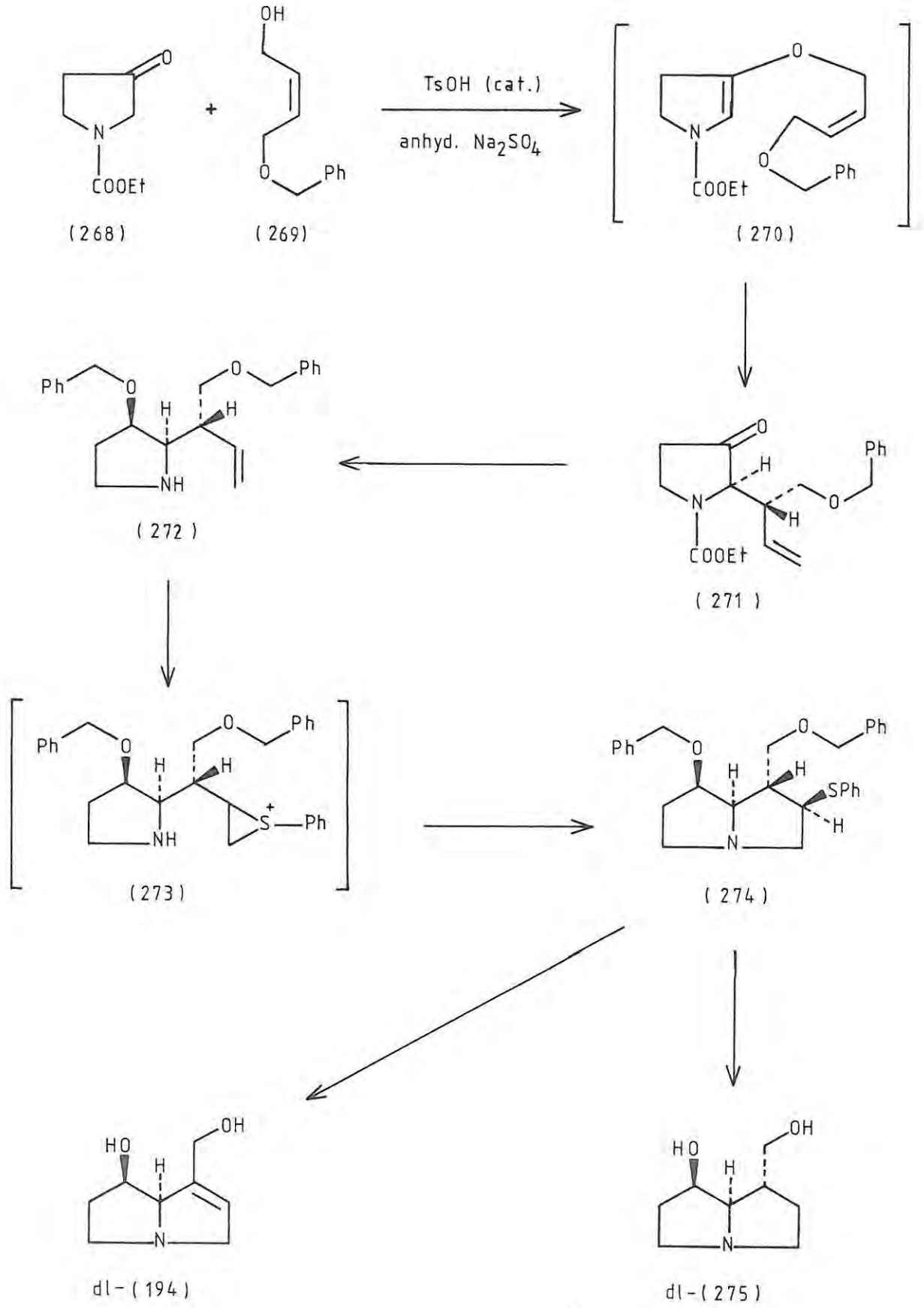
Scheme 22.

The other two groups, Muchowski and Nelson,[178] and Flitsch and Wernsmann[179] independently developed another route, [Scheme 22]. Nucleophilic attack by the succinimide anion on the cyclopropane phosphonium salt (265) generated an ylide which reacted intramolecularly giving the pyrrolizidinone ester (266). This was catalytically reduced to the lactam (267), which was further reduced with hydride to racemic

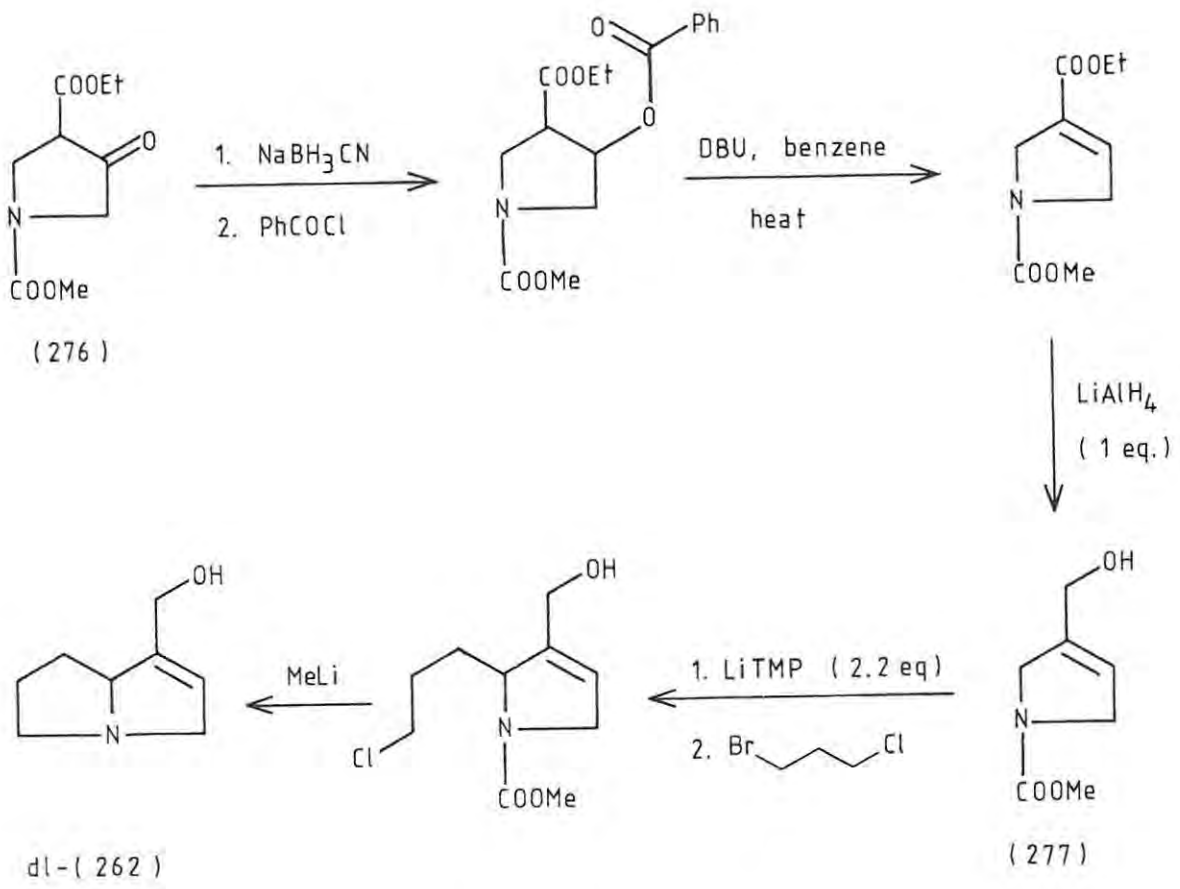
isoretronecanol (178). Alternatively epimerisation of the lactam with 1,5-diazabicyclo[4,3,0,]non-5-ene, (DBN), in refluxing benzene prior to reduction gave racemic trachelanthamidine (179).

More recently Kametani and coworkers[180] have synthesised racemic retronecine, and racemic turneforcidine via an epi-sulphonium ion intermediate. This is the first synthesis of turneforcidine to be reported. Reaction of the N-protected pyrrolidinone (268), [Scheme 23], with the allylic alcohol (269) in the presence of 4-toluenesulphonic acid and anhydrous sodium sulphate gave (271) via a Claisen rearrangement of the presumed intermediate allyl enol ether (270). Reduction and subsequent protection of the alcohol group, followed by removal of the nitrogen protecting group gave (272). Treatment of the hydrochloride of (272) with benzenesulphenyl chloride followed by potassium carbonate and sodium iodide gave the key epi-sulphonium ion intermediate (273), which immediately cyclised to the pyrrolizidine (274). Desulphurisation with Raney nickel and removal of the protecting groups by hydrogenation gave racemic turneforcidine (275). Alternatively oxidation to the sulphoxide using 3-chloroperbenzoic acid followed by elimination and deprotection with lithium in liquid ammonia gave racemic retronecine (194).

The approach used by Macdonald and Narayanan[181] in their synthesis of racemic supinidine is unusual in that these workers chose to introduce the unsaturation and the 9-hydroxymethyl unit into the one ring prior to formation of



Scheme 23.

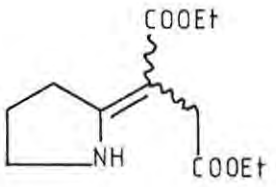


Scheme 24.

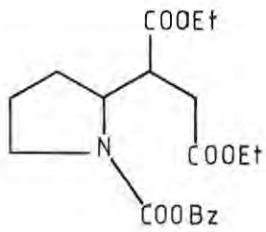
the second ring, [Scheme 24]. Introduction of the carbon-carbon double bond was achieved by reduction of the ketone functionality of (276), followed by benzoylation and subsequent elimination. Selective hydride reduction then provided the complete right-hand portion, (277), of the target molecule. Lithiation and alkylation introduced the required carbons for the remainder of the molecule in a site specific manner. Removal of the N-protecting group by treatment with methyl lithium resulted in spontaneous cyclisation to racemic supinidine (262).

Ring closure of the second ring by formation of a lactam as opposed to N-alkylation has been reported by Pinnick and Chang,[182] and more recently by Shono and coworkers.[183] Both

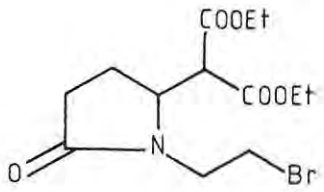
groups synthesised racemic isoretronecanol and racemic trachelanthamidine. The pyrrolizidine precursor in Pinnick's approach is (278), while that used by Shono is (279).



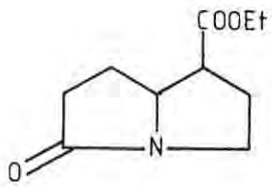
(278)



(279)



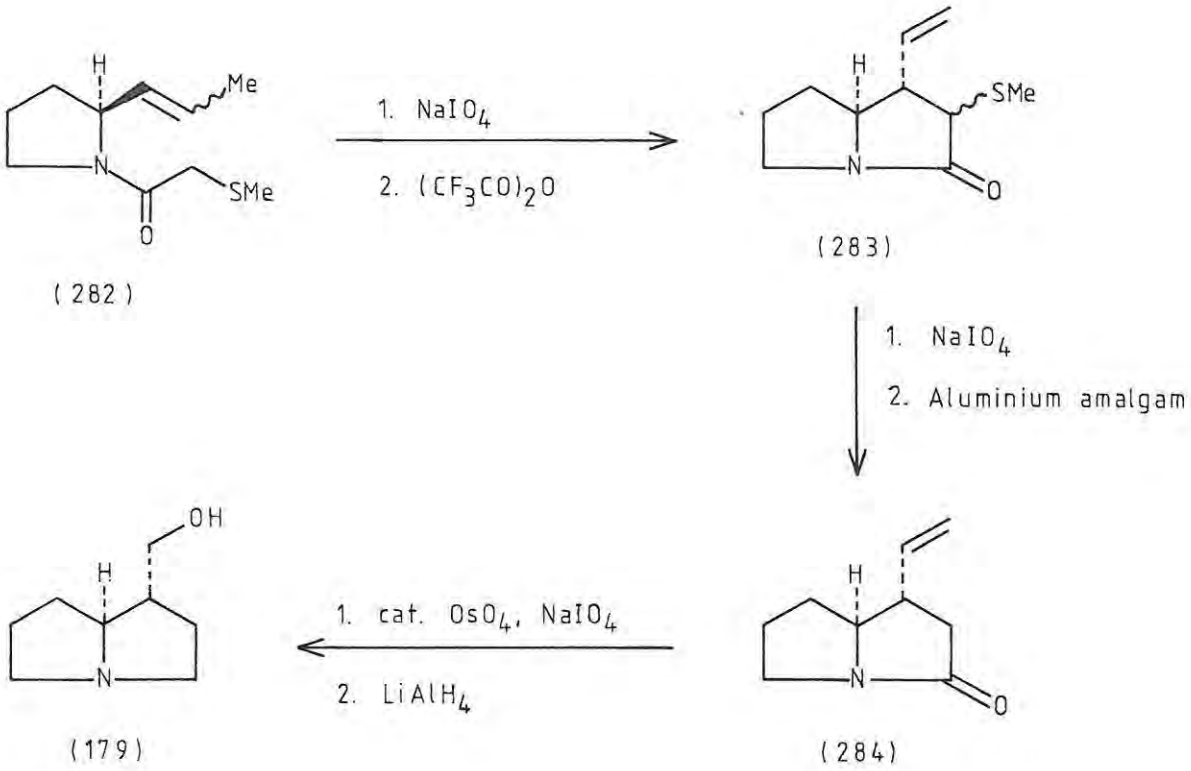
(280)



(281)

Finally a number of routes to the pyrrolizidine ring have involved formation of a carbon-carbon bond as the ring closure step. The simplest of these routes is that of Kraus and Neuenschwander[184] who synthesised the lactam diester (280), and effected cyclisation by a simple alkylation reaction at the proto-C_1 to give, after decarboxylation, the pyrrolizidinone (281) as a mixture of isomers. Separation and reduction gave racemic isoretronecanol and racemic trachelanthamidine.

(-)Trachelanthamidine has been synthesised by Ishibashi and coworkers,[185] who converted L-prolinol into (282) via several steps, [Scheme 25]. This was oxidised with sodium periodate,

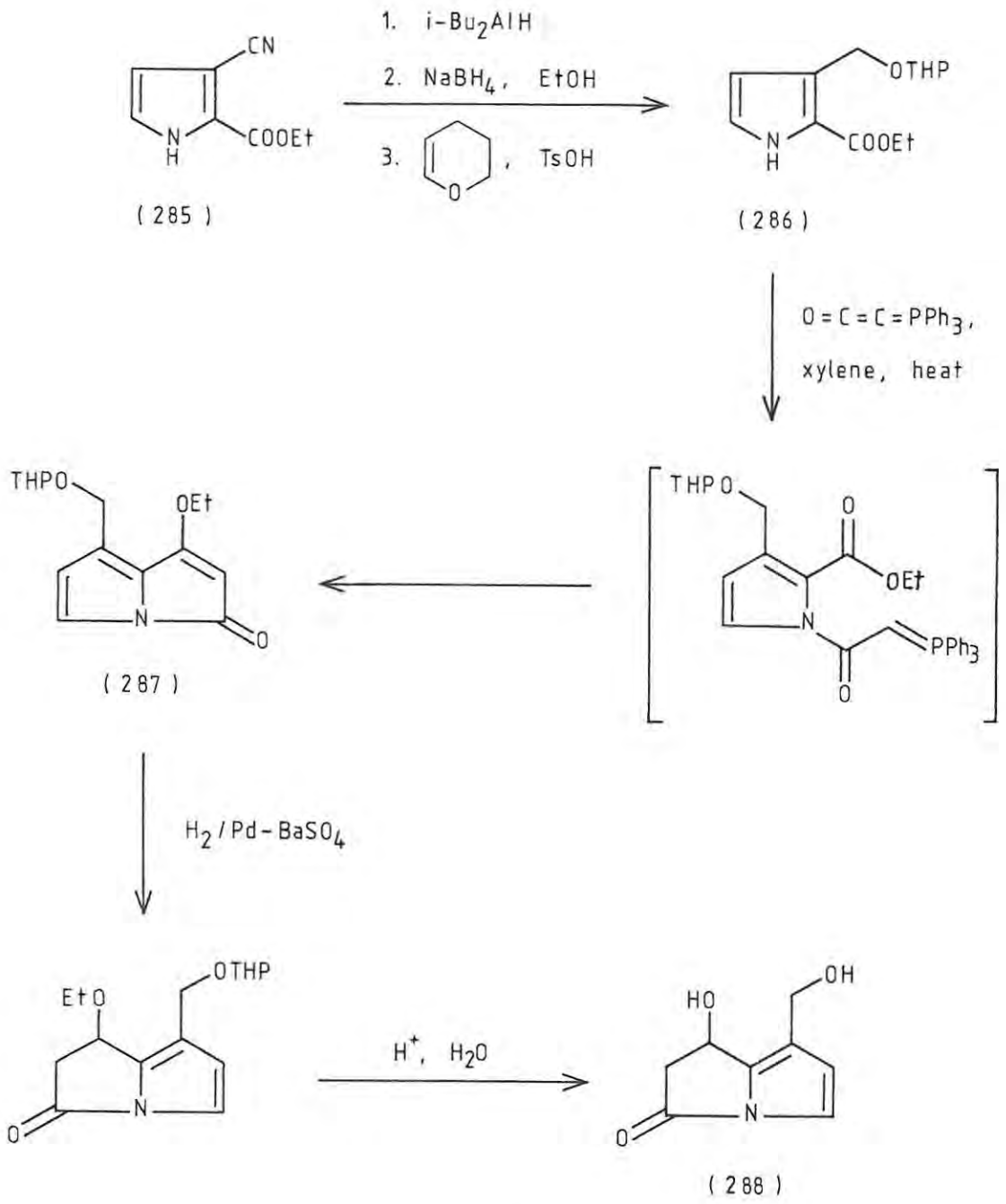


(282) (283) (284) (179)

Scheme 25.

and then cyclised using trifluoroacetic anhydride to the pyrrolizidine (283). Further oxidation with sodium periodate followed by removal of the resultant sulphoxide gave (284). Finally cleavage of the C=C bond and hydride reduction gave the desired (-)trachelanthamidine (179).

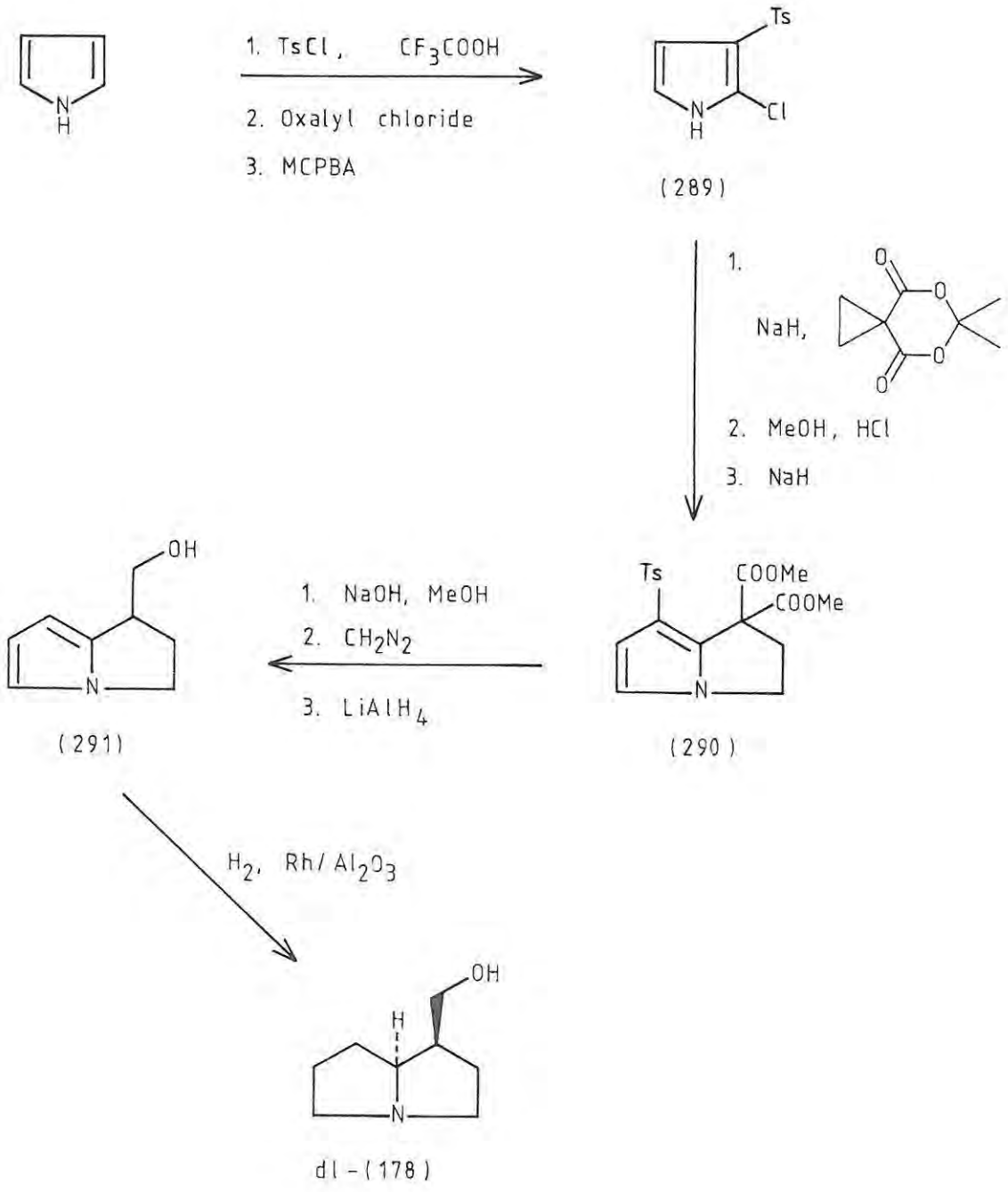
Bohlmann's[186] synthesis of the dihydropyrrolizinone (288), [Scheme 26], is the first such synthesis of necines of this type, and also involves ring closure at C_1. The cyanopyrrole (285) was reduced stepwise to the alcohol which was then protected as the tetrahydropyranyl derivative (286). Reaction with triphenylphosphoranylidine ketene in the Bestmann reaction attached the ketene unit onto the nitrogen with concomitant attack of the resultant ylide on the adjacent ester to form the pyrrolizinone (287). Selective catalytic reduction and hydrolysis gave the required necine (288).



Scheme 26.

Greenhouse and Ortiz also employed a pyrrole ring in their synthesis of isoretronecanol.[187] Pyrrole was converted to (289) by sulphinylation and oxidative chlorination, [Scheme 27]. N-Alkylation of (289), followed by nucleophilic displacement of the chloride gave (290). This ring closure reaction was made possible by the activating effect of the

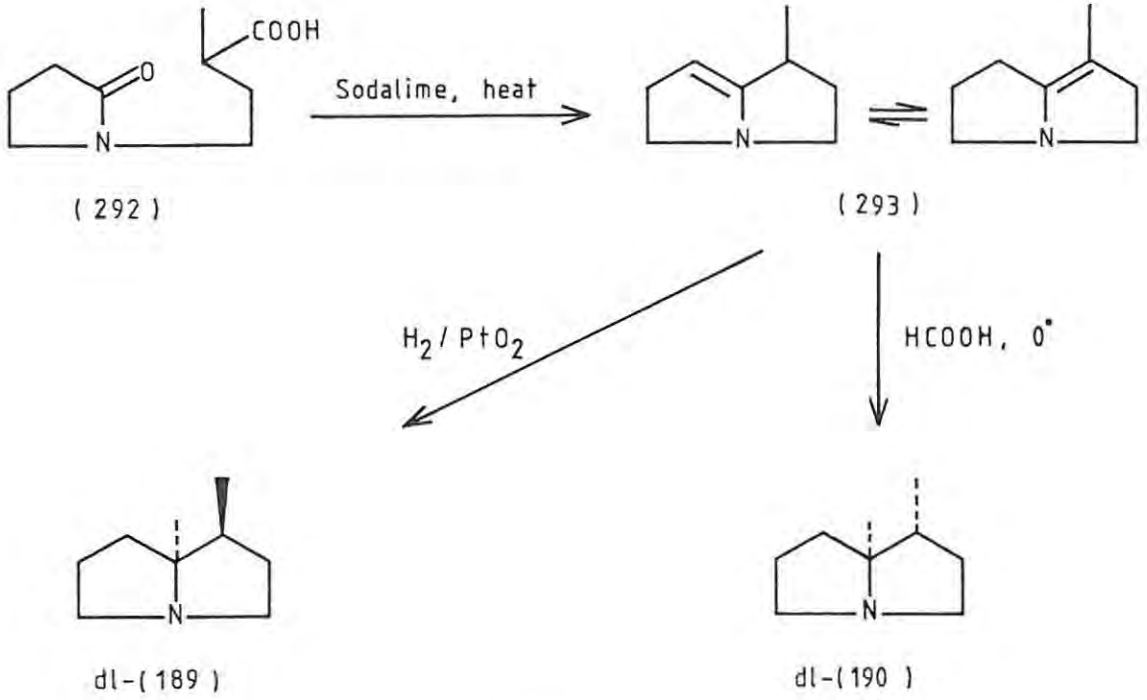
adjacent sulphoxide group. Diester (290) was readily converted to the monoester, and then reduced to (291). Finally hydrogenation gave the required isoretronecanol (178).



Scheme 27.

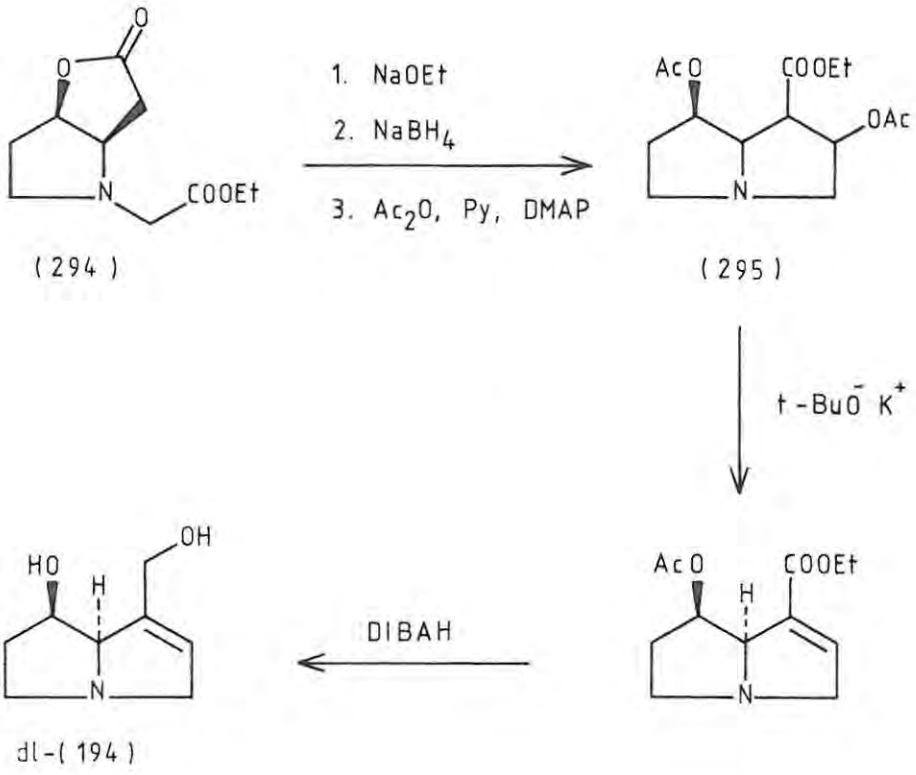
Miyano and coworkers[188] have reported a short and high yielding route to racemic heliotridane and racemic

pseudoheliotridane, [Scheme 28]. Dry distillation of the lactam (**292**) over soda-lime gave the enamine (**293**) which was reduced either by catalytic hydrogenation, or by reaction with formic acid, giving racemic heliotridane (**189**) or racemic pseudoheliotridane (**190**) respectively.



Scheme 28.

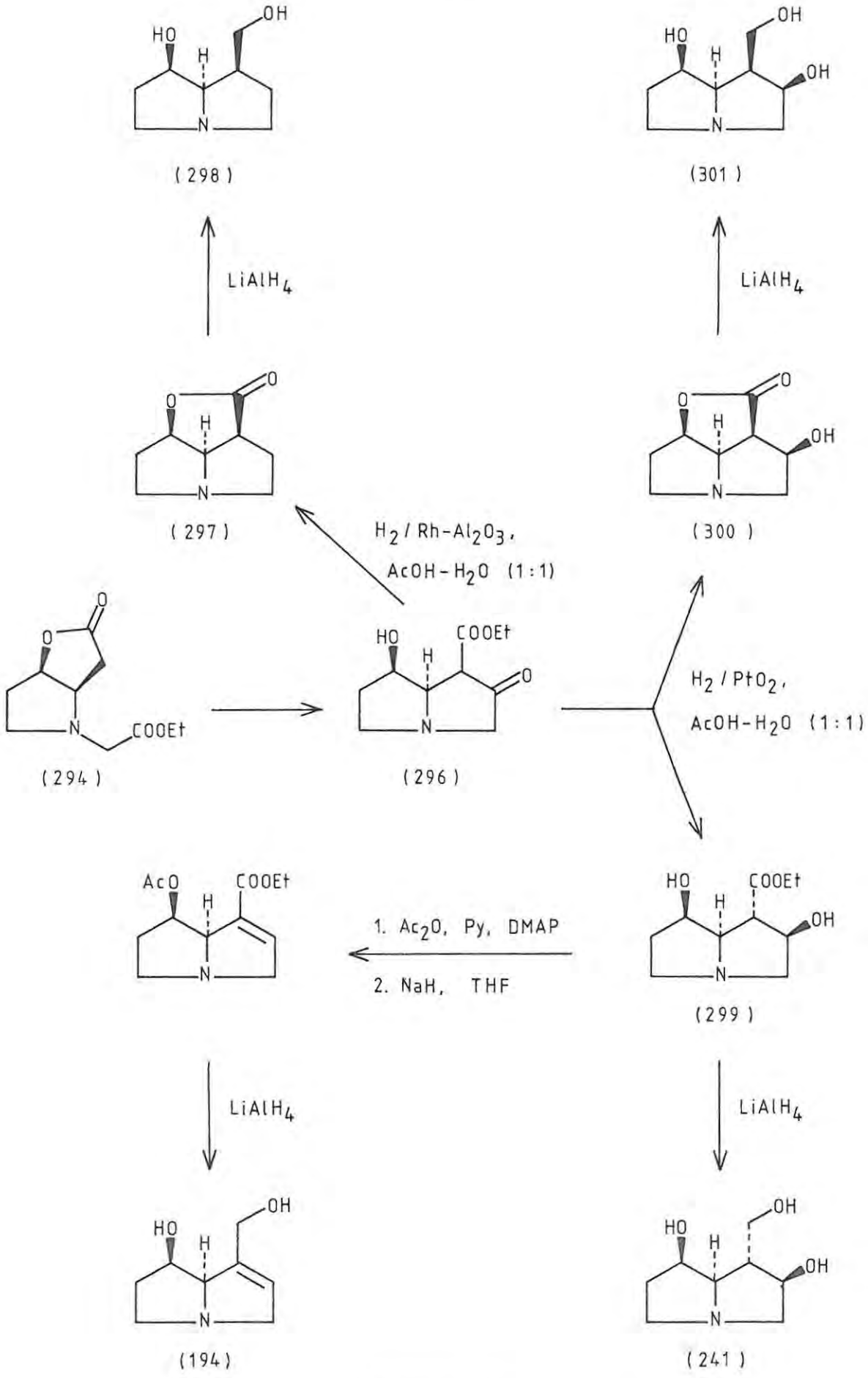
As part of their total synthesis of the macrocyclic alkaloid integerrimine Narasaka and coworkers[189] synthesised racemic retronecine using a modification of the route pioneered by Geissman and Waiss[190]. Formation of the pyrrolizidine ring was achieved by subjecting lactone (**294**), [Scheme 29], to a Dieckmann condensation. Subsequent reduction and acetylation then gave (**295**). Reaction of (**295**) with potassium tert-butoxide introduced the carbon-carbon double bond, and finally a hydride reduction afforded retronecine (**194**).



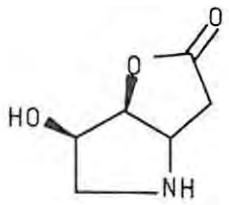
(294) (295) dl-(194)

Scheme 29.

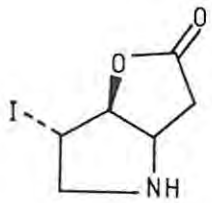
Benn and Rueger[191] have elaborated further modifications to Giessman's method in synthesing four optically active necine bases. Use of potassium ethoxide in toluene at room temperature gave good yields of the ketoester (**296**), [Scheme 30]. Hydrogenation of (**296**) using a rhodium catalyst afforded predominantly lactone (**297**) which was reduced to (-)platynecine (**298**). Replacing the rhodium catalyst by platinum dioxide in the hydrogenation step gave mainly (**299**), reduction of which gave (+)croalbinecine (**241**). Alternatively (**299**) was converted into (+)retronecine (**194**) using Narasaka's approach. Production of a fourth necine arose from the observed slow epimerisation and lactonisation of (**299**) into (**300**), which on hydride reduction gave the C_1-epimer, (**301**), of croalbinecine.


(298)
(301)
LiAlH4
LiAlH4
(297)
(300)
H2 / Rh-Al2O3,
AcOH-H2O (1:1)
(294)
(296)
H2 / PtO2,
AcOH-H2O (1:1)
1. Ac2O, Py, DMAP
2. NaH, THF
(299)
LiAlH4
LiAlH4
(194)
(241)

Scheme 30.



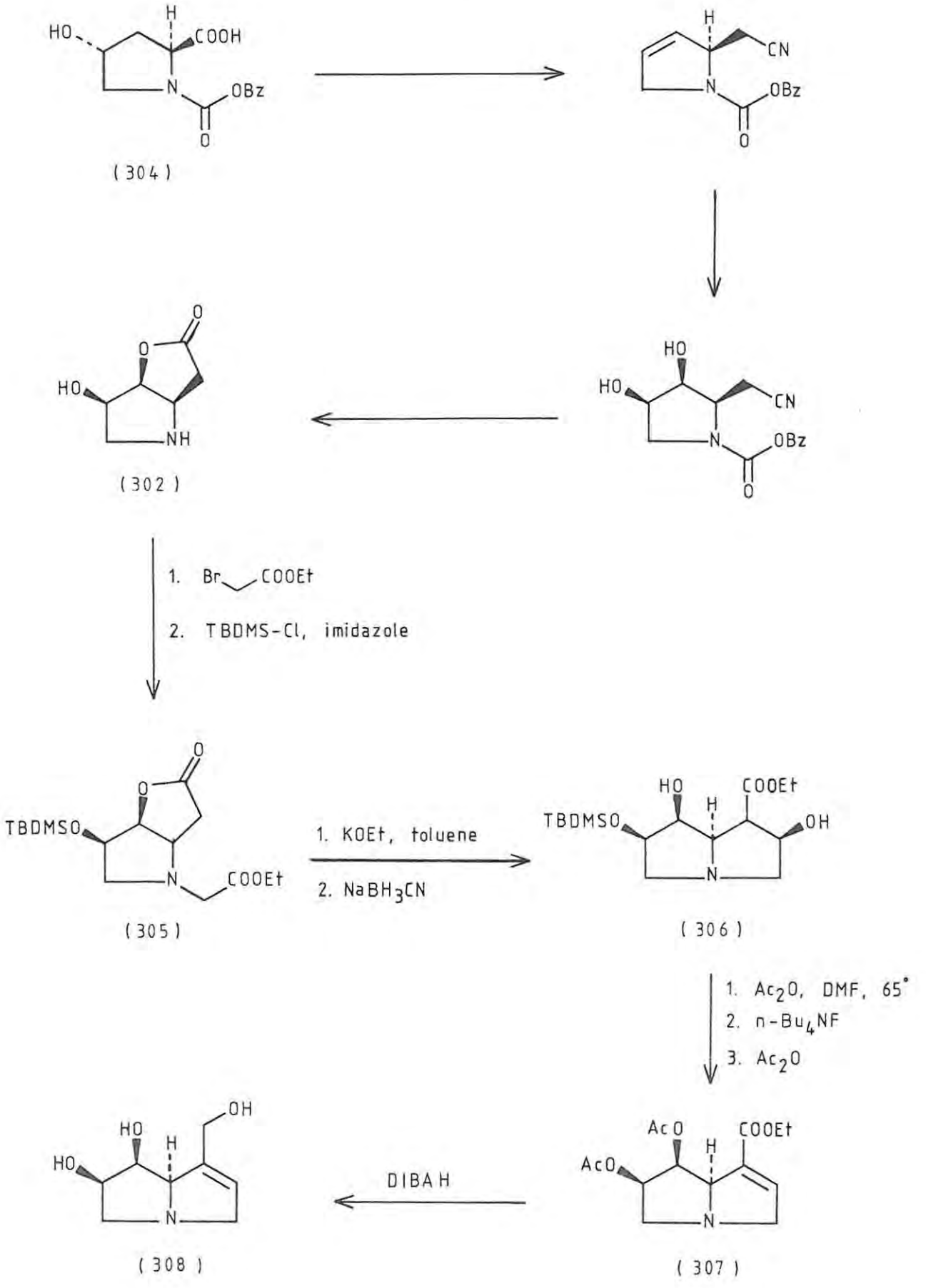
(302)



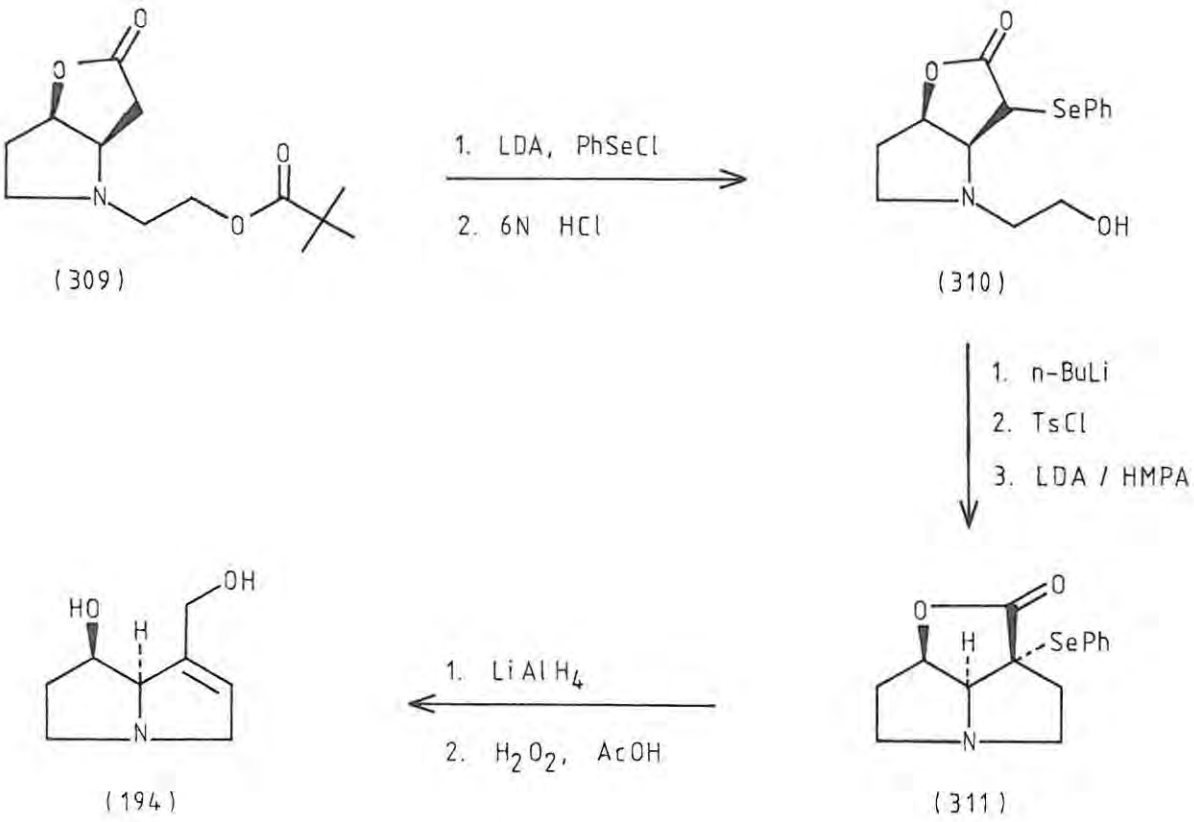
(303)

More recently Benn and coworkers[192] synthesised (+)crotanecine employing (302) as a key intermediate. Synthesis of (302) from the available iodo derivative (303) proved impossible. However (302) could be made from the hydroxyproline (304) by a number of careful manipulations of the attached functional groups, [Scheme 31]. N-Alkylation and silylation of (302) gave (305) which was cyclised and immediately reduced to the saturated pyrrolizidine (306). During the subsequent acetylation/desilyation steps, fortuitous elimination occurred, giving (307), which on reduction gave (+)crotanecine (308).

Most recently Niwa and coworkers[193] have synthesised (+)retronecine via yet another modification of Geissman's lactone, [Scheme 32]. Starting from R-(+)malic acid, this group synthesised (309) via a lengthy sequence. Introduction of the phenylselenide and unmasking of the alcohol gave (310), which was cyclised in a three step procedure to the tricyclic lactone (311). This was reduced to the diol and finally oxidative elimination of the phenylselenide gave (+) retronecine (194).


HO
H
COOH
N
OBz
O
(304)
CN
(302)
1. Br COOEt
2. TBDMS-Cl, imidazole
TBDMSO
1. KOEt, toluene
2. NaBH3CN
(305)
(306)
1. Ac2O, DMF, 65°
2. n-Bu4NF
3. Ac2O
AcO
DIBAH
(308)
(307)

Scheme 31.

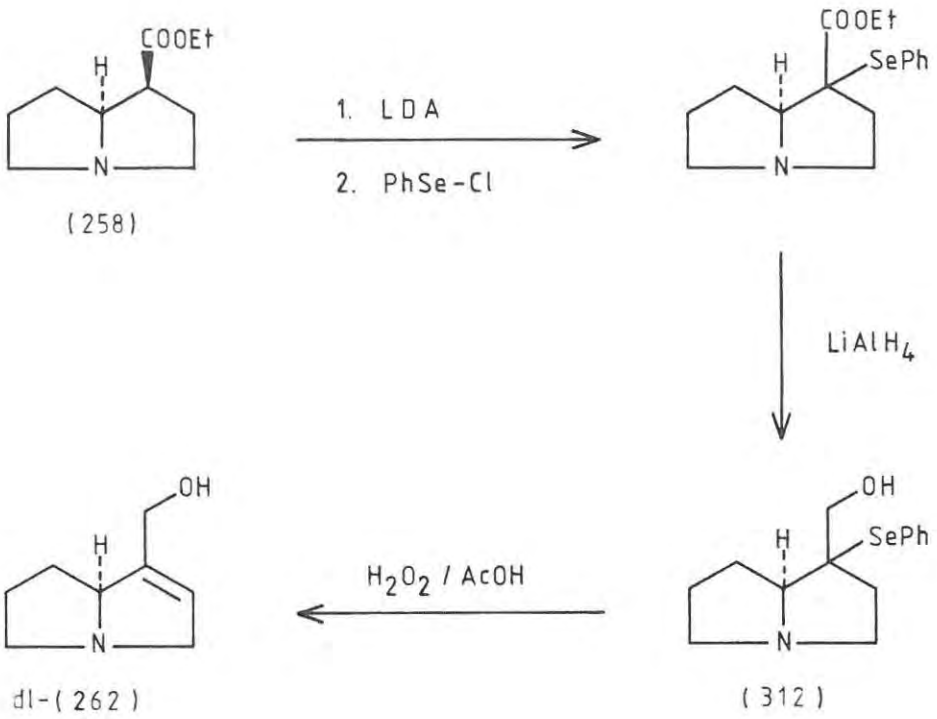


Scheme 32.

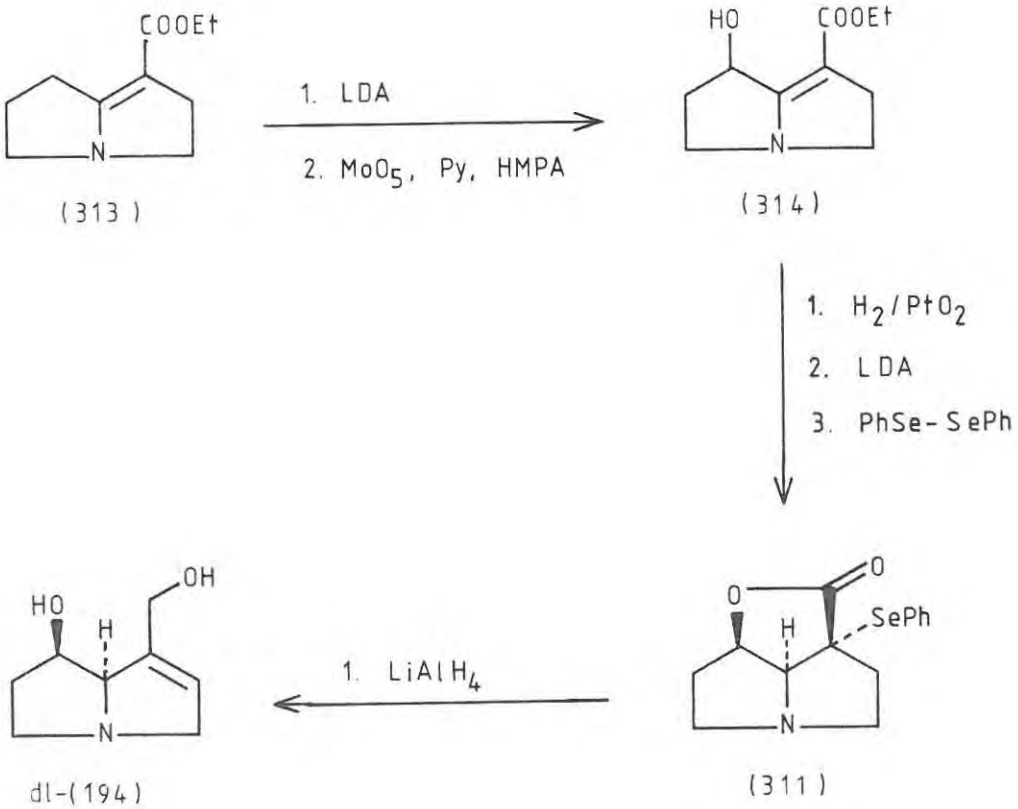
2.1.3. Modification of an existing necine base.

Only a limited number of syntheses of necines have been reported since 1976 which are based on modifications of existing pyrrolizidines. The earliest of these was that of Robins and Sakdarat[194] who converted the pyrrolizidine ester (258) into racemic supinidine (262), [Scheme 33]. Phenyl selenation of (258) followed by reduction of the ester moiety gave (312), which readily underwent oxidation and elimination to give the required supinidine (262).

Recently Yamada's[195] group converted the pyrrolizidine ester (313) into racemic retronecine, [Scheme 34]. Introduction of the hydroxyl group at C_7 was achieved by low temperature oxidation of the lithium enolate of (313) using

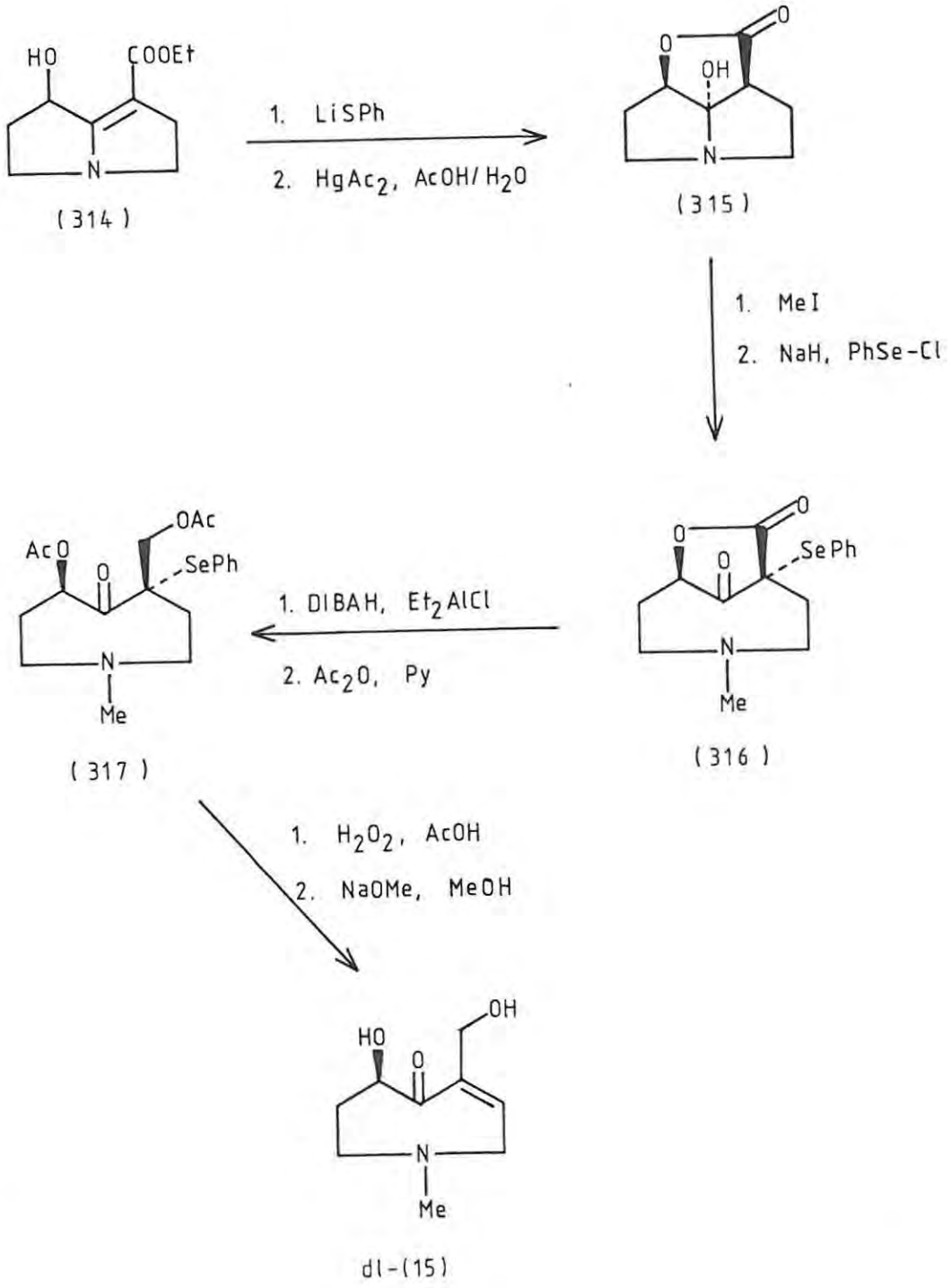


Scheme 33.



Scheme 34.

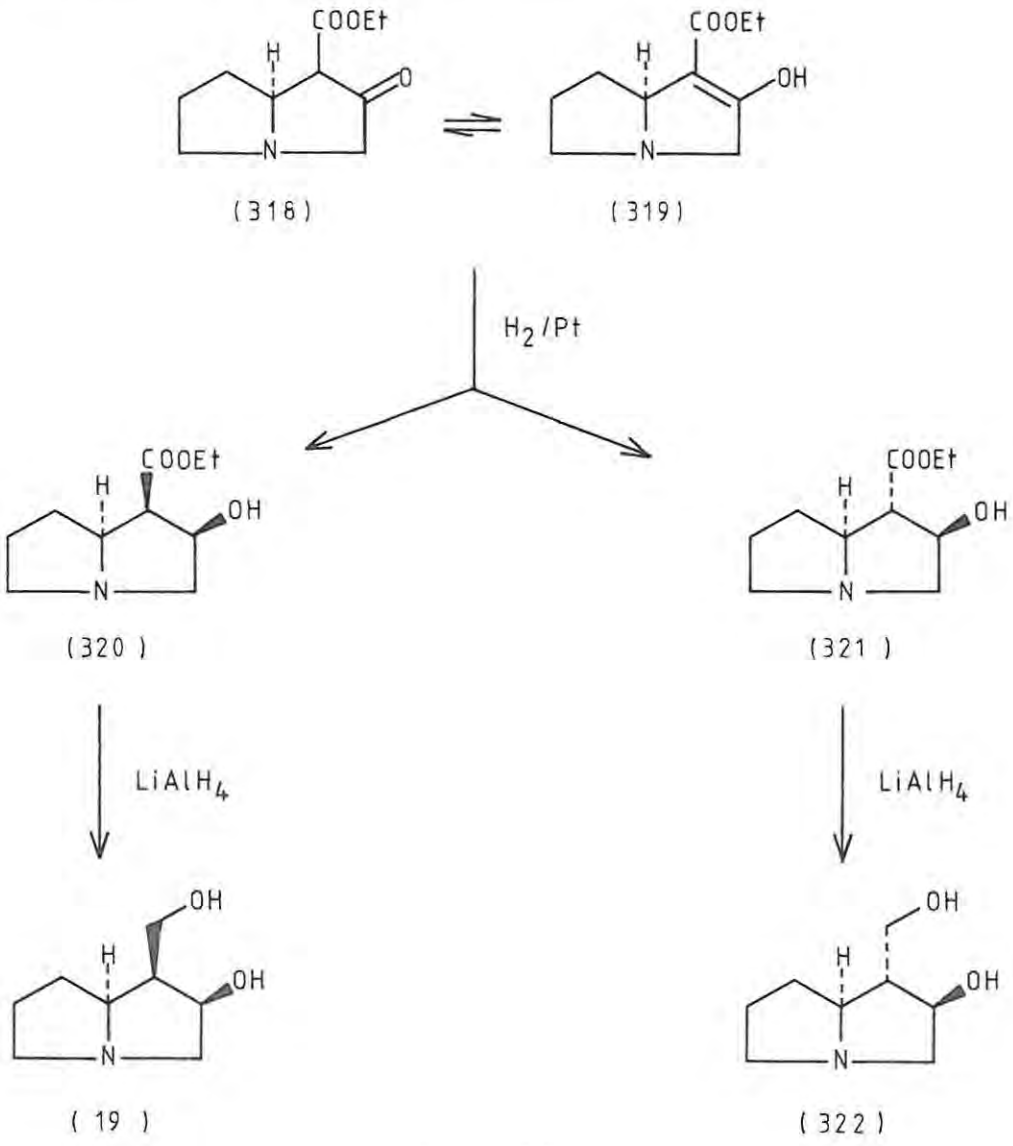
oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide, (MOP). Reduction of the hydroxyester (314) followed by selenation of the resulting lactone gave (311), and thence by oxidative elimination, retronecine (194).



Scheme 35.

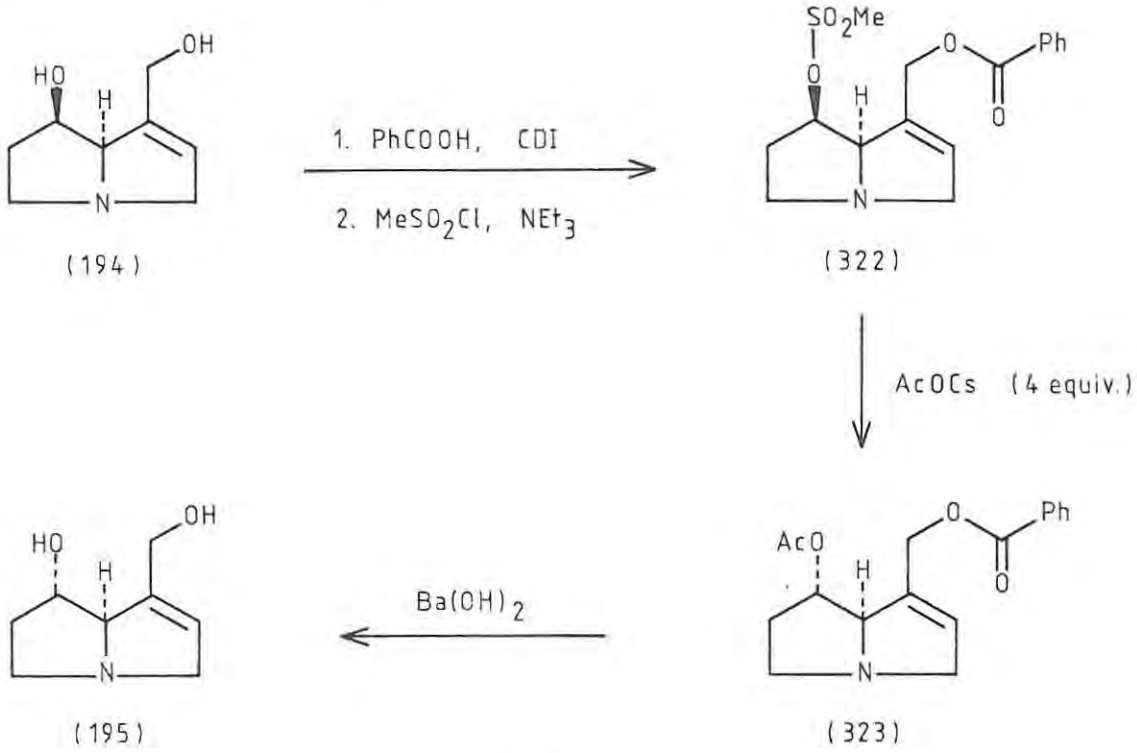
Subsequently Yamada[196] synthesised racemic otonecine (15) from hydroxyester (314), [Scheme 35]. Reaction of (314)

with lithium thiophenolate followed by mercuric diacetate introduced a hydroxyl group at C_8, [(315), Scheme 35], which was oxidised to (316) by formation of the methiodide and subsequent phenylselenation. Hydride reduction in the presence of a Lewis acid, then acetylation, allowed reduction of lactone (316) without incurring loss of the phenylselenyl group. Such a group is prone to reductive elimination due to its proximity to the keto group. Oxidative elimination of the phenylselenyl group of (317) followed by removal of the acetate protecting groups gave otonecine (15).



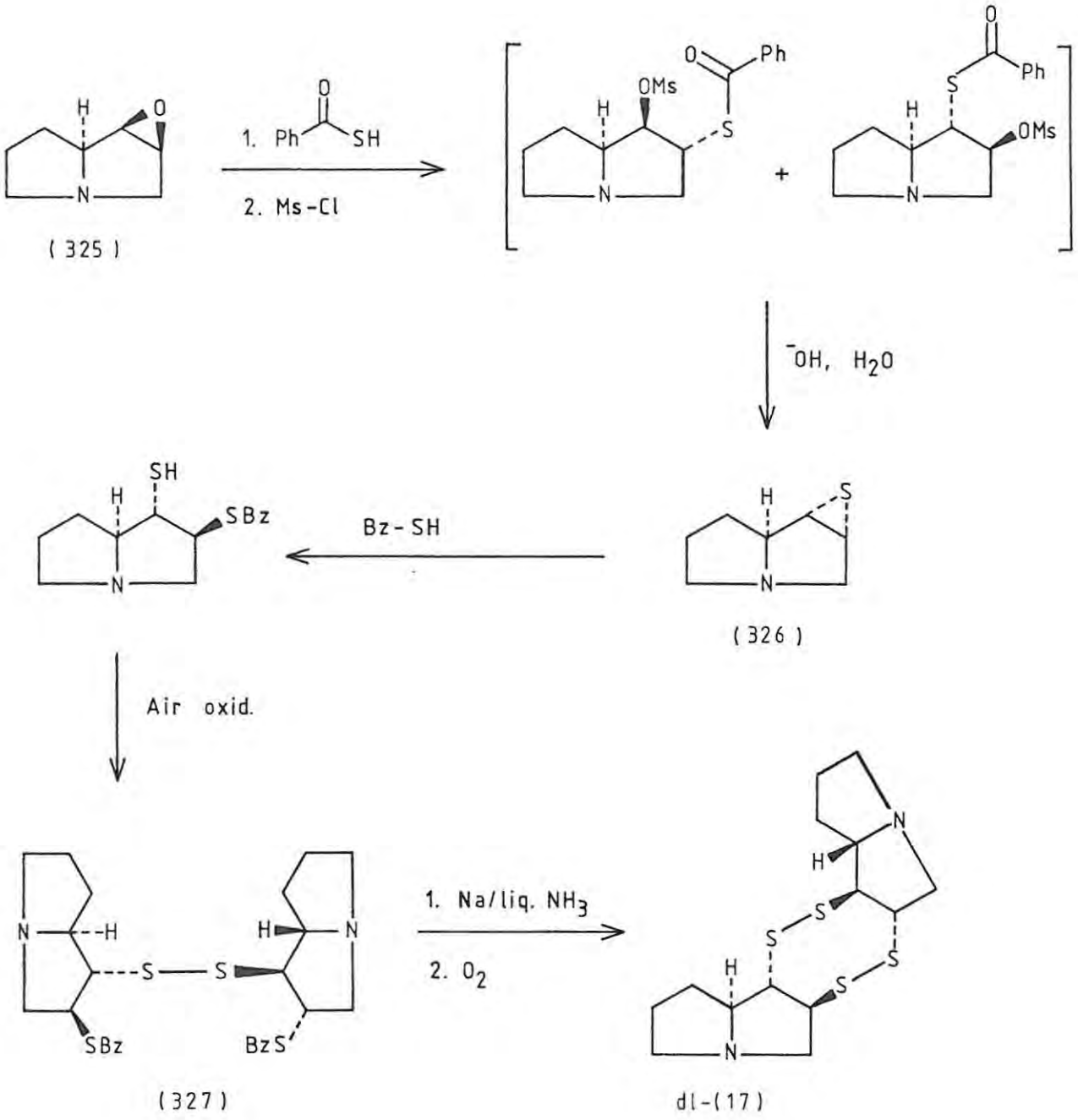
Scheme 36.

Synthesis of the dihydroxy necines, petasinecine (19) and its C_1-epimer (322), has been reported by Benn[197], who started with the ketoester (318), [Scheme 36]. Enol-keto tautomerism and catalytic reduction of (319) gave a mixture of the hydroxyesters (320, 321). However the use of sodium cyanoborohydride afforded (321) exclusively. Separation of the isomers and further hydride reduction gave (-)petasinecine (19) and its (+)C_1-epimer (322).



Scheme 37.

Very recently Zalkow and Glinski converted retronecine into heliotridine.[198] Naturally available (+)retronecine (194) was first converted into the 7-mesyl-9-benzoyl diester (322), [Scheme 37]. Inversion of the stereochemistry at C_7 was effected by treatment with various cesium carboxylates (such as cesium acetate), which gave (323) from which (+)heliotridine (195) was obtained by hydrolysis.



(325) (326) (327) dl-(17)

Scheme 38.

The last synthesis of this type is that of racemic cassipourine by Wrobel[199], [Scheme 38]. The 1,2-epoxy-pyrrolizidine (325) was converted into the thioepoxide (326) by epoxide cleavage with thiobenzoic acid, mesylation and base induced ring closure. Stereospecific cleavage of the thiirane ring with thiobenzyl alcohol followed by air oxidation gave the bis-sulphide (327). Removal of the

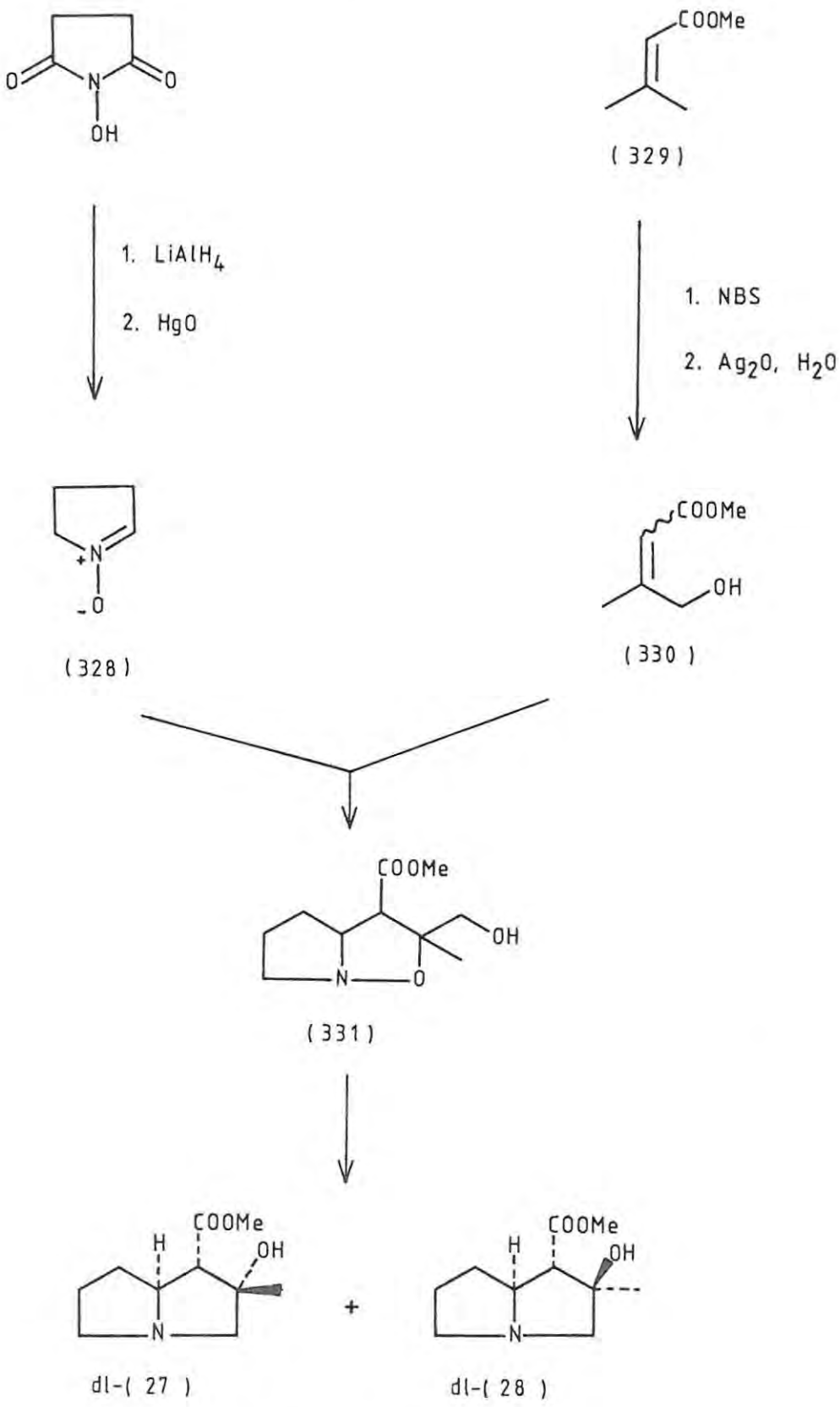
benzyl protecting groups without cleavage of the pyrrolizidine-sulphur or sulphur-sulphur bonds proved possible using sodium in liquid ammonia. The resulting dithiol readily oxidized to racemic cassipourine (17) in the presence of oxygen.

2.2. Necic acids and alkaloids.

Syntheses of the alkaloids and the necic acids are grouped together since in a number of cases synthesis of the acid is integral to the synthesis of the alkaloid.

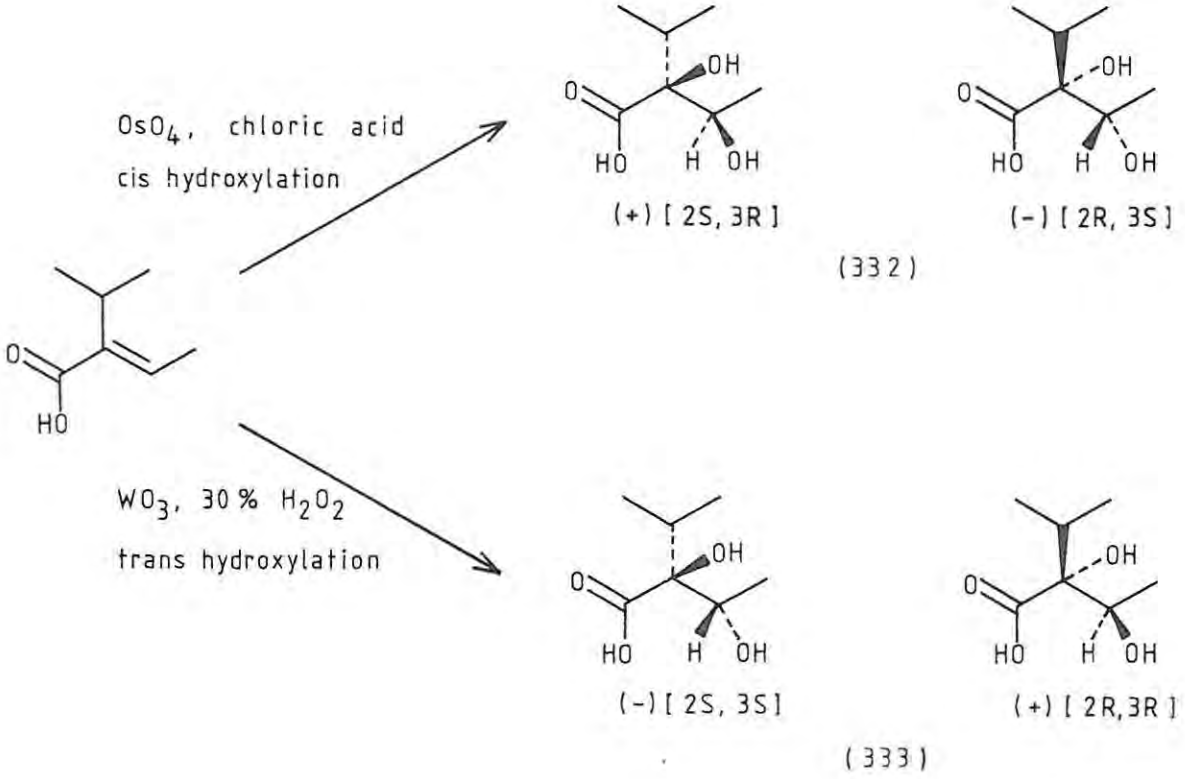
The simplest esters synthesised since 1976 are racemic tussilagine (27) and its C_2-epimer racemic isotussilagine (28), [Scheme 39], reported by Roeder and coworkers.[45] Reduction of N-hydroxysuccinimide followed by mercuric oxide oxidation gave the required pyrrolidine N-oxide (328). Allylic bromination and subsequent hydroxylation of butenoate (329) gave the hydroxybutenoate (330) as a mixture of cis and trans isomers. A 1,3-dipolar cycloaddition with the N-oxide (328) resulted in a mixture of the isoxazolidines (331), which on mesylation and catalytic hydrogenation gave a mixture of the pyrrolizidine esters (27) and (28).

Kochetkov[78] has reported the total synthesis of trachelanthamine (334), lindelofine (335) and viridiflorine (336), and in so doing has determined the relative and absolute stereochemistry of these alkaloids and hence the absolute stereochemistry of a number of related alkaloids.


COOMe
(329)
1. LiAlH4
2. HgO
1. NBS
2. Ag2O, H2O
(328)
COOMe
OH
(330)
COOMe
OH
(331)
COOMe
H
OH
COOMe
H
OH
dl-(27)
dl-(28)

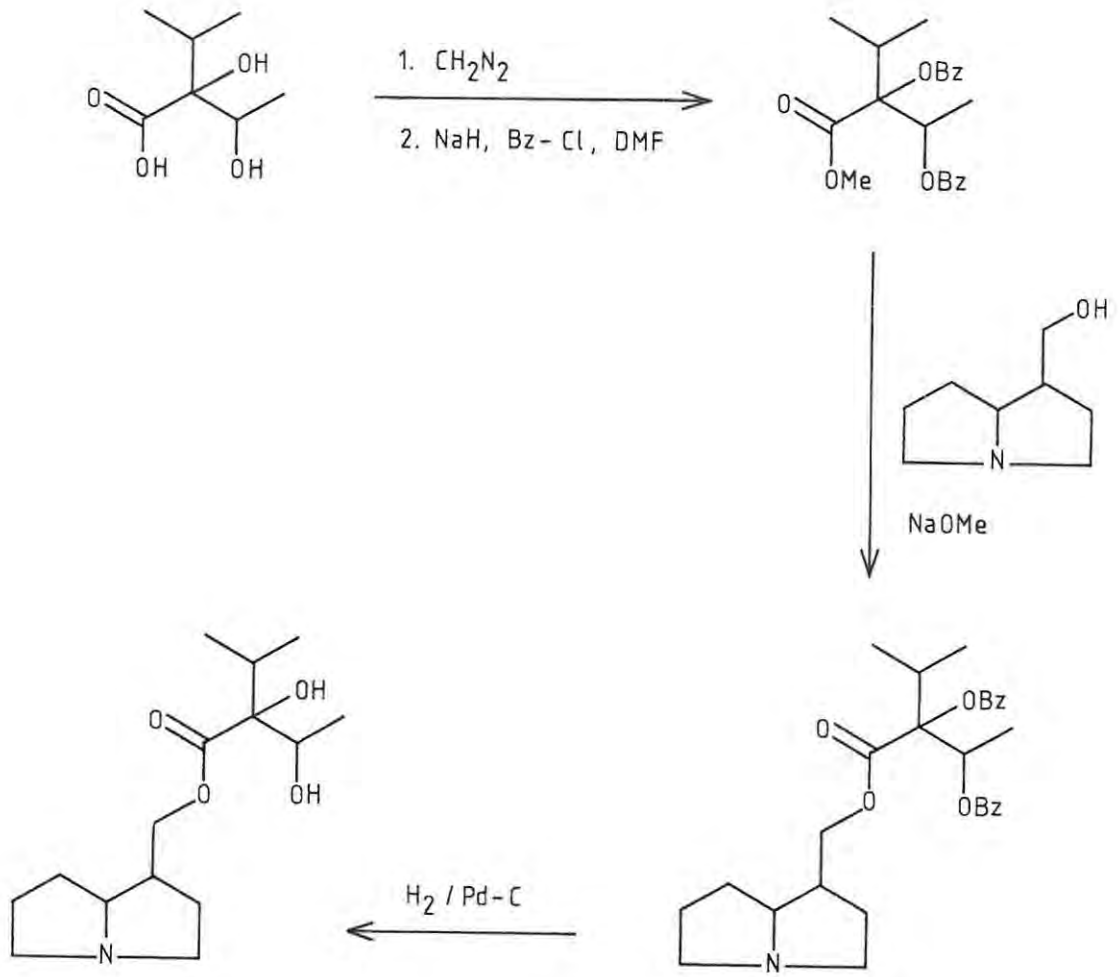
Scheme 39.

The optically active isomers of 2-isopropyl-2,3-dihydroxybutanoic acid were synthesised from trans-2-isopropylbutenoic acid, [Scheme 40], and then resolved.

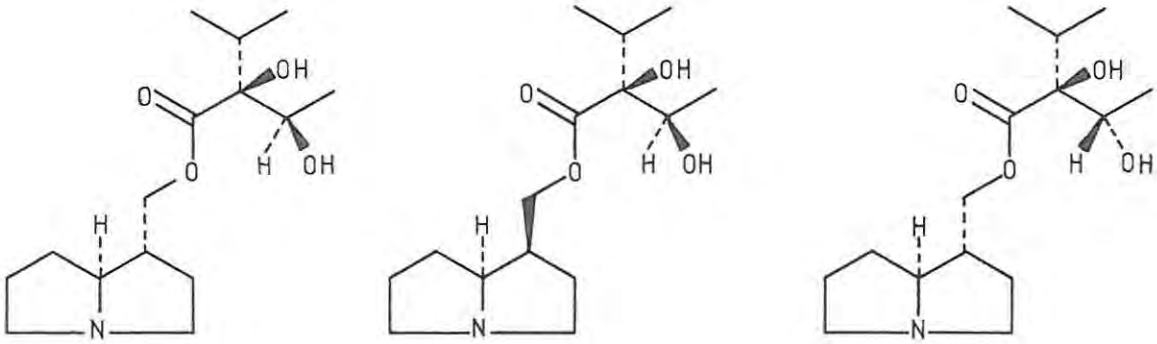


Scheme 40.

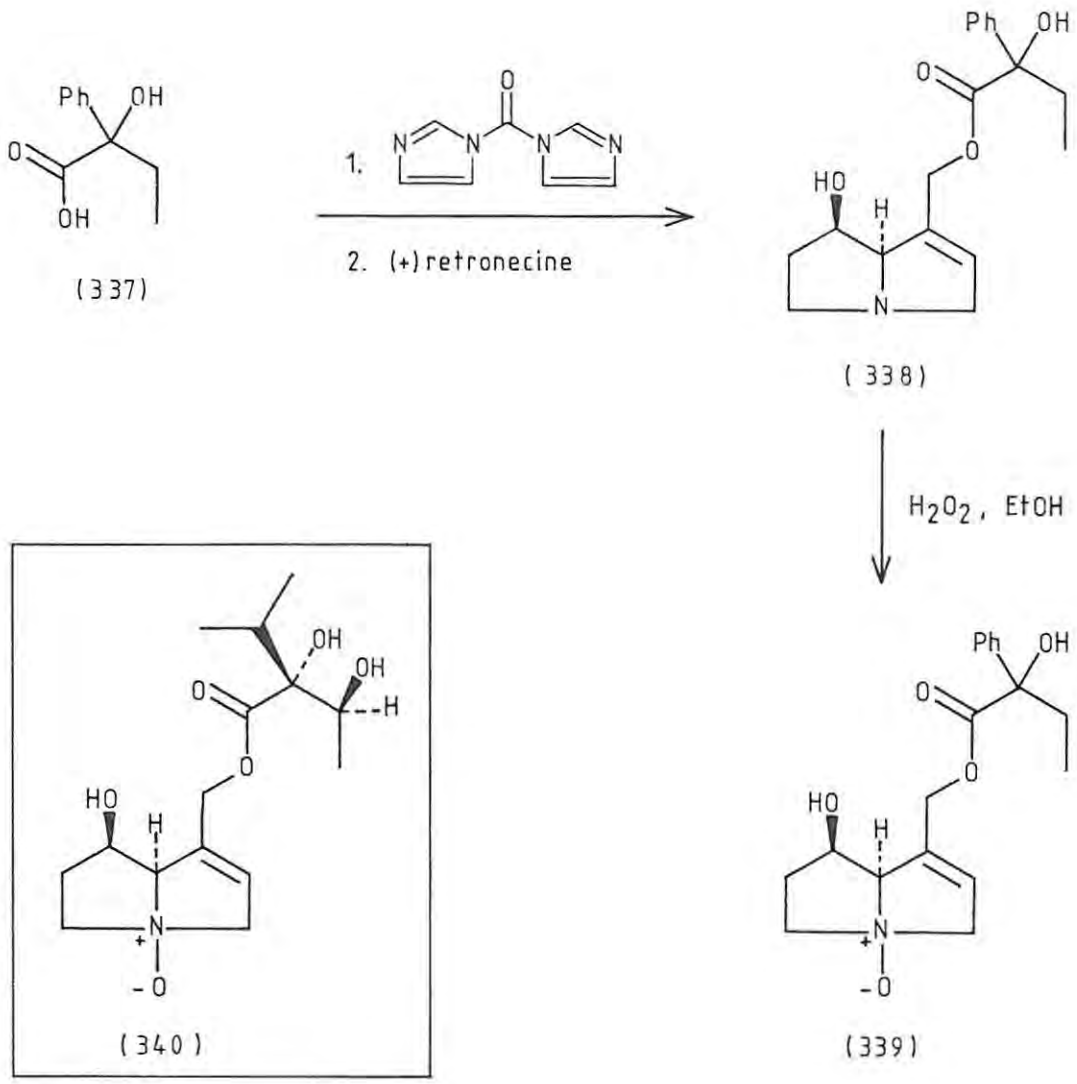
The resolved acids were esterified using diazomethane, [Scheme 41], and the hydroxyl groups protected as their benzyl ethers. Transesterification of a protected ester with an optically active necine in the presence of sodium methoxide gave the dibenzylalkaloid derivative from which the free alkaloid was obtained on hydrogenolysis. Thus esterification of (-)trachelanthamidine with (+)trachelanthic acid (332) gave trachelanthamine (334); (+)isoretronecanol esterified with the same acid gave lindelofine (335), and (-)trachelanthamidine esterified with (-)viridifloric acid (333) gave viridiflorine (336).



Scheme 41.



(334) (335) (336)



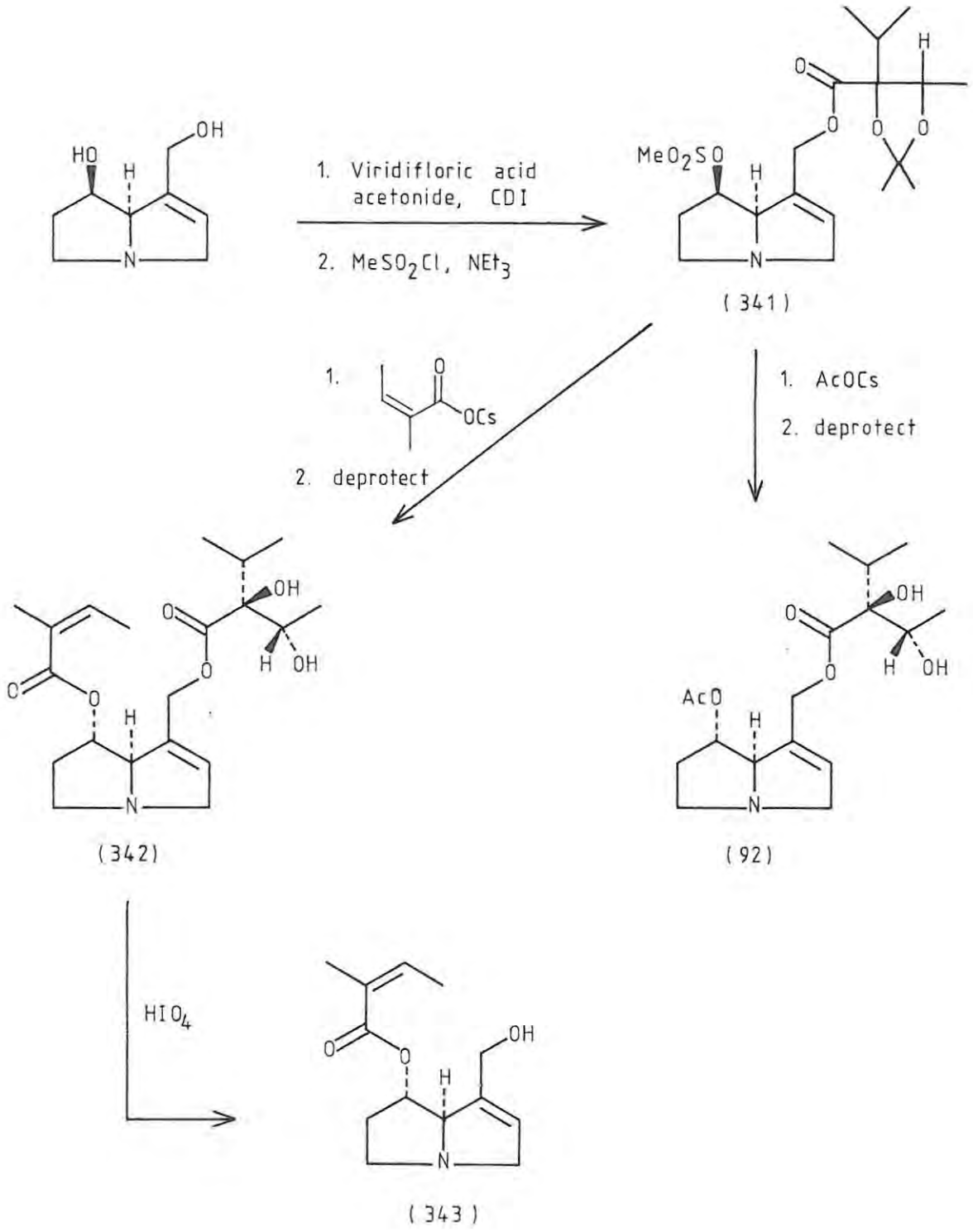
Scheme 42.

In view of the known anticancer activities of a number of pyrrolizidines,[200,201] Zalkow and coworkers[202] synthesised 9-O-(2-hydroxy-2-phenylbutanoyl)retronecine (338), [Scheme 42], as a racemic mixture and as the pure 2'S(+) and 2'R(-) diastereomers. This was accomplished by converting either the racemic or the optically pure acids (337) into the imidazolide, and then allowing the activated acid to react with retronecine (obtained from natural sources). Esterification occurred specifically at the C_9 allylic hydroxyl group of retronecine to give the desired alkaloid

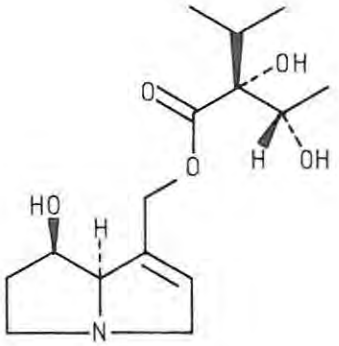
which was subsequently oxidised to the N-oxide (339) with hydrogen peroxide in ethanol. [Subsequent tests showed the N-oxide to have greater anticancer activity than indicine N-oxide (340) on which the synthetic alkaloid was designed.]

Recently Zalkow and Glinski[198] have synthesised 7-acetyl-echinatine (92), 7-angelyl-9-viridiflorylheliotridine (342), and 7-angelylheliotridine (343). Naturally available retronecine was esterified at C_9 with the acetonide of (-)viridifloric acid, and then mesylated to give (341), [Scheme 43]. The stereochemistry at C_7 was then inverted, by reaction with either cesium acetate or cesium angelate, and removal of the actonide gave (92) and (342) respectively. Lastly oxidative cleavage of (342) gave (343).

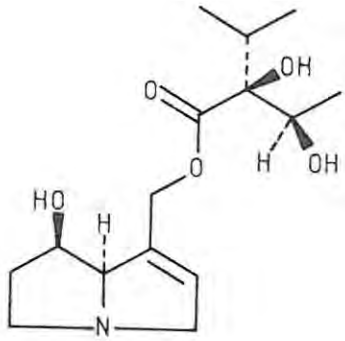
Zalkow's group have also synthesised a number of alkaloids by reaction of various isopropylidene protected dihydroxy acids with retronecine using N,N'-carbonyldiimidazole (CDI) and imidazoylsodium as coupling agents.[203] Mild acid hydrolysis of the isopropylidene protecting groups yielded the free alkaloids indicine (344), intermedine (345), lycopsamine (346) and 9-(+)viridiflorylretronecine (347). These alkaloids, along wih their N-oxides, prepared by treatment with m-chloroperbenzoic acid, were then screened for anticancer activity.


1. Viridifloric acid acetonide, CDI
2. $MeSO_2Cl$, NEt_3
(341)
1.
2. deprotect
1. AcOCs
2. deprotect
(342)
(92)
HIO_4
(343)

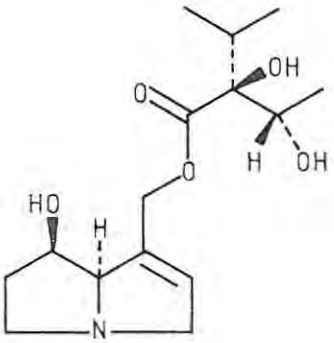
Scheme 43.



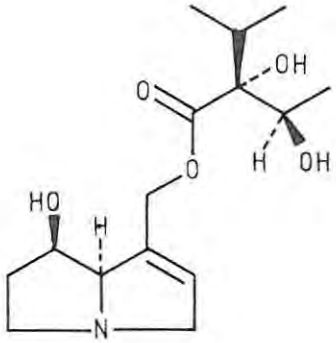
(344)



(345)



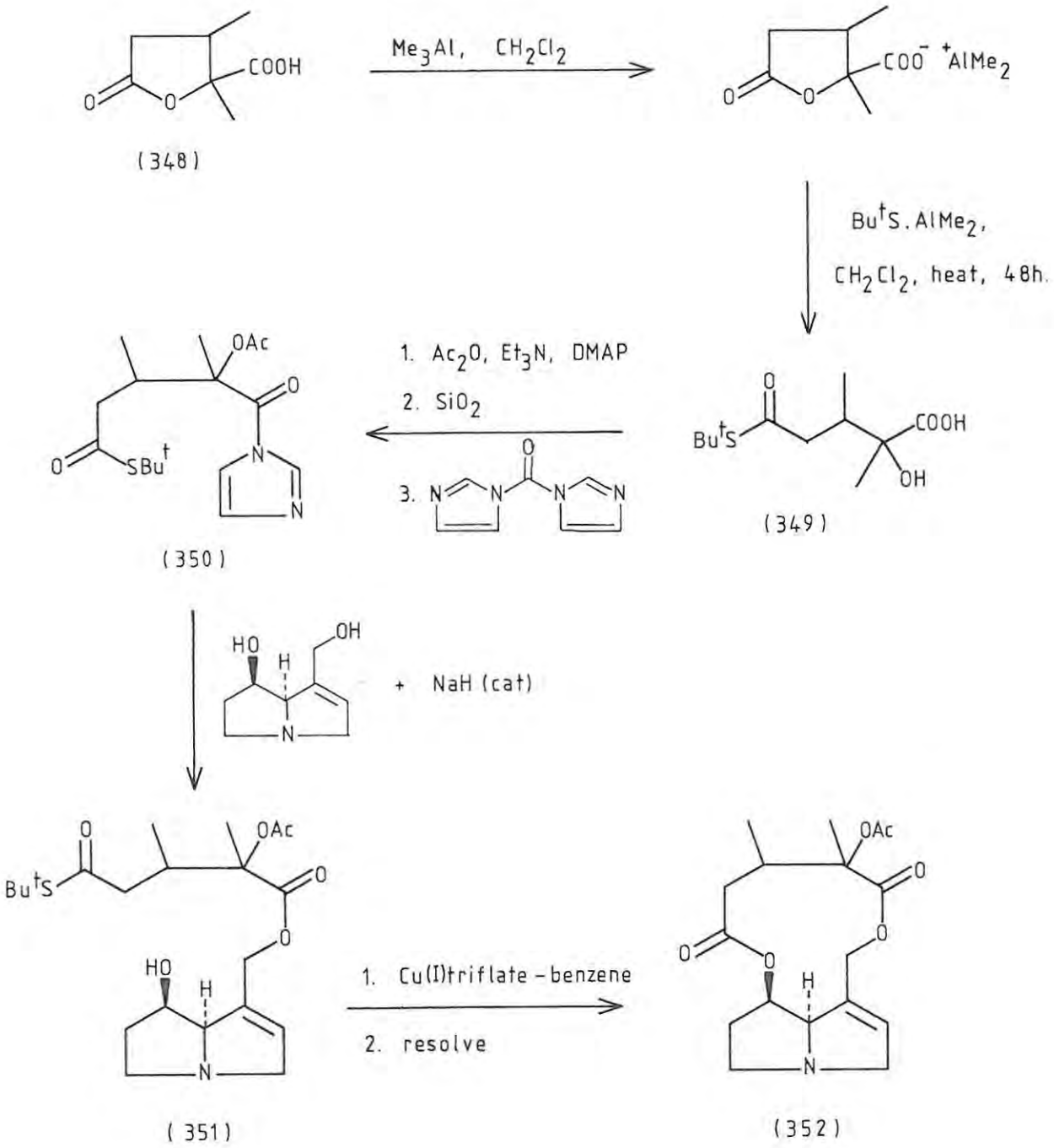
(346)



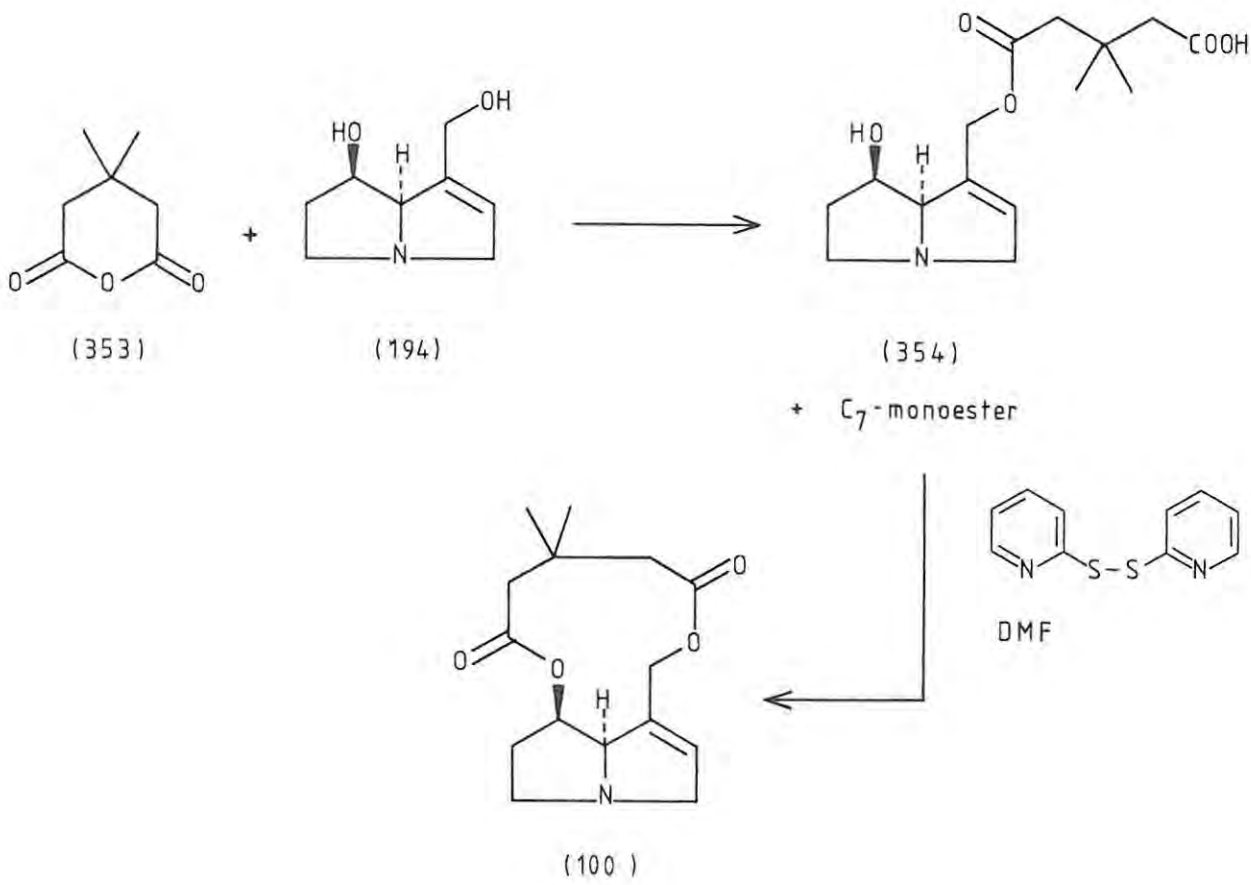
(347)

The macrocyclic pyrrolizidine diester crobarbatine has been synthesised as its acetate by Meinwald and Huang.[204] The starting material, racemic trans-lactone (348), [Scheme 44], was converted into its dimethylaluminium salt, which reacted quantitatively with dimethylaluminium tert-butyl sulphide to give the thioester (349). Attempts to react (349) with (+)retronecine (obtained by isolation and hydrolysis of monocrotaline) led to unwanted reaction of the tertiary alcohol. This was therefore converted into the acetate, the free acid activated as the imidazole (350), and then reacted with the necine in the presence of a catalytic amount of sodium hydride to afford the ester (351). Final cyclisation, by treatment with copper(I) trifluoromethane-

sulphonate-benzene complex gave a mixture of crobarbatine acetate (352) and its diastereomer.



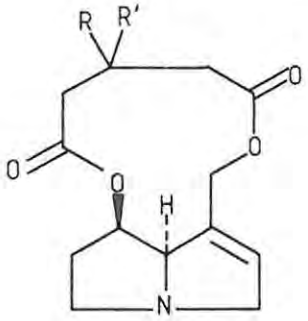
Scheme 44.



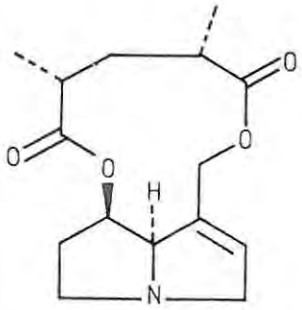
Scheme 45.

In 1980 Robins and Sakdarat[82] developed a route to macrocyclic esters of retronecine, [Scheme 45]. Reaction of (+)retronecine (194) with dimethylglutaric anhydride (353) in chloroform gave a quantitative mixture of the 7- and 9-monoesters (354) of retronecine. The mixture of monoesters was then reacted with 2,2'-dithiodipyridine and triphenylphosphine in dimethylformamide at room temperature, and the resulting thioesters cyclised to the diester (100) by refluxing in dimethylformamide.

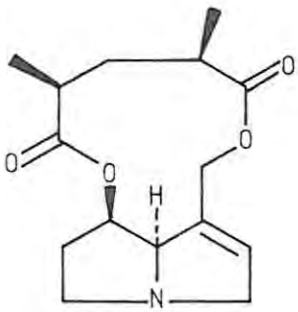
Use of various substituted starting anhydrides[205-207,83] gave the eleven-membered macrocyclic diesters (355-362), and the ten-membered macrocyclic diesters (96-99).[81] Only dicrotaline, (358), occurs naturally.



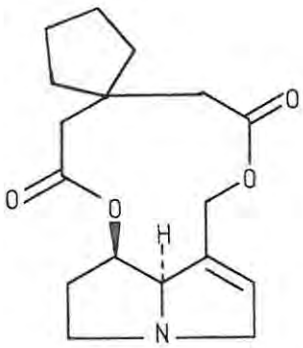
	R	R'
(355)	H	H
(356)	Ph	Ph
(357)	H	Me
(358)	OH	Me
(359)	Me	OH



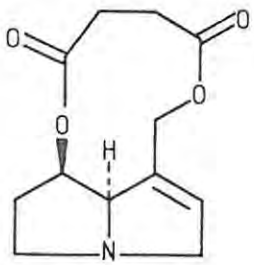
(360 = 101)



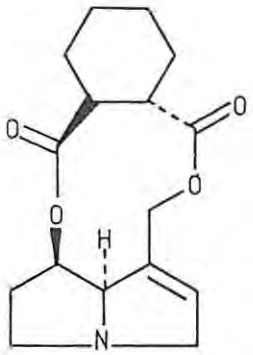
(361 = 102)



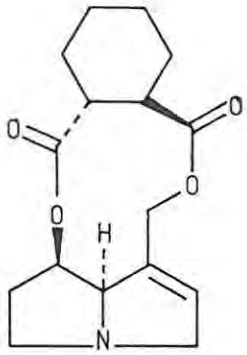
(362)



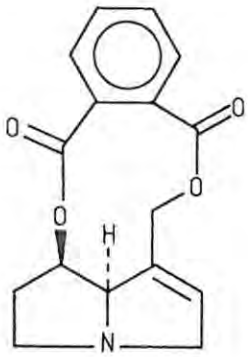
(96)



(97)



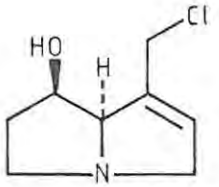
(98)



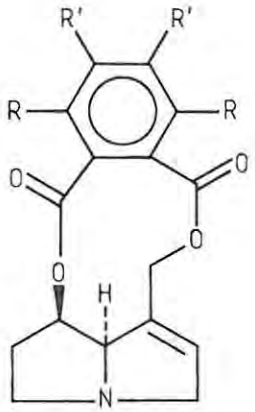
(99)

Very recently Robins and Burton have reported a modified cyclisation procedure.[208] Retronecine was converted to the chloro derivative (363), and this was reacted with a variety of acid anhydrides in the presence of DBU affording the new diesters (364 - 371).

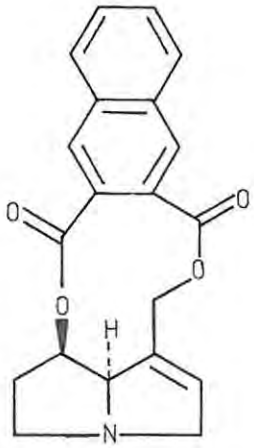
The only other eleven-membered macrocyclic pyrrolizidines to be synthesised are the isomeric alkaloids crispatine and fulvine. These have been prepared by Vedejs and Larsen[209] and require a different cyclisation procedure to that used by Robins[207] and Meinwald.[204] Crispatic acid (372), [Scheme 46], previously synthesised by Matsumoto,[210] was converted into the anhydride by reaction with dicyclohexylcarbodiimide, and the hydroxyl group protected as the methoxymethyl ether. Cleavage of the anhydride with 2-(trimethylsilyl)ethoxy-dimethylaluminium then gave the glutarate monosilyl ester (373, R = H). This was converted to the phosphoric anhydride (373, R = $PO(OEt)_2$) and then coupled with the lithium alkoxide of the racemic silyl protected retronecine (374) to form a mixture of diastereomers (375).



(363)



	R	R'
(364)	H	Cl
(365)	Cl	Cl
(366)	Br	Br



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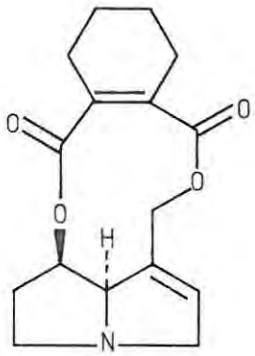

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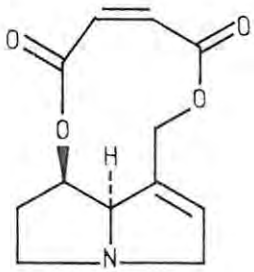

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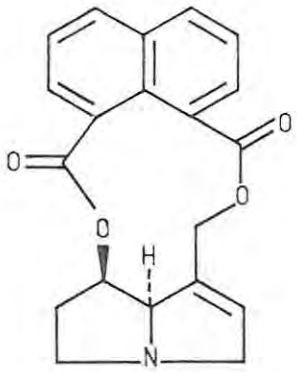
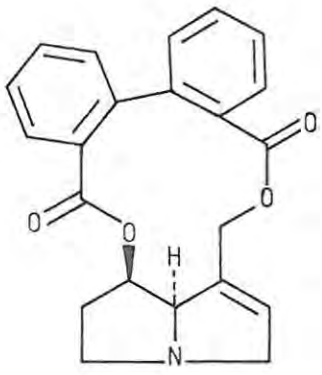


(370)



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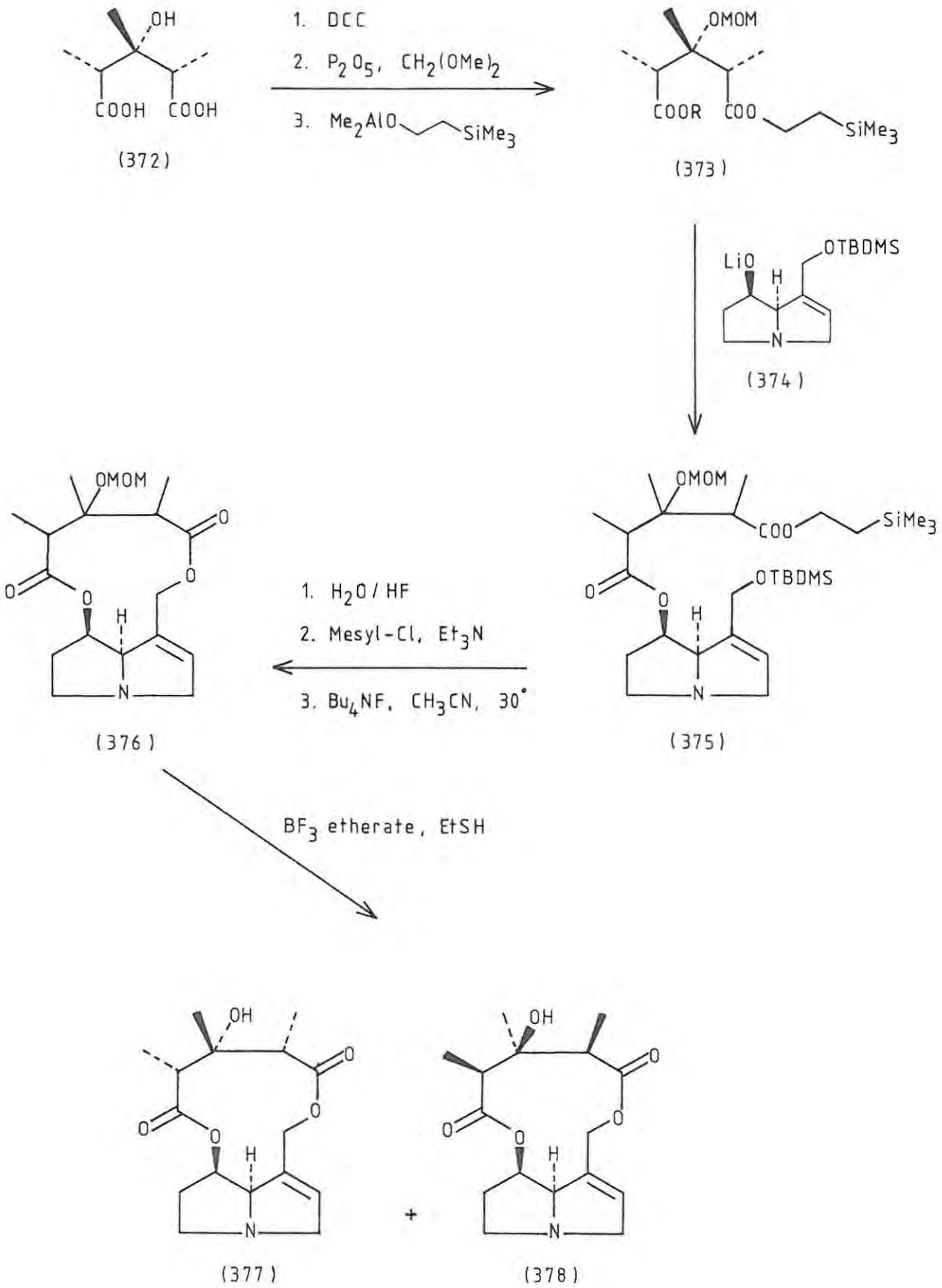
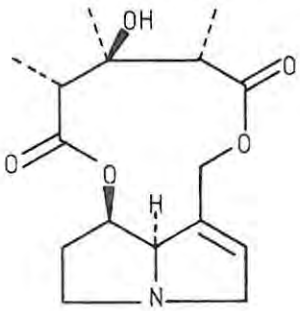
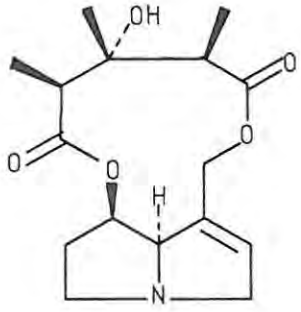

OH
COOH COOH
(372)
1. DCC
2. P_2O_5, $CH_2(OMe)_2$
3. Me_2AlO SiMe3
OMOM
COOR COO SiMe3
(373)
LiO
H
OTBDMS
N
(374)
OMOM
COO SiMe3
OTBDMS
O
H
N
(375)
1. H_2O / HF
2. Mesyl-Cl, Et_3N
3. Bu_4NF, CH_3CN, 30°
OMOM
O
(376)
BF_3 etherate, EtSH
OH
(377)
+
OH
(378)

Scheme 46.

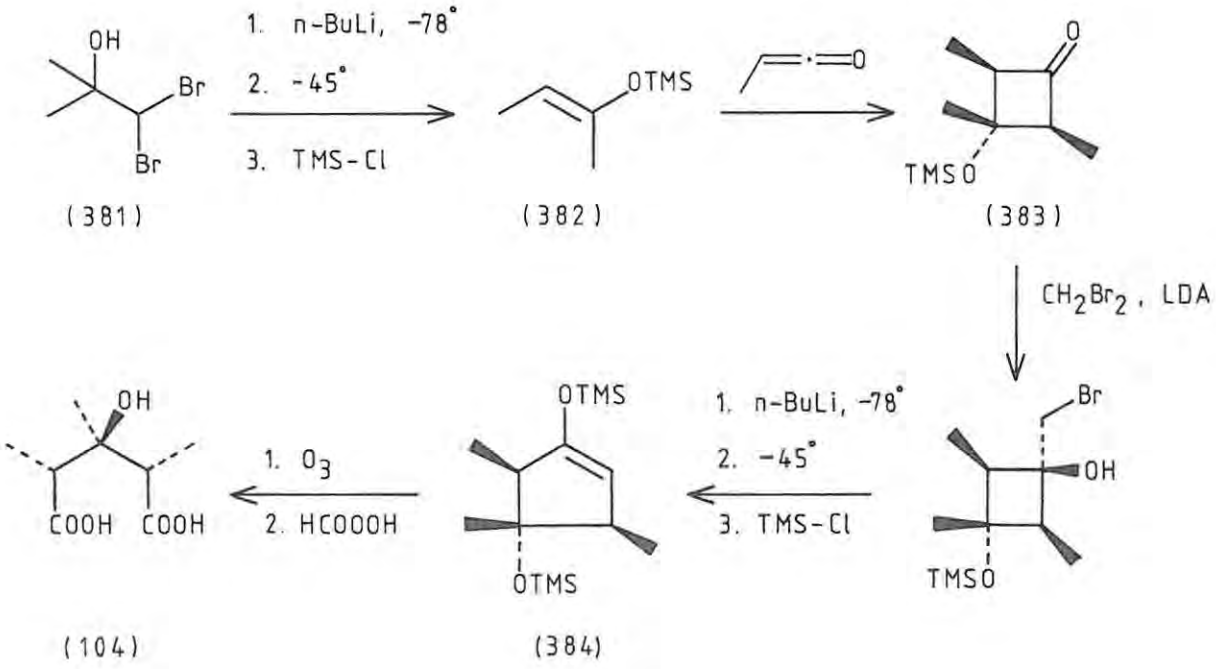
Cyclisation to the diester (376) involved changing the protecting group attatched at C_9 to a methanesulphonate as well as treatment with tetrabutylammonium fluoride in acetonitrile. The diastereomers were separated and the protecting groups removed to give either crispatine (377) or isocrispatine (378). Replacement of crispatic acid by fulvinic acid in the reaction sequence led to fulvine (379) and isofulvine (380).



(379)



(380)

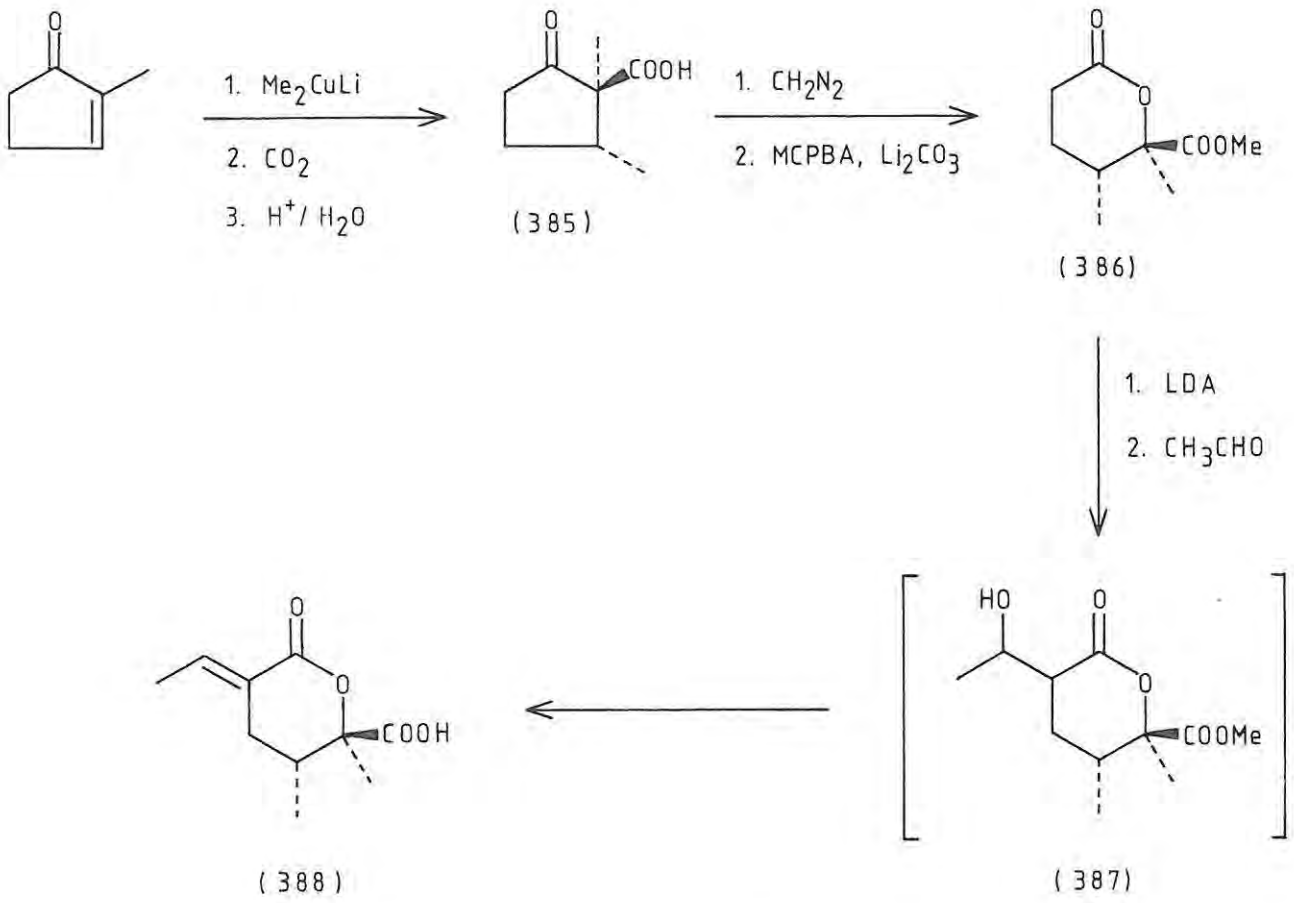


(381) (382) (383) (384) (104)

Scheme 47.

Although fulvinic acid had been synthesised earlier,[210] material for the synthesis of fulvine was obtained by a different sequence, [Scheme 47]. Addition of two equivalents of butyl lithium to dibromide (381) followed by trimethylsilyl chloride gave predominantly the E-enolsilane (382). This underwent a selective [2+2] cycloaddition with methyl ketene to form cyclobutanone (383). Introduction of the dibromomethylene unit followed by a bromocarbenoid ring expansion reaction[211] gave (384) from which fulvinic acid (104) was obtained on oxidative cleavage.

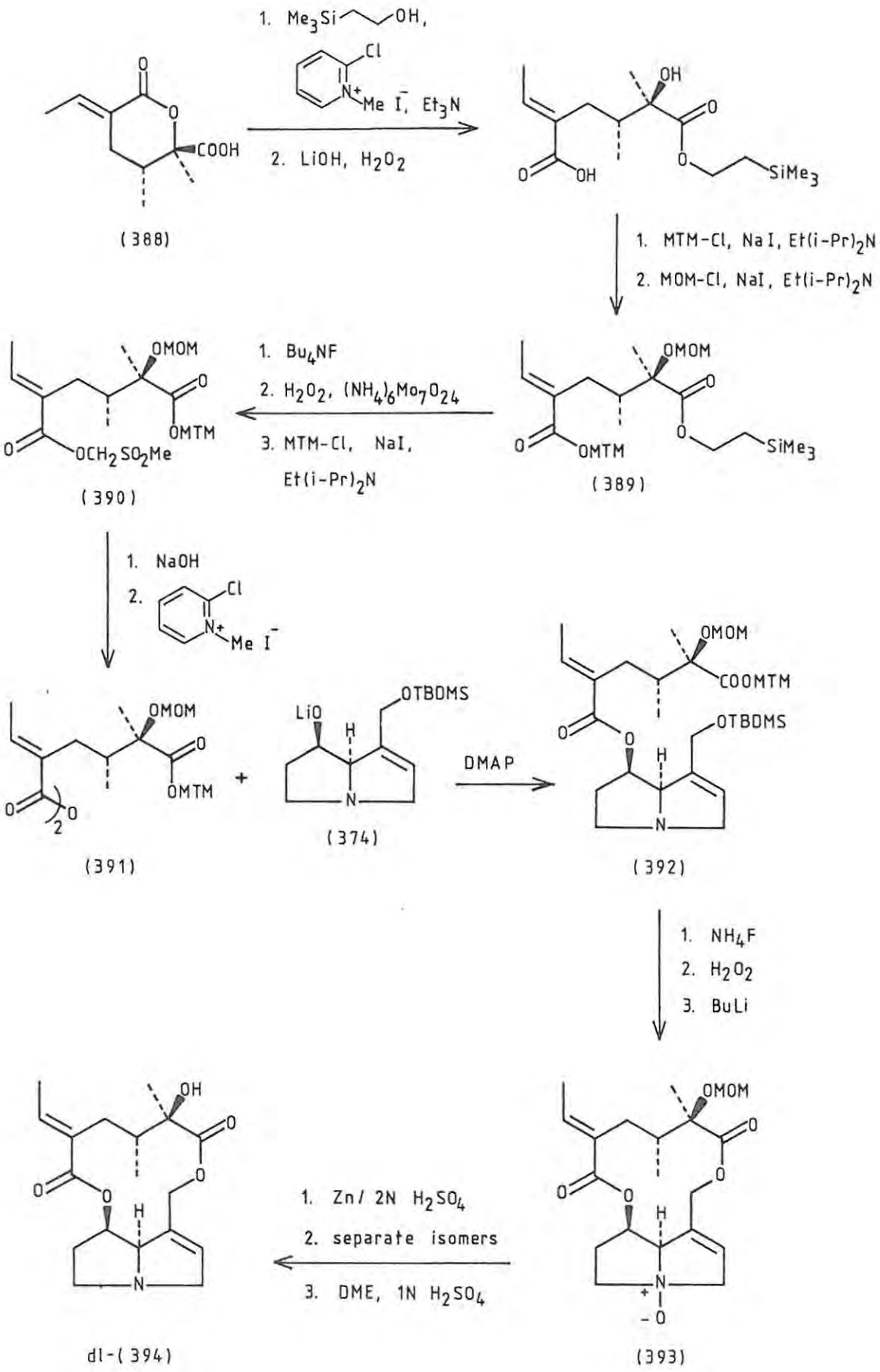
The first twelve-membered macrocyclic pyrrolizidine alkaloid synthesis reported is that of integerrimine by Narasaka and coworkers.[189,212] The required integerrinecic acid lactone was synthesised,[213] [Scheme 48]. Methylation of 2-methyl-2-cyclopentenone with dimethylcopper lithium at 0°C, followed by carboxylation of the resulting lithium enolate at -78°C resulted in stereospecific formation of the ketoacid (385). This was esterified with diazomethane and then subjected to a Baeyer-Villiger oxidation with 3-chloroperbenzoic acid in the presence of lithium carbonate to afford the lactone (386) as the major product. Lithiation and addition of acetaldehyde then gave the aldol product (387), which was not isolated. Dehydration proved difficult and was finally achieved using 2-fluoro-1-methylpyridinium p-toluenesulphonate yielding mainly the (E)-isomer, hydrolysis of which gave racemic integerrinecic acid lactone (388).



Scheme 48.

In preparation for coupling to the base retronecine, the lactone was subjected to a number of protection and deprotection reactions in order to obtain the anhydride (391), [Scheme 49]. Acid protection, ring cleavage and further introdution of protecting groups gave (389) with the acid groups differentially protected. Oxidation of one of these groups and replacement of the second gave (390) from which (391) was obtained by removal of the sulphone group and treatment with 2-chloro-1-methylpyridinium iodide.

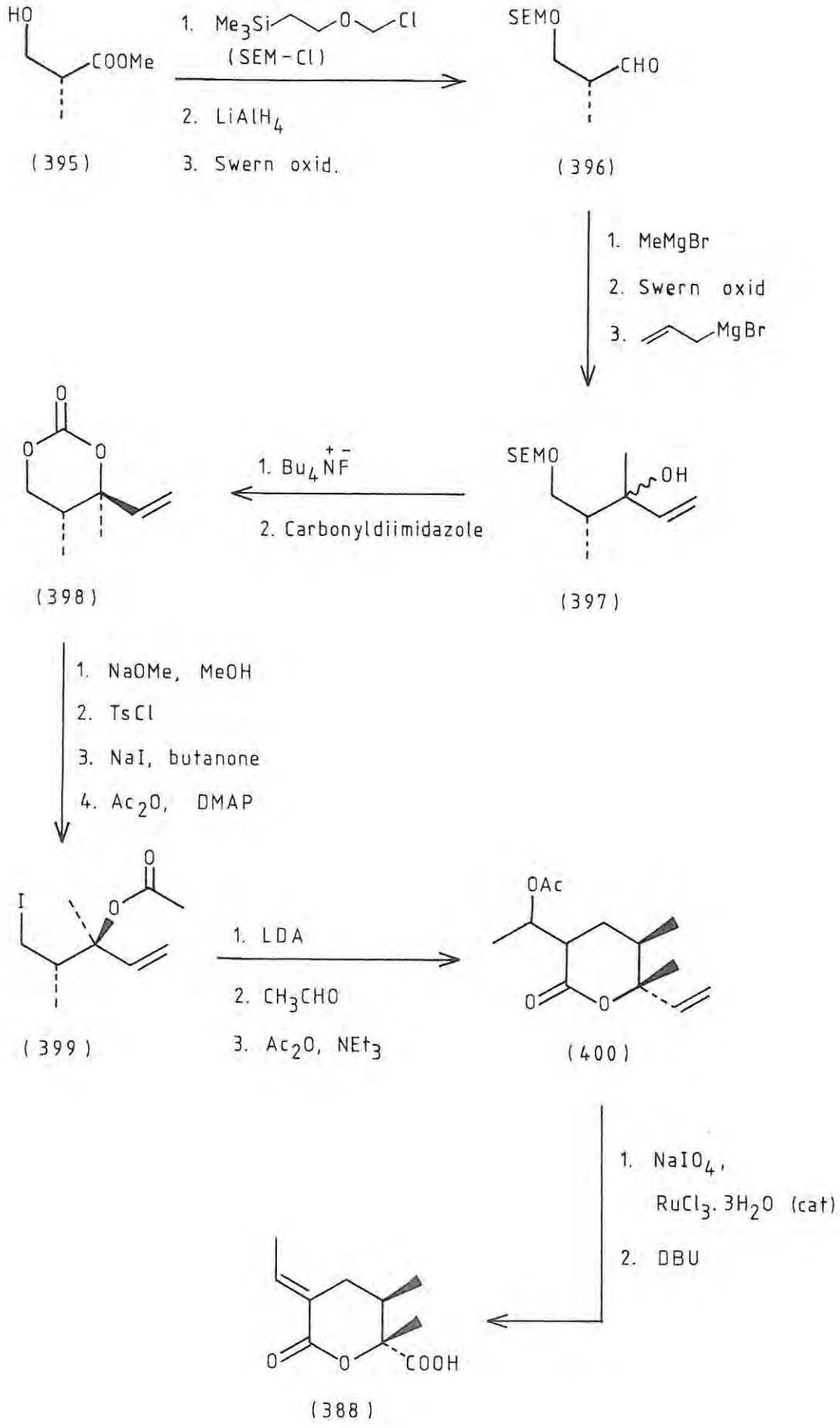
Prior to coupling with anhydride (391), the allylic alcohol of the base retronecine, (obtained via a modification of Geissman's route, Cf. Scheme 29), was protected as the


1. Me3Si-CH2-CH2-OH,
Me I⁻, Et3N
2. LiOH, H2O2
(388)
1. MTM-Cl, NaI, Et(i-Pr)2N
2. MOM-Cl, NaI, Et(i-Pr)2N
1. Bu4NF
2. H2O2, (NH4)6Mo7O24
3. MTM-Cl, NaI,
Et(i-Pr)2N
(389)
(390)
1. NaOH
2.
Me I⁻
(391)
(374)
DMAP
(392)
1. NH4F
2. H2O2
3. BuLi
(393)
1. Zn / 2N H2SO4
2. separate isomers
3. DME, 1N H2SO4
dl-(394)

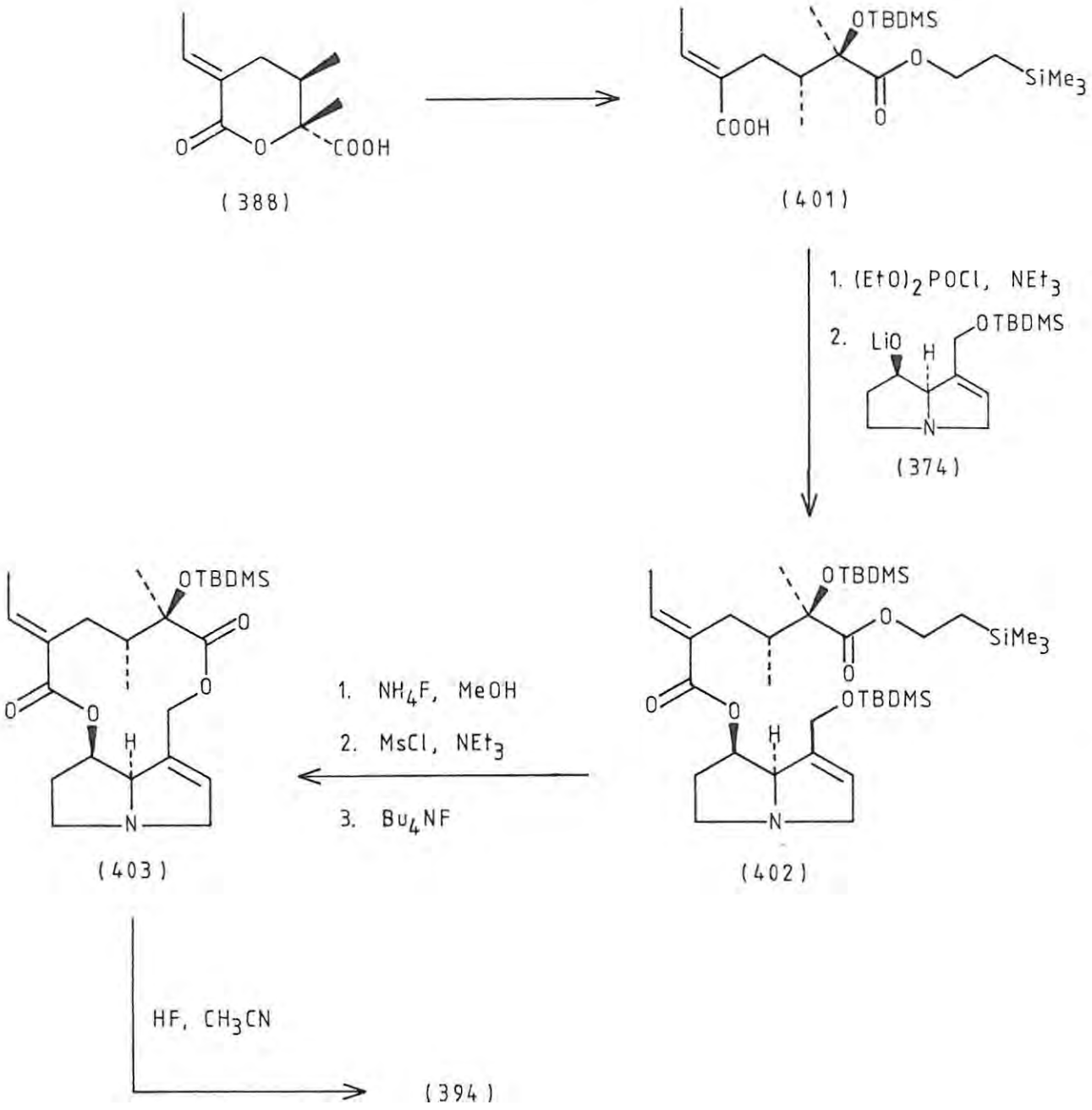
Scheme 49.

tert-butyldimethylsilyl ether. Treatment of anhydride (391) with the lithium salt (374) gave ester (392). Formation of the cyclic diester (393) was then achieved by first oxidising the methoxythiomethyl unit to the sulphone, second, replacing the C_9-silyl protecting group with a lithium alkoxide unit and then finally reacting the sulphone in a nucleophilic diplacement reaction. Since formation of the cyclic diester also induced the formation of the N-oxide, the latter was reduced, and the mixture of diastereomers separated. Hydrolysis of the methoxymethyl protecting group finally gave racemic integerrimine (394).

Recently White and Ohira have reported a stereospecific synthesis of integerrimine, based in part on the above work.[214] Synthesis of the acid portion began with methyl (R)-(-)-3-hydroxy-2-methylpropanoate (395), [Scheme 50]. This was protected, then converted to the aldehyde (396). A Grignard reaction, Swern oxidation and a second Grignard reaction gave (397). Conversion to the cyclic carbonates and separation gave (398) as the major isomer. This was hydrolysed and transformed via the primary tosylate to (399). Lithiation, reaction with acetaldehyde and acetylation gave (400), which on oxidative cleavage and base catalysed elimination generated (388) exclusively. Acid protection and ring cleavage [Scheme 51, Cf. Scheme 49], followed by protection of the alcohol provided (401). Activation of (401) and reaction with (374) led to (402). Conversion of the primary silyl ether to a mesylate followed by deprotection of the ester group resulted in spontaneous cyclisation to (403). Finally removal of the protecting group gave (-)integerrimine (394).

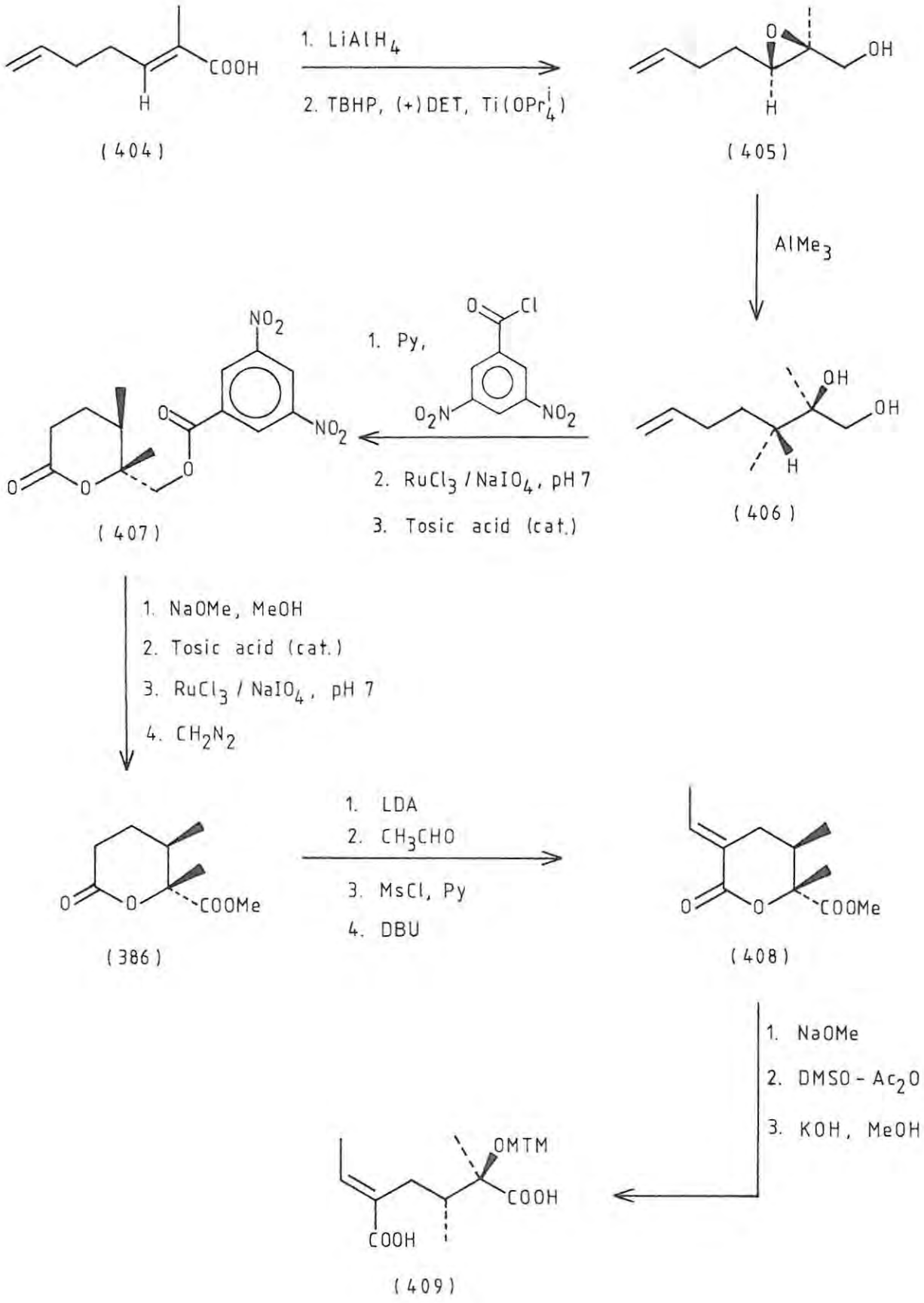

HO
COOMe
1. Me3Si O Cl
(SEM-Cl)
2. LiAlH4
3. Swern oxid.
SEMO
CHO
(395)
(396)
1. MeMgBr
2. Swern oxid
3. MgBr
SEMO
OH
1. Bu4N+F-
2. Carbonyldiimidazole
(397)
(398)
1. NaOMe, MeOH
2. TsCl
3. NaI, butanone
4. Ac2O, DMAP
I
OAc
1. LDA
2. CH3CHO
3. Ac2O, NEt3
(399)
(400)
1. NaIO4,
RuCl3.3H2O (cat)
2. DBU
COOH
(388)

Scheme 50.



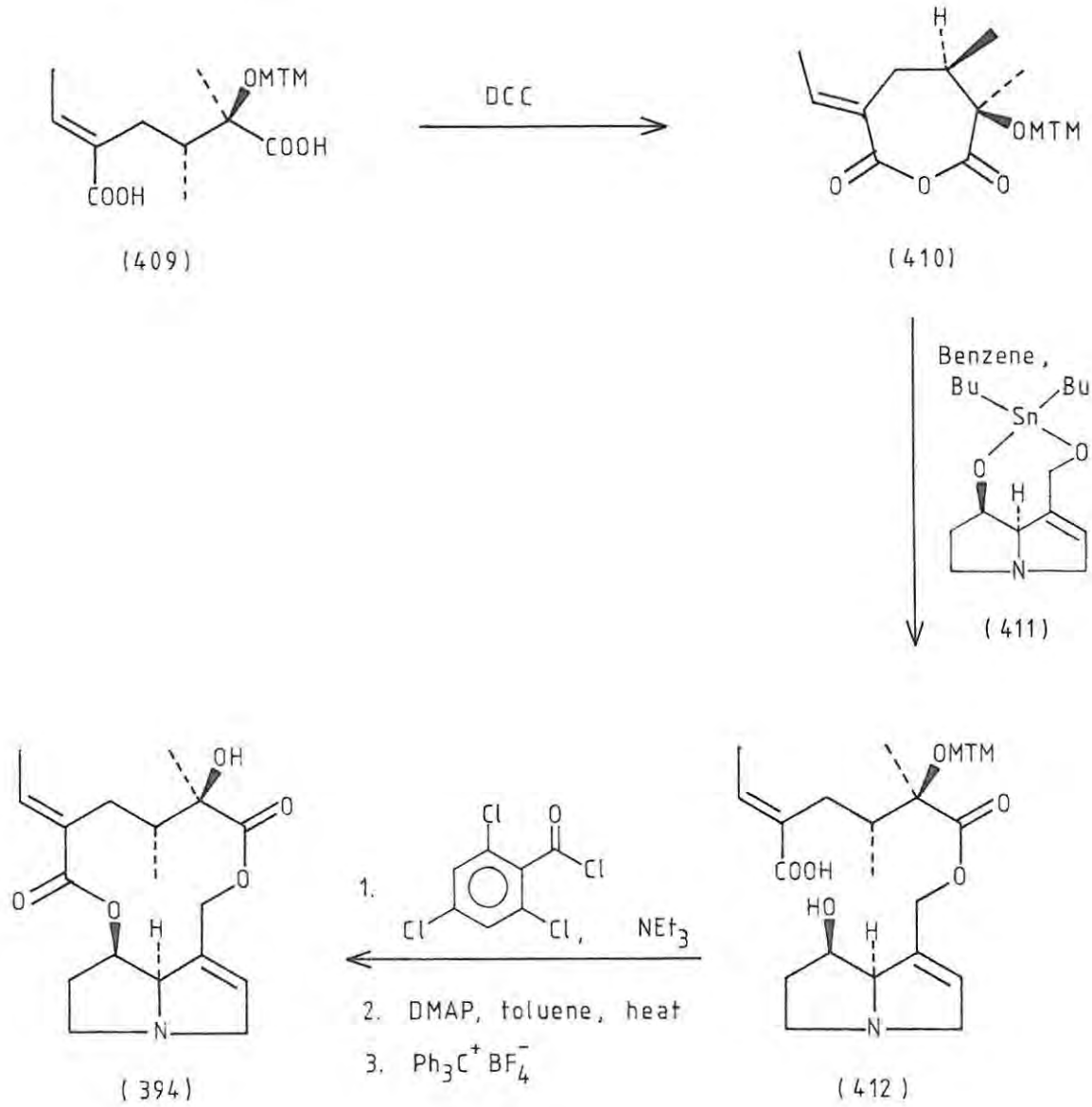
Scheme 51.

A second synthesis of optically pure integerrimine was reported at the same time by Yamada and coworkers.[215,216] The starting point for this synthesis was the dienoic acid (404), [Scheme 52]. Reduction to the alcohol followed by Sharpless epoxidation gave (405), which was converted to the diol (406) using trimethylaluminium. Protection of the primary alcohol, cleavage of the alkene using ruthenium


1. LiAlH4
2. TBHP, (+)DET, Ti(OPr4i)
(404)
(405)
AlMe3
1. Py,
2. RuCl3 / NaIO4, pH 7
3. Tosic acid (cat.)
(406)
(407)
1. NaOMe, MeOH
2. Tosic acid (cat.)
3. RuCl3 / NaIO4, pH 7
4. CH2N2
1. LDA
2. CH3CHO
3. MsCl, Py
4. DBU
(386)
(408)
1. NaOMe
2. DMSO - Ac2O
3. KOH, MeOH
(409)

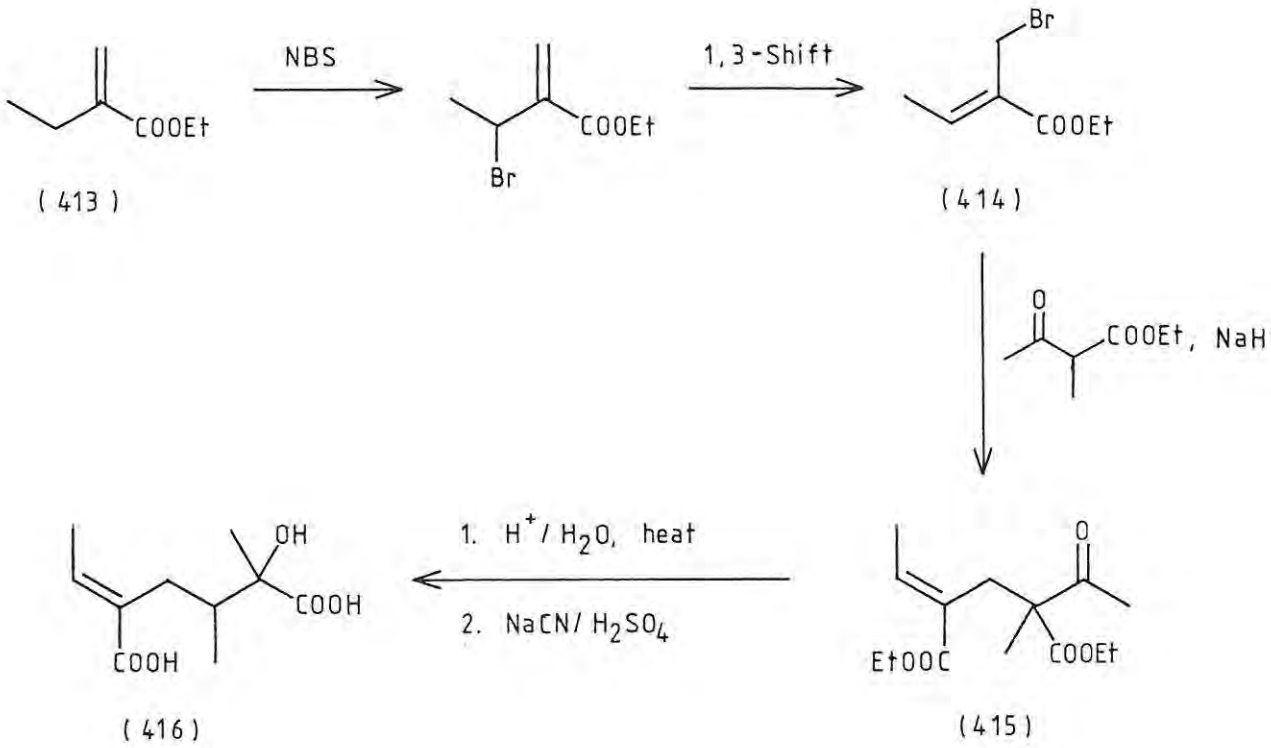
Scheme 52.

tetroxide (generated in situ), and lactonisation afforded (**407**). Deprotection, further oxidation with ruthenium tetroxide, and esterification provided (**386**), from which (**408**) was obtained using a modification of Narasaka's route (Cf. Scheme 48, p119). Cleavage of lactone (**408**) by methanolysis, protection of the hydroxyl group and hydrolysis to the diacid provided (**409**).



Scheme 53.

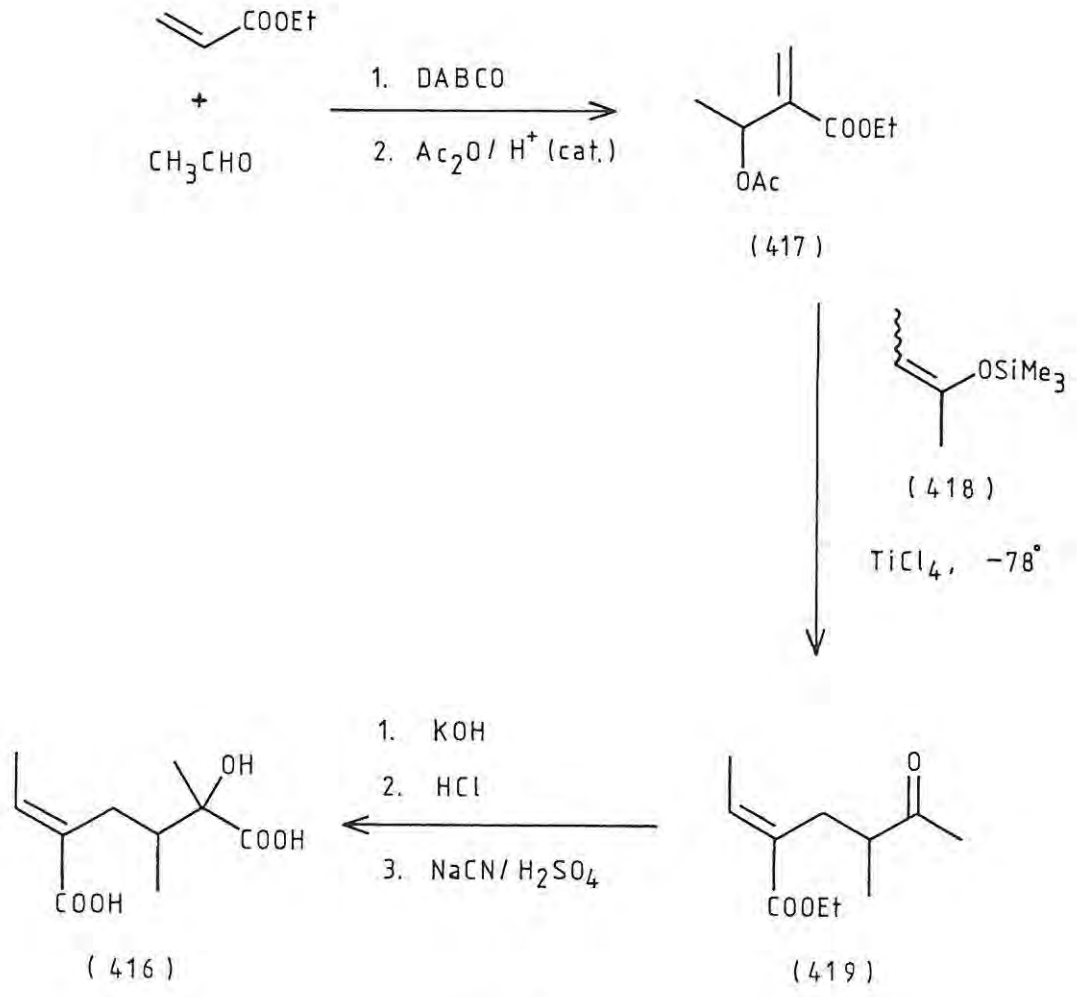
This was cyclised to the anhydride (**410**), [Scheme 53], and reacted with the stannoxane of retronecine (**411**), (obtained by reaction of retronecine with dibutyltin oxide), to form the monoester (**412**). Formation of a mixed anhydride and treatment with dimethylaminopyridine, followed by deprotection of the hydroxyl group gave the required (-)integerrimine (**394**).



Scheme 54.

Three other groups have recently reported syntheses of integerrinecic acid; 1) Pastewka[217] first brominated the unsaturated ester (**413**), [Scheme 54], and then carried out a 1,3-sigmatropic shift to obtain (**414**). This was used to alkylate ethyl methylacetoacetate forming the keto diester (**415**). Hydrolysis and decarboxylation followed by cyanohydrin formation gave the required racemic acid (**416**), albeit in low overall yield, (3%).

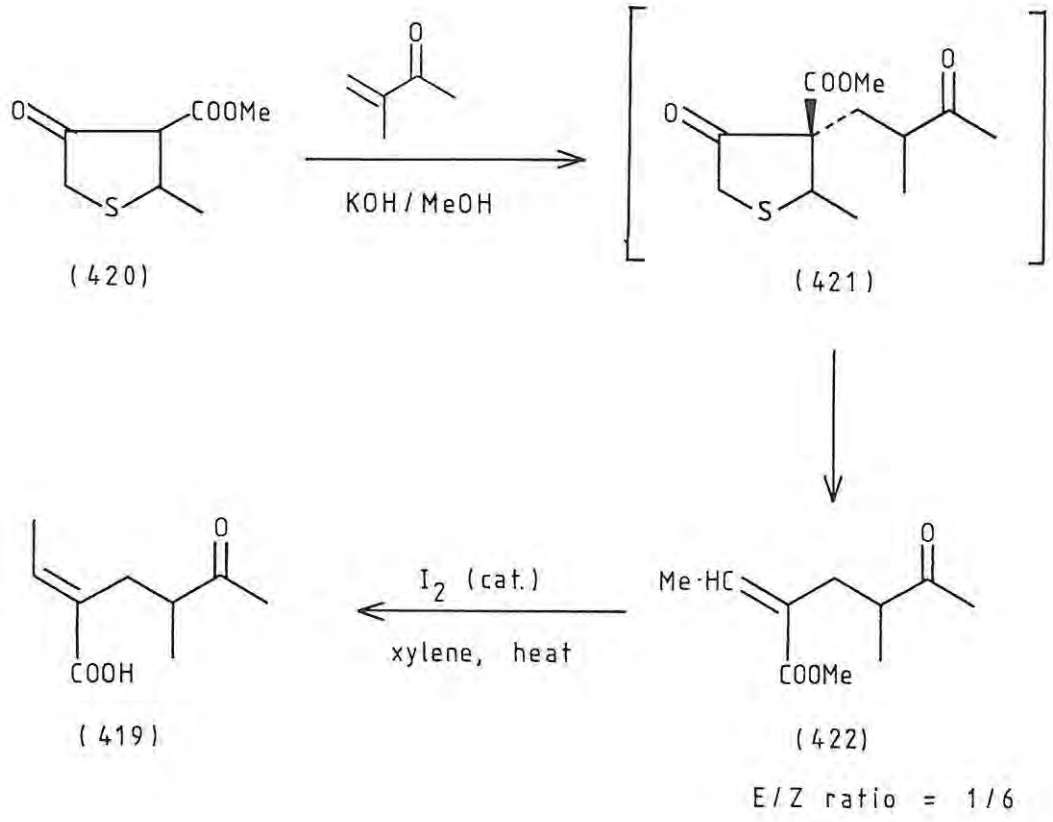
2) Drewes and Emslie[218] used 1,4-diazabicyclo[2,2,2]octane, (DABCO), to condense ethyl acrylate with acetaldehyde, and acetylated the resulting hydroxyl group to give (**417**), [Scheme 55]. This was reacted with silylenol ether (**418**) in the presence of titanium tetrachloride at -78°C to give the keto ester (**419**). This, on mild hydrolysis, followed by treatment with sodium cyanide and further hydrolysis provided racemic integerrinecic acid (**416**) in good overall yield, (18%).



Scheme 55.

3) Pollini's group have introduced the sulphur hetrocycle (**420**), [Scheme 56], as a synthon of an αβ-unsaturated ester, and which allows ready alkylation at the α-carbon.[219] Thus

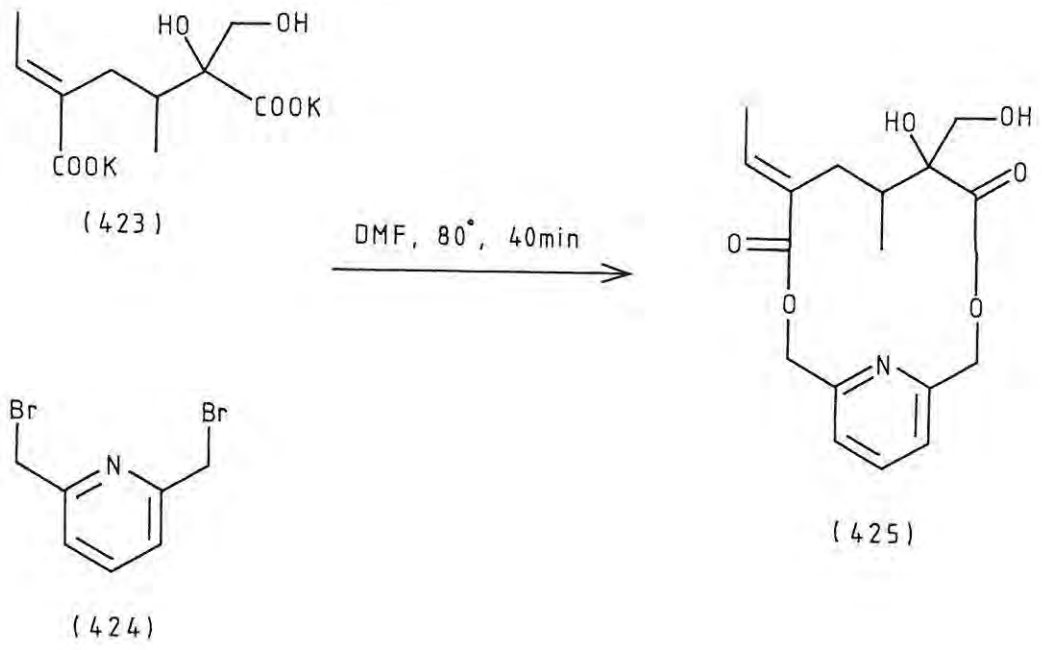
reaction of (**420**) with 3-methylbutenone in the presence of equimolar amounts of methanolic potassium hydroxide gave the Michael addition product (**421**). This, under the reaction conditions, then rearranged to the unmasked keto ester (**422**) as a mixture of E/Z isomers. Refluxing in xylene with a catalytic amount of iodine resulted in complete conversion to the E-isomer (**419**). As this had already been converted into integerrinecic acid[218] this constituted a formal synthesis of the acid.



Scheme 56.

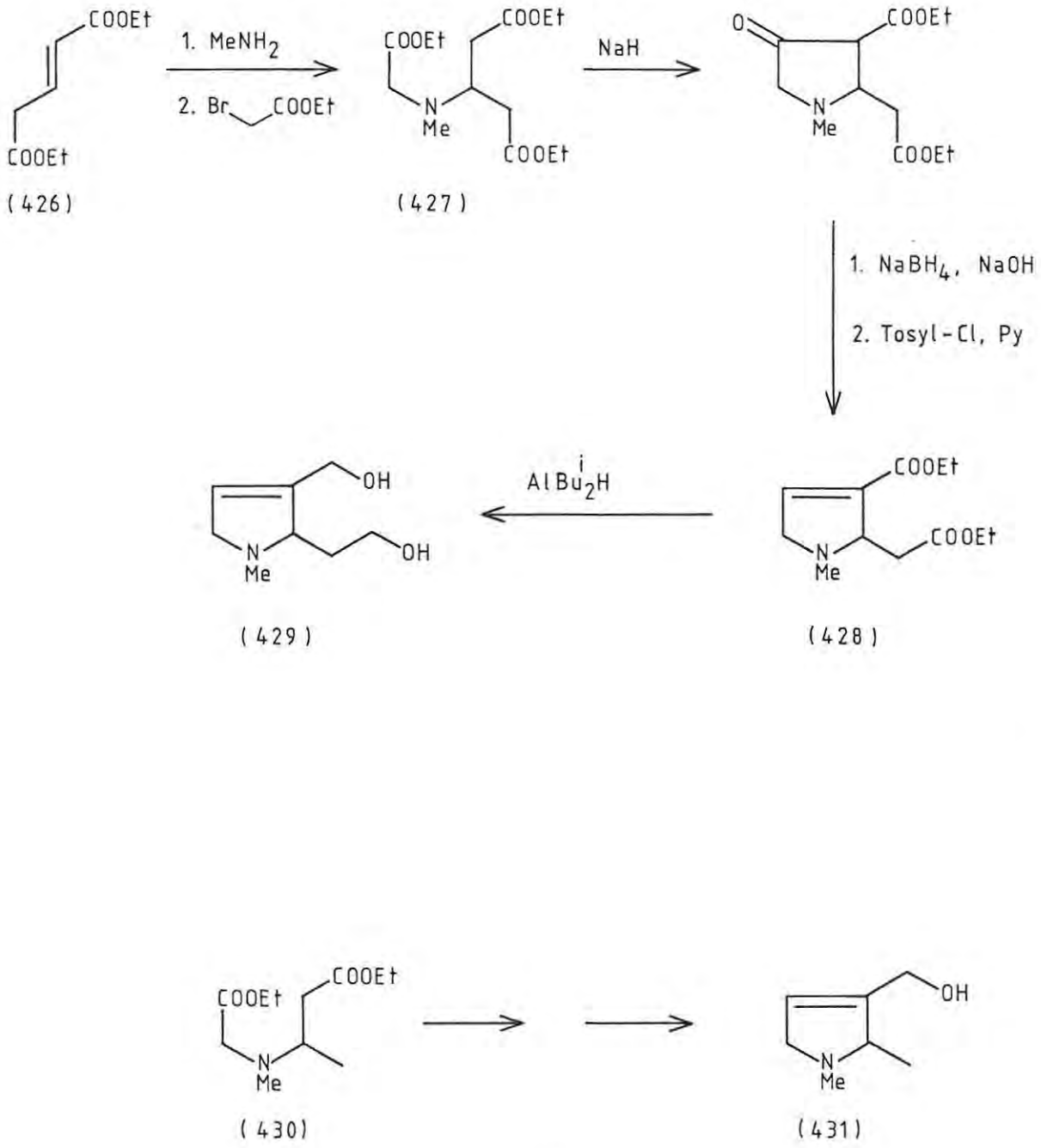
A synthetic alkaloid, pyridine-retronecate (**425**), [Scheme 57], which has the pyridine moiety in place of the pyrrolizidine ring, has been reported by Drewes and Pitchford and found to have similar cytotoxic effects to

retrorsine.[220] The acid portion of the new compound is retronecic acid and was obtained by extraction and hydrolysis of natural retrorsine from Senecio isatideus. Conversion of the acid to the dipotassium salt (**423**) followed by heating in dimethylformide with 2,6-bis(bromomethyl)pyridine (**424**) produced pyridine-retronecate (**425**).



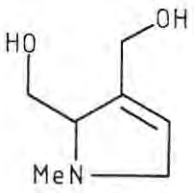
Scheme 57.

Other cytotoxicity studies on pyrrolizidine alkaloids[221] have resulted in the preparation of a range of hydroxymethyl-3-pyrroline analogues which were called synthanecines,[222] [Scheme 58]. Treatment of diethyl glutaconate (**426**) with methylamine then ethyl bromoacetate gave triester (**427**). This was subjected to Dieckmann cyclisation, a reduction and an elimination to give the pyrroline diester (**428**). This on reduction gave synthanecine D (**429**). Similarly synthanecine E (**431**) was prepared from ethyl 3-methylaminobutanoate (**430**).

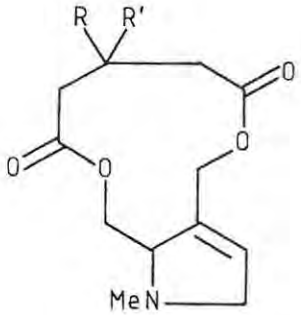


Scheme 58.

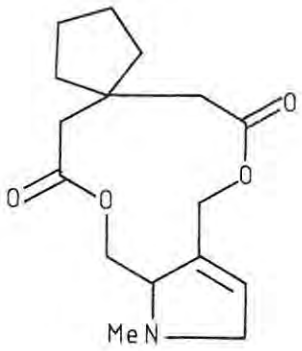
Subseqeuently Robins and Barbour[223] have synthesised the macronecine diesters (433) - (440), which have synthanecine A (432) as the base, using the same approach as had been used earlier[82] for the synthesis of the pyrrolizidine alkaloids (355) - (362) (Cf. Scheme 45).



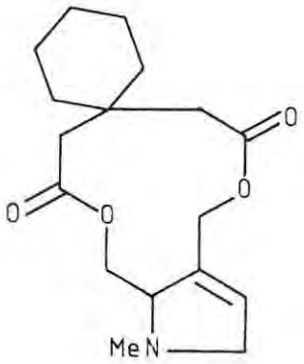
(432)



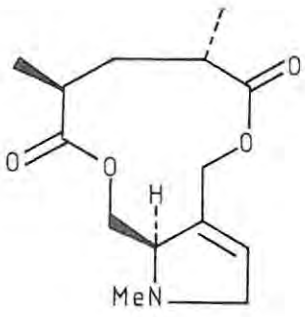
	R	R'
(433)	H	H
(434)	H	Me
(435)	Me	Me
(436)	Me	OH



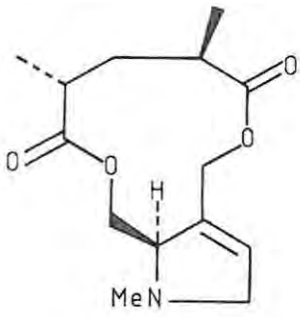
(437)



(438)

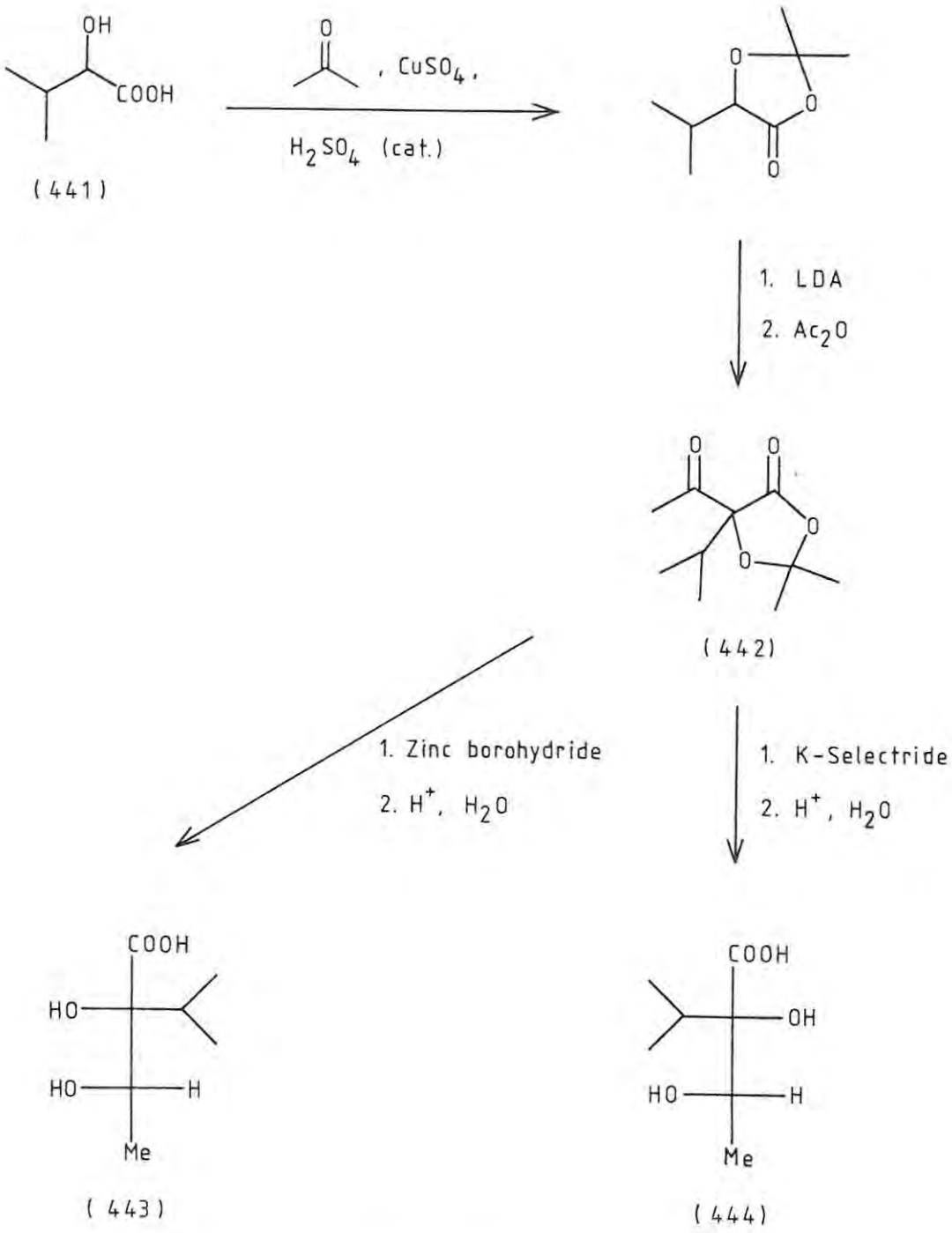


(439)



(440)

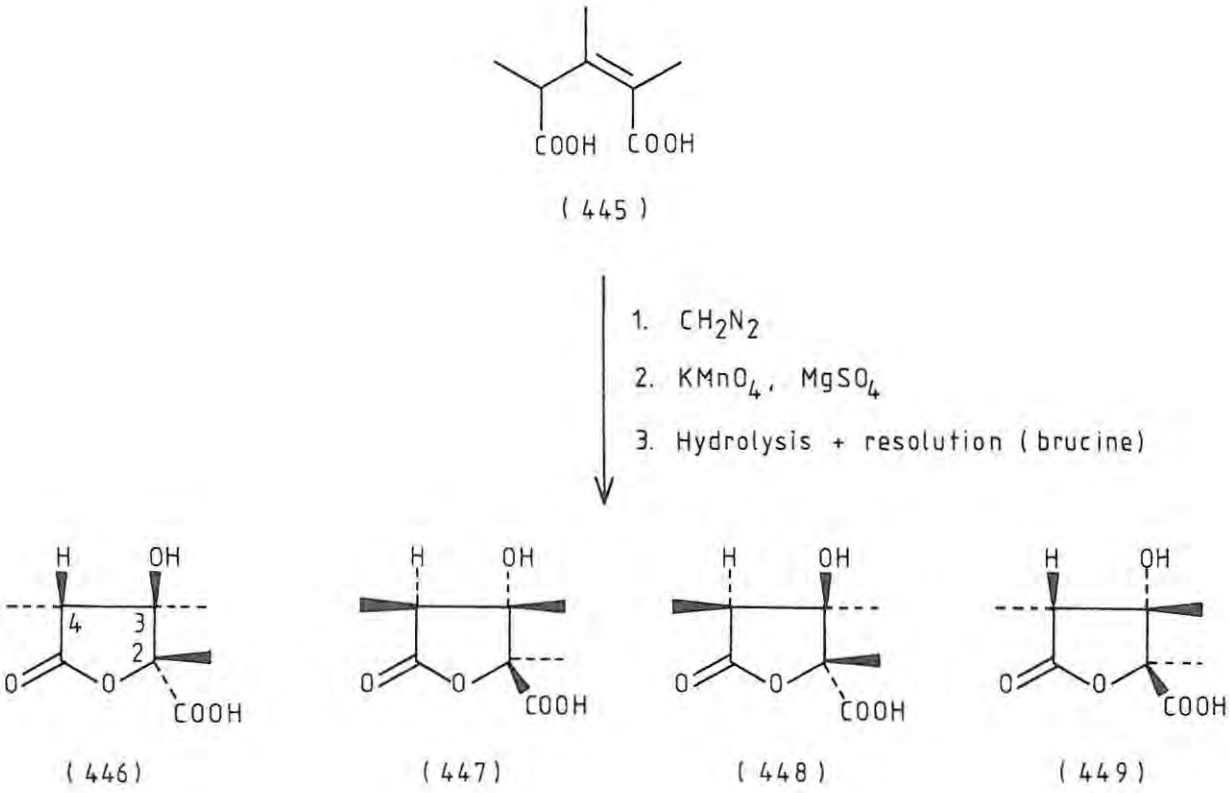
There have been five syntheses of necic acids reported since 1976[58] in addition to the syntheses of integerrinecic and fulvinic acids discussed above. The only synthesis of monocarboxylic necic acids reported recently is that of the diastereomeric trachelanthic and viridifloric acids by Glass and Shanklin.[224]



Scheme 59.

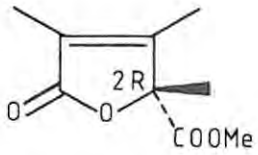
The starting material, 2-hydroxy-3-methylbutanoic acid (**441**), [Scheme 59], was first protected as the acetonide, and then treated with lithium diisopropylamide and acetic anhydride in a Claisen reaction to give ketoester (**442**). This was stereoselectively reduced either with zinc borohydride to

give racemic viridifloric acid (**443**), or with potassium tri-(sec-butyl)borohydride, (i.e. potassium selectride), to give racemic trachelanthic acid (**444**).

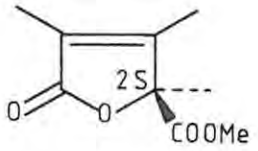


Scheme 60.

Matsumoto and coworkers have synthesised and determined the absolute configurations of all eight stereoisomers of the diacid monocrotalic acid.[225] Synthesis of four of the isomers started with racemic cis-2,3,4-trimethyl-2-penten-dioic acid (**445**), [Scheme 60], which was esterified with diazomethane and converted into the cis-diol with potassium permanganate to give a separable mixture of two racemic γ-lactone esters. Hydrolysis to the acid lactones and resolution with brucine gave the individual isomers (**446**) -(**449**).

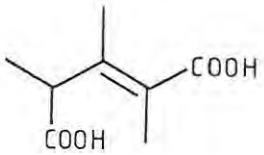


(450)

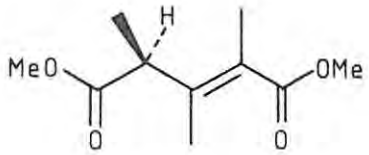


(451)

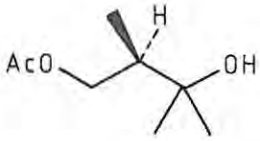
The absolute stereochemistry of each isomer at C_2 was determined by esterification and dehydration to (**450**) or (451) of known [R] or [S] configuration respectively. Since, as a result of the cis-hydroxylation and lactonisation, the C_2 and C_3-methyl groups of all four isomers must be in a trans relationship to each other the stereochemistry at C_3 could be unambiguously defined on the basis of the stereochemistry at C_2. Identification of (**446**) as monocrotalic acid therefore confirmed Crout's[226] earlier assignment of the absolute stereochemistry as (2R, 3R, 4R).



(452)

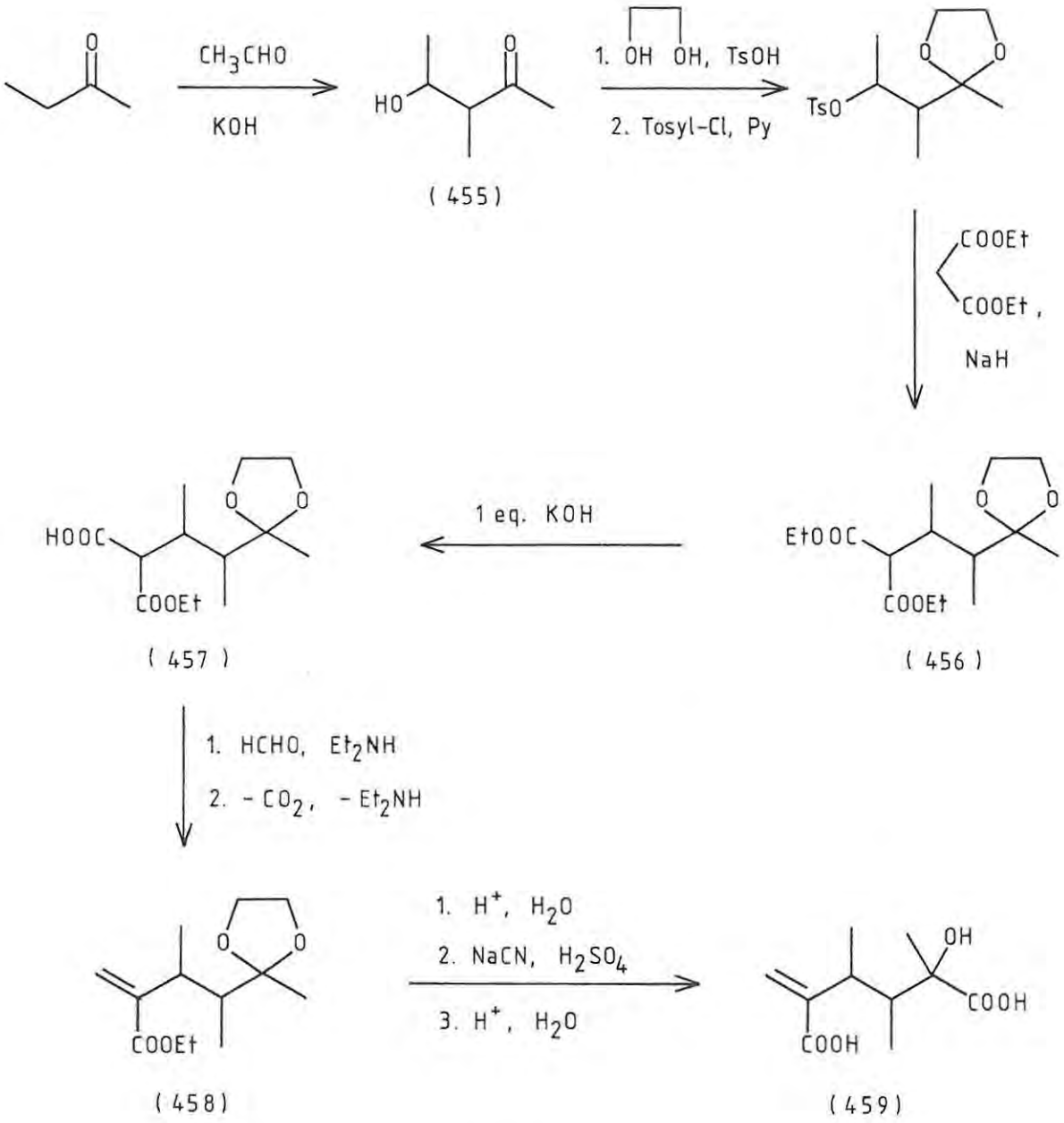


(453)



(454)

By using the (E)-diacid (**452**) which was resolved using cinchonine, the remaining four isomers were synthesised in the same way, and the stereochemistry at C_2 and C_3 determined as before. The stereochemistry at C_4 in these isomers was determined by degradation of the dimethyl ester (**453**) to the monoacetate (**454**) and comparison with material of known stereochemistry.



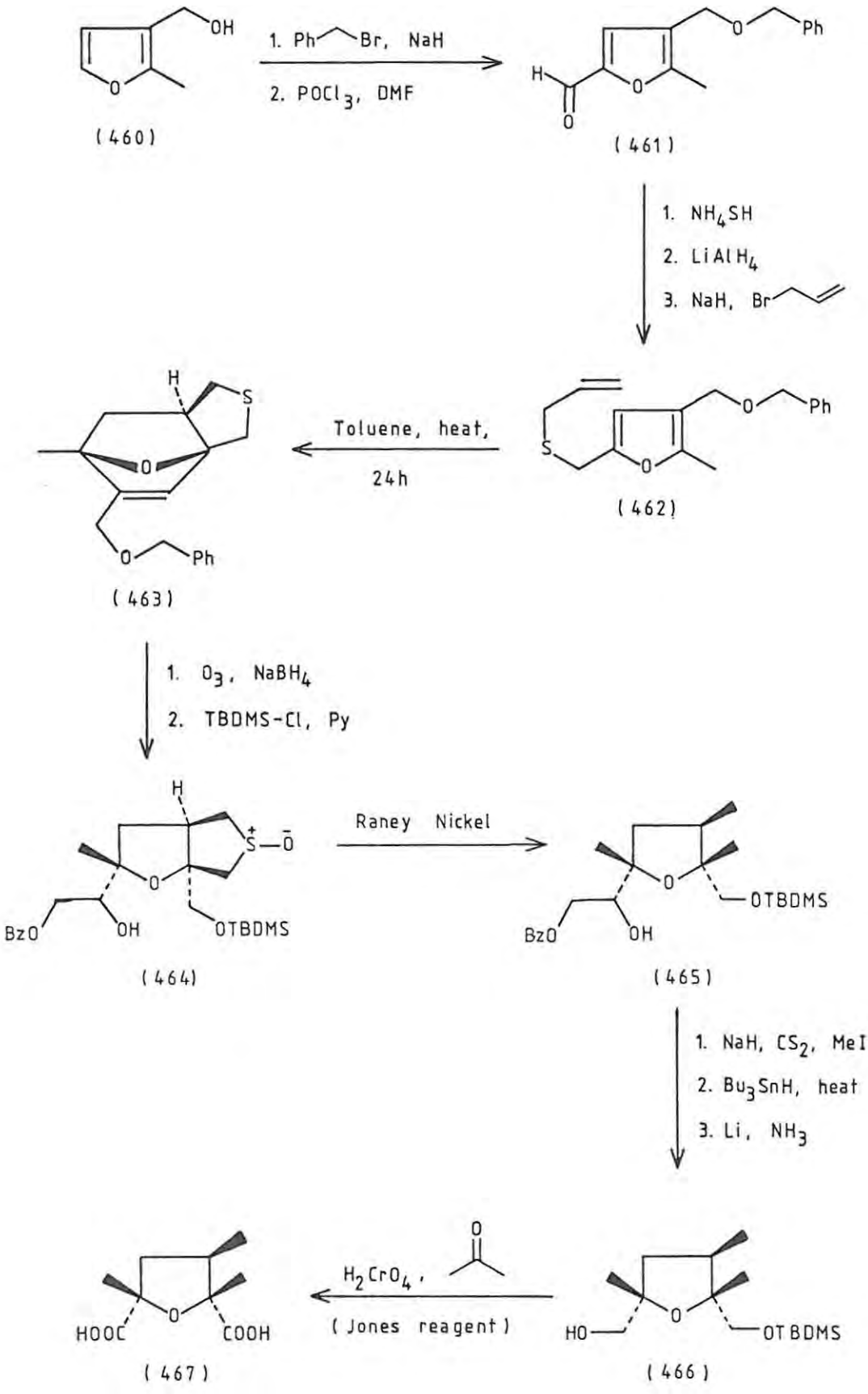
Scheme 61.

Subsequent to their isolation of senecivernine,[101] Roeder's group have synthesised the C_{10}-glutaric acid senecivernic acid from butanone,[102] [Scheme 61]. Reaction with acetaldehyde gave the aldol product (455), which was protected as the ethylene ketal, tosylated and then reacted with diethylmalonate anion to give (456). This was partially hydrolysed with one equivalent of ethanolic

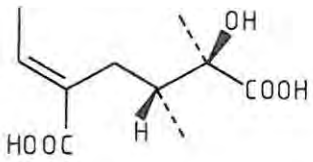
potassium hydroxide to (457). Reaction with formaldehyde and diethylamine in a Mannich reaction gave (458) directly by insertion of a methylene group with concommitant loss of the carboxyl group. Final removal of the ketal protecting group, formation of the cyanohydrin, and subsequent hydrolysis produced racemic senecivernic acid (459).

Nemorensic acid (467), the diacid portion of retroisosenine, has recently been synthesised by Klein[227] from the substituted furan (460), [Scheme 62]. Protection of the alcohol and formylation via a Vilsmeier-Haack reaction gave aldehyde (461). Reaction with ammonium sulphide, followed by immediate reduction and allylation gave the key intermediate (462). This was cyclised to the tricyclic adduct (463) by refluxing with toluene. Cleavage of the carbon-carbon double bond by reductive ozonolysis and subsequent silylation gave the sulphoxide (464) and eventually (465) using Raney nickel. The secondary alcohol group was removed by xanthate formation and reduction using tributyltin hydride, and the benzyl protecting group removed by lithium in ammonia. A final oxidation of the silyl alcohol (466) with Jones' reagent offered cis-nemorensic acid (467).

In view of the fact that many of the necic acids, based on an adipic acid backbone, possess similar structures, (Cf. 416, 468 - 472), it should be possible to develop a 'general synthesis' of these acids.

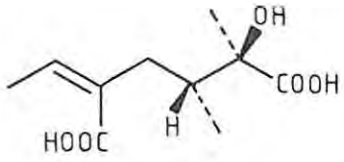

OH
1. Ph Br, NaH
2. POCl3, DMF
(460)
H
O
O
Ph
(461)
1. NH4SH
2. LiAlH4
3. NaH, Br
S
Toluene, heat,
24h
(462)
(463)
1. O3, NaBH4
2. TBDMS-Cl, Py
Raney Nickel
BzO
OH
OTBDMS
(464)
(465)
1. NaH, CS2, MeI
2. Bu3SnH, heat
3. Li, NH3
H2CrO4,
(Jones reagent)
HO
HOOC
COOH
(466)
(467)

Scheme 62.



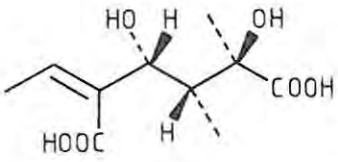
(416)

(+)Integerrinecic acid



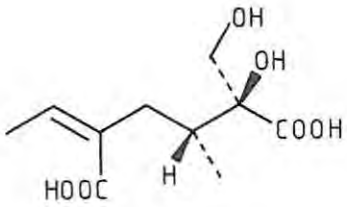
(468)

(+)Senecic acid



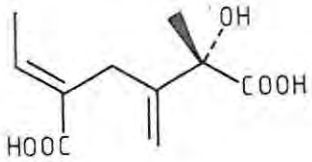
(469)

Hygrophyllinecic acid



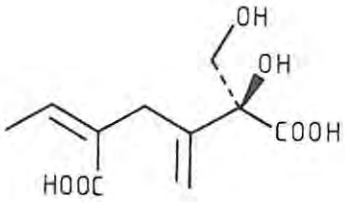
(470)

Retronecic acid



(471)

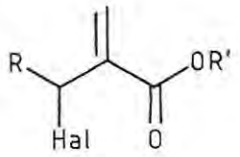
Spartiodinecic acid



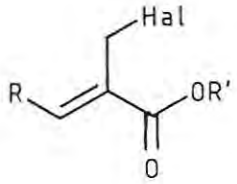
(472)

Riddellic acid

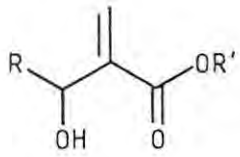
Toward this end Drewes and coworkers[228-230] have investigated the synthesis and utility of a series of halogenated allylic esters, (473) and (474), prepared from the corresponding 3-hydroxy-2-methylenealkanoate esters (475).



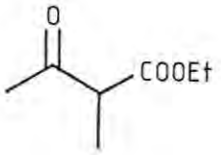
(473)



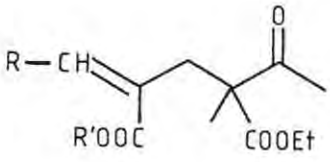
(474)



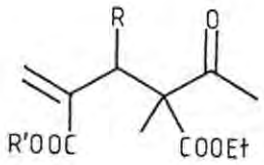
(475)



(476)



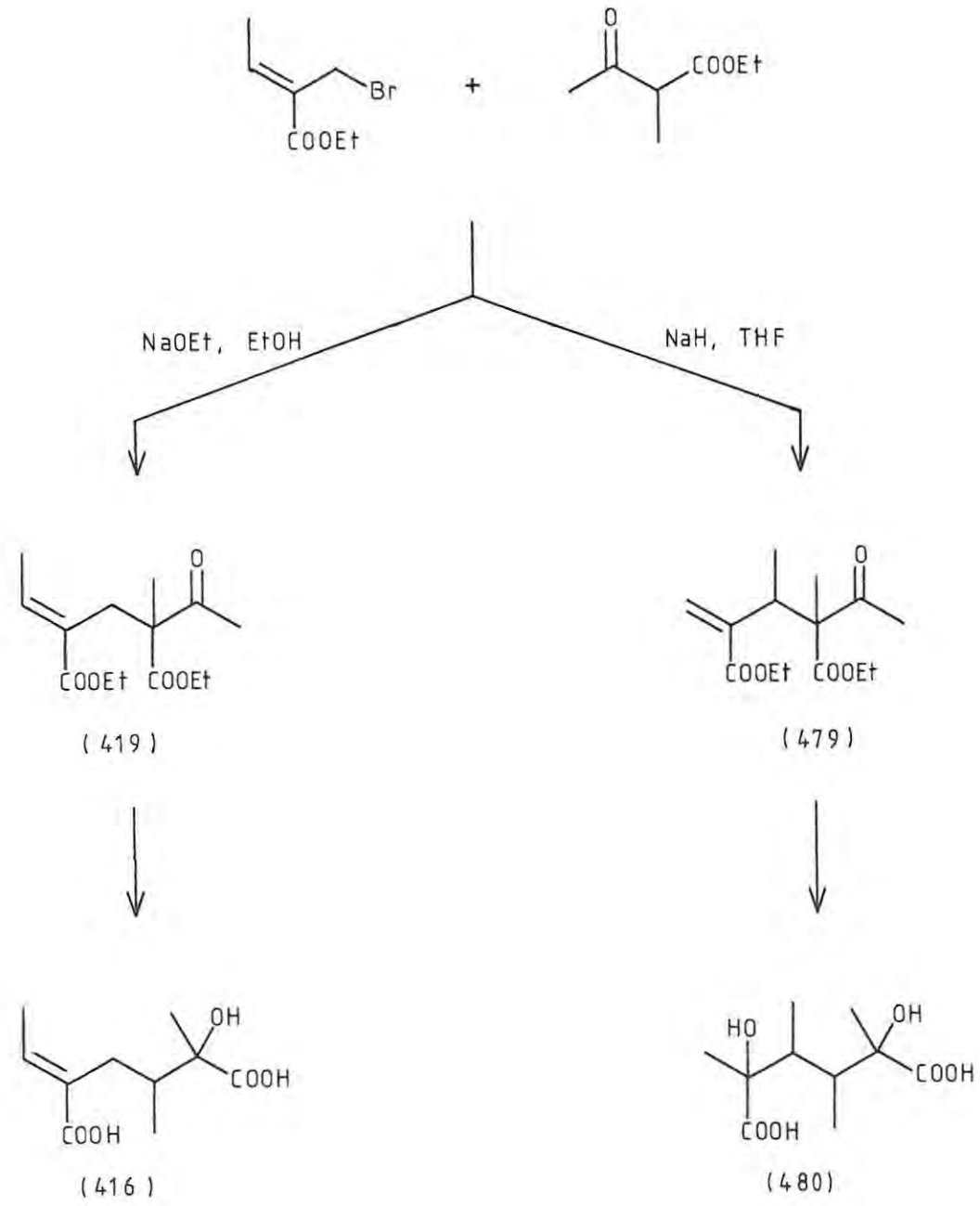
(477)



(478)

Reaction of (475) with $HBr-H_2SO_4$, $HI-H_3PO_4$ or hexachloro acetone - triphenylphosphine, (HCA-Ph_3P), gave the respective bromides, iodides and chlorides, with structure (474) being the favoured and often exclusive product. In the case of the chlorides, either equal amounts of both products were formed, or (473) was produced exclusively.[230] Subsequent reaction of the halides with the enolate anion of the α-keto ester (476) gives rise to two possible products, either via allylic attack giving (477), or via vinylic attack, leading to the rearranged product (478).

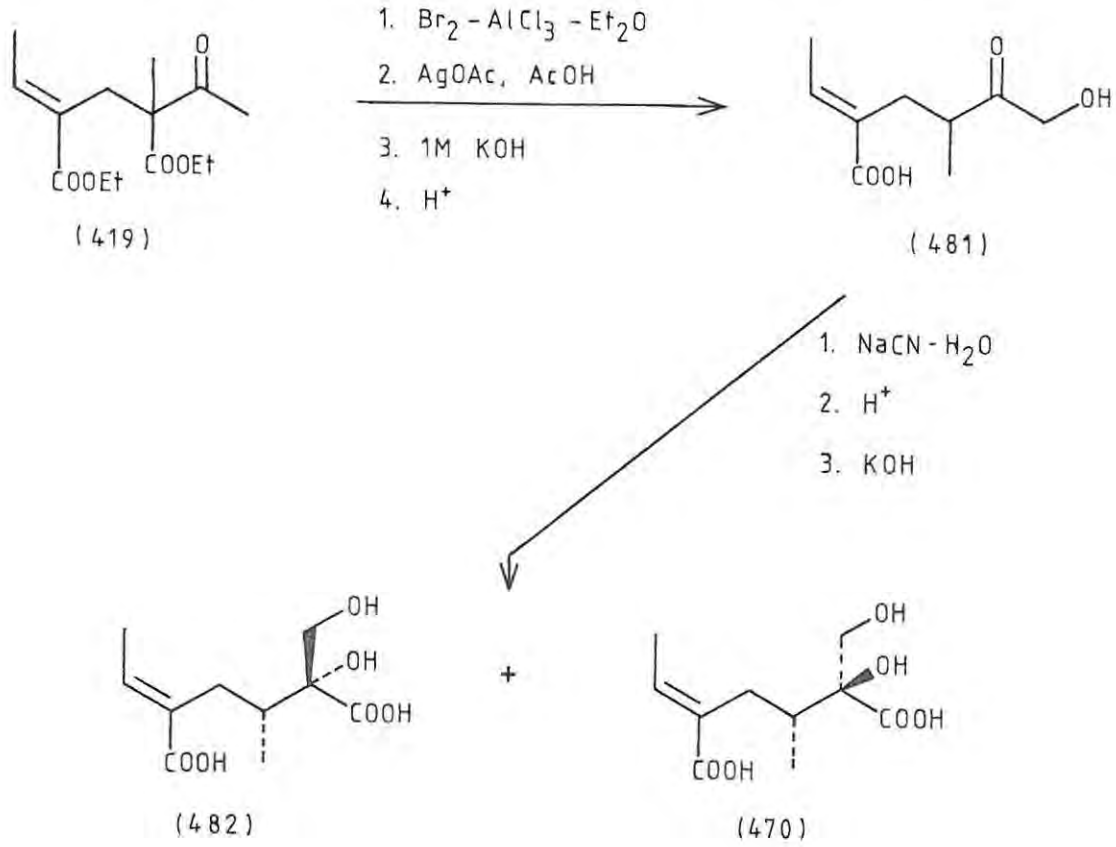
Drewes et al[228,230] have shown that there is regioselectivity in the reaction. Considering halides of type (**474**), allylic attack is enhanced by 1) changing the halide from chlorine to bromine to iodine; 2) increasing the polarity of the base solvent system (i.e. NaH-THF to NaOEt-EtOH); 3) increasing



Scheme 63.

the bulk of the substituents on the halide. The alkene configuration was unaffected. Generally vinylic attack is important only in less-polar solvents and least hindered substrates. Considering chlorides of type (**473**), only products of type (**477**) were observed, but the reaction was no longer stereoselective. Appreciable quantities of the Z-isomers were produced, particularly in the polar solvent system.

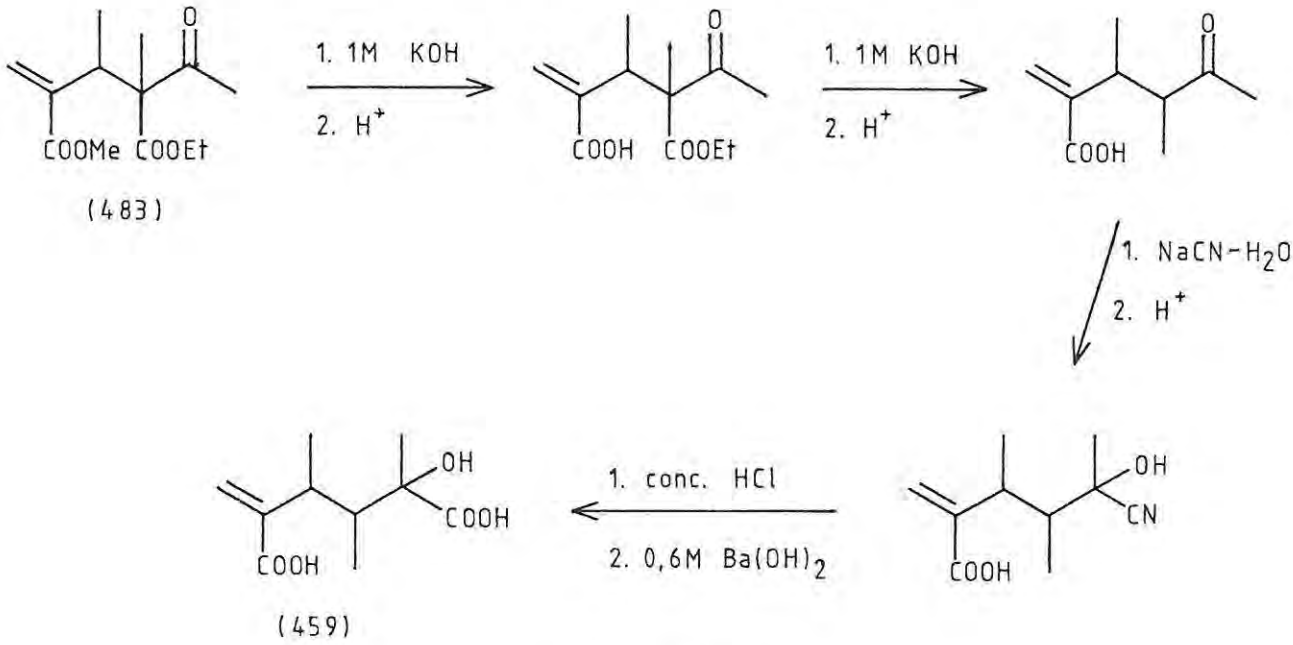
The potential use of the regioselectivity of reactions with these synthons is illustrated, [Scheme 63]. Reaction of ethyl (Z)-2-bromomethyl-2-butenoate with (**476**) leads either to (**419**), a precursor for the synthesis of integerrinecic acid, (Cf. Scheme 55, p127), or to (**479**), a possible precursor for the synthesis of sceleranecic acid (**480**).



Scheme 64.

Subsequently Drewes et al. have synthesised retronecic acid (**470**) and isoretronecic acid (**482**) from (**419**), [Scheme 64], and senecivernic acid (**459**) and its stereoisomers from (**483**, (**478**, R = R' = Me)).[231] Bromination of (**419**), treatment with silver acetate - acetic acid and then hydrolysis and decarboxylation provided (**481**), from which racemic retronecic acid and racemic isoretronecic acid were obtained via cyanohydrin formation and hydrolysis.

Similarly, senecivernic acid and its stereoisomers were obtained from (**483**) by stepwise hydrolysis, cyanohydrin formation and further hydrolysis, [Scheme 65].



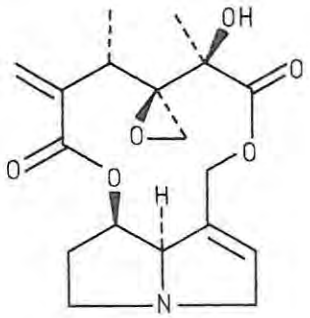
Scheme 65.

The above review completes the syntheses of all necine bases, necic acids and pyrrolizidine alkaloids for the period from 1976 to March 1988.

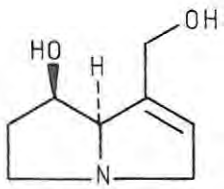
3. APPROACHES TO THE SYNTHESIS OF SWAZINECIC ACID.

3.1. Background.

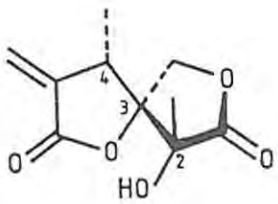
Investigation of Senecio Swaziensis Compton, and later S.barbellatus D.C., by Gordon-Gray and coworkers[232-234] resulted in the indentification of swazine (**484**). This on acid hydrolysis gave the base retronecine (**194**) and swazinecic acid dilactone (**485**). The stereochemistry at the three chiral centres in (**485**) was established by X-ray crystallography.[232]



(**484**)



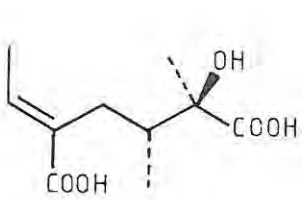
(**194**)



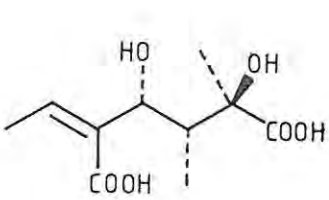
(**485**)

Progress towards the synthesis of swazinecic acid was first made by Gordon-Gray and Whiteley[235] who succeeded in synthesising the unsaturated diacid (**490**) via two routes, [Schemes 66 and 67].

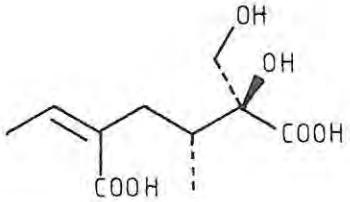
A number of points are of interest in these approaches. Firstly it was intended that any synthesis of swazinecic acid should also constitute a "general approach" to other structurally similar necic acids such as integerrinecic acid (**416**), hygrophyllinecic acid (**469**), and retronecic acid (**470**).



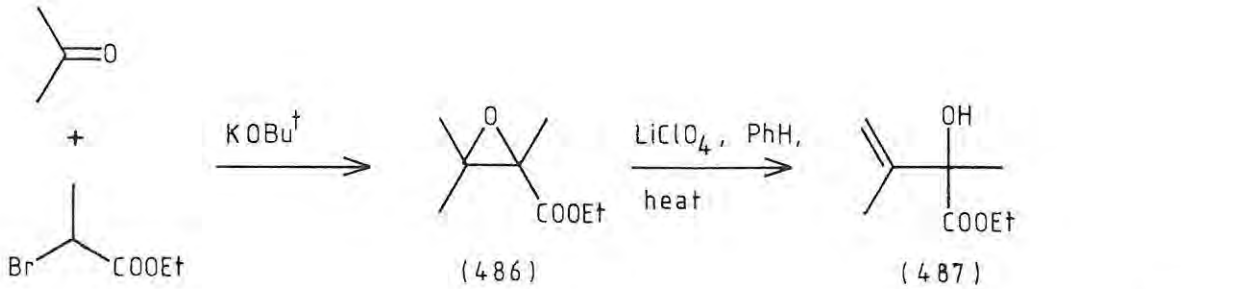
(416)



(469)

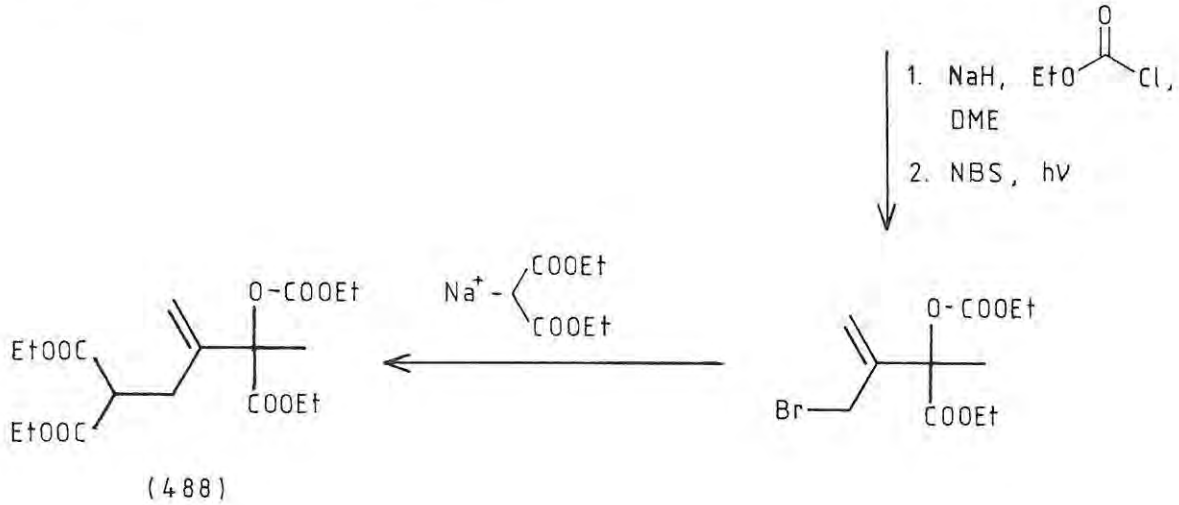


(470)

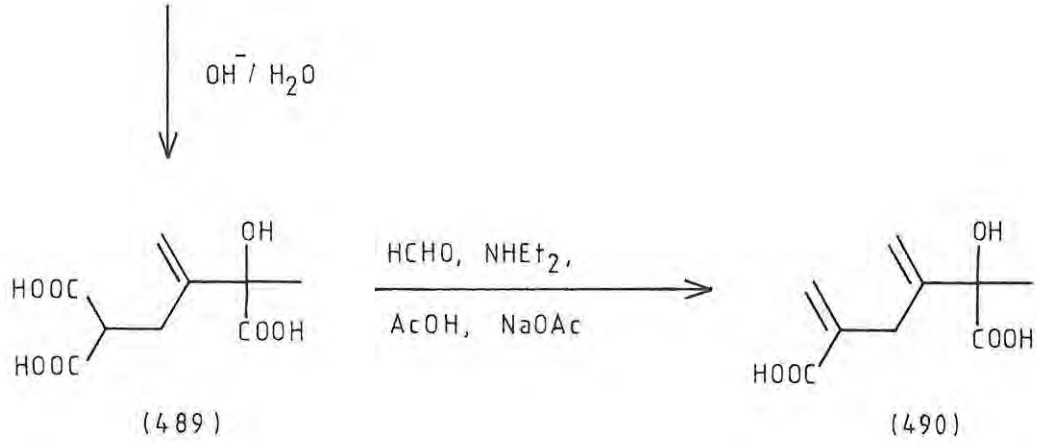


(486)

(487)



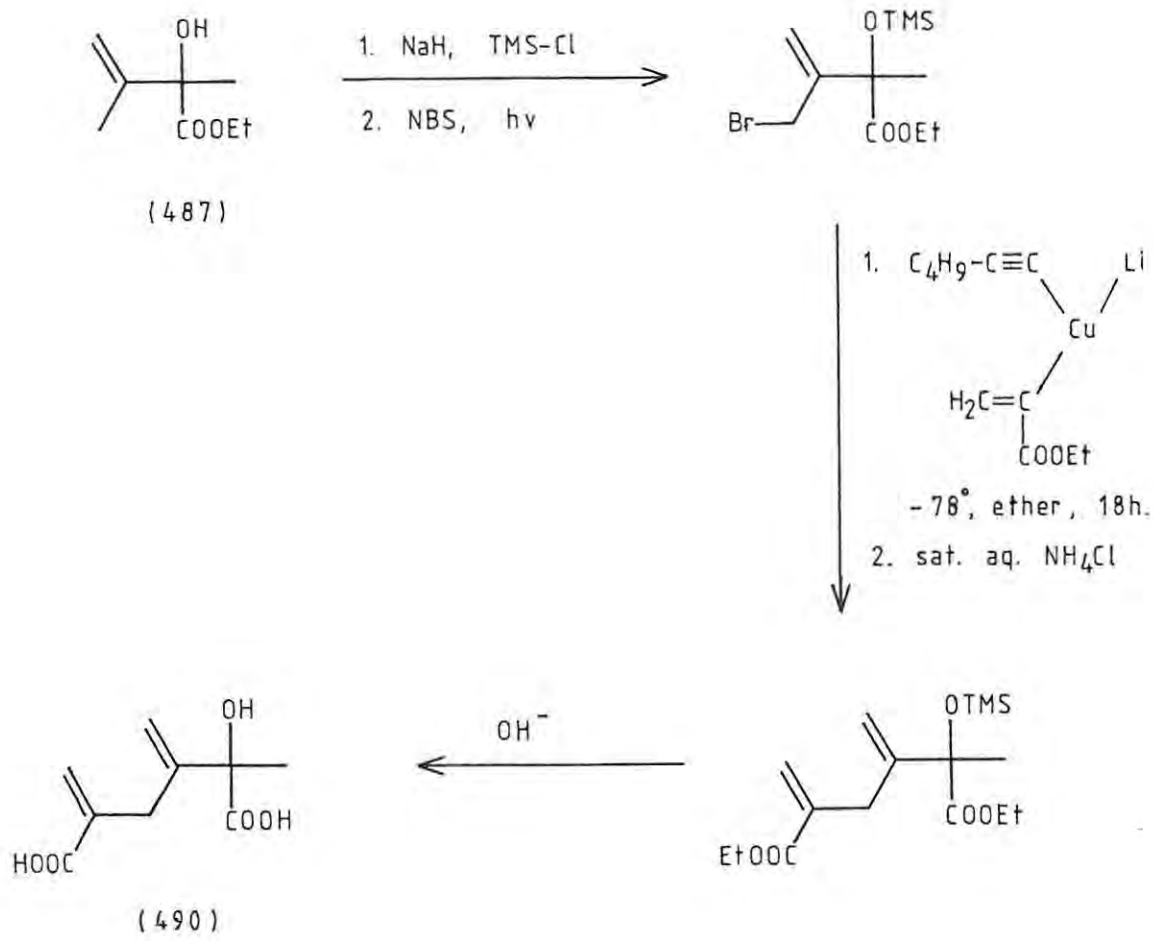
(488)



(489)

(490)

Scheme 66.

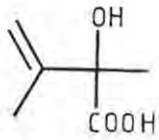


Scheme 67.

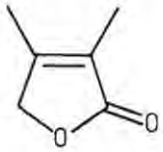
Secondly a number of routes to the allylic α-hydroxy ester (**487**) were explored. Only the route shown, [Scheme 66], which utilises the Darzens reaction followed by a rearrangement, proved successful. Thirdly, protection of the tert-hydroxyl group in (**487**) proved both necessary and difficult.

Lastly, since it was expedient to obtain the correct stereochemistry of all required chiral centres as early as possible after their incorporation into the precursor molecules, attention was given to the resolution of (**487**) which contains the (projected) C_2 asymmetric centre in

swazinecic acid (485). However all standard efforts to effect resolution of the free acid (491), (brucine, cinchonine), failed. Although salts were obtained, they proved to be thermally unstable and rearrangement of the allylic alcohol occurred to produce β-methylangelica lactone (492).



(491)



(492)

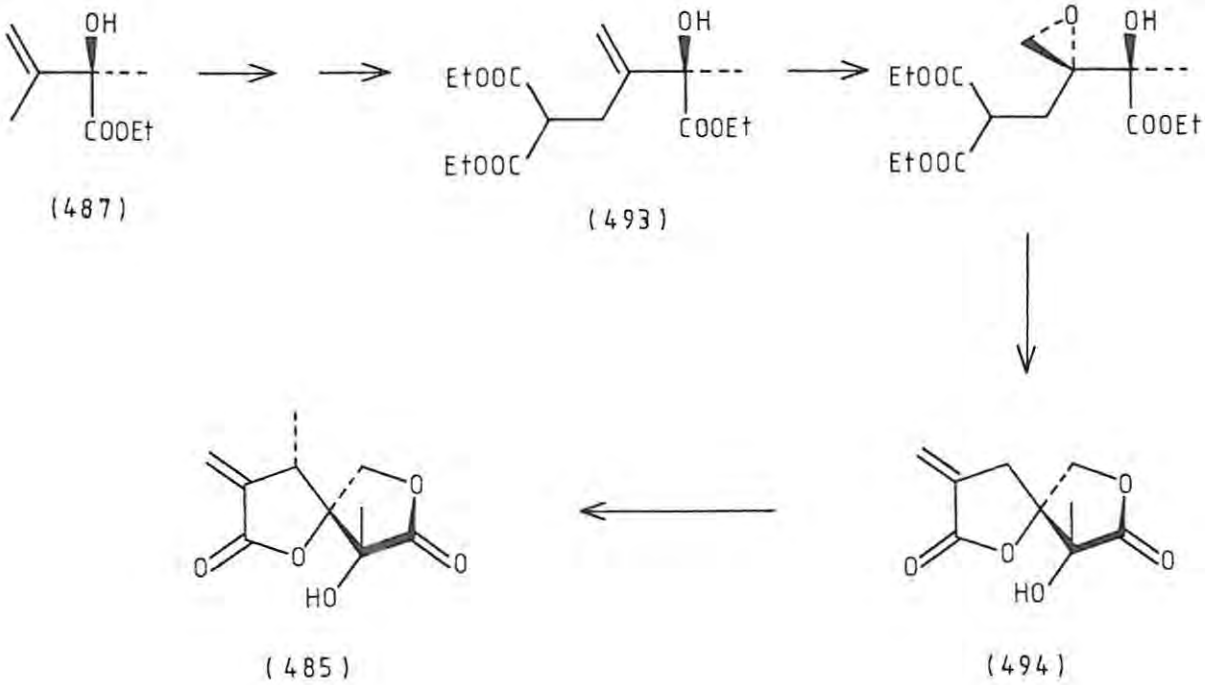
Resolution of the chiral centre in (487) therefore had to be postponed until the allylic alcohol moiety no longer existed. In the event this point was not reached and hence all products shown in Schemes 66 and 67 were racemic.[235]

The overall yield of the diacid (490) from (487) via the route shown in Scheme 66 was 30%, and this, coupled with the unsolved problem of effecting resolution of the existing asymmetric centre, implied that yields of the dilactone (485), when finally synthesised, would be unacceptably low. Accordingly the alternative synthesis of the diacid (490) from (487) was developed [Scheme 67]. This gave an improved overall yield of 60%.

3.2. Scope of the present work.

In the present work it appeared of paramount importance to obtain optically pure α-hydroxy ester (487) for elaboration into swazinecic acid dilactone (485). Since resolution of the free acid (491) via diastereomeric salt formation had not

proved successful due to the instability of the salts formed, it was decided to investigate, 1), the formation of diastereomeric amides via reaction with an appropriate optically active amine, and 2), an asymmetric synthesis of the α-hydroxy ester (**487**), or a derivative thereof. In this regard Meyers' work with oxazolines appeared particularly attractive.[236]

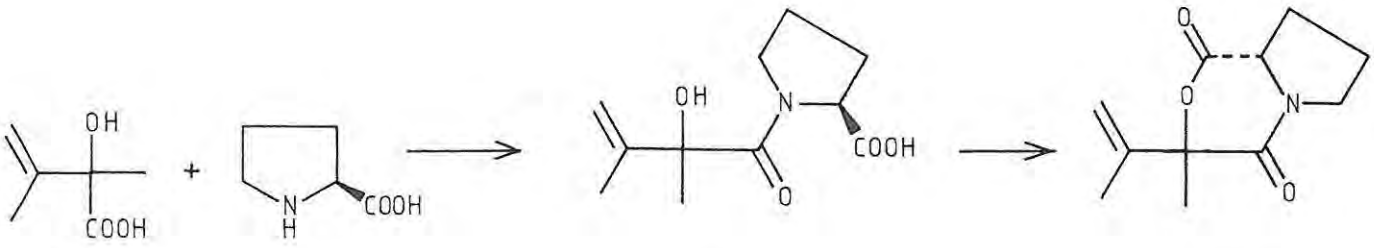


Scheme68.

Once the optically pure hydroxy ester (**487**) (or a synthetic equivalent) became available, the intention was to obtain the triester (**493**) using established procedures, [Scheme 68]. It was anticipated that asymmetric epoxidation of (**493**) would introduce the second of the three chiral centres required. Hydrolysis of the resultant epoxy triester, followed by the introduction of the methylene group by a Mannich reaction would provide the dilactone (**494**), from which swazinecic acid dilactone (**485**) could be obtained on introduction of the methyl group.

3.3. Formation of diastereomeric amides.

At the outset then, attention was therefore given to the use of the readily available amino-acid L-proline (**495**) as a resolving agent. It was anticipated that reaction with (**491**) would lead first to the amide (**496**), [Scheme 69], and subsequently to the bicyclic structure (**497**), with ring closure being assisted by the favourable proximity of the reacting functional groups.



(491) (495) (496) (497)

Scheme 69.

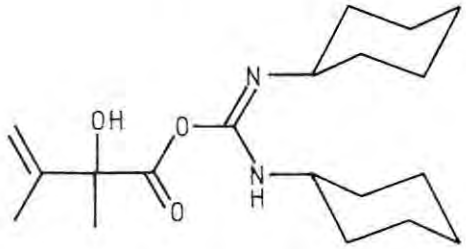
Standard methods for the formation of amides include the reaction of acid anhydrides, acid chlorides, esters or the free acids with the appropriate amine.[237] Of these methods the most widely used involves the use of acid chlorides. The presence of the α-hydroxyl functionality in (**491**) however, made it obvious that formation of the acyl chloride, without concomitant conversion of the alcohol to a chloride, would be very difficult if not impossible, despite it being, in this case, a tertiary alcohol. Protection of the alcohol prior to formation of the acyl chloride also presented considerable difficulties and so the approach to amide (**496**) via an acyl chloride was initially not investigated.

What appeared to be the best route to the required amide (**496**) was the reaction of the free racemic hydroxy acid with L-proline in the presence of a carbodiimide coupling reagent such as dicyclohexylcarbodiimide. These reagents have been widely used as coupling agents in the synthesis of esters and amides.[238,239] The coupling reaction is usually carried out under neutral conditions and is the method of choice for the synthesis of peptides.[240]

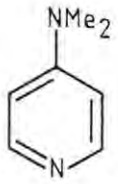
It was anticipated that although both hydroxy acid (**491**) and L-proline (**495**) were difunctional molecules, the different reactivity of the two functionalities in each molecule would be sufficient to allow selective coupling to occur, leading to formation of the required amide (**496**). The reaction of the tert-hydroxyl group of (**491**) with the carboxylic acid of proline was expected to be slower due to the difficulties mentioned earlier.[58]

Accordingly equimolar quantities of the α-hydroxy acid (**491**) and L-proline (**495**) were stirred together with 2,2 equivalents of dicyclohexylcarbodiimide (DCC) in tetrahydrofuran at room temperature. No desired amide (**496**) or cyclic product (**497**) was obtained however, despite modifying the conditions by reflux, addition of triethylamine, changing order of reagents, and use of acetonitrile as solvent. In all cases examination of the gummy residues obtained on workup indicated that although the α-hydroxy acid (**491**) appeared to be reacting with the DCC to form an unstable intermediate, this was not reacting with the L-proline, but was being recovered on workup. The structure of the

intermediate is postulated as (498) since it showed as a single spot on TLC, the peak at 2115 cm^{-1} due to the N=C=N bond in DCC was absent in the infrared, there was a large envelope in the proton NMR corresponding to the dicyclohexyl protons, and lastly, the methylene protons of the C=C bond were visible as a broad doublet just above δ 5 ppm (TMS = δ 0 ppm.). Furthermore, on standing several days, crystalline dicycohexylurea slowly separated out of the residues.



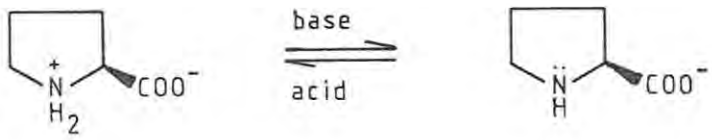
(498)



(499)

It was realised that such reactions have been carried out in the presence of the acylation catalyst 4-(N,N-dimethyl-amino)pyridine, (DMAP, 499). The use of DMAP, either alone, or in combination with DCC, has enabled difficult or previously fruitless acylations to be carried out, often under mild conditions.[241] Using DMAP in the presence of DCC in the present situation, however, again resulted in no reaction.

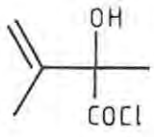
In considering possible reasons for the failure of the reaction thus far, it appeared that the α-hydroxy acid (491) was reacting with the DCC as required, and hence the problem lay with the L-proline. A possible cause of the lack of reactivity could be the ampholytic nature of the amino acid, (in peptide synthesis the ampholytic nature is suppressed by using N-protected amino acids).



(500) (501)

If, under the reaction conditions, L-proline existed as the zwitterion (500), then it would be expected to be resistant to acylation due to the absence of the nitrogen lone pair of electrons. Addition of base to L-proline would produce (501), in which the nitrogen lone pair of electrons is present, thereby enabling coupling with the acid (491). Triethylamine with a pKa of 10,65 would be a suitable base to employ to ensure that the equilibrium is shifted in favour of (501) as the pK_a for the equilibrium reaction between (500) and (501) is 10,6.

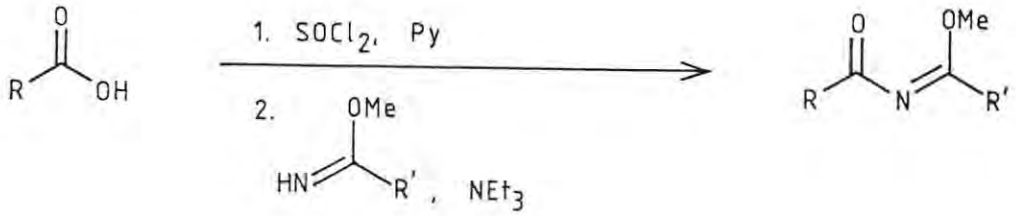
Since triethylamine is known to have an adverse effect on both the rate and the nature of the final product in DCC-mediated reactions,[241] the DCC was omitted, and reliance placed on the catalytic effect of the DMAP alone. Nevertheless no coupling between the L-proline and the acid (491) resulted despite a number of variations to experimental conditions.



(502)

The failure to obtain any of the desired amide (496), or the subsequent cyclised product (497), forced a reconsideration

to generate the acid chloride (**502**). In 1982 Matsuda and coworkers[242] reported a mild conversion of carboxylic acids to acid chlorides using stoichiometric amounts of thionyl chloride in the presence of an excess (up to 2,8 equivalents) of pyridine, [Scheme 70].



Scheme 70.

These reactions took place at room temperature and resulted in rapid and nearly quantitative yields of a number of acid chlorides which were reacted <u>in situ</u> with various imidates to form N-acylimidates. In applying this method to the problem on hand, the thionyl chloride/pyridine reagent was premixed and an aliquot added to hydroxy acid (**491**) followed, after a few minutes, by the L-proline. Analysis of the product of this reaction revealed, however, that the reaction had, once again, failed.

In view of this lack of success and frustrations in obtaining both the cyclic structure (**497**) and the amide (**496**), which is in keeping with the known low reactivity of tertiary carboxylic acids,[243] a new approach was sought.*

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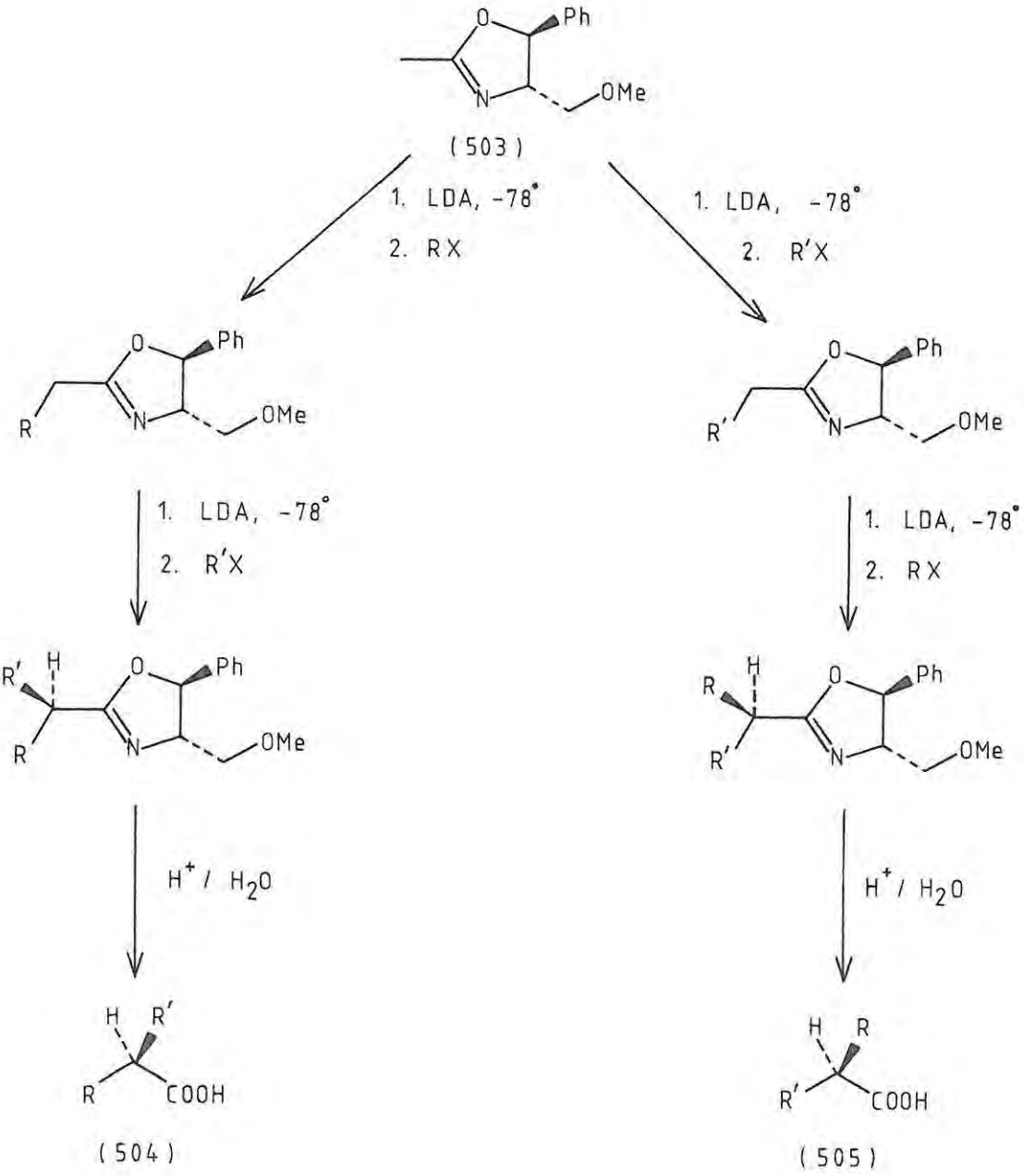
* It was with mixed feelings that the author learnt about the report from Crout et al. that the α-hydroxy acid (**491**) had been resolved via successive formation of the quinone and dicyclohexylammonium salts.[244]

3.4. Approaches using asymmetric oxazolines.

Since the resolution of the α-hydroxy acid (**491**) had proved difficult, attention was directed towards an asymmetric synthesis of the acid. Earlier syntheses of optically active α-hydroxy acids usually used α-keto acids or their esters as substrates.[245-247] The production of the asymmetric centre resulted from the use of various chiral auxiliaries to direct a stereospecific attack on the prochiral centre. Other routes have used αβ-unsaturated acids,[248] and α-keto aldehydes.[249] None of these routes appeared attractive, however, as the reactions were usually restricted in terms of starting materials, reagents, or substituents obtainable.

Routes to asymmetric products usually employ one of several approaches. Firstly a chiral reagent may be reacted with a prochiral substrate. In such reactions approach of the chiral reagent, towards the active site on the substrate is controlled by the steric requirements of the chiral reagent, resulting in a preferred enantiomer of product.[250,251] Secondly, a prochiral substrate, devoid of optical properties, may be converted into an optically active substrate by the attachment of a chiral, frequently bulky, auxiliary. The auxiliary serves to direct the approach of non-chiral reagents to a reactive site by one of two modes. Passive chiral auxiliaries work by sterically restricting the access to a reaction site by reagents. The recent use by Whitesell and coworkers of 8-phenylmenthol as the chiral auxiliary in the synthesis of α-hydroxy acids is an excellent illustration of this method of asymmetric induction.[252,253]

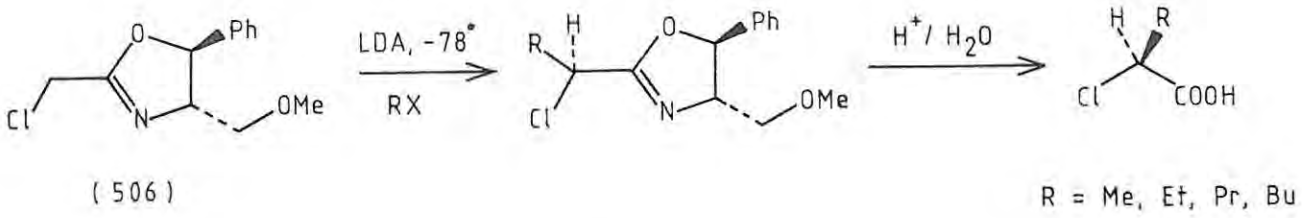
Active chiral auxiliaries, in addition to any inherent steric effect, also actively complex with an approaching reagent and hence the ensuing reaction tends to be highly stereoselective. Meyers' work with oxazolines[236] and Evans' work using oxazolidones[254] are examples of this type of asymmetric control.



Scheme 71.

Of particular interest was Meyers' work with oxazolines. It had been shown that the 2-methyloxazoline, (**503**), [Scheme 71], could be readily alkylated at the α-position, and then hydrolysed to produce α-alkylated acids, (**504** and **505**). The stereochemistry of these α-alkylated acids could be controlled through the order of addition of the alkyl halides to the oxazoline anions.[255]

Furthermore Meyers had also generated chiral α-chloro-carboxylic acids, [Scheme 72], from the α-chloro-oxazoline (**506**) via alkylation and hydrolysis.[256]



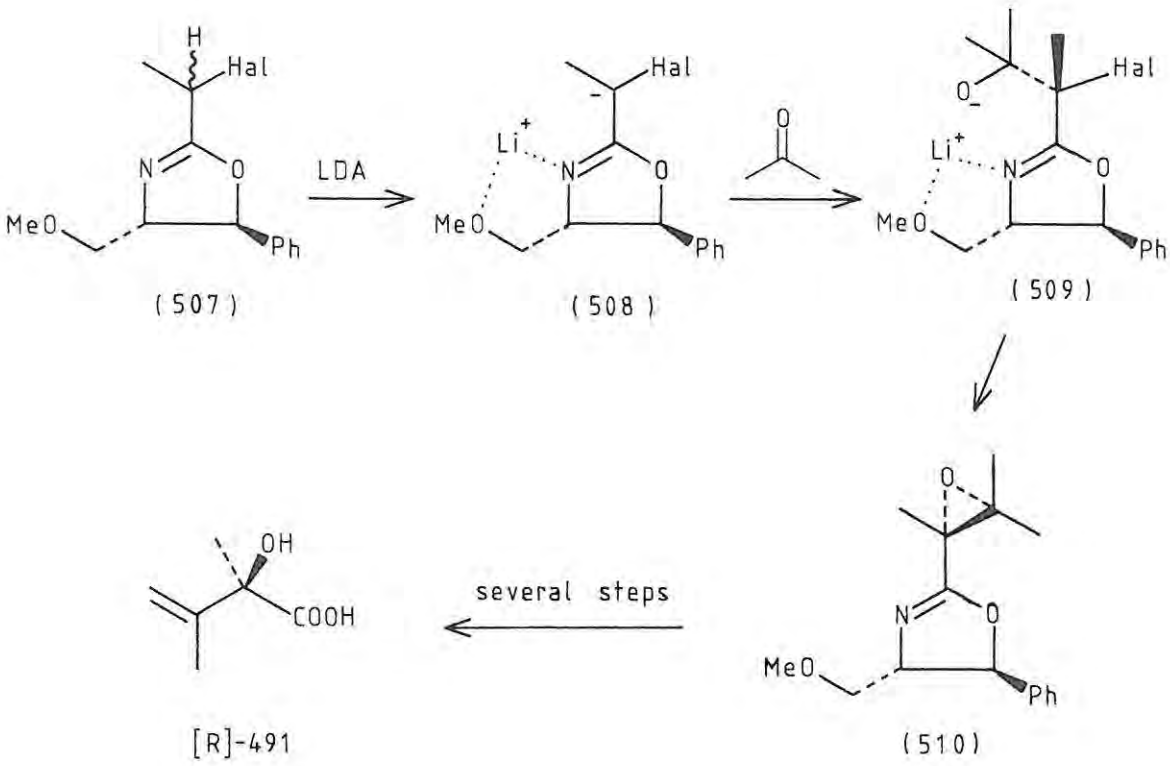
(506)

R = Me, Et, Pr, Bu

Scheme 72.

It therefore appeared feasible to combine the oxazoline chemistry with the Darzens reaction used earlier,[58] (Cf. Scheme 66, p144), as a possible route to the required α-hydroxy acid (**491**).

In theory the stereochemistry at C_2 of the α-hydroxy acid (**491**) would be determined by the halo-oxazoline (**507**) in the following manner [Scheme 73]. Metalation of (**507**) would give the lithio-oxazoline (**508**), with the halogen atom anti to the lithium cation, as the presumed thermodynamically favoured form in accordance with Meyers' results.[255] Approach of this anion to the electrophile would be expected to occur with the carbonyl carbon orientated toward the



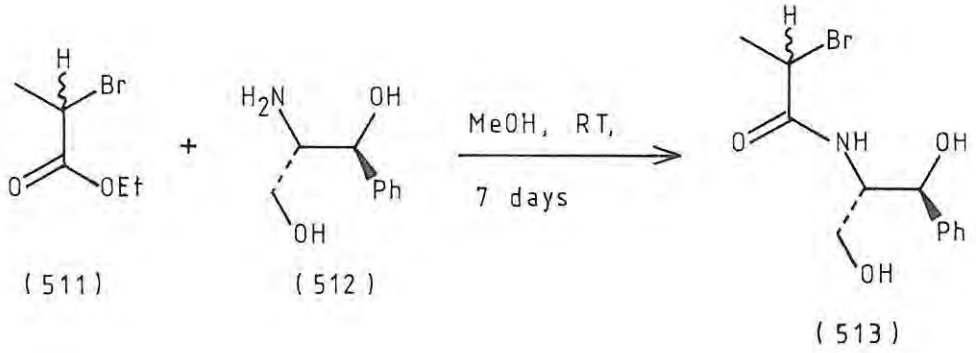
Scheme 73.

α-anion and the oxygen toward the lithium cation. Such an approach is also likely to disrupt any interaction that is possible in (**508**) between the halogen lone pair electrons and the lithium. Attack of the α-anion on the carbonyl would give structure (**509**), which would be expected to undergo a spontaneous S_n2 displacement of the halogen leading to the epoxide (**510**) possessing the required R-configuration at the α-carbon. Removal of the oxazoline ring and rearrangement of the epoxide should then afford the free optically active hydroxy acid (**491**).

This approach also invited the possibility of carrying out the rearrangement of the epoxide (**510**) to the allylic alcohol prior to hydrolysis of the oxazoline group. (Removal of the oxazoline group would thus not be required until much later on in the synthesis.)

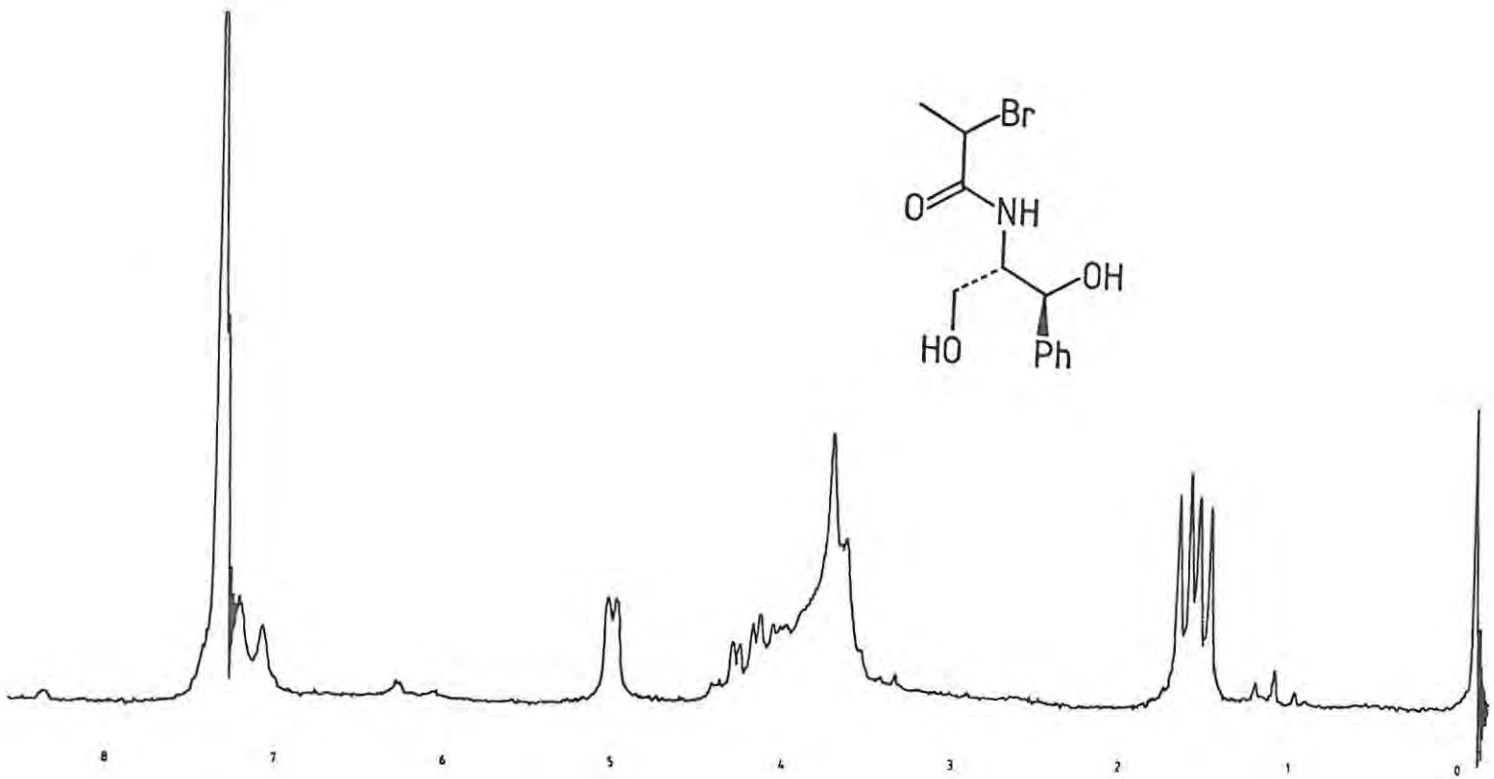
Attention was therefore focussed on the synthesis of the required α-halo-oxazoline (507). Meyers et al[256] had synthesised the homologous 2-(chloromethyl)oxazoline from the imidate of chloroacetonitrile. Unfortunately for the present situation, this approach would require the expensive and unavailable (locally) 2-chloropropanonitrile. A more suitable approach was therefore sought.

Standard methods of preparing 2-alkyloxazolines involve condensing carboxylic acids or derivatives with the appropriate amino alcohol;[257,258] and ring closing hydroxyamides, either by dehydration,[259] or by reaction with thionyl chloride.[260] Simple oxazolines have also been synthesised from aziridines and carboxylic acids.[261]



Scheme 74.

Accordingly ethyl 2-bromopropanoate (511), [Scheme 74], was reacted with the optically active aminodiol (512) resulting in the formation of the bromoamide (513) as a mixture of diastereoisomers. This was clearly revealed in the proton NMR spectrum (p158) by the presence of two overlapping doublets, at δ 1,66 ppm and δ1,75 ppm, due to the protons on the methyl groups. Separation of the diastereoisomers was easily effected using flash chromatography.[262] On the basis



NMR 1: (2'R,1S,2S)- and (2'S,1S,2S)-N(2-Bromopropanoyl)-2-amino-1-phenylpropane-1,3-diols (513)

of the optical rotation values and the circular dichroism spectra, the isomer with the methyl protons resonating at δ1,75 ppm was tentativly identified as the [2'R,1S,2S]-isomer.[263]

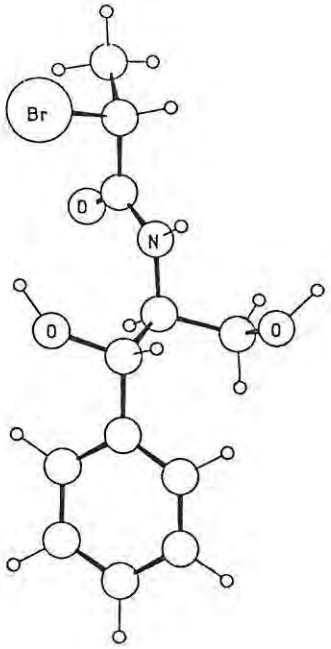


Figure 1. Perspective view of [2'R,1S,2S]-(513)

X-Ray crystallographic analysis[264] confirmed this assignment, [Fig. 1], and also showed the amide to be in the preferred trans conformation, with the amide group and the two neighbouring carbons in a planar arrangement (fig. 2a, p160). This conformation also permits overlap of the nitrogen lone pair of electrons with the σ^* antibonding orbital of the C=O bond, leading to increased stabilisation relative to the cis-configuration (fig. 2b, p 160) where such overlap is not possible. Further, the bromine atom is almost at right angles to the plane of the amide group (Br-C-C-O torsional angle of 92,6°), so placing the methyl group in a syn

relationship to the C=O group (fig. 3a), and is thus deshielded to some extent. In the [2'S,1S,2S]-isomer the methyl group would be gauche to the C=O group (fig. 3b), hence the protons would now be less deshielded, as is observed.

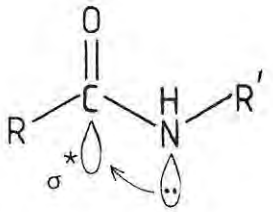


Fig. 2a trans-conformer

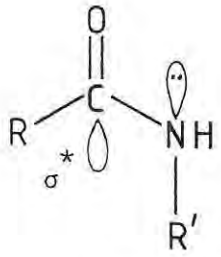


Fig. 2b cis-conformer

Figure 2. Amide conformations showing orbital interactions.

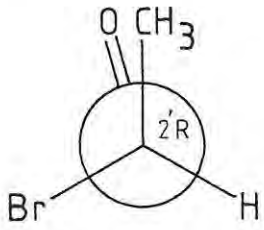


Fig. 3a

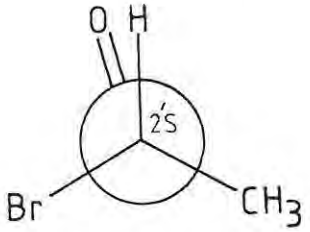
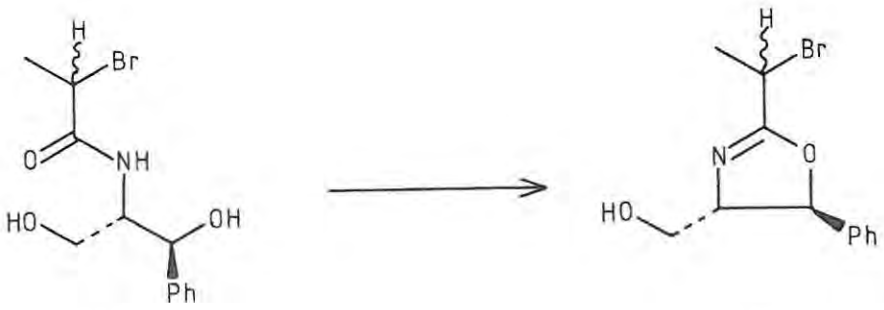


Fig. 3b

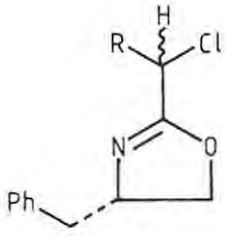
Figure 3. Newman projections about the 2' carbon atom of (513) showing the methyl - carbonyl syn/gauche relationships.

Efforts to cyclodehydrate the bromoamide (513) into the oxazoline (514) met with little success, [Scheme 75]. Heating the amide at atmospheric pressure, either alone, or in the presence of the Lewis acid, anhydrous zinc chloride, resulted in the complete destruction of the bromoamide and the formation of intractable tars. Working under a nitrogen atmosphere and attempting to vacuum distil off any oxazoline which may have been formed prior to decomposition also failed.



(513) (514)

Scheme 75.

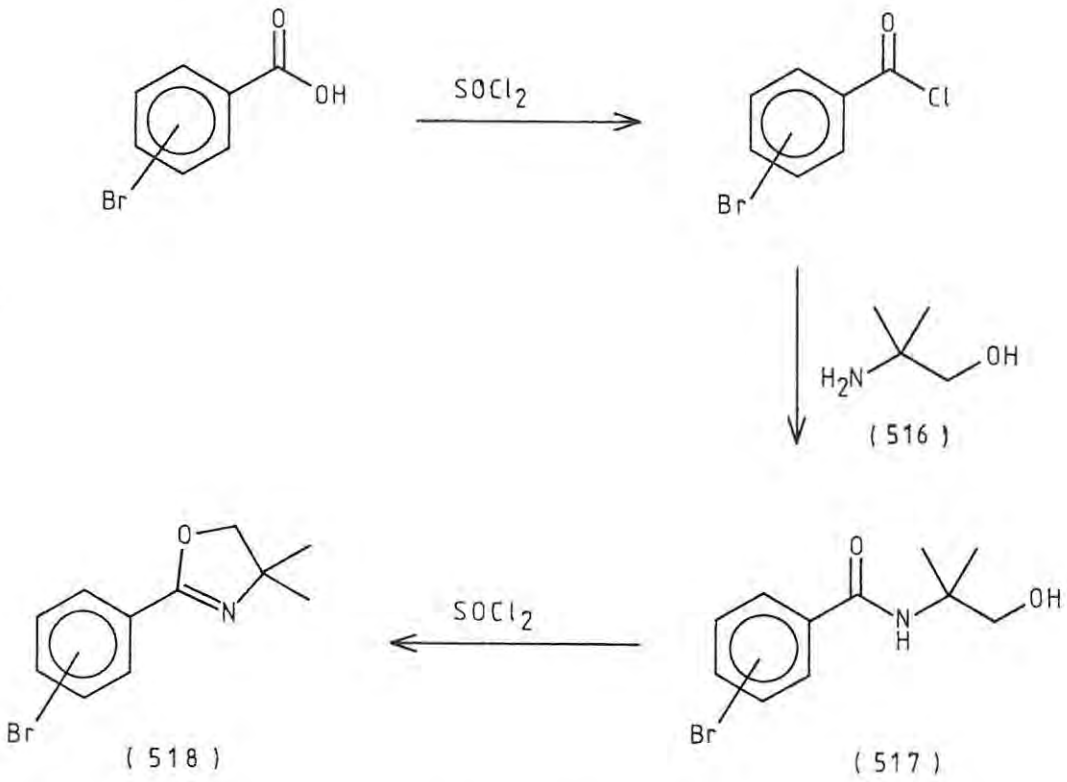


(515)

Although disappointing, this failure was not altogether unexpected as Meyers had also reported difficulties in distilling closely related α-chloro-oxazolines synthesised from chloroimidates.[256] By contrast, Shibata and his coworkers[265] had purified a range of chloro-oxazolines of general structure (515) by distillation, and had not reported any difficulties.

Since it appeared certain that the desired bromoxazoline (514) was heat sensitive, methods of cyclising the bromoamide to the oxazoline at ambient temperature or below were investigated. Other work by Meyers and his coworkers[266] involved the synthesis of a series of bromophenyloxazolines (518) from the parent bromobenzoic acids [Scheme 76]. The acids were first converted into the acid chlorides, which were reacted with the amino alcohol (516) to give the amide

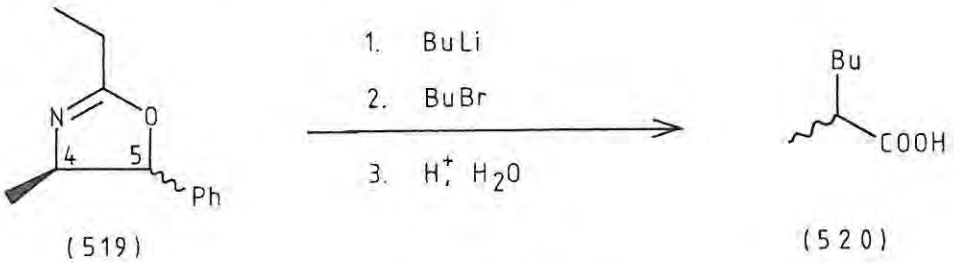
(517). Further treatment with thionyl chloride at room temperature produced the bromophenyloxazolines (518).



Scheme 76.

Three points need to be mentioned in this approach to oxazolines. Firstly, nucleophilic substitution of the bromine atom in the aromatic amide (517) was most unlikely, but could occur with the aliphatic amide (513). This, however, would not be a serious matter, as it was the intention to remove the halide in a subsequent reaction, (Cf. Scheme 73, p156). Secondly, the side chain of bromoamide (513) contains an extra hydroxyl group and hence it was possible that other reactions may occur. Thirdly, it was known that use of thionyl chloride in the synthesis of oxazolines from hydroxyamides resulted in inversion of

configuration at the carbon bearing the oxygen atom.[267] The effect of such an inversion on subsequent asymmetric transformations was uncertain, but the preparation of the [S] and [R]-2-methylhexanoic acids (520) by Meyers and coworkers[255] from the respective 4,5-cis- or 4,5-trans-substituted oxazolines (519), [Scheme 77], indicated that any effect would be minimal. Although the degree of asymmetric induction was low in these reactions, (due to the absence of the methoxy group), the cis-substituted oxazoline gave a slightly better result than the trans-substituted oxazoline.



(519) (520)

Scheme 77.

Nonetheless a dropwise addition of a solution of thionyl chloride in dry dichloromethane to a vigorously stirred solution of the bromoamides (513), also in dichloromethane, at -10°C, followed by work-up and extraction gave a white crystalline product, mp 164-7°. The 60MHz proton NMR spectrum (p166) of this compound showed that, apart from the $CH_3CH(Br)$ moiety still being present, there was a complex pattern in the region δ3,9 - 4,6 ppm due to overlapping signals for the α-methine proton and the (presumed) oxazoline ring protons.

In order to separate the various overlapping signals present in the spectrum, and therefore identify the product, use was

made of a lanthanide shift reagent. These organometallic materials complex with organic compounds by lone pair donation from the organic molecule to unoccupied orbitals of the lanthanide. In so doing, the magnetic environment of the protons in the organic molecule is drastically affected, and hence large changes in chemical shift may be observed. The extent of the shift observed for any one proton signal is proportional to the relative amount of shift reagent present, and to the distance of the protons from the lone pair donor atoms within the molecule.[268]

In the present case, use of the lanthanide shift reagent europium(III) tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione, ($Eu(fod)_3$), in progressively increasing amounts up to 0,7 mole equivalents of $Eu(fod)_3$, caused the overlapping signals to become separated. A plot of the chemical shift value versus mole equivalents of shift reagent for each signal observed provided a series of staight line plots, (Figure 4, p165), from which the shift values in the original spectrum could be determined. The signal pattern so revealed resembled that expected for (514).

The NMR spectrum also showed, however, that the amide was still present, as indicated by a broad doublet at δ 7,1 ppm (p166). This was confirmed by strong absorption peaks in the infrared spectrum at 3350 cm^{-1}, (N-H stretching vibrations), and by two strong bands at 1700 and 1530 cm^{-1} due to the amide. Not seen in the infrared was any peak at 1670 cm^{-1}, characteristic of oxazoline rings. Chemical analysis of the material gave $C_{12}H_{14}BrNO_4S$ as the empirical formula.

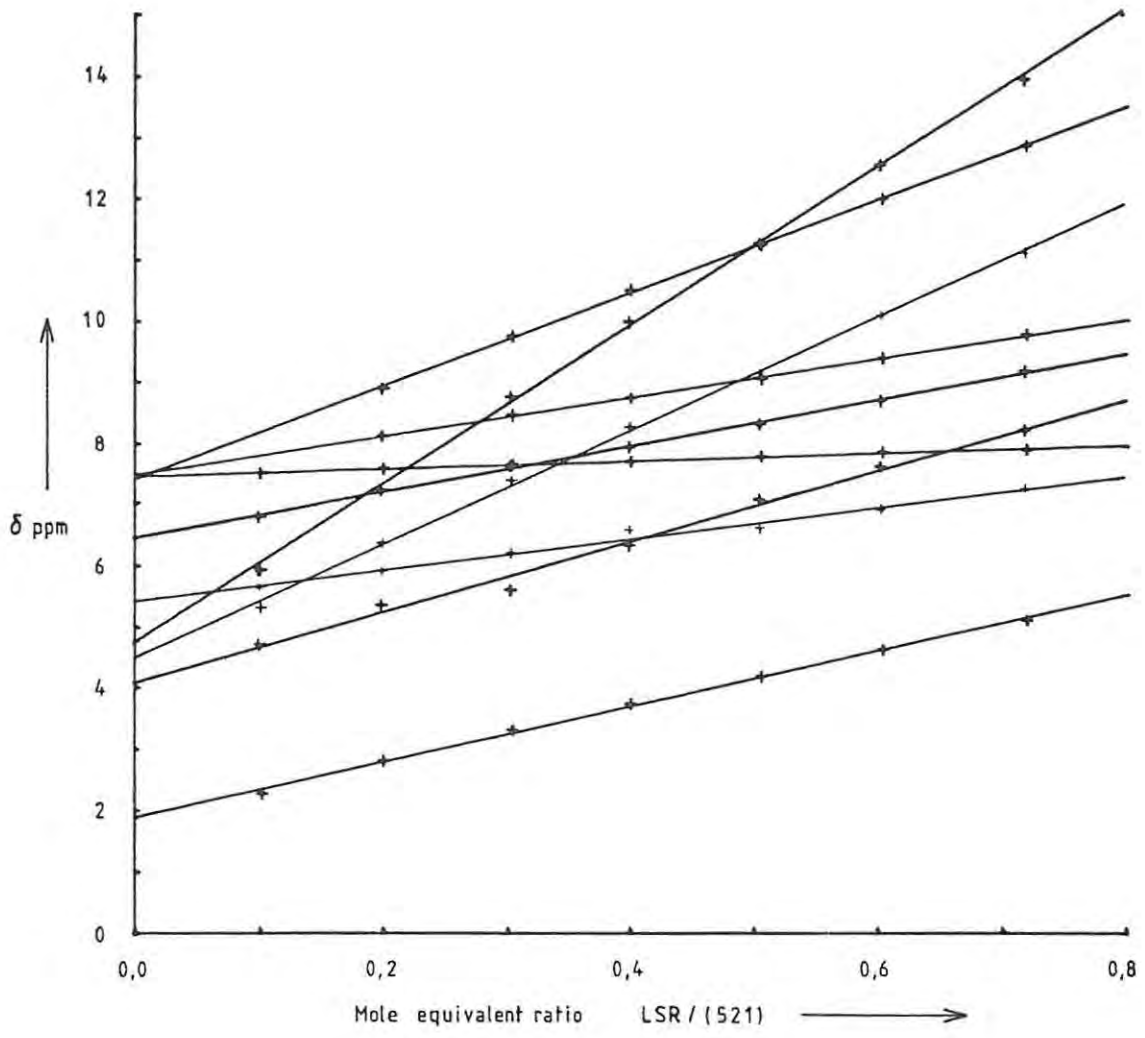
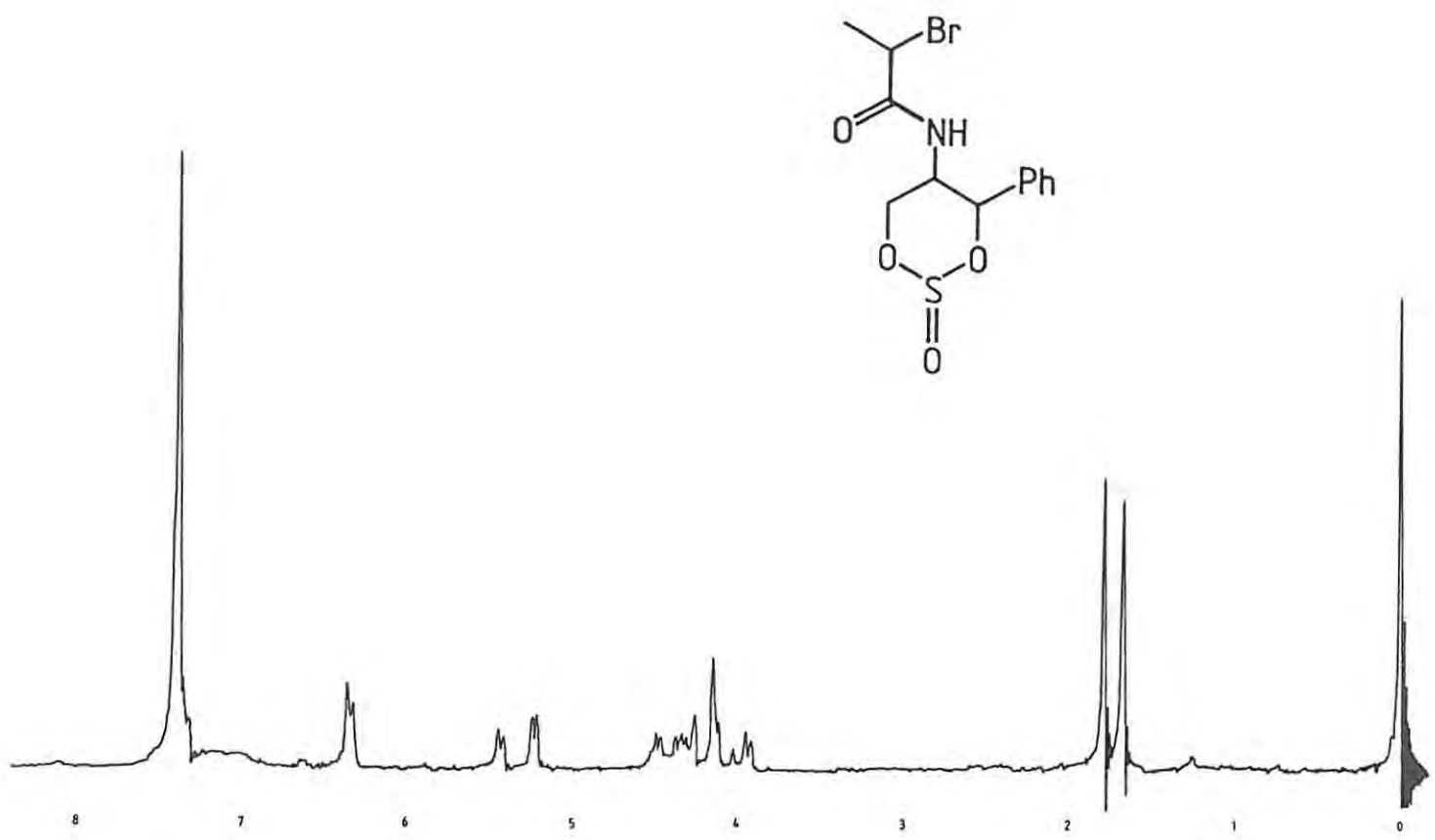
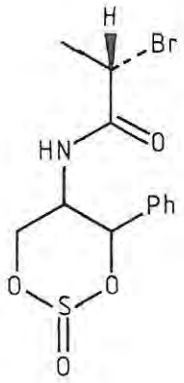


Figure 4: Plot showing the change in chemical shifts for (521) on addition of lanthanide shift reagent $Eu(fod)_3$.



NMR 2: (2'S,5S,6S)-N(2-Bromopropanoyl)-5-amino-6-phenyl-2-oxo-1,3,2-dioxathiane (521)

On the basis of the above information, and the absence of any signals in either the NMR or infrared spectra which could be due to hydroxyl groups, the material was suspected to be a cyclic sulphite (521). X-Ray analysis[264] confirmed this conclusion, and showed the six-membered sulphite ring to be in the chair conformation, with the amide side chain and the S=O bond being in a 1,4-diaxial relationship, and the phenyl ring equatorially orientated, [Figure 5].



(521)

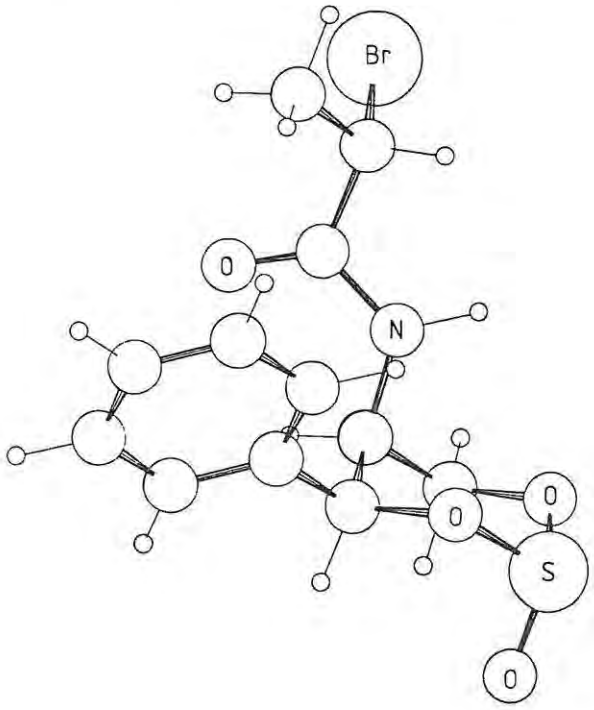


Figure 5. Perspective view of (521)

The axial orientation of the S=O bond is in keeping with previous studies which showed that the stabilisation of an axial S=O bond is due to the anomeric effect and a 'back donation' of lone-pair electrons from an oxygen atom into an anti-bonding orbital.[269] Spatial requirements for the interactions are such that the conformer with the largest number of lone pairs in anti-periplanar positions to electronegative groups is the most stable.

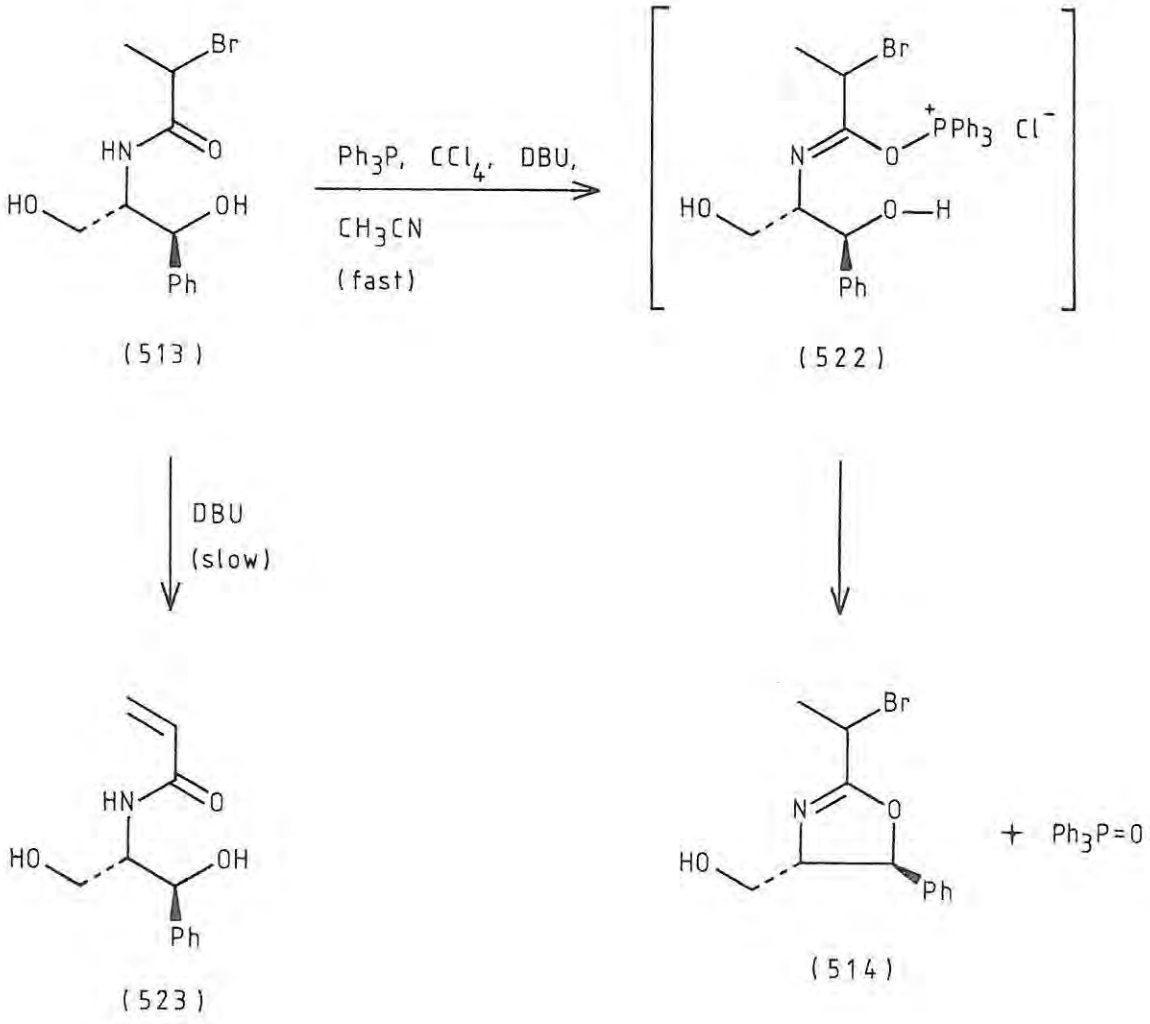
Repeating the reaction at room temperature gave identical results, albeit in lower yields. Interestingly the sulphite (521) proved more resistant to hydrolysis than was anticipated.[270-272] Thus treatment with dilute sodium hydroxide for twenty-four hours at room temperature had no effect. Hydrolysis was eventually effected on treatment with 5M hydrochloric acid at room temperature for twenty-four hours, but this also resulted in extensive hydrolysis of the amide functionality.

Use of freshly distilled phosphorus oxychloride in place of the thionyl chloride in the above reaction resulted in recovery of the starting amide. This is, presumably, due to a rapid hydrolysis of any intermediate 'phosphite' during work-up.

Vorbruggen and Krolikiewicz[273] reported the results of their work on the formation of oxazolines and other heterocycles using the four-component dehydrating system (triphenylphosphine, tetrachloromethane, triethylamine and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in acetonitrile) developed by Appel.[274] Using this methodology they reported that both aliphatic and aromatic acids, when reacted with amino-alcohols, aminothiols or diamines were converted, via the amides, into the respective heterocycles. The reactions had been carried out at room temperature and the yields were reasonable. Of particular interest was the reported insensitivity of the method to the presence of unprotected hydroxyl or amino groups in the starting materials. In our case this route to the required oxazoline appeared most

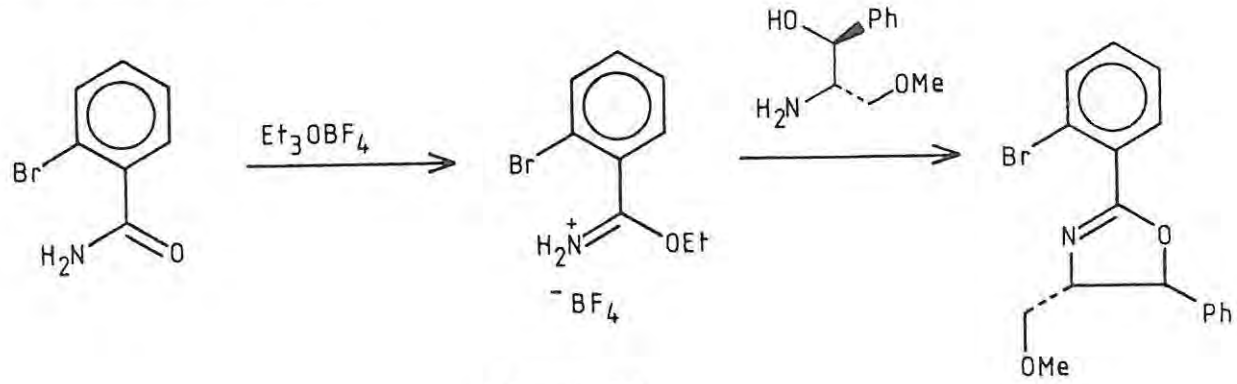
promising, despite the fact that DBU had been used as a dehydrohalogenating reagent.[275]

Although a dehydrobromination reaction to give (523) was possible in the present situation, it was anticipated that the dominant reaction would be the formation of the O-phosphorylated intermediate (522) by the triphenylphosphine/tetrachloromethane adduct reacting with the carbonyl group of the amide (513) [Scheme 78]. This would be followed by cyclisation to the oxazoline (514) and triphenylphosphine oxide.



Scheme 78.

The dropwise addition of three equivalents of triphenylphosphine in dry acetonitrile to a stirred mixture of the bromoamide (513), excess tetrachloromethane and three equivalents each of triethylamine and DBU in dry acetonitrile, followed by stirring overnight at room temperature, gave, on workup, an off-white 'waxy' solid. TLC examination (SiO_2, ethyl acetate) of the solid revealed a single spot. Examination of the product by infrared and NMR spectroscopy, and comparison with standard spectra,[276,277] showed it to be heavily contaminated by triphenylphosphine oxide (obtained during workup by hydrolysis of any triphenylphosphine adducts), the removal of which proved very difficult,[278] and ultimately resulted in the recovery of insignificant amounts of bromoamide (513).



Scheme 79.

The failure of this reaction to provide the required oxazoline was most disappointing, and it appeared that formation of the oxazoline via amide cyclisation was unlikely to succeed. There remained however one possible method of ring closure to be investigated, namely reaction of triethyloxonium tetrafluoroborate (Meerwein's salt)[279] with the amide (513). Meyers and his coworkers[266] have used this approach to synthesise 2-aryloxazolines by reacting various aromatic

amides with the fluoroborate to form aryl imidates; addition of an amino-alcohol then gave the aryloxazolines, [Scheme 79].

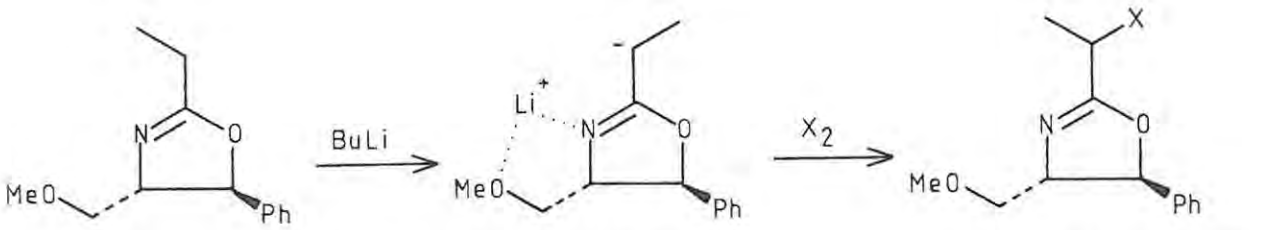
Problems with this approach were still envisaged, however. It was thought that in applying this method to the amide (513), the tetrafluoroborate reagent was likely to react preferentially with the two free hydroxyl groups rather than with the amide carbonyl.

The triethyloxonium tetrafluoroborate was first prepared as a 1M solution in dichloromethane.[280] This was then reacted, under nitrogen, with equimolar quantities of the bromoamide (513) in dichloromethane and the reaction allowed to proceed for twenty-four hours at room temperature. Workup and extraction into dichloromethane afforded a gum in low yield. The NMR spectrum of the gum showed the amide proton to still be present as well as strong signals characteristic of ethoxy groups. It was therefore apparent that the tetrafluoroborate reagent had indeed reacted preferentially with the hydroxyl groups and had not effected cyclisation to the oxazoline.

Further work on the cyclisation of the bromoamide (513) was therefore discontinued, and attention was turned to the possibility of introducing the halogen into an existing oxazoline structure.

In principle this appeared a simple operation, since generation of an oxazoline anion followed by addition of halogen, (bromine or iodine for ease of handling), would be expected to produce the required α-halo-oxazoline, [Scheme

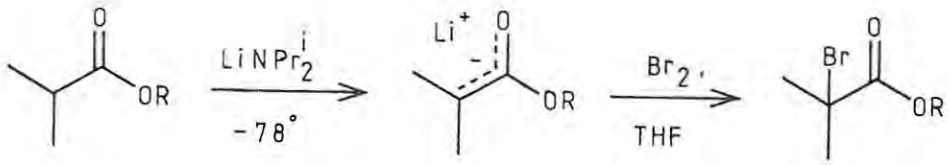
80]. Interestingly, on searching the literature, no examples of such a halogenation could be found.



Scheme 80.

Consequently, commercially available (4S,5S)-2-ethyl-4-hydroxymethyl-5-phenyl-2-oxazoline[281] was methylated, (NaH, MeI),[255] and the resultant methoxyoxazoline (**524**) treated with lithium diisopropylamide (LDA) at -78°C in tetrahydrofuran to give the expected yellow solution of the anion (**525**). Addition of a solution of bromine in tetrahydrofuran to the anion at -78° resulted in immediate decolouration of the bromine. On workup, however, the major product was recovered methoxyoxazoline (**524**). This result was both unexpected and puzzling.

A search of the literature revealed that Arnold and Kulenovic,[282] in their report on the synthesis of α-halo-esters using tetrahalomethanes, had encountered an identical problem with the reaction of carbanions and bromine in tetrahydrofuran, [Scheme 81]. These workers ascribed the failure to be due to formation of HBr from the photochemical bromination of tetrahydrofuran prior to addition to the solution of the ester anion (**526**). Their response to this



(526)

Scheme 81.

problem was to replace the tetrahydrofuran by tetrachloromethane, whereupon they encountered mixed halogenation by the solvent as well as by the bromine. Subsequent investigations then showed that halogenation could be accomplished by the tetrahalomethane alone and that the presence of molecular bromine was not required.

In the present investigation, therefore, two options existed; 1), to find a substitute solvent for tetrahydrofuran, and 2), to investigate the use of a tetrahalomethane as the halogen source. Attention was first turned to finding a substitute solvent for tetrahydrofuran.

Halogenation of the oxazoline was repeated exactly as before using hexane as the solvent. Due allowance was made for the lower solubility of the oxazoline (524) in hexane compared to tetrahydrofuran. Again, however, the starting oxazoline was recovered in quantity along with small amounts of what appeared from infrared and NMR spectroscopy to be diisopropylamine hydrobromide salt.

It appeared that both the hexane and the diisopropylamine were having detrimental effects on the outcome of the reaction. The reaction was thus repeated using ether, and

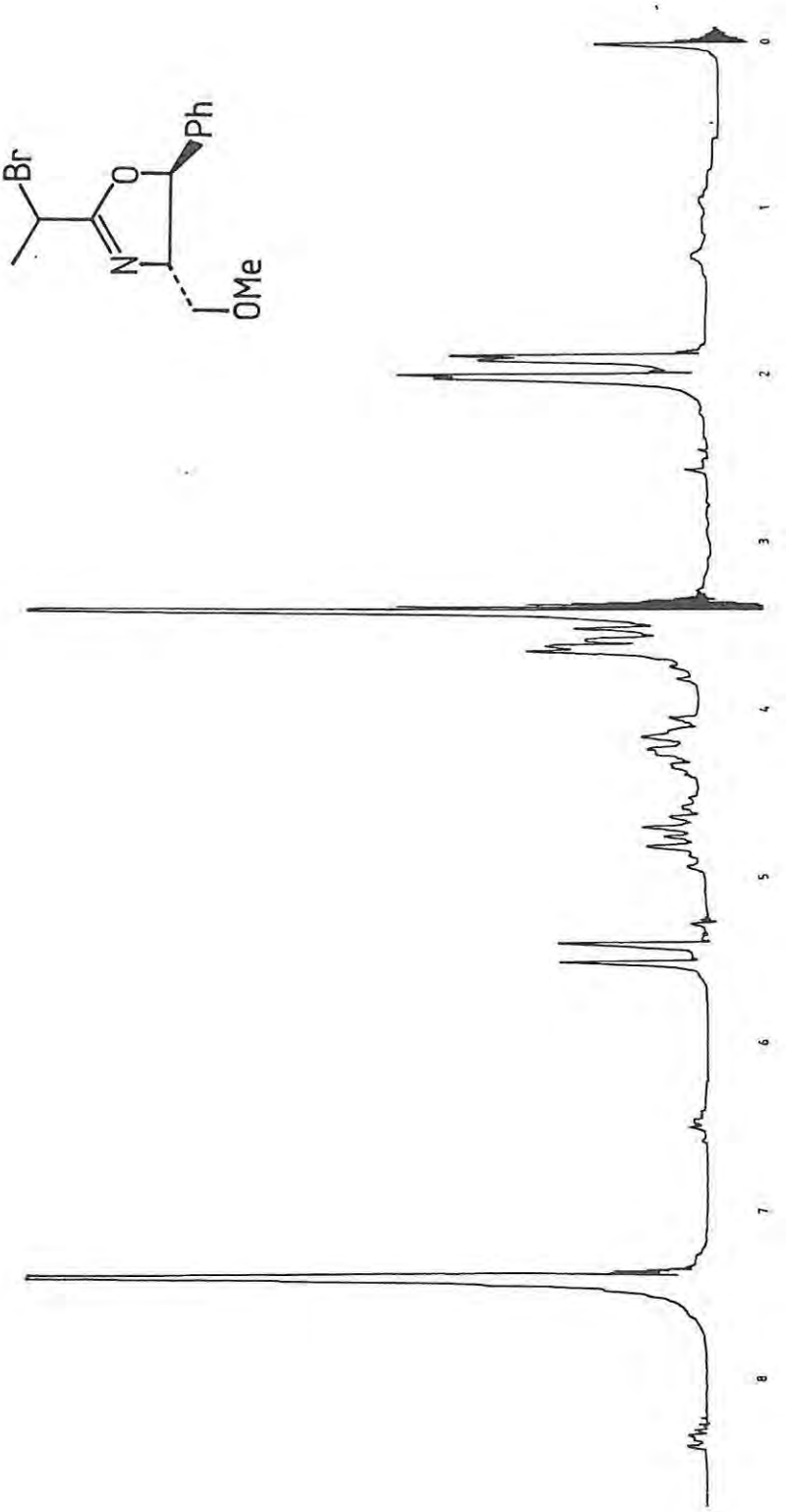
butyllithium (in place of lithium diisopropylamide) to generate the anion (525). On addition of an ethereal bromine solution a thick yellow precipitate formed. Workup of this reaction gave a small amount of a sweet smelling yellow oil quite unlike the starting oxazoline. The product was purified, with difficulty, by flash chromatography.[262]

Spectroscopic examination of the purified product showed it to be the bromo-oxazoline (527). The infrared spectrum confirmed that the oxazoline ring was still intact, (C=N stretch 1670 cm^{-1}), and the NMR spectrum (p175) showed a pair of unequal doublets slightly downfield of, and replacing, the triplet of the methyl group of the parent oxazoline (524). The pair of doublets clearly indicated the presence of the two diastereomeric forms of the bromo-oxazoline.

Omission of the diisopropylamine from the reaction was therefore vindicated. The yield of the purified product was, however, very low.

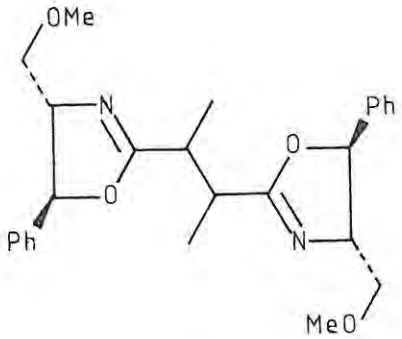
With the intention of avoiding the difficulties of handling bromine, and possibly obtaining a higher yield, the reaction was again repeated, this time replacing the bromine with iodine. Workup of this reaction afforded the desired iodo-oxazoline (528), again in low yield.

Since Arnold and Kulenovic[282] had reported high yields in their syntheses of α-haloesters using tetrachloro- and tetrabromomethanes as the halogen source, it was decided to investigate the use of tetrabromomethane in the oxazoline halogenation reaction. The required tetrabromomethane was

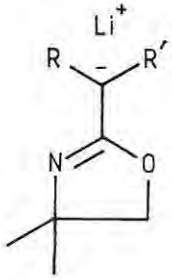


NMR 3: (4S,5S)-2-(1-Bromoethyl)-4-methoxymethyl-5-phenyl-2-oxazolines (527)

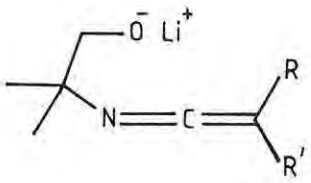
obtained by synthesis based on the reaction of Bell and Ford-Smith in their study of the hydrolysis of tribromomethane.[283] Generation of the oxazoline anion (525) in ether at -78°C using butyllithium, followed by addition of an ethereal solution of tetrabromomethane resulted in the formation of an orange-yellow suspension. On warming to room temperature the colour lightened. Workup and examination of the product showed that only small quantities of the desired bromo-oxazoline (527) had been produced.



(529)



(530)



(531)

Apart from quantities of recovered starting oxazoline (524), the only other product of interest was a pale oil, which after purification, was identified as the dimeric product (529). It was learnt that dimer formation also had prevented Meyers from synthesising the halo-oxazolines by halogenation.[284] In addition, Meyers' group[258] have also shown that oxazoline dimer formation, as well as rearrangement of the oxazoline anion (530) to the ketenimine (531) occurs at ambient temperatures.

In an effort to increase yields of the bromo-oxazoline (527), the reagents were added in reverse order. Thus the lithio-oxazoline (525) in ether at -78°C was added dropwise, via a

double-ended needle, to an ethereal solution of tetrabromomethane at -78°C. Examination of the product obtained, after warming to room temperature and work-up, revealed the bromooxazoline (527) with an improved yield.

The limited success achieved using ethereal solutions of bromine, iodine or tetrabromomethane as the halogenating agents was suspected to be a result of the limited solubility of the reagents in ether at the reaction temperatures. Halogenation at higher temperatures was considered unwise due to anion rearrangement to a ketenimine, or formation of oxazoline dimers.[258] Since solubility had not been a problem with tetrahydrofuran solutions, the use of tetrahydrofuran in the reaction was reconsidered.

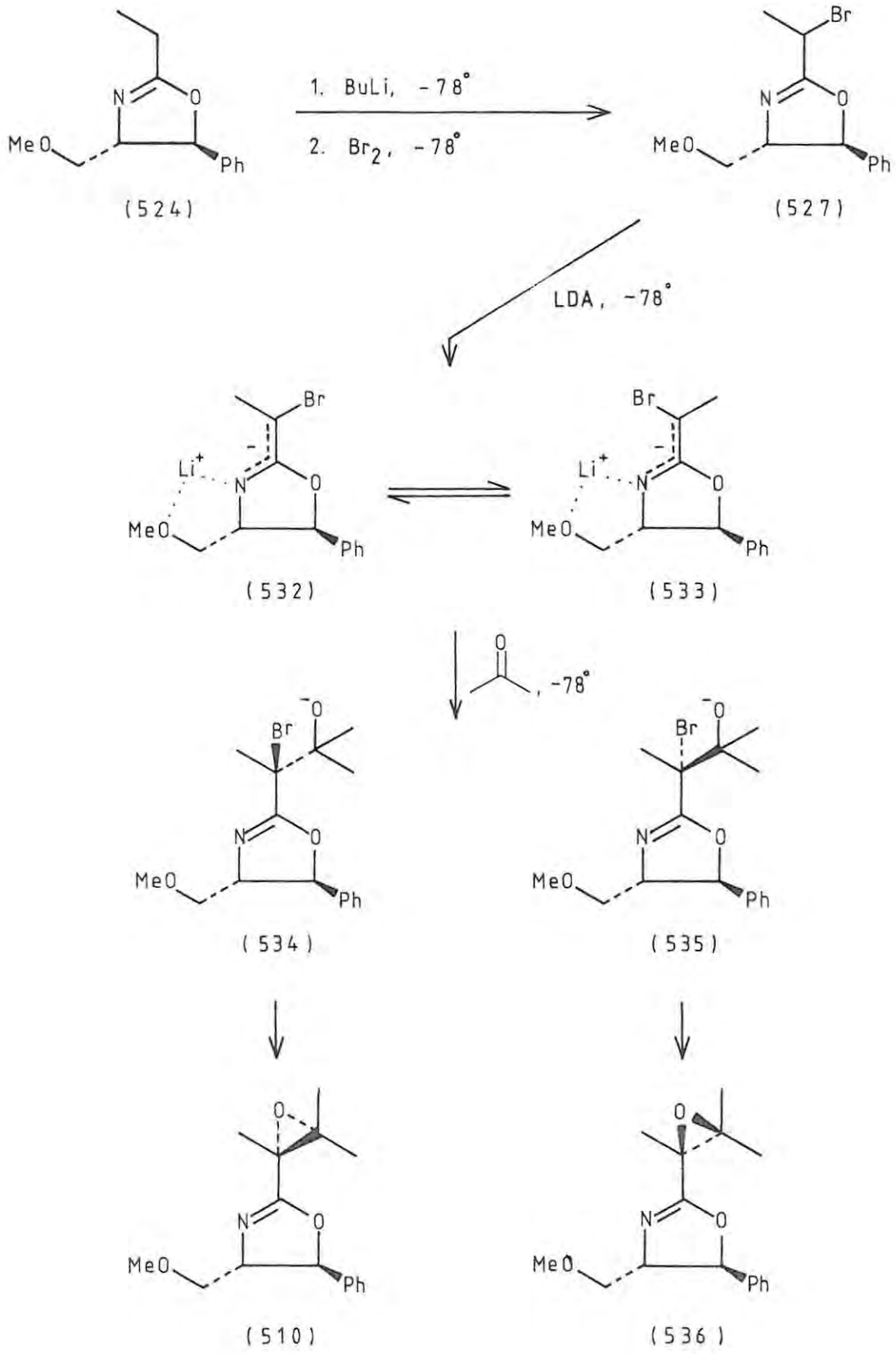
If, as was suspected in the light of Arnold and Kulenovic's work[282] discussed earlier, the bromine (and presumably to a lesser extent, the iodine) was reacting photolytically with the tetrahydrofuran, then this reaction could be minimised, or even eliminated, by preparing and immediately utilising the halogen/tetrahydrofuran solution in total darkness. Furthermore to reduce the possibility of dimerisation of the oxazoline (524) it was decided to add the oxazoline to the butyllithium at -78° instead of the reverse as had been done before.

Addition of the oxazoline (524) to butyllithium in tetrahydrofuran at -78°C gave the expected yellow solution of the anion (525). Attempts to mix bromine and tetrahydrofuran at -78° proved fruitless, as the bromine solidified (mp. -7°)

and solvation in the tetrahydrofuran was extremely slow. This problem was overcome by first mixing the bromine and tetrahydrofuran at room temperature (in the dark), then cooling rapidly to -78°C, followed by dropwise addition of the lithio anion solution to the cold bromine solution. The reaction was kept at this cold temperature for 90 minutes before being allowed to warm to room temperature and worked up. Purification of the crude product gave the bromo-oxazoline (527) in 61% yield, as a diastereomeric mixture, along with 21% recovered methoxyoxazoline (524).

The proton NMR (p175) of the bromo-oxazoline showed a pair of overlapping doublets at δ 1,94 and δ 1,96 ppm due to the β-methyl protons, while the methine protons were visible as a double quartet centred on δ 4,72 ppm. Chromatographic separation of the isomers was achieved with difficulty, and resulted in the isolation of the major isomer with the methyl protons resonating at δ 1,96 ppm. This was assigned as the (1'R,4S,5S)-isomer by comparison with the NMR spectra of the separated isomers of bromo-amide (513) for which the absolute configuration had been determined.

Using the above procedure with iodine in place of bromine produced the corresponding iodo-oxazoline (528) in slightly lower yield, (59%). Following the reaction by gas chromatography showed that halogenation was rapid, with no further change observable twenty minutes after addition of the oxazoline anion (525) to the halide solution. Yields of the bromo-oxazoline (527) were increased to 95% by allowing one hour for complete anion formation, before addition to the



(524) (527) (532) (533) (534) (535) (510) (536)

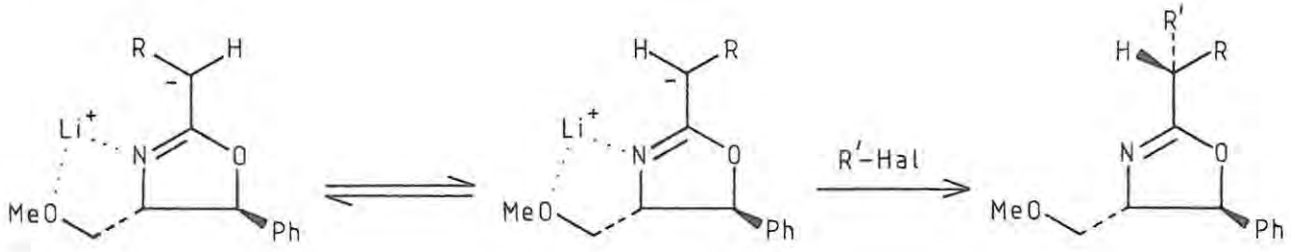
Scheme 82.

bromine solution. This endorsed the fact that the formation of the oxazoline anion (525) is the slow step in the reaction, and is in agreement with earlier work[255] wherein anion preparation times of 30 minutes were used.

With the required bromo-oxazoline (527) now readily available, attention was given to the problem of producing the epoxyoxazoline (510) (Cf. Scheme 73, p156).

While lithiation and subsequent bromination of (524) to produce (527) was assured, it was anticipated that addition of another equivalent of base to (527) would provide the anions (532) and (533) as an equilibrium mixture, [Scheme 82].

Meyers and coworkers[255] had shown that for oxazoline anions of general structure (537) and (538) it had not been possible to detect the two isomers using NMR, since rapid interconversion was occurring, [Scheme 83]. On alkylation, however, the anion isomer (538), with the largest group furthest removed from the lithium ion, was attacked preferentially to give dialkyloxazolines (539) in high optical purity.



(537) (538) (539)

Scheme 83.

Consequently it was thought that the anions (532) and (533) would behave in similar fashion, with anion (532) reacting in preference. The possibility of interaction of the bromide lone pair electrons with the lithium ion resulting in anion (533) becoming the most stable isomer could not, however, be dismissed. Assuming that (532) would be the predominant ion, addition of acetone and attack by the carbonyl carbon from the least hindered (lower) face of the anion, would lead to formation of the oxyanion (534) and hence the epoxy-oxazoline (510) via subsequent S_n2 displacement of the bromine atom.

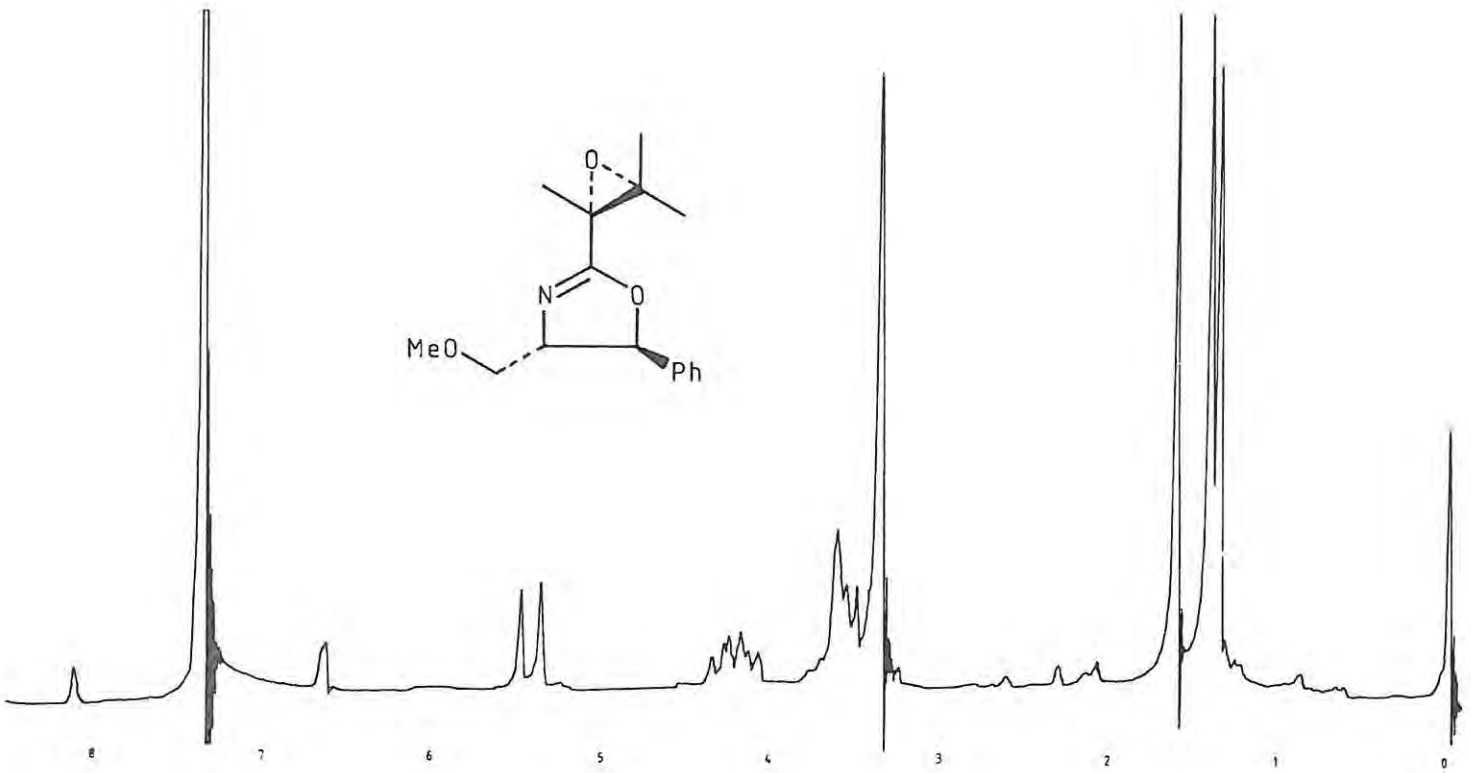
Accordingly the bromo-oxazoline (527) in tetrahydrofuran was lithiated at -78°C using lithium diisopropylamide as the metalating agent. Use of lithium diisopropylamide in place of the butyl lithium used in the formation of (527) was based on Meyers earlier work[255] wherein he showed that the highest enantiomeric excesses were obtained using this reagent. The resulting dark orange-red solution was stirred for ten minutes, followed by rapid addition of dry acetone. The temperature of the reaction was maintained for 25 minutes then allowed to reach 20°C to allow cyclisation to the epoxide.[285] During this time the colour lightened to a pale orange. Workup and separation of the reaction products resulted in the isolation of the desired oxazoline (510), (Yields of 75 - 80%, based on GLC analysis). The main impurity being unreacted halo-oxazoline.) Attempts to purify the crude product mixture resulted in a considerable loss of material regardless of techniques used.

During the course of the above work it became apparent that both the bromo- and the iodo-oxazolines, (527) and (528),

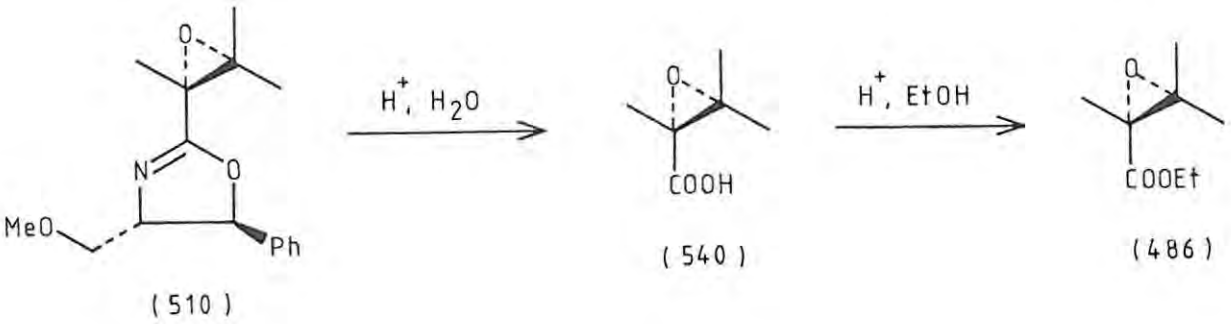
were unstable compounds at room temperature, but could be stored for up to three weeks at 0-4°C. Therefore in view of the limited stability of the halo-oxazolines, and hence the losses which were being incurred on workup and purification, it was decided to attempt a one-pot synthesis of the epoxy-oxazoline (510).

The methoxyoxazoline (524) was lithiated using butyllithium, and then brominated in the dark at -80° by addition of the lithio anion (525) to the bromine in tetrahydrofuran as before. After allowing one hour for complete formation of the bromo-oxazoline (527), the oxazoline was added dropwise to lithium diisopropylamide in tetrahydrofuran at -80° to give a very dark red-brown solution of the lithio bromo-oxazoline. Addition of dry acetone, and slow warming to room temperature gave the desired epoxyoxazoline (510) in 86% yield based on GLC and NMR analysis.

Determination of the specific rotation of (510) gave a value of $[\alpha]^{24} = -46,4°$. Since the ^{1}H NMR spectrum (p183) of the epoxyoxazoline showed no evidence of the presence of diastereoisomers, it suggested that only one isomer had been synthesised. Assuming that the anion (532), [Scheme 82, p179], was the most stable conformer, it implied that the desired [R]-epoxyoxazoline had been produced. Proof of this assumption could be obtained by hydrolysis of the oxazoline ring and esterification of the free acid to give the epoxy ester (486), [Scheme 84], for which the absolute configuration and optical rotation data was known.[286]



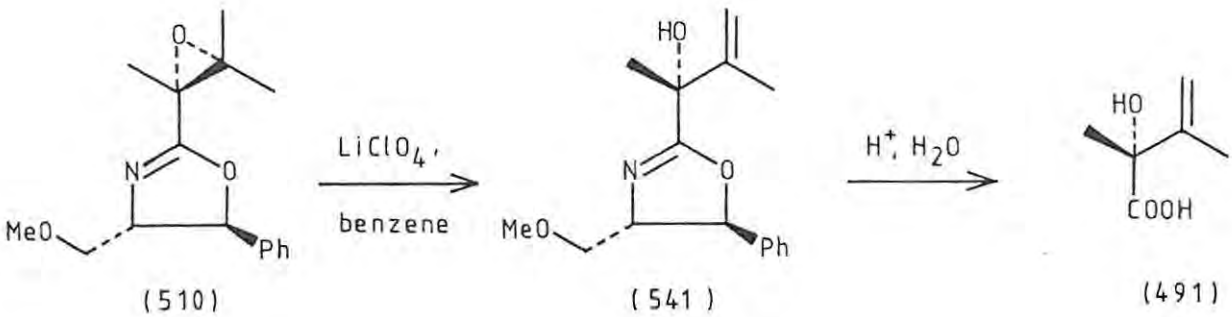
NMR 4: (4S,5S)-2-(1,2-dimethyl-1,2-epoxypropyl)-4-methoxymethyl-5-phenyl-2-oxazoline (510)



(510) (540) (486)

Scheme 84.

A problem with this approach was the likelihood of epoxide ring cleavage occurring in addition to removal of the oxazoline ring. An alternative method of confirming the absolute configuration would therefore be to first rearrange the epoxyoxazoline to the allylic compound (**541**), [Scheme 85, see also Scheme 66, p144], followed by subsequent hydrolysis to the free acid (**491**), for which the absolute configuration and optical rotation data were recently reported.[244]



(510) (541) (491)

Scheme 85.

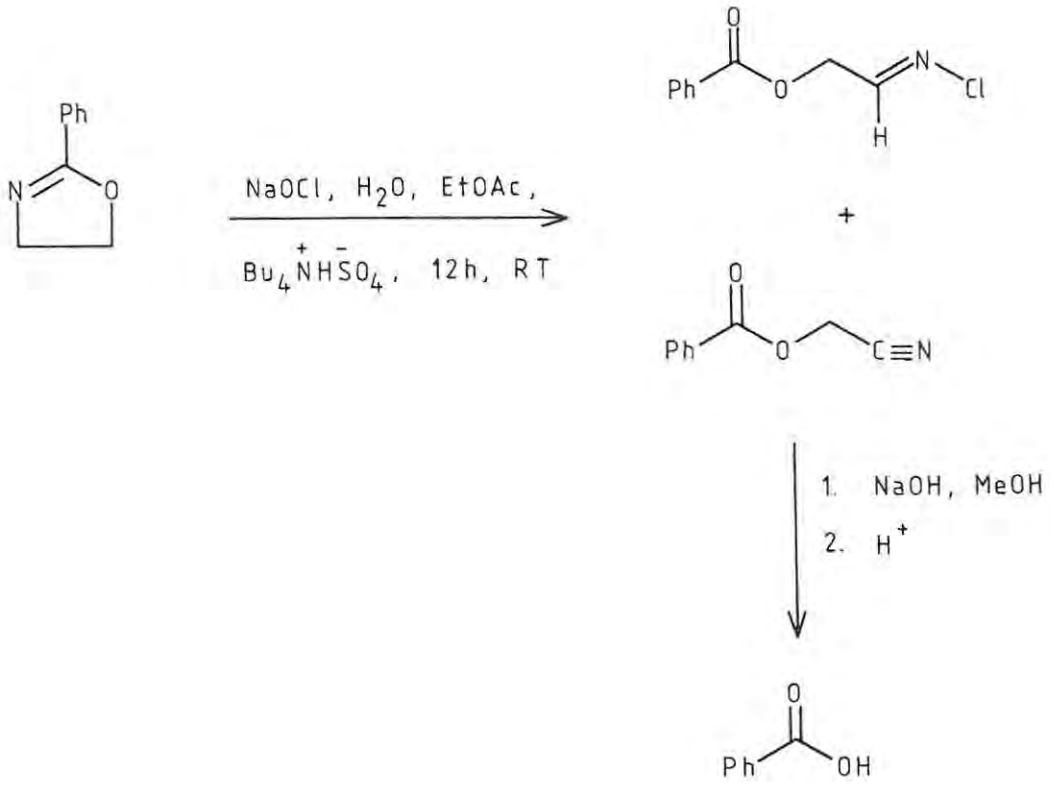
Cleavage of oxazoline rings is usually carried out by refluxing for several hours under acidic conditions.[287,288] A modification of this approach is to first cleave the ring to an aminoester salt by mild acid hydrolysis, then follow

this by treatment with base.[261] The advantage of the two step procedure is an improvement in the optical purity of the diastereomeric product, though at the expense of a small loss in overall yield.

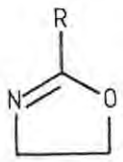
Reaction of the epoxy oxazoline (510) with aqueous acid did indeed cause cleavage of the oxazoline ring, but also resulted in rupture of the epoxide ring. Johnson and Bade,[285] in their work on the synthesis of glycidic acids also encountered great difficulty in isolating their product.

In an effort to avoid decomposition of the epoxide during hydrolysis, the reaction was run at room temperature, using absolute ethanol as solvent. It was anticipated that the desired stable ester (**486**) (Cf. Scheme 84, p184) would be produced directly. On workup, however, none of the desired ester (**486**) was obtained, nor was any of the epoxy oxazoline recovered.

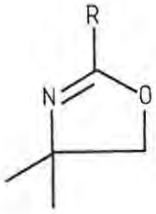
A recently reported ring cleavage reaction of oxazolines, carried out under basic conditions, is that developed by Weinreb and Levin.[289] Reaction of an oxazoline with commercial bleach under phase transfer conditions was shown to result in the formation of a mixture of an N-chloro-iminoester and a nitrile, [Scheme 86]. The reaction occurred at room temperature and the choice of organic solvent was found to be critical, with ethyl acetate being the best solvent. Subsequent base hydrolysis of the intermediate products followed by acidification resulted in isolation of the free acid.



Scheme 86.



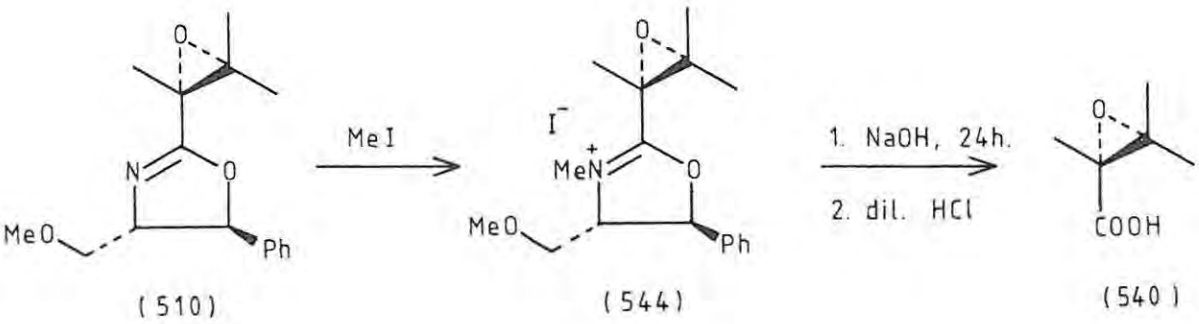
(542)



(543)

Only oxazolines of general structure (542) and (543) were reported,[289] and it was therefore uncertain whether the reaction would proceed using the more highly substituted oxazoline (510). Consequently treatment of the epoxyoxazoline (510) with sodium hypochlorite for sixty hours, subsequent base hydrolysis, and workup of the reaction did not produce any recognisable products. Changing the

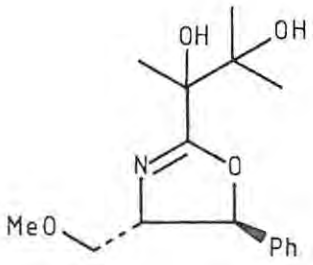
phase transfer catalyst to tetrabutylammonium bromide, using different sources of the hypochlorite, varying the reaction times and work-up procedures were equally unsuccessful.



(510) (544) (540)

Scheme 87.

A second non-acidic method of cleaving oxazoline rings had been mentioned previously.[258] In this procedure the epoxyoxazoline (**510**) was first treated with methyl iodide to produce a methiodide salt (**544**), [Scheme 87]. Removal of volatile material and treatment of the crude methiodide with dilute sodium hydroxide at room temperature for 48 hours once again failed to provide any of the desired product, and total loss of the oxazoline (**510**).



(**545**)

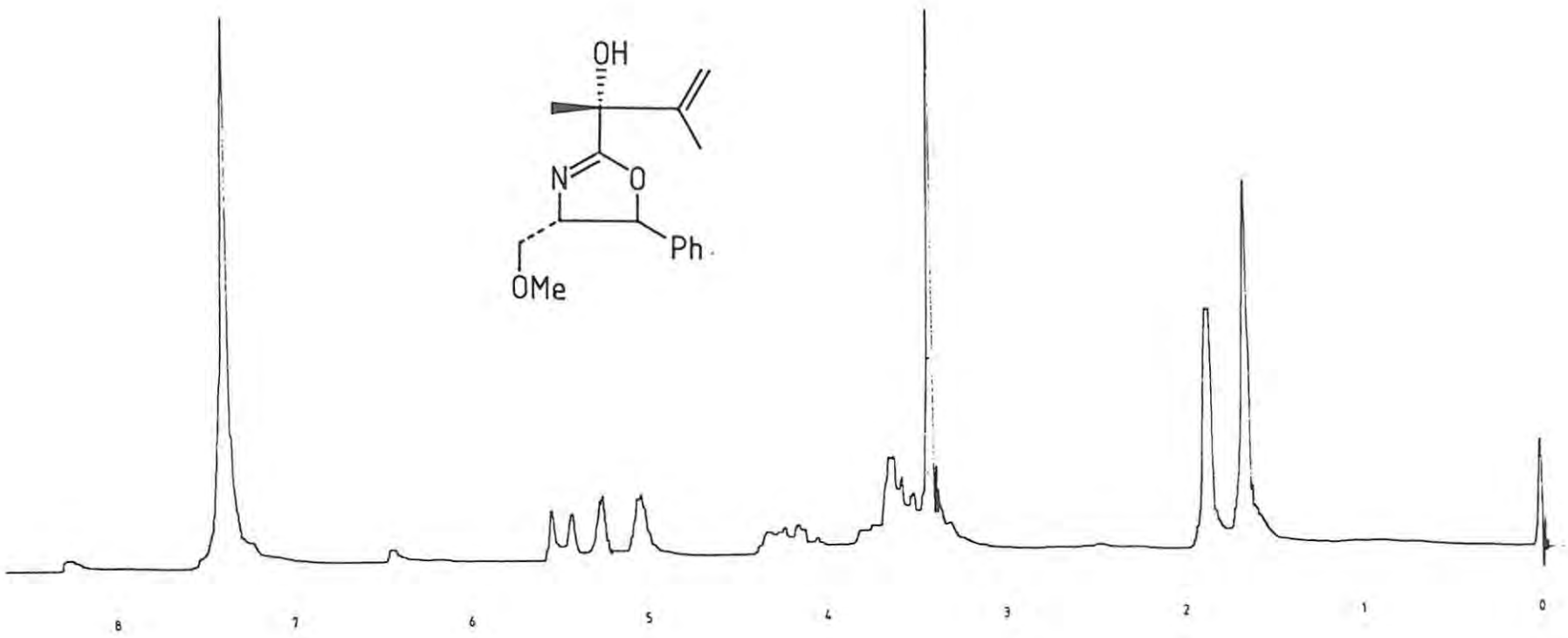
The total failure to obtain any epoxyacid (**542**) or epoxyester (**486**) from these reactions, along with the loss of the starting oxazoline indicated that hydrolysis of both the

oxazoline ring and of the epoxide was occurring. Hydrolysis of the epoxide, under both acidic and basic conditions, would provide the dihydroxyoxazoline (**545**) (or the free acid). It is known that both β-hydroxyacids or esters undergo an extremely facile αβ-cleavage,[290] and in the present case this would lead to the formation of acetone and lactic acid as the end products. Such reversion reactions were in fact encountered by Meyers et al[258] in similar circumstances.

Since it had proved difficult to obtain the epoxyacid (**540**) from the epoxyoxazoline (**510**), attention was turned to obtaining the allylic α-hydroxy acid (**491**) via rearrangement of the epoxyoxazoline and subsequent hydrolysis, [Scheme 85, page 184].

Rearrangement of epoxyester (**486**) to the allylic α-hydroxy ester (**487**) (p144) had been achieved previously by either lithium perchlorate[58] or 4-toluene sulphonic acid.[244] The treatment of epoxyoxazoline (**510**) with lithium perchlorate in refluxing dry benzene for twelve hours was not successful. Use of excess 4-toluenesulphonic acid in place of the lithium perchlorate, however, gave the required allylic hydroxy-oxazoline (**541**) in good yield, as evidenced by the appearance in the proton NMR (p189) of signals at δ5,05 and δ5,26 ppm due to the vinylic protons.

Treatment of (**541**) with hot dilute hydrochloric acid for one hour[287,288] resulted in the disappearance of the water-insoluble oxazoline, thus indicating that ring cleavage had occurred. Work-up and continuous liquid-liquid extraction of the reaction mixture resulted in the recovery of the desired



NMR 5: (1'R,4S,5S)-2-(1-Hydroxy-1,2-dimethyl-2-propenyl)-4-methoxymethyl-5-phenyl-2-oxazoline (541)

hydroxyacid (**491**) as a clear gum (24% yield) which crystallised on standing. Measurement of the specific rotation of (**491**) gave $[\alpha] = -0,5°$. Comparison with the reported[244] value for the R-isomer of $[\alpha] = -18,2°$ indicated that while the required R-isomer was indeed the major product of the epoxidation reaction, the diastereomeric excess of 3% was disappointingly low. The possibility of racemisation of the chiral centre having occurred during the hydrolysis and work-up was discounted, since racemisation of the tertiary alcohol was most likely to proceed with concomitant rearrangement of the C=C bond into conjugation with the carbonyl group. No evidence of any such product had been observed either in the present work, or previously.[58,244]

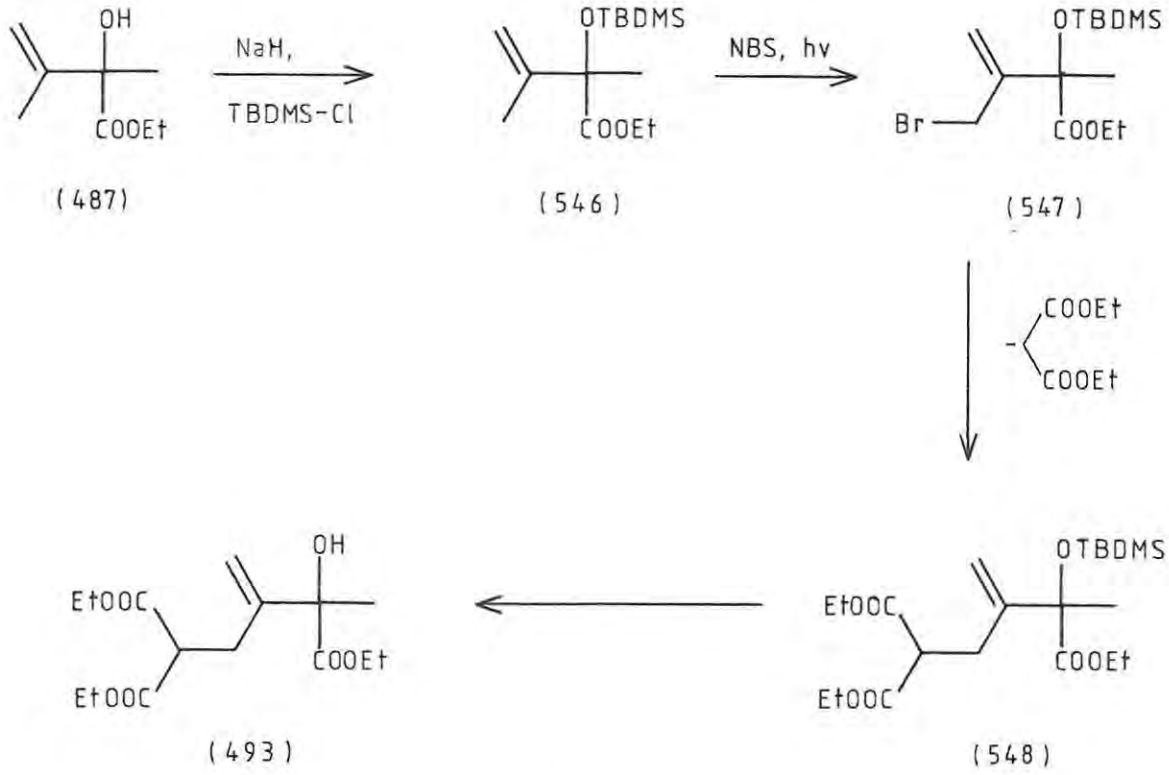
Two possible reasons for the low asymmetric induction achieved during the epoxidation step (Cf. Scheme 82, p179) are postulated. Firstly, it had been anticipated that addition of lithium diisopropylamide to the bromo-oxazoline (**527**) (Cf. Scheme 82, p179) would provide the isomeric lithio anions (**532**) and (**533**) as an equilibrium mixture, with anion (**532**) being the favoured isomer on the basis of least steric crowding, while anion (**533**) would be favoured on the basis of interaction of the halogen lone pair with the lithium ion. It now appeared that anion (**532**) is only marginally favoured, thus indicating that either a significant amount of halogen-lithium interaction was taking place, or that there was insufficient difference in the sizes of the methyl and bromine groups to significantly affect the relative quantities of anions (**532**) and (**533**). Secondly, and less

likely, was the possibility that the anion (**532**) was indeed the major isomer, but that attack by the acetone was not occurring solely from the least hindered (lower) face of the anion.

3.5. Elaboration of the carbon skeleton.

With the hydroxyacid (**491**) to hand, albeit in very low enantiomeric excess, attention was now turned to the synthesis of the remainder of the carbon skeleton of swazinecic acid dilactone (**485**).

In view of the low enantioselectivity obtained for the hydroxyacid via the oxazoline route, subsequent reactions were developed on racemic compounds starting from the allylic hydroxy ester (**487**). This was readily available by



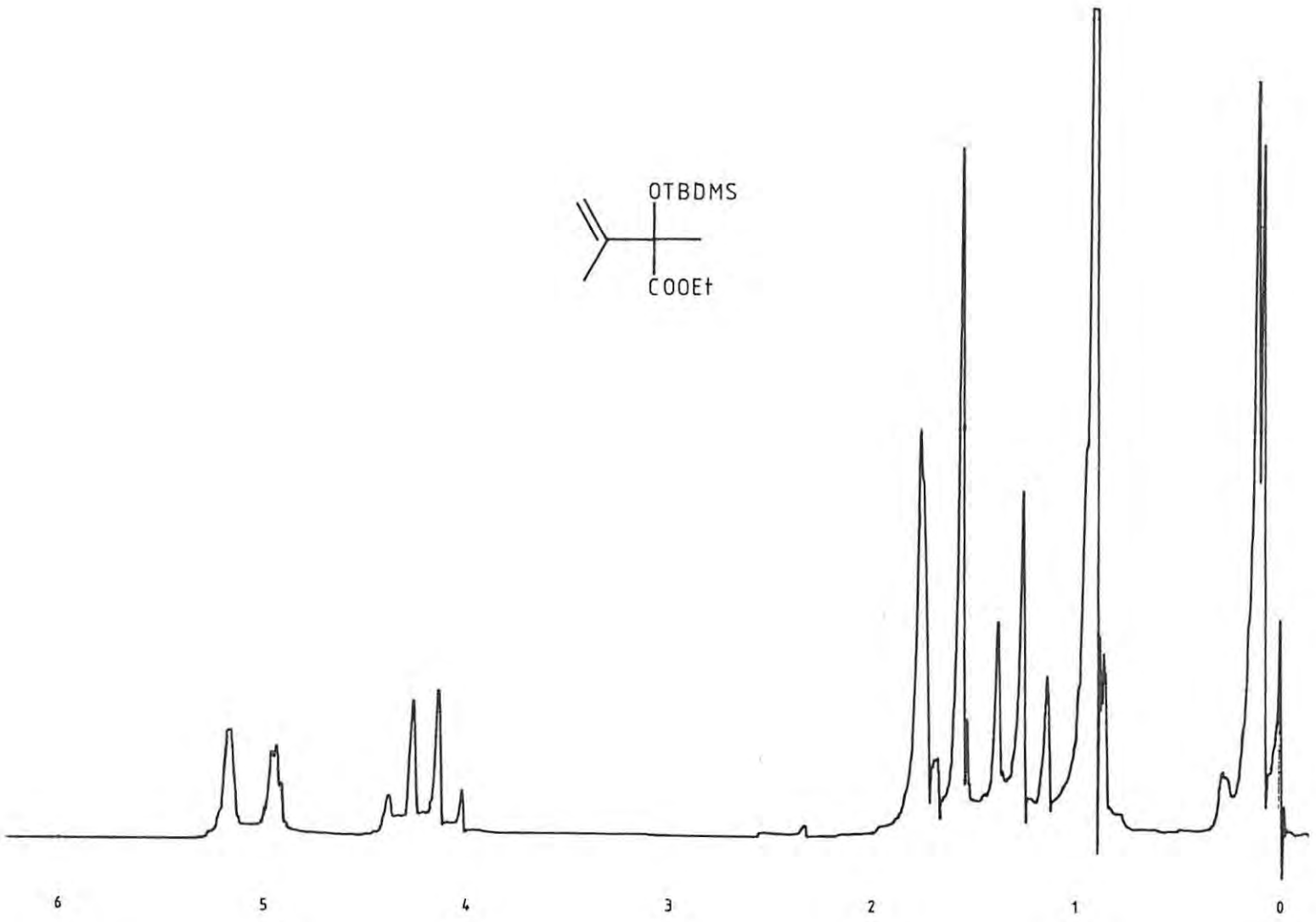
(487) (546) (547) (548) (493)

Scheme 88.

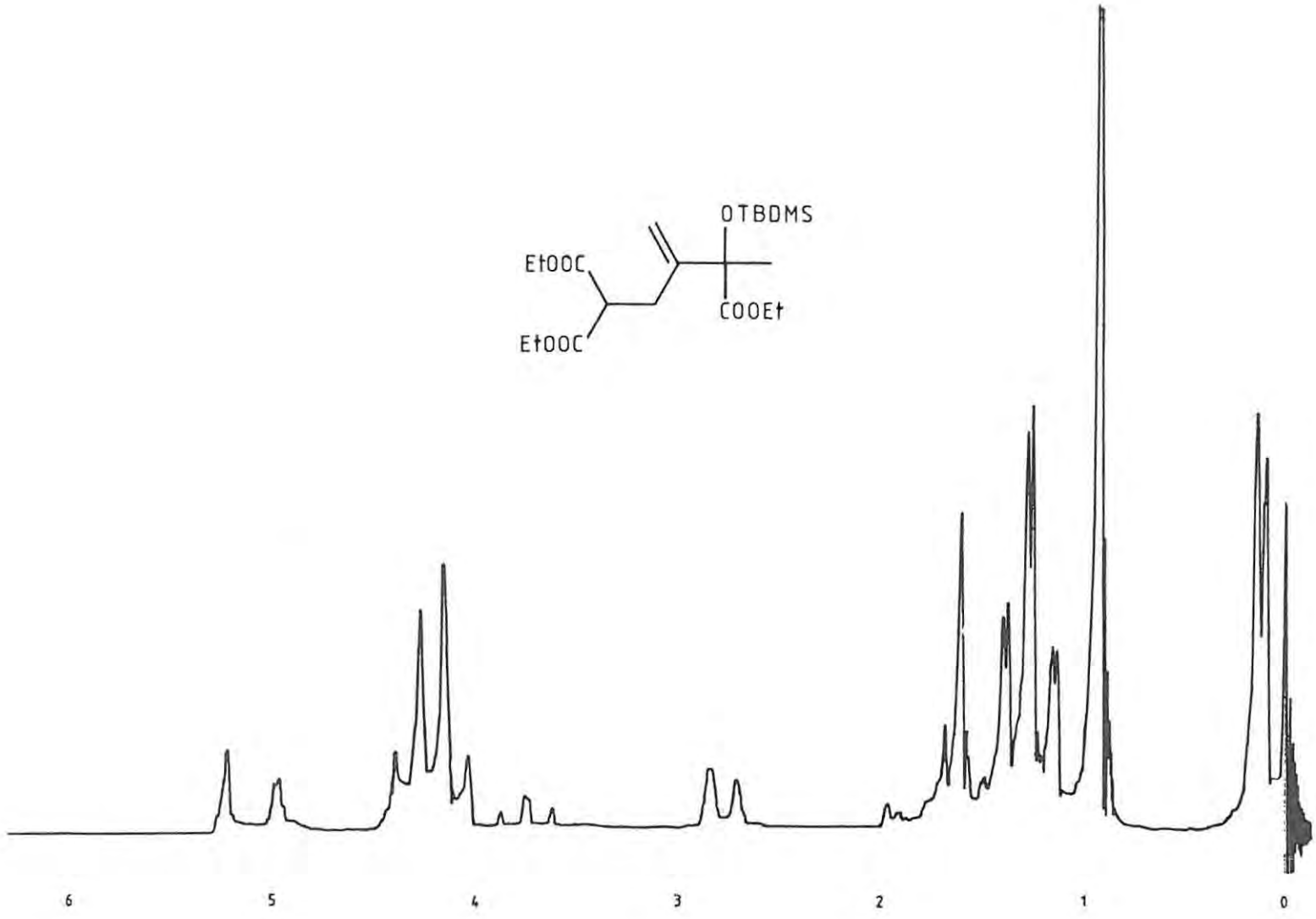
condensing acetone with ethyl 2-bromopropanoate in a Darzens reaction,[235] (Cf Scheme 66, page 144), followed by lithium perchlorate catalysed rearrangement of the resultant epoxy ester (**486**).

Elaboration of the skeleton of (**487**) followed the approach developed earlier.[235] The hydroxyl group was protected as the tert-butyldimethylsilyl ether (**546**), [Scheme 88] (NMR spectrum, p193), (instead of the more labile trimethylsilyl ether used previously (Cf Scheme 67, page 145)). Photolytic bromination using N-bromosuccinimide gave (**547**) which, after purification through a short column of silica gel, was reacted with diethyl malonate anion to give the crude triester (**548**). The pure triester was obtained using flash chromatography,[262] (NMR spectrum, p194).

Attention was now turned to the removal of the silyl protecting group. Reference to Greene's[291] work on protecting groups provided a number of methods which had effected cleavage of the tert-butyldimethylsilyl group, under mild conditions and in high yields. The simplest of these is the use of acetic acid-water-tetrahydrofuran (3:1:1) at 25°C for six hours, giving yields of 96%. Treatment of (**548**) with this system for 21 hours did not, however, result in any cleavage, and the starting triester (**548**) was recovered in quantity. This lack of reactivity can be ascribed to the severe steric crowding in vicinity of the Si-O-C bonds thus making access by attacking nucleophiles very difficult. Hence it was apparent that it would be necessary either to employ forcing conditions, or to use a small, strongly nucleophilic reagent.



NMR 6: Ethyl 2,3-dimethyl-2-O-tert-butyldimethylsilyl-3-butenoate (546)

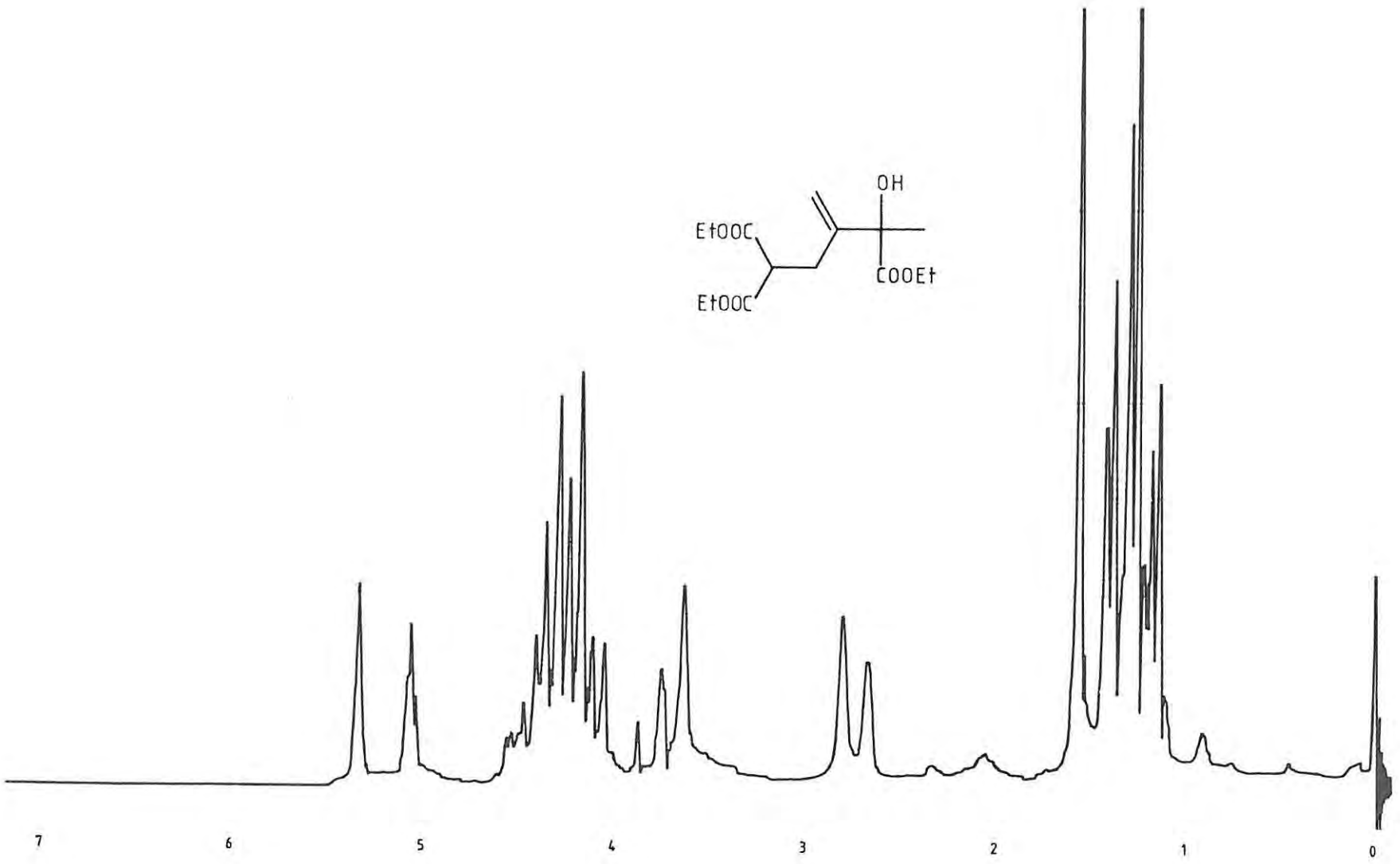


NMR 7: Diethyl 5-carboethoxy-2-methyl-3-methylene-2-O-tert-butyldimethyl-silylhexanedioate (548)

Three of the most effective methods reported to date for cleaving silyl ethers, particularly the more resistant types, are those employing tetra-n-butylammonium fluoride,[292] hydrofluoric acid in acetonitrile,[293] and boron trifluoride etherate.[294] All of these make use of the small size and strong nucleophilic character of the fluoride ion. Of the three methods, the ones using the quaternary ammonium fluoride and boron trifluoride etherate appealed since they both avoided the difficulties associated with handling hydrofluoric acid.

The tetra-n-butylammonium fluoride was prepared *in situ*[295] from potassium fluoride dihydrate and tetra-n-butylammonium chloride in dry acetonitrile, and a three-fold excess reacted with the silyl triester (548) at room temperature for twenty-two hours. Work-up of the reaction revealed that 42% of the silyl triester had undergone cleavage. Repeating the reaction at reflux overnight, however, resulted in complete cleavage to the required hydroxy triester (493, NMR spectrum p196).

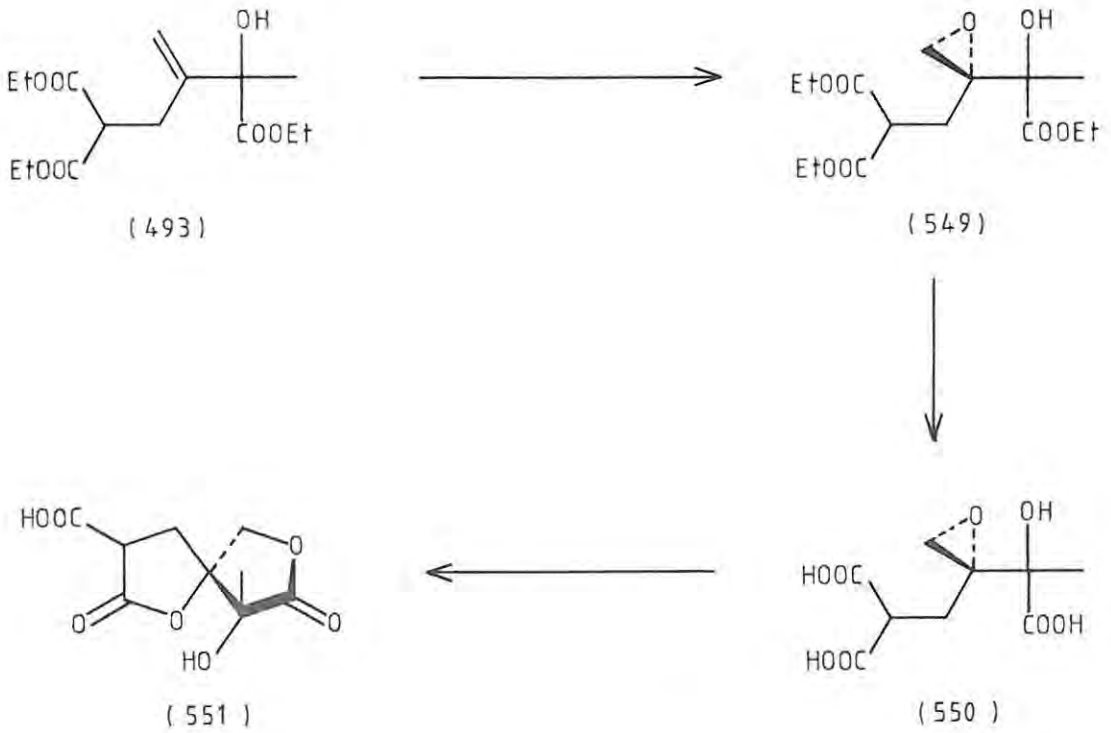
In the second method a solution of (548) in dichloromethane was stirred with a slight excess of boron trifluoride etherate under nitrogen. After fourteen hours the reaction was quenched with dilute aqueous sodium carbonate, and the organic portion removed and concentrated. Examination of the product showed it to be the desired hydroxy ester (493) contaminated by small amount of the unreacted silyl triester (548), with the overall yield being better than 90%.



NMR 8: Diethyl 5-carboethoxy-2-hydroxy-2-methyl-3-methylenehexanedioate (**493**)

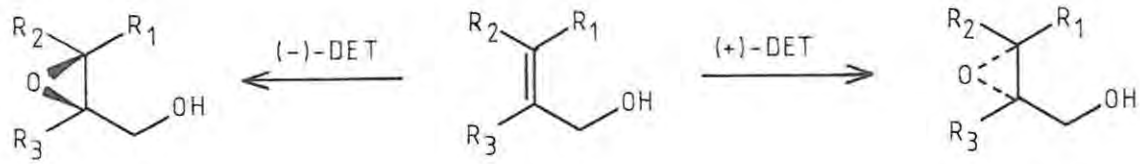
With the synthesis of (493) complete, attention was next turned to epoxidation of the alkene functionality of (493), from which it was intended to obtain the spiro-dilactone (551), [Scheme 89], by ester hydrolysis, epoxide cleavage and cyclisation (Cf. Scheme 68, p147).

Since introduction of the epoxide results in the formation of the second of the three chiral centres present in the target molecule it was highly desirable that the epoxidation be carried out in a stereoselective manner. Although epoxidisation of allylic alcohols has been known for many years,[296] it is only recently, as a result of the work of Sharpless and his coworkers,[297-299] that asymmetric epoxidation (in good enantiomeric and overall yields) has been possible.



Scheme 89.

The earliest asymmetric epoxidations used m-chloroperbenzoic acid as the oxidising agent.[296] More recently this has been replaced by tert-butyl hydroperoxide, and the reactions are catalysed by either molybdenum hexacarbonyl or vanadyl acetoacetonate, with the latter being the preferred choice.[298] Epoxidation with these reagents give markedly better stereoselectivities compared to those obtained using m-chloroperbenzoic acid. In 1981 Sharpless and coworkers[299] discovered that use of titanium tetra-isopropoxide/diethyl tartrate as the 'catalyst' system, and tert-butyl hydroperoxide as the oxidant, allowed for remarkable stereoselectivities. More importantly, the new system provided complete control over the stereochemistry of the epoxide product simply by the use of either the L-(+)- or D-(-)-isomer of diethyl tartrate, [Scheme 90]. In all cases reported to date, use of the L-isomer has led exclusively to delivery of the incoming oxygen atom to the lower face of the alkene (when drawn as in Scheme 90), and conversly for the D-isomer. So effective is the titanium-catalysed reaction that it has become known as the Sharpless asymmetric epoxidation reaction.



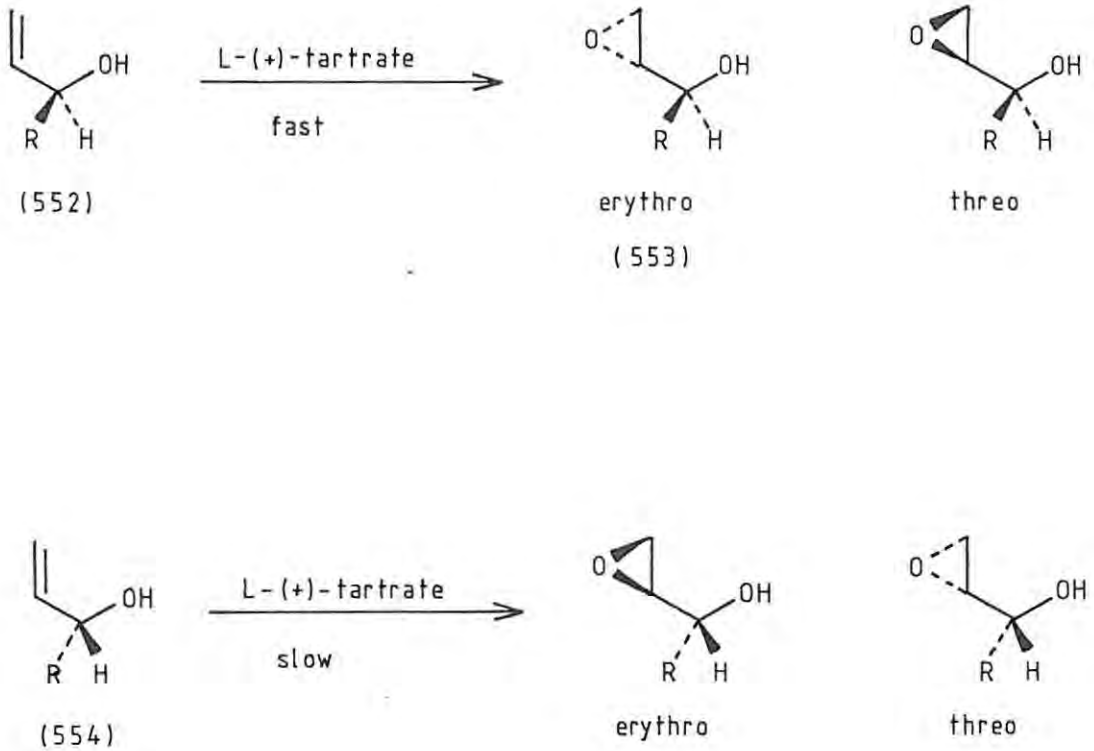
Scheme 90. (Other details (TBHP, Ti(O$\underline{i}$Pr)$_4$, CH_2Cl_2, -20°C) omitted for clarity.)

Other tartrate diesters were found to be as effective, and are of particular use in application where the epoxy alcohols generated are appreciably water soluble.[300] The latest advance has been to reduce the quantities required of the titanium tetra-isopropoxide from a slight molar excess down to truly catalytic amounts by the addition of 4A molecular sieves to the reaction mixture,[301] the principal role of the molecular sieves being to remove traces of water from the reaction mixture, as the activity of the catalyst is known to be seriously degraded by the presence of moisture.

It appeared therefore, that the Sharpless asymmetric epoxidation reaction would be ideal for the conversion of allylic hydroxy ester (493) to the epoxy triester (549), as the correct configuration of the new chiral centre could be unambiguously obtained by using L-(+)-diethyl tartrate as the co-catalyst.

The author was aware, however, of two potential problems with this approach. Firstly, nearly all of the examples of the Sharpless asymmetric epoxidation which had been reported had involved primary allylic alcohols, while the remaining reactions had involved secondary alcohols. In all cases the method had given very high enantiomeric excesses and good yields. Although some of the reactions involving secondary alcohols had required several days reaction time, this was in part due to the (intentionally) reduced amounts of tert-butyl hydroperoxide used.[302] There did not, however, appear to be any reports of the asymmetric epoxidation reaction having been carried out on tertiary allylic alcohols. Secondly, in none of the reported examples of the Sharpless asymmetric

epoxidation had there been an ester group present in the substrate molecule in addition to the allylic alcohol functionality. It was therefore uncertain whether the reaction would be successful on the allylic hydroxy ester (493).



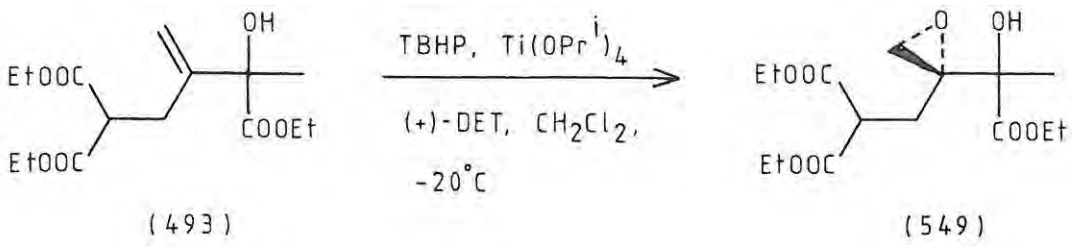
Scheme 91.

Also of interest was the effect of the existing chiral centre, present in (493), on the outcome of the reaction. In their work on secondary alcohols, Sharpless and coworkers[302] had shown that an existing chiral centre had a major effect on both the speed and the stereoselectivity of the epoxidation reaction. Substrates with the substituent on the carbinol carbon ABOVE the plane of the allylic moiety, [structure (552), Scheme 91], underwent rapid reaction in the

presence of L-(+)-tartrate esters to provide the erythro product (553) almost exclusively. The enantiomer with the substituent BELOW the plane underwent a slow reaction to provide a mixture of erythro and threo, the precise ratio of which depended on the substrate used.

By stopping the reaction when slightly more than half of the alcohol had been consumed, it was possible to recover the slower-reacting isomer (ie (554)) in extremely high optical purity and in reasonable yields, while the product was predominately epoxy-alcohol (553). On the assumption that the epoxidation reaction would in fact be successful on the tertiary allylic alcohol system of (493), it appeared likely that it would be possible to obtain the desired enantiomer of (549) in high purity simply by limiting the extent of reaction. In effect the reaction would allow resolution of both chiral centres of (549) in a single step from racemic (493). It remained to be seen, however, if firstly, the reaction would be successful on a tertiary allylic alcohol, and secondly, if any difference in rate of reaction and stereoselectivity occurred in the epoxidation of (493). It was anticipated that the R-isomer of (493) would react faster than the S-isomer, and thus would provide the erythro product.

Accordingly the allylic hydroxy ester (493) was added to a solution of titanium tetra-isopropoxide and L-(+)-diethyl tartrate in dichloromethane under nitrogen at -20°C, [Scheme 92]. This was followed by anhydrous tert-butyl hydroperoxide in dichloromethane,[298] and the reaction stored

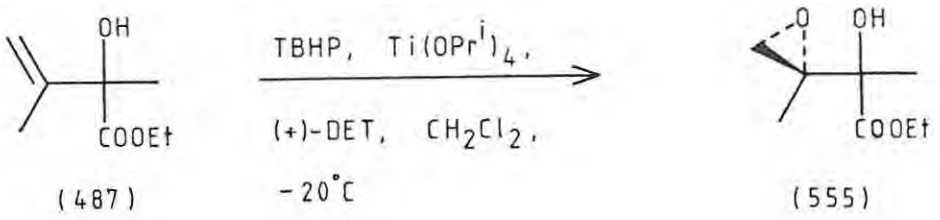


(493) (549)

Scheme 92.

at -23°C for four days. On work-up, however, (493) was recovered in quantity, with no evidence of epoxidation having occurred. Repeating the reaction under a variety of conditions (more catalyst and peroxide, longer reaction times and reaction temperatures of -20°C, 0°C and room temperature) still failed to provide any detectable amount of the desired epoxy-triester (549).

In considering reasons for the failure of the reaction, three possible causes were of interest. Firstly, the steric bulk of the molecule as a whole, and in particular, the diethyl malonate 'tail' could be restricting access to the C=C bond. Secondly, the steric hindrance about the quaternary carbon could be preventing the tertiary alcohol from complexing with the titanium reagent with resultant loss in reactivity. Lastly, the ester attached to the carbinol carbon could be affecting the reaction, both on account of the long range electron withdrawing effect of the carbonyl on the C=C bond, and, more seriously, the possibility of the ester complexing with the titanium catalyst, in a similar manner to the diethyl tartrate, resulting in loss of catalytic action.

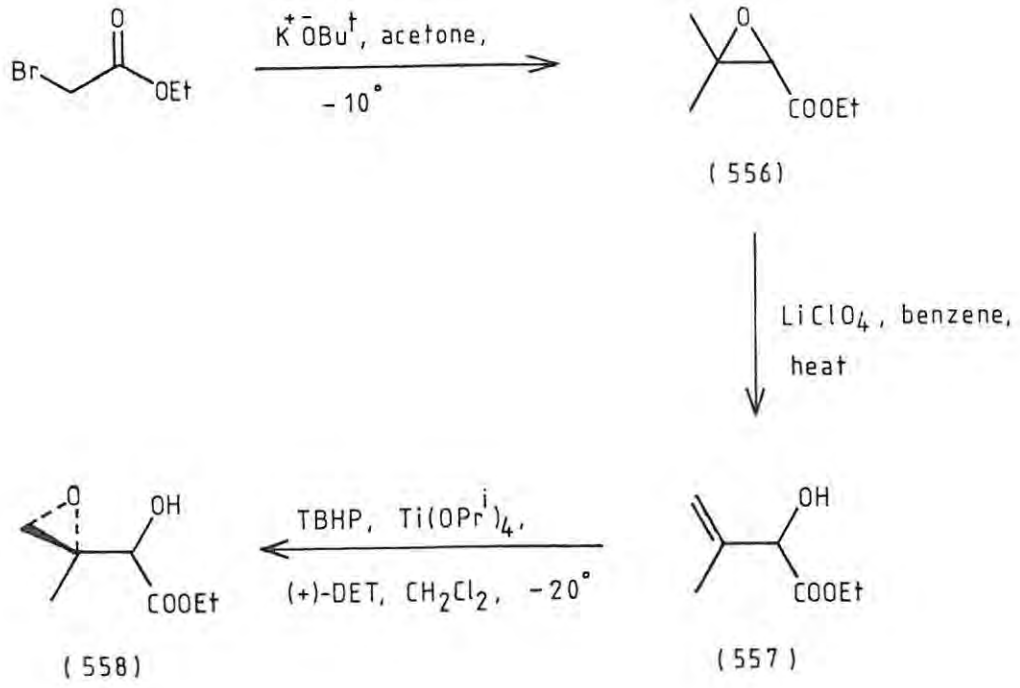


(487) (555)

Scheme 93.

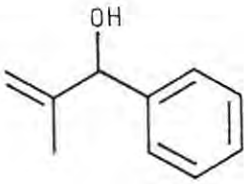
The first possibility, the steric effects of the molecule as a whole, could easily be tested by replacing the triester (**493**) by the precursor monoester (**487**), [Scheme 93]. Once again, however, attempted reaction under the standard conditions (ie -20°C, several days) failed, with the ester (**487**) being recovered in quantity, and none of the required epoxide (**555**). It was therefore clear that the problem lay with the tertiary alcohol and/or the attached ester group.

Since it was known that secondary allylic alcohols reacted well under the reaction conditions used,[302] the effect of the ester group could also be tested easily by using the secondary hydroxy ester (**557**) as a model compound in the reaction. The ester was synthesised [Scheme 94] by reaction of acetone with ethyl bromoethanoate at -10°C in the presence of potassium tert-butoxide in a Darzens reaction, and the resultant epoxy-ester (**556**) rearranged to the allylic hydroxy ester (**557**) by refluxing with lithium perchlorate in dry benzene. Treatment of (**557**) with the Sharpless asymmetric epoxidation reagents at -20°C for twenty-one days resulted in the isolation of a very small amount of material which was identified by NMR as the required epoxy ester (**558**).

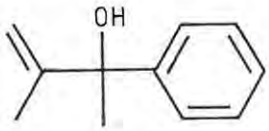


Scheme 94.

In view of the very long reaction time and the low return of epoxide (**558**) compared to the short reaction times and good returns reported in the earlier work,[302] it was apparent that the ester functionality was indeed the primary cause of the difficulties encountered. Although the mechanism of the inhibition of the reaction by the ester group was not investigated, (being outside the scope of the present work), it was suspected that steric factors were also involved since some epoxidation of the secondary allylic hydroxy ester (**557**) had occurred, but not of the tertiary analog (**487**). The steric hindrance aspect was later confirmed by Rugunanan[303] who synthesised and then epoxidised a number of secondary and tertiary allylic alcohols such as (**559**) and (**560**). In all cases tested, the tertiary alcohols could be epoxidised but in very low yields, while the secondary alcohols provided substantially greater quantities of epoxides.



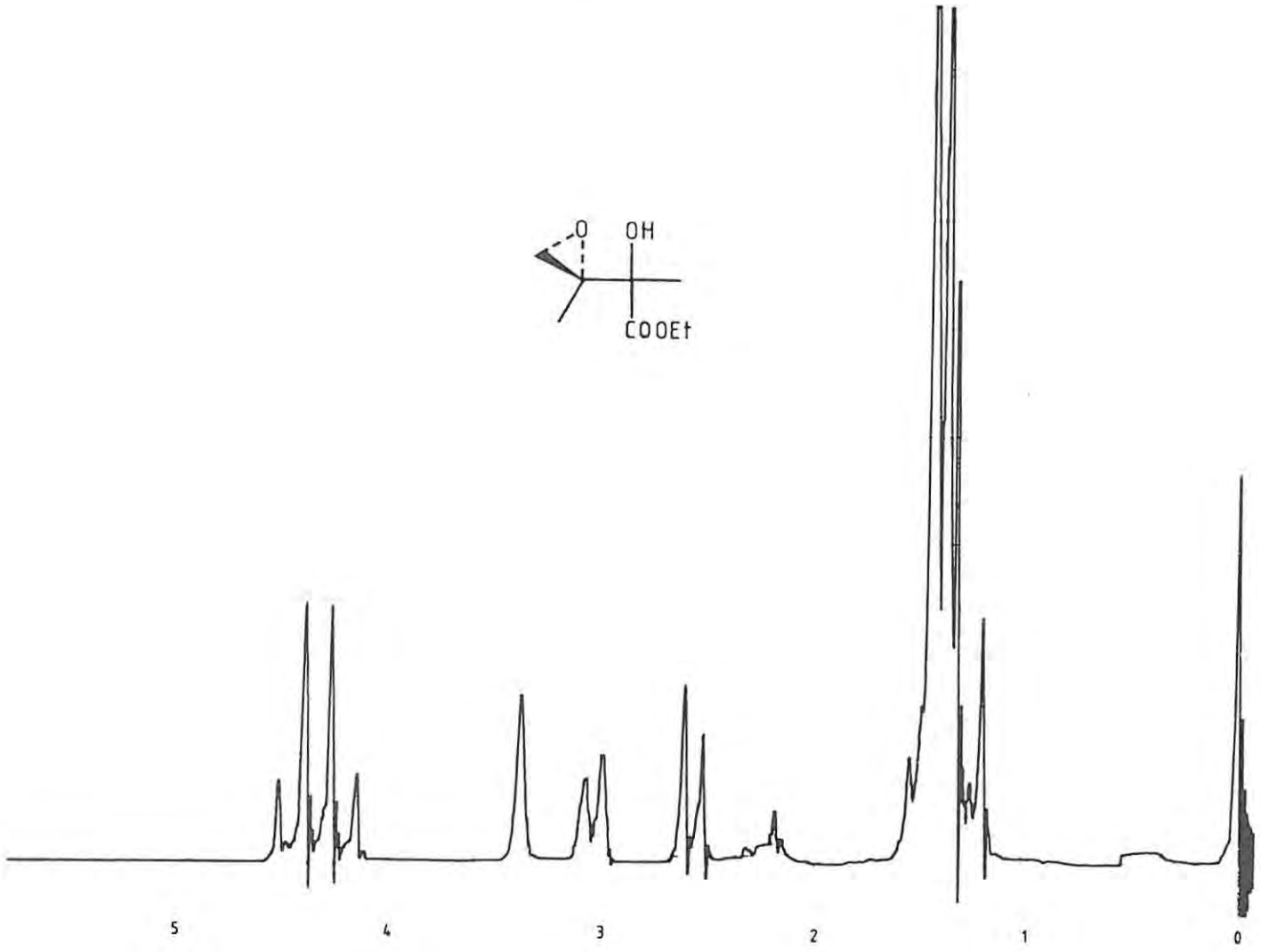
(559)



(560)

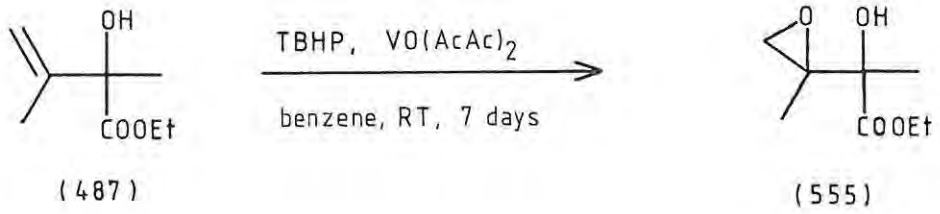
With the failure of the titanium-catalysed epoxidation reactions, attention was turned to the available alternative methods. Since Sharpless and Verhoeven[298] had found that the vanadium catalyst was better than the molydbenum catalyst when applied to allylic alcohols, the use of the vanadium catalyst was investigated, albeit with reservations as to its success!

In the light of the results obtained earlier, the vanadium catalysed reaction was first attempted on the monoester (**487**) rather than on the more elaborate triester (**493**). Addition of vanadyl acetoacetonate to a solution of (**487**) in dry benzene produced the expected characteristic deep blue-green colouration, [Scheme 95], which on addition of tert-butyl hydroperoxide[298] changed to a deep red. The reaction was stirred at room temperature under nitrogen for seven days, during which time the colour of the mixture altered from red to yellow and finally to a light green. Work-up of the reaction and vacuum distillation of the crude material gave a clear oil in 52% yield. The proton NMR spectrum of the oil (p 206) showed that the signals centred on δ5.15 ppm, due to the vinylic protons of (**487**), had disappeared, and had been



NMR 9: Ethyl 2,3-dimethyl-3,4-epoxy-2-hydroxybutanoate (555)

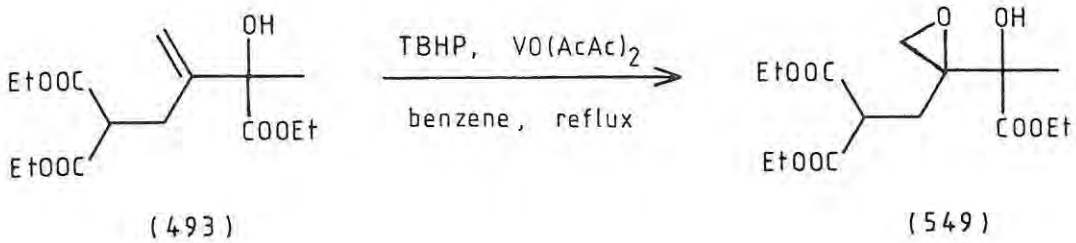
replaced by a pair of complex doublets at δ2,65 ppm and δ2,96 ppm due to the methylene protons on the epoxide ring, while other peaks visible were in agreement with the signals expected for (555).



(487) (555)

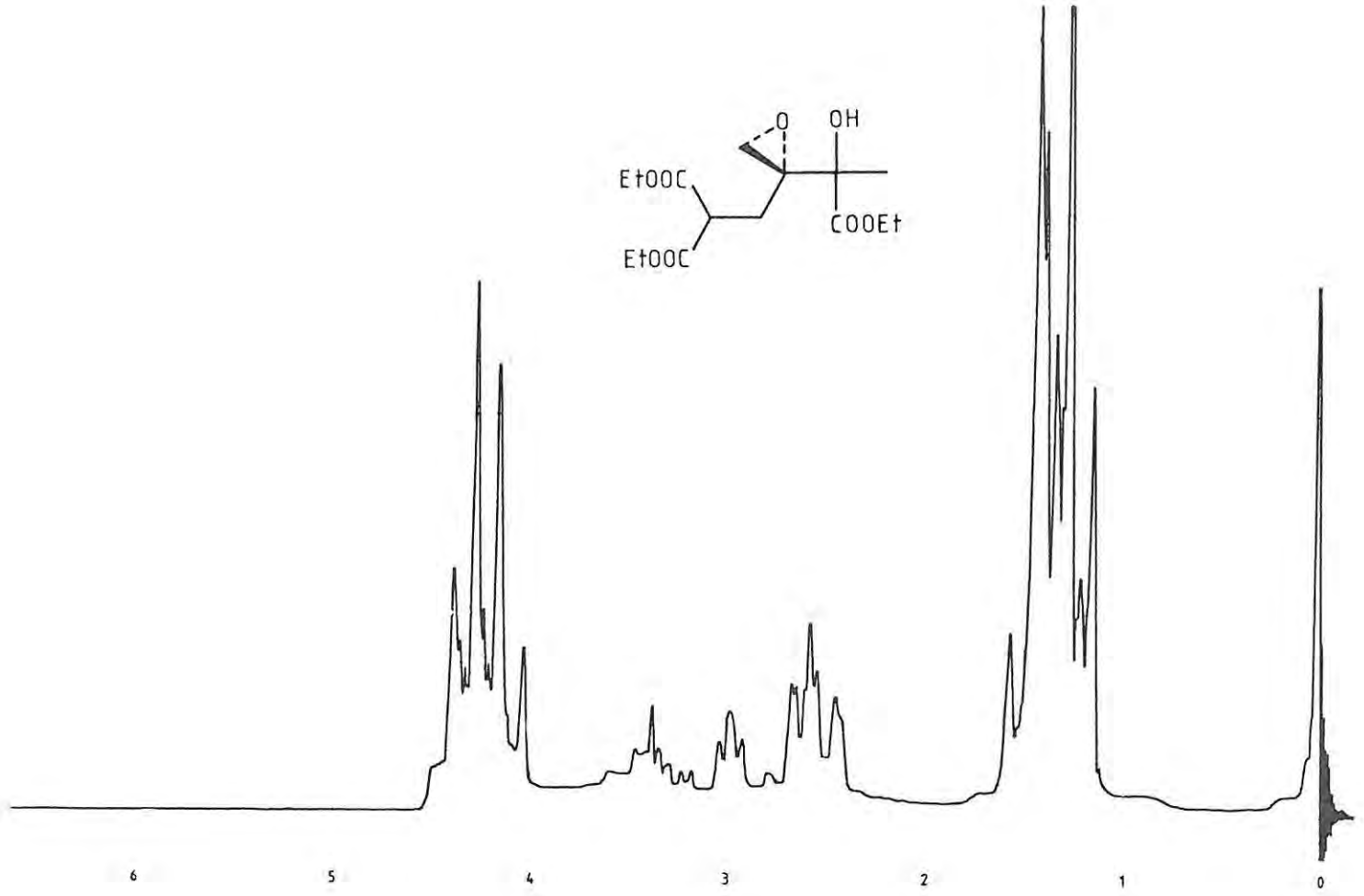
Scheme 95.

Encouraged by this result, the reaction was tried on the triester (493), [Scheme 96]. The reaction was, however, run at reflux rather than at room temperature as previously. After five hours at reflux the green colour reappeared and the reaction was worked up. Vacuum distillation of the crude gave the required epoxy-triester (549) as an oil (74% yield), identified by NMR spectroscopy (p 208).



(493) (549)

Scheme 96.



NMR 10: Diethyl 5-carboethoxy-3-epoxymethylene-2-hydroxy-2-methyl-hexanedioate (549)

Unlike the titanium-catalysed reaction, where the stereochemistry of the product could be controlled by changing the tartrate enantiomer employed,[299] the vanadium-catalysed reaction is not controllable, but usually provides the erythro isomer.[298] Fortuitously, this is the same configuration sought for the epoxy-ester (549), and it was therefore anticipated that the vanadium-catalysed reaction had provided the desired diasteriomer as the major product. This would only be confirmed once the spirodilactone (485) (p 143) was obtained and compared against the authentic material, for which the configuration was known unambiguously.[232,233]

In order to cover the possibility of the incorrect isomer being obtained from the above reaction, the use of m-chloroperbenzoic acid as the epoxidising agent was investigated. The major product with this reagent is usually the threo isomer,[304] although the stereoselectivity is generally not as good as that obtained from the vanadium catalysed reactions, and in some cases negligible.[298]

Excess m-chloroperbenzoic acid in dichloromethane and the triester (493) were stirred together overnight at room temperature. Unreacted peroxide was destroyed by the addition of aqueous sodium sulphite, and the reaction worked up to provide the epoxy ester (549), identical by NMR to that obtained previously. The specific rotation of (549) from this reaction was 0,00°, and therefore, disappointingly, no stereoselectivity had occurred.

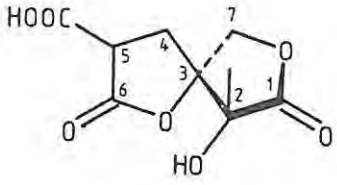
With the epoxy ester (549) to hand, efforts were now made to obtain the spirodilactone (551) (Cf. Scheme 89, p 197). It was anticipated that hydrolysis of (549) would provide the triacid (550), (or the ring opened equivalent), which was expected to spontaneously cyclise to the dilactone (551), in imitation of the formation of swazinecic acid dilactone (485), itself obtained by hydrolysis of swazine (484).[234]

Accordingly the epoxy triester (549) and dilute hydrochloric acid were stirred together at room temperature for two days. The reaction mixture was continously extracted with ether for twenty-four hours, and the solvent removed to provide a very small amount of clear gum. Examination of the gum by NMR revealed, however, that the gum was largely recovered epoxy triester (549), but with the presence of a strong broad peak at δ5,9 ppm and a sharp singlet at δ3,97 ppm.

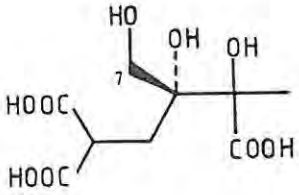
The reaction was repeated, and then carefully neutralised before being freeze-dried, and the solid residue so obtained continously extracted with ether for two days. Once again, however, only trace amounts of material was obtained, which could not be identified.

While acidic hydrolysis had not proved successful it was possible that basic hydrolysis would provide the dilactone (551) more readily. Therefore the epoxy triester (549) and dilute sodium hydroxide were stirred together at room temperature overnight. The reaction mixture was washed with ether to remove any unreacted triester, then acidified and continously extracted with ether to provide a gum in low yield. Over a period of days, the gum crystallised into fine

needles which sublimed very readily (over several weeks very long hair-like crystals were obtained in the sample vial). Testing with aqueous sodium carbonate showed the material to be acidic. The NMR spectrum (run in hexadeutero-acetone) showed a very strong hydroxyl peak at 6,34 ppm, indicative of a hydroxyacid, and a singlet methyl peak at 1.40 ppm. Other signals visible were a singlet at 4,56 ppm, and complex multiplets at 2,7 ppm and 4,05 ppm.



(551)



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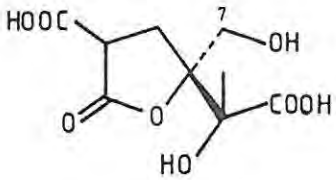


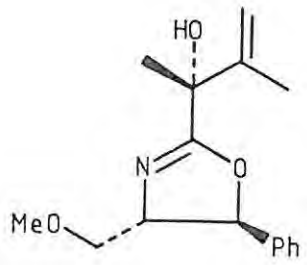
(562)

The NMR data suggested that the material was the trihydroxy-triacid (561) or, more likely, the monolactone (562) rather than the dilactone (551), since the signal at 4,56 ppm was a singlet and not the double doublet expected for the protons on C_7. This is in accordance with the earlier finding that the two rings of swazinecic acid dilactone are of different stability.[234]

Repeating the reaction at reflux, and on a larger scale gave a similar product, and did not result in improved recovery of the material. Attempts to examine the available crystalline material by single crystal X-ray crystallography failed due to the rapid sublimation of the mounted crystal.

The synthesis of the epoxy triester and its hydrolysis product(s) (of uncertain structure) thus concludes the

present contribution to the synthesis of swazinecic acid dilactone. While an asymmetric synthesis of the two chiral centres in (549) is now possible by application of the oxazoline chemistry leading to structure (541), coupled with the chain elaboration and subsequent vanadium-catalysed epoxidation, the precise degree of enantioselectivity achieved at both centres remains uncertain. The major problem thus remains that of a clear-cut and straight forward enantioselective synthesis of the chiral centres present in swazinecic acid dilactone (485).



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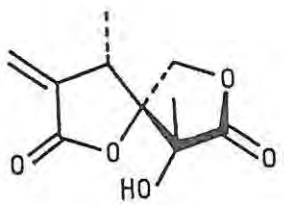


(485)

4. EXPERIMENTAL.

4.1. General methods.

All glassware used in organometallic reactions was thoroughly cleaned and dried at 120°C. Apparatus was assembled at this temperature and allowed to cool under a stream of dry nitrogen (high-purity grade). For reactions involving alkyl lithium reagents, the reaction vessels were additionally flamed while being evacuated, and then allowed to cool under a stream of nitrogen.

Diethyl ether, tetrahydrofuran and hexane were refluxed for several hours over calcium hydride, followed by distillation, under dry nitrogen, from lithium aluminium hydride, just prior to use. Dichloromethane was predried over calcium chloride, and distilled from calcium hydride prior to use.

All dry solvents and air-sensitive materials were transferred by hypodermic syringes or hypodermic tubing according to known methods.[305]

Solutions of butyl lithium were standardised at room temperature according to the procedure of Watson and Eastham, using 1,10-phenanthrolene or 2,2-bipyridyl indicators.[306]

Sodium hydride (50% or 80% dispersion in oil) was washed free of oil with small portions of dry hexane, and the supernatant hexane layer removed by means of a pipette.

Diisopropylamine was distilled from calcium hydride (B.pt = 84°C) and stored over 4A molecular sieve under a nitrogen atmosphere.

Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 180 spectrometer or on a Pye-Unicam SP3-100 spectrometer. Proton NMR spectra were recorded at 60 MHz on a Perkin-Elmer R12A spectrometer unless stated otherwise, and spectra were run in deuterochloroform or in hexadeutero-acetone with tetramethylsilane as internal standard.

4.2. (2'R,1S,2S)- and (2'S,1S,2S)-N(2-Bromopropanoyl)-2-amino-1-phenylpropane-1,3-diols (513)

Ethyl 2-bromopropanoate (5 g, 25 mmol), (1S,2S)-2-amino-1-phenylpropane-1,3-diol (8,0 g, 48 mmol), and a few drops of methanol were allowed to stand at room temperature for 5 days.[257] The volatile components were then removed under reduced prssure, and the residue partitioned between ethyl acetate and 2M hydrochloric acid. The organic phase was washed with water, dried ($MgSO_4$), filtered, and evaporated to provide a diastereomeric mixture of the bromoamides (513) (2,53 g, 57%) as a clear gum which crystallised on standing (several weeks). Separation and purification by flash chromatography,[262] (SiO_2, ethyl acetate), and crystallisation of the separated isomers from hexane-ethyl acetate gave the (2'S,1S,2S)-isomer as colourless needles, Mp. 81-82°C; $[\alpha]_D^{25}$ +3,5° (c 1,96, ethanol); IR (KBr) 3545, 3420, 3300, 3065, 3030, 1650, 1548, 1030, 760 and 695 cm^{-1}; ^1H NMR 60MHz, p158 (mixture of isomers,), (90MHz, δppm): 1,66 (3H, d, J = 7 Hz, CH_3), 2,89 (2H, br s, 2 x OH), 3,82 (2H, d, J = 4,2 Hz, CH_2OH), 3,95-4,27 (1H, m, CHN),4,37 (1H, q, J = 7 Hz, CHBr),

5,1 (1H, d, J = 3,6 Hz, PhCHOH), 7,08 (1H, br d, NH) and 7,34 (5H, s, ArH); Anal. calc. for $C_{12}H_{16}BrNO_3$: C, 47,7; H, 5,34; Br, 26,45; N, 4,64%. Found: C, 45,14; H, 5,16; Br, 26,63; N, 4,40%, and the (2'R,1S,2S)-isomer as colourless needles, Mp. 97-97,5°C; $[\alpha]_D^{25}$ -7,1° (c 0,82, ethanol); IR (KBr) 3520, 3405, 3290, 3070, 3035, 1655, 1555, 1065, 750 and 700 cm^{-1}; ^1H NMR (90MHz, δppm): 1,75 (3H, d, J = 7 Hz, CH_3), 3,3 (2H, br s, 2 x OH), 3,81 (2H, d, J = 4,2 Hz, CH_2OH), 3,95-4,23 (1H, m, CHN), 4,28 (1H, q, J = 7 Hz, CHBr), 5,07 (1H, d, J = 3,6 Hz, PhCHOH), 7,07 (1H, br d, NH) and 7,32 (5H, s, ArH); Anal. found: C, 47,49; H, 4,88; Br, 26,53; N, 4,70%. Details pertaining to the X-ray structural analysis are given in appendix 1.

4.3. (2'S,5S,6S)-N(2-Bromopropanoyl)-5-amino-6-phenyl-2-oxo-1,3,2-dioxathiane (521)

(2'S,1S,2S)-N(2-Bromopropanoyl)-2-amino-1-phenylpropane-1,3-diol (513) (578 mg, 1,92 mmol) in dry dichloromethane (5,0 ml) was stirred at 0°C, and a solution of freshly distilled thionyl chloride (0,4 ml, 5,5 mmol) in dry dichloromethane (2 ml) added dropwise. The reaction was stirred at 0°C for 30 min., and then a further 1h at room temperature. The volatiles were removed under reduced pressure and the residue purified by flash chromatography[262] to afford colourless crystals (125,2 mg), Mp. 164-167°C; IR (KBr) 3250, 3030, 1695, 1530, 1450, 1165, 1020, 928, 808, 740 and 700 cm^{-1}; ^1H NMR (p166, δppm): 1,72 (3H, d, J = 7 Hz, CH_3), 4,06 (1H, dd, J = 12 and 2 Hz, CH_2O), 4,2 (1H, q,

J = 7 Hz, CHBr), 4,25-4,55 (1H, m, CHN), 5,35 (1H, dd, J = 12 and 2 Hz, CH_2O), 6,35 (1H, d, J = 1,8 Hz, PhCHOH), 7,1 (1H, br d, NH), 7,37 (5H, s, ArH); Anal. calc. for $C_{12}H_{14}BrNO_4S$: C, 41,39; H, 4,05; Br, 22,95; N, 4,02; S, 9,21%. Found: C, 41,66; H, 4,07; Br, 22,18; N, 4,07; S, 9,09%. Details pertaining to the X-ray analysis are given in appendix 1.

4.4. Tetrabromomethane

Aqueous 5M sodium hydroxide (50 ml, 250mmol) was cooled in a salt/ice bath to 0°C, and bromine added dropwise to the vigorously stirred solution, while maintaining the temperature, until crystallisation occurred. Bromoform (25 ml, 74,5 g, 290 mmol) was added dropwise and the reaction allowed to warm to room temperature and stirred a further 3h before allowing to stand overnight. The organic layer was separated, washed with water, dried (Na_2CO_3), filtered, and solvent evaporated under reduced pressure to afford crude tetrabromomethane which was recrystallised from ethanol to give off-white crystals (3,89 g) which were pure by TLC, Mp. 80°C (with sublimation), (Lit.[307] Mp. 90°C).

4.5. (4S,5S)-2-(1-Bromoethyl)-4-methoxymethyl-5-phenyl-2-oxazoline (527)

n-Butyl lithium (1,6M solution in hexane, 7,0 ml, 11,2 mmol) was transferred via gas-tight syringe into a flame-dried flask fitted with a rubber septum and purged with nitrogen.

This was cooled to -80°C before adding dry tetrahydrofuran (25 ml). Previously prepared[255] (4S,5S)-2-ethyl-4-methoxymethyl-5-phenyl-2-oxazoline (2,19 g, 1,95 ml, 10.0 mmol) was added dropwise with vigorous stirring to give a yellow solution of the oxazoline anion. The mixture was stirred for 1h at this temperature to allow complete anion formation.

Dry tetrahydrofuran (50 ml) was transferred to a second, flame-dried, nitrogen purged, flask fitted with a rubber septum, and, WORKING IN THE DARK,[282] bromine (1,84 g, 575 l, 11,5 mmol) added at room temperature and then rapidly cooled to -80°C. Without delay, the oxazoline anion solution was added dropwise, via double-ended needle, to the stirred bromine solution. The reaction was allowed to come to room temperature overnight, then quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. The organic layer was washed with water, dried ($MgSO_4$), filtered and the solvents removed under reduced pressure to afford a sweet-smelling yellow oil (2,86 g, 95% pure by GLC and NMR) as a mixture of diastereoisomers, which was further purified (with considerable losses) by flash chromatography[262] (SiO_2, CH_2Cl_2). The pure material was stable for 1-2 days at room temperature, but could be stored for approximately 2 weeks at 4°C. IR (neat) 3065, 3030, 1660, 1495, 1450, 1125 and 700 cm^{-1}; ^1H NMR (p175, δppm): 1,94, 1,96 (3H, dd, J = 7 Hz, CH_3CHBr), 3,4 (3H, s, OCH_3), 3,6 (2H, m, OCH_2), 4,2 (1H, m, C=N-CH), 4,7, 4,75 (1H, dq, J = 7 Hz, CHBr), 5,46 (1H, d, J = 6,5 Hz, O-CH-Ph), 7,4 (5H, s, ArH); ^{13}C NMR (125MHz, δppm): 22,41, 22,5 (CH_3), 36,3, 36,6 (CH-Br), 59,2 (CH_3O),

73,7 (CH_2O), 74,5 (CH-N), 84,01 (CH-O), 125,3, 128,1, 128,6 (aromatic C), 140,3 (quat. aromatic C), 166,6 (C=N); mass spectrum: m/z (Rel. Abun.) 299/297 (21), 254/252 (66), 218 (73), 154/152 (53), 146 (76), 112 (100); Anal. calc. for $C_{13}H_{16}BrNO_2$: C, 52,4; H, 5,37; Br, 26,85; N, 4,69. Found: C, 51,77; H, 5,61; Br, 32,53; N, 4,63. Preparative TLC (SiO_2, hexane/ether, 3/2) of an aliquot gave predominately the (1'R,4S,5S)-isomer, (90% diastereomeric excess by ^1H NMR), δppm 1,96 (3H, d, J = 7Hz, CH_3CHBr), 3,4 (3H, s, OCH_3), 3,6 (2H, m, OCH_2), 4,2 (1H, m, C=N-CH), 4,70 (1H, q, J = 7 Hz, CH-Br), 5,46 (1H, d, J = 6,5 Hz, O-CH-Ph), 7,4 (5H, s, ArH); specific rotation $[\alpha]_D^{24}$ = -25,85° (c 0,53, $CHCl_3$).

4.6. (4S,5S)-2-(1-Iodoethyl)-4-methoxymethyl-5-phenyl-2-oxazoline (528)

This was prepared in a similar manner to the bromo analog (527) described above, but in reduced quantities. Thus starting oxazoline (524) (438 mg, 2,0 mmol) was added dropwise under nitrogen to a stirred mixture of n-butyl lithium (1,45M solution in hexane, 1,45 ml, 2,1 mmol) and dry tetrahydrofuran (10 ml) at -80°C. The deep yellow solution obtained was stirred at temperature for 1h before being added dropwise via double-ended needle to a stirred solution of iodine (508 mg, 2,0 mmol) in dry tetrahydrofuran (20 ml) at -80°C. After 30 min the reaction was quenched by decanting into water (100 ml) containing a crystal of sodium thiosulphate and extracted with dichloromethane. Further work-up and purification as before gave a yellow oil (408 mg,

59%) as a diastereomeric mixture, IR (neat) 3065, 3030, 1655, 1495, 1450, 1200, 1125 and 700 cm^{-1}; ^1H NMR (δppm): 2,09, 2,12 (3H, dd, J = 7 Hz, CH_3CHI), 3,4 (3H, s, OCH_3), 3,6 (2H, m, OCH_2), 4,2 (1H, m, CH-N), 4,77, 4,83 (1H, dq, J = 7 Hz, CH-I), 5,43 (1H, d, J = 6,5 Hz, O-CH-Ph), 7,38 (5H, s, ArH).

4.7. (4S,5S)-2-[(1R)-1,2-Epoxy-1,2-dimethylpropyl]-4-methoxymethyl-5-phenyl-2-oxazoline (510)

a. From (527): n-Butyl lithium (1,6M solution in hexane, 1,4 ml, 2,24 mmol) was added dropwise with stirring to dry diisopropylamine (230 mg, 2,28 mmol) at -80°C in a nitrogen purged flame-dried flask. The flask was brought to room temperature for 5 min, then recooled to -80°C. Dry tetrahydrofuran (10 ml) was added, followed dropwise by a solution of the bromo-oxazoline (527) (585 mg, 1,96 mmol) in dry tetrahydrofuran (5 ml). The deep red-brown solution of the lithio bromo-oxazoline so formed was stirred 10 min at this temperature, then dry acetone (0,5 ml) added rapidly. The reaction was stirred at -80°C for a further 25 min, and then allowed to warm to room temperature to allow cyclisation to the epoxide to occur.[285] The reaction was worked up by decanting into saturated aqueous ammonium chloride and extracted with dichloromethane. The organic layer was washed with water, dried ($MgSO_4$), filtered and solvents removed under reduced pressure to afford a yellow-brown oil. Purification by preparative TLC (SiO_2, ethyl acetate) gave pure epoxyoxazoline (510) as a light yellow oil (415 mg,

77%), IR (neat) 3065, 3030, 1670, 1495, 1450, 1125, 1100 and 700 cm^{-1}; ^1H NMR (p183, δ ppm): 1,35 and 1,40 (6H, 2 x s, $C(CH_3)_2$), 1,63 (3H, s, $N=C-C(CH_3)-O$), 3,4 (3H, s, OCH_3), 3,6 (2H, m, $O-CH_2$), 4,2 (1H, m, C=N-CH), 5,46 (1H, d, O-CH), 7,4 (5H, s, ArH); mass spectrum: m/z (rel. abund.%) 275 (43), 229 (48), 201 (25), 171 (55), 159 (77), 149 (100), 131 (70); $[\alpha]_D^{24}$ = -46,4° (c 0,85, $CHCl_3$).

b. From (528): Use of the iodo-oxazoline (528) (660 mg, 1,92 mmol) in place of the bromo-oxazoline (527) in the above procedure afforded the epoxyoxazoline (510) in reduced yield (322 mg, 61%).

c. From (524) via (527) in a one-pot procedure: Dry tetrahydrofuran (40 ml) was added to n-butyl lithium (1,50M solution in hexane, 9,34 ml, 14,0 mmol) in a flame-dried, nitrogen purged flask at -80°C, followed by dropwise addition, with stirring, of 2-ethyl-4-methoxymethyl-5-phenyl-2-oxazoline (524) (2,53 g, 11,56 mmol). After stirring for 45 min at -80°C the yellow lithio-oxazoline solution was added dropwise via double-ended needle to a stirred solution of bromine (2,32 g, 14,5 mmol) in dry tetrahydrofuran (40 ml) (the bromine solution was mixed and rapidly cooled to -80°C in the dark immediately prior to use). After a further 30 min the solution of the intermediate bromo-oxazoline (527) so formed was added dropwise, via double ended needle, to a stirred solution of lithium diisopropylamide (18,0 mmol, made by adding n-butyl lithium (1,5M in hexane, 12,0 ml, 18,0 mmol) to diisopropylamine (2,53 ml, 18,1 mmol) in tetrahydrofuran (20

ml)) at -80°C. The deep red-brown solution of the lithio anion so formed was in turn added to well stirred dry acetone (1,5 ml, 20,4 mmol) at -80° via double-ended needle and the reaction mixture allowed to warm to room temperature overnight. Workup as before provided the epoxyoxazoline (510) (2,73 g, 86%).

4.8. (1'R,4S,5S)-2-(1-Hydroxy-1,2-dimethyl-2-propenyl)-4-methoxymethyl-5-phenyl-2-oxazoline (541)

(1'R,4S,5S)-2-(1,2-Epoxy-1,2-dimethylpropyl)-4-methoxymethyl-5-phenyl-2-oxazoline (510) (202 mg, 0,73 mmol) and 4-toluenesulphonic acid (75 mg, 0,43 mmol) were refluxed together in dry benzene (5 ml) for 12h. The reaction was cooled, and benzene removed under reduced pressure. The was residue taken up in a mixture of dichloromethane (5 ml) and water (2 ml), and carefully neutralised to pH7 by addition of solid sodium carbonate. The organic layer was separated, dried ($MgSO_4$), filtered and solvent removed under reduced pressure to provide the crude product which was purified by TLC (SiO_2, ethyl acetate) to afford pure (541) (184 mg, 91%), ^1H NMR (p189, δppm): 1,67 (3H, s, CH_3-C-O), 1,88 (3H, s, CH_3-C=C), 3,43 (3H, s, O-CH_3), 3,65 (2H, m, O-CH_2), 4,20 (1H, m, CH-N=C), 5,05 and 5,26 (2H, C=CH_2), 5,49 (1H, d, J = 8 Hz, O-CH-Ph), 7,39 (5H, s, ArH).

4.9. 2-Hydroxy-2,3-dimethyl-3-butenoic acid (491)

(1'R,4S,5S)-2-(1-Hydroxy-1,2-dimethyl-2-propenyl)-4-methoxymethyl-5-phenyl-2-oxazoline (541) (179 mg, 0,65 mmol) was

refluxed with 2M hydrocloric acid (5 ml) for 1h, by which time the mixture was homogeneous. The reaction cooled, and made basic by cautious addition of solid sodium carbonate before being extracted with ether (discarded). The aqueous phase was reacidified by cautious dropwise addition of concentrated hydrochloric acid, and then continously extracted with ether for 18h. The ethereal extracts were dried ($MgSO_4$), filtered and solvent removed under reduced pressure to provide (**491**) (20 mg, 24%) as a clear gum which crystallised on standing, Mp. 88-89°, $[\alpha]_D^{25,5}$ -0,5° (c 1,00, EtOH) (Lit.[244] Mp. racemate 87-88°, R-isomer 93-94°, $[\alpha]_D$ -18,2° (R-isomer, c 1,05, EtOH)); ^1H NMR (δppm): 1,60 (3H, s, CH_3-C-O), 1,85 (3H, br s, CH_3-C=C), 5,05 and 5,25 (2H, apparent singlets, CH_2=C), 7,15 (2H, br s, 2 x OH).

4.10. Ethyl 2,3-dimethyl-2-O-tert-butyldimethylsilyl-3-butenoate (546)

Ethyl 2-hydroxy-2,3-dimethyl-3-butenoate (**487**) (7,90 g, 50 mmol) in dry tetrahydrofuran (20 ml) was added dropwise at room temperature, under nitrogen, to a stirred slurry of sodium hydride (80% dispersion in oil, 1,59 g, 53 mmol) in dry tetrahydrofuran (20 ml). Stirring was continued for 30 min after evolution of hydrogen had ceased, then a solution of tert-butyldimethylsilyl chloride (8,0 g, 53 mmol) in dry tetrahydrofuran (30 ml) was added dropwise at room temperature to the vigorously stirred mixture, and stirring continued for a further 2h. The reaction was decanted into water (50 ml), acidified to pH7 and extracted with

dichloromethane (3 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered, and solvent removed under reduced pressure. The crude product so obtained was vacuum distilled to afford pure (**546**) (7,33 g, 54%), Bpt. 82-84°C at 0,2 mm Hg, ^1H NMR (p193, δppm): 0,07, 0,10 (6H, 2 x s, 2 x Si-CH_3), 0,90 (9H, s, Si-$C(CH_3)_3$), 1,25 (3H, t, J = 7 Hz, O-CH_2-CH_3), 1,55 (3H, s, O-C-CH_3), 1,75 (3H, s, C=C-CH_3), 4,17 (2H, q, J = 7 Hz, COO-CH_2-CH_3), 4,95 and 5,18 (2H, 2x m, C=CH_2).

4.11. Ethyl 3-bromomethyl-2-methyl-2-O-tert-butyldimethylsilyl-3-butenoate (547)

Ethyl 2,3-dimethyl-2-O-tert-butyldimethylsilyl-3-butenoate (**546**) (13,6 g, 50 mmol) and N-bromosuccinimide (9,75 g, 55 mmol) in tetrachloromethane (150 ml) were refluxed together in bright sunlight for 2½h. The mixture was cooled to 0°C, filtered to remove succinimides, and the residual solution purified by passage through a short silica gel column, eluting with chloroform. Removal of solvents under reduced pressure gave a pale oil (16,48 g, 94%) which was used immediately without further purification. ^1H NMR (δppm): 0,07, 0,10 (6H, 2 x s, 2 x Si-CH_3), 0,90 (9H, s, Si-$C(CH_3)_3$), 1,25 (3H,t, J = 7 Hz, O-CH_2-CH_3), 1,64 (3H, s, O-C-CH_3), 4,07 (2H, s, C=C-CH_2-Br), 4,15 (2H, q, J = 7 Hz, COO-CH_2-CH_3), 5,43 (2H, s, C=CH_2).

4.12. Diethyl 5-carboethoxy-2-methyl-3-methylene-2-O-tert-butyldimethylsilylhexanedioate (548)

Diethyl malonate (7,48 g, 46,7 mmol) in dry tetrahydrofuran (20 ml) was added dropwise, under nitrogen, to a stirred slurry of sodium hydride (80% dispersion in oil, 1,40 g, 46,7 mmol) in dry tetrahydrofuran (50 ml). The mixture was stirred until homogeneous (30 min), then ethyl 3-bromomethyl-2-methyl-2-O-tert-butyldimethylsilyl-3-butenoate (547) (16,4 g, 46,7 mmol) in dry tetrahydrofuran (25 ml) added dropwise, and the whole refluxed for 8h. The reaction was cooled, decanted into water (100 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with water, dried (Na_2CO_3), filtered and solvents removed under reduced pressure. The orange liquid so obtained was vacuum distilled to afford a pale liquid (19,5 g, 97%) pure by NMR and TLC. Bpt.142-146°C at 0,5 mm Hg; ^1H NMR (p194, δ ppm): 0,07, 0,13 (6H, 2 x s, 2 x Si-CH_3), 0,90 (9H, s, Si-C(CH_3)$_3$), 1,25 (9H, overlapping triplets, J = 7 Hz, 3 x COO-CH_2-CH_3), 1,56 (3H, s, O-C-CH_3), 2,65 (2H, d, J = 8 Hz, CH-CH_2-C=CH_2), 3,58 (1H, t, J = 8 Hz, CH-CH_2), 4,16 (6H, q, J = 7 Hz, COO-CH_2-CH_3), 4,99 and 5,23 (2H, 2x m, C=CH_2).

4.13. Diethyl 5-carboethoxy-2-hydroxy-2-methyl-3-methylene-hexanedioate (493)

a. Diethyl 5-carboethoxy-2-methyl-3-methylene-2-O-tert-butyldimethylsilylhexanedioate (548) (860 mg, 2,0 mmol) was added, at room temperature to a stirred slurry of tetra-n-

butylammonium chloride (85%, 660 mg, 2,0 mmol) and potasssium fluoride dihydrate (600 mg, 6,4 mmol) in dry acetonitrile (20 ml), and the resulting mixture refluxed for 18h. The reaction was cooled, decanted into 10% aqueous sodium carbonate, and extracted with ether (3 x 20 ml). The ethereal extracts were washed with 2M hydrochloric acid, then water, before being dried ($MgSO_4$) and filtered. The volatiles were removed under reduced pressure, and the residues purified by TLC to provide diethyl 5-carboethoxy-2-hydroxy-2-methyl-3-methylenehexanedioate (493) (566 mg, 89%) as a pale oil, ^1H NMR (60MHz p196, 500MHz, δ ppm): 1,22, 1,23, 1,27 (9H, 3 x t, J = 7 Hz, 3 x $O-CH_2-CH_3$), 1,52 (3H, s, $O-C-CH_3$), 2,68 (2H, m, $CH-CH_2-C=CH_2$), 3,5 (1H, br s, OH), 3,67 (1H, t, J = 7,7 Hz, $CH-CH_2$), 4,14, 4,15, 4,22 (6H, 3 x q, J = 7 Hz, $COO-CH_2-CH_3$), 4,97, 5,23 (2H, $C=CH_2$); ^{13}C NMR (125MHz, δ ppm): 14,0 (3 x $O-CH_2-CH_3$), 24,7 ($O-C-CH_3$), 30,5 ($CH_2-C=CH_2$), 51,1 (CH), 61,33, 61,33, 61,42 (3 x $O-CH_2$), 113,0 ($C=CH_2$), 136,8 (quat C), 146,5 ($C=CH_2$), 168,93, 168,96, 175,27 (3 x C=O).

b. The silyl triester (548) 6,15 g, 14,3 mmol) in dry dichloromethane (10 ml) was added dropwise, under nitrogen and at room temperature, to a stirred solution of boron trifuoride etherate (1,94 g, 15,0 mmol) in dry dichloro-methane (10 ml). The reaction was stirred for 14h, then quenched by addition of 5% aqueous sodium carbonate (30 ml) and stirred vigorously until gas evolution had ceased. The organic layer was separated, the aqueous phase washed once with dichloromethane and the combined organic layers dried

(Na_2CO_3), filtered and evaporated to provide a yellow oil which was further purified by vacuum distillation to afford pure (493) (4,20 g, 93%), Bpt 115°C at 0,05 mm Hg.

4.14. Ethyl 2,3-epoxy-3-methylbutanoate (556)

Ethyl bromoethanoate (16,7 g, 0,10 mol) and dry acetone (5,8 g, 7,4 ml, 0,10 mol) in dry tetrahydrofuran (10 ml) were cooled to -10°C under a nitrogen atmosphere, and a solution of potassium tert-butoxide (11,2 g, 0,10 mol) in dry tetrahydrofuran (60 ml) added slowly with vigorous stirring. On completion of addition the reaction was allowed to warm to room temperature and stirred overnight. Saturated aqueous ammonium chloride was added and the mixture extracted with ether. The organic extracts were dried (Na_2CO_3), filtered and volatiles evaporated to provide a reddish-brown liquid which was distilled under reduced pressure to afford pure (556) as a clear liquid (6,31 g, 44%), Bpt 77-80°C at 16 mm Hg (Lit.[308] 87-89,5°C at 30 mm Hg); ^1H NMR (δppm): 1,30 (3H, t, J = 7 Hz, $O-CH_2-CH_3$), 1,37, 1,42 (6H, 2 x s, 2 x CH_3), 3,35 (1H, s, CH), 4,30 (2H, q, J = 7 Hz, $COO-CH_2-CH_3$).

4.15. Ethyl 2-hydroxy-3-methyl-3-butenoate (557)

Ethyl 2,3-epoxy-3-methylbutanoate (556) (6,3 g, 43,7 mmol) in dry benzene (10 ml) was added dropwise to a stirred suspension of lithium perchlorate (0,5 g) in dry benzene (10 ml) at room temperature. The mixture was stirred for 1h,

then refluxed overnight before being cooled, decanted into water (20 ml), and extracted with dichloromethane. The organic extracts were washed with water, dried ($MgSO_4$), filtered and solvents evaporated. The crude material was purified by flash chromatography[262] and distillation under reduced pressure to afford a colourless liquid (1,96 g, 31%), bpt 72-75°C at 14 mm Hg; ^1H NMR (δppm): 1,30 (3H, t, J = 7 Hz, $O-CH_2-CH_3$), 1,78 (3H, s, $C=C-CH_3$), 3,32 (1H, br s, OH), 4,31 (2H, q, J = 7 Hz, $COO-CH_2-CH_3$), 5,08 and 5,20 (2H, 2x m, $C=CH_2$).

4.16. Ethyl 3,4-epoxy-2-hydroxy-3-methylbutanoate (558)

Using a hypodermic syringe and needle, titanium tetra-isopropoxide (0,59 ml, 2,0 mmol) followed by L-(+)-diethyl tartrate (0,4 ml, 2,28 mmol) was added, with stirring, to dry dichloromethane (30 ml) contained in a flame-dried, nitrogen purged flask at -20°C. After stirring for 5 min at this temperature, ethyl 2-hydroxy-3-methyl-3-butenoate (557) (230 mg, 1,60 mmol) was added to the mixture, followed by tert-butyl hydroperoxide[298] (3,08M in dichloromethane, 1,30 ml, 4,0 mmol) and the reaction stored at -23°C for 21 days. The reaction was quenched by addition of 10% aqueous (+)-tartaric acid (5 ml) to the stirred mixture at -25°C. After 30 min the flask was allowed to warm to room temperature and stirred a further 1h. The organic phase was separated, washed once with 10% aqueous sodium sulphite, then once with water, dried ($MgSO_4$), and volatiles removed under reduced pressure. The residues were dissolved in ether

(15 ml), cooled to 0°C, and stirred with 1N sodium hydroxide (6 ml) for 30 min (to decompose the diethyl tartrate). The ethereal layer was separated, washed once with saturated aqueous sodium chloride, dried ($MgSO_4$) and solvent evaporated to afford a clear oil (28 mg), ^1H NMR (δppm): 1,36 (3H, t, J = 7 Hz, $O-CH_2-CH_3$), 1,40 (3H,s, CH_3-C), 2,69, 2,92 (2H, 2 x d, epoxy CH_2), 3,7 (1H, br s, OH), 4,0 (1H, s, CH-OH), 4,36 (2H, q, J = 7 Hz, $COO-CH_2-CH_3$).

4.17. Ethyl 2,3-dimethyl-3,4-epoxy-2-hydroxybutanoate (555)

Vanadyl acetoacetonate (52,3 mg, 0,2 mmol) was added at room temperature to a stirred solution of ethyl 2,3-dimethyl-2-hydroxy-3-butenoate (**487**) (843 mg, 5,85 mmol) in dry benzene (10 ml) under nitrogen. On addition of tert-butyl hydroperoxide[298] (3,08M in dichloromethane, 2,0 ml, 6,16 mmol) the initially dark green solution turned a deep red colour. The reaction was stirred at room temperature, under nitrogen, for seven days, during which time the colour changed from red to yellow and then to light green. The mixture was shaken with 10% aqueous sodium sulphite (to remove excess peroxide), and the organic phase was separated, washed with water, dried ($MgSO_4$), filtered, and solvents removed under reduced pressure. The residue so obtained was vacuum distilled to provide pure epoxide (555) as a clear liquid (488 mg, 52%), bpt 61°C at 0,75 mm Hg; ^1H NMR (p206, δ ppm): 1,33 (3H,t, J = 7 Hz, $O-CH_2-CH_3$), 1,37 1,43 (6H, 2 x s, 2 x $C-CH_3$), 2,56 (1H, d, J = 5 Hz, epoxy CH), 3,03 (1H, d, J = 5 Hz, epoxy CH), 3,38 (1H, br s, OH), 4,33 (2H, q, J = 7 Hz, $COO-CH_2-CH_3$).

4.18. Diethyl 5-carboethoxy-3-epoxymethylene-2-hydroxy-2-methylhexanedioate (549)

a. Vanadyl acetoacetonate (26,5 mg, 0,1 mmol) was added to a stirred solution of diethyl 5-carboethoxy-2-hydroxy-2-methyl-3-methylene-hexanedioate (**493**) (632 mg, 2,0 mmol) in dry benzene (10 ml) at room temperature, under nitrogen. The bright blue-green solution so formed was heated to reflux and a solution of tert-butyl hydroperoxide[298] (3,08M in dichloromethane, 0,81 ml, 2,5 mmol) added dropwise resulting in the formation of a dark red colour. After refluxing for 5h (during which time the colour changed from red to yellow to green) the reaction was cooled and excess peroxide destroyed by shaking with 10% aqueous sodium sulphite. The organic phase was separated, washed with water, dried ($MgSO_4$), filtered and solvents evaporated to provide essentially pure epoxy triester (**549**) (651 mg, 98%). ^1H NMR (p208, δppm): 1,25, 1,35 (9H, overlapping triplets, J = 7 Hz, $O-CH_2-CH_3$), 1,40 (3H, s, $O-C-CH_3$), 2,5 (2H, dd, J = 8 and 2 Hz, $CH-CH_2-C=CH_2$), 2,62, 2,96 (2H, 2 x d, J = 5 Hz, epoxy CH_2), 3,48 (1H, t, J = 8 Hz, $CH-CH_2$), 3,7 (1H, br s, OH), 4,20 (6H, q, J = 7 Hz, $COO-CH_2-CH_3$).

b. Diethyl 5-carboethoxy-2-hydroxy-2-methyl-3-methylene-hexanedioate (**493**) (1,204 g, 3,81 mmol) and m-chloroperbenzoic acid (85%, 870 mg, 4,29 mmol) in dichloromethane (20 ml) were stirred together at room temperature for 2h. Excess peroxides were destroyed by shaking vigorously with 10% aqueous sodium sulphite (30 ml), and the organic layer

separated, washed with 5% aqueous sodium bicarbonate, then dried ($MgSO_4$) and filtered. Evaporation of solvent gave the crude epoxy-ester (549), which was purified by vacuum distillation (938 mg, 74%). Bpt 125-130°C at 0,35 mm Hg.

5. APPENDICES

5.1 Appendix 1. - Crystallographic data for structures (513) and (521).

Intensity data were collected on a Philips PW 1100 diffractometer using graphite monochromated Cu-K_α radiation. The intensities of three standard reflections, measured every hour, remained constant to within 3% of their mean value. Structure solution by Patterson synthesis, refined by least squares based on F_o; all non-H atoms refined anisotropically, with H atoms at calculated positions refined with common isotropic temperature factors. Both structures were solved with the SHELX 76 program system.[309]

5.1.1 Crystal data and experimental and refinement parameters

crystal data	(513)	(521)
Molecular formula	$C_{12}H_{16}BrNO_3.H_2O$	$C_{12}H_{15}BrNO_4S$
M_r	320,2	348,2
Space group (orthorhombic)	$P2_12_12_1$	$P2_12_12_1$
a/Å	22,124(5)	15,510(5)
b/Å	12,812(5)	9,707(5)
c/Å	4,886(5)	9,457(5)
V/Å^3	1385(2)	1424(2)
Z	4	4
D_x/Mg m^{-3}	1,535(3)	1,624(3)
λ(Cu-K_α)/Å	1,5418	1,5418
μ(Cu-K_α)/mm^{-1}	3,856	5,109
F(000)	656	704

Data collection	(513)	(521)
Crystal dimension/mm	0,2x0,07x0,07	0,1x0,08x0,05
Scan mode	$\omega-2\theta$	$\omega-2\theta$
Scan width/°θ	2	2
Scan speed/°θs^{-1}	0,08	0,08
Range scanned/2θ	12 - 120°	12 - 120°
Number of reflections collected	1260	1270
Number of refections observed	1240 with I>σ(I)	1237 with I>σ(I)
Reflections used: h	0/24	0/18
k	0/14	0/11
l	0/5	0/10
R	0,0525	0,0616
R_w	0,0515	0,0607

5.1.2 Fractional coordinates ($x10^4$) and equivalent isotropic temperature factors ($Å^2 \times 10^3$) for non-H atoms

	x/a	y/b	z/c	U_{eq}/U_{iso}
Structure (513)				
C(1')	-1679(4)	10512(7)	5646(20)	58(5)
C(2')	-1208(3)	10045(6)	7658(17)	45(4)
C(3')	-590(3)	9926(6)	6316(16)	37(4)
C(2)	506(3)	9801(5)	7255(15)	34(4)
C(3)	859(3)	10786(6)	7984(15)	38(4)
C(1)	764(3)	8812(5)	8539(16)	34(3)
C(4)	1411(3)	8583(5)	7738(15)	37(3)
C(5)	1533(3)	7909(6)	5525(18)	48(4)
C(6)	2136(4)	7683(7)	4833(23)	61(5)
C(7)	2601(3)	8147(7)	6176(23)	60(5)
C(8)	2474(4)	8836(7)	8314(21)	82(5)
C(9)	1881(3)	9017(6)	9056(19)	45(4)
N	-127(2)	9939(5)	8077(11)	35(3)
O(1)	-539(2)	9823(5)	3854(11)	57(4)
O(2)	893(2)	10896(4)	10861(12)	44(3)
O(3)	382(2)	7932(4)	7936(11)	47(3)
O(4)	201(3)	12668(5)	12069(11)	55(4)
Br	-1464(0,4)	8634(1)	8695(3)	70(6)

	x/a	y/b	z/c	U_{eq}/U_{iso}
Structure (521)				
C(1')	1749(9)	7973(13)	-2837(10)	83(8)
C(2')	1768(6)	8284(9)	-1249(9)	55(5)
C(3')	1924(5)	6995(9)	-388(8)	46(5)
C(2)	1429(5)	5657(8)	1659(7)	42(4)
C(3)	1290(5)	6066(9)	3199(9)	49(5)
C(1)	731(5)	4591(9)	1222(7)	43(4)
C(4)	764(5)	4196(8)	-333(7)	43(4)
C(5)	1255(6)	3094(8)	-734(9)	52(5)
C(6)	1335(6)	2759(10)	-2172(10)	62(6)
C(7)	917(7)	3524(11)	-3156(9)	68(7)
C(8)	425(6)	4614(11)	-2770(8)	62(6)
C(9)	326(6)	4959(9)	-1345(8)	55(6)
N	1403(4)	6874(6)	775(7)	44(4)
O(1)	424(4)	6628(5)	3411(5)	49(3)
O(2)	-120(3)	5212(6)	1454(5)	49(4)
O(3)	-262(4)	4386(7)	3896(5)	63(4)
O(4)	2454(4)	6137(6)	-709(7)	67(4)
Br	2687(1)	9546(1)	-789(2)	99(10)
S	-363(3)	5625(2)	3055(2)	53(1)

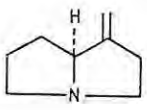
5.1.3 Selected tortion angles for structures (513) and (521)

Atoms	Angle/° (513)	(521)
C(1')-C(2')-C(3')-N	154,5	-135,8
C(1')-C(2')-C(3')-O	-26,0	43,2
Br-C(2')-C(3')-N	-86,9	102,7
Br-C(2')-C(3')-O	92,6	-78,3
C(2')-C(3')-N-C(5)	-	175,82
C(2')-C(3')-N-C(2)	177,77	-
O-C(3')-N-C(5)	-	-3,17
O-C(3')-N-C(2)	-1,73	-
C(3')-N-C(5)-C(6)	-	144,3
C(3')-N-C(2)-C(1)	118,2	-
C(3')-N-C(5)-C(4)	-	-94,5
C(3')-N-C(2)-C(3)	-116,6	-
C(3')-N-C(5)-H(5)	-	23,2
C(3')-N-C(2)-H(2)	0,0	-
O(2)-S-O(1)-C(4)	-	-54,5
O(3)-S-O(1)-C(4)	-	56,6
O(1)-S-O(2)-C(6)	-	56,7
O(3)-S-O(2)-C(6)	-	-55,4
S-O(1)-C(4)-C(5)	-	60,5
S-O(2)-C(6)-C(5)	-	-62,2

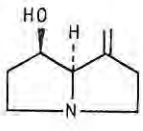
5.2 Appendix 2. - The pyrrolizidine alkaloids

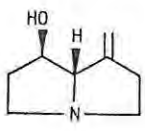
Listed below are the structures and names of the known pyrrolizidine alkaloids as of March 1988, and is an updated version of the listing given by Robins in his review of these alkaloids.[1]

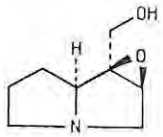
A. Simple pyrrolizidine bases



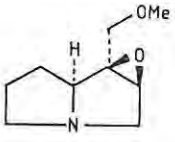
1-Methylenepyrrolizidine



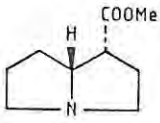




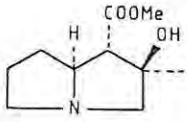
(Ref. 310)



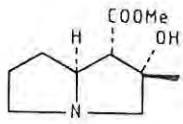
Chysine

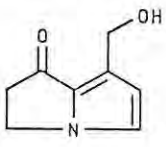


Isotussilagine[45]

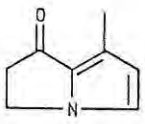


Tussilagine[43,45]

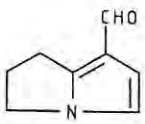




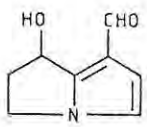
Loroquine



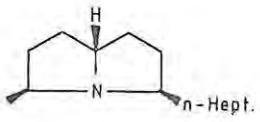
Danaidone[311]



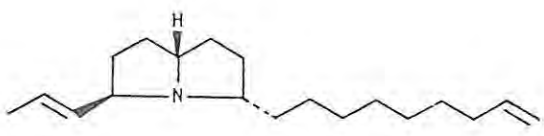
Danaidal



Hydroxydanaidal[27]

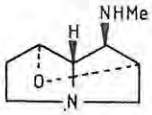


3S,5S,8S-3-Heptyl-5-methyl- pyrrolizidine [30]

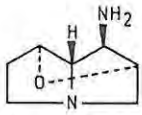


3S,5R,8S-3-(1-non-8-enyl)-5-(E-1-prop-1-enyl)- pyrrolizidine [31]

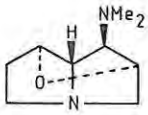
B. Loline Group



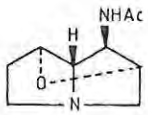
Loline
(Festucine)



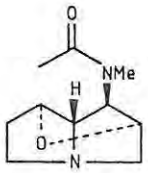
Norloline



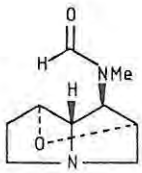
N-Methylloline[312]



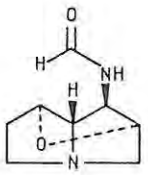
N-Acetylnorloline[312]



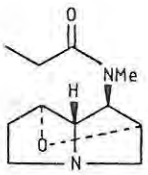
Lolinine



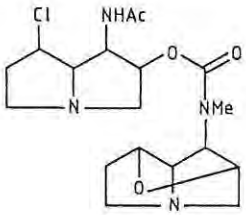
N-Formylloline[312]



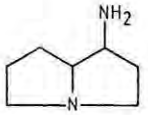
N-Formylnorloline[313]



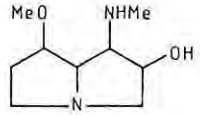
Decorticasine



Lolidine[41]

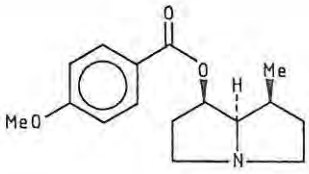


1-Aminopyrrolizidine[10]



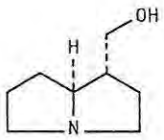
2-Hydroxy-7-methoxy-1-methylaminopyrrolizidine
(Ref. 10)

C. Retronecanol Group

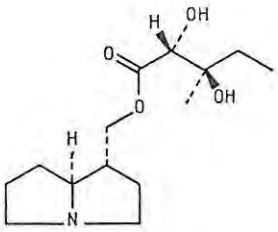


Ehretinine[125]

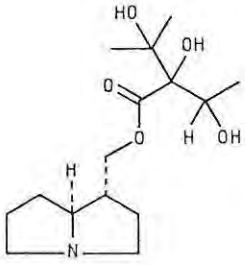
D. (-)Trachelanthamidine Group



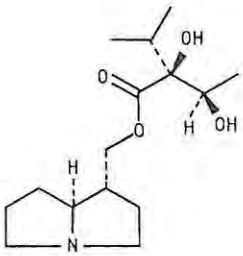
(-)Trachelanthamidine



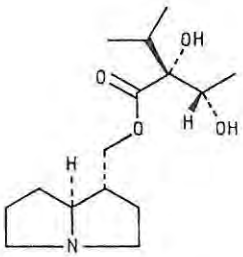
Strigosine[314]
[(-)strigosic acid]



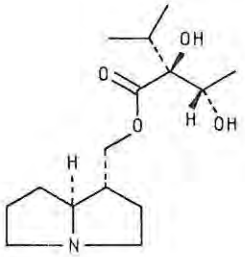
Macrotomine
[echimidinic acid]



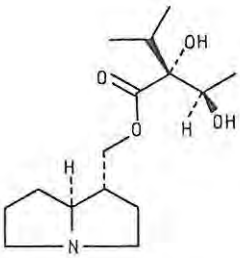
Trachelanthamine[78]
[(+)trachelanthic]
[acid]



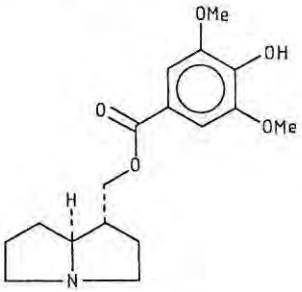
Heliovicine[47]
[(-)trachelanthic]
[acid]



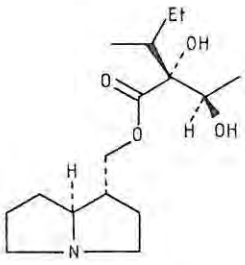
Viridiflorine[78]
[(-)viridifloric]
[acid]



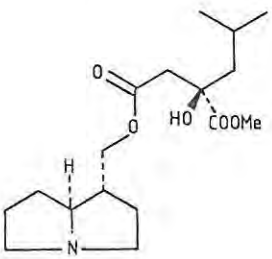
Coromandaline[47]
[(+)viridifloric]
[acid]



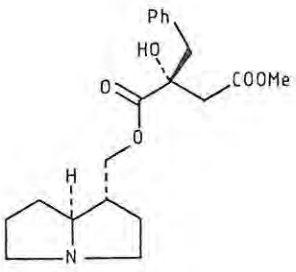
Alafine



Curassavine[62]
[(-)curasavic]
[acid]

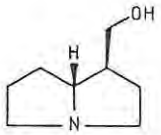


Cornucervine

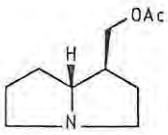


Phalaenopsine T

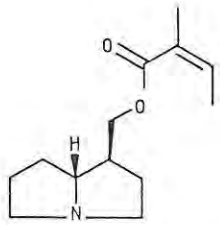
E. (+)Trachelanthamidine (Laburnine) Group



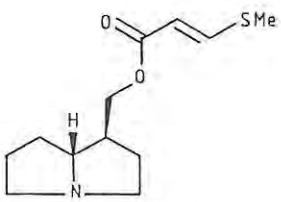
Laburnine



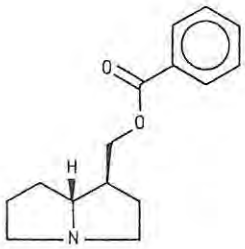
Acetyllaburnine

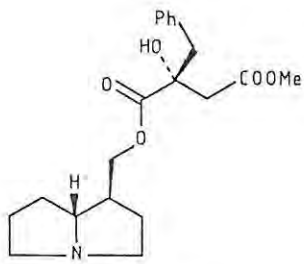


Angelyllaburnine

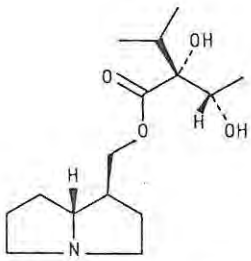


Planchonelline

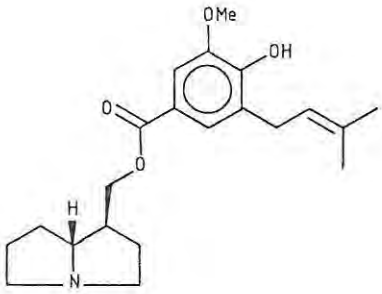




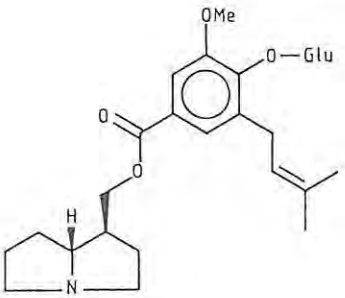
Phalaenopsine LA



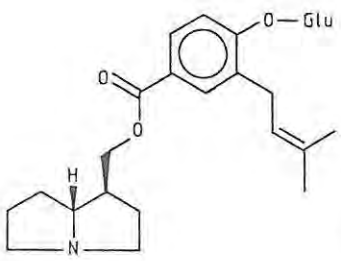
Heliocurassavinine[46]
[(-)trachelanthic acid]



Keitine

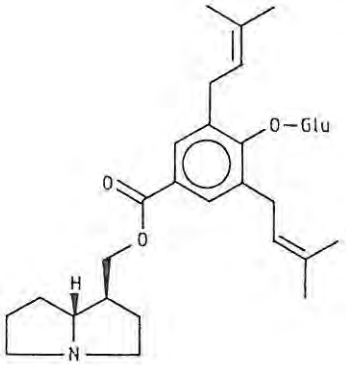


Keitoaine

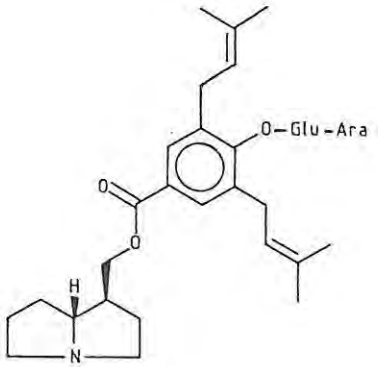


Malaxine

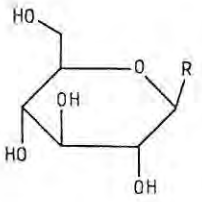
E. (+)Trachelanthamidine Group (continued)



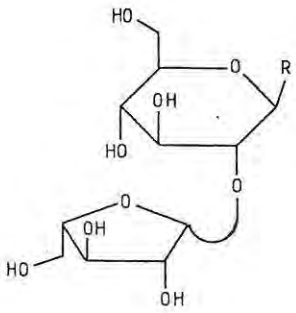
Auriculine



Grandifoline

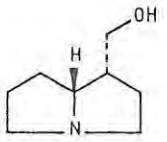


Glu = -D-Glucopyranosyl

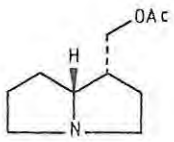


Glu-Ara = 2-O- -D-Glucopyranosyl- -L-arabinosyl

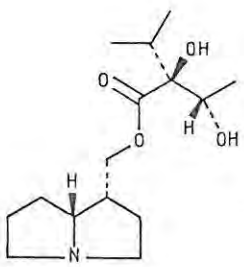
F. (+)Isoretronecanol Group



Isoretronecanol
(Lindelofidine)

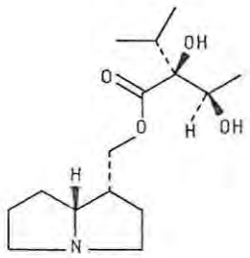


Acetylisoretronecanol

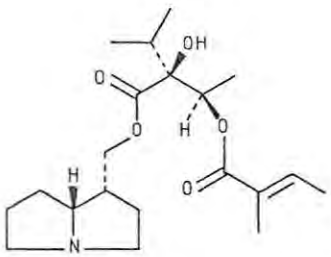


Cynaustraline[78]
[(-)viridifloric acid]

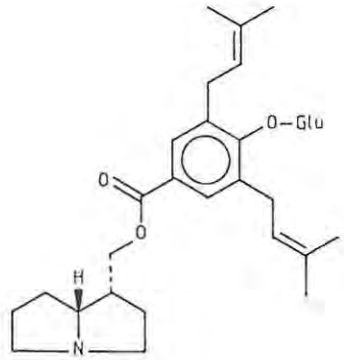
F. (+)Isoretronecanol Group (continued)



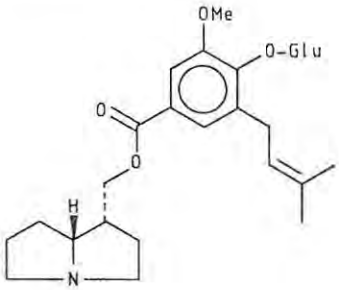
Lindelofine[78]
[(+)trachelanthic acid]



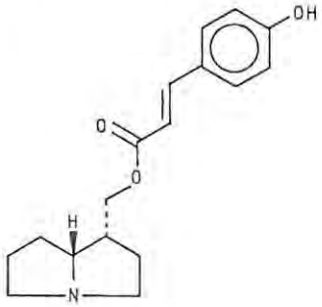
Lindelofamine
[(+)trachelanthic]
[and tiglic acids]



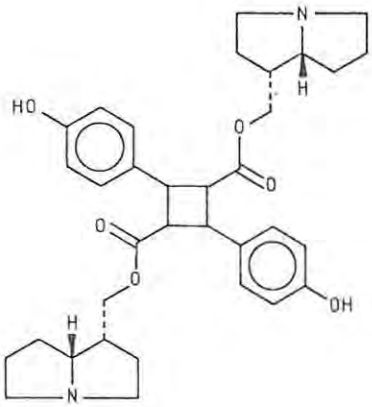
Paludosine



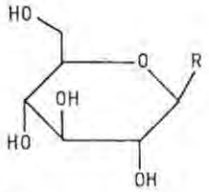
Hammarbine



Thesinine

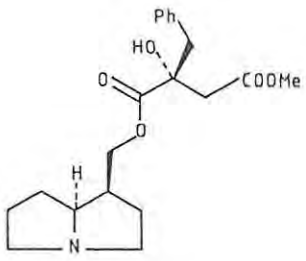


Thesine

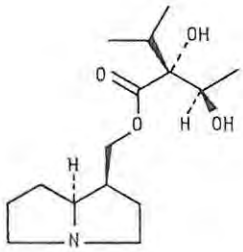


Glu = -D-Glucopyranosyl

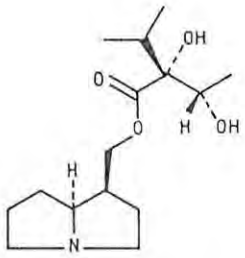
G. (-)Isoretronecanol Group



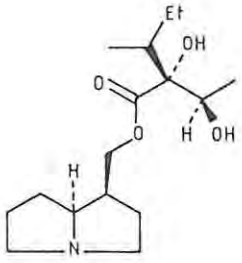
Phalaenopsine IS



Heliocoromandaline[46]
[(+)viridifloric acid]

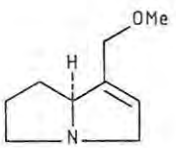


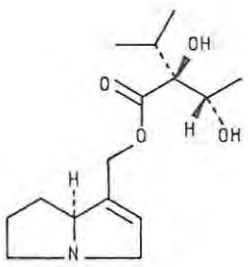
Heliocurassavicine[46]
[(-)trachelanthic acid]



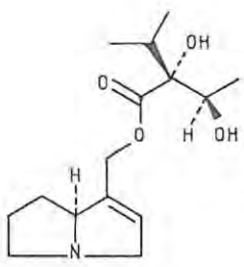
Heliocurassavine[46]
[(-)curassavic acid]

H. (-)Supinidine Group



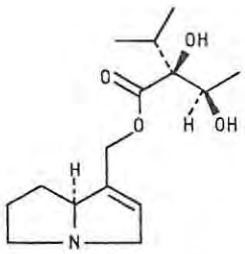


Amabiline
[(-)viridifloric acid]

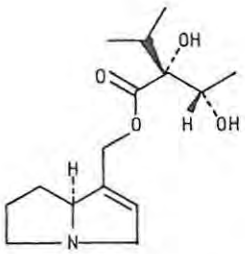


Coromandalinine[46]
[(+)viridifloric acid]

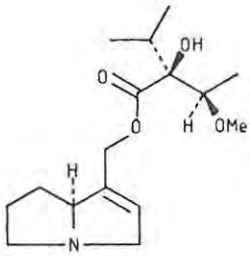
H. (-)Supinidine Group (continued)



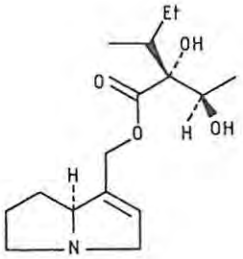
Supinine[315]
[(+)trachelanthic acid]



Heliovinine[46]
[(-)trachelanthic acid]

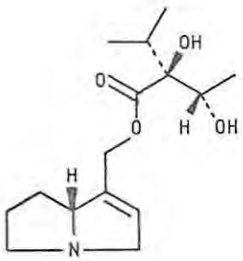


Heleurine[315]
[(-)heliotrinic acid]



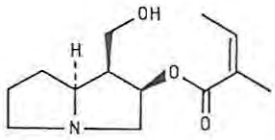
Curassavinine[46]
[(-)curassavic acid]

I. (+)Supinidine Group

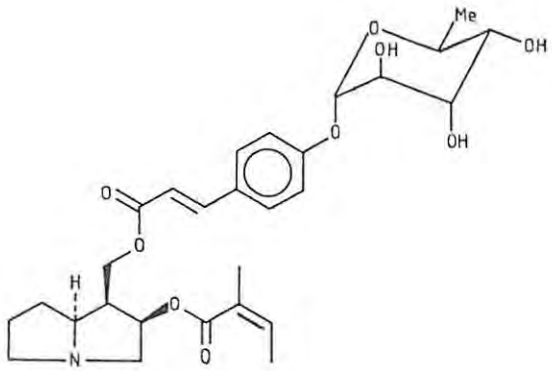


Cynaustine
[(-)viridifloric acid]

J. Petasinecine Group

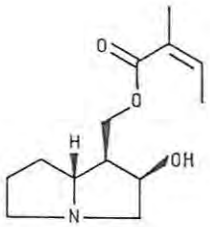


Petasinine[40]



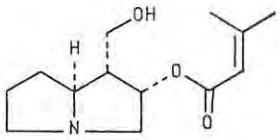
Petasinoside[40]

K. (+)Macronecine Group

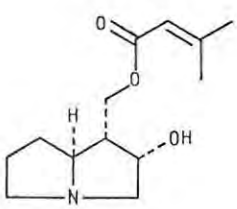


Macrophylline

L. (-)Macronecine Group

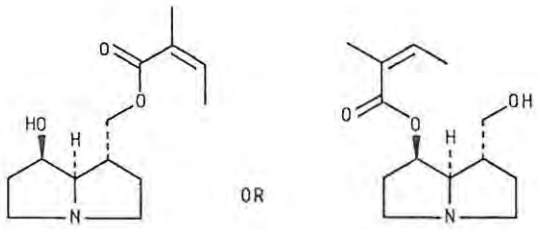


2-Senecioylmacronecine[14]

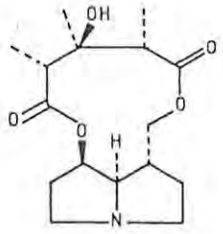


9-Senecioylmacronecine[14]

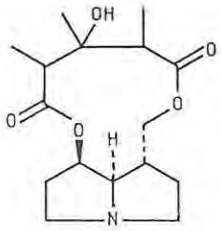
M. (-)Turneforcidine Group



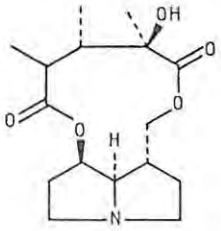
Turneforcine



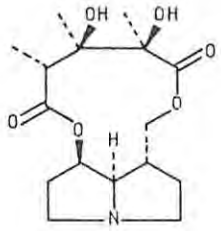
Crocandine[85]
[fulvinic acid]



Isocrocandine[85]

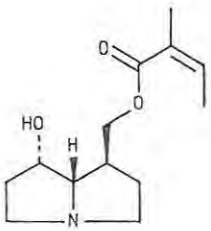


Retusine[94]



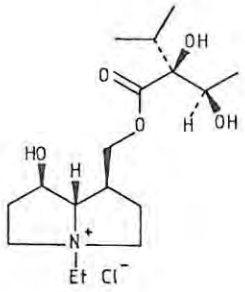
Cropodine[86]

N. (+)Turneforcidine Group

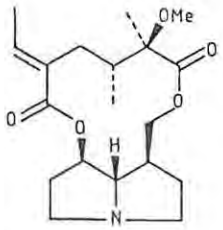


Farfugine[72]
[angelic acid]

O. Hastanecine Group

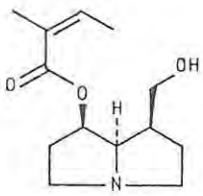


[(+)trachelanthic acid]

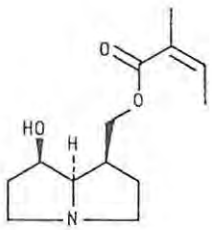


Hastacine

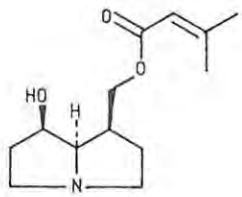
P. Platynecine Group



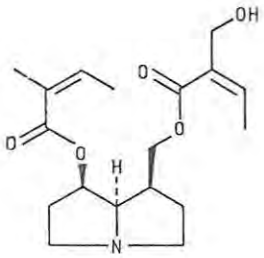
7-Angelylplatynecine[69]



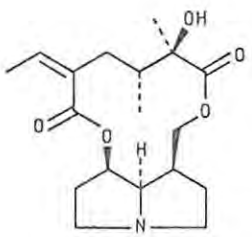
9-Angelylplatynecine[69]



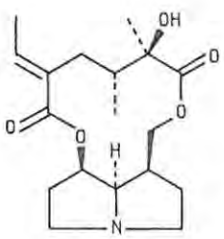
Fuchsisenecionine[68]
[senecioic acid]



Sarracine
[sarracinic and]
[angelic acids]

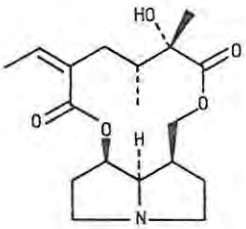


Platyphylline[128]
[(+)senecic acid]

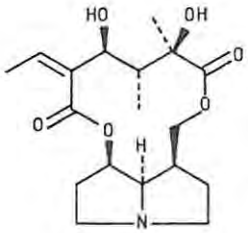


Neoplatyphylline
[(+)integerrinecic acid]

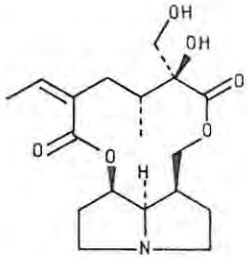
P. Platynecine Group (continued)



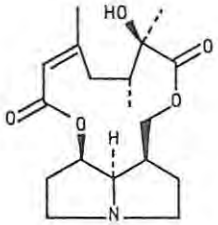
Ligularinine[115]
[(+)neoligularidinecic acid]



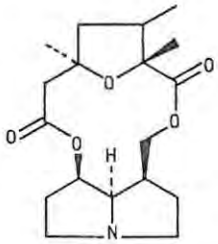
(-)Hygrophylline[316]
[hygrophyllinecic acid]



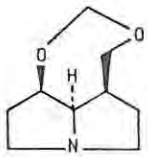
Dihydroretrorsine[124]
[(+)isatinecic acid]



Bulgarsenine[132,134]

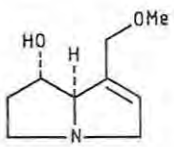


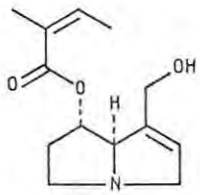
Nemorensine[130,131]
[trans-nemorensic acid]



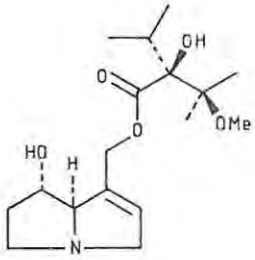
(Ref. 61)

Q. Heliotridine Group



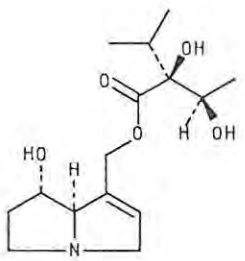


7-Angelylheliotridine

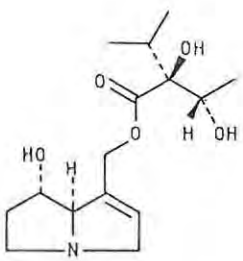


Heliotrine
[(-)heliotrinic acid]

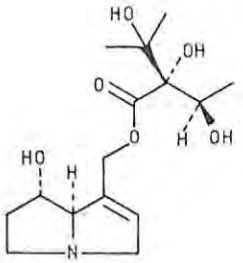
Q. Heliotridine Group (continued)



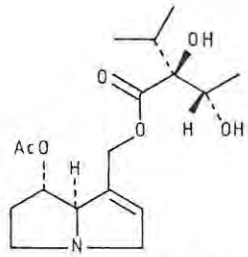
Rinderine
[(+)trachelanthic acid]



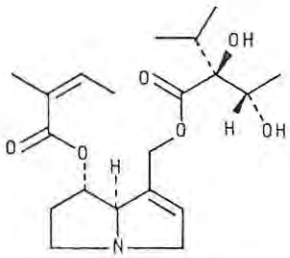
Echinatine
[(-)viridifloric acid]



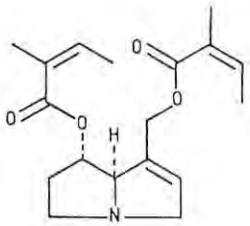
Europine
[(+)lasiocarpic acid]



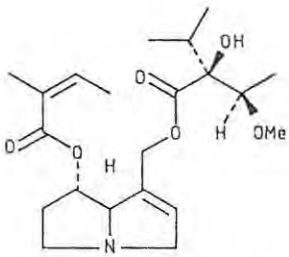
7-Acetylechinatine[80]



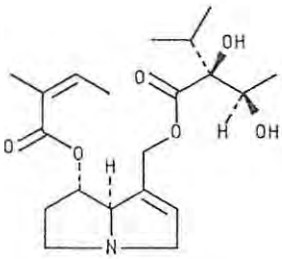
7-Angelylheliotridine
viridiflorate



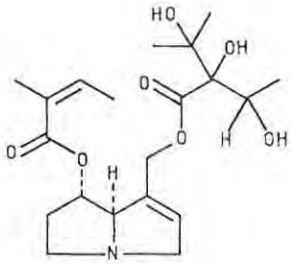
Asperumine
[angelic acid]



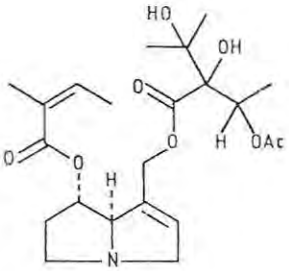
7-Angelylheliotrine[80]



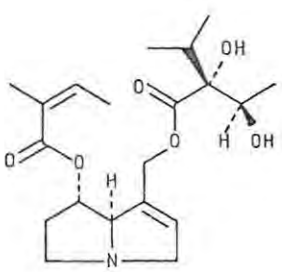
7-Angelylheliotridine
trachelanthate
[(+)trachelanthic acid]



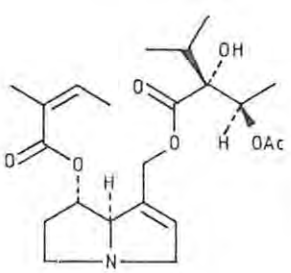
Heliosupine
[?(+)echimidinic acid]



Acetylheliosupine[76]

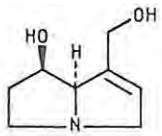


Lasiocarpine
[(+)lasiocarpic acid]

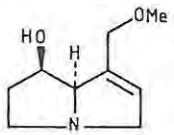


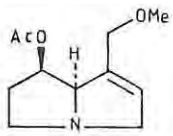
Acetyllasiocarpine[77]

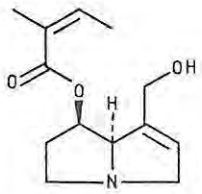
R. Retronecine Group



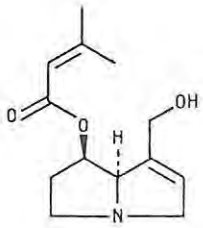
(+)-Retronecine



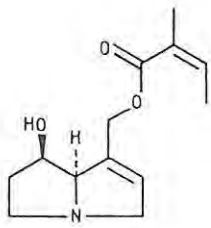




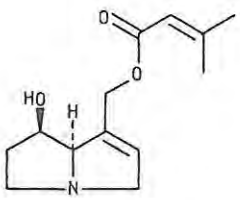
7-Angelylretronecine[317]



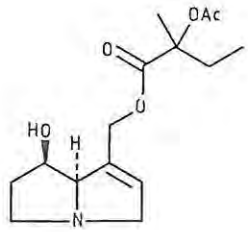
7-Senecioylretronecine[66,67]



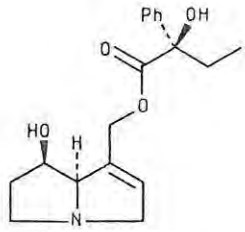
9-Angelylretronecine



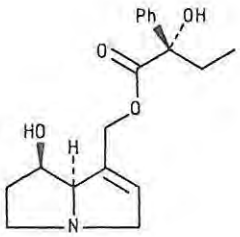
9-Senecioylretronecine[14]



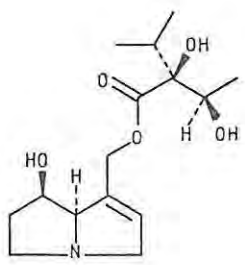
Callimorphine[28]



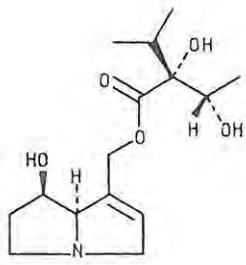
R-9-O(2-hydroxy-2-phenyl-butanoyl)retronecine [203]



S-9-O(2-hydroxy-2-phenyl-butanoyl)retronecine [203]

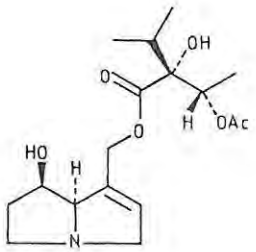


Intermedine
[(+)trachelanthic]
[acid]

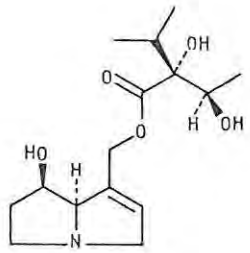


Indicine
[(-)trachelanthic]
[acid]

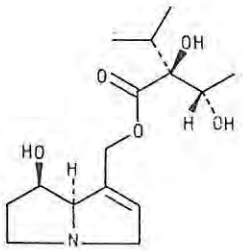
R. Retronecine Group (continued)



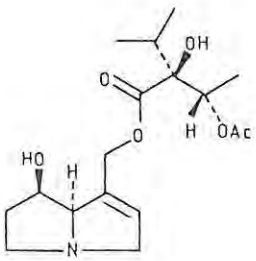
3'-Acetylindicine



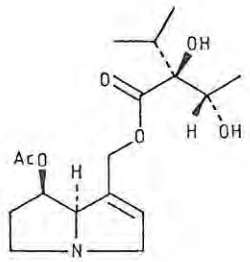
9-(+)viridifloryl- [204]
retronecine



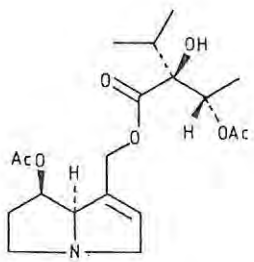
Lycopsamine
[(-)viridifloric]
[acid]



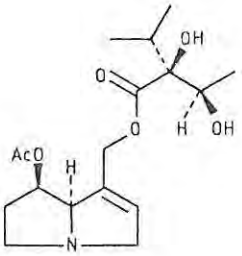
3'-Acetyllycopsamine[64]



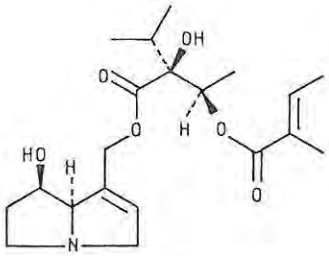
7-Acetyllycopsamine[74]



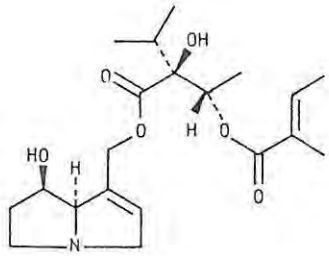
3'7-Diacetyllycopsamine[64]



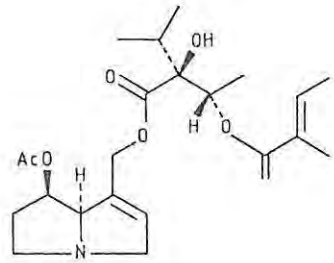
7-Acetylintermedine[74]



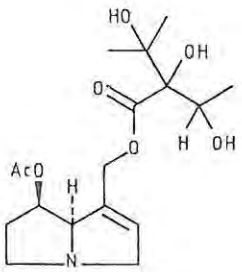
Anadoline
[-tiglyl-(+)trachelanthic]
[acid]



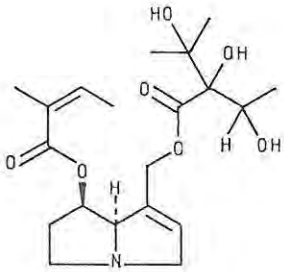
Scorpioidine[4]
[-tiglyl-(-)viridifloric]
[acid]



7-Acetylscorpioidine[4]

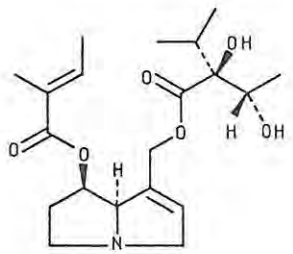


Uplandicine[74]
[echimidinic]

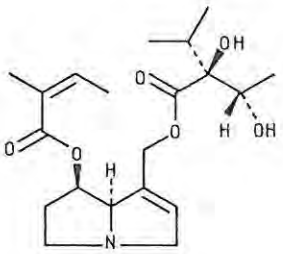


Echimidine
[echimidinic]
[and angelic acids]

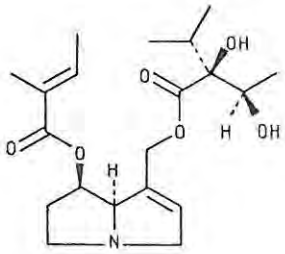
R. Retronecine Group (continued)



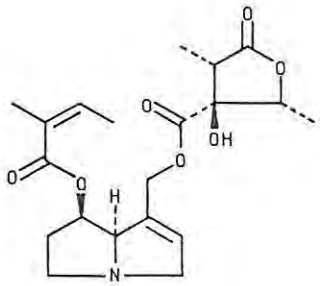
Symphytine[318]
[(-)viridifloric]
[and tiglic acid]



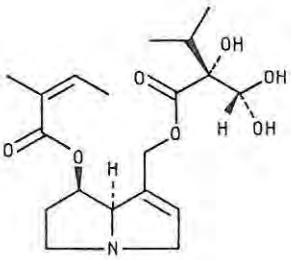
Symlandine[74]
[(-)viridifloric]
[and angelic acid]



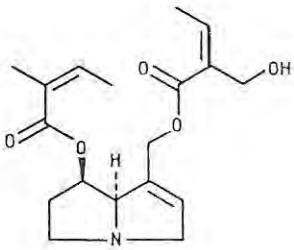
Myoscorpine
[(+)trachelanthic]
[and tiglic acids]



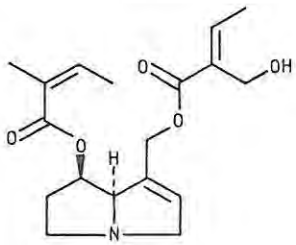
Latifoline[18]
[latifolic and]
[angelic acid]



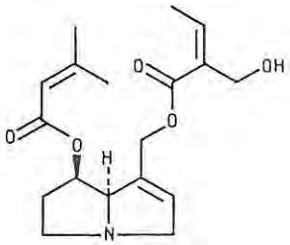
Echiumine
[(-)trachelanthic]
[and angelic acids]



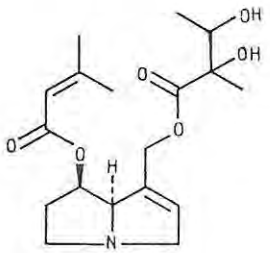
Triangularine[67,75]
[sarracinic and]
[angelic acid]



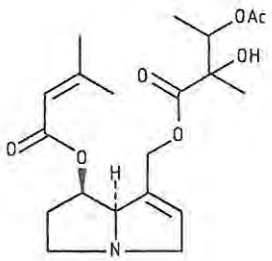
Neotriangularine[75]
[isosarracinic and]
[angelic acids]



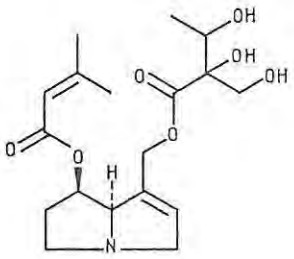
7-Senecioyl-9-sarracinyl- [67]
retronecine



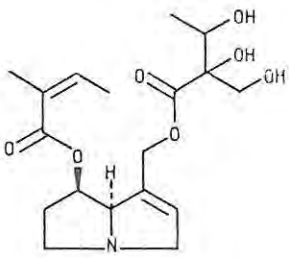
(Ref. 14)



(Ref. 14)

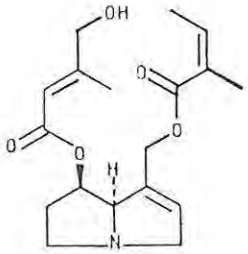


(Ref. 14)

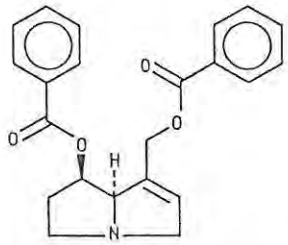


Dihydroxytriangularine[9]

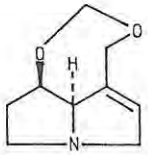
R. Retronecine Group (continued)



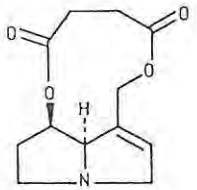
Sencalenine[66]



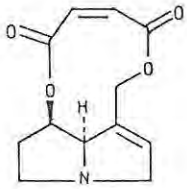
Retronecine 7,9-dibenzoate[73]



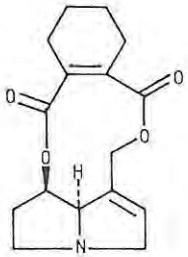
(Ref. 61)



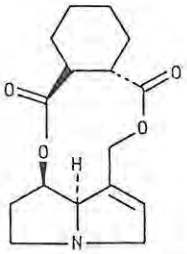
7,9-O,O-(Succinyl)-retronecine [81]



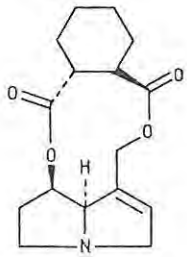
(Ref. 209)



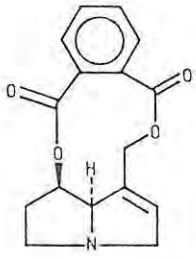
(Ref. 209)



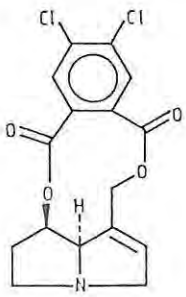
7,9-O,O-[(1S,2S)cyclohexane-1,2-diyl]retronecine (Ref. 81)



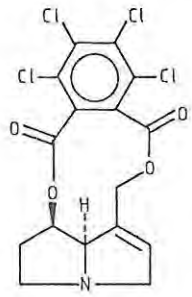
7,9-O,O-[(1R,2R)cyclohexane-1,2-diyl]retronecine (Ref. 81)



7,9-O,O-(Phthaloyl)-retronecine (Ref. 81)



(Ref. 209)



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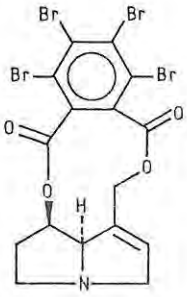
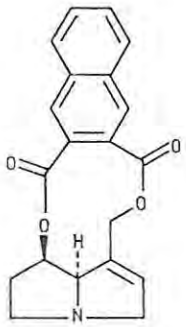


(Ref. 209)

R. Retronecine Group (continued)



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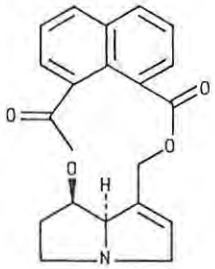

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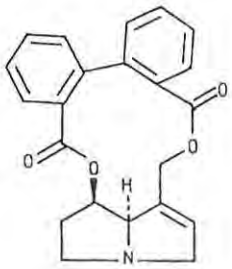

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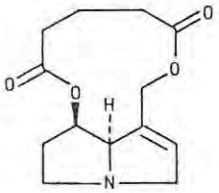
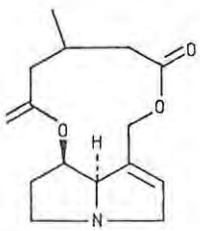
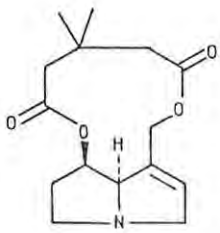


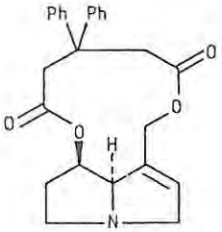
(+)1,2-Didehydro-crotalanine [206]



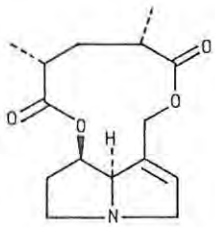
13-Methyl-1,2-di-dehydrocrotalinine [206]



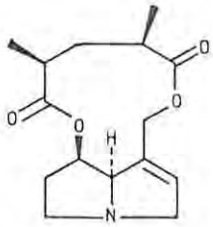
13,13-Dimethyl-1,2-di-dehydrocrotalinine [82]



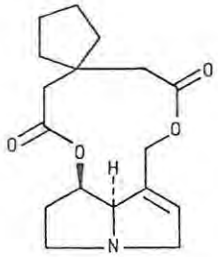
13,13-diphenyl-1,2-di-dehydrocrotalinine [206]



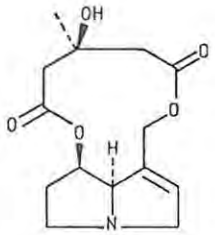
(Ref. 83)



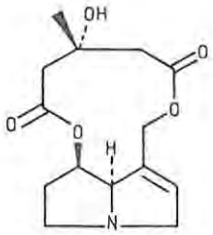
(Ref. 83)



13,13-Tetramethylene-1,2-didehydrocrotalanine [206]

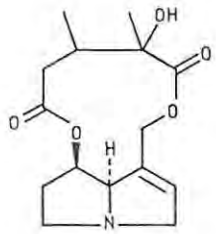


S-(+)Dicrotaline[207]

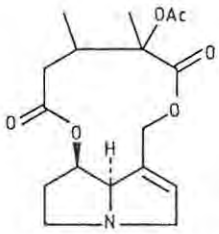


R-(-)Dicrotaline[207]

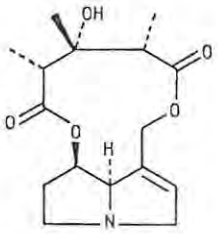
R. Retronecine Group (continued)



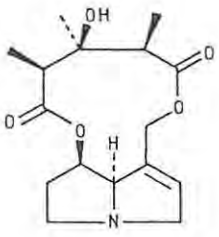
Crobarbatine



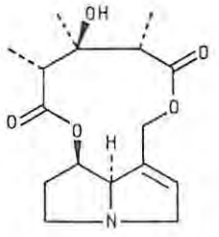
Crobarbatine acetate[205]



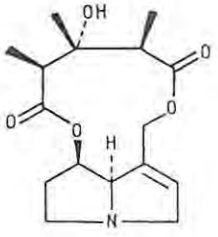
Crispatine[97]



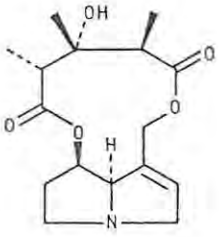
Isocrispatine[210]



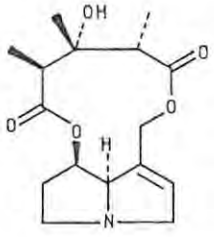
Fulvine[210]



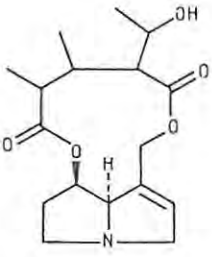
Isofulvine[210]



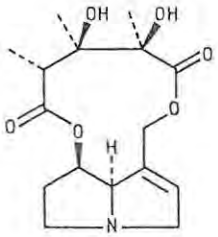
Cromadurine



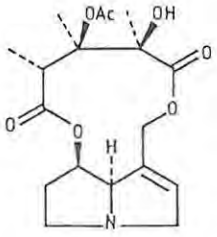
Isocromadurine



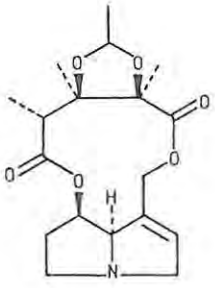
Cronaburmine[87]



Monocrotaline[92]

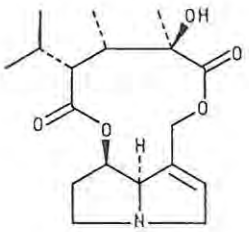


Spectabiline[96]

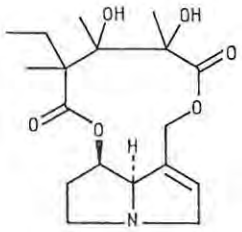


Monocrotalinine[84]

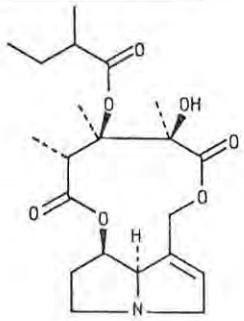
R. Retronecine Group (continued)



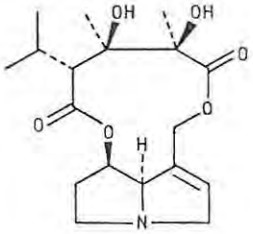
Incanine[93]



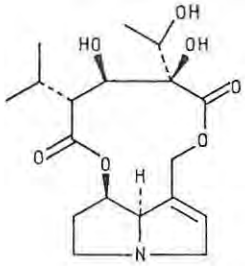
Crotalarine
(Croburhine)



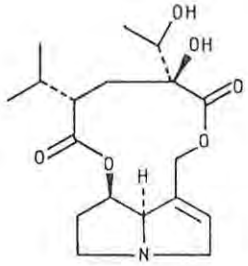
Grahamine



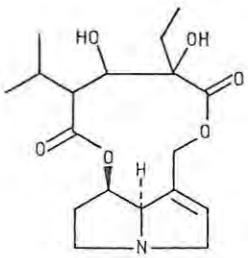
Trichodesmine



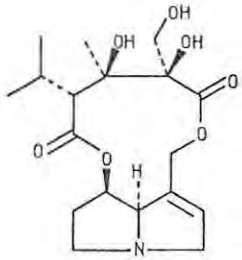
Axillarine



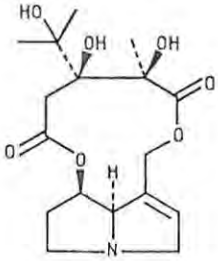
Desoxyaxillarine[91]



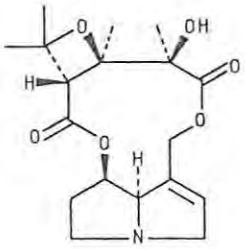
Axillaridine



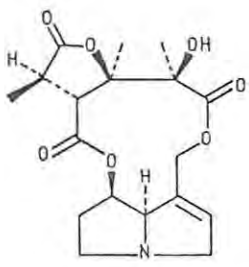
Junceine[95]



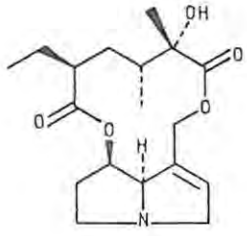
Globiferine[8]



Grantaline[89,90]

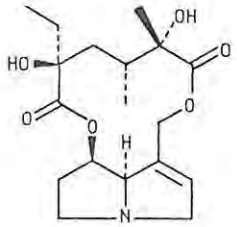


Grantianine[98]

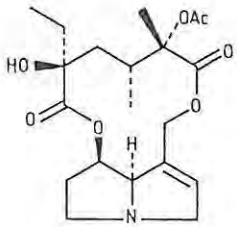


Yamataimine[100]

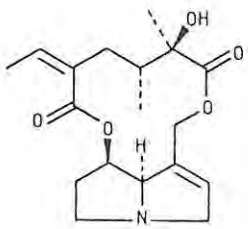
R. Retronecine Group (continued)



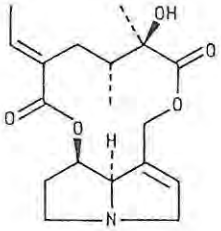
Bisline



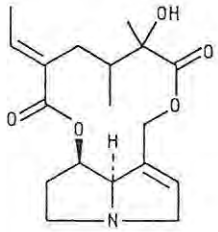
Isoline



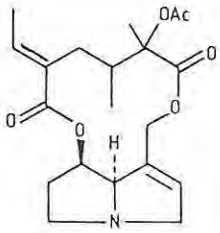
Senecionine



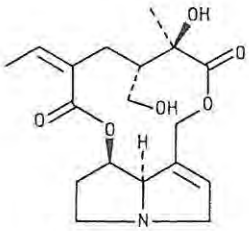
Integerrimine



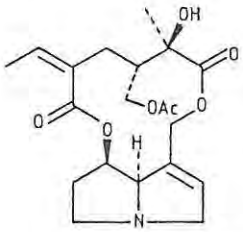
Nilgirine



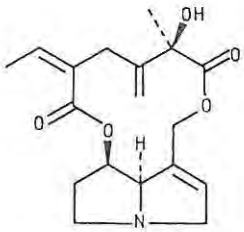
Crotastriatine



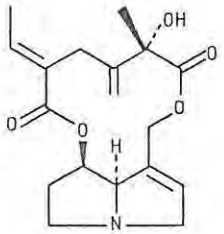
Gynuramine[103]



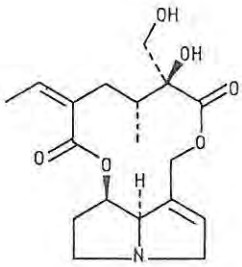
Acetylgynuramine[103]



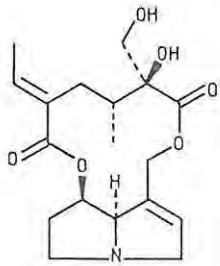
Seneciphylline



Spartioidine

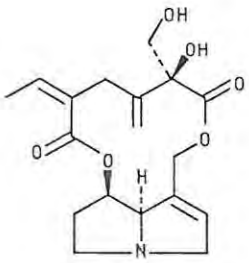


Retrorsine[127]

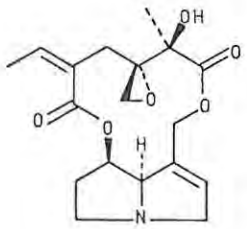


Usaramine
(Mucronatine)

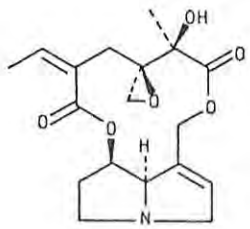
R. Retronecine Group (continued)



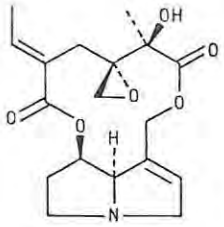
Riddelline



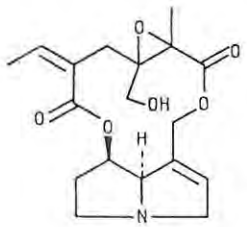
(Ref. 14, 109)



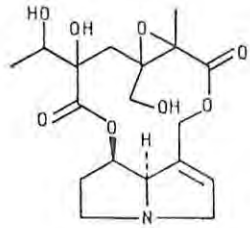
(Ref. 109)



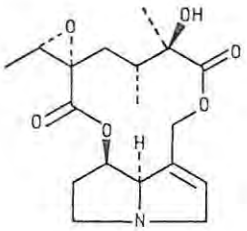
(Ref. 14)



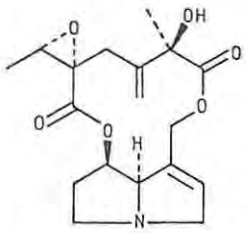
Erucifoline



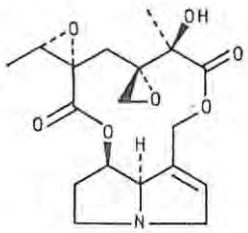
(Ref. 14)



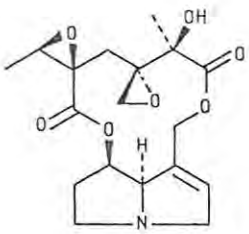
Jacobine



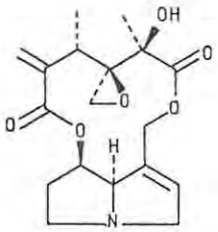
Jacozine[109]



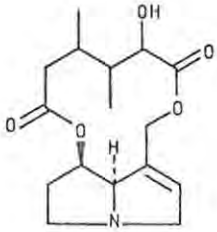
Senecicannabine[108,109]



(Ref. 109)

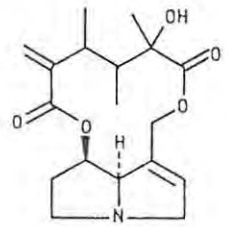


Swazine[233-235]

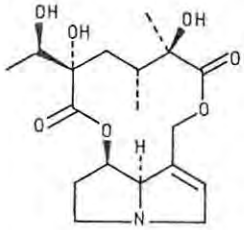


Crotananine[99]

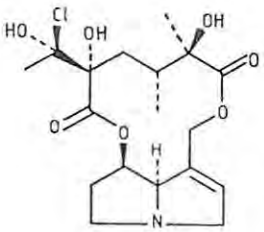
R. Retronecine Group (continued)



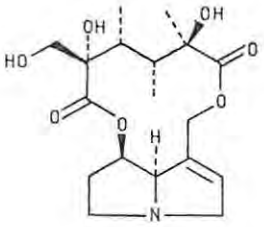
Senecivernine[101]



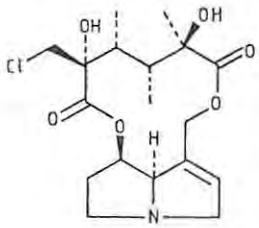
Jacoline



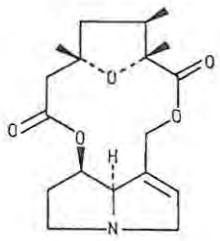
Jaconine



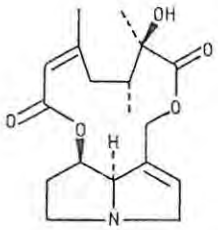
Sceleratine[107]



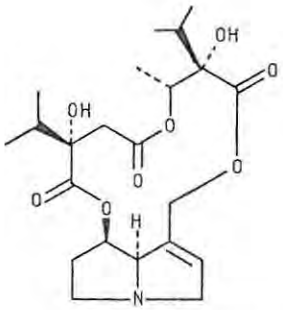
Merenskine[105]



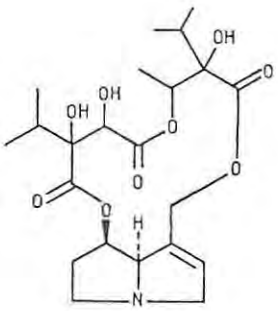
Retroisosenine[132]



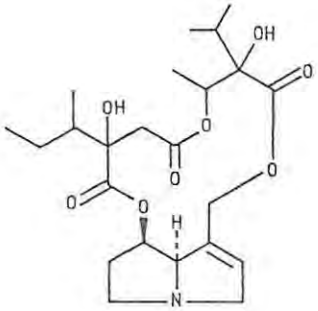
Doronenine[135]



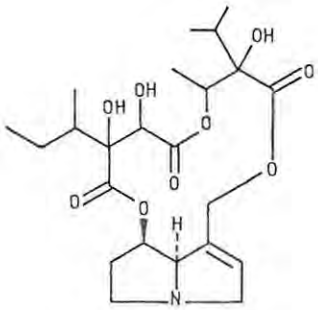
Parsonsine[63,136]



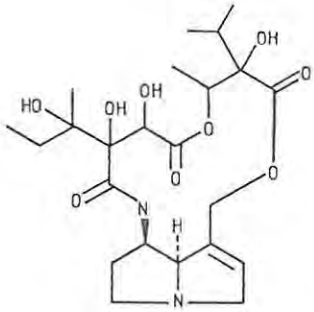
Spiraline[63]



Heterophylline[63]

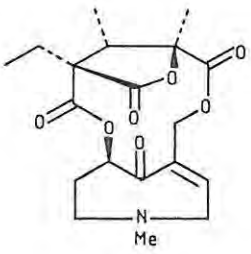


Spiranine[63]

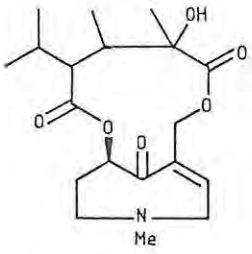


Spiracine[63]

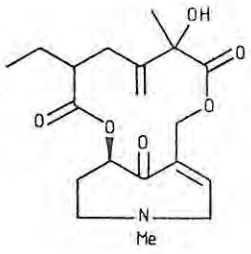
S. Otonecine Group



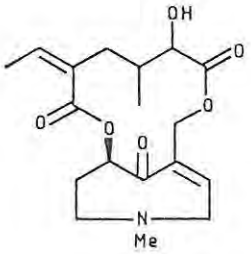
Retusamine



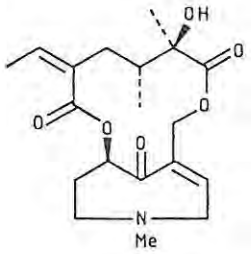
Crosemperine



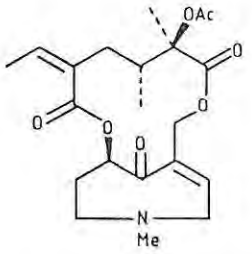
Emiline[319]



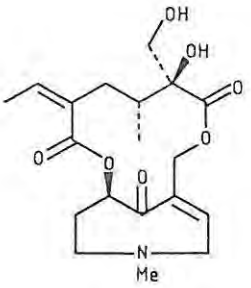
Crotafoline



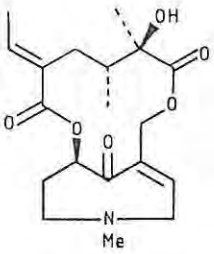
Senkirkine
(Renardine)



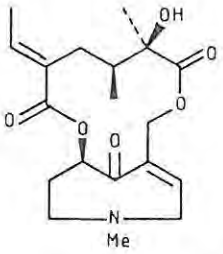
Acetylsenkirkine



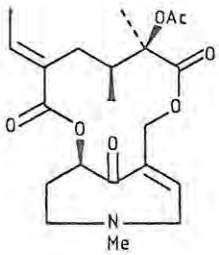
Hydroxysenkirkine



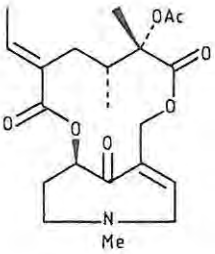
Neosenkirkine



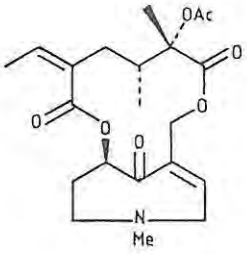
Crotaverrine[116,117]



Acetylcrotaverrine[116,117]

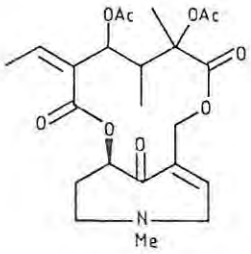


Ligularidine[114,115]

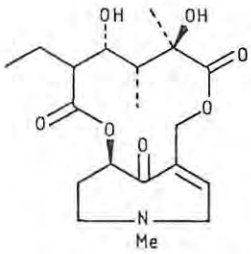


Neoligularidine[115]

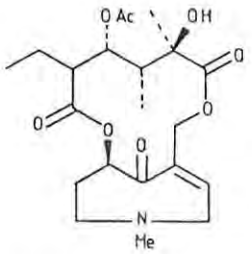
S. Otonecine Group (continued)



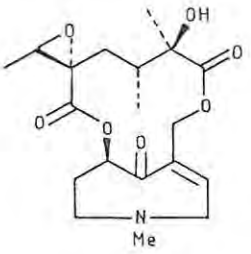
Ligularidine



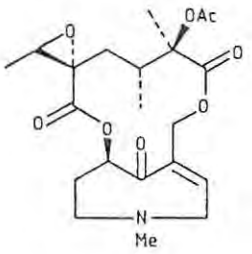
Syneilesine[120,121]



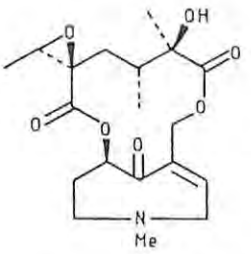
Acetylsyneilesine[120,121]



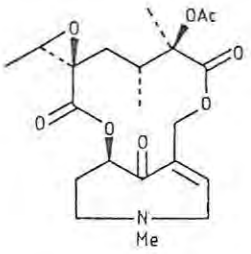
Otosenine



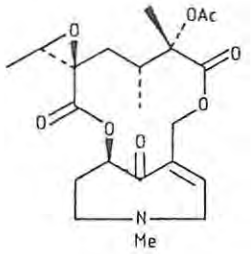
Florosenine



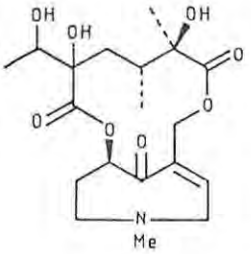
Petasitenine[110-113]
(Fukinotoxin)



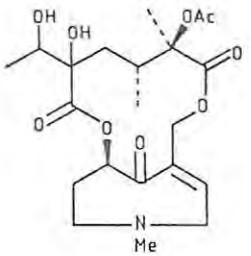
Neopetasitenine[110,112]



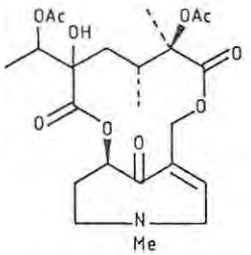
Ligularizine[115]



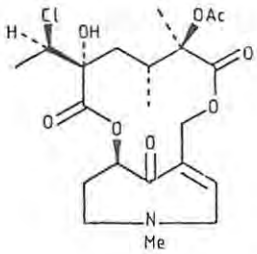
Onetine



Floridanine

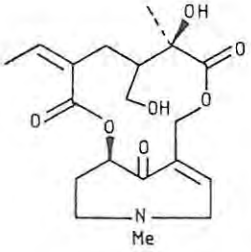


Floricanine

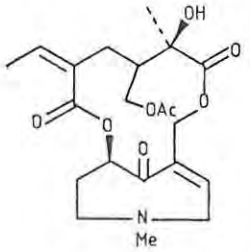


Doronine[122,123]

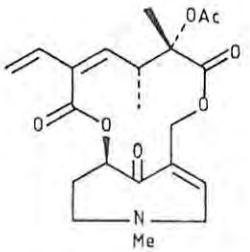
S. Otonecine Group (continued)



18-Hydroxysenkirkine[14]

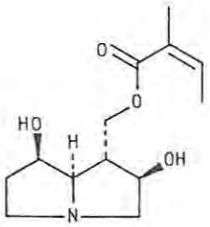


18-Acetoxysenkirkine[14]

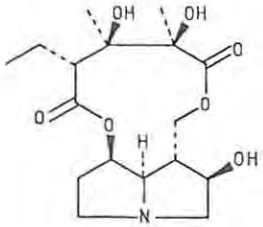


Clivorine

T. Croalbinecine Group

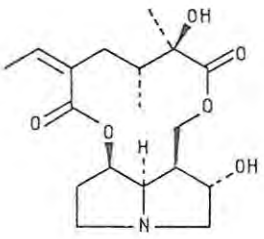


Helifoline[70]

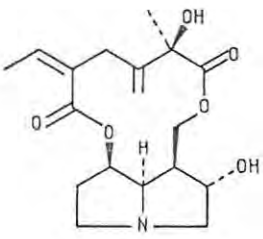


Croalbidine

U. Rosmarinecine Group

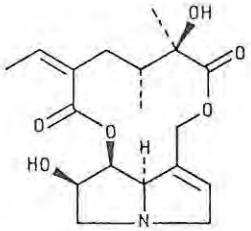


Rosmarinine

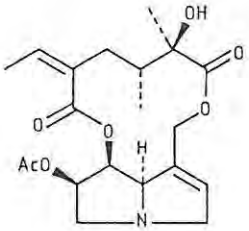


Angularine

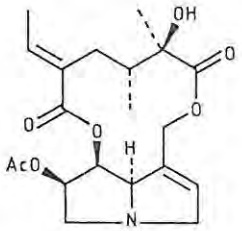
V. Crotanecine Group



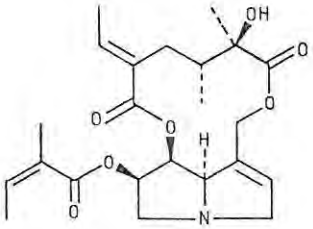
Anacrotine



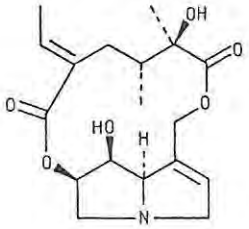
6-Acetylanacrotine



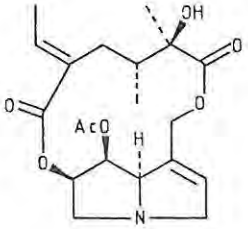
6-Acetyl-trans-anacrotine



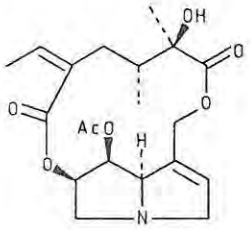
6-Angelyl-trans-anacrotine



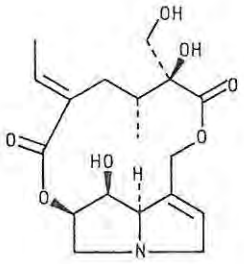
Madurensine



7-Acetylmadurensine

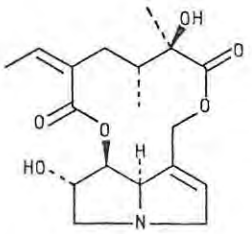


7-Acetyl-cis-madurensine



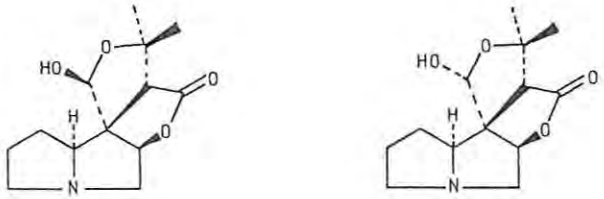
Crotafoline

W. Uspallatinecine Group



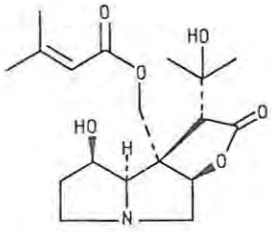
Uspallatine[48]

X. Senecicaudatinal Group

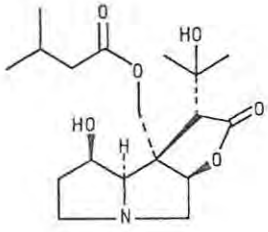


Senecicaudatinal semiacetals[14]

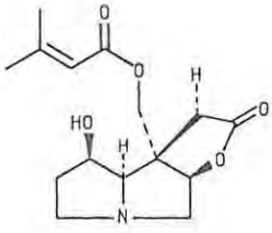
Y. Senecicaudatine Group



9-Senecioylseneci- [14]
caudatine



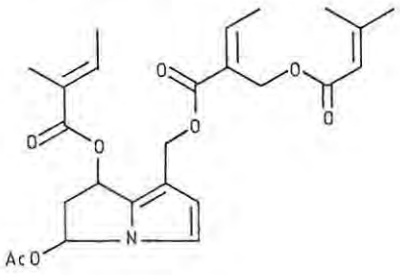
9-Isovalerylseneci- [14]
caudatine

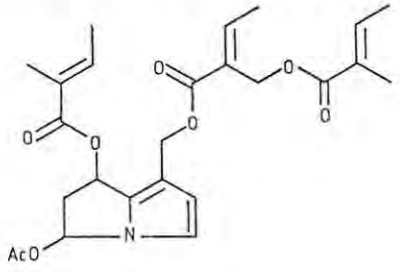


9-Senecioylnorseneci- [14]
caudatine

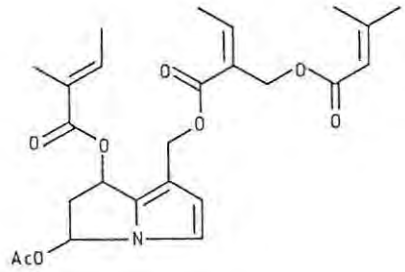
Z. Senampeline Group

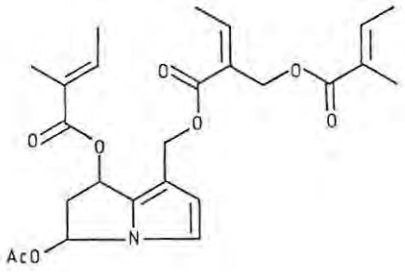
These structures were identified and named as unresolved mixtures of isomers as indicated.



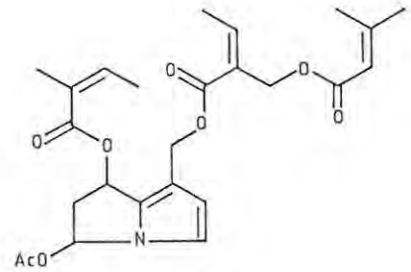


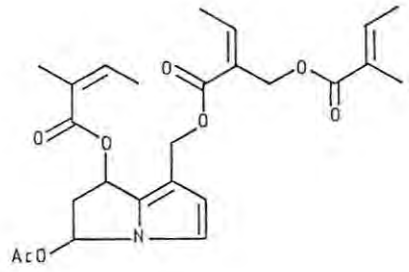
Senampelines A and B (mixture)[52]

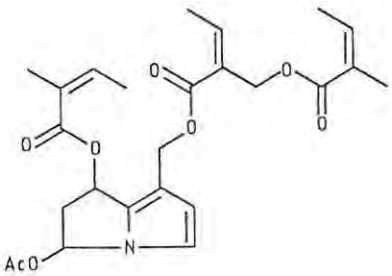




Senampelines C and D (mixture)[52,53]

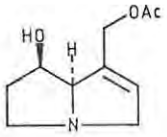


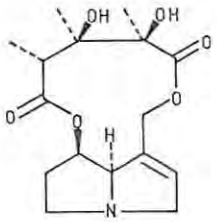




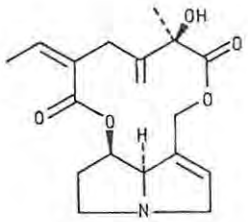
Senampelines E, F and G (mixture)[53]

AA. Dihydropyrrolizine Group[320]

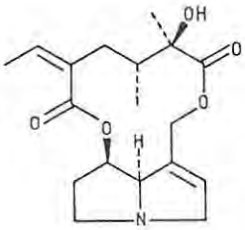




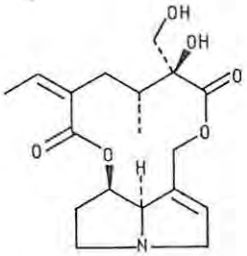
Monocrotaline pyrrole



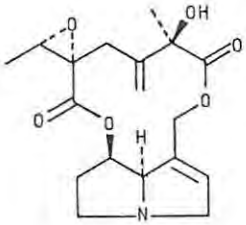
Seneciphylline pyrrole



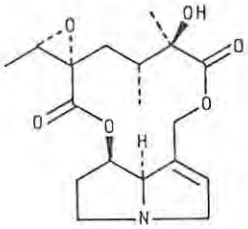
Senecionine pyrrole



Retrorsine pyrrole

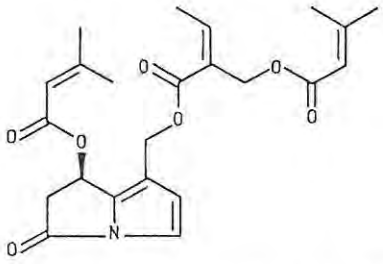


Jacozine pyrrole

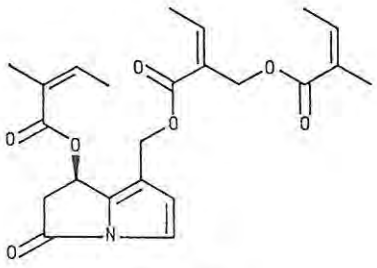


Jacobine pyrrole

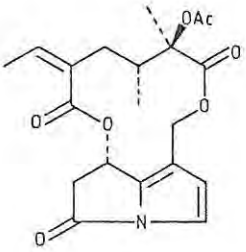
BB. Dihydropyrrolizinone Group



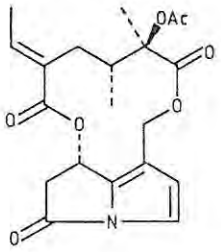
7 -Senecioyloxy-9-(5-senecioyloxy- angelyloxy)-5,8-dehydroheliotridin-5-one [12]



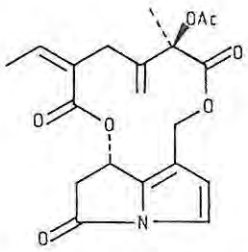
(Ref. 14)



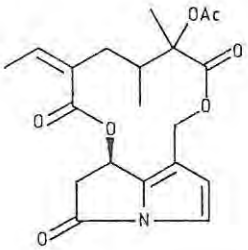
Senaetnine[56]



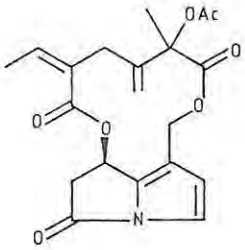
trans-Senaetnine[53]



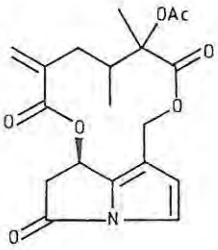
Dehydrosenaetnine[125]



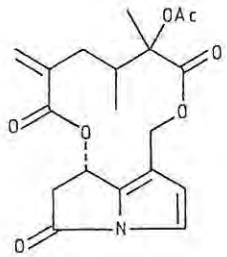
Isosenaetnine[54]



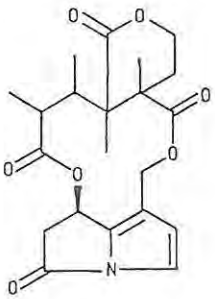
Dehydroisosenaetnine[54,125]



Pterophorine[52]

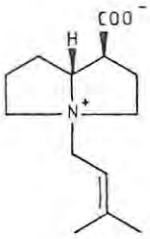


Isopterophorine[55]

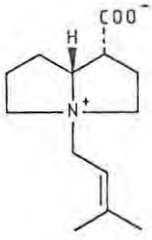


Inaequidenine[56]

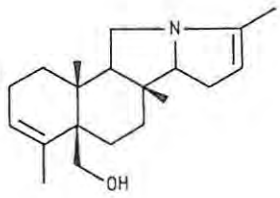
CC. Miscellaneous Group



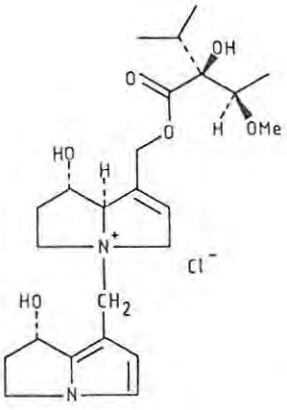
Anodendrine



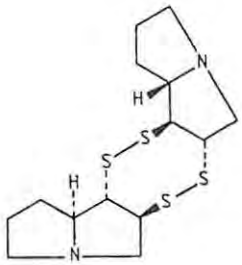
Alloanodendrine



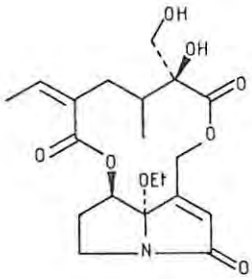
Thelopogine



(not named)

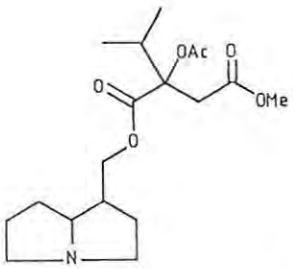


Cassipourine

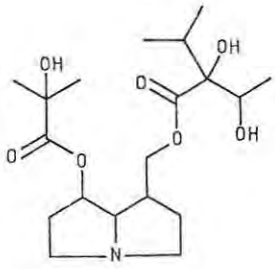


8-Ethoxy-3-oxoretrorsine[51]

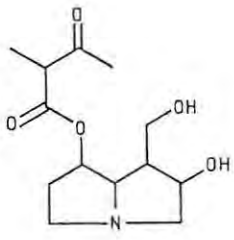
DD. Unidentified Bases



(not named, base is either [63] (+)trachelanthamidine or (+)isoretronecanol)



Uluganine



Procerine[71]

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