APPROACHES TO THE TOTAL SYNTHESIS

OF BICYCLOMYCIN

A thesis presented by

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To my Parents and Elaine

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ABSTRACT

The biological properties of, and synthetic approaches to, the antibiotic bicyclomycin are reviewed.

Novel synthetic approaches to the total synthesis of bicyclomycin, (1S, 6R, 1'S, 2'S)-8,10-diaza-6-hydroxy-5-methylene-1-(2'-methyl-1',2',3'-trihydroxypropyl)-2-oxabicyclo [4.2.2] decan-7,9-dione, have been investigated.

One approach involved conversion of 2-C-methyl-D-ribono-1,4-lactone (available from β-D-fructose) in 4 steps to 2,3-O-isopropylidene-3-C-methyl-L-erythrono-1,4-lactone, a potential intermediate for a chiral acid chloride bearing the trihydroxymethylpropyl side chain of bicyclomycin. Attempted preparation of adducts from α-metalated ethyl isocyanoacetate and β-oxygenated ketones such as 4-hydroxybutan-2-one was unsuccessful. Ethyl acetoacetate was converted in 3 steps into ethyl 5-benzyloxy-2-formylamino-3-oxopentanoate, a precursor for potentially useful isonitriles for coupling with suitable chiral acid chlorides. Model studies on the reaction of simple isonitriles and acid chlorides were not promising.

Another approach involved a proposed α-keto-acid intermediate derived from 2,3-O-isopropylidene-2-C-methyl-D-ribono-1,4-lactone. Oxidative studies on this lactone were low yielding. A synthetic equivalent, 2-[(1S, 4S)-1-acetoxy-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-methyl]-2-(diphenylmethoxy-carbonyl)-1,3-dithiane, was readily available from 2-C-methyl-D-ribono-1,4-lactone in 8 steps. Model 1,3-dithianes were also readily available from the dianion of 2-carboxy-1,3-dithiane. 5-t-Butyldiphenylsilyloxy-2-[(diphenyl-methylene) amino]-3-methylpentanamide was prepared in good yield from commercial materials in 4 steps *via* carbanions derived from N-(diphenylmethylene) glycinamide (reaction with several electrophiles was examined). Coupling of the model 1,3-dithiane synthon and the above mentioned amide was successful, yielding, after further elaboration, 2-(1-acetoxyethyl)-2-[N-(1-carbamoyl-4-hydroxy-3-methylbutyl)

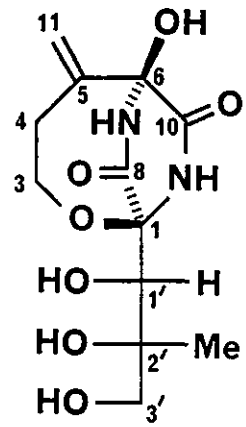
carbamoyl]-1,3-dithiane. Initial silver (I) or mercury (II) mediated bicyclisation studies to give 1-(1-acetoxyethyl)-8,10-diaza-5-methyl-2-oxabicyclo [4.2.2] decan-7,9-dione were not successful.

CONTENTS

INTRODUCTION

Bicyclomycin (1) is an antibiotic which was first isolated by two Japanese groups[1,2] in 1972. Bicyclomycin is produced by various Streptomyces species such as Streptomyces sapporonensis[1,3,4,5,6], Streptomyces No.5879[2], Streptomyces aizunensis[2,7,8], Streptomyces griseoflavus var. bicyclomyceticus[9], and Streptomyces irabensis[10], and its production has been the subject of numerous patents[5,6,8,9,10]. Although bicyclomycin is the most commonly used name for this antibiotic, other names such as Antibiotic No.5879[2], Aizumycin[7], Antibiotic WS-4545[11-16], and Bicozamycin[17] have been used. Systematically bicyclomycin is named (1S, 6R, 1'S, 2'S) - 6-hydroxy-5-methylene-1-(1',2', 3'-trihydroxy-2'-methylpropyl)-2-oxa-7,9-diazabicyclo [4.2.2]decane-8,10-dione.

Bicyclomycin has a unique chemical structure whose relative[18] and absolute[19] configuration has been firmly established by X-ray crystallography. The interesting antibacterial activity and low toxicity of bicyclomycin has prompted much biological research, and several synthetic approaches to bicyclomycin have been reported.



(1)

REVIEW

BIOLOGICAL PROPERTIES OF BICYCLOMYCIN

BIOLOGICAL PROPERTIES OF BICYCLOMYCIN

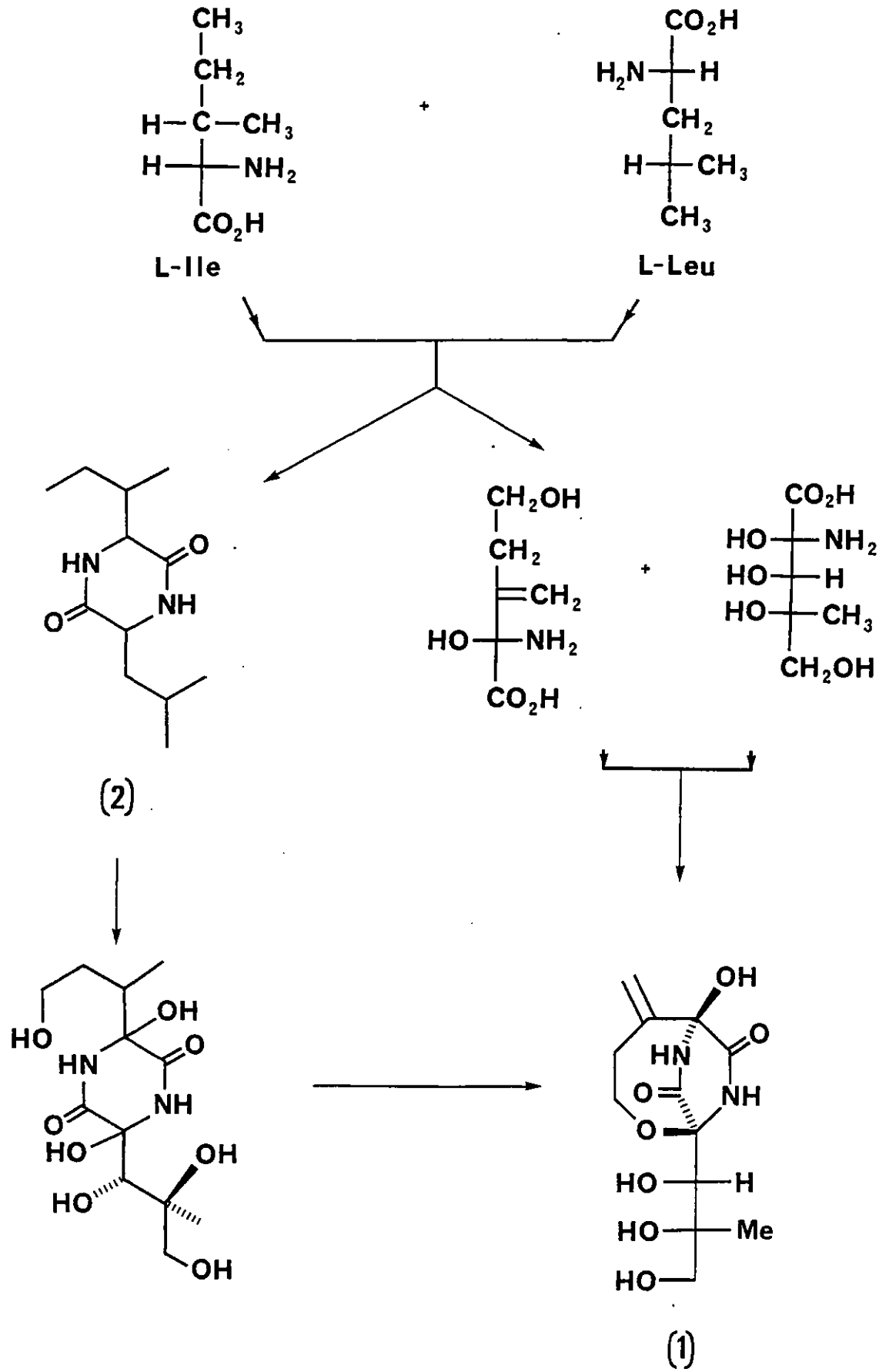
Biosynthesis

The structure of bicyclomycin (1) contains a 2,5-piperazinedione moiety which suggests that biosynthetically bicyclomycin may be derived from two amino-acid components.

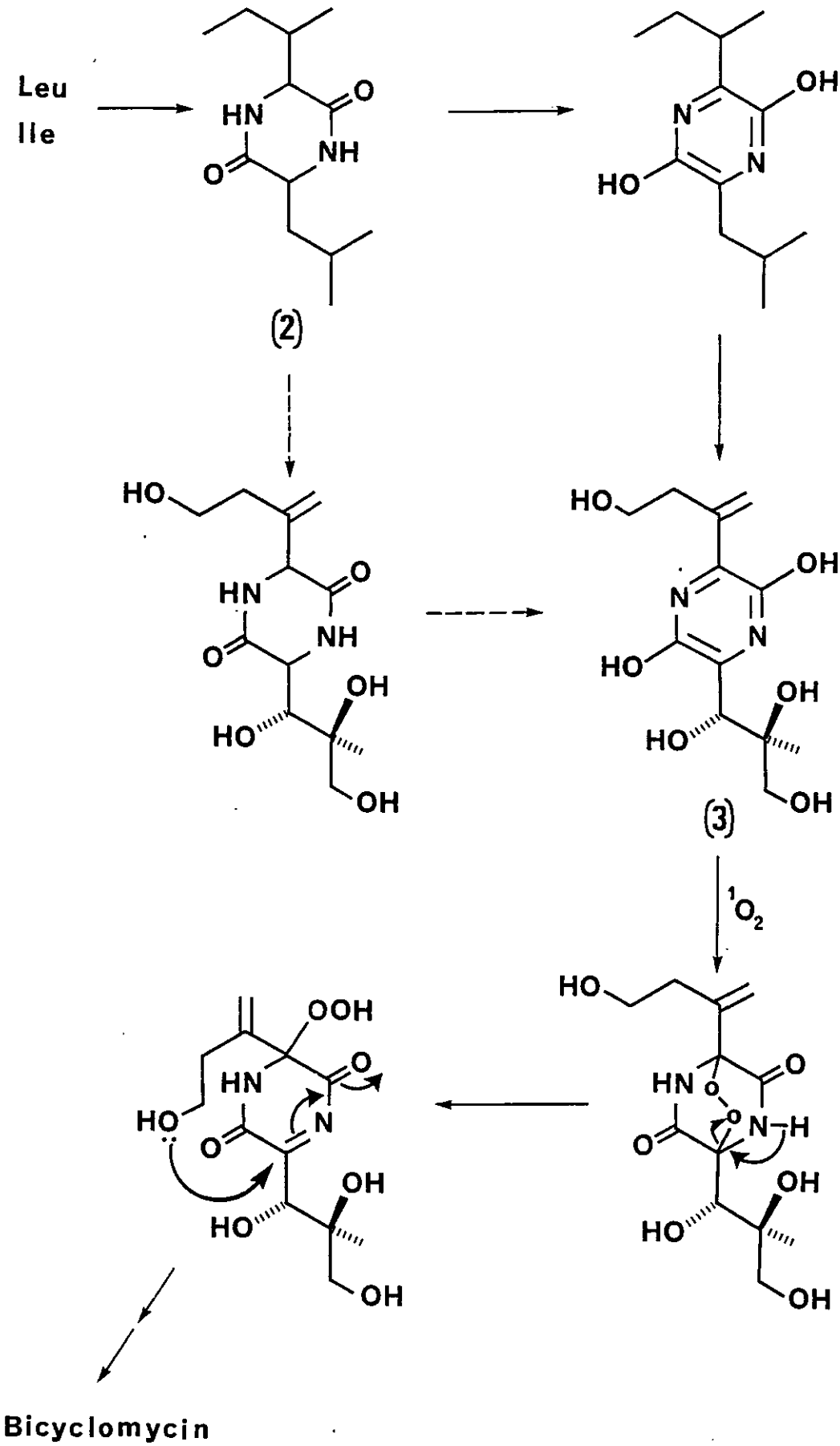
The biosynthesis of bicyclomycin has been probed[20] by observing the production of bicyclomycin from Streptomyces sapporonesis in the presence of various additives. The effect of eighteen different amino-acids was examined and the presence of L-leucine, L-isoleucine, L-phenylalanine and L-glutamic acid was found to stimulate bicyclomycin production. An equimolar mixture of L-leucine and L-isoleucine had the most pronounced effect. Use of radioactive ^{14}C-L-leucine and ^{14}C-L-isoleucine resulted in production of ^{14}C-labelled bicyclomycin, the incorporation of radioactivity being proportional to the concentration of the radioactive amino-acid in the medium. These results support the hypothesis that the biosynthetic pathway begins with L-leucine and L-isoleucine. Of various vitamins investigated nicotinamide was found to be the most effective for bicyclomycin production and the presence of ferrous salts was found to be almost essential. Starch, mannose and fructose were found to be the most effective carbohydrate additives.

These results support the two hypothetical biosynthetic pathways starting from L-leucine and L-isoleucine (Scheme 1). It is proposed that nicotinamide acts as an electron donor required by oxygenases and that ferrous ion may be necessary for hydroxylation reactions.

An alternative proposed[21] biosynthetic pathway involves the same intermediate 2,5-piperazinedione (2) derived from L-leucine and L-isoleucine, followed by subsequent oxidation to a 2,5-dihydroxypiperazine (3), cycloaddition with singlet oxygen and bicyclisation (Scheme 2).

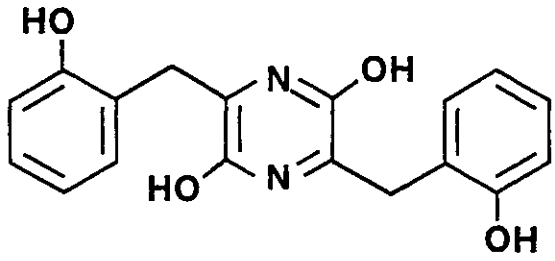


Scheme 1



Scheme 2

As a model system for the proposed intermediate 2,5-hydroxypiperazine (3), the 2,5-hydroxypiperazine (4) was synthesised, but unfortunately photo-oxygenation studies were prohibited by solubility problems[21].



(4)

Much work remains to be done to fully elucidate the biosynthetic pathway(s) to bicyclomycin.

Antibacterial Activity

i) Toxicity

Bicyclomycin has a low toxicity as judged by experiments on mice. It has been reported that mice tolerate an intraperitoneal injection[2] of 400 mg/kg, and intravenous and intraperitoneal injections of 1 g/kg for two weeks[7]. The acute toxicity (LD_0) in mice by intravenous injection[1] was greater than 2 g/kg and by subcutaneous, oral or intraperitoneal administration[1] was greater than 4 g/kg.

ii) In vitro activity

The in vitro activity of bicyclomycin has been extensively studied against various organisms[1,2,7,22,23,24,25], and the results are given in Table 1.

In summary, it has been found that bicyclomycin is active against most gram-negative bacteria including Klebsiella, Salmonella, Escherichia, Shigella, Brucella, Citrobacter, Enterobacter cloacae, and Neisseria gonorrhoeae,

TABLE 1

In Vitro Activity of Bicyclomycin

Organism	MIC / mcg/ml			Ref.
	Bicyclo-mycin	Strepto-mycin	Ampicillin	
E. coli (30 strains)	6.25–50	1.56–>400	3.13–12.5	22
E. coli (Streptomycin resistant)	25	>100	–	22
E. coli (Ampicillin resistant)	25	–	>100	22
E. coli (3 strains)	31.2	–	–	7
E. coli NIHJ JC-2	25	–	–	1
E. coli (86 strains)	6.25–100	–	0.39–100	17
E. coli (3 strains)	12.5–25	–	–	25
Klebsiella (30 strains)	25–>400	3.13–>400	100–>400	22
Klebsiella pneumoniae S	15.6	–	–	7
Klebsiella pneumoniae ST-101	25	–	–	1
Klebsiella pneumoniae 327	25	–	–	25
Klebsiella pneumoniae 327	>100	–	–	25
Shigella (45 strains)	12.5–50	0.78–>400	1.56–12.5	22
Shigella (3 strains)	15.6	–	–	7
Shigella flexneri 1a-2W-A	25	–	–	1
Shigella sonnei (50 strains)	12.5–50	6.25–>800	6.25–12.5	23
Shigella flexneri (50 strains)	6.25–25	6.25–800	6.25–>800	23
Shigella (86 strains)	3.12–100	–	0.20–>100	17
Salmonella (41 strains)	25–100	6.25–>400	0.78–>400	22
Salmonella (3 strains)	7.8–31.2	–	–	7
Salmonella typhosa T-287	25	–	–	1
Salmonella (105 strains)	12.5–100	–	0.2–100	17
Salmonella typhimurium 277	25	–	–	25
Citrobacter (22 strains)	25–200	25–>800	400–20	22

TABLE 1 - cont'd

Organism	MIC (mcg/ml) Bicyclomycin	Streptomycin	Ampicillin	Ref.
Enterobacter cloacae (8 strains)	25-200	3.13->800	800->800	22
Enterobacter cloacae (2 strains)	50	-	-	25
Proteus vulgaris IAM-1025	>800	50	100	22
Proteus vulgaris X-19	>500	-	-	7
Proteus vulgaris IAM-1025	>1,000	-	-	1
Proteus (5 strains)	>100	-	-	25
Pseudomonas aeruginosa IAM 1095	>800	50	>100	22
Pseudomonas aeruginosa 35	>500	-	-	7
Pseudomonas aeruginosa IAM 1095	>1,000	-	-	1
Pseudomonas aeuruginosa(2 strains)	>100	-	-	25
N.gonorrhoeae Matuura	25	1.56	<0.05	22
N.gonorrhoeae 1317/4	>100	-	-	25
N.meningitidis 68	>800	6.25	<0.05	22
N.meningitidis 1316	>100	-	-	25
Staphylococcus aureus (4 strains)	>800	6.25-12.5	0.1-0.39	22
Staphylococcus aureus FDA 209P	500	-	-	7
Staphylococcus aureus 209P JC-1	>1,000	-	-	1
Staphylococcus aureus (2 strains)	>100	-	-	25
Streptococcus hemolyticus S-23	>800	25	0.05	22
Streptococcus pyogenes	>100	-	-	25
Streptococcus faecalis 6733	>800	100	1.56	22
Streptococcus faecalis 1362/3	>100	-	-	25
Streptococcus faecalis 5	>500	-	-	7
Dipl.pneumoniae (3 strains)	>800	12.5-25	0.05-0.1	22
Bacillus subtilis ATCC-6633	>800	0.78	0.1	22
Bacillus subtilis ATCC-6633	>500	-	-	7

TABLE 1 - cont'd

Organism	MIC (mcg/ml) Bicyclomycin	Streptomycin	Ampicillin	Ref.
Bacillus subtilis ATCC-6633	>1,000	-	-	1
Bacillus anthracis 1	>500	-	-	7
Sarcina lutea PCI-1001	250	1.56	0.05	22
Sarcina lutea PCI-1001	62.5	-	-	7
Sarcina lutea PCI-100	250	-	-	1
Corynebacterium diphtheriae (5 strains)	800->800	0.78-6.25	0.1-0.39	22
Mycob. tuberculosis 607	>800	0.1	>800	22
Mycob. phlei 607	>500	-	-	7
Mycob. phlei	>1,000	-	-	1
Brucella melitensis K-3	0.9	-	-	7
Vibrio comma 384	3.9	-	-	7
Serratia marcescens 2	>500	-	-	7
Serratia marcescens 344	>100	-	-	25
Morganella 3	>500	-	-	7
Rettgerella 15	>500	-	-	7
Candida albicans YU-1200	>500	-	-	7
Candida albicans	>1,000	-	-	1
Candida albicans ATCC 11651	>100	-	-	25
Aspergillus niger N-1	>500	-	-	7
Penicillium chrysogenum Q-176	>1,000	-	-	1
Y.enterocolitica (43 strains)	12.5-100	-	≤0.1-25	17
Camp. jejuni (114 strains)	1.56-100	-	≤0.1-100	17
Haemophilus influenzae NCTC 4560	3.1	-	-	25
Treponema hyodysenteriae (23 strains)	100->100	12.5->100	1.56-6.25	24
Clostridium perfringens 194	>100	-	-	25

but inactive against Proteus, Morganella, Rettgerella, Pseudomonas, gram-positive bacteria and fungi. Interestingly, bicyclomycin shows no cross-resistance with typical antibacterial drugs such as streptomycin[23], kanamycin[23], chloramphenicol[23], tetracycline[23], ampicillin[23], nalidixic acid[23], or benzylpenicillin[26].

iii) In vivo activity

The most studied in vivo activity of bicyclomycin appears to be E. coli in mice. Bicyclomycin showed an ED_{50} of 12 mg/kg when administered subcutaneously and an ED_{50} of 102 mg/kg when administered orally twice, immediately after infection and after three hours[25]. Mice (27-30g) infected with E. coli of various strains resistant to typical antibiotics were treated with bicyclomycin subcutaneously once, one hour after infection, giving ED_{50} values of 0.69-4.05 mg/mouse[22].

Bicyclomycin has been shown[27] to decrease the enterobacteria counts in faeces of rats to about 3% of control levels at a dosage of 3 mg/kg orally four times in 40h. Growth of test organisms (E. coli, and Salmonella typhimurium) implanted in the rat jejunum (part of the small intestine between the duodenum and ileum) was also inhibited by bicyclomycin[27]. An ED_{50} of 26 mg/kg was observed for subcutaneous treatment of mice infected by Enterobacter cloacae[25].

Bicyclomycin, or its protein conjugates, have been observed to produce antibodies specific to this antibiotic when injected into rabbits, guinea pigs, or monkeys. However no antibodies were produced on oral administration to rabbits[26]. These results of antigenicity in animals may mean that bicyclomycin possesses a sensitizing activity in man by analogy with penicillins and cephalosporins[26].

The efficacy of orally administered bicyclomycin on shigellosis in rhesus monkeys infected with a lethal dose of Shigella flexneri has been studied[23].

A daily dosage of 40mg/kg for 5 days restored normal faeces in 8.6±1.1 days, compared with 15.3±1.1 days for treatment with kanamycin. Death resulted in 5 out of 7 untreated control monkeys. Studies on human volunteers and monkeys have shown that after oral administration recovery of bicyclomycin in the urine was low, but recovery from the faeces was high[23]. It has also been reported that bicyclomycin does not interfere with the normal protective intestinal flora[27]. These results indicate that bicyclomycin is poorly absorbed from the gastrointestinal tract[23], and that the antibiotic may be of use in the treatment of gastrointestinal infections[23,27].

iv) Pharmacokinetics

If bicyclomycin is administered intramuscularly in mice, rats, rabbits, or dogs the peak levels in blood serum were found to be fairly high[28]. The half-life of bicyclomycin in rabbit serum was 45 minutes after intravenous injection, as compared to 22 minutes for ampicillin[28]. Intramuscular injection into rats indicated that bicyclomycin transfer into the bile was low[28], and that the highest tissue concentrations were in the kidney (403.5mcg/g after a dose of 100mg/kg) followed by the liver, lung, heart and spleen[28].

The excretion of bicyclomycin has been extensively studied in both animals and humans. Intramuscular administration to rats, rabbits, dogs, and humans resulted in recovery of bicyclomycin in the urine of 93,77,74, and 95-96% respectively in 24h[28]. No metabolite (except bicyclomycin) possessing antimicrobial activity was found in the urine from human volunteers. Excretion after oral administration has been studied in rats, monkeys and humans[23,28]. In rats, after an oral dose of 100mg/kg, 24% of the antibiotic was excreted in the urine during 24 hours[28], but in monkeys[23] and humans[28] doses of 40mg/kg and 1g respectively produced low urinary excretions of 3.1 and 2.9% respectively. However, oral administration to monkeys[23] and humans[28] produced high faecal excretions of 46 and 73% respectively.

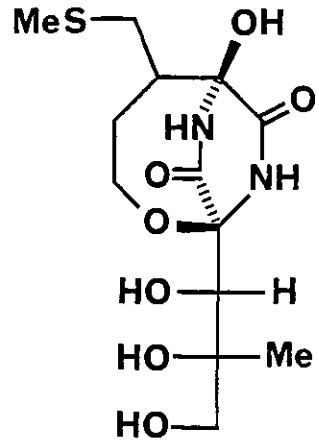
In summary, these results indicate that bicyclomycin is absorbed well in rats, dogs, rabbits and humans by intramuscular injection, but only weakly absorbed in rats and very poorly absorbed by monkeys and humans after oral administration.

At present metabolic pathways of bicyclomycin in vitro and in vivo have not been determined.

v) Morphological changes induced in bacterial cells and mode of action.

Electron microscopic studies[29,30] on E. coli have shown that bicyclomycin inhibits septum formation resulting in filamentous cells and causes high undulation and numerous blebs of the outer membrane. Breakage of the outer membrane or the blebs led to cell lysis[29]. Formation of the elongated cells was induced at a level of 12.5 µl /ml of bicyclomycin, and osmotically fragile spheroplast-like cells were induced at a lethal concentration of 25 µl /ml.

The mechanism of action of bicyclomycin has been studied[30,31,32,33] and reviewed[34]. Bicyclomycin binds to the inner membrane proteins of E. coli and the olefinic double bond is proposed[31] to react with a sulphydryl group at the receptor protein. Binding was inhibited by the presence of dithiothreitol and 2-mercaptoethanol and treatment of bicyclomycin with sodium methanethiolate yielded an adduct (5). It is believed that bicyclomycin inhibits the biosynthesis of the bound form of lipoprotein covalently linked to peptidoglycan[34]. The exact mechanism of this inhibition has not been determined but may proceed by one of three mechanisms: 1) interference with the biosynthesis of the free form lipoprotein, resulting in incapability of binding to peptidoglycan, 2) the inhibition of the cross-link reaction of free form lipoprotein and peptidoglycan, or 3) the formation of an unusual peptidoglycan, lacking the ability to bind with free-form lipoprotein.



(5)

Miscellaneous properties

An unusual property of bicyclomycin is its ability to promote the growth of animals[35]. Incorporation of 1-200 ppm bicyclomycin into the feed of chickens and swine stimulates growth. For example, 1-day old chickens fed a diet with and without 3 ppm bicyclomycin for 8 weeks had weight increases of 1842 and 1707 g respectively.

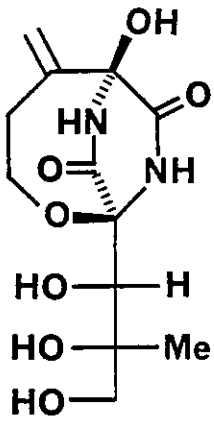
Semi-synthetic derivatives of bicyclomycin

Numerous semi-synthetic derivatives of bicyclomycin (1) have been prepared and reported principally in the patent literature[36-49], although some reports in the chemical literature have appeared[4,25]. Of the large number of derivatives only a few will be mentioned here.

Bicyclomycin itself is poorly absorbed from the gastrointestinal tract, but it was found that various 3′-acyl derivatives[4,25] were absorbed and excreted in the urine as bicyclomycin. In contrast 2′,3′-diacyl derivatives were excreted unmetabolized, and the activity of such derivatives[4] was low.

Derivatives of structural type (6),(7), and (8) were generally inactive *in vitro*[25] (MIC >100 mcg/ml). However, compounds (6) (R^1-R^5=H, R^6=COEt;

R^1-R^5=H, R^6=THP; R^1-R^3,R^5-R^6=H, R^4=COPh; R^1-R^4=H, R^5/R^6=$C(CH_3)_2$) showed ED_{50} values for E.coli in mice[25,40] of 30,30,60, and 65 respectively compared to 12 mg/kg for bicyclomycin (1)



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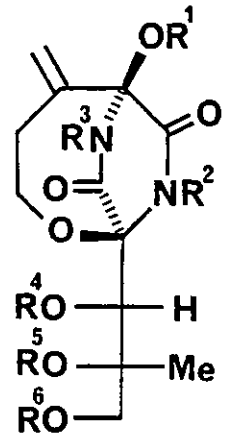
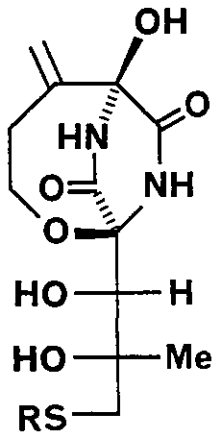


R^{1-6} = H, alkyl, Ⓟ

(6)



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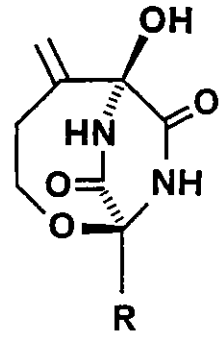


R = R′C=X

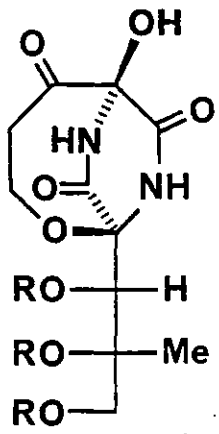
= R′C=CR′$_2$

= R′$_2$COH

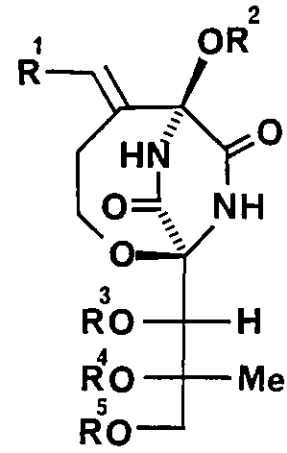
(8)

Perhaps the most significant derivatives of bicyclomycin are those derived from 5-norbicyclomycin-5-one (9) such as compounds of type (10)[25,49] and (11)[25,39,36,46]. Some of the 5-alkylidene (10) and 5-imino (11) compounds exhibited a broader range of biological activity in vitro than bicyclomycin and

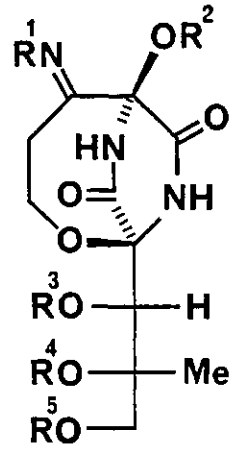
were active against Proteus[25], the most active being (10)(R^1=CO_2Me, R^2-R^5=H). Compounds of type (12) are generally inactive or weakly active[25].



(9) R=H, Ⓟ

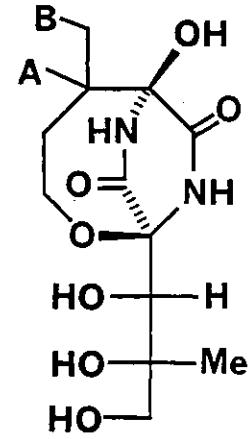


(10) R^1=CO_2R, COR, CN
R^2-R^5=H, Ⓟ



R^1= OH, OR, NR_2
R^2-R^5=H, Ⓟ

(11)



A=B=H, Br, OH
A/B=

(12)

However results on compounds of this type (12) cast some doubts on the proposed mechanism of action of bicyclomycin[31] which involves addition of a sulphydryl group onto the 5-exocyclic double bond. It has been reported that dihydrobicyclomycin (12) (A=B=H) exhibits no significant activity (no details given)[31], but another report indicates that dihydrobicyclomycin has antimicrobial

activity against E. coli, Salmonella typhosa, and Shigella flexneri[47]. Another apparent anomaly is the activity of 5,11-dibromo-5,11-dihydrobicyclomycin (12) (A=B=Br) which has been reported to have ED_{50} values[25,48] of 65 and 60 mg/kg for E. coli in mice (s.c.). It is, of course, possible that bicyclomycin and its derivatives act by a different mechanism or are metabolised.

On the basis of the limited biological data in the patent literature it seems that most derivatives of bicyclomycin are either inactive, or less active than the parent compound, although the 5-alkylidene and 5-imino derivatives do show promising activity.

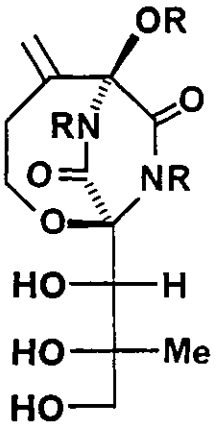
REVIEW

SYNTHETIC APPROACHES TO

BICYCLOMYCIN

SYNTHETIC APPROACHES TO BICYCLOMYCIN

From 1980 onwards bicyclomycin (1) has been the subject of intense synthetic effort, and numerous synthetic approaches to bicyclomycin have been reported[50-65]. The most successful fully reported approach is the synthesis of (±)-N,N',O-trimethylbicyclomycin (13)[57], although the total synthesis of bicyclomycin has now been achieved by two groups, as judged by material presented in lectures[58,63].



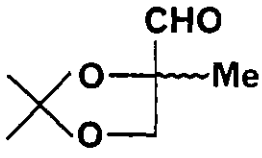
(1) R = H

(13) R = Me

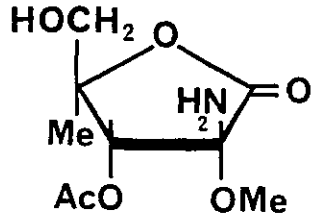
a) Approaches to synthons for the trihydroxypropyl side chain

Generally [57,58,62] racemic 2,3-O-isopropylidene-2-C-methyl-DL-glyceraldehyde (14) has been used as the synthon for this portion of bicyclomycin and its use will be discussed subsequently.

In the abstract literature[64] the sugar 4-C- methyl-2-O-methyl-2-C-amino-DL-ribono-1,4-lactone (15) has been described as a potential intermediate.

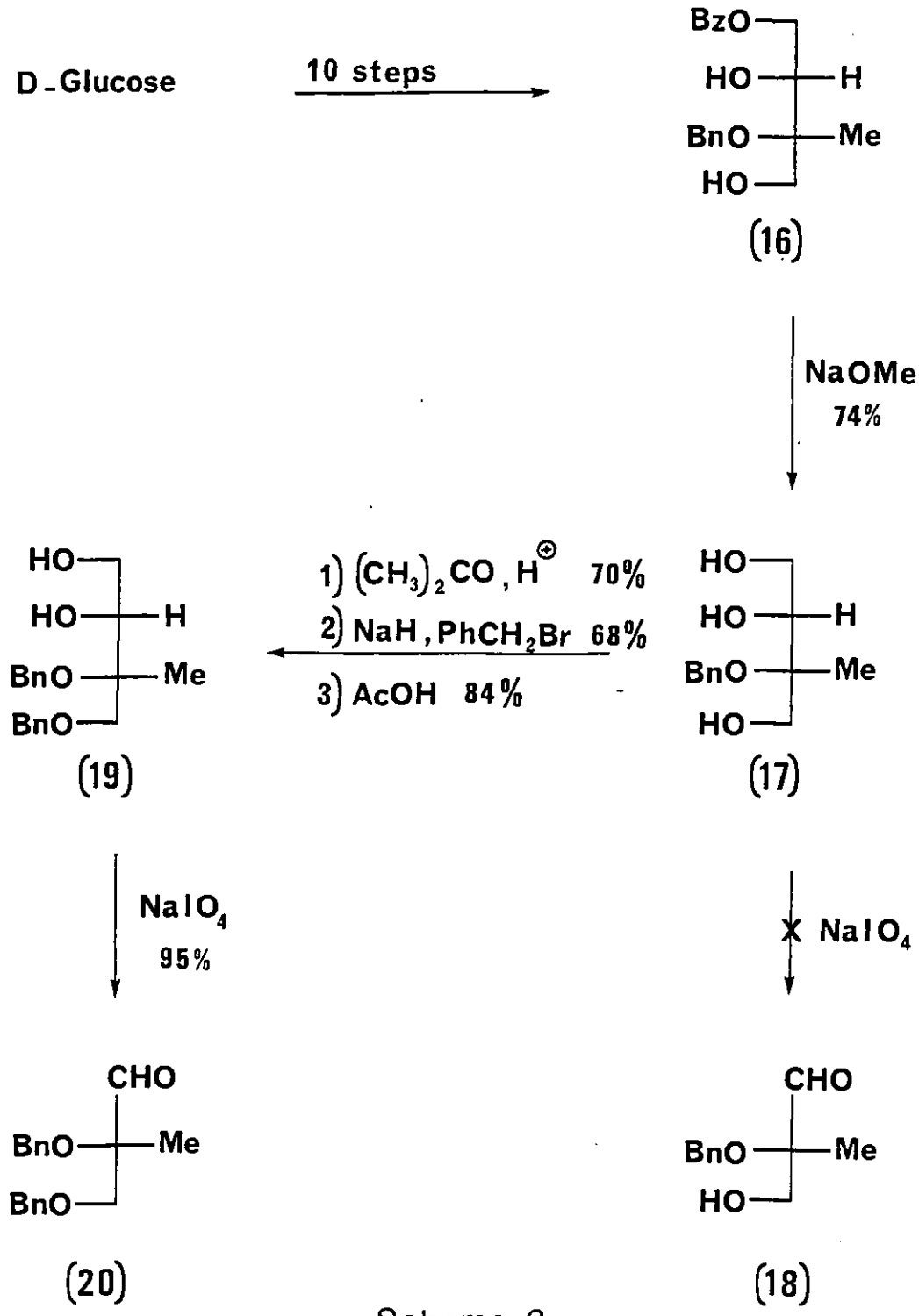


(14)

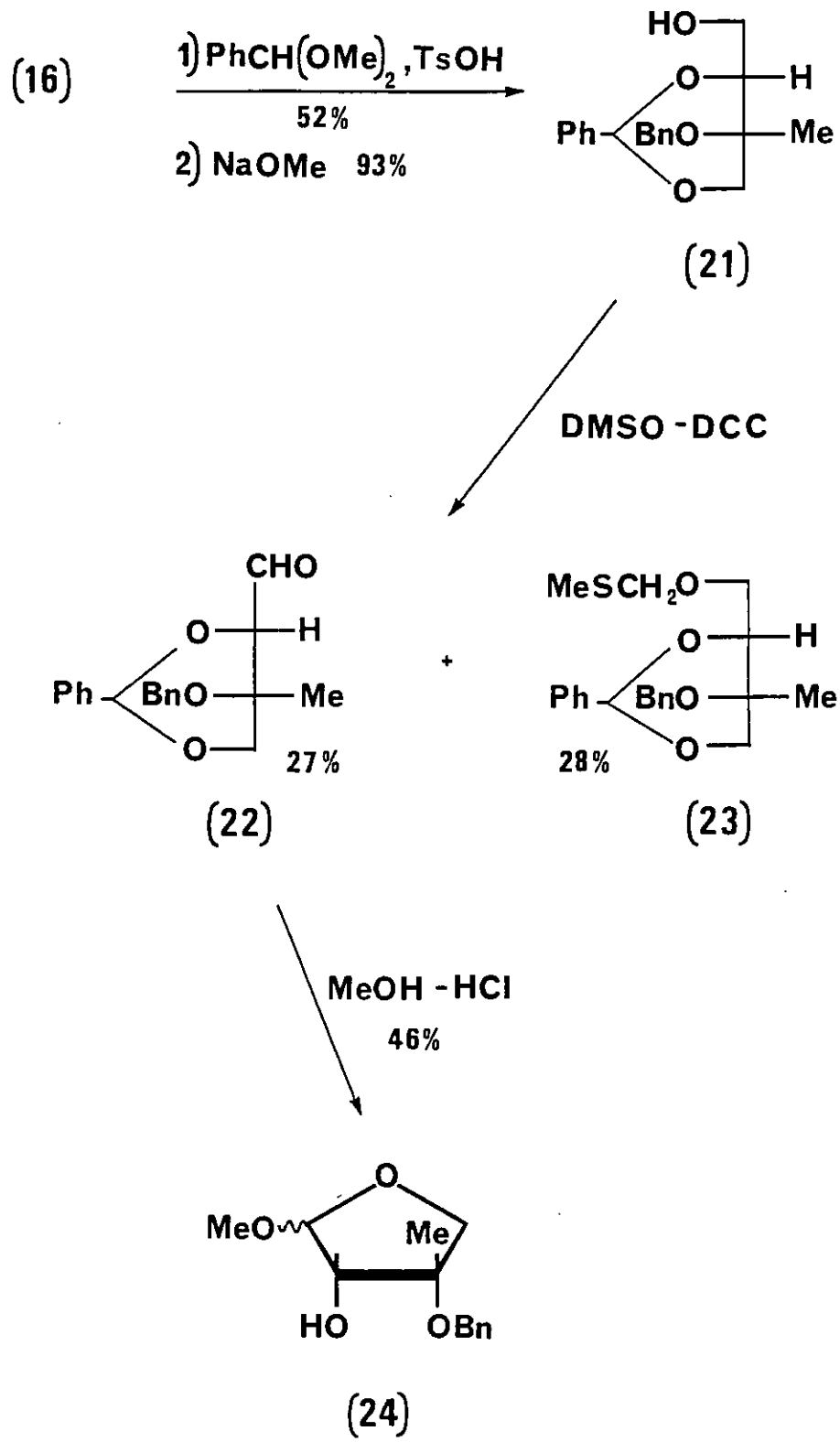


(15)

Work by Yoshimura[65] has provided some potentially useful chiral sythons for bicyclomycin synthesis. However, the routes to these compounds are rather long (Scheme 3), and the stability of the glyceraldehyde derivatives (18) and (20) seems to be low. Thus (18) was unstable and (20) was only stable at room temperature "for a few hours", although aldehyde (22) appears to be stable.



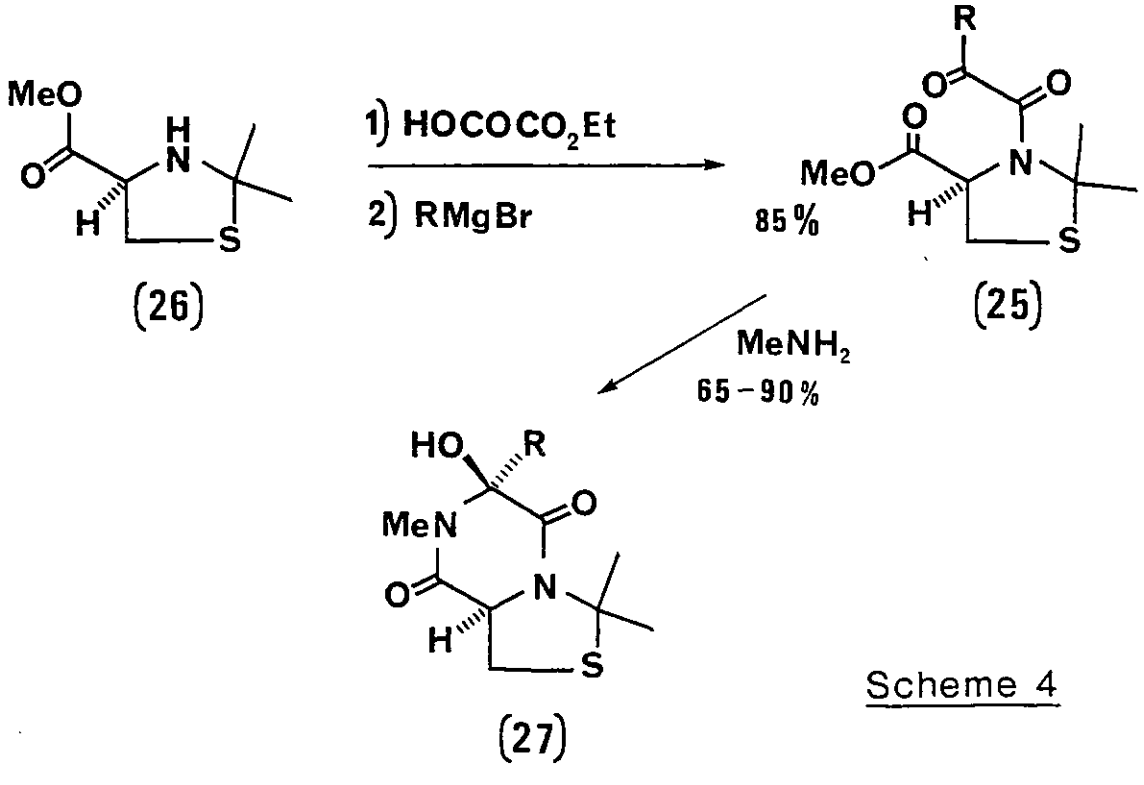
Scheme 3



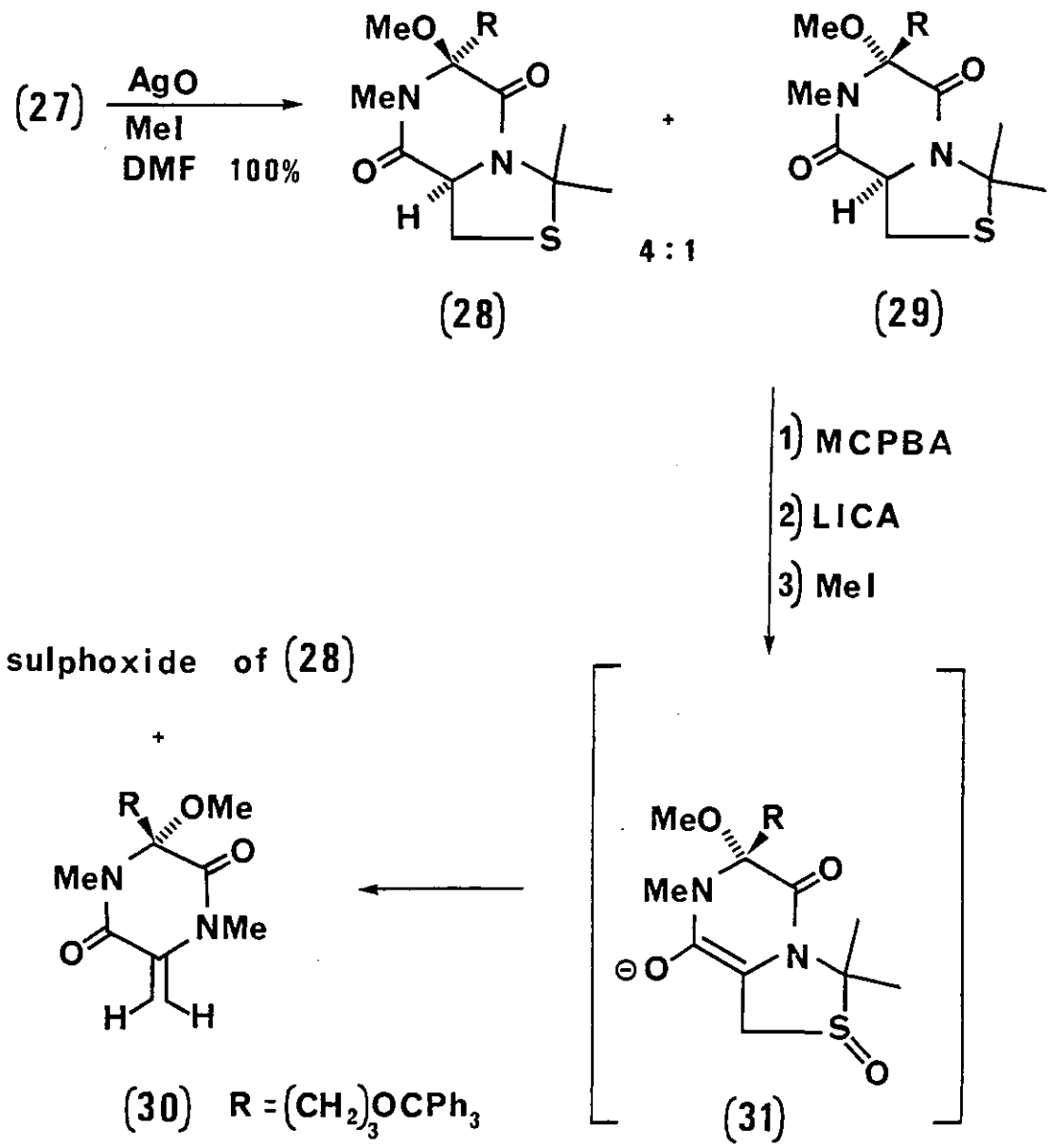
Scheme 3 cont'd

b) Approaches involving construction of the 2,5-piperazinedione moiety at a late stage.

The first synthetic approach to bicyclomycin was published by Dunkerton[52] and involved the construction of the 2,5-piperazinedione moiety by reaction of α-keto-amide (25) (derived from L-cysteine thiazolidine methyl ester (26)) with a suitable amine such as methylamine to give (27) exclusively (Scheme 4). Subsequent methylation resulted in some racemisation (60-80% retention) to give (28) and (29) (4:1). Treatment of this mixture with m-chloroperbenzoic acid (MCPBA) and subsequent elimination with lithium N-cyclohexylisopropylamide (LICA) and methylation (MeI) gave 6-alkylidene-2,5-piperazinedione (30) and unreacted diasteriomeric sulphoxide of (28). This diastereoselectivity is proposed to arise from lithium chelation with the methoxy group followed by syn intramolecular proton abstraction giving enolate (31). The yield of (30) is quoted as 100%, but must be very low since the reacting diastereomer of the mixture (28) and (29) (4:1) is the minor component. It was planned[53] to form bicyclic systems from the epoxide derived from (30). This approach to bicyclomycin systems is far less elegant than subsequently published approaches involving 6-alkylidene-2,5-piperazinediones, and no further work on this approach has been published.

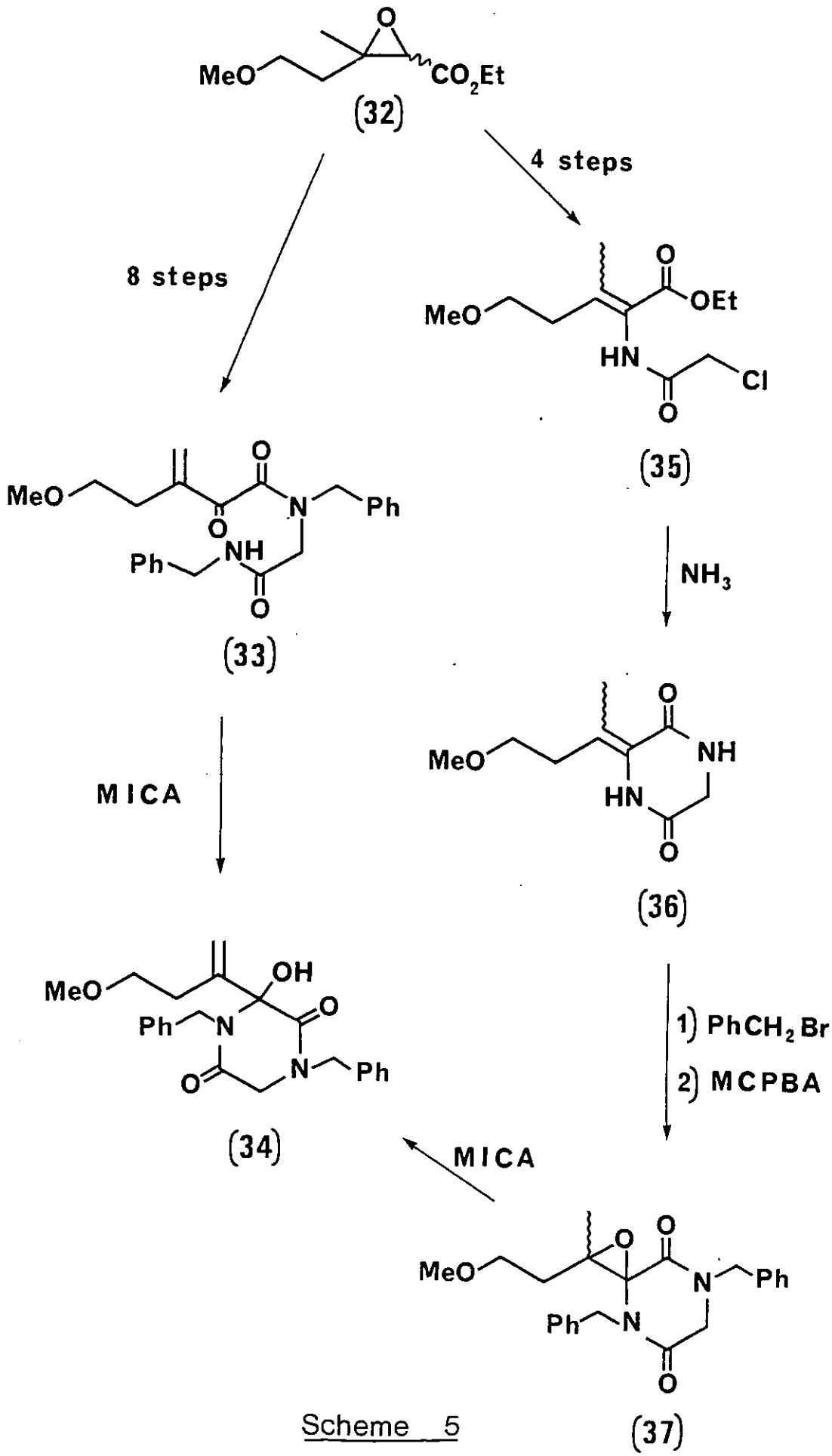


Scheme 4



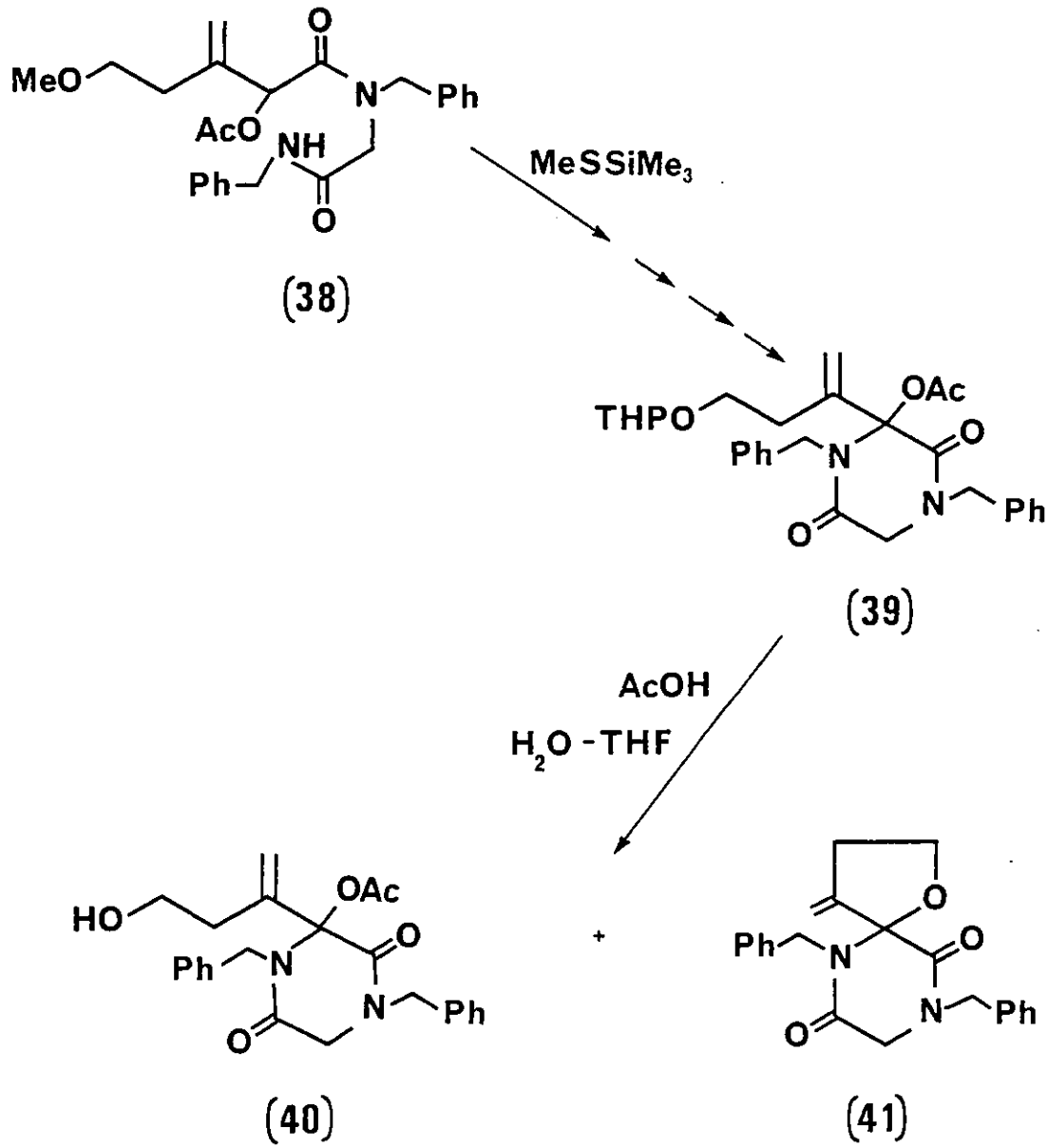
Scheme 4 cont'd

Another approach[51] (Scheme 5) to the construction of the 2,5-piperazine-dione moiety also involved cyclisation of an α-keto-amide, this time intra-molecularly with an amide. Glycidate (32) (available from 4-methoxybutan-2-one and ethyl chloroacetate) was converted in 8 steps to α-keto-amide (33) which was cyclised with magnesium cyclohexylisopropylamide (MICA) to give 2,5-piperazinedione (34) in 11% overall yield from (32). (34) was also synthesised from (32) in 6% overall yield via (35), (36), and (37). The conversion of epoxide (37) into (34) is an elegant method of introducing the exocyclic methylene and tertiary alcohol.


MeO
CO2Et
(32)
4 steps
8 steps
MeO
OEt
HN
Cl
(35)
MeO
N
Ph
NH
Ph
(33)
NH3
MeO
NH
HN
(36)
MICA
MeO
OH
Ph
N
N
Ph
(34)
1) PhCH2Br
2) MCPBA
MICA
MeO
N
Ph
Ph
N
(37)

Scheme 5

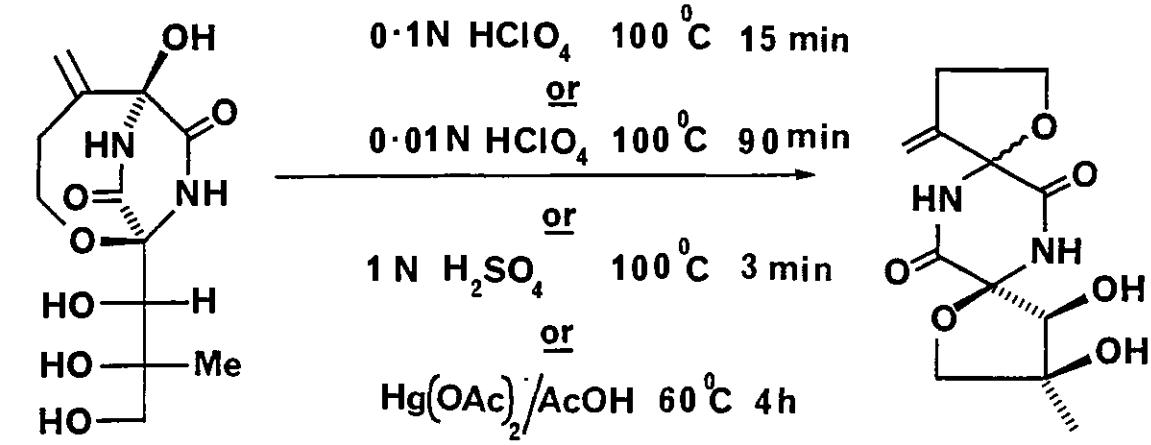
Further elaboration of (34) was not possible due to difficulties encountered on deprotection with trimethylsilyl iodide. However, demethylation of intermediate (38) with methylthiotrimethylsilane was successful and subsequent reaction as previously yielded the tetrahydropyranyl ether (39) (Scheme 6). Attempted deprotection of (39) with acetic acid led to the desired alcohol (40) along with spiro-compound (41) in a ratio of 3:1.



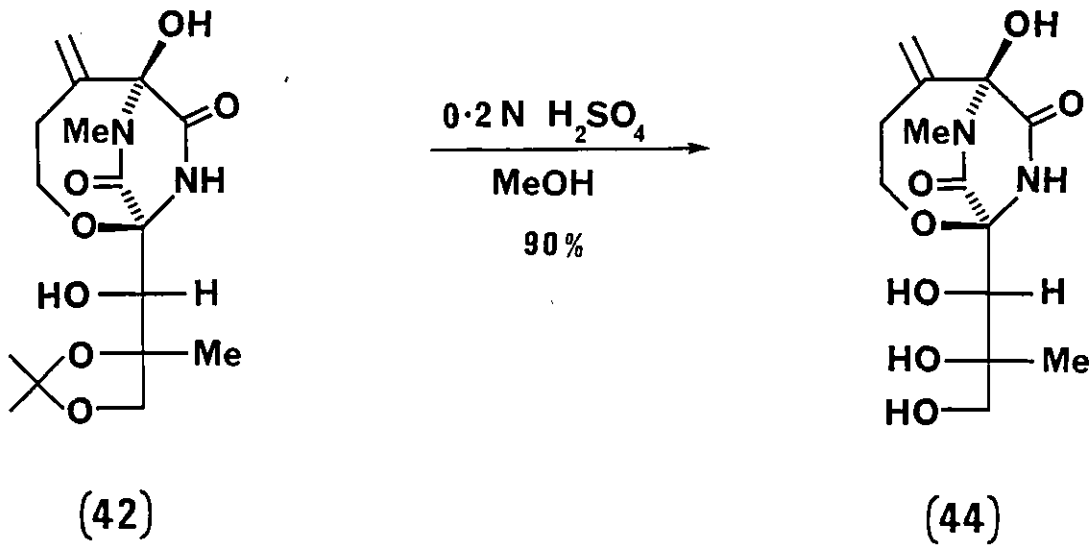
Scheme 6

Formation of spiro-compound (41)(Scheme 6) highlights the necessity of avoiding excessively acidic conditions when designing the synthesis of bicyclomycin. N-methylbicyclomycin (44) is stable to very dilute acid such as 0.2N

sulphuric acid in methanol as shown by the deprotection of acetonide[25] (42) (Scheme 7), but bicyclomycin is unstable to strong acids and decomposes to the diastereomeric spiro-compound (43).



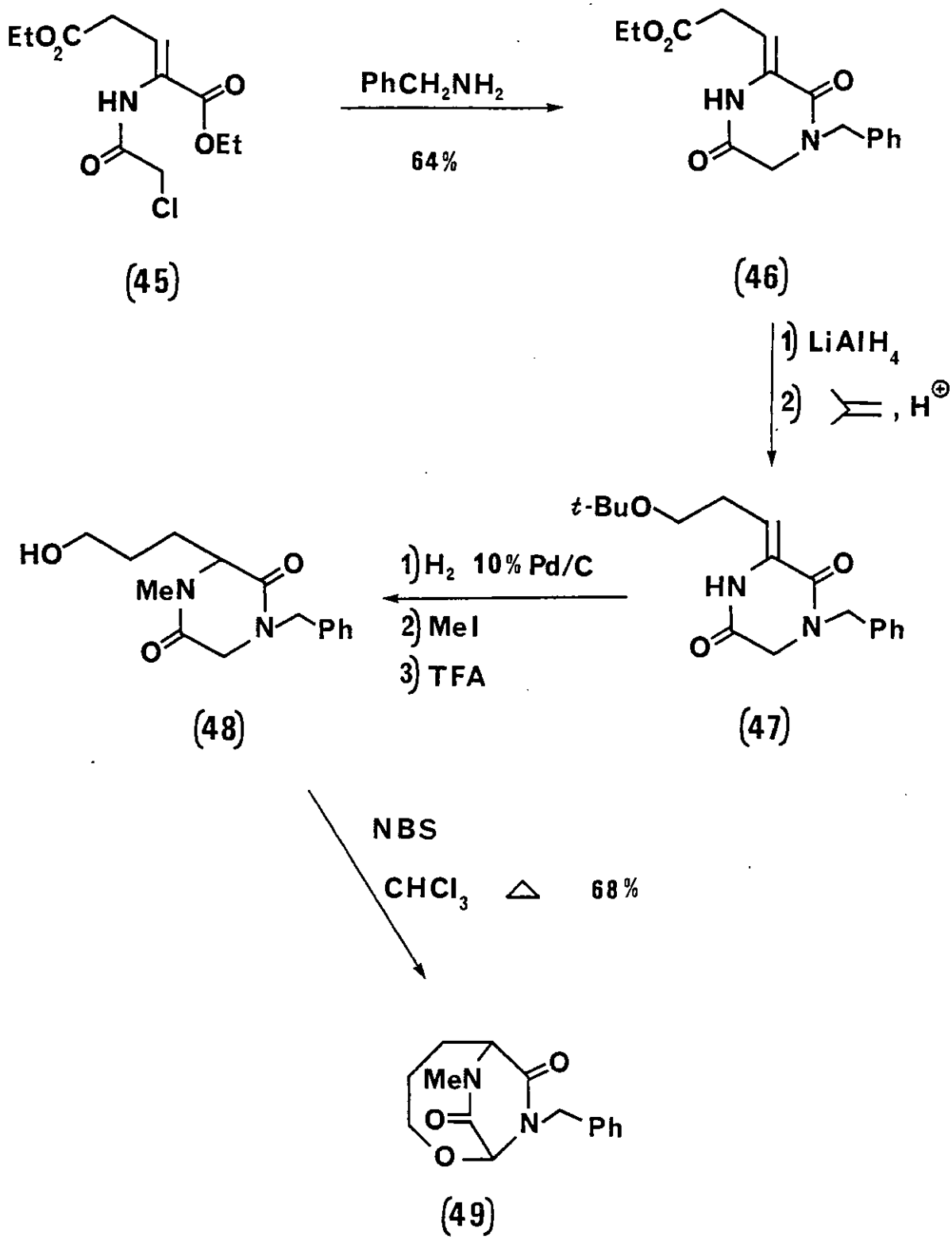
(1) (43)



(42) (44)

Scheme 7

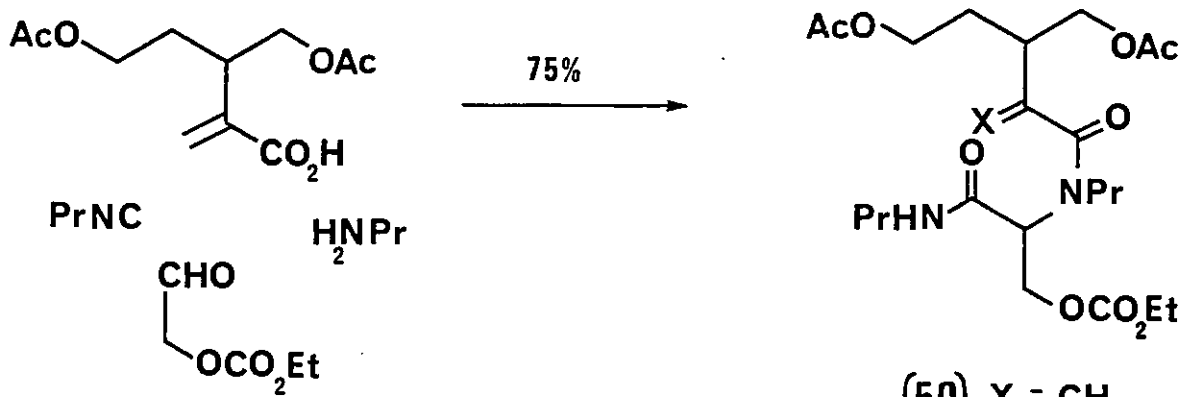
The 2,5-piperazinedione moiety of bicyclomycin has also been constructed by reaction of an amine with an α-chloro-amide by Shin[54] (Scheme 8). Thus α-chloroamide (45) (derived from ethyl 4-ethoxycarbonyl-2-oxobutanoate and


EtO2C
HN
O
OEt
O
Cl
PhCH2NH2
64%
EtO2C
HN
O
N
Ph
O
(45)
(46)
1) LiAlH4
2)
, H⊕
t-BuO
HN
O
N
Ph
O
1) H2 10% Pd/C
2) MeI
3) TFA
HO
MeN
O
N
Ph
O
(47)
(48)
NBS
CHCl3
68%
MeN
O
N
Ph
O
O
(49)

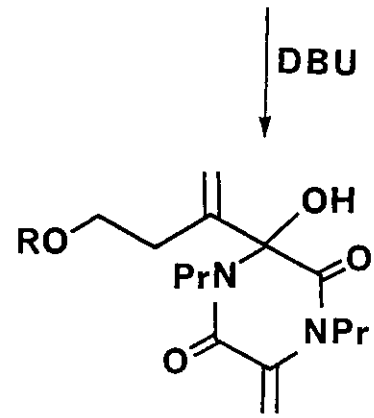
Scheme 8

chloroacetamide) was treated with benzylamine to give 3-alkylidene-2,5-piperazinedione (46) in 64% yield. Reduction of the ester group and protection of the resulting alcohol gave t-butyl ether (47). Hydrogenation, methylation and deprotection gave alcohol (48) in 83% yield from (47). Cyclisation of (48) with N-bromosuccinimide in chloroform at reflux gave the bicyclic model compound (49) in 68% yield. Interestingly no production of the corresponding spiro-compound was reported.

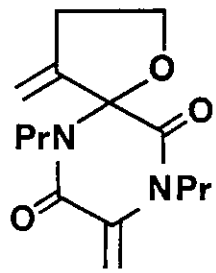
An interesting approach by Fukuyama[50] also led to bicyclic systems. The 2,5-piperazinedione moiety of bicyclomycin was again constructed from an α-keto-amide (51) by intramolecular addition of an amide (Scheme 9). The basic acyclic skeleton was established by a versatile Ugi four-component condensation reaction to give amide(50) which was ozonised to give the α-keto-amide (51). Treatment of (51) with DBU resulted in three transformations - elimination of acetic acid, cyclisation to form the 2,5-piperazinedione ring, and elimination of carbonate to give the 3-alkylidene-2,5-piperazinedione (52) in 55% yield from (50). Hydrolysis yielded alcohol (53) which was found to be very acid sensitive, yielding the spiro-compound (54) on treatment with hydrochloric acid in dichloromethane. However, cyclisation induced by pyridinium hydrobromide perbromide or phenylselenyl chloride yielded bicyclic derivatives (55) and (56) respectively in 65 and 70% yield. The bromide (55) was synthetically useless for SN2 type reactions. The selenide (56) was converted by oxidation, Pummerer rearrangement, and hydrolysis to the aldehyde (57). (57), a potentially versatile intermediate, was reacted with a suitable Wittig reagent yielding (58). Reaction of aldehyde(57), generated *in situ* by reaction of the intermediate acetoxyselenide derived from (56), with isopropenyllithium gave alcohol (59). Further elaboration of (58) and (59) to bicyclomycin analogues was not reported. This approach, therefore, demonstrates an interesting bicyclisation reaction, but suffers from the disadvantage (as with many of the published approaches) of using alkyl-amide protecting groups.



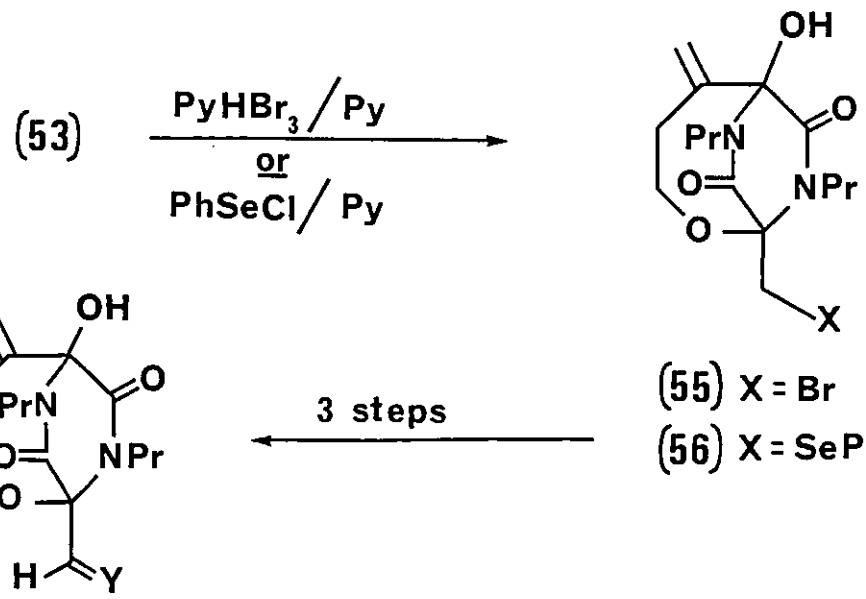
(50) X = CH_2
(51) X = O



(52) R = Ac
(53) R = H



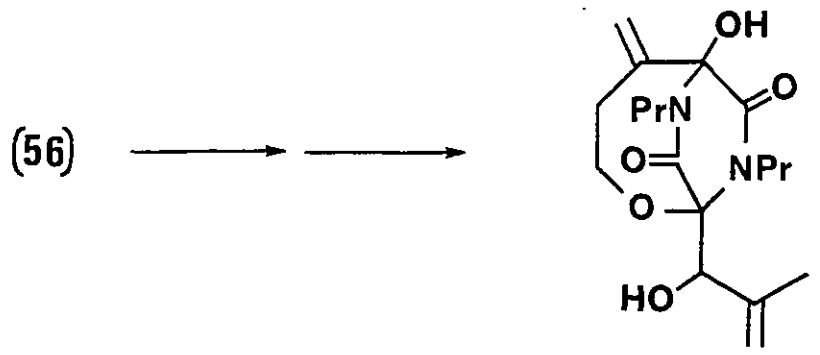
(54)



(55) X = Br
(56) X = SePh

(57) Y = O
(58) Y = $C(CH_3)CO_2Et$

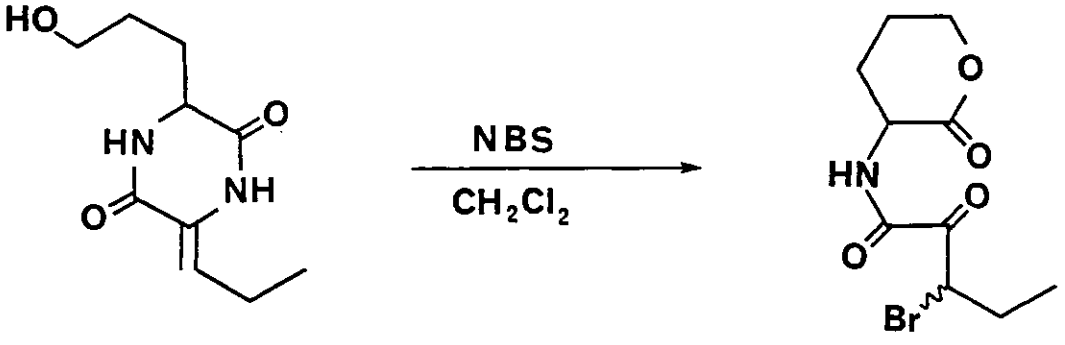
Scheme 9



(59)

Scheme 9 cont'd

A brief report by Dirlam[60] also mentioned bicyclisation studies on 3-alkylidene-2,5-piperazinediones (Scheme 10). However, in this case, treatment of (60) with N-bromosuccinimide failed to yield any bicyclic compound but gave the lactone (61), presumably by amide cleavage and subsequent hydrolysis on work up.



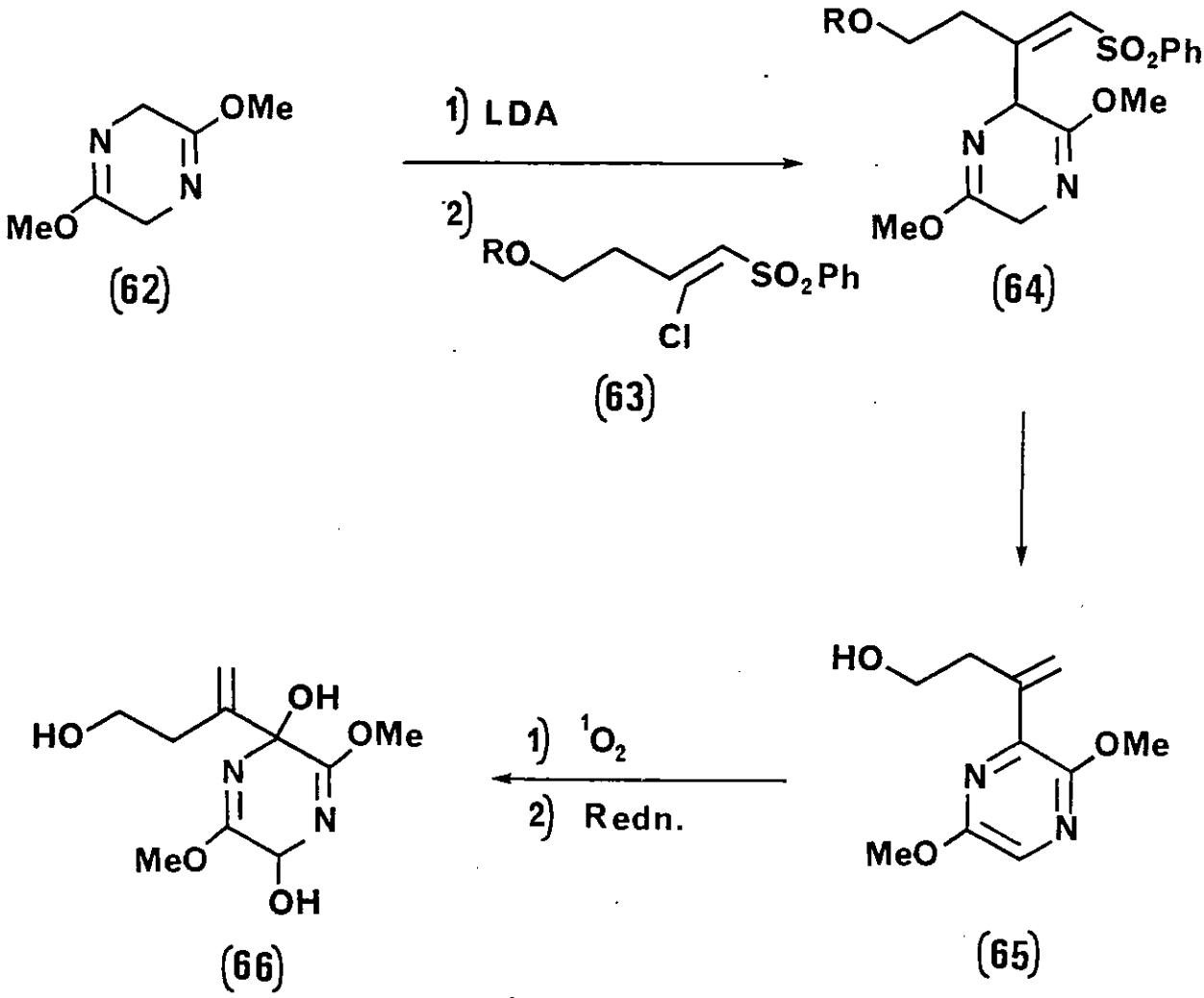
(60) (61)

Scheme 10

c) Approaches involving carbanions of 2,5-piperazinedione derivatives

The most widely used approach to bicyclomycin is to construct the precursors for bicyclisation via the use of carbanions derived from 2,5-piperazinediones or their equivalents.

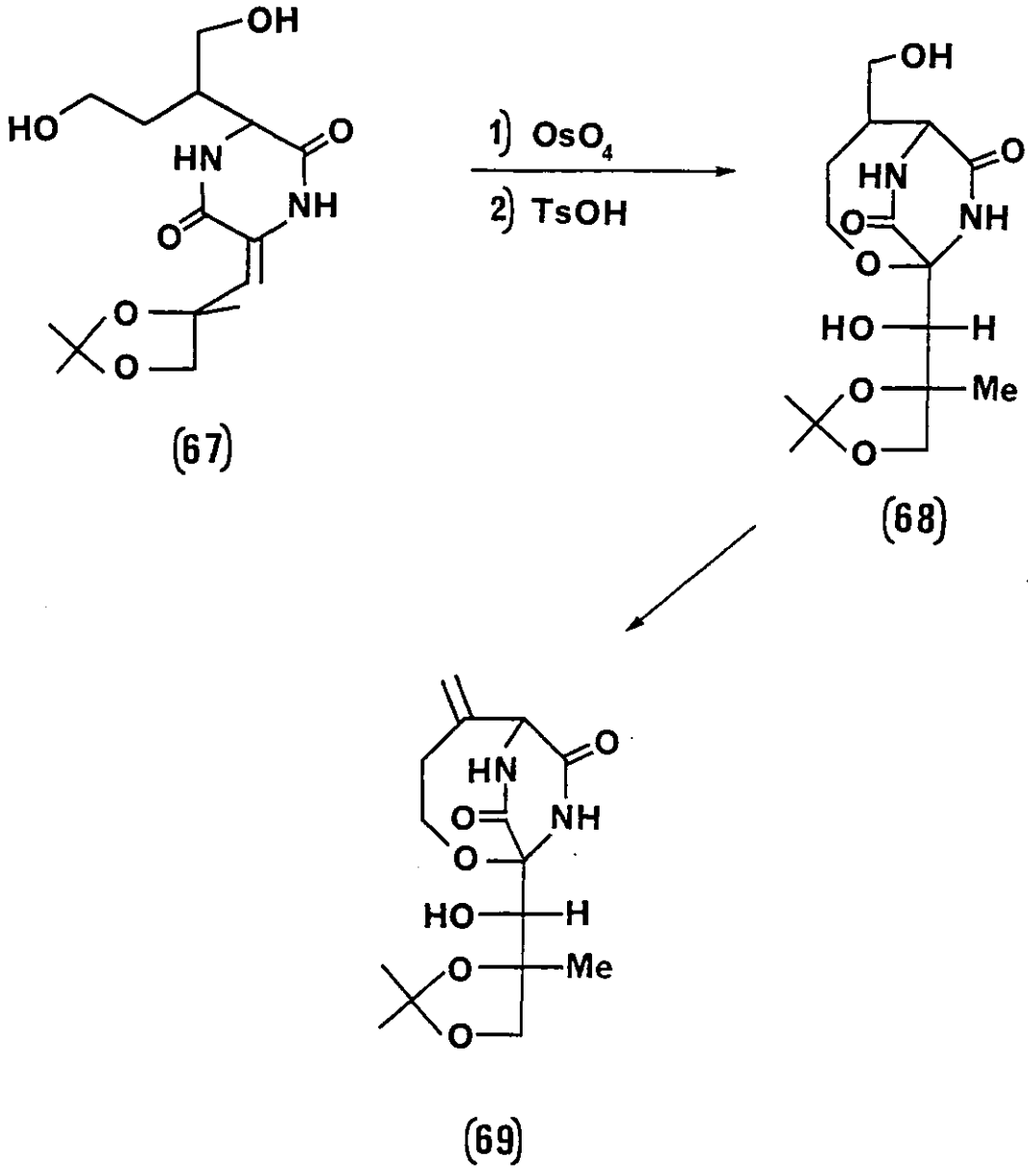
One approach described in lecture form by Sammes[59], was to use the carbanion derived from 3,6-dimethoxy-2,5-dihydropyrazine (62) which on reaction with vinyl-chloride (63) lead to adduct (64) (Scheme 11). Subsequent elimination of the sulphone group and deprotection led to pyrazine (65) in 50% yield from (62). Cycloaddition of pyrazine (65) with singlet oxygen and reduction (mimicking a proposed [21] biosynthetic pathway to bicyclomycin) gave triol (66). Bicyclisation studies on triol (66) were not reported and no published material has been forthcoming.



Scheme 11

Carbanion chemistry of 2,5-piperazinediones was used by Maag[55] to prepare the 3-alkylidene-2,5-piperazinedione (67) (Scheme 12). Oxidation with osmium tetroxide and cyclisation with p-toluenesulphonic acid yielded (68) (no yield available) which was further elaborated to give racemic 6-desoxy-

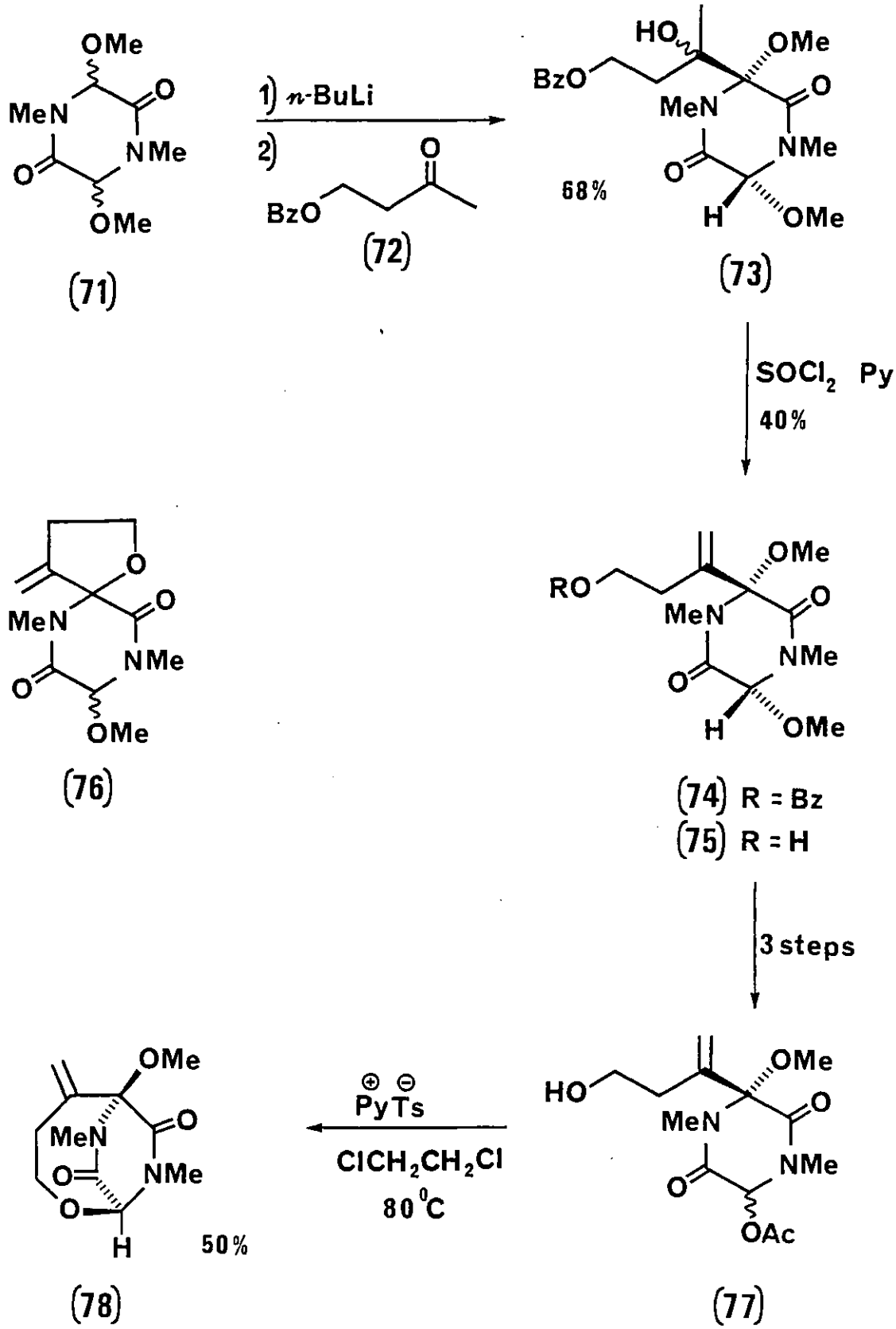
bicyclomycin derivative (69). No details of this synthesis have been published.



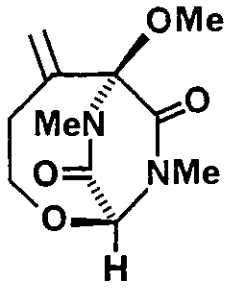
(67) (68) (69)

Scheme 12

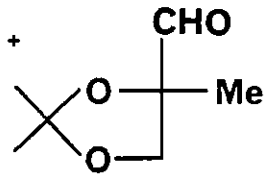
One of the major contributions to the field of bicyclomycin synthesis is the work[56-58] of Nakatsuka. The synthesis[56,57] of N,N',O-trimethylbicyclomycin (70) has been achieved, commencing with the stereoselective reaction of the carbanion of 3,6-dimethoxy-2,5-piperazinedione (71) with ketone (72) to give alcohol (73) (Scheme 13). Dehydration with thionyl chloride gave the exo-olefin (74) in low yield (40%) along with corresponding endo-olefin (33%). Hydrolysis of (74) gave alcohol (75). Interestingly attempted cyclisation of (75) with camphorsulphonic


OMe
MeN
O
NMe
O
OMe
(71)
1) n-BuLi
2)
O
BzO
(72)
HO
OMe
BzO
MeN
O
NMe
O
H
OMe
68%
(73)
SOCl2 Py
40%
OMe
RO
MeN
O
NMe
O
H
OMe
(74) R = Bz
(75) R = H
3 steps
OMe
HO
MeN
O
NMe
O
OAc
(77)
⊕ ⊖
PyTs
ClCH2CH2Cl
80 °C
OMe
MeN
O
NMe
O
O
H
50%
(78)
O
MeN
O
NMe
O
OMe
(76)

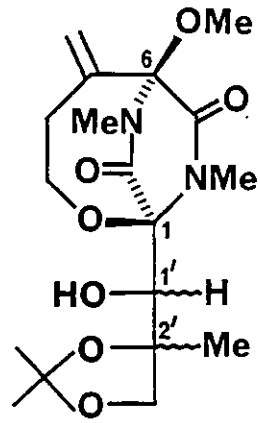
Scheme 13



(±)(78)



(±)(79)



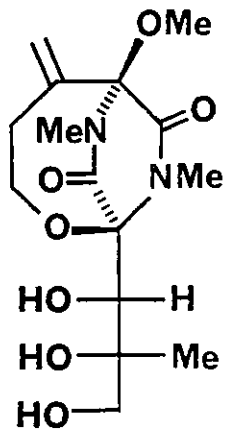
(80)

a) 1S,6R,1'S,2'S

b) " , " ,1'R, "

c) " , " ,1'S,2'R

d) " , " ,1'R, "



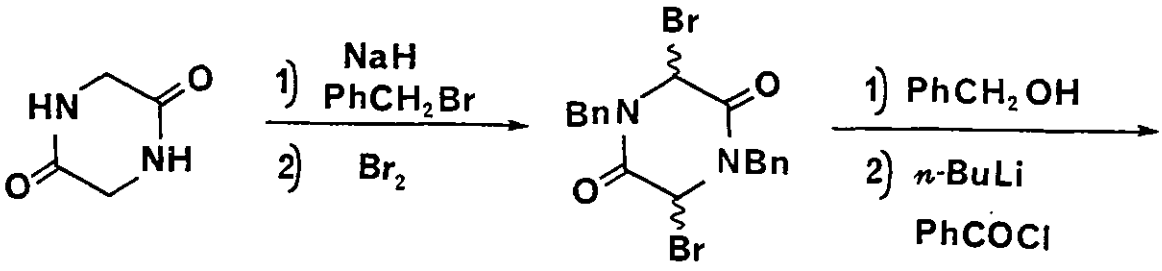
(70)

Scheme 14

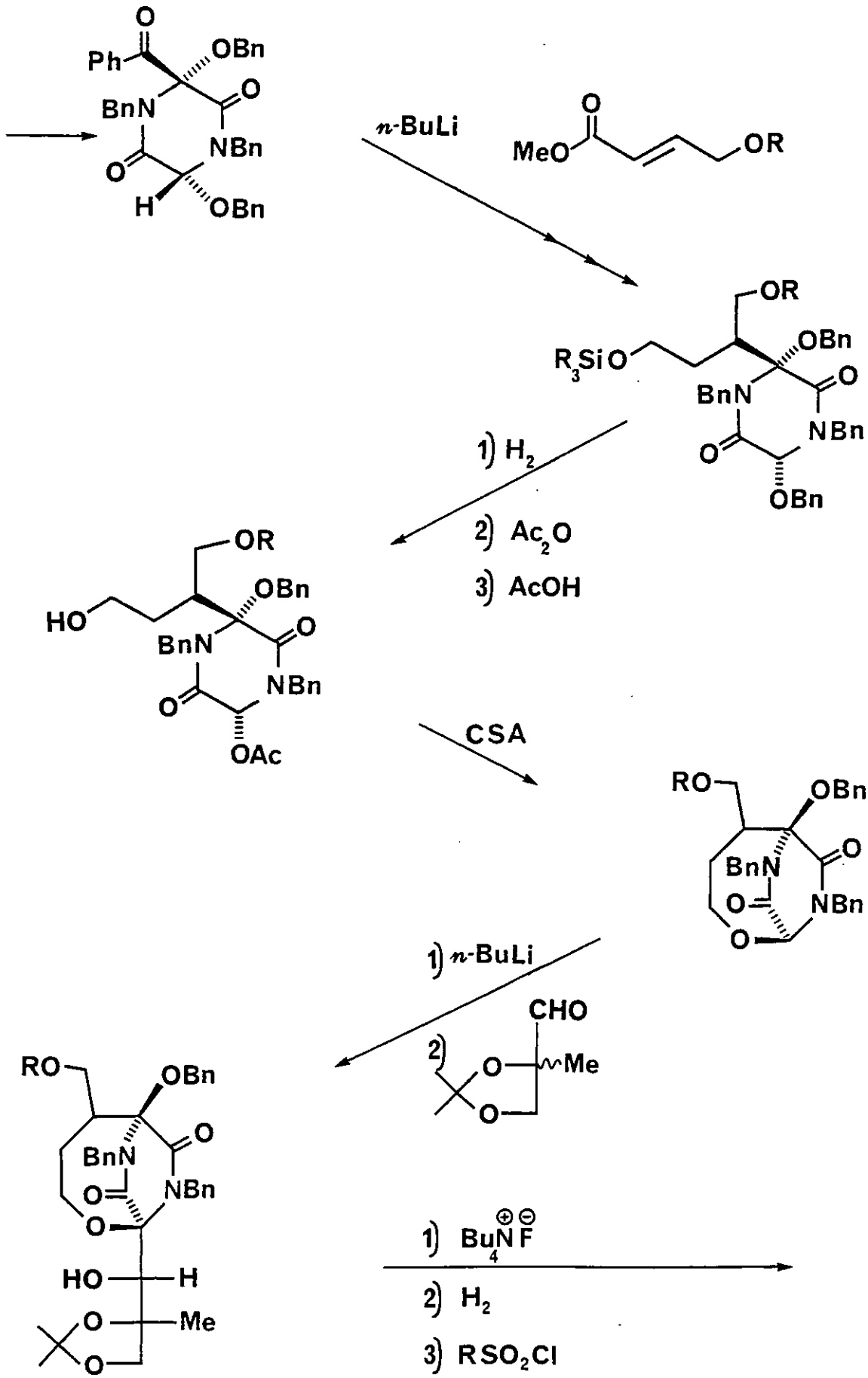
acid in methanol at reflux afforded spiro-compound (76) (40% compared to 20% of desired bicycle (78)), again indicating the acid instability of the bicyclic system of bicyclomycin[19]. Thus (75) was converted into acetate (77) and cyclised effectively with pyridinium p-toluenesulphonate in dichloroethane at 80°C to give bicyclic compound (78). (78) was also found to be unstable to camphor-sulphonic acid, rearranging to spiro-compound (76) (80%).

Formation of the bridgehead carbanion from racemic (78) was effected with LDA and reaction[57] with racemic glyceraldehyde derivative (79) yielded alcohol (80) as a mixture of diastereomers in a ratio of 9:3:3:1 (Scheme 14). For simple aldehydes such as i-butyraldehyde and methacrolein a stereoselectivity of 4:1 was observed, and this is attributed to steric approach control induced by the N-methyl group on the 2,5-piperazinedione (78). Aldol condensation with glyceraldehyde derivative (79) gave an improved ratio of 9:3:3:1 where the combination of chiral centres C-1′ and C-2′ appear to exert some degree of mutual stereo-control. However it must be said that the yield of the combined isomers was low (46%). The separated major isomer (80a) was hydrolysed to give (±)N,N′,O-trimethylbicyclomycin (70).

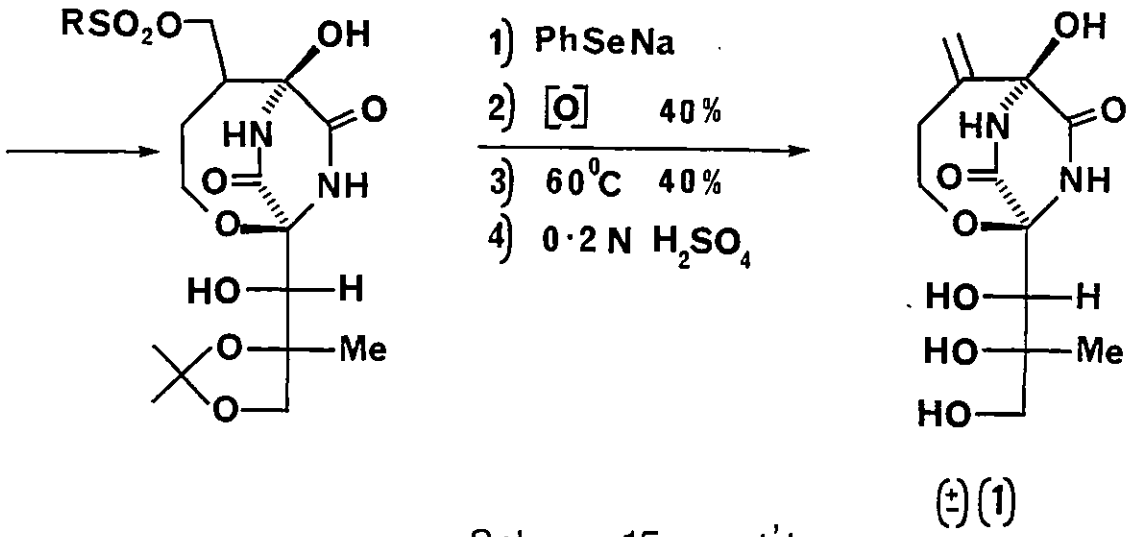
Use of basically the same strategy has been reported[58] in a lecture by Nakatsuka to yield (±)-bicyclomycin (1). Reports in the chemical literature are awaited. The basic approach leading to (±)-bicyclomycin is outlined below (Scheme 15).



Scheme 15

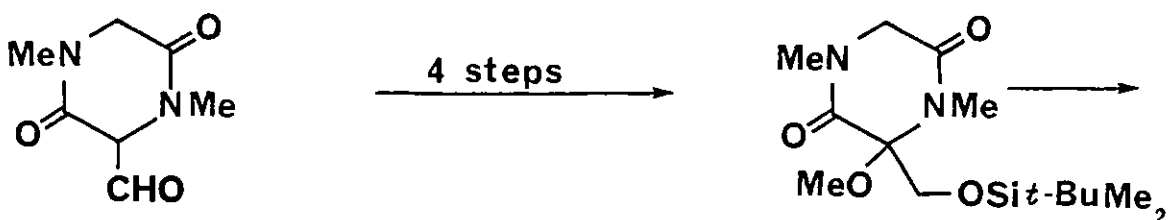


Scheme 15

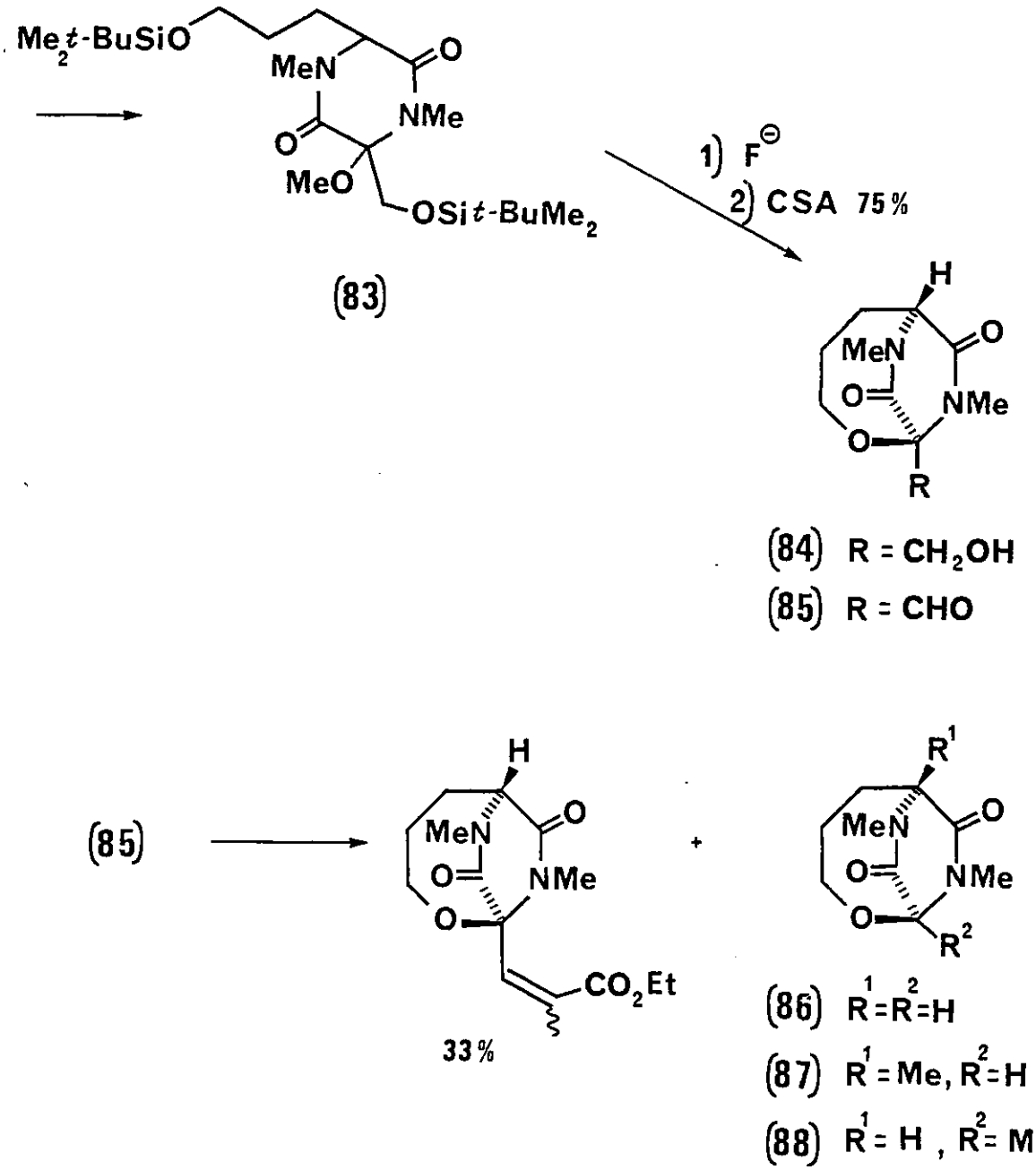


Scheme 15 cont'd

The other major contributor to bicyclomycin synthesis has been Williams, whose strategies[61-63] have again revolved around carbanions derived from 2,5-piperazinedione derivatives. One procedure leading to bicyclic models commenced with 2,5-piperazinedione (81) (available in four steps from (82)), which on deprotonation with LDA and reaction with t-butyldimethylsilyoxy-3-iodopropane gave adduct (83) as a diastereomeric mixture (Scheme 16). Desilylation and cyclisation with camphorsulphonic acid, in a similar precedure to that of Nakatsuka[56], led to bicyclic compound (84). Interestingly, treatment of the corresponding aldehyde (85) with Horner-Emmons reagents led to a low yield of the desired olefin (33%), giving an equal amount of the deformylated derivative (86) (34%). This result indicated the stability of the bridgehead carbanion of (86). It was found that the bridgehead proton α to the ethereal oxygen is slightly less acidic than the other bridgehead proton in (86). Thus methylation gave a 3:1 mixture of products, (87) and (88).



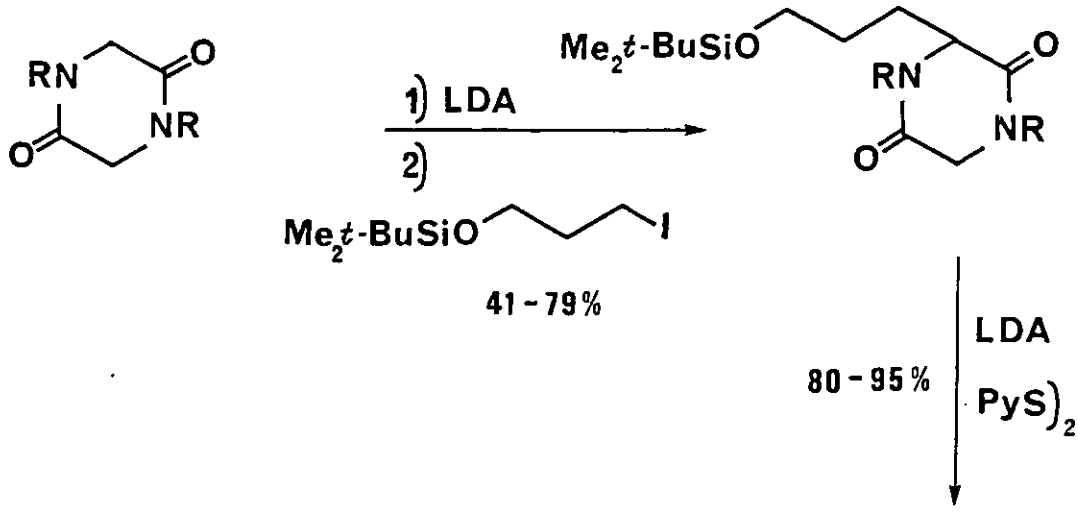
(82) Scheme 16 (81)

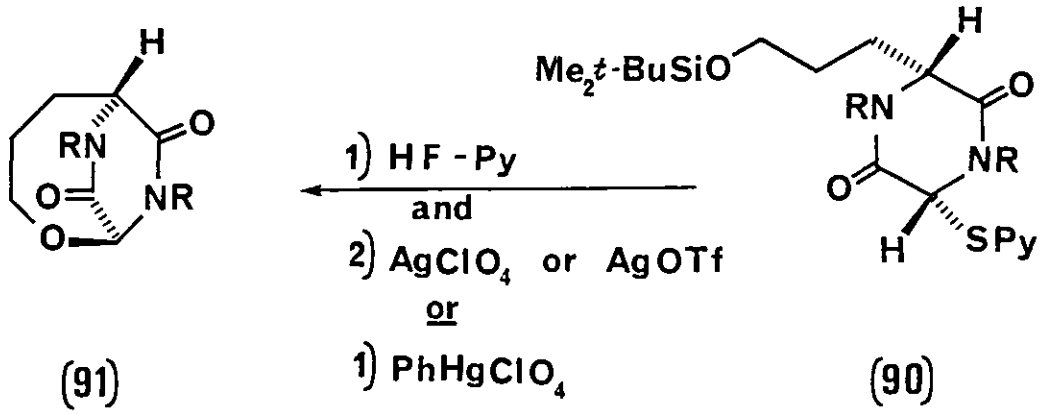


Scheme 16 cont'd

Use of this strategy was later extended[62] by Williams in the elegant synthesis of N,N´-dimethyl-5-desmethylenebicyclomycin (89) (Scheme 17). The overall strategy is outlined below (Scheme 17). The bicyclisation step ((90)to (91)) involving the metal-mediated intramolecular cyclisation of pyridyl-

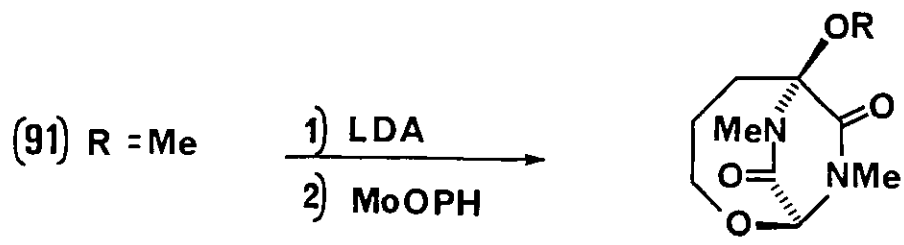
thioethers is of particular note. Bridgehead carbanions were used to introduce the 6-hydroxyl group and the trihydroxymethylpropyl side chain.





(91) (90)

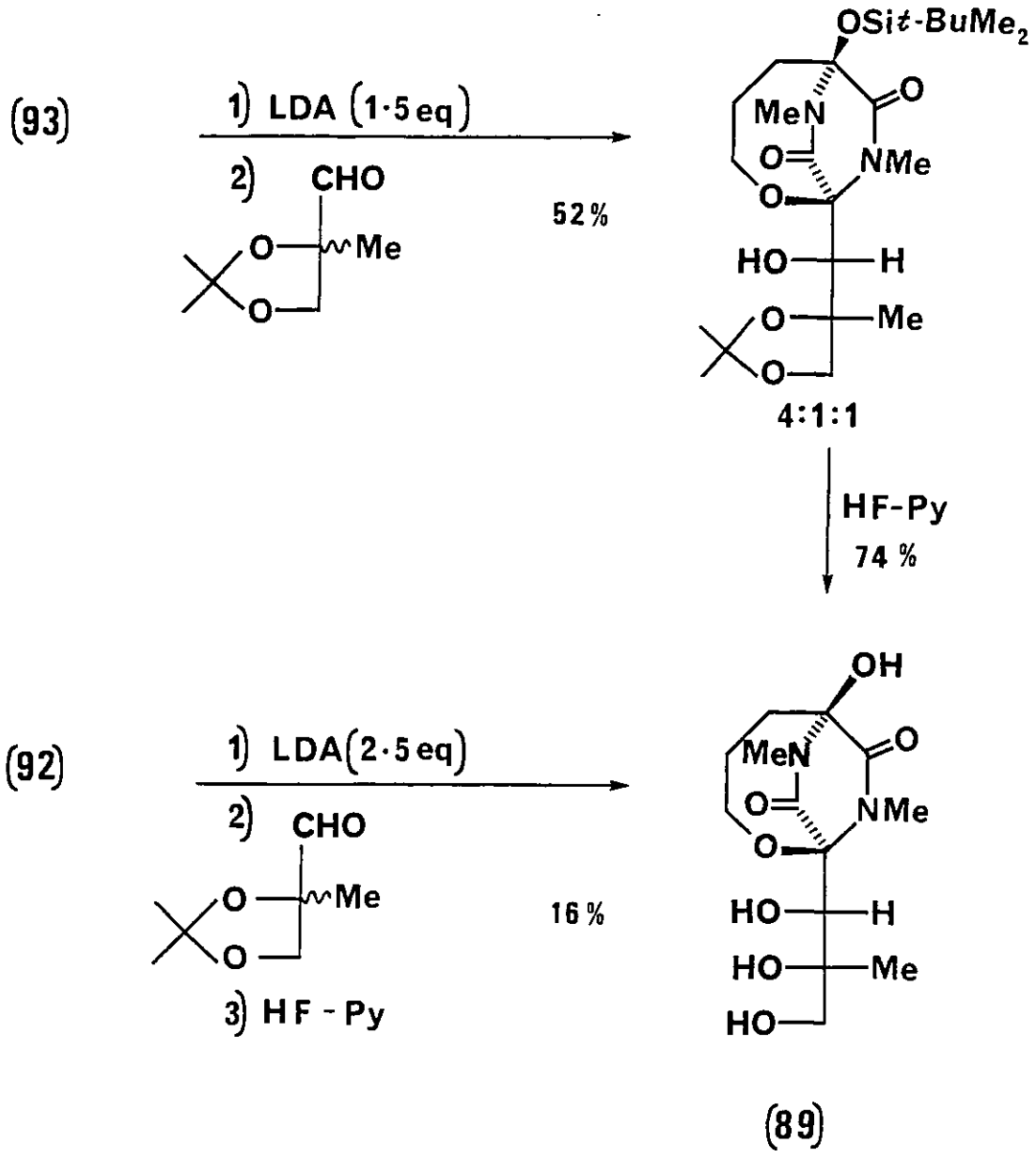
R = Me, $PhCH_2$, CH_2OMe



(92) R = H

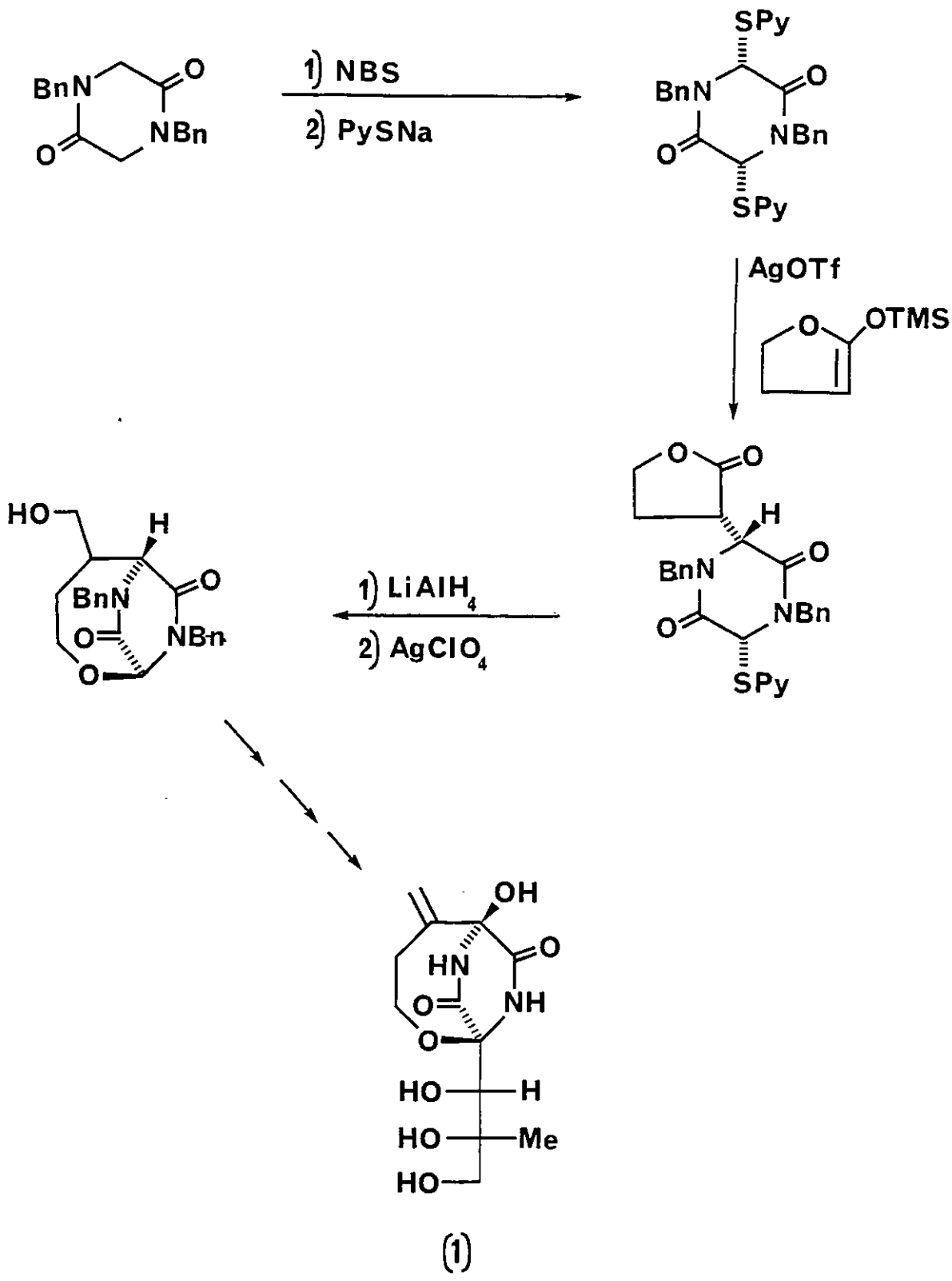
(93) R = OSi t-Bu Me_2

Scheme 17



Scheme 17 cont'd

Williams's strategy has been further extended to "an entantiospecific total synthesis of (+)-bicyclomycin (1)" as reported in lecture form recently[63]. A new selenium-mediated bridgehead oxidation reaction and an asymmetric synthesis of the C-1´-C-3´ side chain moiety of bicyclomycin was presented, but no specific details are yet available, although the overall approach has been outlined[63] (Scheme 18).


BnN
NBn
1) NBS
2) PySNa
SPy
AgOTf
OTMS
HO
H
1) LiAlH4
2) AgClO4
OH
HN
NH
HO
Me

(1)

Scheme 18

In conclusion, it can be seen that numerous very different synthetic approaches to bicyclomycin have been investigated. Several very efficient cyclisation procedures to produce the 2-oxa-7,9-diazabicyclo [4.2.2] decane-8, 10-dione ring system have been developed, by far the most promising, elegant and versatile being Williams' procedure using pyridyl-thioethers[62-63]. However, the synthesis of optically pure bicyclomycin by a short versatile route has yet to be fully reported in the chemical literature.

RESULTS AND DISCUSSION

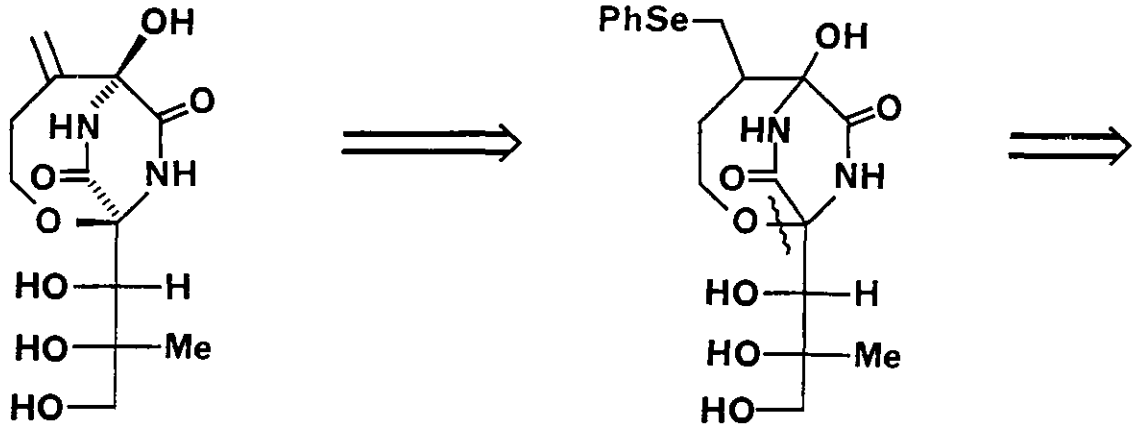
RESULTS AND DISCUSSION

Introduction

Four main synthetic strategies for the proposed total synthesis of bicyclomycin (1) have been investigated. All these strategies involve construction of the 2,5-piperazinedione moiety at a late stage and subsequent, or concomitant, bicyclisation to give the 2-oxa-7,9-diazabicyclo[4.2.2]decane-8,10-dione ring system found in bicyclomycin. In all the approaches studied, the trihydroxymethylpropyl side chain of bicyclomycin was to be derived in chiral form from carbohydrate sources. Each strategy will be discussed in turn.

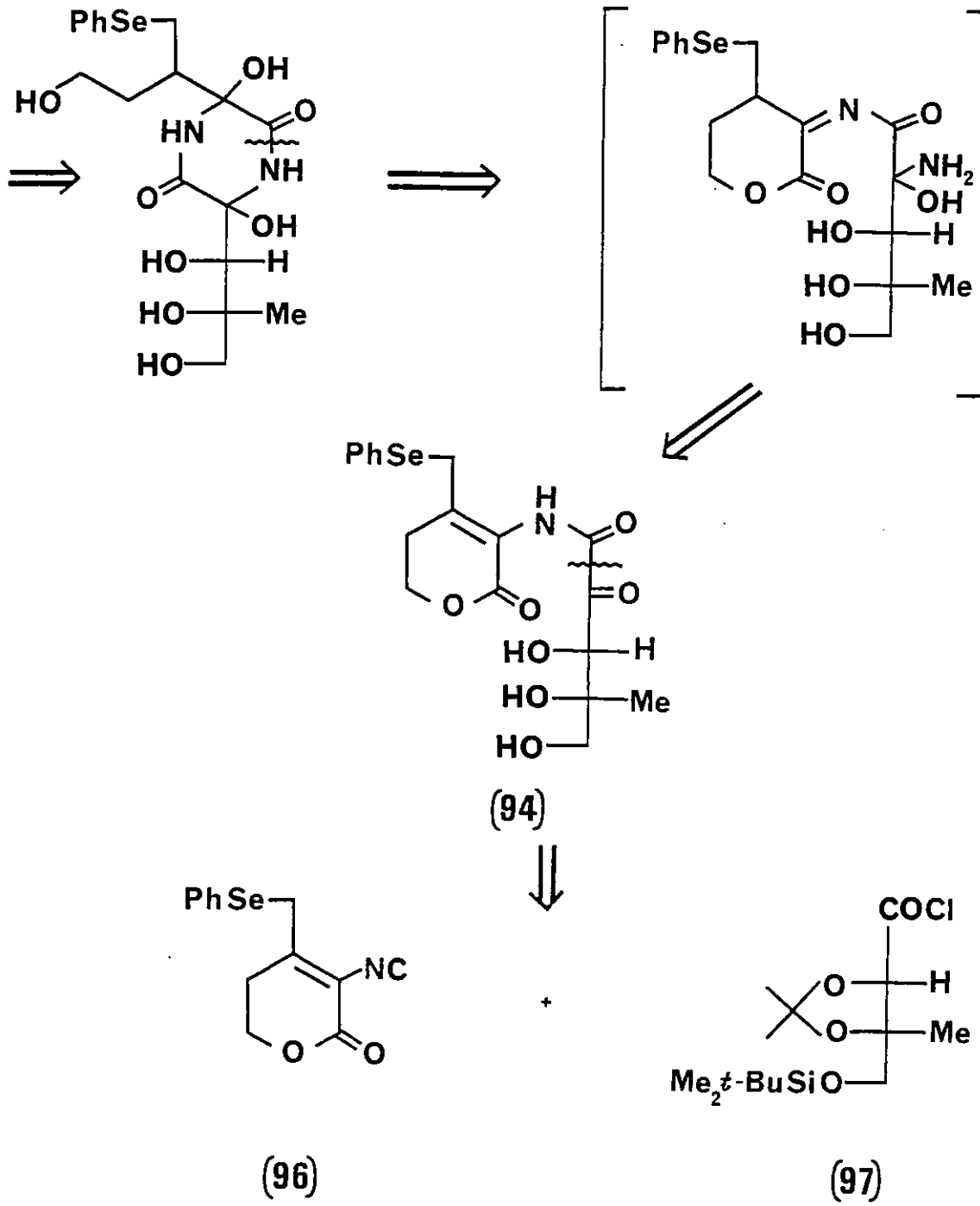
1) STRATEGY A

The first strategy investigated is outlined retrosynthetically below (Scheme 19). The exocyclic double bond of bicyclomycin (1) should be available by a selenoxide elimination. The key proposed reaction is conversion of α-keto-amide (94) into bicyclic compound (95) by treatment with aqueous ammonia via carbinolamine formation, enamide isomerisation and hydration, lactone aminolysis and finally bicyclisation. Based on this retrosynthetic analysis the initial target compounds were isonitrile (96) and acid chloride (97).



(1) (95)

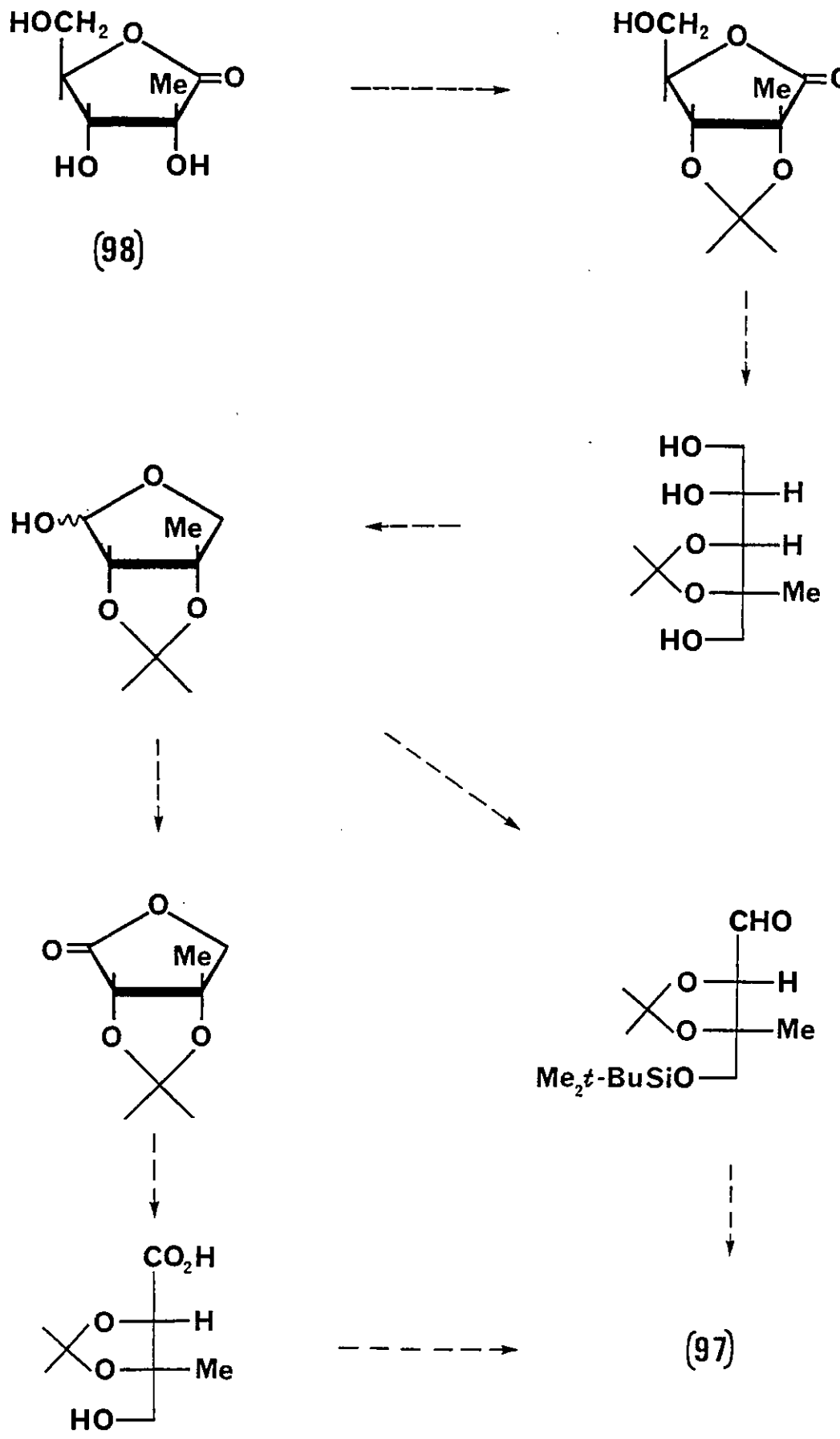
Scheme 19



Scheme 19 cont'd

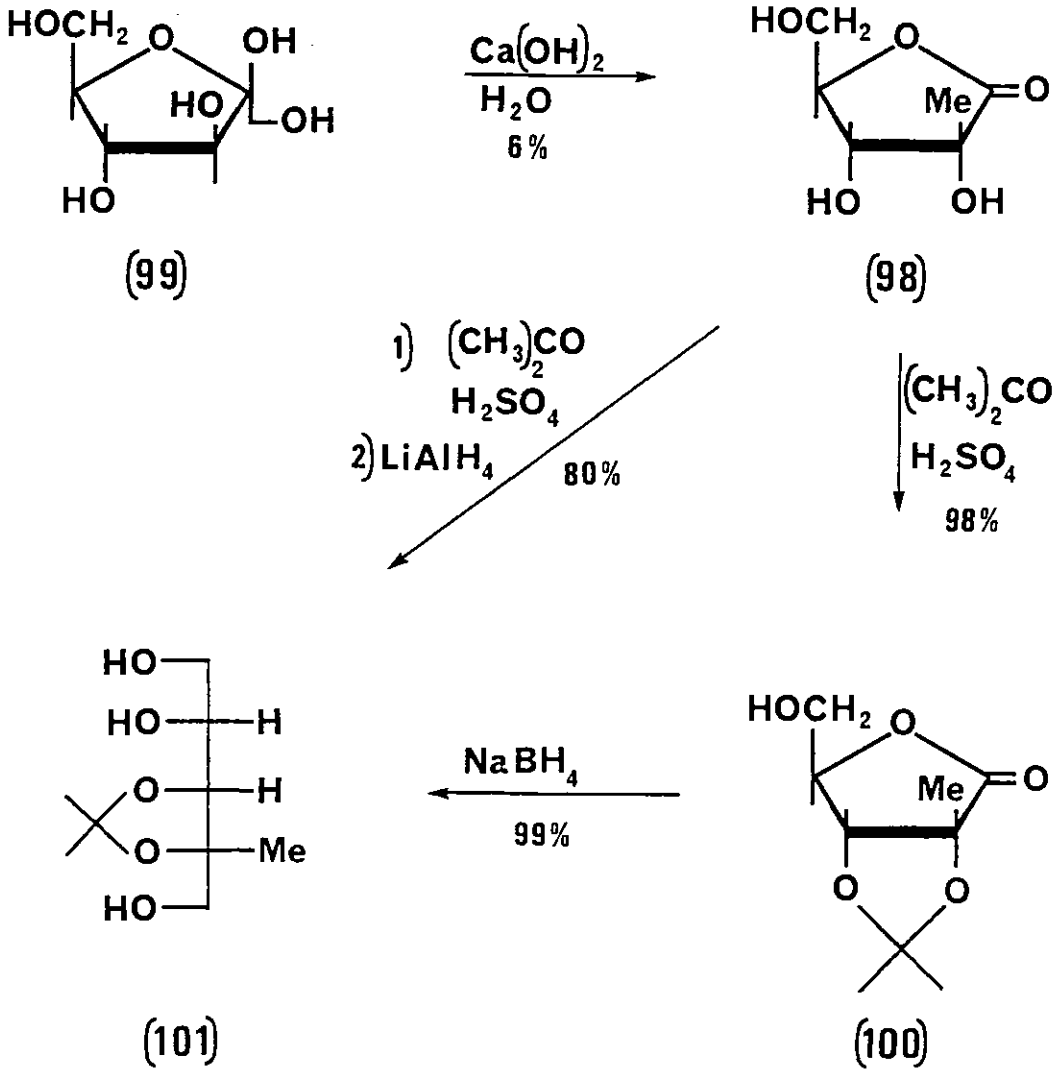
a) Synthetic approaches to acid chloride (97)

A route to the acid chloride (97) was proposed using as the chiral starting material the known lactone (98), which is available from β-D-fructose (Scheme 20).


HOCH2
O
Me
O
HO
OH
(98)
HOCH2
O
Me
O
O
O
HO
HO
H
O
H
O
Me
HO
O
HO
Me
O
O
O
Me
O
O
CHO
O
H
O
Me
Me2t-BuSiO
CO2H
O
H
O
Me
HO
(97)

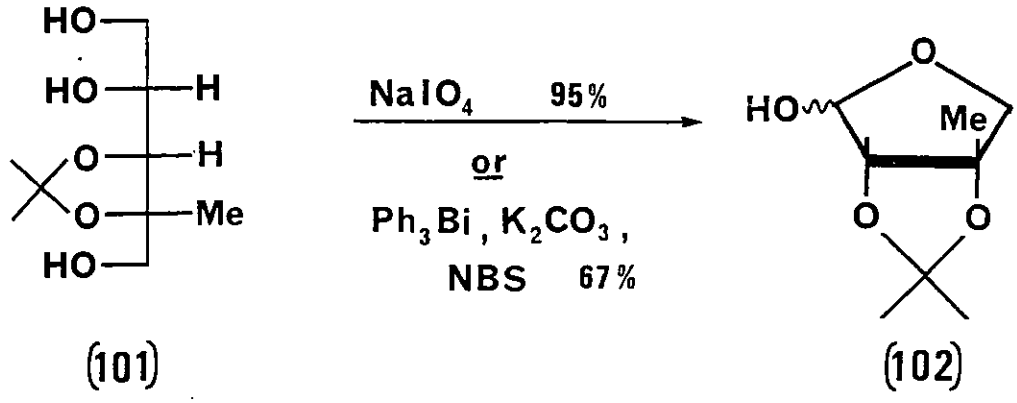
Scheme 20

Thus treatment of β-D-fructose (99) with aqueous calcium hydroxide for 10 weeks at room temperature according to the literature procedure[66] gave lactone (98) in low yield (6%) (Scheme 21). Treatment of lactone (98) with acetone and sulphuric acid gave the corresponding acetonide (100) in 98% yield. Reduction of lactone (100) was most easily achieved with sodium borohydride in ethanol to give ribitol (101) in 99% yield. Ribitol (101) was also available by reduction of lactone (100) with lithium aluminium hydride in diethyl ether to give ribitol (101) in 80% overall yield from lactone (98), but use of sodium borohydride was more convenient and higher yielding (Scheme 21).

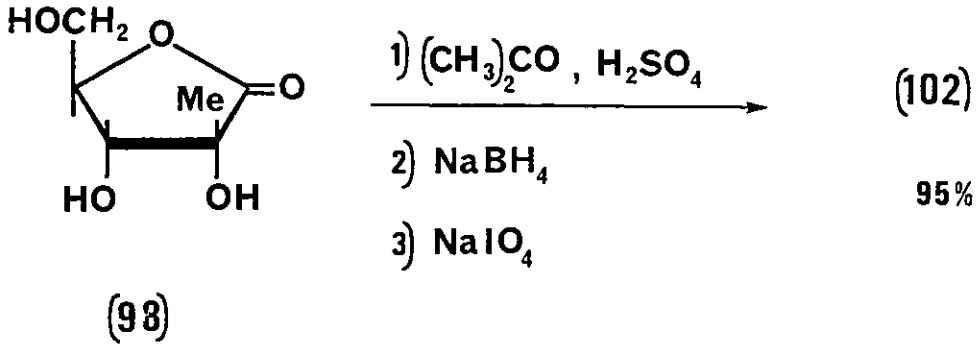


Scheme 21

Glycol cleavage of ribitol (101) was achieved with sodium periodate in aqueous tetrahydrofuran (THF) to give lactol (102) in good yield (95%) (Scheme 22). Lactol (102) could also be prepared from ribitol (101) by Barton's[67] glycol cleavage system of triphenylbismuth, potassium carbonate and N-bromosuccinimide, but the yield was only 67%. Lactol (102) was routinely prepared from lactone (98) without purification of intermediates (100) and (101) in 95% overall yield (Scheme 22).



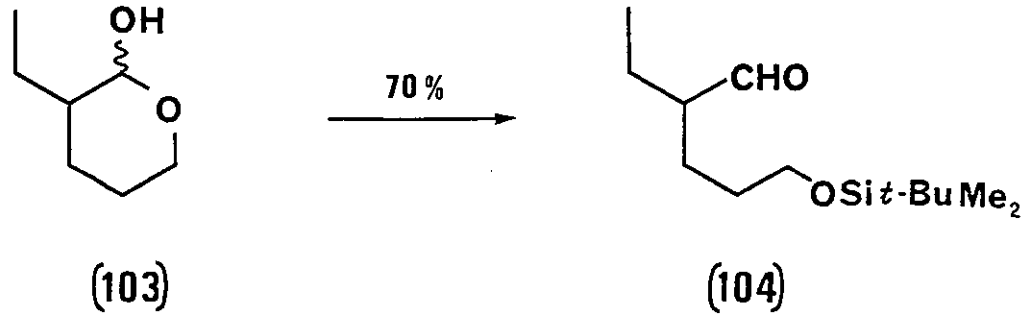
(101) (102)



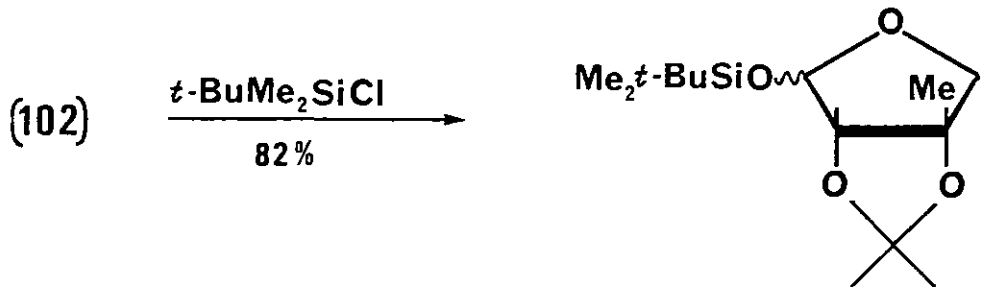
(98)

Scheme 22

Nicolaou [68] has reported that lactol (103) may be trapped mostly in the aldehyde-form (104) by silylation with t-butyldimethylsilyl chloride (Scheme 23). With this precedent in mind, the chiral lactol (102) was treated with t-butyldimethylsilyl chloride and imidazole in N,N-dimethylformamide (DMF) at 0°C and then room temperature. Unfortunately the only isolable product was silylated lactol (105) in 79% yield, and no aldehydic products could be detected. Reaction at room temperature with a very slow rate of addition of t-butyldimethylsilyl chloride also failed to yield any aldehydic products, merely increasing the yield of isolated silylated lactol (105) to 82%. Presumably the furanose ring of lactol (102) is more favoured than inthe examples quoted by Nicolaou [68], and in fact the infra-red spectrum of (102) does not show a carbonyl stretch.



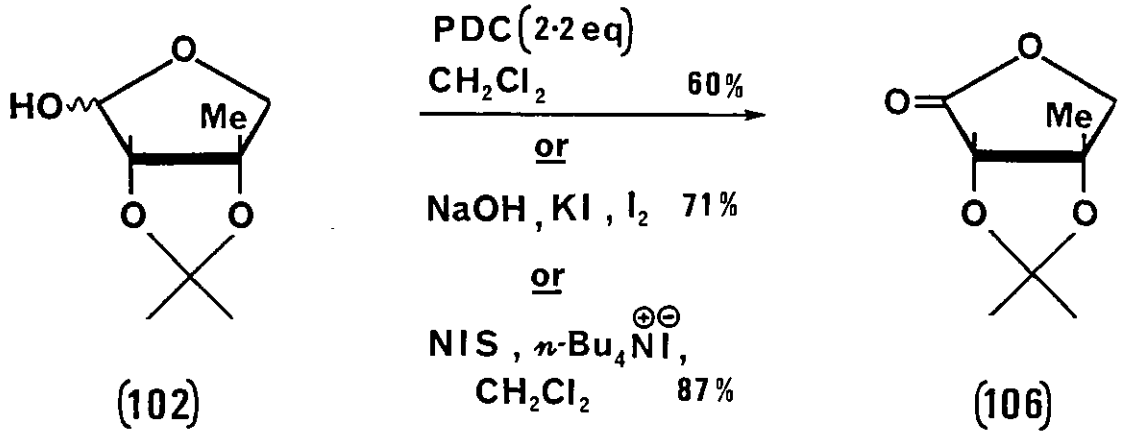
(103) (104)



(105)

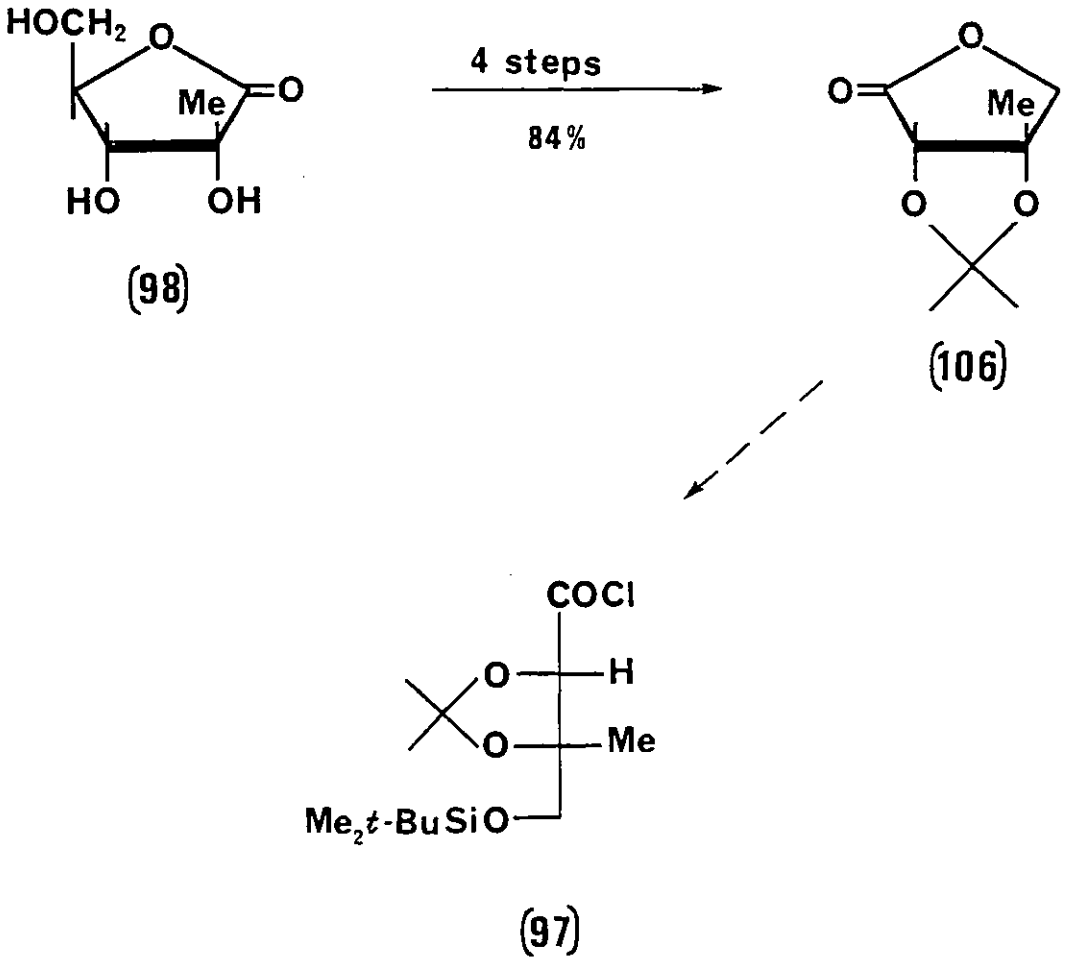
Scheme 23

The other proposed route to acid chloride synthon (97) was via lactone (106) (Scheme 24). Initial attempts to oxidise lactol (102) with ruthenium tetroxide[69] or dimethylsulphoxide-acetic anhydride[70] gave no reaction and an intractable mixture respectively. The first successful oxidant to be used was pyridinium dichromate (PDC)[71] in dichloromethane which yielded lactone (106) in 60% yield (Scheme 24). This reaction was very slow and was complicated by the presence of significant amounts of a less polar unidentified product. Pure lactone (106) was however stable to excess PDC and so the by-products presumably arose from decomposition of the starting lactol (102). These problems were initially overcome by oxidation of lactol (102) with alkaline aqueous potassium iodide-iodine[72] which yielded lactone (106) in 71% yield, but the oxidant of choice was found to be N-iodosuccinimide-tetrabutylammonium iodide[73] which gave lactone (106) in 87% yield (Scheme 24).



Scheme 24

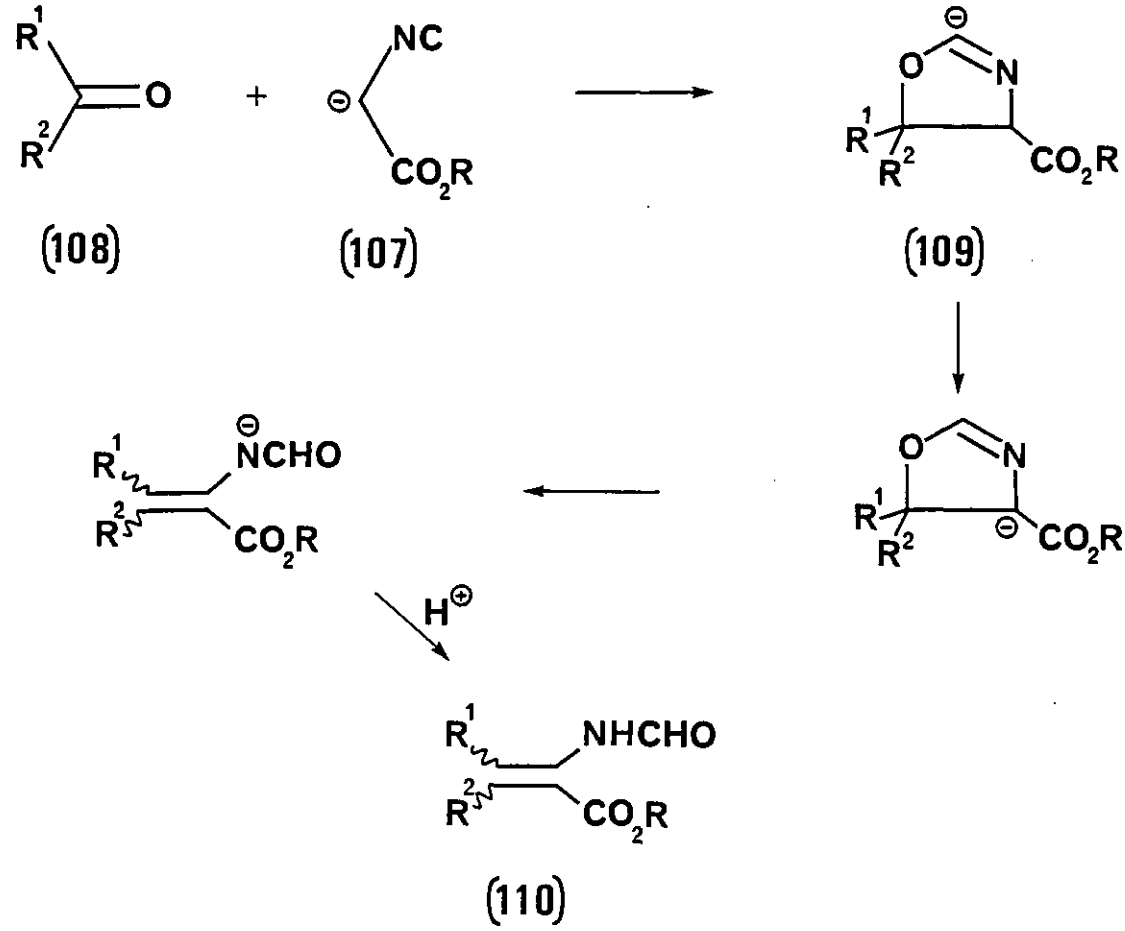
Further elaboration of lactone (106) to the target acid chloride (97) was not studied due to difficulties encountered in the synthesis of other synthons in Strategy A. However, a short and efficient route for the conversion of lactone (98) into lactone (106), a potential precursor to synthon (97), had been developed (Scheme 25).



Scheme 25

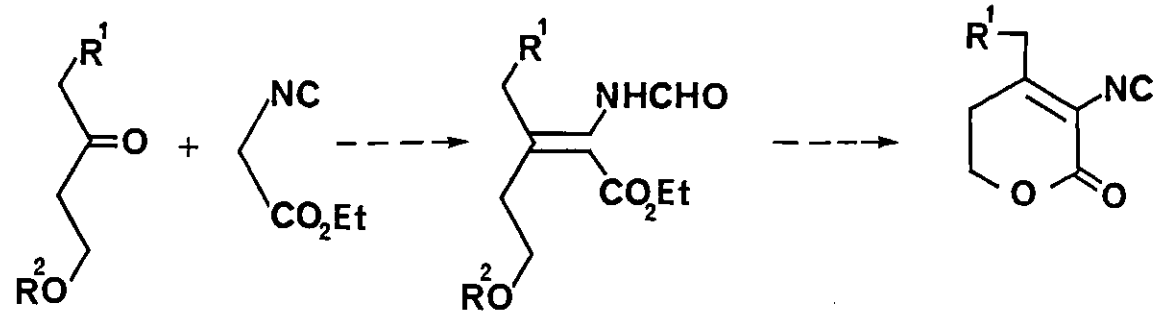
b) Synthetic approaches to model compounds of isonitrile (96)

Approaches to isonitrile (96) were based on the use of α-metalated isonitriles[74]. Schöllkopf has found that α-metalated isonitriles such as (107) react with ketones (108) to give, initially, 2-metalated oxazolines (109) which, by proton transfer, electrocyclic ring opening and protonation, finally yield N-alkenylformamides (110) as the isolated products (Scheme 26).



Scheme 26

On the basis of Schöllkopf's work a route to isonitrile (96) was designed using ketones of general type (111) (Scheme 27).

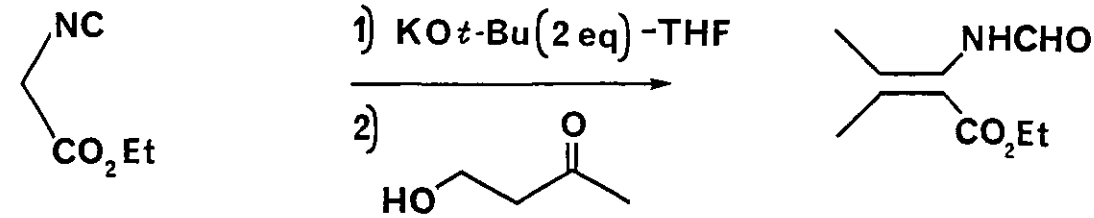


(111) R^1 = PhSe, R^2 = H
(113) R^1 = R^2 = H

(96) R^1 = PhSe
(112) R^1 = H

Scheme 27

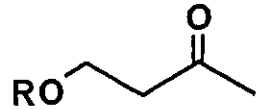
As a model study, simplified ketone 4-hydroxybutan-2-one (113) was chosen with a view to preparing adduct (112) (Scheme 27). Ketone (113) has been prepared in the literature from acetone and formaldehyde by aldol condensation. In our hands only very low yields (up to 12%) of (113) could be obtained due to extensive decomposition on distillation. Ethyl isocyanoacetate (114) was prepared from glycine ethyl ester hydrochloride in two steps (82 and 61%) via the corresponding formamide as described in the literature[76]. Treatment of isonitrile (114) with two equivalents of potassium t-butoxide in THF and subsequent reaction with ketone (113) gave a very complex mixture of products (t.l.c.), including significant amounts of formamide (115) (as judged by comparison with an authentic sample (t.l.c., n.m.r.)) (Scheme 28).



(114) (113) (115)

Scheme 28

Production of formamide (115) indicated that a retro-aldol reaction was occurring at some stage. Protection of the hydroxyl group in ketone (113) was seen as a method of overcoming this problem. Treatment of (113) with dihydropyran in acidic conditions failed to yield a pure sample of tetrahydropyranyl ether (116), due in part to the difficulty experienced in preparing a pure sample of (113). However, acetoxy-ketone (117) was conveniently prepared[77] in low yield (31%) from methyl vinyl ketone and acetic acid in the presence of a catalytic amount of water. Application of this procedure to prepare pivaloyl-ketone (118) was not successful due to polymerisation on attempted distillation of the crude material believed to be (118).

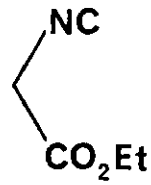


(113) R = H

(116) R = THP

(117) R = Ac

(118) R = *t*-BuCO

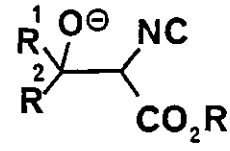


(114)

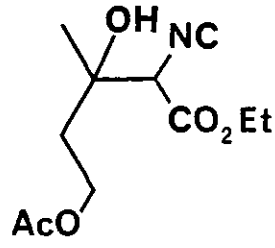
Attempted condensation of isonitrile (114) with acetoxy-ketone (117) in THF with potassium t-butoxide as base resulted in a very slow consumption of starting isonitrile (i.r.) and gave a complex mixture (t.l.c.). Use of sodium hydride in THF or potassium t-butoxide in DME failed to consume starting material (i.r.). A reaction with lithium hexamethyldisilazide as base in THF resulted in consumption of the starting isonitrile (i.r.), but from the complex mixture produced (t.l.c.) none of the required adduct could be detected (mass spectrometry). One possible explanation for these poor results was that acetoxy-ketone (117) was decomposing under the basic conditions to give methyl vinyl ketone.

Isonitrile (114) is known[78] to undergo conjugate addition to Michael acceptors. However, a reaction of isonitrile (114) and acetoxy-ketone (117) with two equivalents of potassium t-butoxide as base gave a complex mixture (t.l.c.) and no products from conjugate addition were isolable.

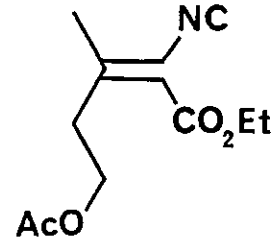
It is known[79] that the initial alkoxide adducts, such as (119), derived from ketones and α-metalated isonitriles can be trapped as the corresponding alcohols by quenching at low temperature with acetic acid. Isolation of an adduct (120) and subsequent dehydration would lead to the target model isonitrile (121).



(119)



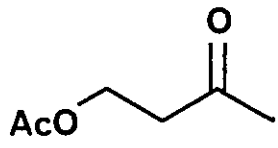
(120)



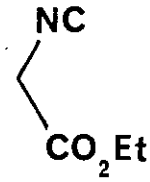
(121)

Attempted preparation of isonitrile (120) by quenching at low temperature with acetic acid gave low yields (15-31%) of an adduct believed to be (120). However, this adduct was not fully characterised by elemental analysis.

Acetoxy-ketone (117) is known[77] to undergo Reformatsky reaction with the zinc enolate from methyl bromoacetate. Therefore, the zinc enolate[80] of isonitrile (114) was prepared and reacted with acetoxy-ketone (117), but this failed to give an improved yield of the adduct believed to be (120) and only resulted in production of a complex mixture (t.l.c.).

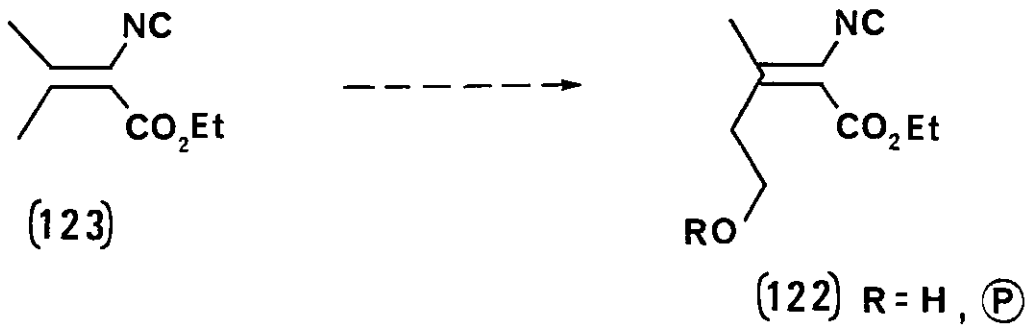


(117)



(114)

Due to the difficulties encountered using α-metalated derivatives of isonitrile (114) with β-oxygenated ketones such as (117) (possibly because of competing β-elimination) an alternative approach to the target model isonitriles of type (122) was investigated (Scheme 29).

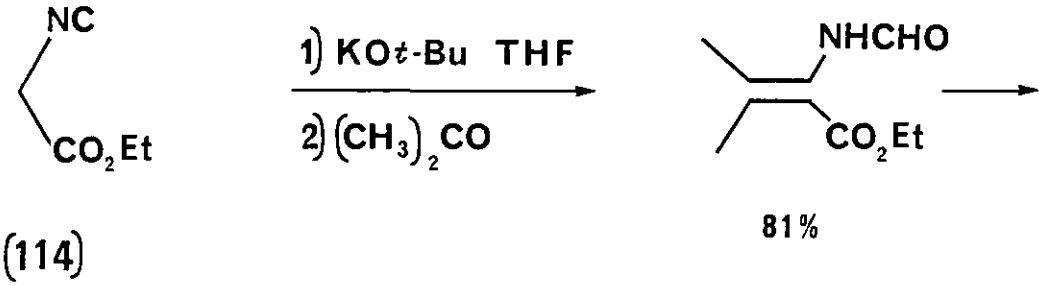


(123)

(122) R = H, Ⓟ

Scheme 29

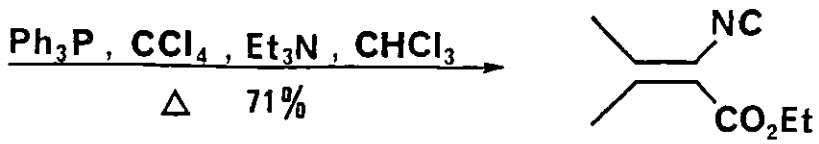
Isonitrile (123) was available in two steps (81 and 71%), as described in the literature[81], from isonitrile (114) and acetone (Scheme 30).



(114)

81%

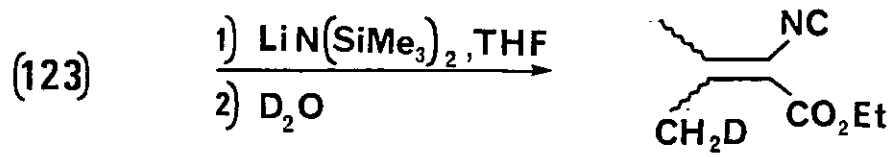
Scheme 30



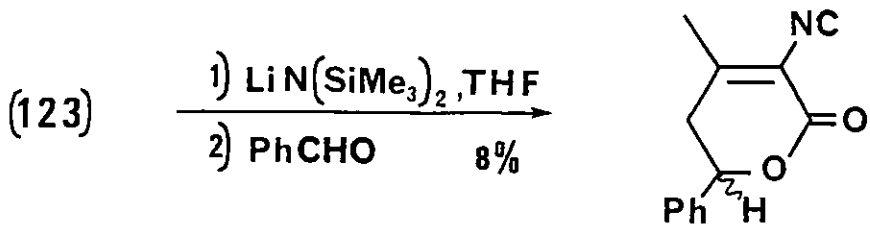
(123)

Scheme 30 cont'd

Reaction of isonitrile (123) with lithium hexamethyldisilazide in THF led to γ-deprotonation as judged by quenching with deuterium oxide, although which methyl group had incorporated deuterium was not established. Despite the reaction appearing to be very clean (t.l.c.), only a low yield (32%) of deuterium incorporated isonitrile (124) was obtained after column chromatography (Scheme 31). Quenching of the carbanion derived from (123) with different electropliles was examined. Use of ethyl formate yielded mainly starting material, and para-formaldehyde gave a complex mixture (t.l.c.), surprisingly containing no isonitrile component (i.r.). Quenching with propanal gave a polymeric mixture (n.m.r.) although use of benzaldehyde (where no proton transfer is possible) did yield very small amounts (8%) of an adduct believed to be lactone (125) (Scheme 31).



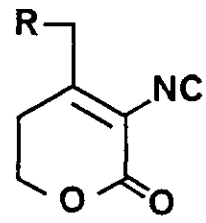
(124)



(125)

Scheme 31

However, these results were very disappointing and so approaches to isonitriles of type (96) and (112) were abandoned and an alternative, but similar, strategy (B) was investigated.

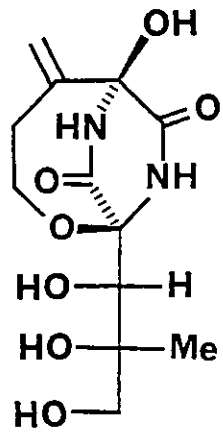


(96) R = PhSe

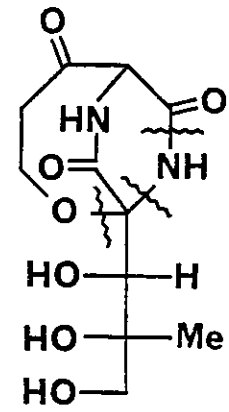
(112) R = H

2) STRATEGY B

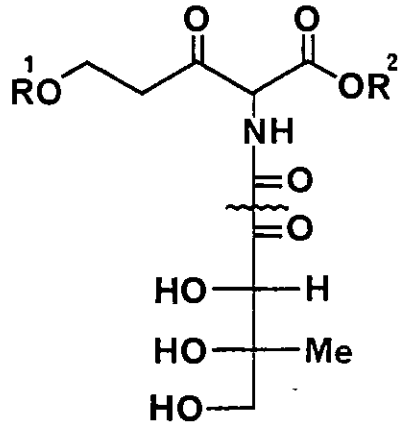
The second strategy considered towards the total synthesis of bicyclomycin is outlined retrosynthetically below (Scheme 32). Ketone intermediates of type (126) or (127) would be versatile compounds, allowing the introduction of the bridgehead hydroxyl group and the exocyclic methylene found in bicyclomycin (1) either by Wittig reaction and subsequent oxidation, or by oxidation via a trimethylsilyl enol ether and subsequent Wittig reaction.



(1)

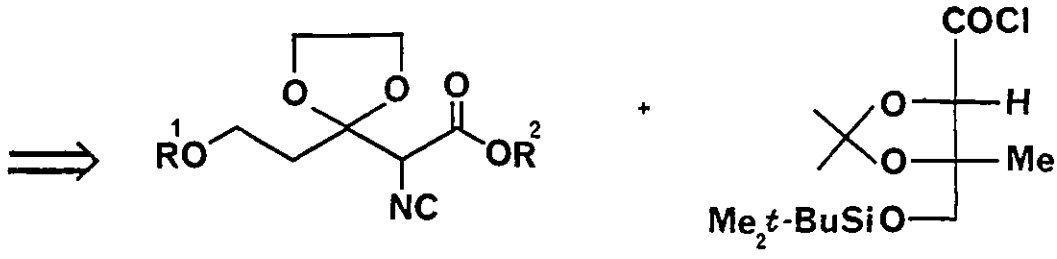


(126)



(127)

Scheme 32



(128) (97)

R^1 = H, Ⓟ

R^2 = alkyl

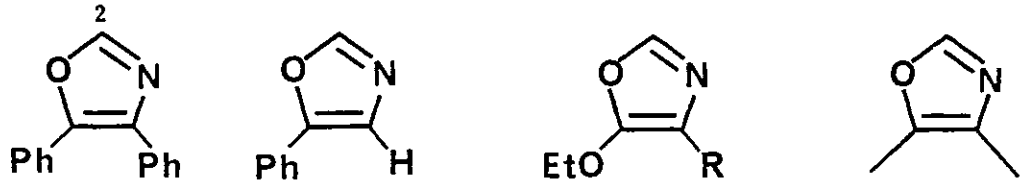
Scheme 32 cont'd

Acid chloride synthon (97) is the same as the synthon in Stragety A. The overall strategy is similar as regards the construction of the bicyclic system, but, as already mentioned, the proposed method for introducing the 5-exocyclic methylene group and 6-hydroxyl group was markedly different.

On the basis of the above retrosynthetic analysis, isonitrile (128), or its equivalent, became the target compound.

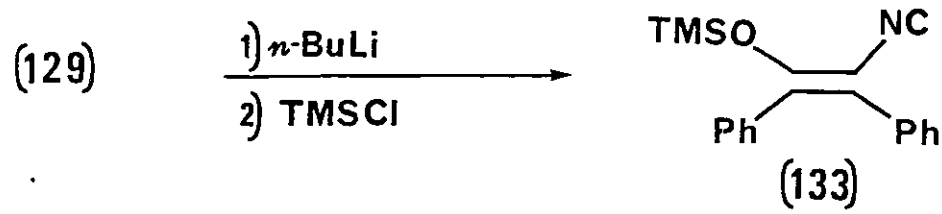
a) Synthetic approaches to isonitriles of type (128)

It is known[82,83] that oxazoles (129), (130), (131), and (132) may be deprotonated with n-butyllithium in the 2-position. Reaction of oxazole (129) with electrophiles such as deuterium oxide and benzaldehyde occurs at the 2-position, but quenching with trimethylsilyl chloride on oxygen has been shown to yield isonitrile (133) (Scheme 33).



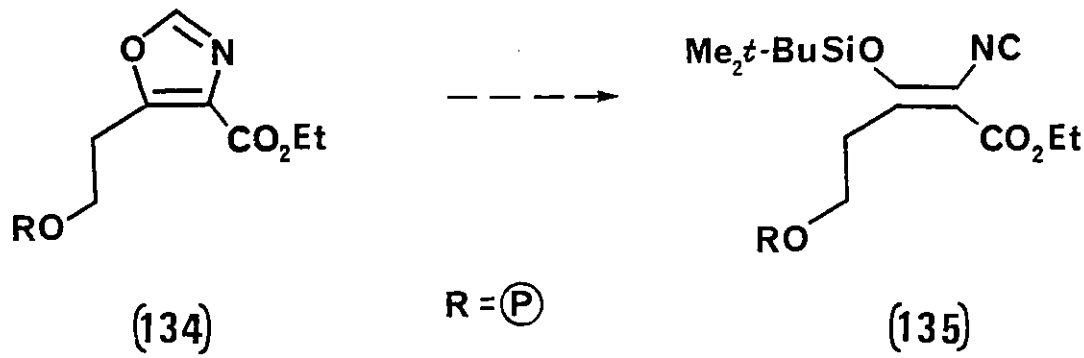
(129) (130) (131) (132)

R = H, Me



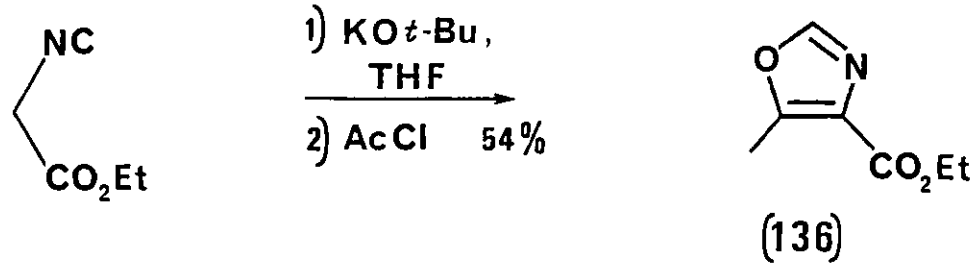
Scheme 33

On the basis of these results reaction of a suitably functionalised oxazole such as (134) should yield isonitrile (135) as a useful synthetic intermediate (Scheme 34).



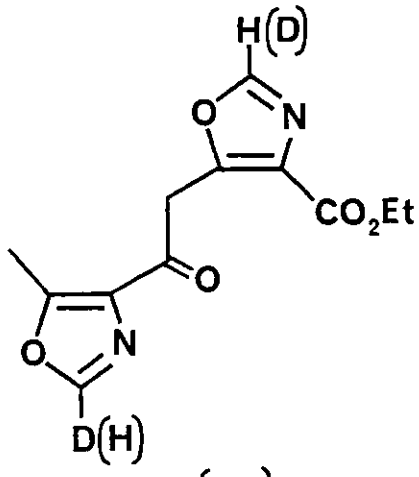
Scheme 34

As a model study, oxazole (136) was prepared as described in the literature[82] from ethyl isocyanoacetate and acetyl chloride with potassium t-butoxide as base (Scheme 35).



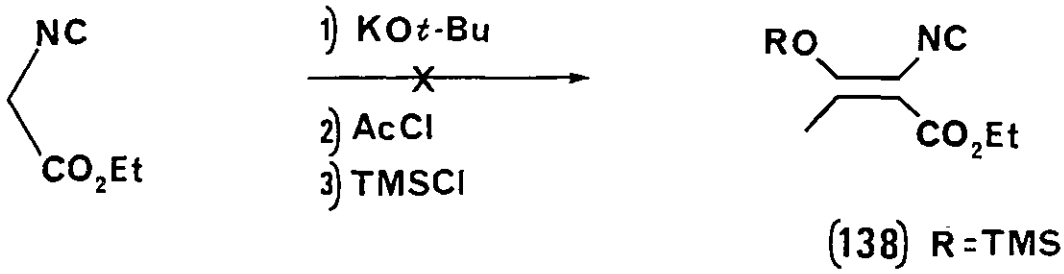
Scheme 35

Treatment of oxazole (136) with n-butyllithium in THF at 0°C and subsequent addition of t-butyldimethylsilyl chloride failed to yield any isonitrile containing products (i.r.) and resulted in destruction of the ethyl ester moiety (n.m.r.). Use of the less nucleophilic base lithium hexamethyldisilazide again gave a complex mixture (t.l.c.), including starting material (n.m.r.) but not containing an isonitrile (i.r.). To check whether carbanion formation was occurring, oxazole (136) was treated with lithium diisopropylamide and then deuterium oxide. No deuterated oxazole (136) was observed (t.l.c.) and the major product is believed to be oxazole (137) (the position of deuteration was not determined). Presumably, for this particular oxazole (136), the methyl protons are more acidic than the ring proton and the resulting carbanion condenses with the starting oxazole (136).



(137)

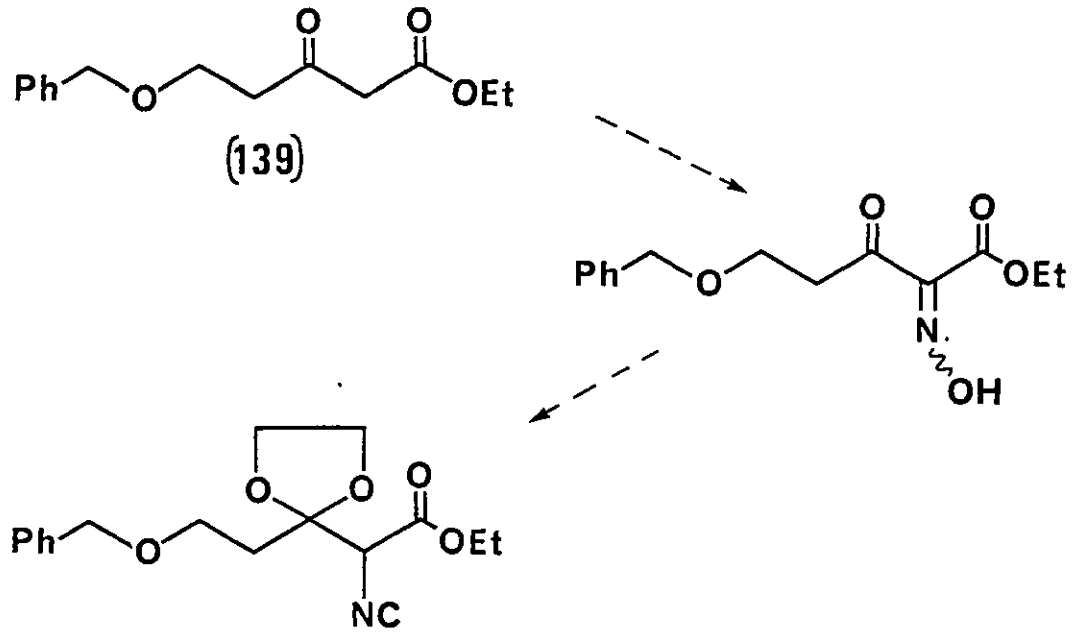
An attempt to prepare trimethylsilyl-isonitrile (138) from ethyl isocyanoacetate, potassium t-butoxide, acetyl chloride and trimethylsilyl chloride yielded oxazole (136) as the only recognisable product (Scheme 36).



(138) R=TMS

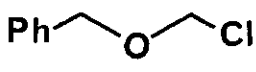
Scheme 36

Due to these disappointing results a new approach to isonitriles of type (128) was investigated. This approach commenced with β-keto-ester (139) which has been described in the literature[84] (Scheme 37).



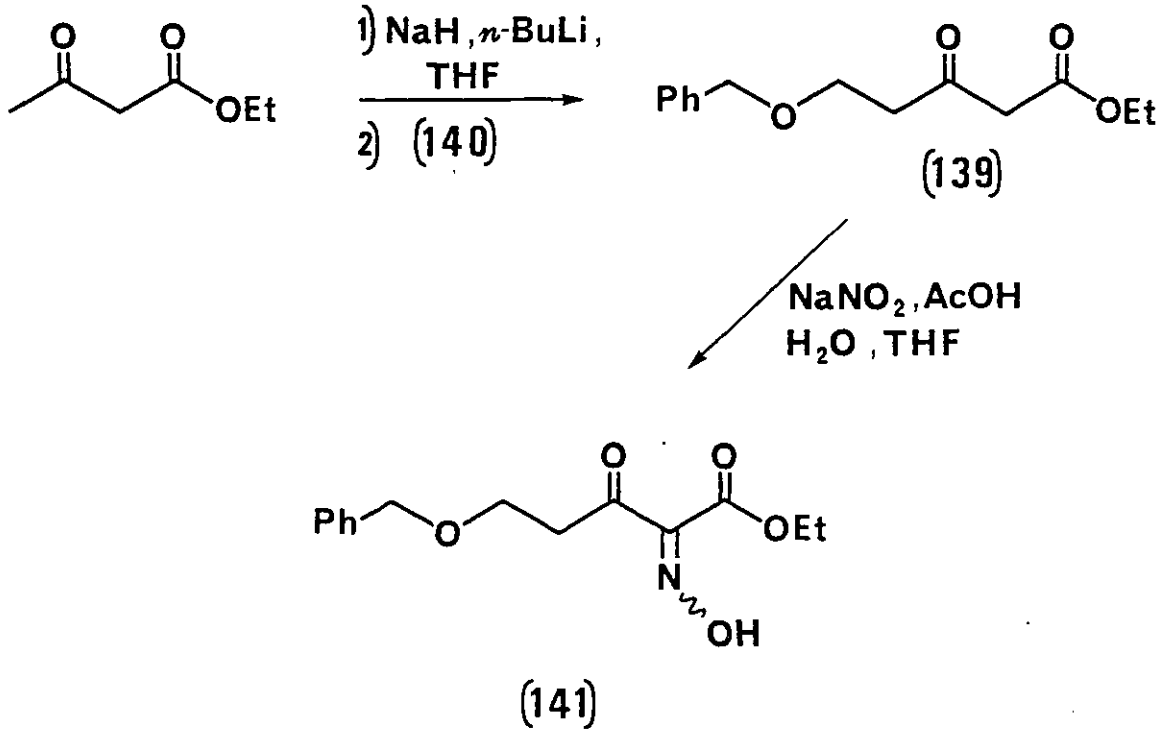
Scheme 37

Preparation of benzyl chloromethyl ether (140) from benzyl alcohol formaldehyde solution and hydrogen chloride by the method[85] in "Organic Synthesis" was not reproducible in our hands. On several occasions attempted distillation resulted in extensive polymerisation. ^{1}Hn.m.r. spectroscopy of the crude material indicated that significant amounts of benzyl chloride were present. It was found that use of excess formaldehyde, in a modified procedure based on the original literature[86] and "Organic Synthesis"[85], gave a crude product containing no benzyl chloride (n.m.r.). Subsequent distillation proceeded smoothly to give benzyl chloromethyl ether (140) in 71% yield.



(140)

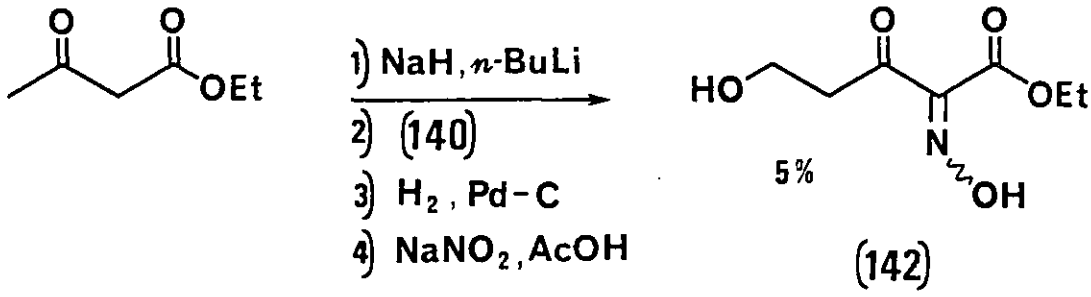
The dianion of ethyl acetoacetate was prepared using sodium hydride and n-butyllithium and reacted[84] with benzyl chloromethyl ether (140) (Scheme 38). The resulting β-keto-ester (139) was very difficult to purify. Distillation failed to remove benzylic impurities (n.m.r.) and so (139) was used crude (after evaporation of excess ethyl acetoacetate) in all subsequent reactions. Treatment of crude (139) with sodium nitrite and acetic acid In aqueous THF gave the oxime (141) in rather low yield (39% from ethyl acetoacetate) (Scheme 38).



Scheme 38

Oximes of β-keto-esters have been reduced by catalytic hydrogenation[87] to the corresponding amine salts. Hydrogenation of oxime (141) over 10% palladium on carbon in ethanolic hydrogen chloride at 5 atmospheres for 4h or 12 atmospheres for 15h failed to consume oxime (141) (t.l.c.). Hydrogenation at 2 atmospheres for 1 day did result in consumption of starting material (t.l.c.), but no recognisable products could be isolated either directly or after attempted acetylation (acetic anhydride-triethylamine).

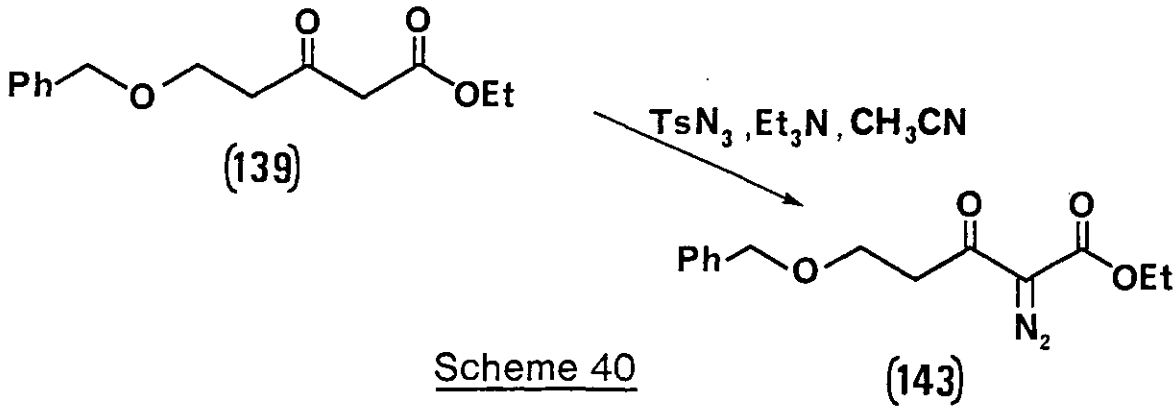
Hydrogenation of oxime (141) may have resulted in removal of one or both of the benzyl and oxime functionality, and this may have contributed to the isolation difficulties encountered. As a simplification it was decided to remove the benzyl group first. Thus, the adduct derived from the dianion of ethyl acetoacetate and benzyl chloromethyl ether was hydrogenated over 10% palladium on carbon, and treated with sodium nitrite and acetic acid to give oxime (142) (Scheme 39).



Scheme 39

However, the overall yield of (142) was extremely low (5%) and this prohibited hydrogenation studies.

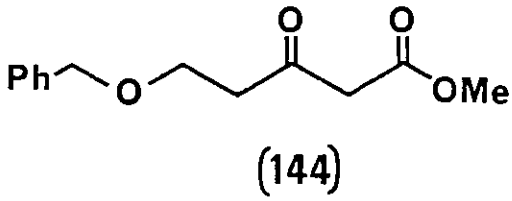
At this stage another means of introducing functionality into β-keto-ester (139) suitable for elaboration to an isonitrile was required. It is known that β-keto-esters react readily with diazo-transfer reagents[88] to give the corresponding diazo-compounds. Treatment of crude β-keto-ester (139) with triethylamine and p-toluenesulphonyl azide[89] (available[90] from p-toluenesulphonyl chloride and sodium azide) in dry acetonitrile gave the diazo-compound (143) in low overall yield (34% from ethyl acetoacetate) (Scheme 40).



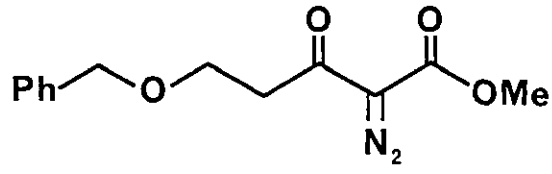
Scheme 40

Use of other diazo-transfer conditions such as p-toluenesulphonyl azide - sodium carbonate - tetrabutylammonium bromide or iodide[91] failed to improve the yield of (143).

In the hope of obtaining improved yields the β-keto-methyl ester (144) was prepared in an analogous manner to β-keto-ester (139). A small portion of (144) was obtained in a good state of purity by distillation. Diazo-transfer with p-toluenesulphonyl azide and triethylamine on both crude and distilled (144) gave the corresponding diazo-compound (145) in 24% (from methyl acetoacetate) and 62% (from (144)) yields respectively.



(144)



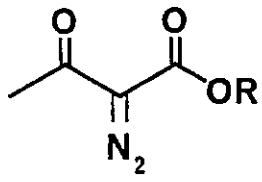
(145)

These results indicated that the low yield of diazo-compound (143) was probably not due to the diazo-transfer step, and so various alternative routes to (143) were investigated.

One problem associated with the preparation of the intermediate β-keto-esters (139) or (144) may have been competitive O-alkylation with benzyl chloromethyl ether. It was thought that this problem may be reduced by use of the corresponding

iodide. However, attempts to prepare benzyl iodomethyl ether from benzyl chloromethyl ether with sodium iodide-acetone, magnesium iodide[92], or tetrabutylammonium iodide failed to give clean reactions. Also, use of two equivalents of LDA instead of sodium hydride-n-butyllithium on methyl acetoacetate failed to yield samples of β-keto-ester (144) of higher purity.

Another approach to diazo-compound (143) was envisaged by making use of the known carbanions of diazoacetoacetate esters (146), (147), and (148). These carbanions have found application in β-lactam chemistry, although yields of alkylation products are generally poor[93].



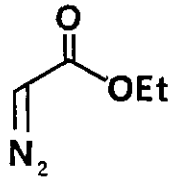
(146) R = Et

(147) R = $PhCH_2$

(148) R = *t*-Bu

Thus, diazo-compound (146) was prepared as described in the literature[89] from ethyl acetoacetate and p-toluenesulphonyl azide in 83% yield. Metalation with lithium hexamethyldisilazide and reaction with benzyl chloromethyl ether resulted in much decomposition and no diazo-compound (143) was detectable (n.m.r.).

Diazo-compounds of β-keto-esters have also been prepared[94] from ethyl diazoacetate (149) and a suitable acid chloride (150).

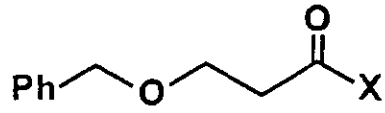


(149)

RCOCl

(150) R = alkyl, aryl

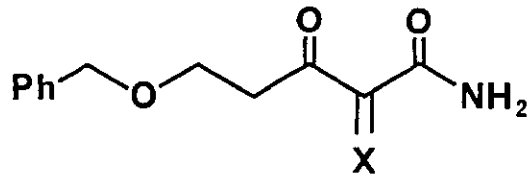
With this in mind approaches to the acid chloride (151) were investigated. Carboxylic acid (152) was readily available by reaction of β-propiolactone with benzyl alcohol (72%) as described in the literature[95]. It has been reported[95] that acid chloride (151) was not formed from acid (152) by treatment with thionyl chloride. We found that use of triphenyl phosphine-carbon tetrachloride[96] was not successful, but that sodium hydride and subsequently oxalyl chloride did give acid chloride (151) in 63% yield.



(151) X = Cl
(152) X = OH

Treatment of acid chloride (151) with ethyl diazoacetate[97] did in fact give the desired diazo-compound (143) but the yield was poor (21%).

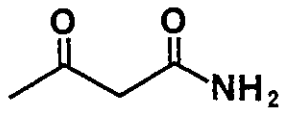
Other potentially useful intermediates of this type would be β-keto-amides such as (153) or (154).



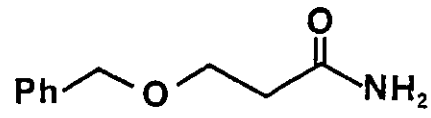
(153) X = N_2
(154) X = NOH

Routes to compounds of this type were briefly examined. However, acetoacetamide (155) (available[98] in low yield from diketene and ammonia) was not suitable for conversion to the corresponding trianion as judged by experiments with sodium hydride-n-butyllithium, or LDA. Also, considerable difficulty was

experienced in attempts to prepare (153) or (154) from the corresponding ethyl esters. Thus,oxime (141) on treatment with ammonia gave a very complex mixture (t.l.c.), and diazo-compound (143) gave a compound initially believed to be (153) (i.r.,n.m.r.) which subsequently decomposed to simple amide (156).

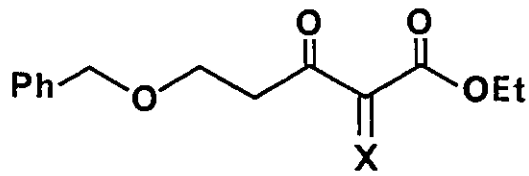


(155)



(156)

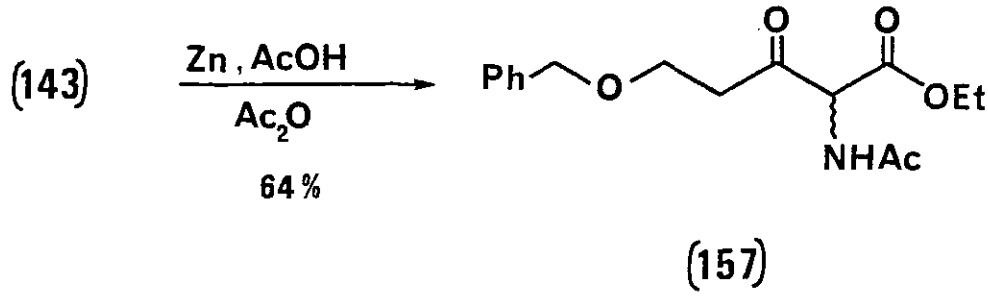
Although we were unable to find high yielding routes to diazo-compound (143) or oxime (141) the dissolving metal reduction of both compounds was studied.



(141) X = NOH

(143) X = N_2

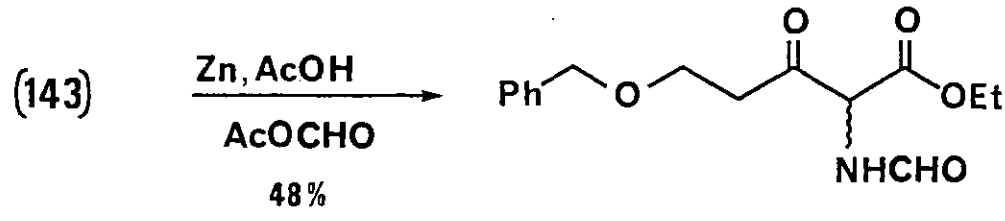
Reduction of diazo-compound (143) with zinc and acetic acid in the presence of acetic anhydride was found to proceed smoothly to give acetamide (157) in 64% yield (Scheme 41). Reduction of oxime (141) under similar conditions also yielded (157) but several other components were present as well (t.l.c.). It was later found that acetic acid need not be used as a solvent, and that reduction of diazo-compound (143) with zinc, acetic anhydride and 5 equivalents of acetic acid in THF proceeded to give acetamide (157) in 42% yield. In this latter reaction some β-keto-ester (139) (30%) was also isolated (Scheme 41).



(157)

Scheme 41

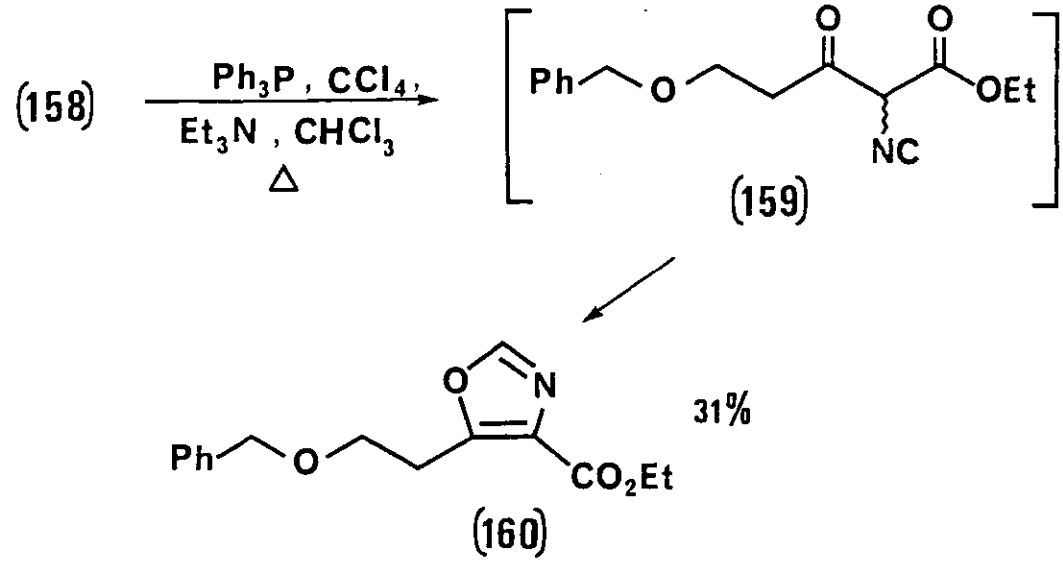
On the basis of these encouraging results reduction of diazo-compound (143) with zinc and acetic acid in the presence of the mixed anhydride formic acetic anhydride[99] was investigated. It was found that formamide (158) was produced in 48% yield along with β-keto-ester (139) (21%)(Scheme 42).



(158)

Scheme 42

As structural confirmation, and to show the transient intermediacy of isonitrile (159), formamide (158) was dehydrated with triphenylphosphine-carbon tetrachloride to give oxazole (160) in an unoptimised yield of 31% (Scheme 43).

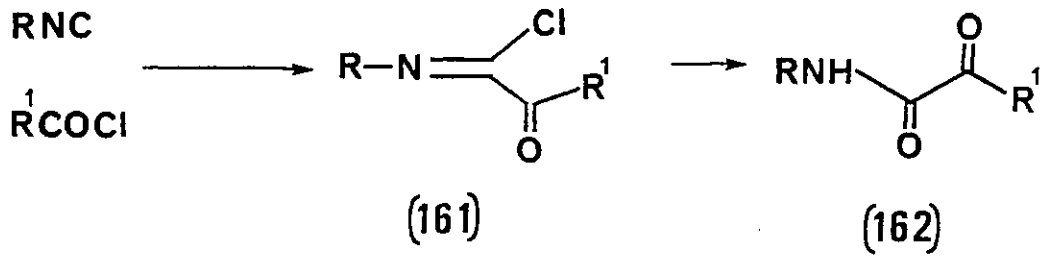


Scheme 43

We now had a low yielding route to formamide (158) which is a synthetic equivalent to the target synthon, isonitrile (128). However, further elaboration along this route was not attempted partly due to the low yields, but mainly due to the unexpected and disappointing results obtained on model studies of isonitriles with acid chlorides. The success of such a reaction would of course be critical to the success of this proposed strategy (B).

b) Model studies on the reaction of isonitriles with acid chlorides

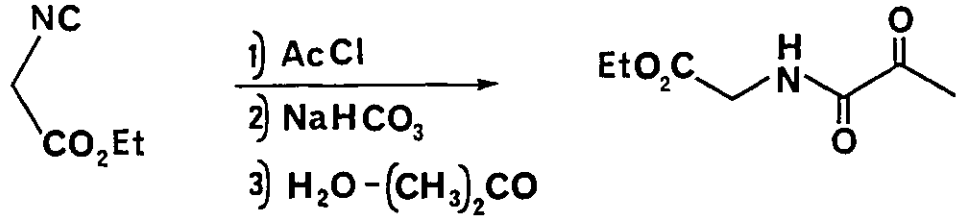
The addition reactions of simple isonitriles to simple acid chlorides, to give initially α-keto-imidoylchlorides (161) and, after hydrolysis, α-keto-amides (162), has been studied by Ugi[100] (Scheme 44).



(161) (162)

Scheme 44

We examined the reactions of two isonitriles which were better models for our proposed intermediates. Thus, ethyl isocyanoacetate (114) was treated with acetyl chloride and subsequently sodium hydrogen carbonate (1 equivalent) in aqueous acetone. The α-keto-amide (163) was isolated in low yield (19%) and characterised as its 2,4-dinitrophenylhydrazone (Scheme 45). Use of excess sodium hydrogen carbonate (as in the original procedure [100]) increased the amount of by-products (t.l.c.). A reaction using a pH 7 buffer as the hydrolysing medium failed to minimise these by-products (t.l.c.).



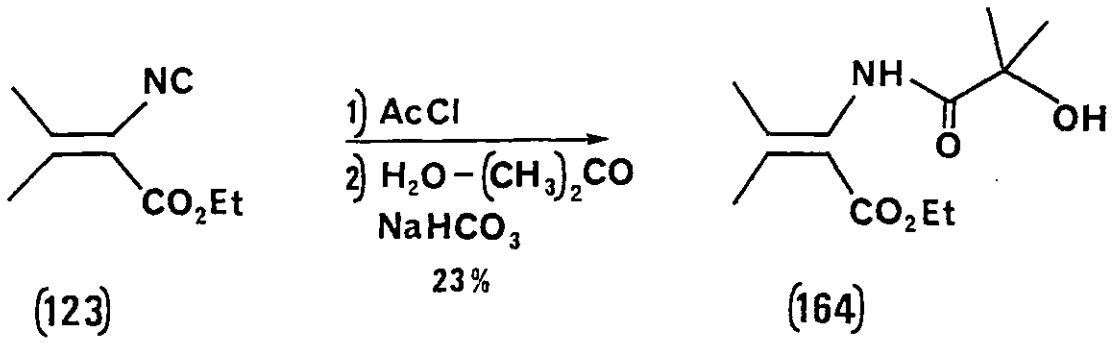
(114) (163)

Scheme 45

Brief attempts to further characterise (163) by conversion to a 2,5-piperazinedione by reaction with benzylamine were unsuccessful. The presence of the corresponding imine was indicated (mass spectrometry) but no adduct could be isolated.

Reaction of the model isonitrile (123) with acetyl chloride was also examined.

Very surprisingly the product isolated after hydrolysis was not the expected α-keto-amide but tertiary alcohol (164), which was fully characterised (Scheme 46). All isonitrile (123) was consumed (i.r. and mass spectroscopy) prior to hydrolysis. To test if this alcohol (164) was acetone derived, a repeat reaction using THF as solvent was carried out, but the same tertiary alcohol (164) was produced (t.l.c.). Further work on this unusual reaction was not carried out.



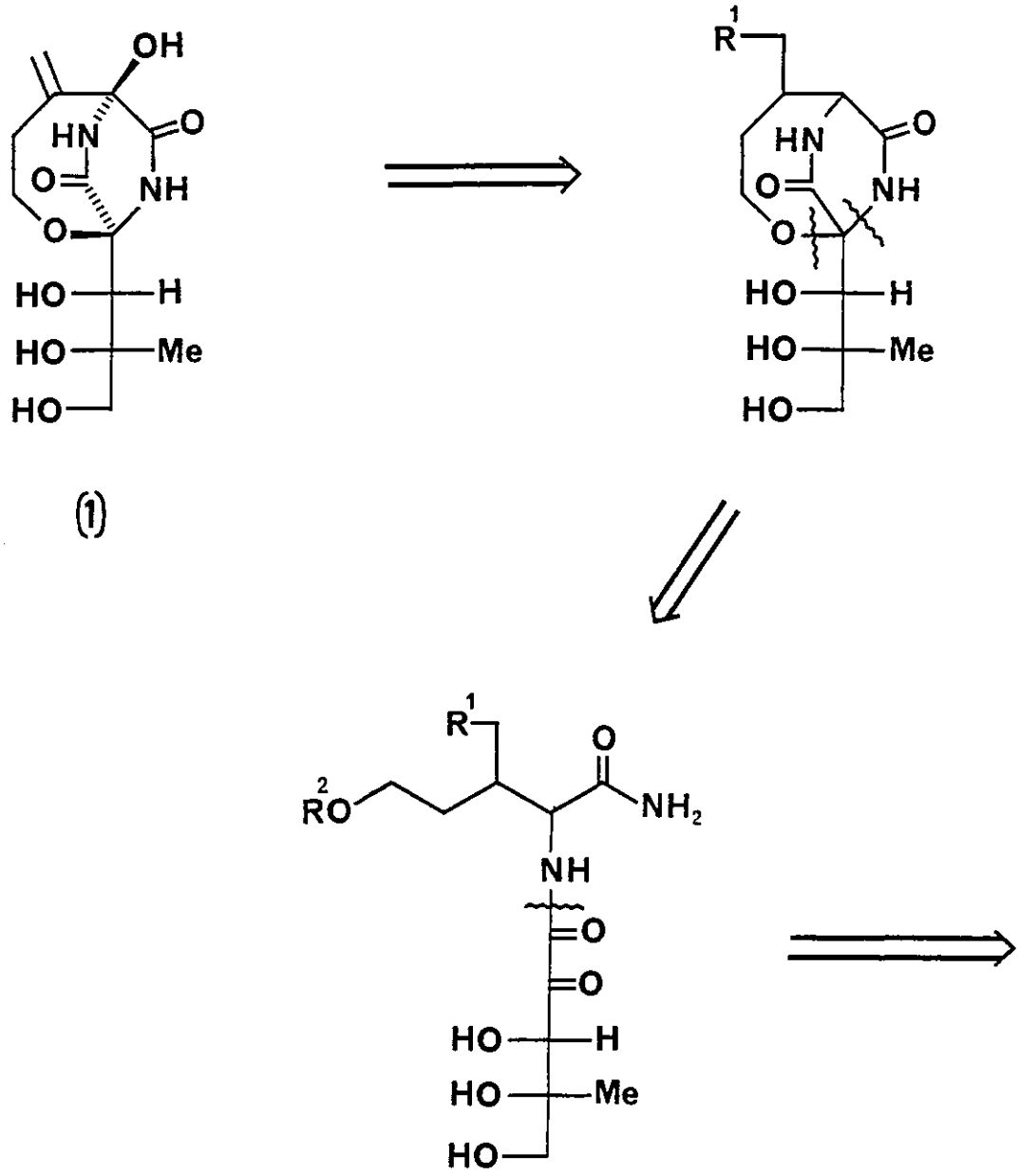
(123) (164)

Scheme 46

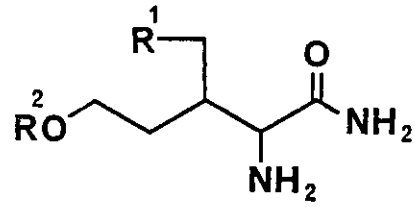
These model studies indicated that the reaction of isonitriles (114) and (123) with acid chlorides is not an efficient or reliable reaction. These and other factors, already discussed, led to the abandonment of Strategies A and B.

3) STRATEGY C

The third strategy (C) (Scheme 47) proposed for the total synthesis of bicyclomycin (1) again involved an intermediate α-keto-amide (165) and subsequent bicyclisation to bicyclomycin type ring systems. However, the proposed construction of α-keto-amide (165) was not via isonitriles but via an amino-amide (166) and an α-keto-acid derivative (167). Thus synthons of type (166) and (167) became the first target compounds for this strategy.



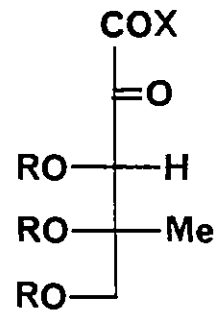
Scheme 47



(166) R^1 = H, PhSe, OH

R^2 = Ⓟ

⟹ +



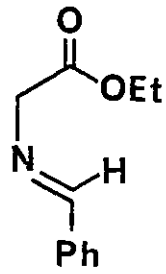
(167) X = OH, Cl

R = Ⓟ

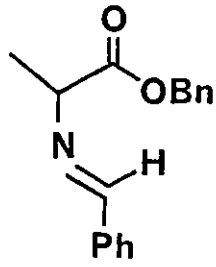
Scheme 47 cont'd

a) Synthetic approaches to amino-amides of type (166)

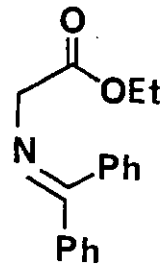
Much work has been published on the synthesis of α-alkyl-α-amino acids via alkylation of carbanions derived from glycine derivatives. For example, benzylidene esters such as (168)[101,102] and (169)[103] and diphenylmethylene esters and nitriles such as (170)[104,105] and (171)[106] have been successfully used.



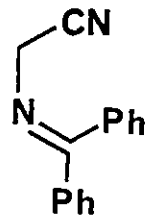
(168)



(169)

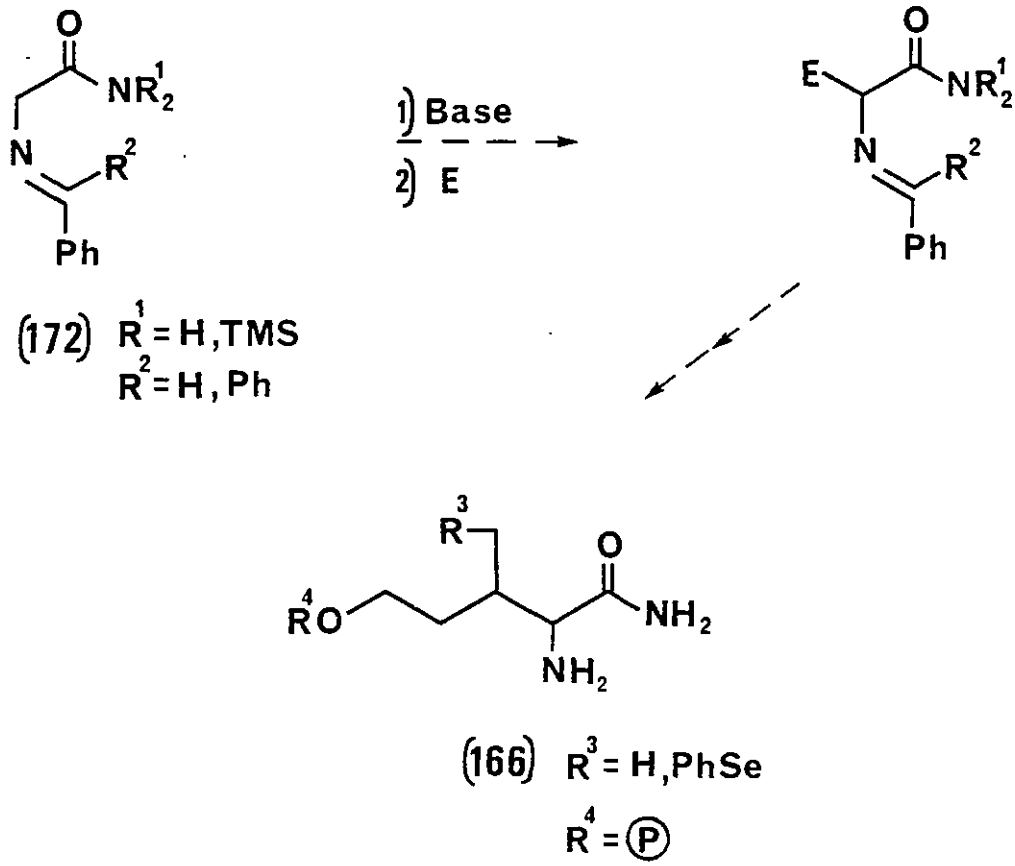


(170)



(171)

On the basis of these benzylidene and diphenylmethylene derivatives we envisaged a generalised synthesis of target amino-amide (166) via novel carbanions derived from amides of general type (172) and suitable electrophiles (E) (Scheme 48).

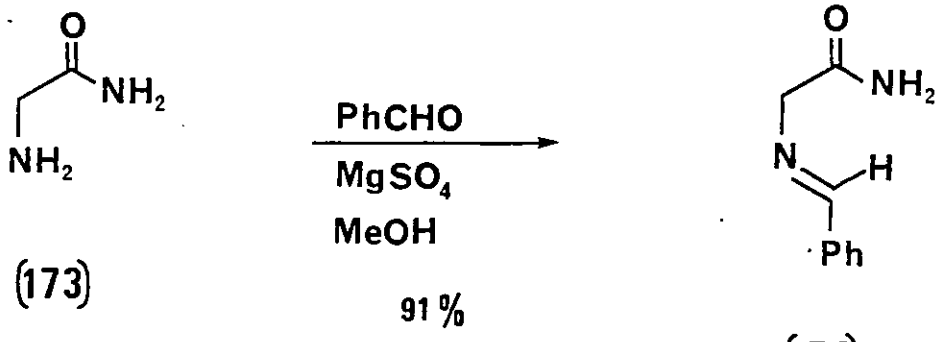


(172) R^1 = H, TMS
R^2 = H, Ph

(166) R^3 = H, PhSe
R^4 = (P)

Scheme 48

Glycinamide (173) (available[107] from glycine ethyl ester hydrochloride, triethylamine and ammonia) was treated with benzaldehyde and magnesium sulphate in dichloromethane, using the conditions Stork[101] employed to prepare ester (168). However, only a low yield (25%) of benzylidene-amide (174) was obtained. A non-aqueous work-up increased this to 32%, but use of methanol as solvent produced a more pronounced improvement giving amide (174) in 91% yield (Scheme 49).



(173) (174)

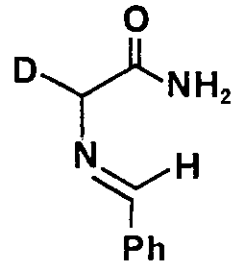
Scheme 49

Carbanions derived from bis-O,N-trimethylsilylacetamide (175)[108] have been used successfully in alkylation reactions[109]. With this in mind an attempt was made to prepare protected amide (176) under identical conditions[109], however, a very complex mixture resulted (n.m.r.).

(175) (176)

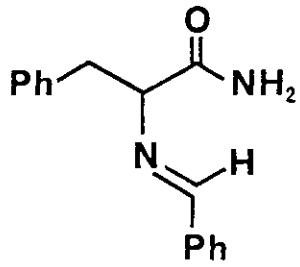
In fact, it was found to be unnecessary to protect the amide funtionality in

amide (174) prior to carbanion formation. Treatment of amide (174) with 1·1 equivalents of LDA in THF at -78°, and quenching with deuterium oxide yielded deuterated amide (177) (in 89% crude yield), indicating that mono-deprotonation on carbon occurs (n.m.r., and mass spectrometry).

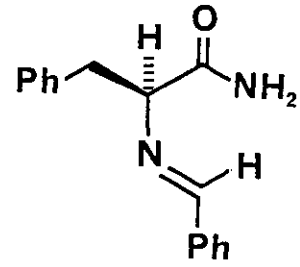


(177)

As a model study the carbanion of amide (174) was quenched with benzyl bromide to give adduct (178), as judged by comparison (t.l.c., n.m.r.) with an authentic sample of amide (179) (available by treatment of commercial L-phenylalanine amide with benzaldehyde and magnesium sulphate in dichloromethane). However, purification of crude amide (178) was not possible due to its instability on silica gel and alumina, and its failure to crystallise from the solvents used to purify authentic amide (179).



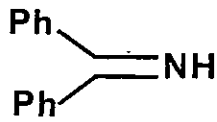
(178)



(179)

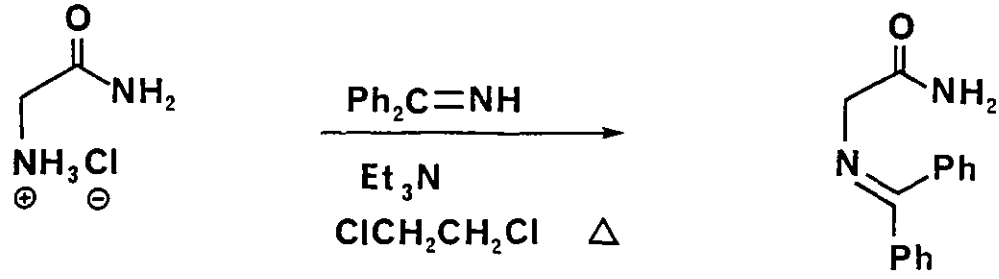
The carbanion derived from amide (174) with LDA failed to react cleanly when benzaldehyde or benzoyl chloride were used as electrophiles.

To overcome the problems found in isolation of the adducts from amide (174) with various electrophiles, it was concluded that a more stable alkylidene derivative would be advantageous. It was, therefore, decided to use diphenylmethylene imines (benzophenone Shiff bases) instead of the benzylidene derivatives. O'Donnell[104] has found that diphenylmethylene derivatives of amino-acid esters are most easily prepared by imine-transfer with diphenylmethylenimine (180) (available[110] from benzonitrile and phenyl magnesium bromide).



(180)

Thus, by analogy, commercial glycinamide hydrochloride (181) was treated with diphenylmethylenimine (180) in dichloromethane, but t.l.c. analysis showed an incomplete reaction. Addition of triethylamine failed to give further reaction (t.l.c.). Use of methanol as the solvent, instead of dichloromethane, did yield the desired amide (182) in reasonable yield (41%) (Scheme 50), but treatment of amide (181) with diphenylmethylenimine (180) and triethylamine in 1,2-dichloroethane at reflux proved to be the method of choice, giving amide (182) in 76% yield (Scheme 50).

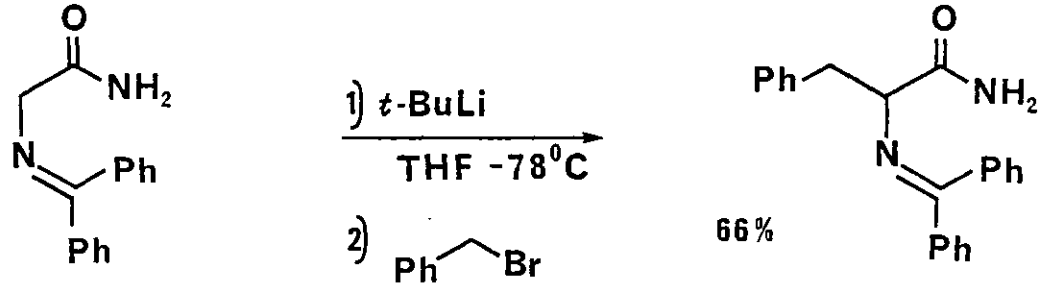


(181) (182)

Scheme 50

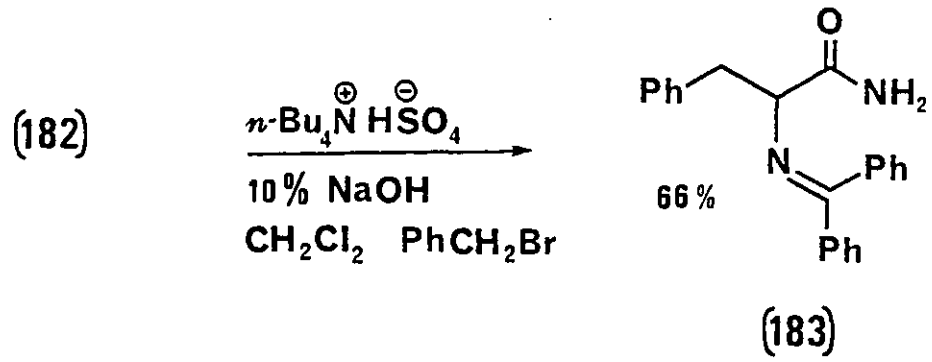
With amide (182) in hand, studies on the formation of the corresponding carbanion were undertaken. Use of 1·2 equivalents of LDA as base under a variety of conditions (see Experimental Section for details) gave poor results in this case (42–53% deuterium incorporation). The fact that all the incorporations were approximately 50% indicated that dianion formation (on carbon and nitrogen) may be a problem. However, the use of 2·2 equivalents of LDA failed to give a significantly improved deuterium incorporation (66% D).

It was subsequently found that amide (182) could be successfully alkylated by using t-butyllithium as base or using phase transfer conditions. Thus, amide (182) on treatment with t-butyllithium (1·1 equivalents) in THF at -78°C for 3h, and subsequently with benzyl bromide gave amide (183) in 66% yield (Scheme 51). The imine functionality was unstable to silica gel, but was sufficiently stable to alumina to enable isolation of amide (183) by column chromatography. It was also found that amide (183) was conveniently produced in good yield (66%) by a phase transfer reaction with amide (182), tetrabutylammonium hydrogen sulphate, 10% aqueous sodium hydroxide, and dichloromethane (Scheme 51).



(182) (183)

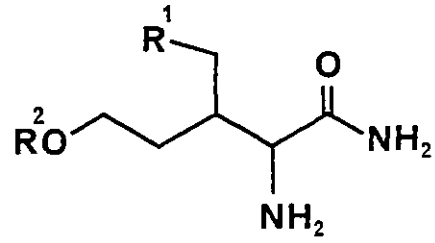
Scheme 51



(183)

Scheme 51 cont'd

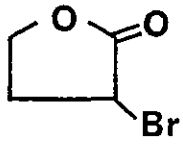
Having obtained successful alkylation procedures for amide (182) and shown that the adducts were sufficiently stable for isolation, we now needed to synthesise various electrophiles with suitable functionality for subsequent elaboration of their adducts with amide (182) to target compounds (166).



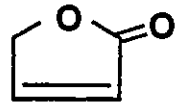
(166) R^1 = OH , PhSe

R^2 = H , Si*t*-Bu Ph_2

2-Bromobutyrolactone (184) and 2-buten-4-olide (185) were considered suitable because sodium borohydride reduction and deprotection of their adducts with amide (182) would have yielded target compound (166) (R^1=OH,R^2=H). Lactones (184) and (185) were prepared as described in the literature[111] from butyrolactone.

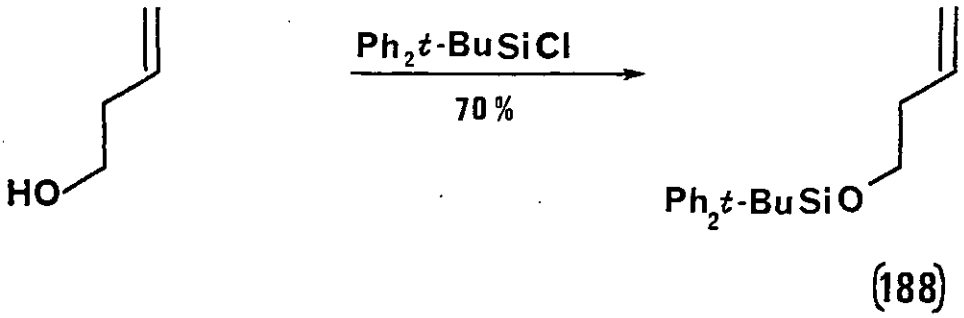


(184)

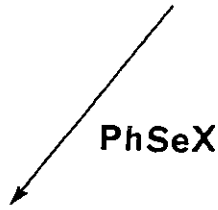


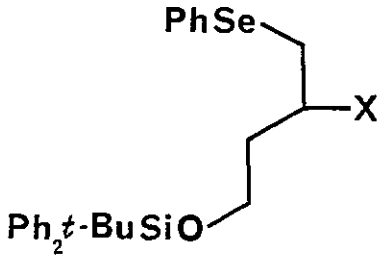
(185)

Compounds such as chloride (186) and bromide (187) would also be useful electrophiles. They were available from commercial 3-buten-1-ol by silylation with t-butyldiphenylsilyl chloride to give (188) in 70% yield, and subsequent reaction with the respective phenylselenyl halide (Scheme 52). Halides (186) and (187) were somewhat unstable which prohibited their full characterisation.



(188)



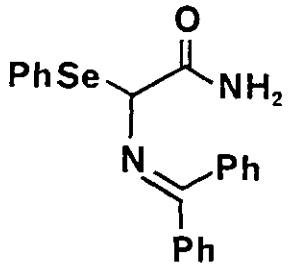


(186) X = Cl

(187) X = Br

Scheme 52

Use of electrophiles (184), (185), (186), and (187) with amide (182) was first examined by the phase-transfer alkylation method. It was found that the lactonic electrophiles (184) and (185) gave no reaction at all (t.l.c.), and it was subsequently shown that these electrophiles were unstable to the hydrolytic conditions. Use of the phenylselenyl electrophiles (186) and (187) was hampered by the formation of large amounts of diphenyl diselenide (t.l.c.). Chloride (186) gave no isolable products, but bromide (187) gave a major product believed to be amide (189). Full characterisation of (189) was not possible due to its facile decomposition to produce diphenyl diselenide (t.l.c.).

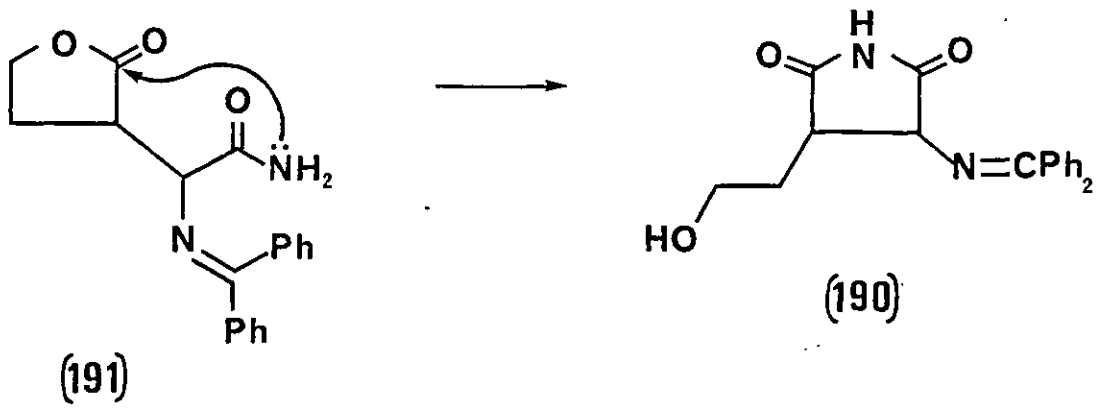


(189)

If phenylselenyl-amide (189) was formed then this indicates a tendency for the carbanion of amide (182) to react with the selenium atom of (187) as the electrophilic centre. Because of these poor results with the phenylselenyl electrophiles, and their propensity to decompose, the use of (186) and (187) as electrophiles was not further studied.

The lactonic electrophiles (184) and (185) were reacted with the carbanion of amide (182) formed by treatment with t-butyllithium. The attempted 1,4-addition to butenolide (185) yielded a very complex mixture (t.l.c.), but lactone (184) gave a reasonably clean reaction and an adduct was isolated. Unfortunately, the isolated compound was imide (190) (38%) and not the desired adduct (191). Presumably imide (190) is more thermodynamically stable (Scheme 53). Although formation of imide (190) was interesting, it was, however, synthetically useless as far as

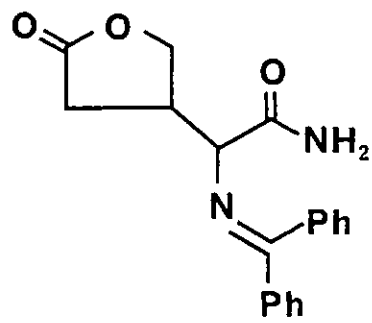
Strategy C was concerned.



(191) (190)

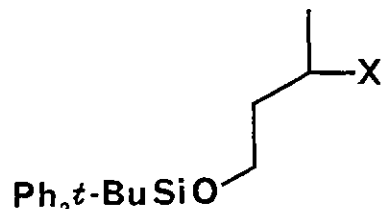
Scheme 53

Stork[101] has reported the successful conjugate addition of amide (168) to various electrophiles in the presence of catalytic sodium ethoxide. Use of these conditions with amide (182) and butenolide (185) failed to produce the desired adduct (192) and showed no detectable reaction (t.l.c.).



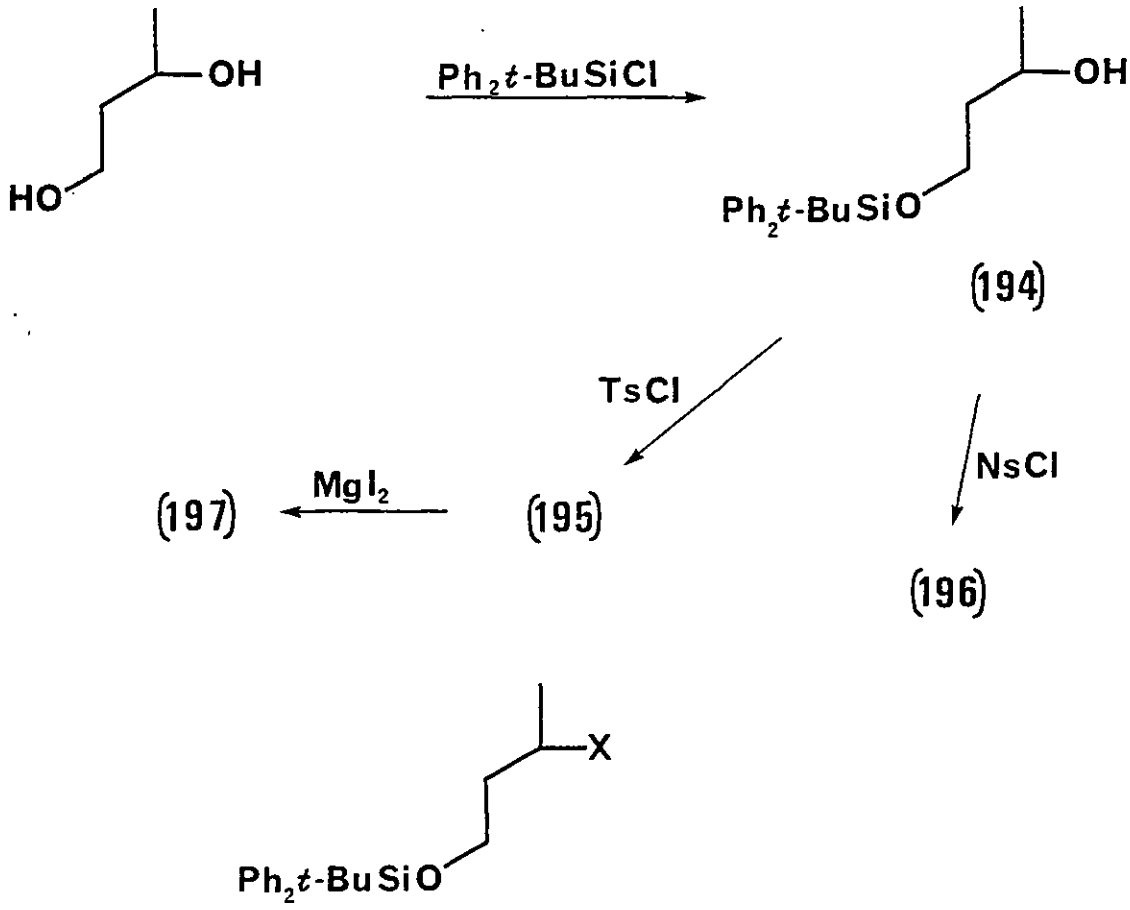
(192)

Due to the difficulties encountered with the highly functionalised electrophiles previously investigated, a simplified electrophile was sought. Electrophiles such as (193) (where X is a leaving group) would provide useful models, subsequent oxidation of which may give access to systems suitable for bicyclomycin synthesis.



(193)

A range of suitable electrophiles were found to be readily available from butan-1,3-diol. Selective silylation of butan-1,3-diol with t-butyldiphenylsilyl chloride proceeded smoothly to give alcohol (194) (Scheme 54). Tosylation of crude alcohol (194) under standard conditions yielded p-toluenesulphonate (195) in 75% overall yield from butan-1,3-diol (Scheme 54). Similarly, reaction of crude alcohol (194) with p-nitrobenzenesulphonyl chloride at -15°C yielded p-nitrobenzenesulphonate (196) in 72% overall yield (Scheme 54). p-Toluenesulphonate (195) was converted into the corresponding iodide (197) with magnesium iodide[112], and iodide (197) was used crude in subsequent reactions.



(195) X = OTs

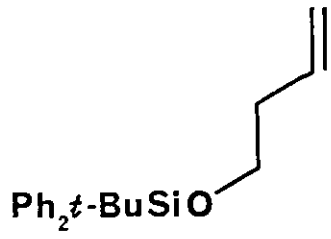
(196) X = ONs

(197) X = I

Scheme 54

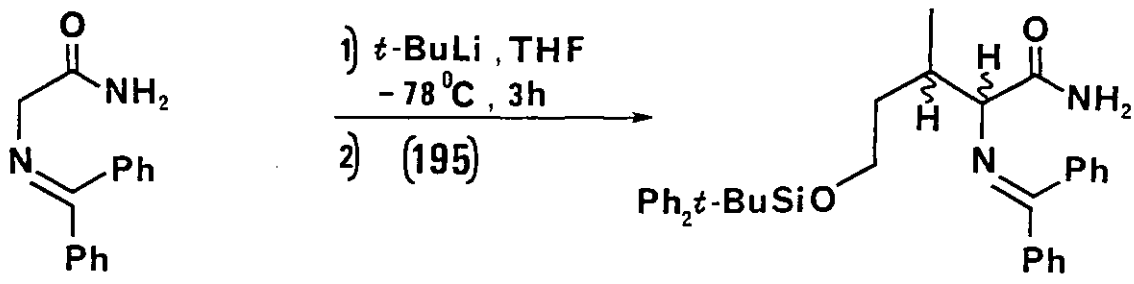
Reaction of p-toluenesulphonate (195) with amide (182) under the phase transfer conditions previously described was unsuccessful and no reaction was detected (t.l.c.).

Reaction of all three electrophiles (195), (196), and (197) was examined with the carbanion derived from amide (182) with t-butyllithium. Initially iodide (197) was tried, but (197) was observed to decompose to alkene (188) under the reaction conditions.



(188)

The use of the corresponding p-toluenesulphonate has been reported to give less elimination than the iodide in other systems[113], and p-toluenesulphonates are reported to be more reactive towards substitution than the corresponding halides[114]. This was in fact found to be the case because reaction of p-toluenesulphonate (195) with the carbanion of amide (182) did give the desired adduct (198), albeit in low yield (25%) (Scheme 55).



(182) (198)

Scheme 55

It was hoped to improve the yield of amide (198) by use of p-nitrobenzenesulphonate (196) as the electrophile because it has been reported[115] that p-nitrobenzenesulphonate is a significantly better leaving group than p-toluenesulphonate. However, use of (196) failed to yield any traces of amide (198) (t.l.c.) and only a very intensely coloured dark red-brown solution was observed. Possibly the carbanion was attacking the electron deficient aromatic ring to give a Meisenheimer complex.

Several experiments were conducted with p-toluenesulphonate (195) as the electrophile to optimise the yield of the desired amide (198) (Table 2).

TABLE 2

Preparation of amide (198)

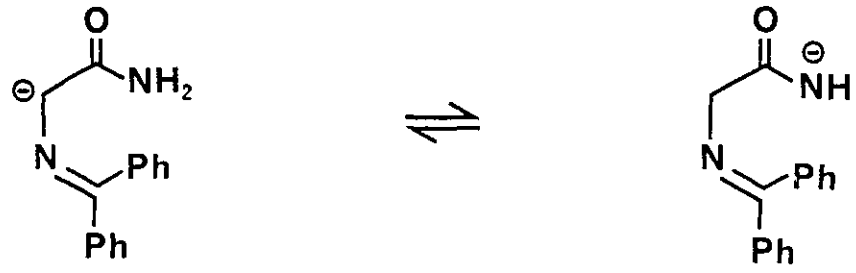
No. Equivs. ^{t}BuLi	Solvent	Additive	Conditions after addition (195)	% yield (198)
1.1	THF	-	RT/17h	25
1.1	THF	TMEDA	RT/2d	0 (t.l.c.)
1.1	THF	DMPU	RT/19h	0 (t.l.c.)
1.1	DME	-	RT/2d	0 (t.l.c.)
2.2	THF	-	RT/18h	39
2.2	Et_2O	-	RT/16h	54
2.2	Et_2O	-	RT/2.5d	84

THF = tetrahydrofuran DME = 1,2-dimethoxyethane

DMPU = N,N´-dimethylpropylurea TMEDA = N,N,N´,N´-tetramethylethylenediamine

The results shown in Table 2 were somewhat surprising at first. Addition of TMEDA or DMPU, or use of a more polar solvent (DME) had a dramatic effect on the yield of adduct (198). Possibly such changes shifted the equilibrium of carbanion (199) and (200) over to the right (Scheme 56). p-Toluenesulphonate (195) would be a sluggish electrophile compared to benzyl bromide (which was used

for the model reactions) and one possibility is that (199) is the kinetic anion and (200) is the thermodynamic anion at the higher temperatures needed for reaction with p-toluenesulphonate (195).

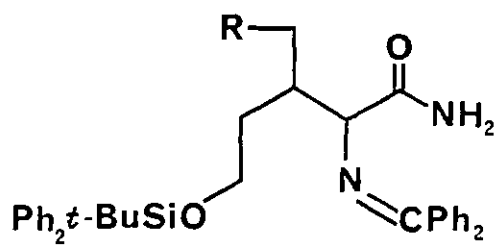


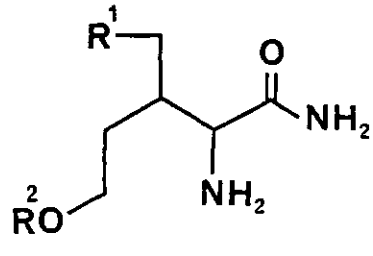
(199) (200)

Scheme 56

In an attempt to test this hypothesis, the dianion of amide (182) was prepared and treated with p-toluenesulphonate (195), but this gave adduct (198) in only a slightly improved yield (39% as compared to 25% for the monoanion) (Table 2). A more dramatic improvement of yield was obtained by using the dianion of amide (182) in a less polar solvent, such as diethyl ether, which gave adduct (198) in 54-84% yield (Table 2).

Therefore, we now had access to amide (198) in good yield although routes to more synthetically versatile amides such as (201) or (202) are still needed. (198) serves as a synthetic equivalent to the generalised target amino-amide (166).





(198) R = H

(201) R = PhSe

(202) R = OH

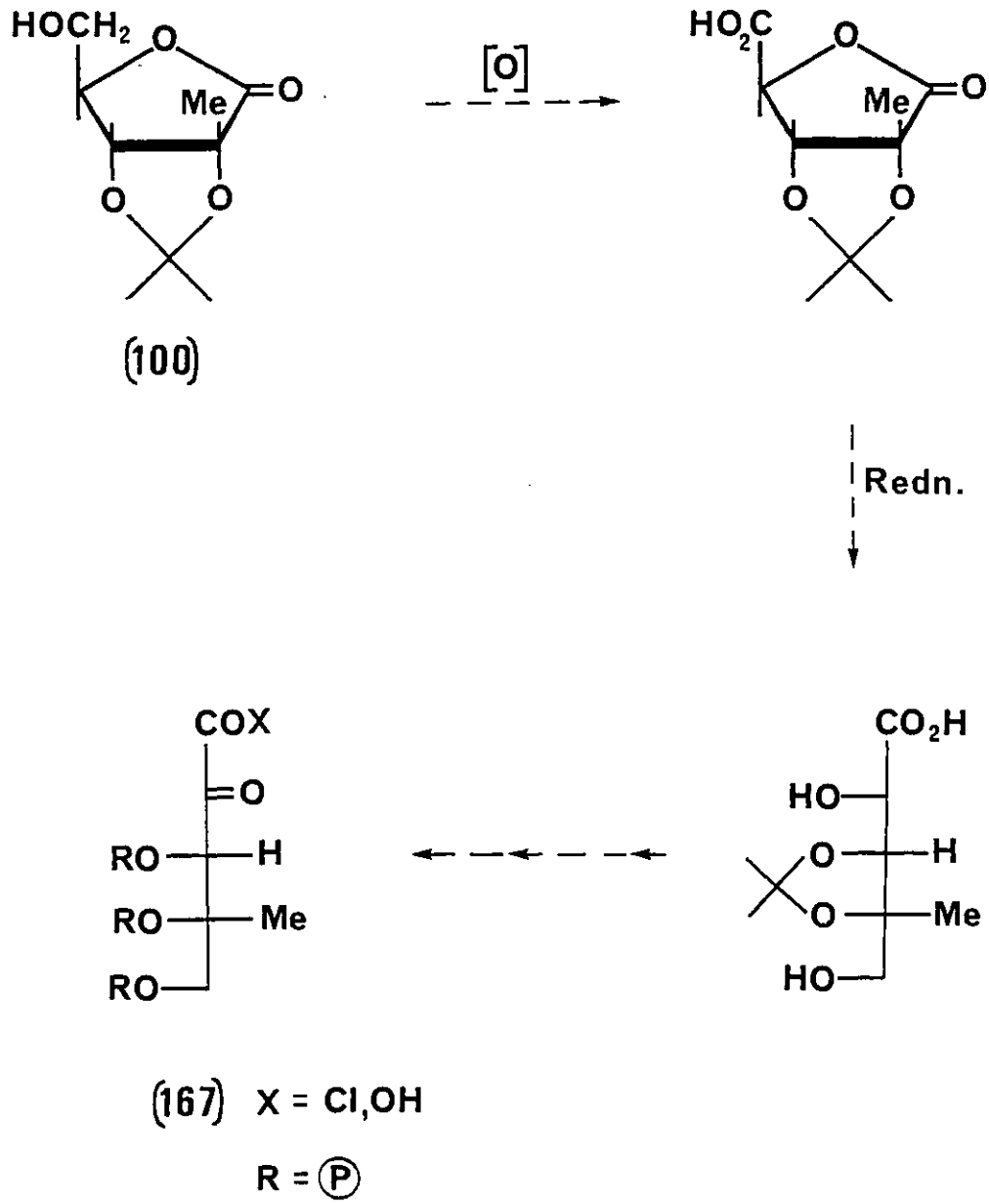
(166) R^1 = H, PhSe, OH

R^2 = Ⓟ

Further elaboration of amide (198) will be discussed as part of Strategy D.

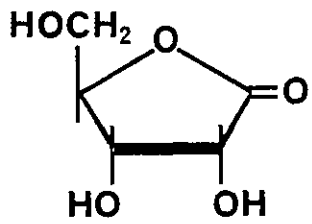
b) Synthetic approaches to α-keto-acid derivative (167).

It was thought that the target α-keto-acid synthon (167) of Strategy C should be available from the previously described lactone (100) (Scheme 57).

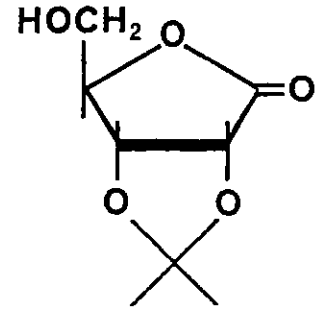


Scheme 57

As a model study D-(+)-ribono-1,4-lactone (202) was chosen as a readily available starting material and converted cleanly in 99% yield to the isopropylidene derivative (203) with concentrated sulphuric acid and acetone.

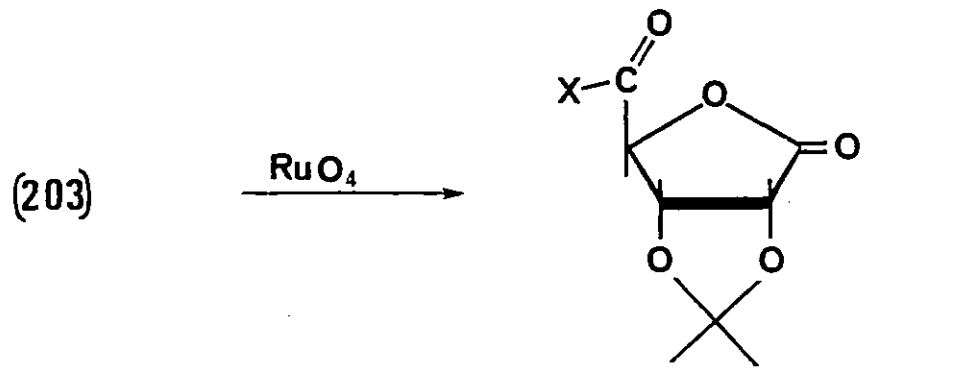


(202)



(203)

Conversion of (203) into the corresponding carboxylic acid (204) with ruthenium tetroxide[116] was not a clean reaction, and acid (204) was isolated as its diphenylmethyl ester (205) (by treatment with diphenyldiazomethane[117] in diethyl ether) in low yield (14% overall) (Scheme 58). Attempted oxidation of (203) with potassium permanganate-tetrabutylammonium bromide[118] failed to yield any isolable products.



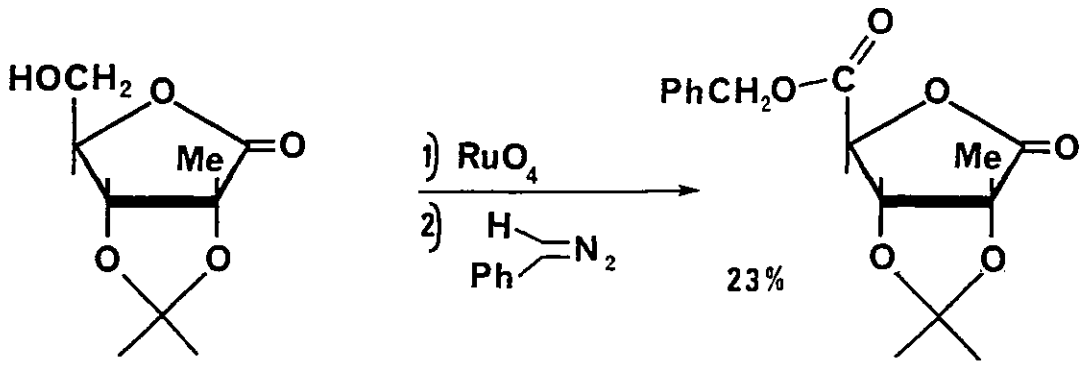
(204) X = OH

(205) X = $OCHPh_2$

Scheme 58

Similarly, oxidation of lactone (100) with ruthenium tetroxide and isolation with phenyldiazomethane (available from N-benzyl-p-toluenesulphonamide[119] via

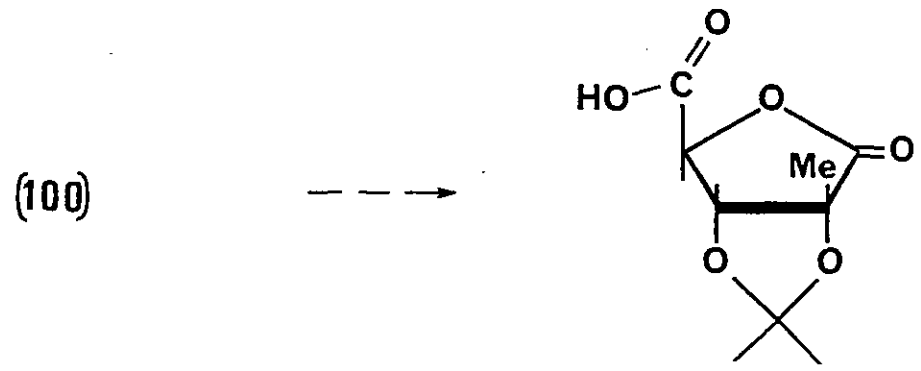
N-benzyl-N-nitroso-p-toluenesulphonamide[120]) gave benzyl ester (206) in low yield (23% overall) (Scheme 59).



(100) (206)

Scheme 59

Although use of ruthenium tetroxide obviously did yield carboxylic acid (207) a higher yielding route was needed for this approach to α-keto-acid derivatives to be useful (Scheme 60).



(207)

Scheme 60

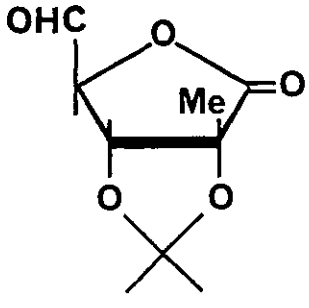
Conversion of alcohol-lactone (100) into acid (207) requires an oxidant which is neither too acidic (to prevent loss of the isopropylidene group) nor too basic (to prevent hydrolysis of the lactone). Numerous oxidants which meet these demanding criteria were tried but with very little success (Table 3).

TABLE 3

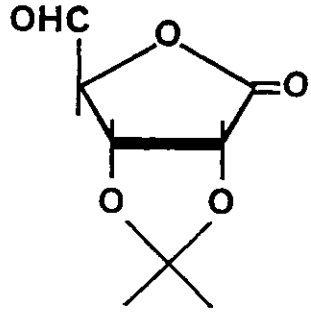
Oxidant	Reference	Result
PDC-DMF	121	Trace amounts of acid (207)(n.m.r.)
$KMnO_4$-H_2O	122	Complex mixture (t.l.c.)
AgO-H_2O	123	Starting material (t.l.c.)
AgO-H_2O-THF	124	Starting material (t.l.c.)
13% Pt/C - air	125	Starting material (t.l.c.)
13% Pt/C - O_2	126	Starting material (t.l.c.)

PDC = pyridinium dichromate DMF = N,N-dimethylformamide

Due to the difficulties encountered in obtaining a good yield of acid (207) by direct oxidation, a route involving a two step oxidation via aldehyde (208) was investigated. Analogous aldehyde (209) has been reported in the literature[127] to be available by oxidation of the corresponding alcohol under Pfitzner-Moffatt conditions.



(208)



(209)

Attempted preparation of aldehyde (208) was examined using a variety of mild reagents (Table 4).

TABLE 4

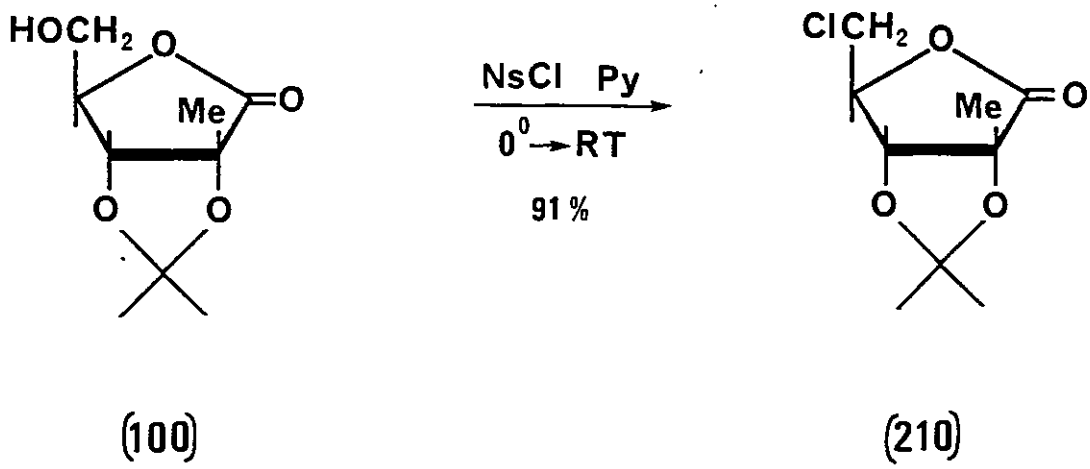
Oxidant	Reference	Result
PDC-CH_2Cl_2	121	Decomposition (t.l.c.)
PCC-CH_2Cl_2	128	Starting material (t.l.c.)
PDC-3Å mol.sieves	129	Rapid conversion to less polar unstable product (M^+, 400 or 385)
PCC-3Å mol.sieves	129	
DMSO-DCC-TFA-py	127	Only trace amounts of aldehydic products (n.m.r.)
DMSO-$(COCl)_2$	130	Complex mixture (t.l.c.)
DMSO-Ac_2O	131	Complex mixture (t.l.c.)

PDC = pyridinium dichromate PCC = pyridinium chlorochromate

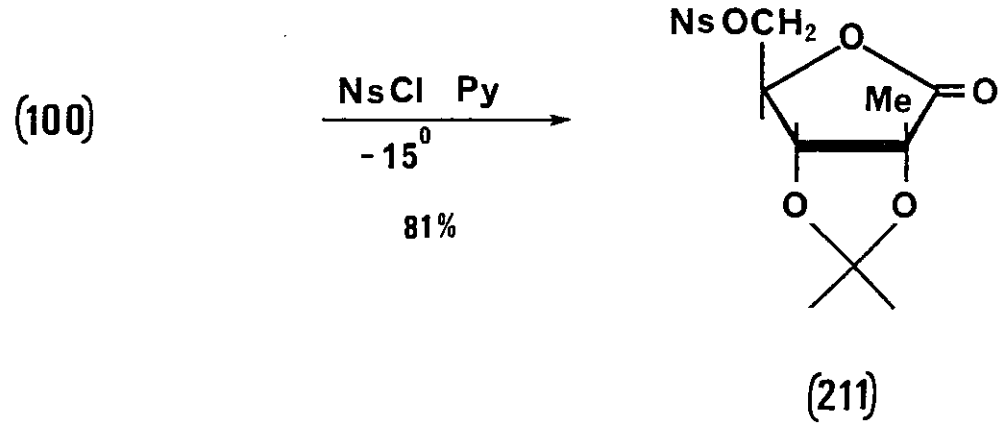
DMSO = dimethyl sulphoxide DCC = N,N'-dicyclohexylcarbodiimide

TFA = trifluoroacetic acid py = pyridine

As can be seen from Table 4 none of the conditions tried yielded the desired aldehyde (208). A slightly different oxidative approach to (208) was briefly examined. It has been reported that Kornblum[132] type oxidations can be achieved under much milder conditions if p-nitrobenzenesulphonates are used in place of the more usual p-toluenesulphonates[133]. To this end, alcohol-lactone (100) was treated with p-nitrobenzenesulphonyl chloride in pyridine at 0°C to room temperature, but the product isolated in good yield (91%) was the chloride (210) and not the p-nitrobenzenesulphonate (211) (Scheme 61). Presumably p-nitrobenzenesulphonate is such a good leaving group that displacement occurs by chloride ion from the pyridinium hydrogen chloride formed in the course of the reaction. This unwanted reaction is surpressed if the reaction is conducted at -15°C and the desired p-nitrobenzenesulphonate (211) is obtained in 81% yield (Scheme 61).



(100) (210)



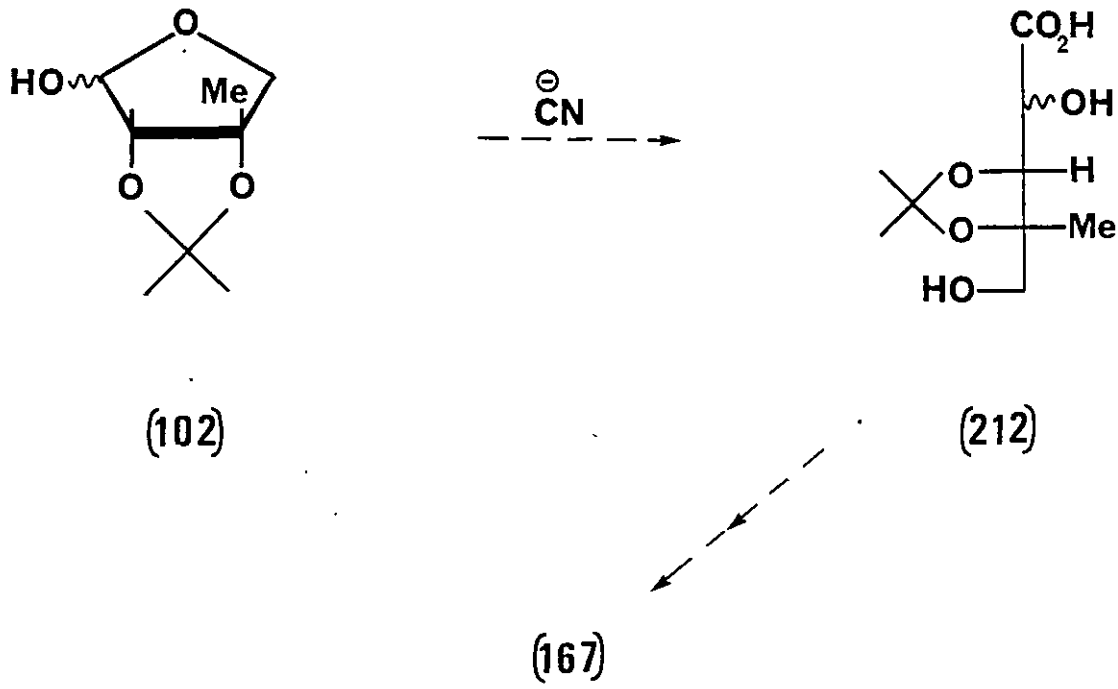
(211)

Scheme 61

However, attempted Kornblum type oxidation of (211) with DMSO and sodium hydrogen carbonate[133] gave no aldehydic products (n.m.r.).

On the basis of this result and previous results it was concluded that isolation of aldehyde (208) was not possible in our hands, although (208) may be have been formed in some reactions and subsequently decomposed.

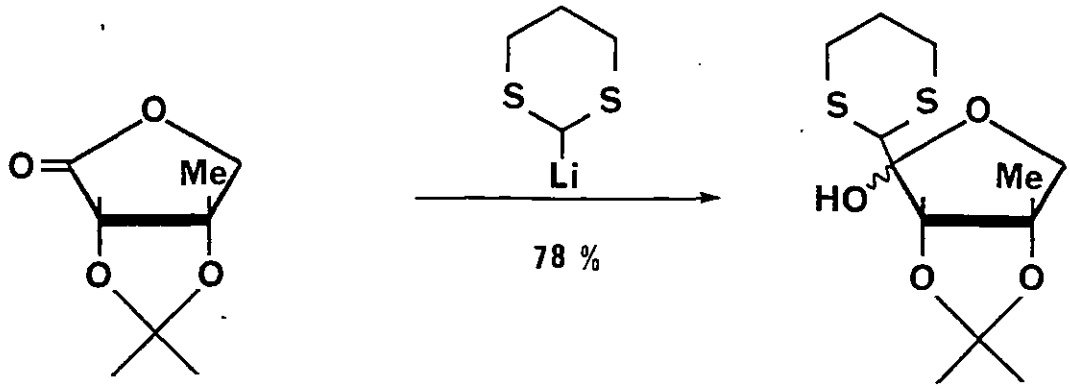
Another approach to α-keto-acid derivatives of type (167) was briefly examined. It was anticipated that reaction of the previously prepared lactol (102) with sodium cyanide should yield α-hydroxy-acid (212) after hydrolysis (Scheme 62).



Scheme 62

Thus lactol (102) was treated with sodium cyanide and the assumed intermediate cyanohydrin hydrolysed by an aqueous reflux. A complex mixture resulted containing no isopropylidene components (n.m.r.). Use of a basic (Na_2CO_3) hydrolysis medium failed to alleviate the problem, again giving a complex mixture of lactonic products (t.l.c.).

In the search for another approach to α-keto-acid derivatives of type (167) an interesting and potentially useful reaction was carried out on lactone (106). Thus treatment of lactone (106) with 2-lithio-1,3-dithiane smoothly yielded the adduct (213) in 78% yield (Scheme 63).

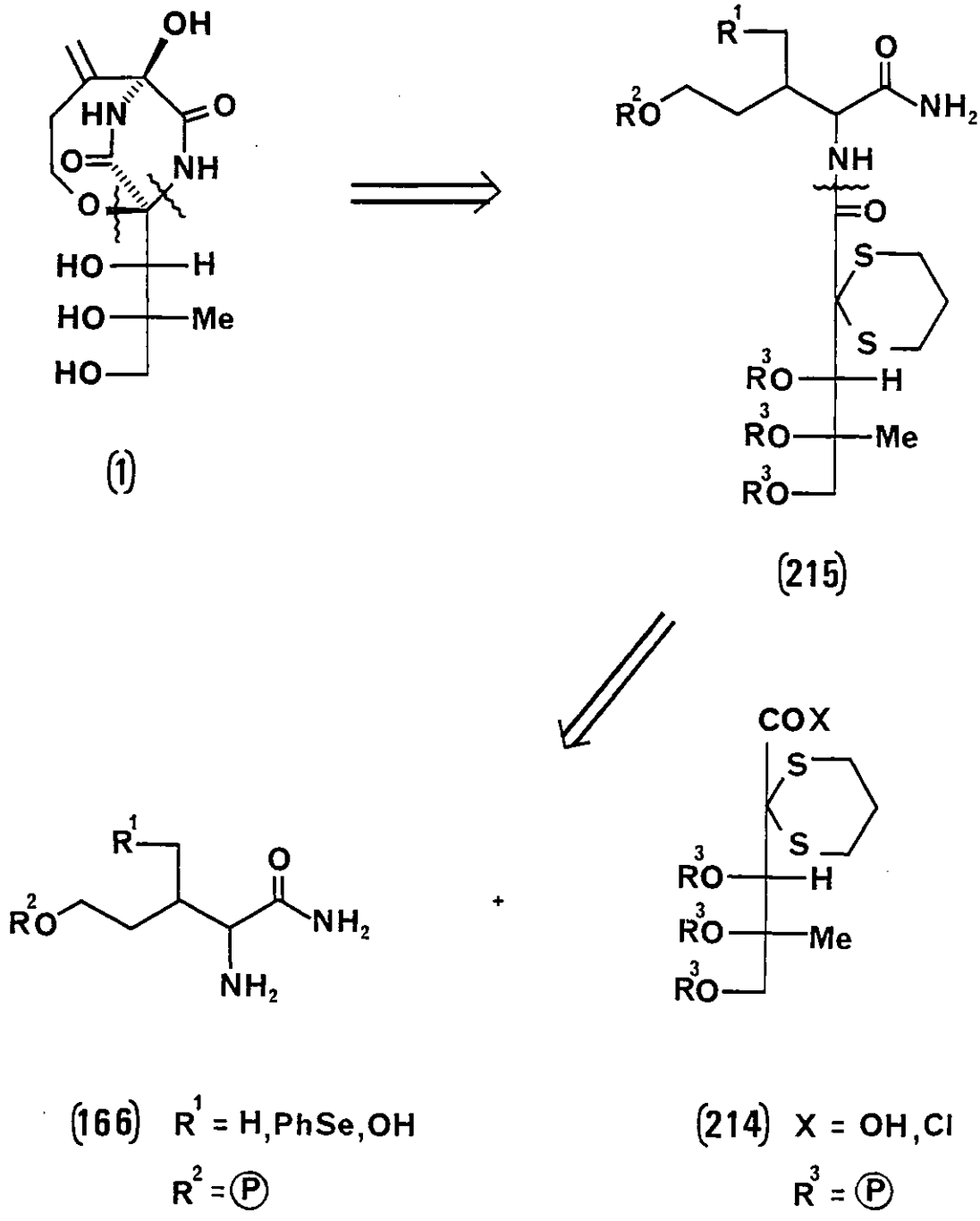


(106) Scheme 63 (213)

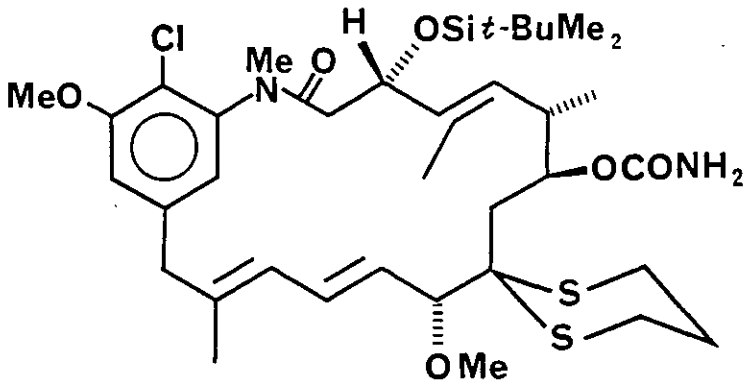
Substituted 1,3-dithianes have been converted into acids or esters by the sequence of metalation, reaction with dimethyl disulphide, and hydrolysis in the presence of mercury (II) salts[134]. However, elaboration of (213) was not attempted due to the success of other strategies (notably D) undertaken at the same time.

4) STRATEGY D

The final strategy (D) proposed for the total synthesis of bicyclomycin was fairly similar to Strategy C. Strategy D is outlined retrosynthetically below (Scheme 64) and again makes use of amino-amide synthons of type (166). However, it was proposed to couple (166) with a 1,3-dithiane derivative of type (214) bearing the chiral trihydroxymethylpropyl side chain found in bicyclomycin.

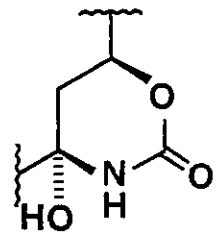


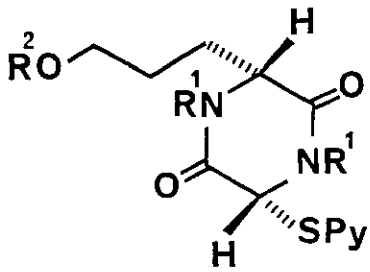
Scheme 64



$HgCl_2$, $CaCO_3$, H_2O, CH_3CN

(216)



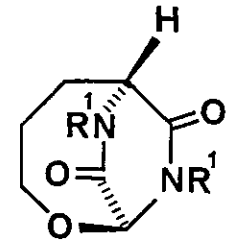


(217) R^1 = Me, $PhCH_2$, CH_2OMe ; R^2 = Si t-BuMe$_2$

(218) R^1 = Me, $PhCH_2$, CH_2OMe ; R^2 = H

(217) $\xrightarrow{PhHgClO_4}$

(218) $\xrightarrow[\underline{or}\ AgClO_4]{AgOTf}$

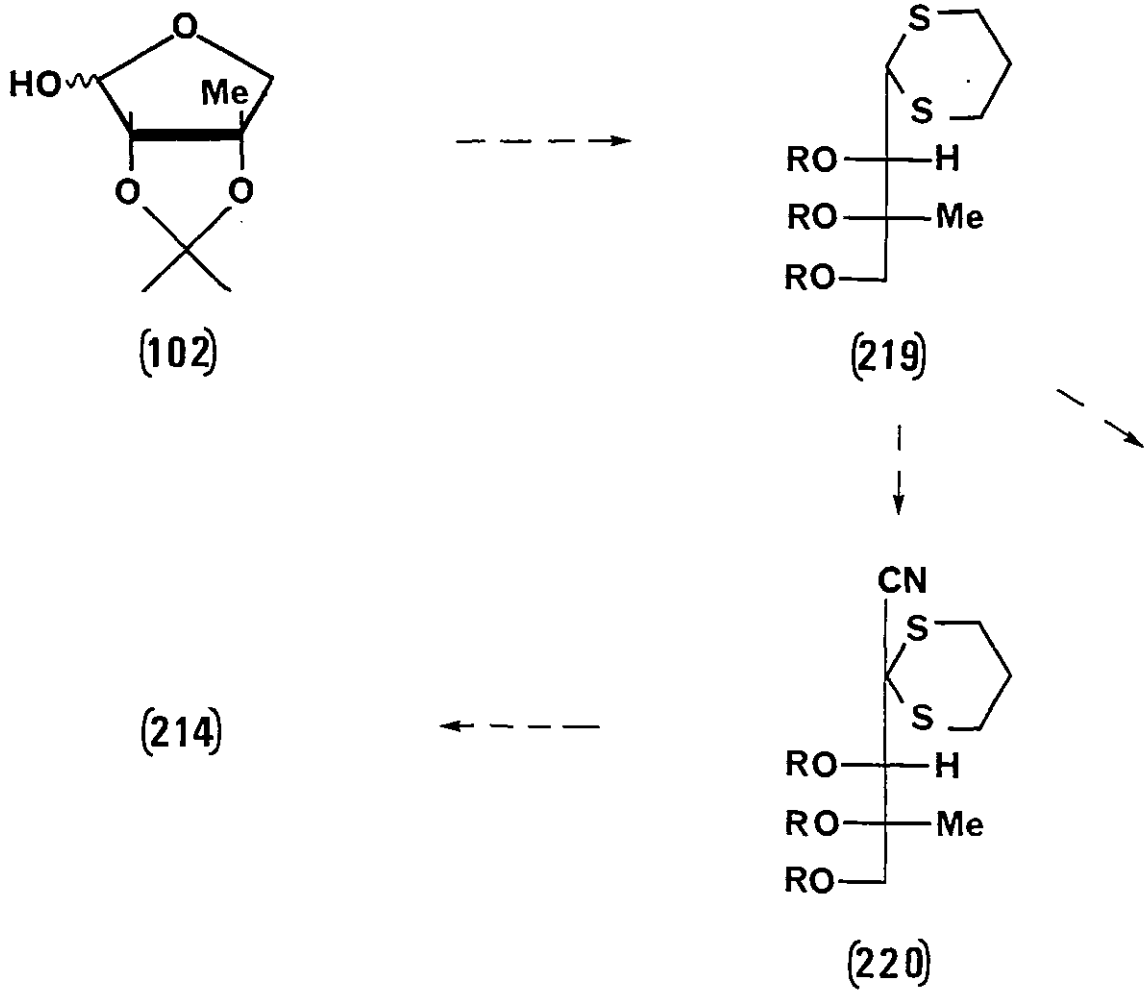


Scheme 65

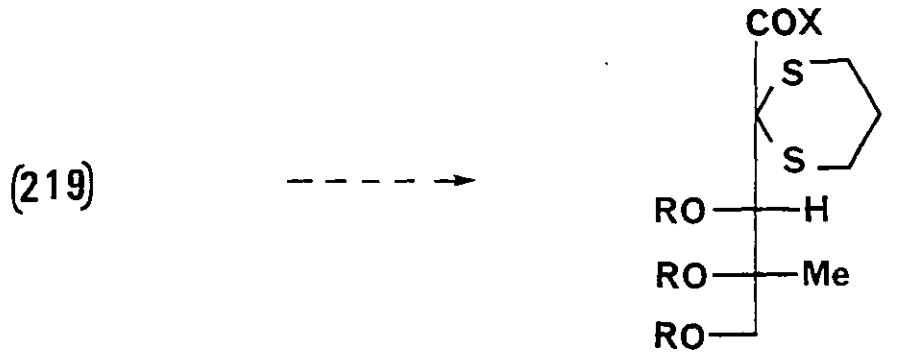
The key step in this strategy (D) was the proposed bicyclisation of (215) in the presence of mercury (II) or silver (I) salts under anhydrous conditions. Some literature precedent does exist for such a reaction. Corey used mercury (II) chloride to cyclise carbamate-1,3-dithiane (216) in a synthesis of maytansine[135], and also, more recently, Williams[62] has cyclised pyridyl-thioethers of type (217) and (218) (Scheme 65).

a) Synthetic approaches to 1,3-dithianes of type (214)

Synthetic approaches to 1,3-dithianes of type (214) were based on conversion of 1,3-dithianes such as (219) into (214) by one of two routes - a) treatment of an electrophilic equivalent of 1,3-dithiane (219) with cyanide ion to give (220) and subsequent hydrolysis or, b) treatment of a carbanion derived from (219) with carboxylating agents (Scheme 66).



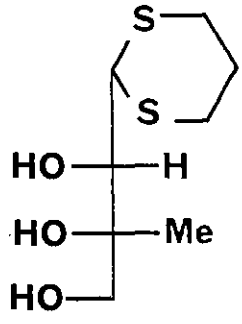
Scheme 66



(214) X = OH, Cl
R = H, Ⓟ

Scheme 66 cont'd

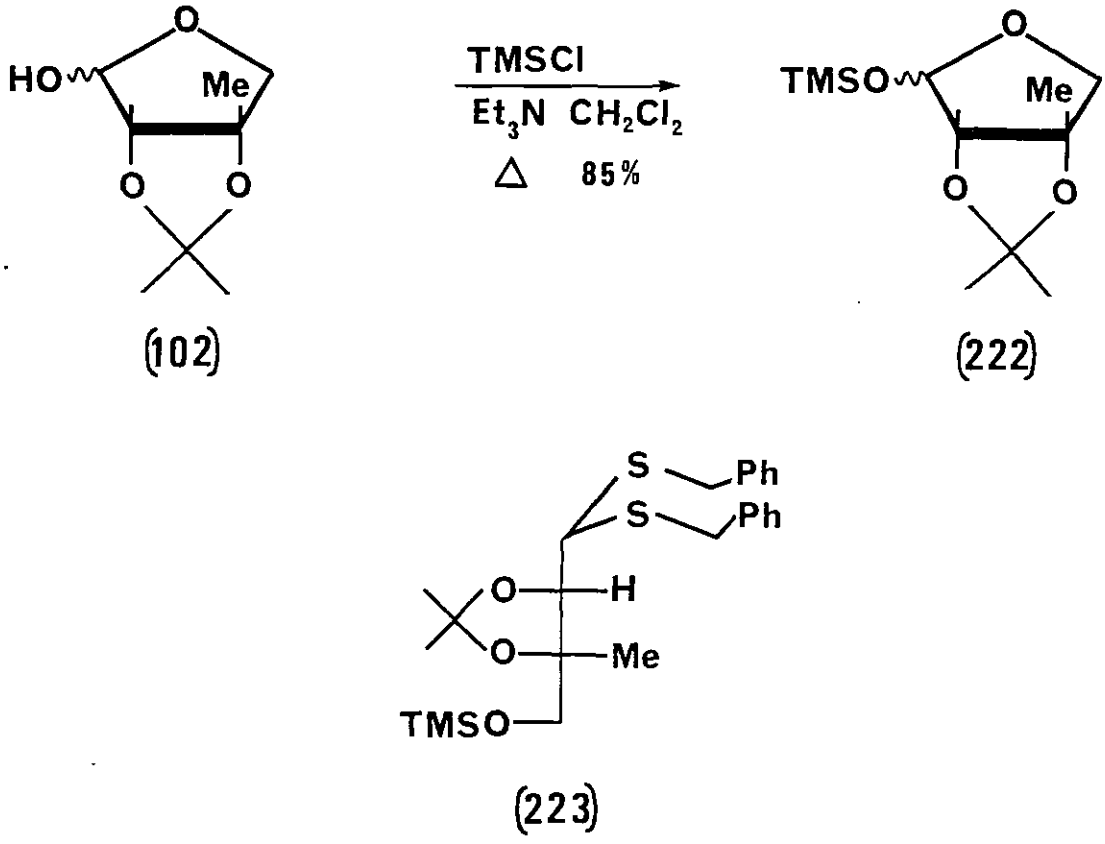
Suitable 1,3-dithianes were available from the previously described lactol (102). Initially lactol (102) was treated with 1,3-propanedithiol in dichloromethane with concentrated sulphuric acid as catalyst, but considerable decomposition resulted (t.l.c.). Use of boron trifluoride etherate as catalyst did yield the 1,3-dithiane (221) in low yield (40%)with concommitant loss of the isopropylidene moiety.



(221)

It has been reported that alkylthiosilanes react with aldehydes or ketones to give the corresponding thioketals in the presence of Lewis acids such as zinc iodide[136] and trimethylsilyl trifluoromethanesulphonate[137]. With this in mind, trimethylsilyl lactol (222) was prepared from lactol (102) in 85% yield (Scheme 67). Treatment of trimethylsilyl lactol (222) with benzylthiotrimethylsilane in the presence of trimethylsilyl trifluoromethanesulphonate yielded a compound believed to be (223)

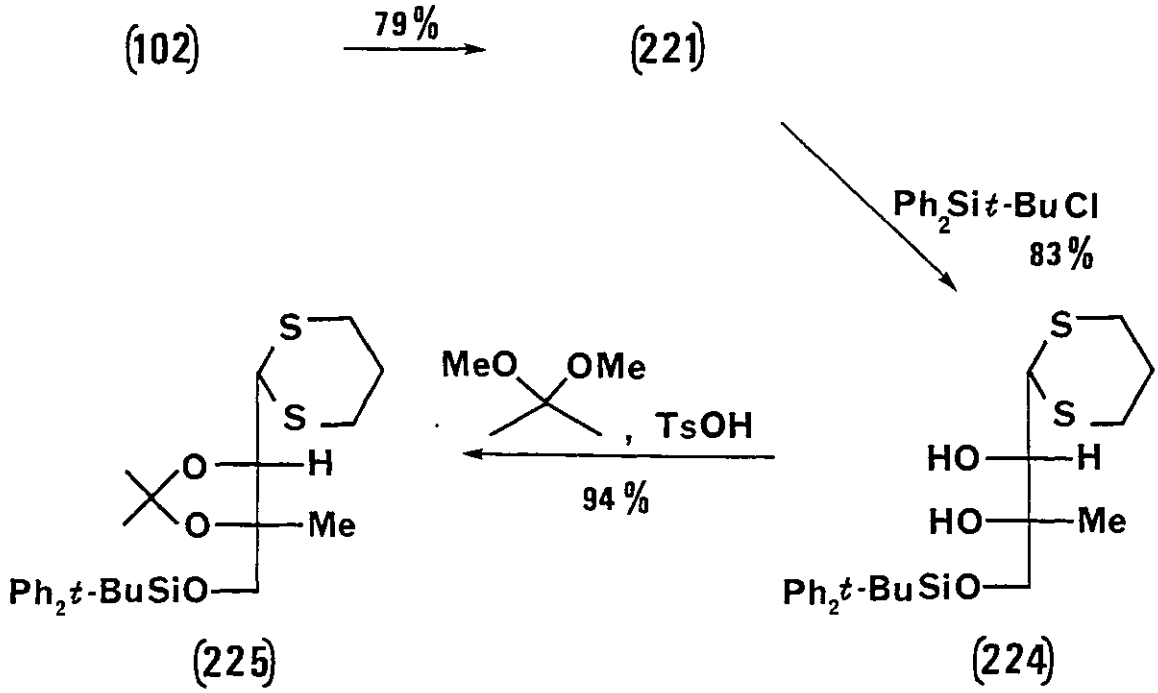
in 56% yield from a trial very small scale (0.14 mmol) reaction, but repetition of this reaction on preparatively useful scales was not possible. Use of zinc iodide as catalyst was also unsuccessful giving a complex mixture (t.l.c.).



(102) (222) (223)

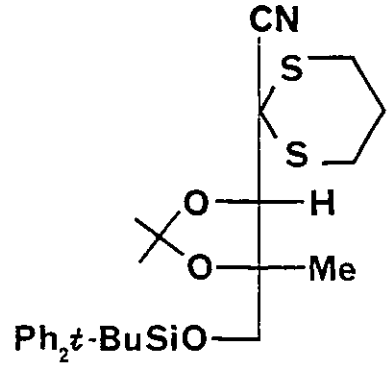
Scheme 67

It was finally found that treatment of lactol (102) with 1,3-propanedithiol in the presence of boron trifluoride etherate at a lower temperature (0°C), and using a methandic triethylamine solution during work-up yielded 1,3-dithiane (221) in good yield (79%). A similar reaction with an aqueous potassium hydroxide work-up gave no isolable products. Selective silylation of (221) proceeded smoothly to give 1,3-dithiane (224) in 83% yield which was further protected as the corresponding isopropylidene derivative (225) in 94% yield (Scheme 68).



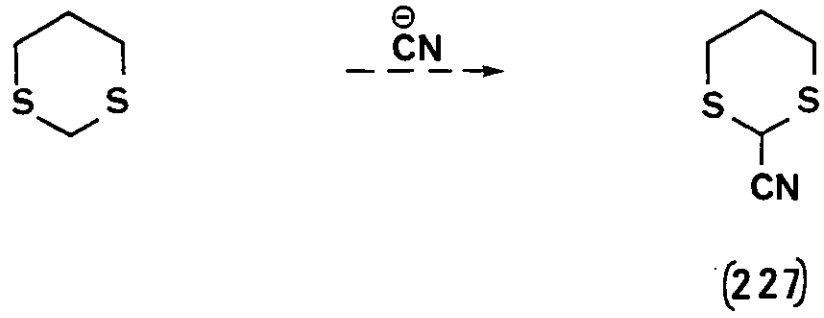
Scheme 68

Treatment of 1,3-dithiane itself with N-chlorosuccinimide is known to yield 2-chloro-1,3-dithiane in which the 2-position of the 1,3-dithiane ring is electrophilic and thus reactive towards sulphur -, oxygen -, nitrogen -, and carbon-nucleophiles[138]. On the basis of this precedent, the 1,3-dithiane (225) was treated with N-chlorosuccinimide and then sodium cyanide, but a complex mixture resulted (t.l.c.). Treatment of (225) with cyanogen bromide or mercury (II) cyanide-iodine[139] also failed to yield the target nitrile (226) and starting material (225) remained (t.l.c.).

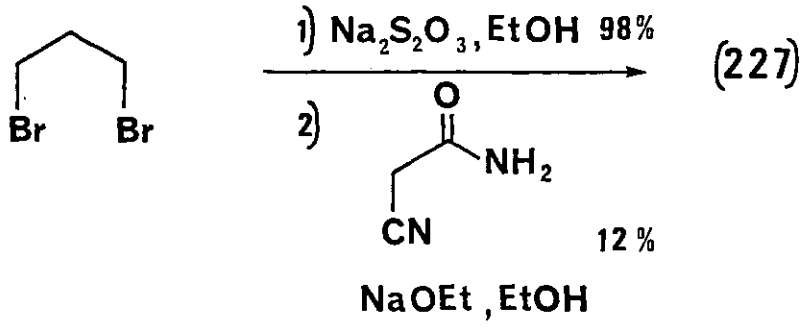


(226)

As a model study it was decided to investigate the transformation of 1,3-dithiane itself into the known[140,141] compound, 2-cyano-1,3-dithiane (227) by means of electrophilic 1,3-dithiane derivatives (Scheme 69). An authentic sample of 2-cyano-1,3-dithiane was prepared as described in the literature[141,142] from 1,3-dibromopropane (Scheme 69).



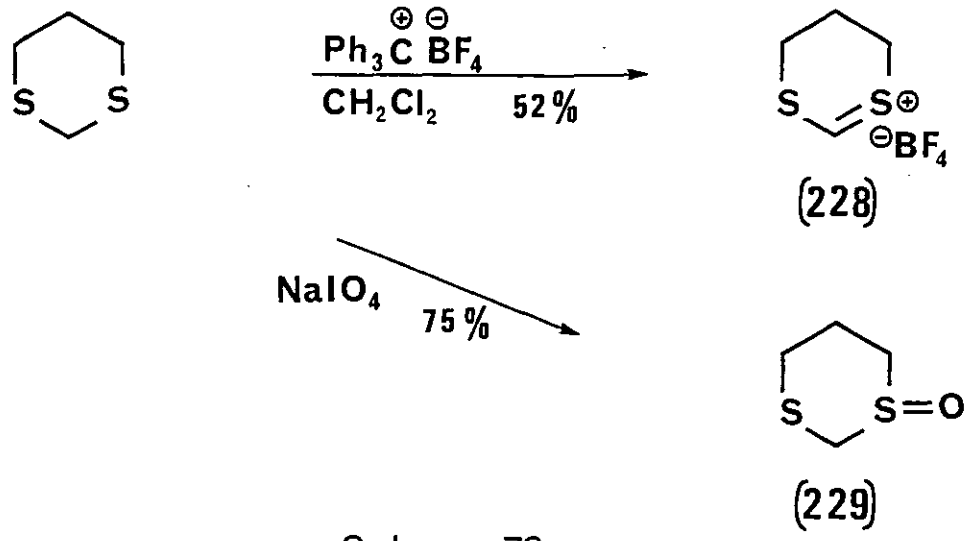
(227)



(227)

Scheme 69

The electrophilic 1,3-dithiane derivatives chosen for study were the known 1,3-dithienium tetrafluoroborate (228)[143,144] and 1,3-dithiane-1-oxide (229)[145] which were prepared by procedures similar to those described in the literature (Scheme 70).

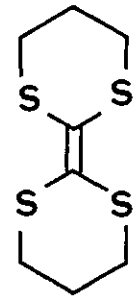


(228)

(229)

Scheme 70

Treatment of tetrafluoroborate (228) with various cyanide sources was investigated. Use of Amberlite IRA-400 (CN^-) resin[146] gave no 2-cyano-1,3-dithiane (227) (t.l.c.), and use of Amberlyst A-26 (CN^-) resin, potassium cyanide -18-crown-6[147], sodium cyanide-DMF[148], or tetrabutylammonium cyanide[149] gave only trace amounts or small amounts of (227) (t.l.c.). Work-up of the tetrabutylammonium cyanide reaction gave 2-cyano-1,3-dithiane (227) (9%) along with a compound believed to be dimer (230) (6%).

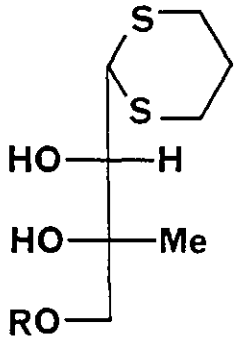


(230)

Attempted conversion of 1,3-dithiane-1-oxide (229) into 2-cyano-1,3-dithiane (227) also proved problematical. Attempted Pummerer rearrangement with trifluoroacetic anhydride in the presence of tetrabutylammonium cyanide gave a complex mixture not including any nitrile (227) (t.l.c.), and use of trimethylsilyl cyanide, Hünigs base, and imidazole or trimethylsilyl trifluoromethanesulphonate failed to consume starting material (t.l.c.). On the basis of

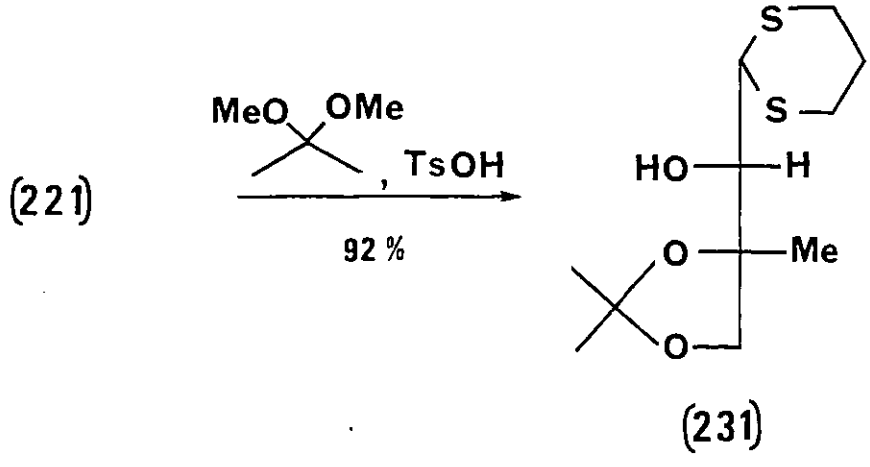
these results the approach to 1,3-dithianes of type (214) via the use of electrophilic 1,3-dithiane derivatives was discontinued.

The approach to compounds of type (214) via carbanions derived from suitable 1,3-dithianes was more successful. 1,3-Dithiane (224) was available as previously described from triol (221) (Scheme 71). Treatment of triol (221) with acetone and anhydrous copper (II) sulphate gave the isopropylidene derivative (231) in 57% yield, but use of 2,2-dimethoxypropane, acetone and p-toluenesulphonic acid gave (231) in an improved yield of 92% (Scheme 71).

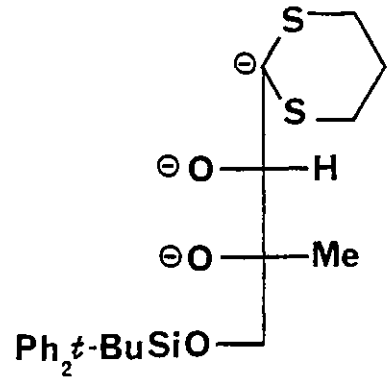


(221) R=H

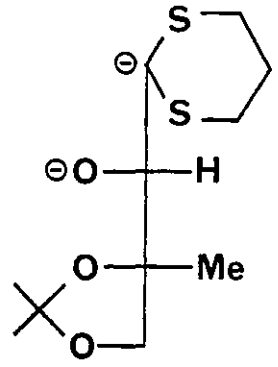
(224) R=Si*t*-BuPh$_2$



Scheme 71

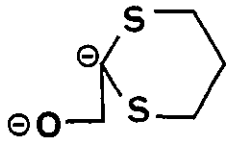


Trianion of (224)

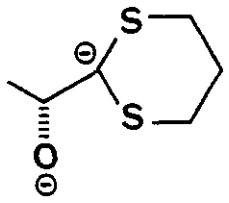


Dianion of (231)

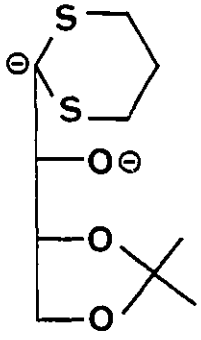
Formation of the trianion of (224) and the dianion of (231) was investigated. It has been reported that 1,3-dithiane anions of derivatives bearing an α-oxygen atom protected as an ether, ester or acetal eliminate to give ketene dithioacetals and decomposition products[150-153]. To prevent such eliminations α-oxygen atoms must be protected as their alkoxide anions, and so 1,3-dithiane polyanions are used. Several anions of this type are known such as (232)[152,154] and (233)[150,151] which have been used very successfully, and (234)[154], (235)[154], (236)[155] and (237)[156] which have met with limited or no success.



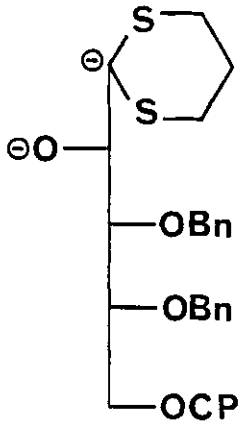
(232)



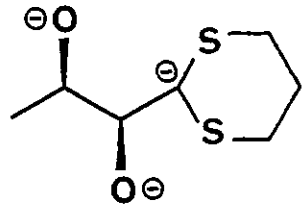
(233)



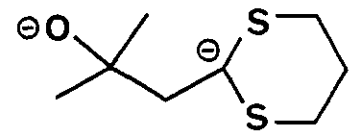
(234)



(235)



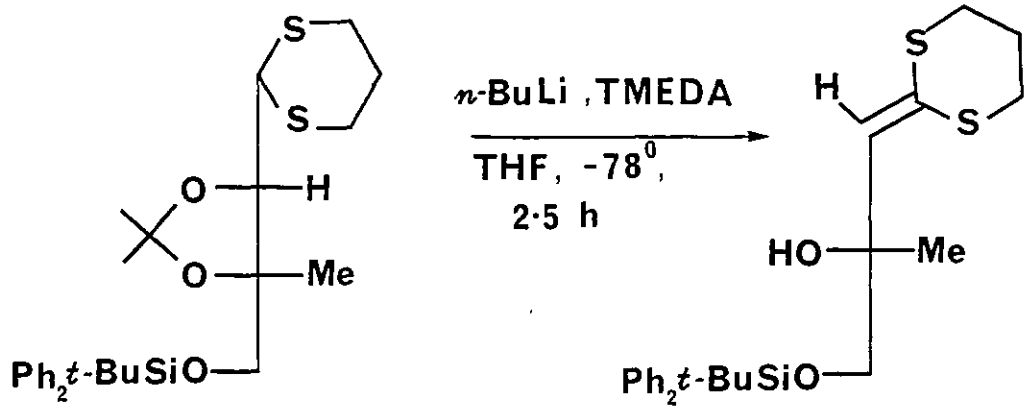
(236)



(237)

Attempts to form the trianion of our dithiane (224) with n-butyllithium or t-butyllithium under a wide variety of conditions (see Experimental Section for details) gave very poor results (16-50% deuterium incorporation). Warming to higher temperatures caused decomposition (t.l.c.). One possible explanation for these very poor results was thought to be the formation of sterically demanding highly chelated systems in solution. If this hypothesis was correct then using a base with a potassium cation should give improved results, but a reaction with potassium hexamethyldisilazide gave poor results (<10% deuterium incorporation).

It was thought that formation of the dianion from dithiane (231) should be more facile. However, considerable difficulty was again encountered and the best result (68% D incorporation) (see Experimental Section for details) required the drastic metalation conditions of n-butyllithium-TMEDA (4 equivalents) in THF at -20°C for 2.5 days. This sluggish deprotonation on carbon of dithiane (231) is in stark contrast to the deprotonation of fully protected dithiane (225) which decomposes quantitatively (t.l.c.) to a compound believed to be ketene thioacetal (238) under the same basic conditions but at low temperature (-78°C) and in only 2.5h (Scheme 72). A reaction at -20°C produced complete decomposition (t.l.c.). An attempt to control this decomposition by cooling to -100°C merely resulted in an approximately equimolar mixture of decomposition product (238) and non-deuterated starting material (t.l.c., n.m.r.).

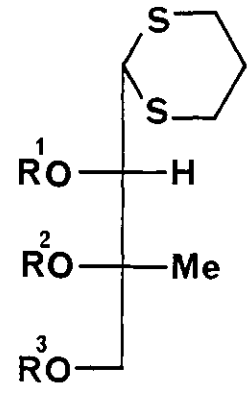


(225) (238)

Scheme 72

One experiment aimed at the preparation of the tetra-anion of triol (221) not surprisingly (on the basis of previous results) gave no deuterium incorporation on carbon.

The observed results with dithianes (221), (224), (231), and (225) clearly indicate that the more hydroxyl groups present on these molecules the less facile deprotonation on carbon becomes.



Apparent ease of deprotonation ↓

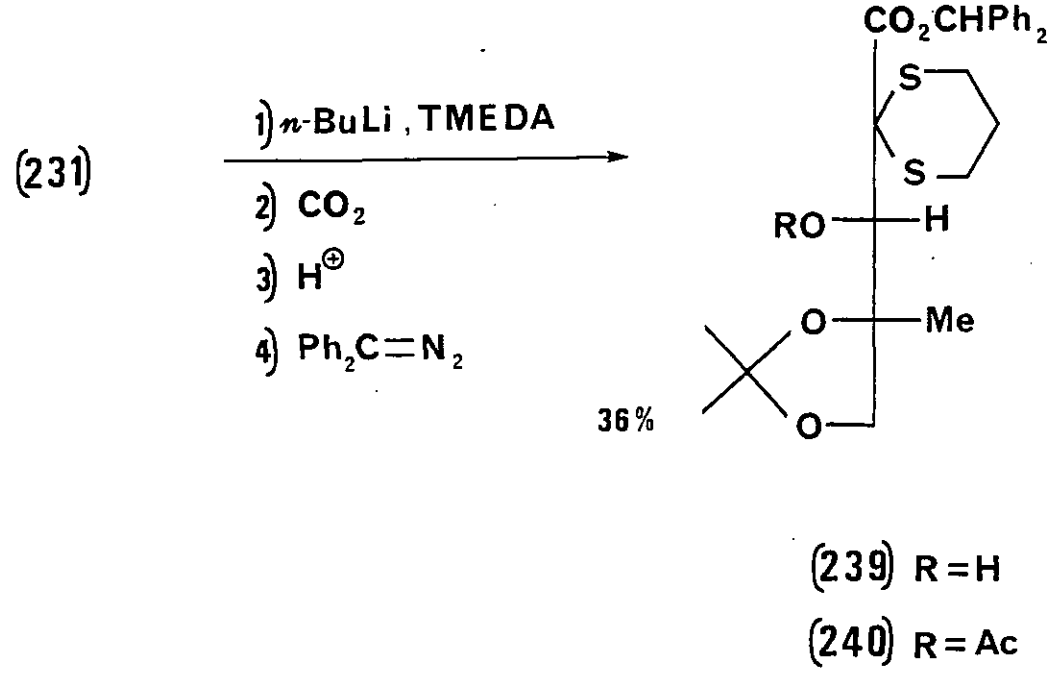
(221) $R^1 - R^3 = H$.

(224) $R^1 = R^2 = H$; $R^3 = Si\,t\text{-}BuPh_2$

(231) $R^1 = H$; $R^2, R^3 = C(CH_3)_2$

(225) $R^1, R^2 = C(CH_3)_2$; $R^3 = Si\,t\text{-}BuPh_2$

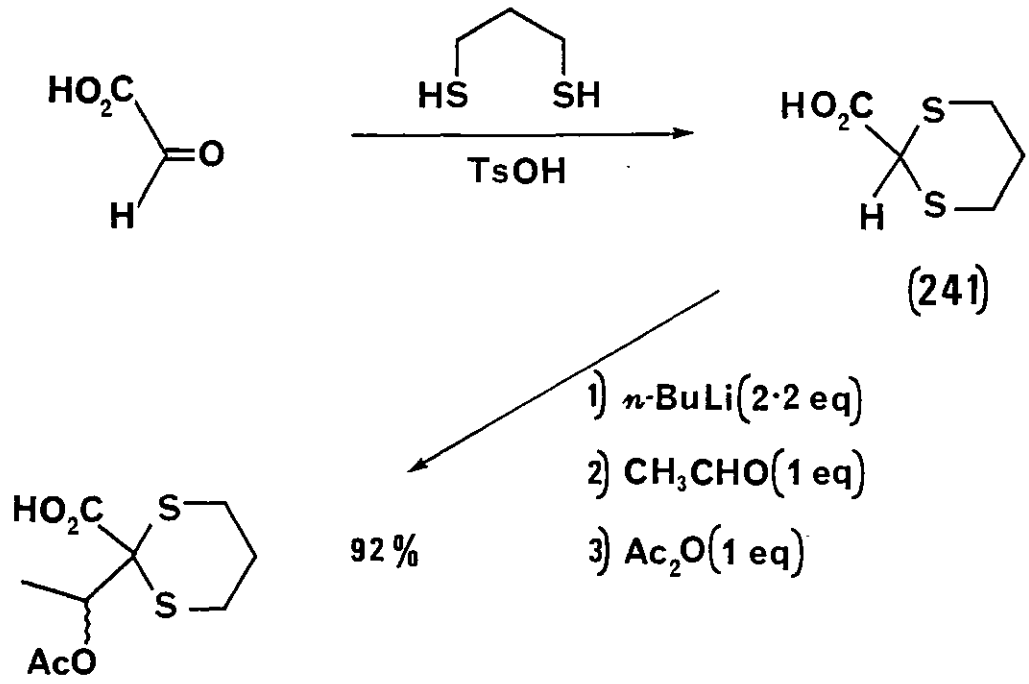
It was, therefore, decided to pursue the most promising carbanion, that is, the dianion of (231). Carboxylation of this dianion with gaseous carbon dioxide, followed by treatment with hydrochloric acid and diphenyldiazomethane gave the required dithiane (239) in 35-36% overall yield (Scheme 73). To complete the synthesis of an equivalent to target compound (214) it was necessary to protect the final hydroxyl group of (239). Attempted silylation with t-butyldiphenylsilyl chloride produced no reaction (t.l.c.), presumably due to steric hinderance, but acetylation with acetic anhydride, 4-dimethylaminopyridine and pyridine cleanly gave acetate (240) in 80% yield (Scheme 73).



Scheme 73

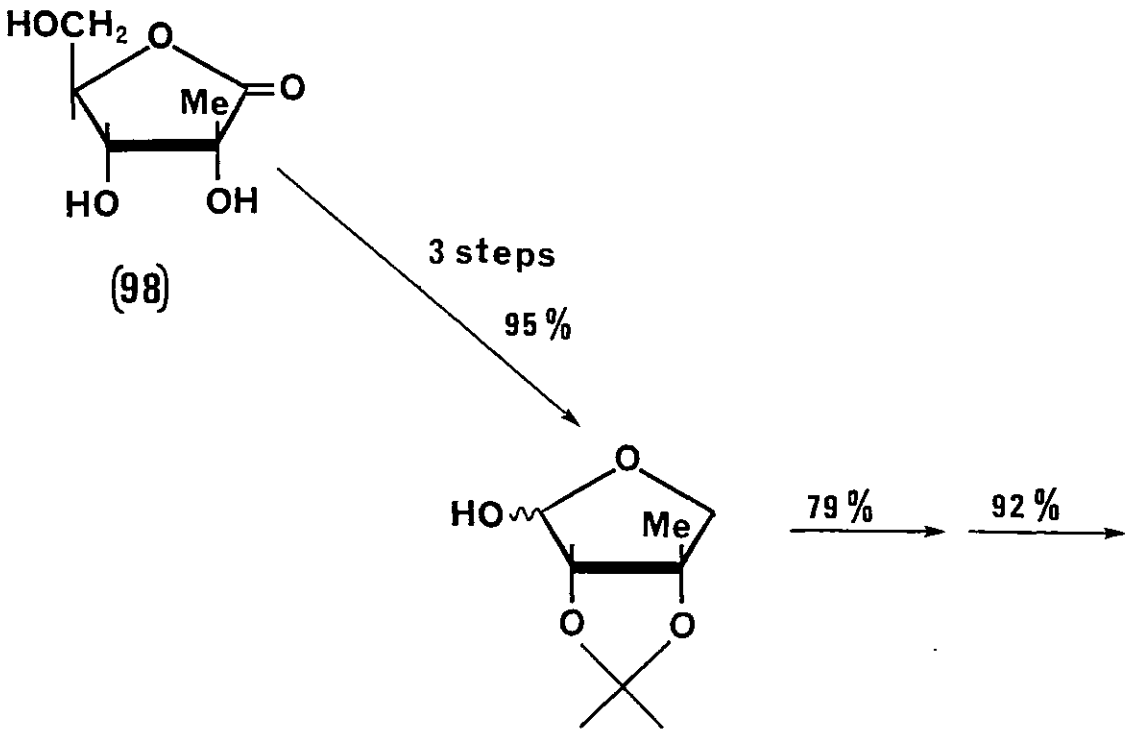
From the point of view of making potentially biologically active analogues of bicyclomycin a short versatile route to simpler analogues of dithiane (240) would be very useful. To this end, dithiane-acid (241) was prepared as described in the literature[113] from glyoxillic acid (Scheme 74). Treatment of (241) with 2 equivalents of n-butyllithium and quenching of the resulting dianion with

acetaldehyde and then acetic anhydride smoothly yielded dithiane-acid (242) in 92% yield (Scheme 74).

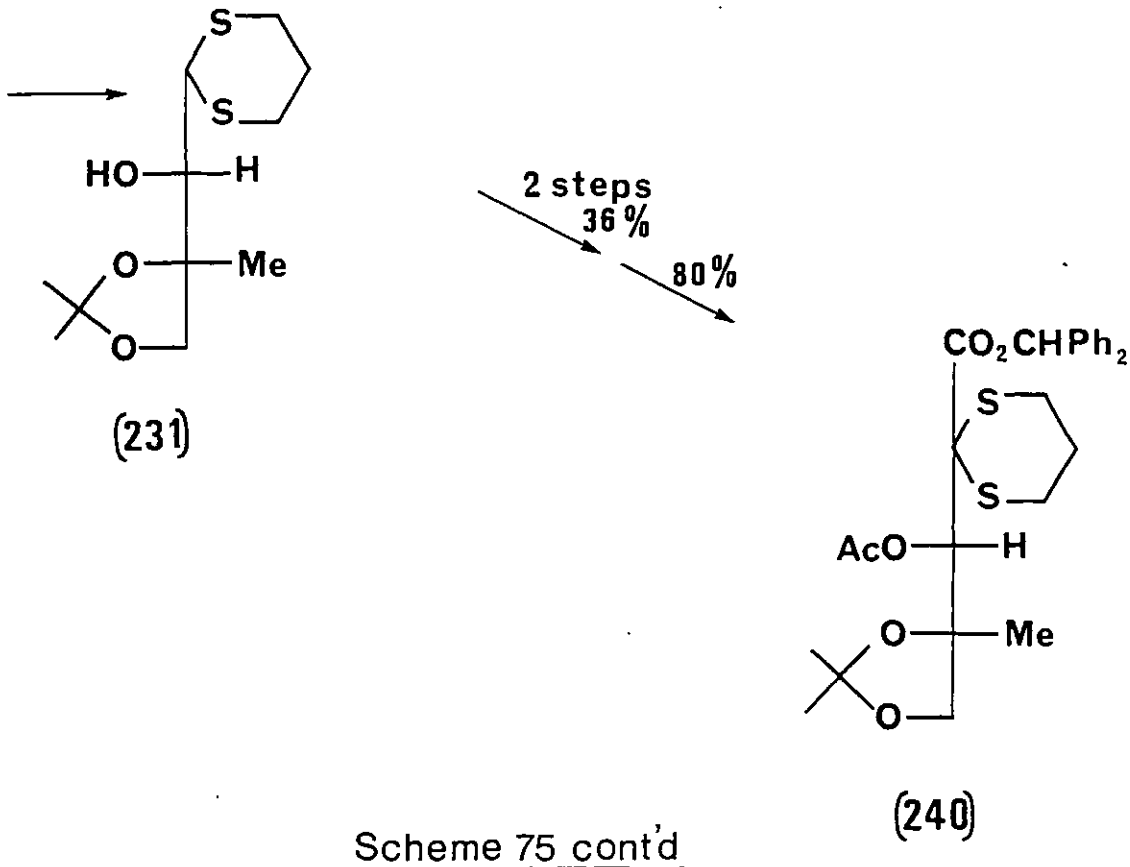


Scheme 74

In summary, we now had a synthetic route to the required 1,3-dithiane synthon (240) in chiral form from carbohydrate lactone (98) (Scheme 75).



Scheme 75 (102)

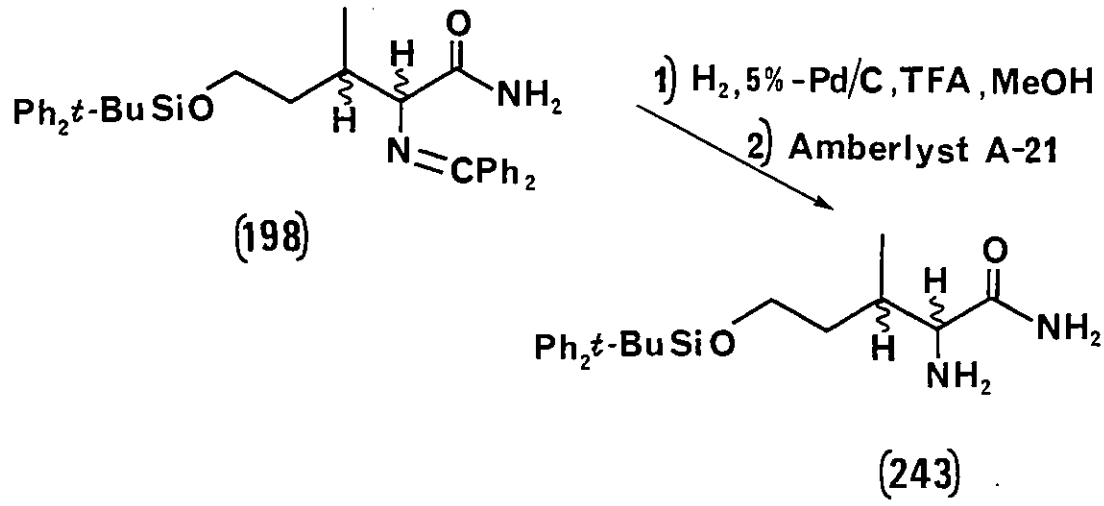


Scheme 75 cont'd

b) Preparation of model compounds for initial bicyclisation studies.

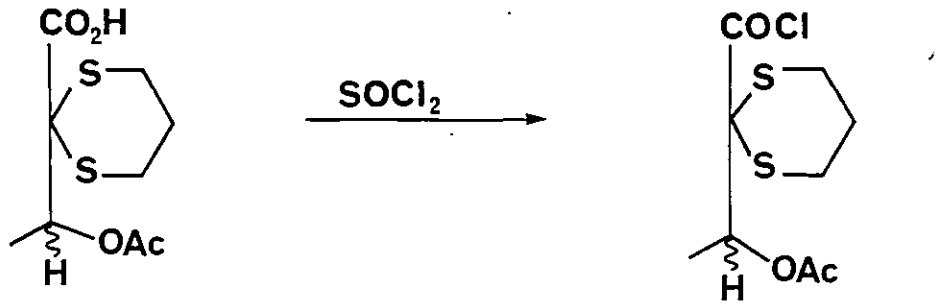
As a model study, it was decided to couple amide synthon (198) and model 1,3-dithiane-acid (242). Prior to coupling reactions it was necessary to remove the diphenylmethylene amino-protecting group in amide (198). Acid hydrolysis of (198) proved problematical. Use of 0·1N hydrochloric acid in diethyl ether[104] or 15% aqueous acetic acid in THF failed to consume starting material (t.l.c.). Reaction of amide (198) with 0·1N hydrochloric acid in methanol did result in hydrolysis but examination of the crude material indicated that the t-butyl-diphenylsilyl grouping had also been removed (n.m.r.). However, it was found that the imine group in amide (198) could be selectively removed by hydrogenation over 5% palladium on carbon in methanol containing one equivalent of trifluoroacetic acid to give amino-amide (243) after treatment with a basic resin (Amberlyst A-21) (Scheme 76). The presence of trifluoroacetic acid was found to be essential for hydrogenation to occur. The by-product, diphenylmethane, was readily removed.

Crude (243) was treated with crude acid chloride (244) (derived from acid (242) with thionyl chloride) in the presence of triethylamine to give the desired amide (245) in 44-61% yield (from amide (198)) (Scheme 76).



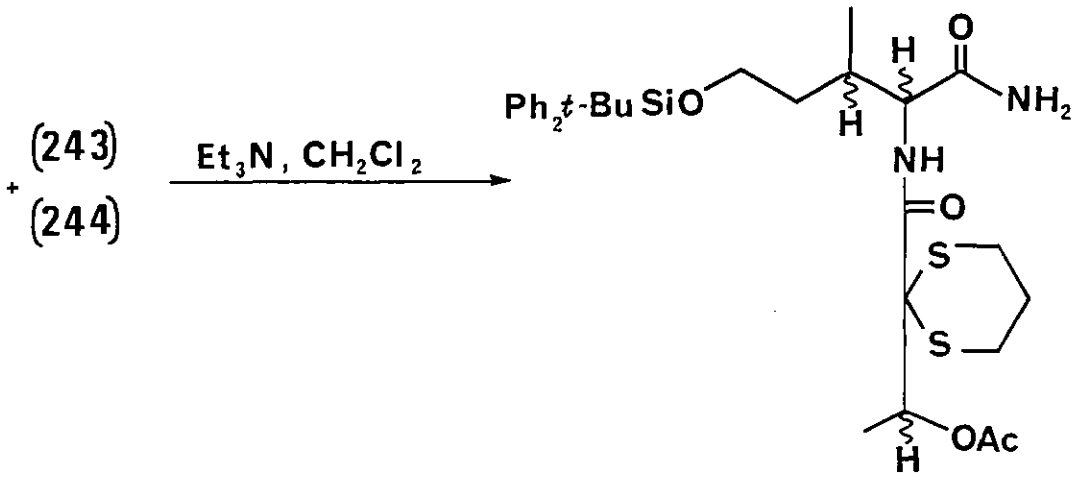
(198)

(243)



(242)

(244)

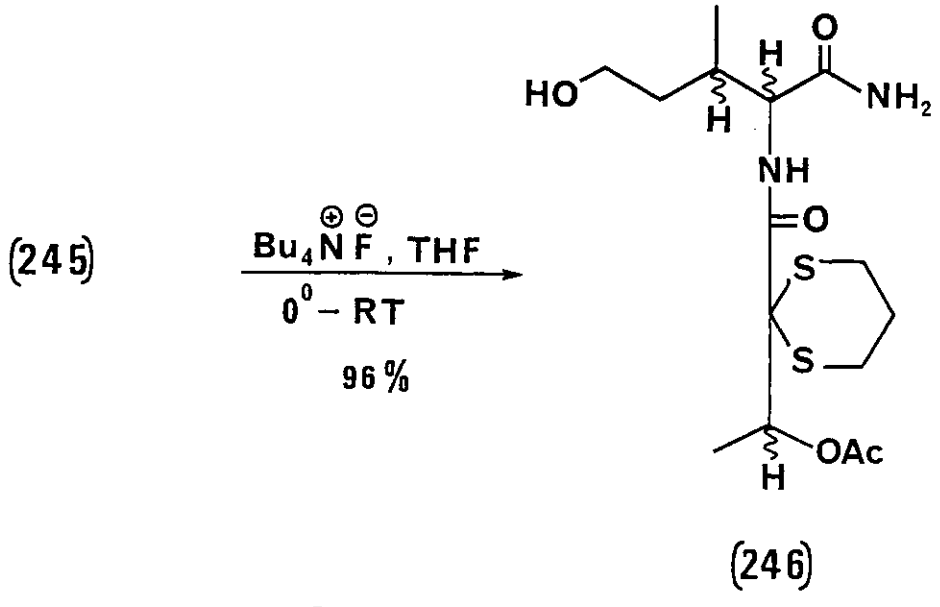


Scheme 76

(245)

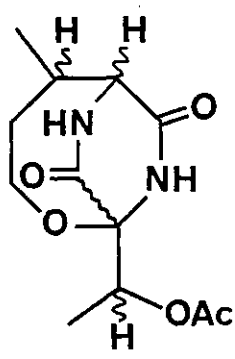
Attempted bicyclisation of amide (245) with phenyl mercury (II) perchlorate according to the method used by Williams[62] (Scheme 65) failed to give any reaction (t.l.c.). Presumably the perchlorate does not remove the t-butyldiphenylsilyl group in (245). The compounds that Williams[62] cyclised contained t-butyl-dimethylsilyl groups.

To overcome these difficulties it was decided to remove the silyl group in (245) prior to bicyclisation studies. This apparently trivial reaction proved to be very troublesome. Treatment of amide (245) with 2 equivalents[157] of tetrabutylammonium fluoride in THF at room temperature only gave a very low yield (40%) of the desired alcohol (246) and considerable amounts of another unidentified product. Reaction of (245) with tetrabutylammonium fluoride (2 equivalents) at -78°C, tetrabutylammonium fluoride (1 equivalent) at -28°C, or potassium fluoride (2 equivalents) in methanol at room temperature gave no reaction (t.l.c.). The product (246) was found to be unstable to excess tetrabutylammonium fluoride and to decompose to the unidentified by-product previously mentioned. ^{1}H n.m.r. analysis of this by-product indicated the loss of the CH_3COAc grouping found in the starting material (245). This problem was finally overcome by use of tetrabutylammonium fluoride (1 equivalent) initially at 0°C and then room temperature to give the required alcohol (246) in good yield (96%) (Scheme 77).



Scheme 77

Finally, a few very small scale model bicyclisation reactions on amide (246) were carried out with the aim of preparing the bicyclomycin anologue (247).



(247)

Use of the reagents and solvents used by Williams[62] (Scheme 65 and Review Section) was not successful. Thus, treatment of amide (246) with silver (I) trifluoromethanesulphonate or silver (I) perchlorate in dichloromethane produced no sign of reaction (t.l.c.). Use of silver (I) perchlorate in acetonitrile led to partial consumption of starting material (t.l.c.), and silver (I) trifluoromethanesulphonate in diethyl ether or mercury (II) trifluoromethanesulphonate in THF led to complete consumption of starting material (t.l.c.) but no products were isolable. It was noticed that both silver (I) perchlorate and trifluoromethanesulphonate were insoluble in dichloromethane which may account for the lack of reactivity observed.

A full investigation of the bicyclisation of alcohol-amide (246) was not possible and further work is necessary to draw any firm conclusions.

In conclusion, several synthetic approaches to bicyclomycin have been investigated. The most promising approach (Strategy D) resulted in the synthesis of the highly functionalised alcohol-amide (246), metal-mediated bicyclisation of which should yield a bicyclic analogue of bicyclomycin. Precursors, such as ester (240), for the synthesis of alcohol-amides bearing the chiral trihydroxy-

methylpropyl side chain found in bicyclomycin have been described. Also, a short versatile route to precursors of alcohol-amides bearing diverse side chains *via* the dianion of 2-carboxy-1,3-dithiane (241) has been illustrated. Application of this methodology will be further investigated in these laboratories with a view to the synthesis of bicyclomycin itself, and/or structural analogues.

EXPERIMENTAL

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 157 G, 257, or 298 grating infrared spectrometers. ^{1}H n.m.r. spectra were recorded with tetramethylsilane as internal standard on Varian T-60, Varian EM-360 A or Perkin-Elmer R12 spectrometers at 60 MHz, on a Perkin-Elmer R32 spectrometer at 90 MHz, and on a Bruker WM250 spectrometer at 250 MHz. ^{1}H n.m.r. spectra are recorded at 60 or 90 MHz unless stated otherwise. Mass spectra were recorded on AE1 MS12, V.G. Micromass 7070B and V.G. 7070F mass spectrometers. Optical rotations were determined using a Perkin-Elmer 141 polarimeter, where possible, on microanalytical samples. Microanalyses were determined by the appropriate laboratory at Imperial College.

Analytical thin layer chromatography (t.l.c.) was performed on Merck precoated GF_{254} silica plates or Merck precoated F_{254} (Type E or Type T) alumina plates. Column chromatography on silica gel refers to medium-pressure chromatography on Merck Kieselgel H (type 60) silica. Column chromatography on alumina refers to either medium-pressure chromatography on Merck F_{254} (Type T) alumina or chromatography by gravity on neutral alumina (Brockman Grade). Solvent gradients were generally used for elution during column chromatography in the following order, petroleum ether (or toluene), dichloromethane, diethyl ether, ethyl acetate, and methanol-chloroform mixtures. Preparative layer chromatography was performed on either freshly prepared or precoated Merck GF_{254} silica plates.

Solvents and reagents - petroleum ether refers to (40-60°C) petroleum ether. Ethanol and methanol were AnalaR grade. Petroleum ether and ethyl acetate were purified by distillation at all times. Diethyl ether was dried over sodium wire. Tetrahydrofuran (THF) was dried by distillation under nitrogen from potassium benzophenone ketyl. N,N-dimethylformamide(DMF), diisopropylamine and hexamethyldisilazane were distilled from calcium hydride or

4Å molecular sieves onto 4 Å molecular sieves. Pyridine was dried by storage over potassium hydroxide or 4 Å molecular sieves. Ethanol and methanol were dried, when required, by 4 Å molecular sieves, or by distillation from magnesium and iodine. Acetone was dried by storage over anhydrous potassium carbonate for at least 5 days, followed by distillation. Toluene was dried, when required, over sodium wire. Acetonitrile and dichloromethane were dried by distillation from phosphorus pentoxide. N,N,N′,N′-tetramethylethylenediamine (TMEDA) and triethylamine were dried over sodium wire. Trimethylsilyl chloride was dried by distillation from calcium hydride. Boron trifluoride etherate was redistilled prior to use. Ethyl and methyl acetoacetate, benzyl bromide, benzaldehyde and butane-1,3-diol were dried over 4 Å molecular sieves. Acid free acetyl chloride was obtained by distillation from phosphorus pentachloride and subsequent distillation from quinoline. Acetic anhydride was purified by distillation from quinoline. Carbon dioxide was dried by passage through calcium chloride. Other reagents were purified by standard techniques[162] if necessary.

During work-up solvents were generally evaporated using a rotary evaporator at, or below, 35°C. Reactions using water or oxygen sensitive compounds were conducted under an atmosphere of dry oxygen-free nitrogen or argon. Reaction temperatures generally refer to bath temperatures.

2-C-Methyl-D-ribono-1,4-lactone (98)

The title compound was prepared from β-D-fructose according to the method of Whistler[66]. If crystallisation failed, the product was purified by continuous extraction with diethyl ether and recrystallisation from acetone. Thus β-D-fructose (1000 g) yielded the title lactone (98) (50.3 g, 6%), m.p. 159-160°C (from acetone) (lit.[66], 160-161°C); $[\alpha]_D^{20}$ +92.9° (c 1.2 in H_2O) (lit.,[66] $[\alpha]_D^{20}$ + 93° (in H_2O)); R.f. 0.1 (silica gel, Et_2O).

2,3-O-Isopropylidene-2-C-methyl-D-ribono-1,4-lactone (100)

Lactone (100) was prepared from lactone (98) by essentially the method of Snowden[158], except that Amberlyst A-21 resin was used during work-up. Thus lactone (98) (4.86 g, 30 mmol) yielded lactone (100) (5.96 g, 98%), m.p. 60-61°C (from benzene-petroleum ether) (lit.,[158] 62-63°C); $[\alpha]_D^{20}$ -38.5° (c 0.73 in $CHCl_3$) (lit.,[158] $[\alpha]_D^{25}$ - 38.4° (c 3.4 in $CHCl_3$)); $\nu_{max.}$ (film) 1775 cm^{-1} (CO); δ_H ($CDCl_3$) 4.58 (2 H, br s, 2 xCH), 4.0 - 3.6 (3H, br d, CH_2 and OH), 1.65 (3 H, s, CH_3), and 1.42 (6 H, s, $(CH_3)_2$ C); R.f.0.9 (silica gel, Et_2O).

2,3 -O-Isopropylidene -2-C-methyl-D-ribitol (101)

a) To a stirred solution of lactone (100) (2.02 g, 10 mmol) in absolute ethanol (60 ml) was added sodium borohydride (1.16 g, 31 mmol) at room temperature. After 16h at room temperature the reaction was quenched with Amberlite IR-120 (H^+) resin to neutrality. Dilution with methanol, filtration and evaporation yielded a syrupy residue. Co-distillation (Büchi) with methanol (3x) yielded a syrup of constant weight which crystallised on seeding to give ribitol (101) as a white solid (2.04 g, 99%) which was further purified by column chromatography (silica gel, diethyl ether), m.p. 64-65°C (Found: C, 52.14; H, 8.65. $C_9H_{18}O_5$ requires C, 52.41; H, 8.80 %); $[\alpha]_D^{20}$ - 16.7° (c 0.32 in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 3380 cm^{-1} (OH); δ_H ($CDCl_3$) 4.0 - 3.3 (9 H, br m, 2 x CH, 2 x CH_2, and 3 x OH), 1.43 (3 H, s, CH_3), and 1.36 (6 H, s, $(CH_3)_2$ C); m/z 207 (M + 1), 191 (M-CH_3), 173, 149, 131, 117, and 113; R.f.0.7 (silica gel, Et_2O).

b) Reduction of lactone (100) with lithium aluminium hydride also yielded ribitol (101) in 50% overall yield from lactone (98).

2,3-O-Isopropylidene-3-C-methyl-L-erythrose (102)

a) From ribitol (101) with sodium periodate

A mixture of ribitol (101) (0.214 g, 1.04 mmol) and sodium periodate (0.242 g, 1.1 mmol) in aqueous THF (50%, 20 ml) was vigorously stirred with exclusion of light for 17h. Evaporation of the solvent, extraction with diethyl ether, filtration, and evaporation of the filtrate yielded erythrose (102) (0.170 g, 95%) vide infra.

b) From ribitol (101) with triphenylbismuth[67]

To a stirred solution of ribitol (101) (0.174 g, 0.84 mmol) in dry acetonitrile (10 ml) was added potassium carbonate (1.27 g, 8.4 mmol) and triphenylbismuth (7.4 mg, 0.017 mmol) at room temperature. To this suspension in the absence of light was added N-bromosuccinimide (0.17 g, 0.93 mmol) in dry acetonitrile (10 ml) over 1.5h. After 22h filtration and evaporation of the solvent gave a slightly yellow oil. A dichloromethane solution was filtered, evaporated, and purified by column chromatography (silica gel, dichloromethane to 20% diethyl ether - dichloromethane) to give erythrose (102) (0.098 g, 67%) vide infra.

c) From lactone (98)

Erythrose (102) was prepared from lactone (98) without isolation of any intermediates by the following modified method.

A stirred suspension of lactone (98) (4.86 g, 0.03 mol) in dry acetone (200 ml) was cooled to 0°C and concentrated sulphuric acid (1 ml) added dropwise. After 26h at room temperature, passage through Amberlyst A-21 resin (30 ml) with acetone as eluant, and evaporation of the solvent gave crude lactone (100) (6.91 g) which was dissolved in ethanol (150 ml). Sodium borohydride (1.67 g, 45 mmol) was added in portions at 0°C and the reaction stirred for 18h at room temperature. Neutralisation with Amberlite IR-120 (H^+) resin, dilution with methanol, filtration, evaporation of the solvent, and co-distillation (Büchi) with

methanol (3 x 200 ml) gave crude ribitol (101) (7.22 g). To a stirred solution of crude ribitol (101) in aqueous THF (50%, 150 ml) was added sodium periodate (7.06 g, 33 mmol) in small portions at room temperature. After 18h the THF was evaporated and the aqueous residue extracted with dichloromethane (3 x 100 ml). The dried (Na_2SO_4) extracts were evaporated and column chromatography (silica gel, 30% diethyl ether-dichloromethane as eluant) yielded pure erythrose (102) (4.97 g, 95%), b.p. 80°C (0.03 mmHg) (Found: C, 55.03; H, 8.23. $C_8H_{14}O_4$ requires C, 55.16; H, 8.10%); $[\alpha]_D^{20}$ + 72.0° (c 0.21 in $CHCl_3$); $\nu_{max.}$ (film) 3420 cm^{-1} (OH); δ_H (90 MHz; $CDCl_3$) 5.39 (1H, s, 1-H), 4.29 (1H, br s, OH), 4.20 (1H, s, 2-H), 3.93 and 3.87 (2H, q, $\underline{J}_{AB}$ 11 Hz, CH_2), 1.52 (3H, s, 3-Me), 1.43 (3H, s, $C\underline{H}_3C\ CH_3$), and 1.38 (3H, s, $C\underline{H}_3\ C\ CH_3$); m/z 173 (M + 1), 159 (M - CH_3), 116, 115, 99, 85, 70, and 59; R.f.0.5 (silica gel, 30% Et_2O - CH_2Cl_2).

<u>1-O-(tert-Butyldimethylsilyl)-2,3-O-isopropylidene-3-C-methyl-L-erythrose (105)</u>

a) To a stirred solution of erythrose (102)(0.35 g, 2 mmol) and imidazole (0.34 g, 5 mmol) in dry DMF (10 ml) under nitrogen was added a solution of <u>tert</u>-butyldimethylsilyl chloride (0.33 g, 2.2 mmol) in dry DMF (10 ml) over 350 min. at room temperature. After 20h diethyl ether (200 ml) and water (50 ml) were added. The organic phase was washed with water (2 x 20 ml), dried ($Mg\ SO_4$) and evaporated to give a colourless oil (0.79 g). Column chromatography on silica gel (13 g, petroleum ether to dichloromethane as eluant) yielded <u>silyl - erythrose (105)</u> (0.47 g, 82%) which could be further purified by distillation, b.p. 90°C (0.5 mmHg) (Found: C, 58.43; H, 10.02. $C_{14}\ H_{28}\ Si\ O_4$ requires C, 58.29; H, 9.78%); $[\alpha]_D^{20}$ + 76.7° (c 0.48 in $CHCl_3$); $\nu_{max.}$ (film) 1380, 1260, 1255, 1140, 1085, and 845 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 5.35 and 5.31 (1H, 2 x s, ratio 3:1, 1-H), 4.13 (1H, s, 2-H), 3.92 and 3.78 (2H, q, $\underline{J}_{AB}$ 10Hz, CH_2), 1.53,

1.45, and 1.38 (9H, 3 x s, 3 x CH_3 C), 0.88 (9H, s, $(CH_3)_3$ C), 0.11 and 0.10 (6H, 2 x s, $(CH_3)_2Si$); R.f. 0.6 (silica gel, CH_2Cl_2).

b) A reaction as in a) but at 0^oC with an addition time of 15 minutes and a reaction time at room temperature of 6h yielded silyl-erythrose (105) in 79% yield.

Attempted preparation of 2,3-O-Isopropylidene-3-C-methyl-L-erythrono-1,4-lactone (106)

a) With ruthenium tetroxide

Treatment of erythrose (102) with ruthenium tetroxide under the conditions of Hall[69] gave no reaction (t.l.c.).

b) With dimethyl sulphoxide - acetic anhydride

Reaction of erythrose (102) with dimethyl sulphoxide and acetic anhydride[70] yielded no isolable products.

2,3-O-Isopropylidene-3-C-methyl-L-erythrono-1,4-lactone (106)

a) With pyridinium dichromate[71]

To a stirred solution of erythrose (102) (0.237 g, 1.4 mmol) in dry dichloromethane (15 ml) was added pyridinium dichromate (0.563 g, 1.5 mmol) at room temperature. After 8 days a further portion of pyridinium dichromate (0.563 g, 1.5 mmol) was added. After 3 days the reaction was diluted with diethyl ether, filtered through a silica gel pad and the solvent evaporated to give a

colourless oil which crystallised on standing. Column chromatography on silica gel (10 g, dichloromethane as eluant) yielded lactone (106) as a crystalline solid (0.142 g, 60%) which could be further purified by sublimation (80°C at 0.03 mmHg), m.p. 82.0 - 82.5 °C (Found: C, 55.57; H, 6.97. $C_8H_{12}O_4$ requires C, 55.81; H, 7.03%); $[\alpha]_D^{20}$ + 112.1° (c 0.07 in $CHCl_3$); $\nu_{max.}$ (nujol) 1770 cm^{-1} (CO); δ_H ($CDCl_3$) 4.42 (1H, s, CH), 4.42 and 4.22 (2H, q, J_{AB} 10 Hz, CH_2), 1.52, 1.50, and 1.41 (9H, 3 x s, 3 x CH_3); m/z 173 (M + 1), 157 (M - CH_3), 129, 115, 99, and 97; R.f.0.8 (silica gel, 10% Et_2O - CH_2Cl_2).

b) With iodine-potassium iodide-sodium hydroxide[72]

To a stirred solution of erythrose (102) (0.170 g, 0.98 mmol) in water (10 ml) was added alternately aqueous iodine/potassium iodide (0.1N iodine and 0.25N potassium iodide, 22 ml in 2 ml portions) and aqueous sodium hydroxide (0.1N, 33 ml in 3 ml portions) at room temperature. After 1h and cooling to 0°C, Amberlite IR-120(H^+) resin (12 ml) was added and the mixture stirred at 0°C for 2h. Repetitive extraction with dichloromethane, washing of the extracts with sodium thiosulphate solution and evaporation of the dried (Na_2SO_4) extracts yielded lactone (106) (0.119 g, 71%).

c) With N-iodosuccinimide-tetrabutylammonium iodide[73]

To a stirred solution of erythrose (102) (0.174 g, 1 mmol) in dry dichloromethane (3 ml) was added N-iodosuccinimide (1.13 g, 5 mmol) and tetrabutylammonium iodide (0.37 g, 1 mmol) in dry dichloromethane (10 ml) at room temperature. The dark brown solution was stirred for 6h. After washing with saturated aqueous sodium thiosulphate and water, the dried (Na_2SO_4) organic phase was evaporated. An ethereal solution of the residue was filtered through silica gel and concentrated to give lactone (106) (0.149 g, 87%).

Ethyl formylaminoacetate

The title compound was prepared in 82% yield from glycine ethyl ester hydrochloride according to the procedure of Hartman[76]; b.p. 110-114°C (0.19 mmHg) (lit.,[76] 94-97°C (0.05 mmHg)).

Ethyl isocyanoacetate (114)

The title compound was prepared in 61% yield from ethyl formylaminoacetate according to the procedure of Hartman[76]; b.p. 79-80°C (10 mmHg) (lit.,[76] 89-91°C (11 mmHg)).

4-Hydroxybutan-2-one(113)

a) The title compound was prepared by a method based on that of Hager[75]:-

To a strongly refluxing solution of acetone (34.8 g, 0.6 mol) and aqueous citric acid solution (10%, 1 ml) heated to 130°C was added aqueous formaldehyde solution (37-41%, 15.8 ml, adjusted to pH 10.1 with 10% sodium hydroxide solution). The formaldehyde solution was added over 45 min. down a 12" spiral water condenser and a 3' x ¾" column packed with glass beads (5.5 to 6.5 mm) heated to 65-70°C. After addition was complete, reflux was maintained for 10 min. Evaporation of the solvent and distillation of the residue yielded impure (^{1}H n.m.r.) 4-hydroxybutan-2-one (113) (1.87 g, 11% based on formaldehyde), b.p. 70-73°C (9.5 mmHg) (lit.,[75] 73-76°C (12 mmHg)). Extensive polymerisation occurred on distillation, no totally pure sample could be obtained (n.m.r.).

b) Distillation of crude 4-hydroxybutan-2-one(113) in the presence of di-n-butyl phthalate failed to prevent polymerisation.

c) Use of Amberlite CG-50 (H^+) resin in place of citric acid failed to improve the yield of 4-hydroxybutan-2-one (113).

Ethyl 2-(formylamino)-3-methyl-2-butenoate (115)[81]

To a stirred solution of potassium t-butoxide (3.334 g, 30 mmol) in dry THF (45 ml) at 0°C under nitrogen was added ethyl isocyanoacetate (3.364 g, 30 mmol) in dry THF (15 ml) over 10 min. The solution became cloudy and yellow during the addition. Acetone (1.727 g, 30 mmol) in dry THF (10 ml) was added over 15 min. Warming to room temperature and evaporation of the solvent gave an orange oil which was treated with water (15 ml) and acetic acid (1.7 ml). Extraction with dichloromethane and evaporation of the dried (Na_2SO_4) extracts gave formamide (115) (4.108 g, 81%) as a white solid, m.p. 69.5-70.5°C (from benzene-petroleum ether) (lit.,[81] 77-78°C); $\nu_{max.}$ (nujol) 3240 (NH), 1710 (CO ester), 1662 (CO formamide), and 1630 cm^{-1} (C=C); δ_H ($CDCl_3$) 8.18 (1H, s, CHO), 6.92 (1H, br s, D_2O exch., NH), 4.26 (2H, q, J 7 Hz, OCH_2), 2.24, 2.22 1.98, 1.87 (6H, 4 x s, $(CH_3)_2$ C = C), and 1.29 (3H, t, J 7 Hz, CH_3 CH_2O).

Attempted preparation of Ethyl 2-(formylamino)-5-hydroxy-3-methyl-2-pentenoate (110, $R^1 = CH_3$, $R^2 = CH_2CH_2OH$, R=Et)

Reaction of ethyl isocyanoacetate with two equivalents of potassium t-butoxide and quenching with 4-hydroxybutan-2-one using the conditions described above for the preparation of (115) yielded many components (t.l.c.), including ethyl 2-(formylamino)-3-methyl-2-butenoate (115) (t.l.c., n.m.r.).

4-Acetoxybutan-2-one (117)[77]

Methyl vinyl ketone (6.53 g, 93 mmol), acetic acid (28 ml) and water (1 drop) were refluxed under nitrogen with stirring for 18h. Evaporation of excess acetic acid, and distillation (twice) yielded 4-acetoxybutan-2-one (117) (3.76 g, 31%), b.p. 52-54°C (2 mmHg)(lit.,[77] b.p. 78-84°C (15 mmHg)); $\nu_{max.}$(film) 1735 (CO ester) and 1720 cm^{-1} (CO ketone); δ_H ($CDCl_3$) 4.33 (2H, t, J 6Hz, CH_2OAc), 2.77 (2H, t, J 6Hz, CH_2CO), 2.19 (3H, s, CH_3CO), and 2.03 (3H, s, CH_3CO_2C).

Attempted preparation of 4-pivaloxybutan-2-one (118)

Use of pivalic acid instead of acetic acid in a method identical with the preparation of 4-acetoxybutan-2-one (see procedure above) failed to yield 4-pivaloxybutan-2-one (118) due to polymerisation on work-up.

Attempted preparation of 4-tetrahydropyranyloxybutan-2-one (116)

No pure sample of (116) could be prepared from 4-hydroxybutan-2-one and dihydropyran under standard conditions.

Attempted preparation of Ethyl 5-acetoxy-2-(formylamino)-3-methyl-2-pentenoate (110, $R^1 = CH_3$, $R^2 = CH_2CH_2OAc$, R=Et)

Ethyl isocyanoacetate was reacted with 4-acetoxybutan-2-one and various bases under standard conditions.

a) With potassium t-butoxide (1 eq.) - THF

Use of potassium t-butoxide (1 eq.) in THF at 0°C, and then reflux, gave a slow consumption of starting isonitrile (t.l.c.), resulting in an intractable mixture (t.l.c.).

b) With potassium t-butoxide (2 eq.) - THF

Use of potassium t-butoxide (2 eq.) in THF initially at -78°C and then room temperature resulted in consumption of starting isonitrile (i.r.) and production of a complex mixture (t.l.c.).

c) With potassium t-butoxide (1 eq.) - DME.

Use of potassium t-butoxide (1 eq.) in DME initially at 0°C and then room temperature failed to consume starting isonitrile (i.r.).

d) With sodium hydride (1 eq.) - THF.

Use of sodium hydride (1 eq.) in THF at room temperature failed to consume starting isonitrile (i.r.).

e) With lithium hexamethyldisilazide (1·1 eq.) - THF.

Use of lithium hexamethyldisilazide (1·1 eq.) in THF initially at -78°C and then room temperature resulted in loss of starting isonitrile (i.r.) but failed to yield any of the desired adduct (110, $R^1 = CH_3$, $R^2 = CH_2CH_2OAc$) (mass spectrometry).

Attempted preparation of Ethyl 5-acetoxy-3-hydroxy-2-isocyanopentanoate (120)

a) To a stirred solution of n-butyllithium (3.16 ml, 4.4 mmol) in dry THF (15 ml) at -72°C was added ethyl isocyanoacetate (0.452 g, 4 mmol) in dry THF (4 ml). After 10 min. a solution of 4-acetoxybutan-2-one (0.52 g, 4 mmol) in dry THF (4 ml) was added. After 1h at -72°C, acetic acid (0.28 ml) in dry THF (2 ml) was added. On warming to room temperature water was added and the aqueous phase extracted with dichloromethane. The dried extracts (Na_2SO_4) were evaporated and the residue purified by column chromatography on silica gel (dichloromethane as eluant) to give recovered ethyl isocyanoacetate (0.047 g, 10%) and an oil tentatively assigned as alcohol (120) (0.300 g, 31%) (Found: M^++1, 244.1179. $C_{11}H_{17}NO_5$ requires M+1, 244.1185); $\nu_{max.}$ (film) 3460 (OH), 2160 (NC), and 1740 cm^{-1} (CO); δ_H ($CDCl_3$) 4.5-4.2 (5H, m, CH_2O, CHNC, $OC\underline{H}_2CH_3$), 3.3 (1H, br s, OH), 2.3-1.8 (5H, m, CH_3CO, CH_2C), and 1.5-1.2 (6H, m, $C\underline{H}_3CH_2O$, CH_3C); m/z 244 (M + 1), 184, 156, 131, 128, and 114. A satisfactory elemental analysis could not be obtained.

b) A 5 mmol scale reaction as in a) above only yielded alcohol (120) in 15%.

c) Attempts to trap alcohol (120) by work-up with p-toluene sulphonyl chloride instead of the acetic acid used in method a) failed.

d) Use of DME instead of THF as in method a) failed to improve the amount of alcohol (120) produced (t.l.c.).

e) Addition of anhydrous zinc chloride after the addition of ethyl isocyanoacetate as in method a) gave a complex mixture of products (t.l.c.).

Ethyl 2-isocyano-3-methyl-2-butenoate (123)

Isonitrile (123) was prepared by the method of Schöllkopf[81] as outlined below in modified form.

Ethyl 2-(formylamino)-3-methyl-2-butenoate (115) (4.00 g, 23 mmol), triphenylphosphine (7.35 g, 28 mmol), carbon tetrachloride (2.3 ml , 23 mmol) were refluxed under nitrogen in chloroform (23 ml) with stirring for 3h. Further triphenylphosphine (3.67 g, 14 mmol) and carbon tetrachloride (1·1 ml, 11.5 mmol) was added and,after 14h at room temperature, evaporation of the solvent gave a red oil which was stirred with petroleum ether. Filtration, washing of the solid with petroleum ether, and evaporation of the combined filtrate and washings gave a brown oil. Column chromatography on alumina (petroleum ether as eluant) gave the title isonitrile (123) as a pale yellow oil (2.53 g, 71%); $\nu_{max.}$ (film) 2110 (NC), 1720 (CO), and 1620 cm^{-1} (C = C); δ_H ($CDCl_3$) 4.28 (2H, q, J 7Hz, CH_2O), 2.28 and 2.14 (6H, 2 x s, $(CH_3)_2C$ = C), and 1.33 (3H, t, J 7Hz, CH_3CH_2); m/z 153 (M^+), 125, 108 (M - OEt), and 97.

Metalation of Ethyl 2-isocyano-3-methyl-2-butenoate (123) and reaction with various electrophiles

a) With deuterium oxide

To a stirred solution of hexamethyldisilazane (0.23 ml, 1.1 mmol) in dry THF (10 ml) at 0°C under nitrogen was added n-butyllithium (0.72 ml, 1 mmol, total base 1.14 mmol). After 15 min., and cooling to -78°C, ethyl 2-isocyano-3-methyl-2-butenoate (123) (0.153 g, 1 mmol) in dry THF (5 ml) was added. After 1h at -78°C, the solution was warmed to 0°C and deuterium oxide (0.018 ml, 1 mmol) added followed by acetic acid (0.122 ml, 2.14 mmol) 1 minute later. Evaporation of the solvent gave a brown oil consisting of one major component

(t.l.c.). Column chromatography on alumina (petroleum ether as eluant) gave a compound believed to be ethyl [4-^{2}H]-2-isocyano-3-methyl-2-butenoate (124) (50 mg, 32%); δ_H ($CDCl_3$) 4.30 (2H, q, J 7Hz, CH_2O), 2.30 and 2.15 (5H, m, CH_2D, CH_3), and 1.35 (3H, t, J 7Hz, CH_3CH_2); m/z 154 (M^+), 126, 109, and 98.

b) With ethyl formate

A reaction as described in procedure a) but with ethyl formate as the electrophile yielded mainly starting material (123).

c) With propanal

A reaction as described in procedure a) but with propanal as the electrophile gave a complex mixture with appeared to be polymeric (n.m.r.).

d) With formaldehyde

A reaction as described in procedure a) but with paraformaldehyde as the electrophile yielded a complex mixture containing no isonitrile products (i.r.).

e) With benzaldehyde

A reaction as described in procedure a) but with benzaldehyde as the electrophile yielded a crude product containing many products (t.l.c.) from which small amounts of an adduct tentatively assigned as 2-isocyano-3-methyl-5-phenyl-2-penten-5-olide (125) (16 mg, 8%) (Found: M^+, 213.0790. $C_{13}H_{11}NO_2$ requires M, 213.0790); $\nu_{max.}$ 2110 (NC), 1730 (CO), and 1610 cm^{-1} (C = C); δ_H ($CDCl_3$) too dilute for full analysis - no CO_2Et present; m/z 301 (v. weak), 213, 187, 167, and 107.

4-Ethoxycarbonyl-5-methyloxazole (136)

The title compound was prepared in 54% yield by the method of Schöllkopf[82] from ethyl isocyanoacetate and acetyl chloride.

Attempted preparation of Ethyl 3-(t-butyldimethylsilyloxy)-2-isocyano-3-methyl-2-butenoate (138, R =Si ^{t}BuMe$_2$)

a) Reaction of oxazole (136) with n-butyllithium in THF at 0°C and treatment with t-butyldimethylsilyl chloride yielded no isonitrile containing products (i.r.), and resulted in destruction of the ester moiety (n.m.r.).

b) A reaction following method a) but using lithium hexamethyldisilazide as the base yielded no isonitrile containing products (i.r.), and t.l.c. analysis showed several components including oxazole (136).

Attempted preparation of Ethyl 2-isocyano-3-methyl-3-trimethylsilyloxy-2-butenoate (138, R=TMS)

Use of the same procedure[82] as that used in the preparation of oxazole (136) but using trimethylsilyl chloride in place of acetic acid yielded only oxazole (136) as a recognisable product (t.l.c., n.m.r.).

[^{2}H]-4-Ethoxycarbonyl-5-[ethyl-2'-oxo-2'-(5''-methyloxazoloyl)]-oxazole (137)

To a stirred solution of LDA (5.5 mmol) in dry THF under nitrogen was added 4-ethoxycarbonyl-5-methyl-oxazole (136) (0.775 g, 5 mmol) in dry THF at 0°C. After 2h a portion of the resulting dark red/orange solution was quenched with excess deuterium oxide, followed by acetic acid at 0°C. Extraction with diethyl ether, washing with water, and evaporation of the dried (Mg SO_4) extracts, followed by purification by preparative layer chromatography on silica gel (diethyl ether - dichloromethane as eluant) yielded the major component, believed to be oxazole (137) (Found: M^+, 265.0830. $C_{12}H_{11}D_1N_2O_5$ requires M, 265.0815); $\nu_{max.}$ (CH_2Cl_2) 1730-1700 and 1600 cm^{-1}; δ_H ($CDCl_3$) 7.81 (1H, s, CH = N), 4.82 (2H, s, CH_2CO), 4.38 (2H, q, J 7Hz, OCH_2), 2.66 (3H, s, CH_3 C = C), and 1.35 (3H, t, J 7Hz, CH_3CH_2).

Benzyl chloromethyl ether (140)

a) Use of the method described in "Organic Synthesis"[85] on several occasions was unsuccessful due to extensive polymerisation on distillation.

b) Benzyl chloromethyl ether (140) was successfully prepared by a method based on that used by Hill[86].

Through a mechanically stirred mixture of benzyl alcohol (20.00 g, 0.185 mol) and aqueous formaldehyde solution (40%, 48.00 g, 0.6 mol) was passed dry (concentrated sulphuric acid) hydrogen chloride at 0 - 10°C for 6h. After separating the layers, the upper layer was dried ($CaCl_2$) and evaporated to give a colourless liquid with contained no benzyl chloride (n.m.r.). Distillation gave pure benzyl chloromethyl ether (140) (20.49 g, 71%), b.p. 56-57°C (0.07 mmHg) (lit.,[85] b.p. 53-56°C (1.5 mmHg); δ_H ($CDCl_3$) 7.32 (5H, s, Ph), 5.48 (2H, s, CH_2Cl), and 4.71 (2H, s, CH_2O).

Ethyl 5-benzyloxy-3-oxopentanoate (139)

The title compound was prepared by the method of Taylor[84] from ethyl acetoacetate and benzyl chloromethyl ether with sodium hydride and n-butyllithium as bases. Purification by distillation failed to produce (139) free of benzylic impurities (n.m.r.), and (139) was thus used crude (after evaporation of excess ethyl acetoacetate) in subsequent reactions.

Ethyl 5-benzyloxy-2-hydroxyimino-3-oxopentanoate (141)

To a stirred solution of crude β-keto-ester (139) (3.00 g, 12 mmol) in THF (25 ml) was added acetic acid (0.78 g, 13 mmol) at 0°C, followed by sodium nitrite (95%, 0.96 g, 13 mmol) in water (6 ml) over 0.5h. The two phase mixture was vigorously stirred at room temperature for 12h. After extracting with diethyl ether (100 ml, and 50 ml), the ethereal solution was successively washed with water (20 ml), dilute aqueous sodium hydrogen carbonate (4 x 20 ml), and water (20 ml). The dried (Na_2SO_4) solution was evaporated to give a yellow oil (3.33 g). Repeated column chromatography on silica gel (25 g, 10% petroleum ether - dichloromethane to dichloromethane to 5% diethyl ether-dichloromethane as eluant) gave oxime (141) (1.88 g, 39% from ethyl acetoacetate) as an oil. Further purification by p.l.c. on silica gel gave an analytical sample (Found: C, 60.07; H, 6.29; N, 4.89. $C_{14}H_{17}NO_5$ requires C, 60.21; H, 6.14; N, 5.02%); $\nu_{max.}$ (film) 3300-3200 (OH), 1740 (CO ester), 1695 (CO ketone), and 1630 cm^{-1} (C = N); δ_H ($CDCl_3$) 10.9 (1H, br s, OH), 7.27 (5H, s, Ph), 4.56 (2H, s, $PhC\underline{H}_2O$) 4.34 (2H, q, J 6Hz, $OC\underline{H}_2CH_3$), 3.84 (2H, t, J 7Hz, $OC\underline{H}_2CH_2$), 3.19 (2H, t, J 7Hz, $CH_2C\underline{H}_2CO$), and 1.30 (3H, t, J 6Hz, $C\underline{H}_3CH_2O$); m/z 280 (M + 1), 252 (M - OH), 232, 172 (M - OCH_2Ph), and 91; R.f. 0.3 (SiO_2, 5% diethyl ether-dichloromethane, visualisation with copper (II) chloride).

Attempted hydrogenation of Ethyl 5-benzyloxy-2-hydroxyimino-3-oxopentanoate (141)

a) Hydrogenation of oxime (141) at 5 atmospheres over 10% palladium on carbon in ethanolic hydrogen chloride gave no reaction (t.l.c.) after 4h.

b) A reaction as in a) but at 12 atmospheres resulted in essentially no reaction (t.l.c.) after 15h.

c) A reaction as in a) but for 24h at 2 atmospheres resulted in loss of starting material (t.l.c.), but no recognisable products were isolable.

d) A reaction as in c), followed by subsequent reaction with acetic anhydride and triethylamine gave no recognisable products (n.m.r., t.l.c.).

Ethyl 5-hydroxy-2-hydroxyimino-3-oxopentanoate (142)

Reaction of the dianion of ethyl acetoacetate (50 mmol) at 0°C for 1h with benzyl chloromethyl ether as previously described gave β-keto-ester (139) (9.26 g). Hydrogenation of a portion of crude (139) (1.00 g) at atmospheric pressure over 10% palladium on carbon (200 mg) in absolute ethanol (50 ml) gave an orange oil (0.61 g), believed to be ethyl 5-hydroxy-3-oxopentanoate; $\nu_{max.}$ (film) 3510 - 3410 (OH), 1730 (CO ester), and 1710 cm^{-1} (CO ketone); δ_H ($CDCl_3$) 4.24 (2H, q, J 7Hz, $OC\underline{H}_2CH_3$), 3.90 (2H, t, J 6Hz, $C\underline{H}_2OH$), 3.53 (2H, s, $C\underline{H}_2CO_2Et$), 2.82 (2H, t, J 6Hz, CH_2CO), and 1.27 (3H, t, J 7Hz, $C\underline{H}_3CH_2O$).

To a stirred solution of a portion of crude alcoholic product (0.525 g, 3.3 mmol) in THF (25 ml) was added acetic acid (0.21 g, 3.6 mmol) in water (6 ml). After stirring for 24h at room temperature the mixture was extracted with diethyl ether (2 x 100 ml). The ethereal extracts were washed successively with water

(25 ml), dilute aqueous sodium hydrogen carbonate (3 x 25 ml), and water (25 ml). Evaporation of the dried (Na_2SO_4) extracts gave an oil (0.313 g) which after column chromatography on silica gel (12 g, dichloromethane to 40% diethyl ether-dichloromethane as eluant) gave oxime (142) as an oil (46 mg, 5% from ethyl acetoacetate). Crystallisation from dichloromethane at low temperature gave a white solid, m.p. 96-97°C (from dichloromethane) (Found: C, 44.69; H, 5.82; N, 7.33. $C_7H_{11}NO_5$ requires C, 44.45; H, 5.86; N, 7.40%); $\nu_{max.}$ (CH_2Cl_2) 3600, 3520, 3200 (OH), 1740 (CO ester), 1720 (sh, CO ketone), 1695 (C = N), and 1630 cm^{-1} (C = C aryl); δ_H ($CDCl_3$) 11.0 (1H, br s, HON = C), 4.38 (2H, q, J 7Hz, $OC\underline{H}_2CH_3$), 4.00 (2H, t, J 6Hz, $C\underline{H}_2OH$), 3.12 (2H, t, J 6Hz, CH_2CO), and 1.34 (3H, t, J 7Hz, $C\underline{H}_3CH_2O$); R.f. 0.4 (silica gel, 40% diethyl ether - dichloromethane).

p-Toluenesulphonyl azide

p-Toluenesulphonyl azide was prepared from p-toluenesulphonyl chloride and sodium azide according to the procedure of Doering[90] in 50% yield; δ_H ($CDCl_3$) 7.82 and 7.36 (4H, q, J_{AB} 8Hz, C<u>H</u> - aryl) and 2.44 (3H, s, CH_3).

Ethyl 5-benzyloxy-2-diazo-3-oxopentanoate (143)

a) To a stirred solution of crude β-keto-ester (139) (7.50 g, 30 mmol) in dry acetonitrile (50 ml) was added a mixture of triethylamine (3.33 g, 33 mmol) and p-toluenesulphonyl azide (6.50 g, 33 mmol) in acetonitrile (10 ml) over 1 min. at room temperature. After 20h at room temperature all soluble material was extracted with diethyl ether (100 ml). The insoluble material was mainly p-toluenesulphonamide (n.m.r.). The diethyl ether extracts were concentrated

and cooled to -78°C. The orange precipitate was filtered off to give diazo compound (143) (3.10 g, 34% from ethyl acetoacetate), m.p. 58-59°C (from diethyl ether) (Found: C, 60.72; H, 5.80; N, 9.98. $C_{14}H_{16}N_2O_4$ requires C, 60.86; H, 5.84; N, 10.14%); $\nu_{max.}$ (nujol) 2140 (N = N), 1710 (CO ester), and 1645 cm^{-1} (CO ketone); δ_H ($CDCl_3$) 7.36 (5H, s, Ph), 4.56 (2H, s, $PhC\underline{H}_20$), 4.30 (2H, q, J 7Hz, $OC\underline{H}_2CH_3$), 3.83 (2H, t, J 6Hz, $OC\underline{H}_2CH_2$), 3.17 (2H, t, J 6Hz, $C\underline{H}_2CO$), and 1.32 (3H, t, J 7Hz, $C\underline{H}_3CH_20$); m/z 277 (M + 1), 248 (M - N_2), 202 (M - EtOH - N_2), 201, 175, 171, 125, and 91; R.f. 0.5 (silica gel, CH_2Cl_2).

b) Use of p-toluenesulphonyl azide in the presence of sodium carbonate and tetrabutylammonium iodide or bromide[91] failed to give diazo-compound (143) in yields higher than in a).

Methyl 5-benzyloxy-3-oxopentanoate (144)

a) The title compound was prepared from methyl acetoacetate and benzyl chloromethyl ether as described for the corresponding ethyl ester (139). Like (139), ester (144) was difficult to purify. A small amount of distilled (144) was obtained, b.p. 140° (1 x 10^{-6} mmHg.).

b) Use of LDA as base failed to yield (144) in an improved state of purity.

Methyl 5-benzyloxy-2-diazo-3-oxopentanoate (145)

a) From distilled β-keto-ester (144)

To a stirred solution of distilled β-keto-ester (144) (0.236 g, 1 mmol) in dry acetonitrile (10 ml) was added a mixture of p-toluenesulphonyl azide (0.20 g,

1 mmol) and triethylamine (0.10g, 1 mmol) in acetonitrile (5 ml) at room temperature. After 20h, evaporation of the solvent followed by column chromatography on silica gel (10 g, 50% petroleum ether – dichloromethane to dichloromethane as eluant) gave diazo-compound (145) (0.162 g, 62%) as a colourless oil (Found: C,59.75; H, 5.49; N, 10.26. $C_{13}H_{14}N_2O_4$ requires C, 59.54; H, 5.38; N, 10.68%); $\nu_{max.}$ (film) 2140 (N=N), 1720 (CO ester), and 1660 cm^{-1} (CO ketone); δ_H ($CDCl_3$) 7.25 (5H, s, Ph), 4.45 (2H, s, $PhCH_2$), 3.75 (5H, s + t superimposed, J 6Hz, CH_3O, OCH_2CH_2), and 3.15 (2H, t, J 6Hz, CH_2CO); m/z 263 (M + 1), 234 (M – N_2), 219, 202 (M – N_2 – MeOH), 175, 174, 108, 107, and 91; R.f. 0.4 (silica gel, CH_2Cl_2).

b) From crude β-keto-ester (144)

Use of crude β-keto-ester (144) as in procedure a) above gave diazo-compound (145) in 24% overall yield from ethyl acetoacetate.

Ethyl diazoacetoacetate (146)

The title compound was prepared according to the method of Regitz[89] in 83% yield from ethyl acetoacetate and p-toluenesulphonyl azide.

3-Benzyloxypropionic acid (152)[95]

A mixture of β-propiolactone (14.4 g, 0.2 mol) and benzyl alcohol (136 g, 1.26 mol) was heated to 80°C and stirred with exclusion of moisture ($CaCl_2$). After 20 h no lactone remained (n.m.r.). Benzyl alcohol was removed by distillation (b.p. 64°C (1 mmHg)) and the residue distilled to yield acid (152) (26.08 g, 72%), b.p. 113–120°C (1×10^{-6} mmHg) (lit.,[95] 125–130 (0.01 mmHg)); $\nu_{max.}$ (film) 3650–2400 (OH) and 1715 cm^{-1} (CO); δ_H ($CDCl_3$) 10.2–10.0 (1H, br, s, CO_2H), 7.35 (5H, s, Ph), 4.55 (2H, s, $PhCH_2$), 3.75 (2H, t, J 6Hz, OCH_2CH_2), and 2.65 (2H, t, J 6Hz, CH_2CO_2H).

3-Benzyloxypropionyl chloride (151)

a) Reaction of 3-benzyloxypropionic acid (152) with triphenylphosphine - carbon tetrachloride[96] failed to yield acid chloride (151) (i.r.).

b) To a stirred suspension of sodium hydride (0.053 g, 2.2 mmol) in dry toluene (20 ml) was added 3-benzyloxypropionic acid (152) (0.36 g, 2 mmol) in toluene over 5 min. at room temperature. After consumption of all the sodium hydride, and cooling to 0°C, oxalyl chloride (0.19 ml, 2.2 mmol) was added. The mixture was stirred at room temperature for 24h, filtered, and the filtrate evaporated to give essentially pure acid chloride (151) (0.248 g,63%) as a colourless liquid; $\nu_{max.}$ (film) 1800 cm^{-1} (CO); δ_H ($CDCl_3$) 7.30 (5H, s, Ph), 4.48 (2H, s, $PhC\underline{H}_2$), 3.68 (2H, t, $\underline{J}$ 6Hz, $OC\underline{H}_2CH_2$), and 3.05 (2H, t, $\underline{J}$ 6Hz, CH_2COCl). Acid chloride (151) was used crude in subsequent reactions.

Ethyl diazoacetate (149)

The title compound was prepared by the method of Searle[97].

Alternative routes to ethyl 5-benzyloxy-2-diazo-3-oxopentanoate (143)

a) From ethyl diazoacetoacetate (146)

Treatment of ethyl diazoacetoacetate with lithium hexamethyldisilazide in THF at -78°C followed by reaction with benzyl chloromethyl ether failed to yield any traces of adduct (143) (n.m.r.).

b) From ethyl diazoacetate (149)

Crude 3-benzyloxypropionyl chloride (151) (0.396 g, 2 mmol) and ethyl diazoacetate (149) (0.228 g, 2 mmol) were mixed neat at room temperature in the presence of antibumping granules (5). After 7 days under argon in the dark no acid chloride (151) remained (i.r.). Column chromatography on silica gel (10 g, 50% petroleum ether - dichloromethane to dichloromethane as eluant) gave diazo-compound (143) (0.118 g, 21%).

Attempted preparation of benzyl iodomethyl ether

Benzyl chloromethyl ether on treatment with sodium iodide - acetone, magnesium iodide[92] - diethyl ether, or tetrabutylammonium iodide - diethyl ether failed to yield benzyl iodomethyl ether and complex mixtures resulted (n.m.r.).

5-Benzyloxy-2-diazo-3-oxopentanamide (153), and decomposition to 3-benzyloxypropanamide (156)

a) To a stirred solution of ethyl 5-benzyloxy-2-diazo-3-oxopentanoate (143) (0.276 g, 1 mmol) in ethanol (20 ml) was added concentrated aqueous ammonia (c 0.88, 0.24 g, 5 mmol). Further portions of ammonia (4.61 g, approx.95 mmol) were added over 4 days. Evaporation of the solvent yielded a brown oil. Extraction with diethyl ether and evaporation gave an orange oil consisting of three components (t.l.c.). Column chromatography on silica gel (10 g, dichloromethane to diethyl ether to ethyl acetate as eluant) gave the major component, believed to be amide (153), (84 mg, 34%) as a pale yellow solid; $\nu_{max.}$ (CH_2Cl_2) 3500, 3405 (NH), 2140 (N = N), 1685 (CO ketone), and 1660 cm^{-1}

(CO amide); δ_H ($CDCl_3$) 7.28 (5H, s, Ph), 6.50-6.0 (2H, br s, NH_2), 4.50 (2H, s, Ph $C\underline{H}_2$), 3.68 (2H, t, $\underline{J}$ 6Hz, $OC\underline{H}_2CH_2$), and 2.45 (2H, t, $\underline{J}$ 6Hz, $C\underline{H}_2$ CO); R.f. 0.1 (silica gel, EtOAc). Attempted purification by recrystallisation resulted in decomposition to amide (156), m.p. 60°C (from diethyl ether) (Found: C, 66.92; H, 7.27; N, 7.81. $C_{10}H_{13}NO_2$ requires C, 67.02; H, 7.31; N, 7.82%); $\nu_{max.}$ (CH_2Cl_2) 3480, 3380 (NH), and 1675 cm^{-1} (CO); δ_H (250 MHz; $CDCl_3$) 7.35 (5H, s, Ph), 6.25 (1H, br s, NH), 5.48 (1H, br s, NH), 4.57 (2H, s, $PhC\underline{H}_2$), 3.76 (2H, t, $\underline{J}$ 7Hz $OC\underline{H}_2CH_2$), and 2.55 (2H, t, $\underline{J}$ 7Hz, $C\underline{H}_2CONH_2$); m/z 180 (M + 1), 162, 161, 149, 135, and 91; R.f. 0.2 (silica gel, EtOAc).

b) The above decomposition occurred on a repeat run of procedure a).

Attempted preparation of 5-benzyloxy-2-hydroxyimino-3-oxopentamide (154)

Reaction of ethyl 5-benzyloxy-2-hydroxyimino-3-oxopentanoate (141) with ammonia by the procedure used in the attempted preparation of amide (153) gave an intractable mixture.

Acetoacetamide (155)

Acetoacetamide was prepared by the method of Kato[98] in low yield (18%) from diketene and ammonia, m.p. 51°C (from diethyl ether) (lit.,[98] 54°C); δ_H ($CDCl_3$) 7.05 (1H, br s, NH), 6.55 (1H, br s, NH), 3.40 (2H, s, CH_2), and 2.22 (3H, s, CH_3). Reproducible yields were difficult to achieve and yields varied from 0 - 18%.

Attempted preparation of the trianion derived from acetoacetamide (155)

a) Use of sodium hydride (1 eq.) and n-butyllithium (2 eq.) in THF and quenching with excess benzyl bromide failed to produce any recognisable products. (mass spectrometry).

b) Use of LDA (3 eq.) as base as in procedure a) gave no recognisable products.

Ethyl 2-acetylamino-5-benzyloxy-3-oxopentanoate (157)

a) From diazo-compound (143)

To a stirred solution of diazo-compound (143) (0.080 g, 0.29 mmol) in glacial acetic acid (1 ml) was added acetic anhydride (0.102 g, 1 mmol) and zinc dust (0.20 g, 3 mmol) in acetic acid (2 ml) at room temperature. After stirring for 6h the mixture was filtered and the zinc washed with dichloromethane. The combined filtrate and washings were washed with dilute aqueous sodium hydrogen carbonate (until effervescence ceased), water, dried (Mg SO_4), and evaporated to give a yellow oil (0.123 g). Column chromatography on silica gel (10 g, dichloromethane to diethyl ether as eluant) gave acetamide (157) (57 mg, 64%) (Found: C, 62.43; H, 6.90; N, 4.36. $C_{16}H_{21}NO_4$ requires C, 62.53; H, 6.89; N, 4.56%); $\nu_{max.}$ (CH_2Cl_2) 3420 (NH), 1750 (CO ester), 1720 (CO ketone), and 1685 cm^{-1} (CO amide); δ_H ($CDCl_3$), 7.24 (5H, s, Ph), 6.7 (1H, br s, NH), 5.20 (1H, d, J 6Hz, CHN), 4.45 (2H, s, $PhC\underline{H}_2O$), 4.16 (2H, q, J 7Hz, $C\underline{H}_2CH_3$), 3.70 (2H, t, J 6Hz, $OC\underline{H}_2CH_2$), 2.95 (2H, t, J 6Hz, CH_2CO), 2.02 (3H, s, $C\underline{H}_3$ CONH), and 1.26 (3H, t, J 7Hz, $C\underline{H}_3CH_2O$); m/z 308 (M + 1), 289 (M - H_2O), 277, 262 (M - OEt), 243, 216 (M - $PhCH_2$), 201, 176, 145, 144, 102, 91, and 43; R.f. 0.7 (silica gel, Et_2O).

b) From oxime (141)

Treatment of oxime (141) as in procedure a) above resulted in formation of acetamide (157) (t.l.c.) but purification was complicated by by-products of similar polarity.

c) From diazo-compound (143) - THF

To a stirred mixture of diazo-compound (143) (0.276 g, 1 mmol), acetic anhydride (0.30 g, 3 mmol) and zinc dust (0.53 g, 8 mmol) in THF (25 ml) was added acetic acid (0.30 g, 5 mmol) dropwise with ice-cooling. After 20 min., the reaction was filtered and the zinc washed with diethyl ether (70 ml). The combined filtrate and washings were washed with saturated aqueous sodium hydrogen carbonate (20 ml), water (2 x 10 ml), and dried ($MgSO_4$). Evaporation of the solvent gave a yellow oil (0.30 g). Column chromatography on silica gel (15 g, dichloromethane to 20% diethyl ether - dichloromethane as eluant) yielded β-keto-ester (139) (76 mg, 30%) and acetamide (157) (128 mg, 42%).

Formic acetic anhydride

Formic acetic anhydride was prepared from acetyl chloride and sodium formate in 55% yield, according to the method of Krimen[99].

Ethyl 5-benzyloxy-2-formylamino-3-oxopentanoate (158)

a) From diazo-compound (143)

To a stirred solution of diazo-compound (143) (0.223 g, 0.8 mmol) in glacial acetic acid (2 ml) was added formic acetic anhydride (0.21 g, 2.4 mmol) with

cooling (ice-water), followed by zinc dust (0.40 g, 6.4 mmol). Effervescence was observed, and the mixture became warm. After 10 min., the reaction was warmed to room temperature and stirred for 6h. Zinc was removed by filtration and washed with dichloromethane. The combined filtrate and washings were washed with dilute aqueous sodium hydrogen carbonate, water, dried ($MgSO_4$) and evaporated to give a colourless oil (0.225 g). Column chromatography on silica gel (10 g, dichloromethane to 60% diethyl ether-dichloromethane as eluant) gave β-keto-ester (139) (41 mg, 21%) and formamide (158) (113 mg, 48%) as a colourless oil; $\nu_{max.}$ (CH_2Cl_2) 3410 (NH), 1750 (CO ester), 1730 (CO ketone), and 1690 cm^{-1} (CO amide); δ_H ($CDCl_3$) 8.22 (1H, s, CHO), 7.32 (5H, s, Ph), 7.2-7.0 (1H, br d, J 7Hz, NH), 5.37 (1H, d, J 7Hz, $CH CO_2Et$), 4.50 (2H, s, $PhCH_2$), 4.24 (2H, q, J 7Hz, OCH_2CH_3), 3.78 (2H, t, J 6Hz, OCH_2CH_2), 3.00 (2H, t, J 6Hz, CH_2CO), and 1.25 (3H, t, J 7Hz, CH_3CH_20); m/z 294 (M + 1), 293 (weak M^+), 275 (M - H_20), 248 (M - OEt), 229, 202 (M - $PhCH_2$), 194, 131, 122, 107, 106, 105, and 91; R.f. 0.6 (silica gel, Et_20). Formamide (158 was further characterised by transformation to oxazole (160) (see below).

b) From oxime (141)

Oxime (141) was treated as in procedure a) above to yield formamide (158) in 68% yield after careful column chromatography to remove two impurities of very similar polarity.

5-(2'-Benzyloxyethyl)-4-ethoxycarbonyloxazole (160)

A mixture of formamide (158) (0.078 g, 27 mmol), triethylamine (0.027 g 0.27 mmol), carbon tetrachloride (0.041 g, 0.27 mmol), triphenylphosphine (0.085 g, 0.32 mmol) in chloroform (3 ml) was refluxed under nitrogen for 14h. A further 2 equivalents of all reagents were added and reflux continued for 3 days.

Evaporation of the solvent gave a brown oil (0.553 g). Column chromatography on silica gel (diethyl ether as eluant) gave triphenylphosphine oxide (0.209 g) and oxazole (160) (23 mg, 31%) as an oil which was further purified by p.l.c. on silica gel (diethyl ether as eluant) (Found: C, 65.56; H, 6.31; N, 5.26. $C_{15}H_{17}NO_4$ requires C, 65.44; H, 6.22; N, 5.09%); $\nu_{max.}$ (CH_2Cl_2) 1715 (CO) and 1610 cm^{-1}; δ_H ($CDCl_3$) 7.74 (1H, s, 2 - H), 7.26 (5H, s, Ph), 4.50 (2H, s, $PhC\underline{H}_2$), 4.36 (2H, q, J 6Hz, $OC\underline{H}_2CH_3$), 3.78 (2H, t, J 6Hz, $OC\underline{H}_2CH_2$), 3.36 (2H, t, J 6Hz, $CH_2C = C$), and 1.37 (3H, t, J 6Hz, $C\underline{H}_3CH_2O$); m/z 276 (M + 1), 275 (M^+), 256, 229 (M - EtOH), 202 (M - CO_2Et), 198, 184 (M - $PhCH_2$), 169, 138, 123, and 91; R.f. 0.4 (silica gel, diethyl ether).

Ethyl 2-pyruvoylaminoacetate (163)

a) To a stirred solution of ethyl isocyanoacetate (0.650 g, 5 mmol) in dry dichloromethane (6 ml) was added acetyl chloride (0.790 g, 10 mmol) at 0°C. After 15h at reflux no isonitrile remained (i.r.). Evaporation of the solvent gave a brown residue which was treated with aqueous acetone (1:1, 4 ml) with stirring at 0°C. After 3h, solid sodium hydrogen carbonate (0.420 g, 5 mmol) was added at 0°C. Extraction with dichloromethane (3 x 10 ml) and evaporation of the dried ($Mg SO_4$) extracts gave a brown oil (1.18 g). Column chromatography on silica gel (dichloromethane as eluant) gave α-keto-amide (163) as the major isolable component (0.166 g, 19%); $\nu_{max.}$ (CH_2Cl_2) 3410 (NH), 1740 (CO), and 1685 cm^{-1} (CO amide); δ_H ($CDCl_3$) 7.6 (1H, br s, NH), 4.5-4.1 (4H, m, $C\underline{H}_2NH$, $OC\underline{H}_2CH_3$), 2.5 (3H, 2 x s, CH_3CO), and 1.4 (3H, t, J 8Hz, $C\underline{H}_3CH_2$); m/z 197 (v. weak) 173 (M^+), 155, 145, and 130; R.f. 0.5 (silica gel, 10% Et_2O - CH_2Cl_2).

α-Keto-amide (163) was further characterised as its 2,4-dinitrophenylhydrazone, m.p. 149-150°C (from EtOH) (Found: C, 44.18; H, 4.20; N, 19.55. $C_{13}H_{15}N_5O_7$ requires C, 44.19; H, 4.25; N, 19.85%); δ_H ($CDCl_3$) 7.18 (1H, d,

J 4Hz, CH - aryl), 8.02 - 7.97 (2H, m, CH - aryl), 4.35-4.17 (4H, m, CH_2NH, CH_2CH_3), 2.33 (3H, s, CH_3CO), and 1.33 (3H, t, J 7Hz, CH_3CH_2); m/z 353 (M^+), 307 (M - OEt), and 280 (M - CO_2Et).

b) Use of a pH7 buffer in place of sodium hydrogen carbonate as in procedure a) above failed to reduce the production of by-products (t.l.c.).

Reaction of Ethyl 2-pyruvoylamino-acetate (163) with benzylamine

Reaction of α-keto-amide (163) with benzylamine in deuteriochloroform, toluene at reflux, or aqueous ethanol at reflux, failed to produce any diketo-piperazines. The only recognisable product was believed to be the corresponding imine (mass spectrometry).

Attempted preparation of ethyl 3-methyl-2-pyruvoylamino-2-butenoate leading to ethyl 2-(2'-hydroxy-2'-methylpropionylamino)-3-methyl-2-butenoate (164)

a) To a stirred solution of ethyl 2-isocyano-3-methyl-2-butenoate (123) (0.153 g, 1 mmol) in dry dichloromethane (1 ml) was added acetyl chloride (hydrogen chloride free, 0.14 ml, 2 mmol) at 0°C. After stirring for 28h at room temperature no isonitrile (123) remained (i.r.). Evaporation of the solvent gave a brown oil; m/z 213 (M^+ for ethyl 3-methyl-2-pyruvoylamino-2-butenoate), 167 (M - OEt), 142, 125, 114, and 97. The residue was cooled to 0°C and aqueous acetone (1:1, 2 ml) added. After 4h at 0°C, sodium hydrogen carbonate (0.084 g, 1 mmol) in water (1 ml) was added at 0°C. Extraction with dichloromethane (3 x 15 ml) and evaporation of the dried (Mg SO_4) extracts gave a yellow solid (0.226 g, 99%). Recrystallisation gave alcohol (164) (53 mg, 23%) as a white solid, m.p. 114-116°C

(from dichloromethane - petroleum ether) (Found: C,57.72; H, 8.43; N, 6.11; M^+, 229.1313. $C_{11}H_{19}NO_4$ requires C, 57.62; H, 8.35; N, 6.11%; M, 229.1314); $\nu_{max.}$ (CH_2Cl_2) 3600 (OH), 3410 (NH), 1715 (CO ester), and 1685 cm^{-1} (CO amide); δ_H ($CDCl_3$) 8.06 (1H, br s, NH), 4.25 (2H, q, J 7Hz, $OC\underline{H}_2CH_3$), 3.25 (1H, br s, OH), 2.18 and 1.80 (6H, 2 x s, $(CH_3)_2$ C = C), 1.50 (6H, s, 2 x $C\underline{H}_3$ COH), and 1.28 (3H, t, J 7Hz, $C\underline{H}_3CH_2$); δ_c (250 MHz; $CDCl_3$) 175.10 (s), 164.72 (s) 144.87 (s), 120.99 (s), 73.71 (s), 60.71 (t), 27.60 (q), 22.22 (q), 21.13 (q), and 14.10 (q); m/z 229 (M^+), 214 (M - 15), 183 (M - EtOH), 143, 114, and 97; R.f. 0.6 (silica gel, 50% Et_2O - CH_2Cl_2).

b) Use of the THF in place of acetone in a procedure similar to a) resulted in production of the same product (164) (t.l.c.). Attempted trapping of any intermediate α-keto-amide with benzylamine gave no identifiable products.

Glycinamide (173)

To a stirred solution of glycine ethyl ester hydrochloride (27.10 g, 0.19 mol) in methanol (150 ml) was added triethylamine (19.61 g, 0.19 mol). The mixture was diluted with ether (1200 ml), cooled in an ice-salt bath, and triethylamine hydrochloride removed by filtration. After evaporation of the filtrate, the residue was added to a saturated solution of ammonia in methanol (300 ml) and stirred for 1 day at room temperature. Evaporation of the solvent gave a straw-coloured solid which was recrystallised to give glycinamide (173) (4.00 g, 28%) as a white solid, m.p. 48-49°C (from diethyl ether - chloroform) (lit.,[107] 67-68°C); δ_H ($CDCl_3$) 7.3 (1H, br s, D_2O exch., CONH), 6.85 (1H, br s, D_2O exch., CONH), 3.26 (2H, s, CH_2), and 1.78 (2H, s, D_2O exch., NH_2); m/z 74 (M^+), 44 ($CONH_2^+$), and 30 (M - $CONH_2$).

N-(Phenylmethylene) glycinamide (174)

a) A mixture of glycinamide (173) (0.74 g, 10 mmol), benzaldehyde (1.06 g, 10 mmol), and anhydrous magnesium sulphate (1.00 g) in dry methanol (20 ml) was stirred at room temperature for 19h. After filtration, the solid was washed with dichloromethane. Evaporation of the combined filtrate and washings gave a white solid which was extracted with dichloromethane. Filtration of the extracts and evaporation of the filtrate yielded a white solid which was washed with petroleum ether to give imine (174) (1.47 g, 91%), m.p. 122-123°C (from CH_2Cl_2) (Found: C, 66.70; H, 6.22; N, 17.33. $C_9H_{10}N_2O$ requires C, 66.65; H, 6.21; N, 17.27%); $\nu_{max.}$ (nujol) 3400, 3200-3160 (NH), 1645 (CO), and 1635 cm^{-1} (C = N); δ_H ($CDCl_3$) 8.2 (1H, br t, CH = N), 7.78-7.25 (5H, m, Ph), 7.0-5.7 (2H, br, NH_2), and 4.23 (2H, d, J 1.5Hz, CH_2); m/z 163, 162 (M^+), 161, 118 (M - $CONH_2$), 104 (M - $CONH_2$-CH_2), and 91.

b) Use of the procedure described by Stork[101] gave imine (174) in 25% yield.

c) Use of procedure b) but with a non-aqueous work-up as in a) gave imine (174) in 32% yield.

Attempted preparation of bis-Trimethylsilyl-N-(phenylmethylene) glycinamide (176)

Treatment of N-(phenylmethylene) glycinamide (174) with triethylamine and trimethylsilyl chloride in a procedure[108] analogous to that used to prepare bis-O,N -trimethylsilylacetamide gave a complex mixture of silylated products (n.m.r.).

Metalation of N-(Phenylmethylene) glycinamide (174) and reaction with various electrophiles.

a) With Deuterium oxide

To a stirred solution of diisopropylamine (0.31 ml, 2.2 mmol) in dry THF (30 ml) was added n-butyllithium (1.57 ml, 2.2 mmol, total base 2.8 mmol) at 0°C under nitrogen. After 45 min. at 0°C, and cooling to -78°C, a solution of imine (174) (0.324 g, 2 mmol) in THF (10 ml) was added over 16 min. to give an intense blood-red solution. After 1h at -78°, and warming to 0°C, deuterium oxide (0.044 g, 2.2 mmol) in THF (2 ml) was added. After 2 min, acetic acid (0.264 g, 4.4 mmol) in THF (2 ml) was added and the reaction warmed to room temperature. Evaporation of the solvent, partitioning between dichloromethane and water, and evaporation of the dried (Na_2SO_4) organic phase gave a pale yellow solid believed to be N-(Phenylmethylene)-[2-^{2}H]-glycinamide (177) (0.290 g, 89%) (Found: M^+ 163.0858. $C_9H_9D_1N_2O$ requires M, 163.0856); δ_H ($CDCl_3$) 8.20 (1H, s, CH = N), 7.8-7.1 (5H, m, Ph), 6.90-5.90 (2H, 2 x br s, NH_2), 4.20 (1H, d, J 2Hz, CHD), and 1.7-0.7 (traces of butyl containing impurities); m/z 163 (M^+), 162, 119, 118, 106, 105, 92, and 91.

b) With benzyl bromide

A reaction using procedure a) but with benzyl bromide as the electrophile gave a crude adduct containing desired amide (178) (as shown by ^{1}H n.m.r. comparison with an authentic sample of amide (179)). Purification was not possible due to instability on silica gel and alumina.

c) With benzaldehyde

A reaction using procedure a) above but with benzaldehyde as the electrophile gave a complex mixture (t.l.c.).

d) With benzoyl chloride

A reaction using a procedure similar to a) above but using an inverse addition of the carbanion solution to benzoyl chloride yielded an intractable mixture (t.l.c.).

N-(Phenylmethylene)-L-phenylalaninamide (179)

To a stirred solution of L-phenylalanine amide (0.164 g, 1 mmol) in dry dichloromethane (5 ml) was added benzaldehyde (0.106 g, 1 mmol) and anhydrous magnesium sulphate (0.20 g) under argon. After 19h at room temperature, filtration (Celite), and evaporation of the solvent gave amide (179) (0.198 g, 79%) as a white solid, m.p. 105-107°C (from CH_2Cl_2 - petroleum ether) (Found: C, 76.20; H, 6.48; N, 11.25. $C_{16}H_{16}N_2O$ requires C, 76.16; H, 6.39 N, 11.10%); $[\alpha]_D^{20}$ - 166.2° (c 0.57 in $CHCl_3$); $\nu_{max.}$ (nujol) 3420, 3310 - 3150 (NH), and 1675 cm^{-1} (CO); δ_H ($CDCl_3$) 7.68 - 7.15 (11H, m, 2 x Ph and CH=N), 6.82 (1H, br s, NH), 6.20 (1H, br s, NH), and 3.92., 3.61 and 2.92 (3H, 12 lines, J_{ABX} 13, 10 and 4Hz, CH_2CH); m/z 252 (M^+), 208 (M - $CONH_2$), 161 (M - $PhCH_2$), 149, 118 and 91.

Diphenylmethylenimine (180)

Diphenylmethylenimine was prepared by the method of Pickard[110] from benzonitrile and phenylmagnesium bromide in 70% yield, b.p. 89-91°C (0.2 mmHg) (lit.,[110] 127-128°C (3.5 mmHg)).

N-(Diphenylmethylene) glycinamide (182)

a) A mixture of glycinamide hydrochloride (2.22 g, 20 mmol), diphenylmethylenimine (3.62 g, 20 mmol), and triethylamine (2.22 g, 22 mmol) in 1,2-dichloroethane (40 ml) was refluxed under nitrogen for 18h. The cooled mixture was poured into dichloromethane and, after washing with water (3 X) and drying (Na_2SO_4), the organic phase was evaporated to give an orange solid. Recrystallisation from dichloromethane - petroleum ether gave amide (182) (3.62 g, 76%) as a light yellow solid, m.p. 163.0-164.5°C (from CH_2Cl_2 - petroleum ether) (Found: C, 75.58; H, 5.92; N, 11.76. $C_{15}H_{14}N_2O$ requires C, 75.61; H, 5.92; N, 11.76%); $\nu_{max.}$ (nujol) 3420, 3135 (NH), 1690 (CO), and 1625 cm^{-1} (C = N); δ_H ($CDCl_3$) 7.68-6.95 (10H, m, Ph), 6.4-5.9 (2H, br s, NH_2), and 3.96 (2H, s, CH_2); m/z 238 (M^+), 194 (M - $CONH_2$),180 (M - CH_2CONH_2), 166 (Ph_2C^+), 161 (M - Ph), 149, 116, 104, and 91; R.f. 0.2 (alumina, Et_2O).

b) Treatment of glycinamide hydrochloride with diphenylmethylenimine in dichloromethane with or without triethylamine present gave incomplete reactions (t.l.c.).

c) A reaction following procedure a) but using methanol as solvent gave amide (182) in 41% yield.

3-Buten-1-yl tert-butyldiphenylsilyl ether (188)

A solution of 3-buten-1-ol (0.72 g, 10 mmol), imidazole (1.70 g, 25 mmol) and tert-butyldiphenylsilyl chloride (2.9 ml, 11 mmol) in dry DMF (7 ml) was stirred at room temperature under nitrogen for 41h. After pouring into diethyl ether (100 ml) and washing with water (3 x 100ml) the dried (Na_2SO_4) ethereal phase

was evaporated to give a pale yellow liquid (3.90 g). Column chromatography on silica gel (25 g, petroleum ether to 20% dichloromethane - petroleum ether) yielded silyl ether (188) (2.16 g, 70%) as a colourless liquid (Found: C, 77.27; H, 8.43. $C_{20}H_{26}OSi$ requires C, 77.36; H, 8.44%); $\nu_{max.}$ (film) 3070, 2960, 2930, 2890, 2860, 1640, 1590, 1470, 1465, 1430, 1385, 1360, 1100, 1090, 990, 915, 825, 735, 705, 690, and 615 cm^{-1}; δ_H ($CDCl_3$) 7.9-7.1 (10H, m, Ph), 6.15-5.40 (1H, m, $CH = CH_2$), 5.12-4.75 (2H, m, $CH_2 = CH$), 3.68 (2H, t, J 6Hz, OCH_2), 2.48-2.18 (2H, m, CH_2CH), and 1.06 (9H, s, ^tBu); m/z 269, 253 (M - ^tBu), 235, 225, 223, 211, 199, 197, 183, 181, 175, 145, 137, 135, 122, 104, 91, and 77; R.f. 0.5 (silica gel, 20% CH_2Cl_2 - petroleum ether).

2-Chloro-1-phenylseleno-4-butyl tert-butyldiphenylsilyl ether (186)

To a stirred solution of phenylselenyl chloride (0.191 g, 1 mmol) in dry acetonitrile (6 ml) at room temperature was added 3-buten-1-yl tert-butyldiphenylsilyl ether (188) (0.310 g, 1 mmol) in dry acetonitrile (3 ml). After 4h under nitrogen the solution became colourless. After 31h the solvent was evaporated to give an almost colourless oil (0.56 g) believed to be crude chloride (186). Full characterisation was not attempted due to the instability of chloride (186). ^1H n.m.r. showed loss of vinylic protons, and t.l.c. analysis showed one major selenium containing component along with diphenyl diselenide. Chloride (186) was used crude in subsequent reactions.

2-Bromo-1-phenylseleno-4-butyl tert-butyldiphenylsilyl ether (187)

To a stirred solution of diphenyl diselenide (0.156 g, 0.5 mmol) in dry acetonitrile (10 ml) was added bromine (26.5 µl, 0.5 mmol) at room temperature

under nitrogen. After 10 min. a solution of 3-buten-1-yl tert-butyldiphenylsilyl ether (188) (0.310 g, 1 mmol) in dry acetonitrile was added at room temperature to give an orange solution. After 2h the solvent was evaporated to give an orange oil (0.600 g) believed to be bromide (187). Full characterisation was not possible due to the facile decomposition of crude (187) to diphenyl diselenide. ^{1}H n.m.r. spectroscopy showed loss of the vinylic protons and t.l.c. analysis showed 2 major components, one of which was diphenyl diselenide. Crude bromide (187) was used in subsequent reactions.

2-Bromobutyrolactone (184)

2-Bromobutyrolactone (184) was prepared from butyrolactone by the method of Price[111] in 46% yield, b.p. 112-117°C (5 mmHg) (lit.,[111] 125-127°C (13 mmHg)).

2-Buten-4-olide (185)

2-Buten-4-olide (185) was prepared from 2-bromobutyrolactone (184) by the method of Price[111] in 42% yield, b.p. 92-96°C (16 mmHg) (lit.,[111] 107-109°C (24 mmHg)).

1-tert-Butyldiphenylsilyloxy-3-butyl p-toluenesulphonate (195)

A solution of dried (4 Å molecular sieves) butan-1,3-diol (0.90 g, 10 mmol), imidazole (1.70 g, 25 mmol), and tert-butyldiphenylsilyl chloride (2.60 ml, 10 mmol) in dry DMF (10 ml) was stirred under nitrogen for 18h at room temperature. The mixture was poured into diethyl ether, washed with water (2 X), dried (Na_2SO_4), and the solvent evaporated to give a colourless oil (3.73 g) believed to be

4-tert-butyldiphenylsilyloxy-2-butanol (194) (R.f. 0.2, silica gel, CH_2Cl_2). To a solution of crude alcohol (194)(3.73 g) in dry pyridine (10 ml) was added p-toluenesulphonyl chloride (2.10 g, 11 mmol) in small portions over 10 min. at 0°C. After stirring for 20h at room temperature under nitrogen, the reaction mixture was poured into aqueous citric acid solution and extracted with dichloromethane. The extracts were washed successively with aqueous saturated citric acid, aqueous saturated sodium hydrogen carbonate, water, and dried ($Na_2 SO_4$). Evaporation of the solvent gave a colourless oil (4.84 g) which was purified by column chromatography on silica gel(70 g, 20% CH_2Cl_2- petroleum ether to 70% CH_2Cl_2 - petroleum ether) to give p-toluenesulphonate (195) (3.60 g, 75%) as a colourless syrup (Found: C, 67.51; H, 7.35. $C_{27}H_{34}S\ Si\ 0_4$ requires C, 67.18; H, 7.10%); $\nu_{max.}$ (film) 3080, 3060, 2920, 2900, 2885, 1600, 1595, 1470, 1435, 1360, 1180, 1110-1080, 990, 900, 820, 740, 710, 695, and 660 cm^{-1}; δ_H ($CDCl_3$) 7.74-7.06 (14H, m, CH-aryl), 4.95-4.57 (1H, m, CHOTs), 3.49 (2H, t, J 5Hz, $CH_2$0 Si), 2.33 (3H, s, aryl - CH_3), 1.93-1.46 (2H, m, CH_2CH), 1.30 (3H, d, J 6Hz, CH_3CH), and 1.01 (9H, s, ^{t}Bu); m/z 425 (M - ^{t}Bu), 353, 348 (M - ^{t}Bu-Ph), 318,293,270,253,224, 199, 175, 135, 123, 105, 91, and 77; R.f. 0.3 (silica gel, 50% CH_2Cl_2 - petroleum ether).

3-Iodo-1-butyl tert-butyldiphenylsilyl ether (197)

To a stirred suspension of magnesium turnings (0.24 g, 10 mmol) in dry diethyl ether was added iodine (0.279 g, 2.2 mmol) at room temperature in small portions. After stirring for 1h at room temperature under nitrogen the iodine colouration dissipated. The supernatant solution was removed by syringe and transferred to another flask, and to this solution was added 1-tert-butyldiphenylsilyloxy-3-butyl p-toluenesulphonate (195) (0.482 g, 1 mmol) in dry diethyl ether at room temperature under nitrogen. After 1.5h t.l.c. analysis indicated complete reaction, giving an ethereal solution of proposed iodide (197) which was used crude

in subsequent reactions; R.f. 0.9 (silica gel, 50% CH_2Cl_2- petroleum ether).

1-tert-butyldiphenylsilyloxy-3-butyl p-nitrobenzenesulphonate (196)

A mixture of butan-1,3-diol (0.90 g, 10 mmol), tert-butyldiphenylsilyl chloride (2.60 ml, 10 mmol), and imidazole (1.70 g, 25 mmol) in dry DMF (5 ml) was stirred under nitrogen at room temperature for 24h. Partitioning between diethyl ether and water, washing of the ethereal layer with water (3 X), and evaporation of the dried ($Na_2 SO_4$) extracts yielded crude 4-tert-butyldiphenylsilyloxy-2-butanol (194) (3.55 g). To a solution of crude alcohol (194) (1.78 g) in dry pyridine at -15°C was added recrystallised p-nitrobenzenesulphonyl chloride (1.66 g, 7.5 mmol) in small portions over 0.5h. After 24h at -15°C (in freezer) further p-nitrobenzenesulphonyl chloride (1.11 g, 5 mmol) was added. After a further 24h at -15°C, the reaction mixture was poured into cold aqueous saturated citric acid and extracted with dichloromethane. The extracts were washed with cold saturated aqueous citric acid, water, dried ($Na_2 SO_4$) and evaporated to give an orange foam (2.48 g). Column chromatography on silica gel (30 g, 10% CH_2Cl_2 - petroleum ether to 80% CH_2Cl_2 - petroleum ether as eluant) gave p-nitrobenzenesulphonate (196) (1.85 g, 72%) as a white foamy solid, m.p. 97.0-98.5°C (Found: C, 60.71; H, 6.11; N, 2.68. $C_{26}H_{31}NO_6S Si$ requires C, 60.79; H, 6.08; N, 2.73%); $\nu_{max.}$ (nujol) 2960-2860, 1610, 1530, 1310, 1190, 1110, 1085, 900, 745, and 710 cm^{-1}; δ_H ($CDCl_3$) 8.18 and 7.98 (4H, ABq, J_{AB} 9Hz, CH -p-nitrobenzenesulphonate), 7.60-7.18 (10H, m, Ph), 5.16-4.70 (1H, m, CH O S), 3.53 (2H, t, J 5Hz, CH_2 O), 2.06-1.57 (2H, m, CH_2), 1.40 (3H, d, J 6Hz, CH_3CH), and 1.01 (9H, s, ^tBu); m/z 469, 387, 372 (base), 330, 285, 270, 211, 186, and 91; R.f. 0.5 (silica gel, 70% CH_2Cl_2 - petroleum ether).

Metalation of N-(Diphenylmethylene) glycinamide (182) and reaction with various electrophiles

a) Lithium diisopropylamide (LDA) as base.

Glycinamide (182) was treated with LDA using standard conditions and quenched with electrophiles as summarised below. Purification was by column chromatography on alumina. % deuterium incorporation (%D) was determined by ^1H n.m.r. spectroscopy.

No. equivs of base	Solvent	°C	Time /h	Electrophile	Recovery %	D %
1.2	THF	- 78	3.5	AcOD	72	42
1.2	THF	- 20	3.5	AcOD	66	51
1.2	THF	0	1	D_2O	44	47
1.2	THF-DMPU	- 78	3.5	CD_3CO_2D	76*	45
1.2	THF	- 78	3.5	CD_3CO_2D	71	53
2.2	THF	- 78	3.5	CD_3CO_2D	75	66

* crude recovery.

b) Sodium hydroxide-tetrabutylammonium hydrogen sulphate

Glycinamide (182) was treated with various electrophiles under phase transfer conditions using sodium hydroxide-tetrabutylammonium hydrogen sulphate in dichloromethane as summarised below. Representative experimental procedures are given below.

Electrophile	Result
Lactone (184)	No reaction. Electrophile decomposed.
Lactone (185)	No reaction. Electrophile decomposed.
p-Toluenesulphonate (195)	No reaction (t.l.c.).
Bromide (187)	Low yield selenide (189)
Chloride (186)	No isolable products
Benzyl bromide	Amide (183) in 66% yield.

N-(Diphenylmethylene)-phenylalaninamide (183)

To a stirred solution of N-(diphenylmethylene)glycinamide (182) (0.238 g, 1 mmol), tetrabutylammonium hydrogen sulphate (0.407 g, 1.2 mmol), and benzyl bromide (0.14 ml, 1.2 mmol) in dichloromethane (10 ml) was added aqueous sodium hydroxide (10%, 5 ml) at room temperature. After 0.5h the organic phase was separated, washed with saturated aqueous sodium chloride, dried (Na_2SO_4) and evaporated to give an oil (0.888 g). Column chromatography on alumina (15 g, 50% CH_2Cl_2 -petroleum ether to CH_2Cl_2 to Et_2O as eluant) yielded amide (183) as a white solid (0.217 g, 66%), m.p. 154.5-155.5°C (from CH_2Cl_2 - petroleum ether) (Found: C, 80.34; H, 6.28; N, 8.50. $C_{22}H_{20}N_2O$ requires C, 80.46; H, 6.14; N, 8.53%); $\nu_{max.}$ (nujol) 3430, 3120 (NH), and 1680 cm^{-1} (CO); δ_H (60 MHz; $CDCl_3$) 7.6-6.05 (17H, m, 3 x Ph and NH_2), 4.2-4.0 (1H, dd, J 5 and 5Hz, CH), and 3.36-2.75 (2H, m, CH_2); δ_H (250 MHz; $CDCl_3$) 7.60-7.00 and 6.45 (15H, m, 3 x Ph), 6.77 (1H, br s, NH), 6.25 (1H, br s, NH), 4.15, 3.22 and 3.05 (3H, 12 lines ABX, J_{ABX} 10, 3, and 13 Hz, $PhCH_2CH$); m/z 328 (M^+), 284 (M - $CONH_2$), 237 (M - $PhCH_2$), 194 (M - $CONH_2$- $PhCH_2$), 182, 165, 105, 91, and 71; R.f. 0.1 (alumina, CH_2Cl_2).

Attempted preparation of 5-tert-butyldiphenylsilyloxy-2-[N-(diphenylmethylene) amino]-3(1´-phenylseleno-methyl)-pentanamide (201) leading to N-(diphenyl-methylene)-2-phenylseleno-glycinamide (189)

Reaction of glycinamide (182) with crude 2-bromo-1-phenylseleno-4-butyl tert-butyldiphenylsilyl ether(187) by the above general method yielded a compound believed to be selenide (189). Full characterisation was not possible due to the instability of this compound; δ_H ($CDCl_3$) 7.8-6.5 (22H, m), 6.0 (2H, br s, NH_2), and 5.30 (1H, s, CH); m/z 394 (M^+), 337, 314 ($Ph_2Se_2^+$), 234, 199, 182, 157, 155, 154, 105, 78,and 77.

c) Catalytic sodium ethoxide as base

A mixture of glycinamide (182), 2-buten-4-olide (185) and catalytic sodium ethoxide in ethanol failed to produce any reaction (t.l.c.).

d) tert-Butyllithium as base

Glycinamide (182) was treated with tert-butyllithium at -78°C for 3h under standard conditions and quenched with various electrophiles (-78° to RT) as summarised below. Representative experimental procedures are given subsequently.

No.Equivs ^tBuLi	Solvent	Additive	Electrophile	Time at RT	Product %
1.1	THF	-	Benzyl bromide	1 h	Amide (183) 66%
1.1	THF	-	Lactone (184)	1 h	Imide (190) 38%
1.1	THF	-	Lactone (185)	1.5 h	Complex mixture (t.l.c.)
1.1	THF	-	Iodide (197)	4 days	Alkene (188) (t.l.c.)
1.1	THF	-	p-nitrobenzene-sulphonate (196)	3 days	No reaction (t.l.c.)
1.1	THF	-	p-toluene-sulphonate (195)	17 h	Amide (198) 25%
1.1	THF	TMEDA	"	2 days	Amide (198) 0% (t.l.c.)
1.1	THF	DMPU	"	19 h	"
1.1	DME	-	"	2 days	"
2.2	THF	-	"	18 h	Amide (198) 39%
2.2	Et_2O	-	"	16h	Amide (198) 54%
2.2	Et_2O	-	"	2.5 days	Amide (198) 84%

For example:-

a) Attempted preparation of 2-(butyrolactono)-N-(diphenylmethylene)glycinamide (191) leading to 1-[N-(diphenylmethylene) amino]-2-(2'-hydroxyethyl)-succinimide (190)

To a stirred solution of N-(diphenylmethylene) glycinamide (182) (0.238 g, 1 mmol) in dry THF (20 ml) was added tert-butyllithium (1.09 ml, 1.1 mmol, total

base 1.99 mmol) at -78°C under nitrogen. Initially a red colouration dissipated to a yellow solution, but after addition of 0.9 ml tert-butyllithium the red colouration persisted. After 3h at -78°C, 2-bromobutyrolactone (184) (0.17 ml, 2 mmol) was added at -78°C and the reaction warmed to room temperature. After 1h, the solvent was evaporated, the residue partitioned between dichloromethane and water, and the dried (Na_2SO_4) organic phase evaporated to give a yellow oil (0.58 g). Column chromatography on alumina (13 g, $CHCl_3$ to 2% MeOH-$CHCl_3$ to 5% MeOH-$CHCl_3$ as eluant) gave imide (190) (0.121 g, 38%) as a foamy solid, m.p. 86-87°C (from CH_2Cl_2-petroleum ether at -20°C) (Found: C, 70.57; H, 5.54; N, 8.66. $C_{19}H_{18}N_2O_3$ requires C, 70.79; H, 5.63; N, 8.69%); $\nu_{max.}$ (film) 3410, 3200 (NH), 1775 (CO), 1710 (CO), 1615, and 1600 cm^{-1}; δ_H ($CDCl_3$) 7.70-7.00 (10H, m, 2 x Ph), 4.52, 4.40, 4.30, 4.24 (1H, 4 lines, CHN), and 3.5-1.5 (7H, m, $HOCH_2CH_2CH$, NH); m/z 322 (M^+), 278, 245, 205, 193, 181, 165, 104, 91, and 77; R.f. 0.3 (alumina, 3% MeOH-$CHCl_3$).

b) N-(Diphenylmethylene) phenylalaninamide (183)

Reaction as in procedure a) above but using benzyl bromide as the electrophile and column chromatography on alumina (15g, $PhCH_3$ to 50% CH_2Cl_2-$PhCH_3$ to CH_2Cl_2 to Et_2O to EtOAc as eluant) yielded amide (183) in 66% yield. Spectral properties were identical to the sample previously prepared (see earlier).

c) 5-tert-Butyldiphenylsilyloxy-2-[N-(diphenylmethylene) amino]-3-methylpentanamide (198)

To a stirred suspension of N-(diphenylmethylene) glycinamide (182) (0.714 g, 3 mmol) in dry diethyl ether (20 ml) at -78°C was added tert-butyllithium (4.92 ml, 6.6 mmol, total base 7.98 mmol) to give an intense blood-red solution. After 3h at -78°C, 1-tert-butyldiphenylsilyloxy-3-butyl p-toluenesulphonate (195) (3.84 g, 7.98 mmol) in dry diethyl ether was added over 15 min. at -78°C. After 1h at 0°C, the reaction was stirred at room temperature for 2.5 days to give a

slightly yellow suspension. After quenching at -78°C with acetic acid (282 µl, 4.98 mmol) the solvent was evaporated and the residue partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (1 X), and the combined organic extracts dried (Na_2SO_4) and evaporated to give a brown oil. Column chromatography on alumina (Grade 1, 210 g, $PhCH_3$ to CH_2Cl_2 to Et_2O to EtOAc to MeOH as eluant) (lower activity alumina was used routinely with $PhCH_3$ to CH_2Cl_2 to Et_2O as eluant) gave, after evaporation, solution indichloromethane, filtration and evaporation, amide (198) as a foam (1.38 g, 84%) (Found: C, 76.25; H, 7.37; N, 5.03. $C_{35}H_{40}N_2O_2Si$ requires C, 76.60; H, 7.35; N, 5.10%); $\nu_{max.}$ (nujol) 3430, 3340-3120 (NH), 1675 (CO), 1615, and 1575 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.84-7.00 (20H, m, 4 x Ph), 6.58-6.46 (1H, br m, NH), 5.73-5.62 (1H, br m, NH), 3.89 and 3.86 (1H, 2 x d, J 3.6 and 3.2 Hz, CHN, mixture of diasteriomers), 3.68-3.44 (2H, m, CH_2OSi), 2.3-1.2 (3H, m, CH_2CH), 1.05 and 0.85 (3H, 2 x d, J 2.4 Hz, CH_3CH as mixture of diasteriomers), and 1.05-1.00 (9H, 2 x s, ^tBu as mixture of diasteriomers); δ_H (60 MHz; $CDCl_3$) 7.8-6.85 (20H, m, 4 x Ph), 6.5 (1H, br s, NH), 5.7 (1H, br s, NH), 3.9-3.38 (3H, m, CH_2OSi, CHN), 2.55-0.75 (15H, m, CH_3CH CH_2, ^tBu); m/z 549, 548 (M^+), 504 ($M - CONH_2$), 491 ($M - {}^tBu$), 473, 446 ($M - {}^tBu - CONH_2 - H$), 248, 199, 182, 180, 167, 165, 135, 104, 91, and 77; R.f. 0.5 (alumina, Et_2O), 0.5 (alumina, Et_2O-EtOAc, 1:1).

2,3-O-Isopropylidene-D-ribono-1,4-lactone (203)

Lactone (203) was prepared by a different procedure to that published by Hough[159].

To a stirred solution of D-ribono-1,4-lactone (5.00 g, 34 mmol) in dry acetone (200 ml) was added concentrated sulphuric acid (1 ml) at room temperature. After 20h the yellow solution was passed through Amberlyst A-21 resin (25 ml) with

acetone as eluant and evaporated to give lactone (203) (6.27 g, 99%) as a white solid, m.p. 138-139°C (lit.,[159] 138-139°C); $[\alpha]_D^{20}$ - 67.7° (c 0.10 in $CHCl_3$), $[\alpha]_D^{20}$ - 63.1° (c 0.48 in pyridine) (lit., [159] $[\alpha]_D^{24}$ - 65.7° (c 2.13 in pyridine)); δ_H ($CDCl_3$) 4.75 (2H, s, 2 x CH), 4.58 (1H, s, CH), 3.90 (2H, br s, CH_2), 2.6 (1H, br t, D_2O exch., OH), 1.48 (3H, s, CH_3), and 1.40 (3H, s, CH_3); R.f. 0.5 (silica gel, Et_2O).

N-Benzyl-p-toluenesulphonamide

N-Benzyl-p-toluenesulphonamide was prepared from benzylamine and p-toluenesulphonyl chloride by the method of Ingold[119] in 80% yield.

N-Benzyl-N-nitroso-p-toluenesulphonamide

The title compound was prepared from N-benzyl-p-toluenesulphonamide with acetic acid, acetic anhydride and sodium nitrite by the method of Overberger[120] in 75% yield.

Attempted oxidation of 2,3-O-Isopropylidene-D-ribono-1,4-lactone (203)

a) With potassium permanganate

Reaction of lactone (203) with potasium permanganate-tetrabutylammonium bromide[118] failed to yield any isolable products.

b) With ruthenium tetroxide

Reaction of lactone (203) with ruthenium tetroxide did yield the crude corresponding acid which was characterised as its benzhydryl ester (see next experiment).

Diphenylmethyl 2,3-O-isopropylidene-D-ribono-1,4-lactono-uronate (205)

To a stirred solution of 2,3-O-isopropylidene-D-ribono-1,4-lactone (203) (0.94 g, 5 mmol) in aqueous acetone (2:1 , 150 ml) was added potassium periodate (2.85 g,12.5 mmol) and ruthenium dioxide dihydrate (25 mg). After stirring for 20h at room temperature in the dark, the mixture was filtered (Celite) and the acetone evaporated. The aqueous solution was saturated with ammonium sulphate, extracted with chloroform, and the dried (Na_2SO_4) organic extracts evaporated to give a yellow oil (0.48 g). To a stirred solution of a portion of this oil (0.188 g) in dry diethyl ether (30 ml) was added diphenyldiazomethane[117] (0.175 g, 0.9 mmol) in dry diethyl ether at room temperature. After 18 h at room temperature, evaporation of the solvent and column chromatography on silica gel (petroleum ether to 10% petroleum ether-CH_2Cl_2 as eluant) gave the title ester (205) (98 mg, 14%) as an oil (Found: M^+, 368.1260. $C_{21}H_{20}O_6$ requires M, 368.1260); $\nu_{max.}$(film) 1805 (CO lactone) and 1755 cm^{-1} (CO ester); δ_H ($CDCl_3$) 7.30 (10H, s, 2 x Ph), 6.90 (1H, s, Ph_2CH), 5.04 (1H, s, CH O CO), 4.67 (2H, s, 2 x CH), 1.48 (3H, s, CH_3), and 1.37 (3H, s, CH_3); m/z 368 (M^+), 353 ($M-CH_3$), 183 (Ph_2CHO^+), 167 (Ph_2CH^+), 105, and 77; R.f. 0.4 (silica gel, CH_2Cl_2). Elemental analysis was not possible due to trace impurities of a very similar polarity to ester (205).

Attempted oxidation of 2,3-O-Isopropylidene-2-C-methyl-D-ribono-1,4-lactone (98) to the corresponding carboxylic acid (207)

a) With ruthenium tetroxide[116]

Reaction of lactone (98) with ruthenium tetroxide did yield the corresponding acid (207) which was characterised as the corresponding benzyl ester (206) (see later) in low yield.

b) With pyridinium dichromate-DMF[71]

Reaction of lactone (98) with pyridinium dichromate in dry DMF gave only trace amounts of acid (207) (n.m.r.).

c) With potassium permanganate[122]

Reaction of lactone (98) with potassium permanganate in water consumed starting lactone (98) but yielded a complex mixture (t.l.c.).

d) With silver (II) oxide[123,124]

Reaction of lactone (98) with silver (II) oxide (freshly prepared[160]) in water[123] or aqueous THF[124] failed to consume starting material (t.l.c.).

e) With 13% platinum on carbon

Reaction of lactone (98) with 13% platinum on carbon[125], sodium hydrogen carbonate and air or oxygen[126] failed to consume lactone (98) (t.l.c.).

Benzyl 2,3-O-isopropylidene-2-C-methyl-D-ribono-1,4-lactono-uronate (206)

To a stirred solution of 2,3-O-isopropylidene-2-C-methyl-ribono-1,4-lactone (98) (0.202 g, 1 mmol) in acetone-water (1:2, 30 ml) was added potassium periodate (0.57 g, 2.5 mmol) and ruthenium dioxide dihydrate (5 mg). After 15h in the dark at room temperature the acetone was evaporated and the aqueous phase saturated with ammonium sulphate, extracted with chloroform, and the dried (Na_2SO_4) extracts evaporated to give crude acid (207) (0.188 g).

To a stirred mixture of sodium methoxide (1 mmol) in methanol (2 ml) and ether (12 ml) was added N-benzyl-N-nitroso-p-toluenesulphonamide (0.290 g, 1 mmol) over 45 min. After 1h at room temperature and 20 min. at reflux, the cooled solution was poured into water. The ethereal layer was dried (Na_2SO_4) and added to an ether solution of crude acid (207). After 2 days at room temperature the colourless solution was evaporated to give an oil (0.210 g) consisting of five components (t.l.c.). Column chromatography on silica gel (10 g, petroleum ether to CH_2Cl_2 as eluant) yielded the title ester (206) (70 mg, 23%) as an oil which eventually crystallised, m.p. 59-60°C (Found: C, 62.75; H, 5.98. $C_{16}H_{18}O_6$ requires C, 62.74; H, 5.92%); $[\alpha]_D^{20}$ - 17.8° (c 0.18 in $CHCl_3$); $\nu_{max.}$ (film) 1800 (CO lactone) and 1755 cm^{-1} (CO ester); δ_H ($CDCl_3$) 7.30 (5H, s, Ph), 5.18 (2H, s, $PhCH_2$), 4.90 (1H, s, CHOCO), 4.35 (1H, s, CH), 1.46 (3H, s, CH_3), 1.40 (3H, s, CH_3), and 1.36 (3H, s, CH_3); m/z 291 ($M-CH_3$), 229, 220, 215 ($M - PhCH_2$), 161, 149, 143, 137, 114, 107, 98, and 91; R.f. 0.5 (silica gel, CH_2Cl_2).

Attempted oxidation of 2,3-O-isopropylidene-2-C-methyl-D-ribono-1,4-lactone (98) to the corresponding aldehyde (208)

Reagents	Reference	Results
PDC-CH_2Cl_2	121	Decomposition (t.l.c.)
PCC-CH_2Cl_2	128	Starting material remained (t.l.c.)
PDC-3Å molecular sieves-CH_2Cl_2	129	Rapid reaction to less polar unstable product (M^+ 400 or 385)
PCC-3Å molecular sieves-CH_2Cl_2	129	"
DMSO-DCC-TFA-py	127	Starting material consumed (t.l.c.). Trace amounts aldehydic products (n.m.r.)
DMSO-$(COCl)_2$	130	Starting material consumed (t.l.c.) Complex mixture (t.l.c.)
DMSO-Ac_2O	131	"

PDC - pyridinium dichromate
PCC - pyridinium chlorochromate
DMSO - dimethyl sulphoxide
DCC - N,N´-dicyclohexylcarbodiimide
TFA - trifluoroacetic acid
py - pyridine

5-chloro-5-deoxy-2,3-O-isopropylidene-2-C-methyl-D-ribono-1,4-lactone (210)

To a stirred solution of 2,3-O-isopropylidene-2-C-methyl-D-ribono-1,4-lactone (98) (0.303 g, 1.5 mmol) in dry pyridine (5 ml) at 0°C was added solid p-nitrobenzenesulphonyl chloride (0.366g, 1.65 mmol) in small portions. After 2h at 0°C further p-nitrobenzenesulphonyl chloride (0.366 g, 1.65 mmol) was added. After 1h at 0°C the reaction was warmed to room temperature and stirred for 17h. After pouring into water the mixture was extracted with diethyl ether and the dried (Na_2SO_4) extracts evaporated to give chloride (210) as a straw coloured solid (0.300 g, 91%), m.p. 78-79°C (from Et_2O - petroleum ether) (Found: C, 49.08; H, 6.03. $C_9H_{13}ClO_4$ requires C, 48.99; H, 5.94%); $[\alpha]_D^{20}$ -36.6° (c 0.13 in $CHCl_3$); $\nu_{max.}$ (nujol) 1775 cm^{-1} (CO); δ_H (250 MHz; $CDCl_3$) 4.72 (1H, ddd, J

5.7, 3.6, and 1.0 Hz, CHCH$_2$), 4.51 (1H, d, J 1.0 Hz, CH), 3.80 and 3.69 (2H, dd, J 12.0 and 3.6 Hz and dd, J 12.0 and 5.7 Hz, CH$_2$), 1.68 (3H, s, CH$_3$), and 1.46 (6H, s, 2 x CH$_3$); δ_H (60 MHz; CDCl$_3$) 4.76 (1H, br t, J 5 Hz, CHCH$_2$), 4.55 (1H, br s, CH), 3.85-3.73 (2H, m, CH$_2$), 1.70 (3H, s, CH$_3$),and 1.44 (6H, s, 2 x CH$_3$); m/z 223, 221 (M + ^{35}Cl), 207, 205 (M - CH$_3$), 165, 163, 145, 143, 120, 118, 105, 103, 85, 83, and 43; R.f. 0.3 (silica gel, CH_2Cl_2).

2,3-O-Isopropylidene-5-O-p-nitrobenzenesulphonyl-2-C-methyl-D-ribono-1,4-lactone (211)

To a stirred solution of 2,3,O-isopropylidene-2-C-methyl-D-ribono-1,4-lactone (98) (0.202 g, 1 mmol) in dry pyridine (2 ml) at -15°C was added p-nitrobenzenesulphonyl chloride (0.289 g, 1.3 mmol) in small portions over 10 min. After 3.5h further p-nitrobenzenesulphonyl chloride (0.222 g, 1 mmol) was added and the mixture stored at -15°C (in freezer) for 24h. The mixture was poured into cold (0°C) water - saturated aqueous citric acid (1:1) and extracted with dichloromethane. The organic phase was washed successively with water - saturated aqueous citric acid (1:1, 2 x), and water (2 x), dried (Na_2SO_4) and evaporated to give a pale yellow solid (0.390 g). Recrystallisation of a portion (0.285 g) yielded the title sulphonate (211) (0.229 g,81%) as a white solid, m.p. 145.5-146.5°C (from CH_2Cl_2-Et_2O) (Found: C, 46.55; H, 4.50; N, 3.61. $C_{15}H_{17}N\,O_9S$ requires C, 46.51; H, 4.42; N, 3.62%); $[\alpha]_D^{20}$ + 11.2° (c 0.13 in $CHCl_3$); $\nu_{max.}$ (nujol) 1775 cm^{-1} (CO); δ_H (250 MHz; $CDCl_3$) 8.46 (2H, d, J 9.6 Hz, 2 x CH - aryl), 8.10 (2H, d, J 8.3 Hz, 2 x CH - aryl), 4.62 (1H, dt, J 2.9 and 0.8 Hz, 4 - H), 4.50 (1H, d, J 0.8 Hz, 3 - H), 4.42 (1H, dd, J 11.2 and 2.7 Hz, 5 - H), 4.29 (1H, dd, J 11.2 and 3.1 Hz, 5 - H), 1.63 (3H, s, CH$_3$), 1.43 (3H, s, CH$_3$), and 1.42 (3H, s, CH$_3$); δ_H (60 MHz; $CDCl_3$) 8.45 (2H, d, J 9 Hz, 2 x CH - aryl), 8.07 (2H, d, J 9 Hz, 2 x CH- aryl), 4.65 (1H, br, t, J

3 Hz, 4 - H), 4.52 (1H, s, 3- H), 4.42-4.33 (2H, m, CH_2),1.65 (3H, s, CH_3), and 1.44 (6H, s, 2 x CH_3); m/z 387 (M^+), 372 (M - CH_3), 357 (M - NO), 342 (M - CH_3- NO), 330, 186 ($SO_2C_6H_4NO_2^+$), 173, 156, 143, 126, 121, 114, 99, and 83; R.f. 0.2 (silica gel, CH_2Cl_2).

Attempted preparation of 5-deoxy-2,3-O-isopropylidene-2-C-methyl-D-ribono-1,4-lactone 5-aldehyde (208) from p-nitrobenzenesulphonate (211)

A solution of p-nitrobenzenesulphonate (211) (0.074 g, 0.2 mmol) and sodium hydrogen carbonate (34 mg, 0.4 mmol) in dry DMSO (0.5 ml) was stirred at room temperature for 18h. No reaction occurred (t.l.c.). Use of further sodium hydrogen carbonate (68 mg, 0.8 mmol) and heating to 75°C for 1 day failed to produce any aldehydic products (n.m.r.).

Attempted preparation of 1-C-carboxy-2,3-O-isopropylidene-3-C-methyl-L-erythrose (212)

a) To a stirred solution of 2,3-O-isopropylidene-3-C-methyl-L-erythrose (102) (87 mg, 0.5 mmol) in water (5 ml) at 0°C was added sodium cyanide (45 mg, 0.93 mmol) in an aqueous solution (1 ml). The mixture was stirred at room temperature for 18 h. T.l.c. analysis showed loss of starting material. The mixture was refluxed for 2 days until evolution of alkaline gas ceased. After cooling to room temperature, Amberlite IR-120(H^+) resin (4 ml) was added and the mixture stirred for 1.5h. Filtration and evaporation of the solvent gave a brown oil which was insoluble in dichloromethane or ethyl acetate. A methanolic solution was dried (Na_2SO_4) and evaporated to give a red-brown residue (54 mg). ^1H n.m.r. analysis showed loss of the isopropylidene grouping and t.l.c. analysis showed

three lactonic components (hydroxylamine-ferric chloride detection), and numerous u.v. active components.

b) A mixture of erythrose (102) (0.103 g, 0.59 mmol), sodium cyanide (29 mg, 0.59 mmol), sodium metabisulphate (0.112 g, 0.59 mmol) and water (2 ml) was stirred for 5 days at room temperature. Sodium carbonate (60 mg) was added and the mixture heated to 50°C for 2 days until the alkaline gas evolution ceased. After cooling to 0°C, Amberlite IR-120 (H^+) resin (3 ml) was added and stirring continued for 1.5h. Evaporation, solution in methanol, and evaporation of the dried (Na_2SO_4) solvent yielded a brown residue (141 mg). T.l.c. analysis showed at least 4 lactonic products.

1-C-(1',3'-Dithian-2'-yl)-2,3-O-isopropylidene-3-C-methyl-L-erythrose (213)

To a stirred solution of 1,3-dithiane (60 mg, 0.5 mmol) in dry THF (10 ml) was added n-butyllithium (0.36 ml, 0.55 mmol, total base 0.7 mmol) at -20°C under argon. After 1.5h at -20 to -10°C and 0.5h at -78°C, a solution of 2,3-O-isopropylidene-3-C-methyl-L-erythrono-1,4-lactone (106) (86 mg, 0.5 mmol) in dry THF (1 ml) was added at -78°C over 1 min. After 3h at -78°C the reaction was quenched by addition of glacial acetic acid (42 mg, 0.7 mmol) in dry THF at -78°C, and the mixture warmed to room temperature. The solvent was evaporated, the residue partitioned between dichloromethane and water, and the dried (Na_2SO_4) organic phase evaporated to give a colourless oil (0.142 g). Column chromatography on silica gel (10 g, 80% petroleum ether - CH_2Cl_2 to 10% Et_2O- CH_2Cl_2 as eluant) gave the title erythrose (213) (0.144 g,78%) as a syrup which partially crystallised on prolonged standing (Found: C, 49.53; H, 7.21. $C_{12}H_{20}O_4S_2$ requires C, 49.29; H, 6.89%); $\nu_{max.}$ 3420 cm^{-1} (OH); δ_H ($CDCl_3$) 4.70-3.52 (4H, m, CHS, CH, CH_2O), 3.08-2.72 (4H, m, 2 x CH_2S), 2.20-1.70 (2H, m,

CH_2CH_2S), 1.55 (3H, s, CH_3), 1.50 (3H, s, CH_3), and 1.40 (3H, s, CH_3); m/z 292 (M^+), 277 (M - CH_3), 275 (M - OH), 261, 234 (M - $CH_3)_2CO$), 217, 203, 175, 145, 119, 118, 87, 85; R.f. 0.7 (silica gel, 10% Et_2O - CH_2Cl_2).

2-[(1S,2S)-2-Methyl-1,2,3-trihydroxypropyl]-1,3-dithiane (221)

a) To a stirred solution of 2,3-O-isopropylidene-3-C-methyl-L-erythrose (102) (0.75 g, 4.3 mmol) in dry dichloromethane (40 ml) was added dry 1,3-propanedithiol (1.27 ml) followed by dropwise addition of boron trifluoride etherate (1.03 ml) at 0°C under nitrogen. After 2.5h at 0°C, triethylamine (2.79 g) in methanol (10 ml) was added at 0°C and the mixture stirred for 0.5h at room temperature. Evaporation of the solvent gave a syrupy residue which was purified by column chromatography on silica gel (17 g, CH_2Cl_2 then Et_2O as eluant) to give the title dithiane (221) (0.76 g, 79%) as a colourless syrup which crystallised on seeding, m.p. 84-85°C (from CH_2Cl_2- petroleum ether) (Found: C, 42.47; H, 7.24. $C_8H_{16}O_3S_2$ requires C, 42.83; H, 7.19%); $[\alpha]_D^{20}$ + 39.3° (c 0.05 in $CHCl_3$); $\nu_{max.}$ (nujol) 3420-3240 cm^{-1} (OH); δ_H (250 MHz; $CDCl_3$) 4.03 (1H, dd, J 8 and 2 Hz, CHOH), 3.89 (1H, d, J 8 Hz, CHS), 3.78 (1H, br d, J 12 Hz, OH), 3.57 (2H, br d, J 7Hz, CH_2OH), 3.11 - 2.98 (2H, m, CH_2S), 2.79 - 2.63 (2H, m, CH_2S), 2.44 (1H, br s, OH), 2.12-2.02 (2H, m, CH_2CH_2S), 1.63-1.60 (1H, br s, OH), and 1.23 (3H, s, CH_3); δ_H (60 MHz; $CDCl_3$) 4.12-3.34 (7H, m, CHCOH, CHS), CH_2OH, and 3 x OH), 3.20-2.77 (4H, m, 2 x CH_2S), 2.13-1.78 (2H, m, CH_2-dithiane), and 1.17 (3H, s, CH_3); m/z 224 (M^+), 206 (M - H_2O), 175 (M - H_2O - CH_2OH), 150, 149, 123, 119, 86, 84, 49, 47, 43, and 41; R.f. 0.2 (silica gel, Et_2O).

b) Use of boron trifluoride etherate at 0°C using method a), but using an aqueous potassium hydroxide work-up[154] gave no isolable products.

c) Use of boron trifluoride etherate at room temperature as in procedure a) gave dithiane (221) in lower yield (40%).

d) Use of sulphuric acid as in procedure c) in place of boron trifluoride etherate gave considerable decomposition (t.l.c.)

2,3-O-Isopropylidene-3-C-methyl-1-O-trimethylsilyl-L-erythrose (222)

To a stirred solution of 2,3-O-isopropylidene-3-C-methyl-L-erythrose (102) (0.234 g, 1.34 mmol) in dry dichloromethane (5 ml) was added dry triethylamine (0.404 g, 4 mmol). After stirring at room temperature under argon for 18h, evaporation of the solvent and distillation (Kugelrohr) gave the title erythrose (222) (0.210 g, 85%), b.p. 70°C (k) (1 mmHg) (Found: C,53.43; H 9.01. $C_{11}H_{22}O_4Si$ requires C, 53.63; H, 9.00%); $[\alpha]_D^{20}$ +71.4° (c 0.32 in $CHCl_3$), δ_H ($CDCl_3$) 5.46 (1H, s, CHOSi), 4.23 (1H, s, CHO), 4.05 and 3.85 (2H, ABq, J 12 Hz, CH_2), 1.67 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.52 (3H, s, CH_3), and 0.32 (9H, s, 3 x CH_3Si); m/z 231 (M - CH_3, weak), 185, 184 (M - CH_3)$_2$CO), 170, 159, 99, 85, 73 (Me_3Si^+), and 59.

Attempted preparation of 2,3-O-Isopropylidene 3-C-methyl-L-erythrose dibenzyldithioacetal leading to 2,3-O-isopropylidene-3-C-methyl-4-O-trimethylsilyl-L-erythrose dibenzyldithioacetal (223)

a) With trimethylsilyl trifluoromethanesulphonate

To a solution of 2,3-O-isopropylidene-3-C-methyl-1-O-trimethylsilyl-L-erythrose (222) (34 mg, 0.14 mmol) in deuteriochloroform in an n.m.r. tube was added trimethylsilylbenzyl mercaptan (0.143 g, 0.73 mmol) and trimethylsilyl

trifluoromethanesulphonate (0.060 g, 0.27 mmol) at room temperature. After 2 days at 60°C the reaction was quenched with dry pyridine (0.3 g) and poured into saturated aqueous sodium hydrogen carbonate (10 ml). After extraction with diethyl ether, washing with saturated aqueous sodium hydrogen carbonate and drying (Na_2SO_4), the organic solvent was evaporated to give an oil (83 mg). Column chromatography on silica gel (1 g, petroleum ether to CH_2Cl_2) gave the major product believed to be 2,3-O-isopropylidene-3-C-methyl-4-O-trimethylsilyl-L-erythrose dibenzyldithioacetal (223) (37 mg, 56%) although full characterisation was not possible; $\nu_{max.}$ (film) 2970, 2950, 2930, 1495, 1455, 1370, 1250, 1215, 1195, 1090, 870, 840, 750, and 700 cm^{-1}; δ_H ($CDCl_3$) 7.45-7.30 (10H, m; 2 x Ph), 4.20, 4.02, and 3.90 (6H, m, 2 x CH_2S, CHS, and CHO), 3.40 (2H, s, CH_2O), 1.58 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.40 (3H, s, CH_3),and 0.15 (9H, s, $(CH_3)_3Si$); m/z 476 (M^+), 469, 461, 418, 401, 385 (M - $PhCH_2$), 352 (M - Ph CH_2SH), 327, 315, 295, 259, 225, 193, 164, 140, and 91.

b) A reaction as in procedure a) but on a larger scale (0.55 mmol) in chloroform gave none of the trimethylsilyl- ether (223) (t.l.c.) but a complex mixture (t.l.c.).

c) With zinc iodide

Use of procedure (a) with zinc iodide instead of trimethylsilyl trifluoromethanesulphonate gave a complex mixture (t.l.c.) from which no pure components could be isolated.

2-[(1S, 2S)-3-tert-Butyldiphenylsilyloxy-1,2-dihydroxy-2-methylpropyl]-1,3-dithane (224)

To a stirred solution of 2-[(1S, 2S) -2-methyl-1,2,3-trihydroxypropyl]-1,3-dithiane (221) (0.500g, 2.2 mmol) and tert-butyldiphenylsilyl chloride (0.62 ml, 2.4 mmol) in dry DMF (15 ml) was added imidazole (0.381 g, 5.6 mmol) at room temperature. After 18h at room temperature under nitrogen, the mixture was poured into diethyl ether (100 ml) and washed with water (3 X). The aqueous phase was re-extracted with diethyl ether, and the combined ethereal extracts washed with water (1 X), dried (Na_2SO_4) and evaporated to give a residue (1.06 g). Column chromatography on silica gel (15 g, 50-60% CH_2Cl_2 - pentane to CH_2Cl_2 to 10% Et_2O-CH_2Cl_2 as eluant) gave the title silyl-ether (224) (0.86 g, 83%) as a colourless syrup (Found: C, 62.29; H, 7.42. $C_{24}H_{34}O_3S_2Si$ requires C, 62.29; H, 7.41%); $[\alpha]_D^{20}$ + 14.0° (c 0.07 in $CHCl_3$); $\nu_{max.}$ (film) 3430 cm^{-1} (OH); δ_H (250 MHz; $CDCl_3$) 7.71-7.36 (10H, m, 2 x Ph), 4.32 (1H, d, J 4Hz, CHS), 3.94 and 3.91 (1H, dd, J 6 and 4 Hz, CH), 3.79 and 3.60 (2H, ABq, J 10 Hz, CH_2OSi), 2.99-2.65 (6H, m, 2 x CH_2S, 2 x OH), 2.12-1.88 (2H, m, CH_2), 1.23 (3H, s, CH_3), and 1.09 (9H, s, ^tBu); δ_H (60 MHz; $CDCl_3$) 7.66-7.13 (10H, m, 2 x Ph), 4.23 (1H, d, J 4Hz, CHS), 3.93-3.75 (1H, m, CH), 3.71 and 3.47 (2H, ABq, J 10 Hz, CH_2OSi), 2.90-2.59 (6H, m, 2 x CH_2S, 2 x OH), 2.10-1.71 (2H, m, CH_2), 1.27 (3H, s, CH_3), and 1.06 (9H, m, ^tBu); m/z 462 (M^+), 444 (M - H_2O), 405 (M - ^tBu), 387, 366, 327, 309, 297, 255, 199, 177, 175, 119, 86, 84, 57, 55, 49, 47, 43, and 41; R.f. 0.5 (silica gel, 5% Et_2O-CH_2Cl_2).

2-[4S, 5S) -5- tert-Butyldiphenylsilyloxymethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl]-1,3-dithiane (225)

To a stirred solution of 2-[(1S,2S)-3-tert-butyldiphenylsilyloxy-1,2-dihydroxy-2-methyl-propyl]-1,3-dithiane (224) (0.353 g, 0.76 mmol) in 2,2-

dimethoxypropane (6 ml) was added p-toluenesulphonic acid (25 mg) at room temperature. After stirring under nitrogen for 15h, the reaction mixture was poured into chloroform, washed with dilute aqueous potassium hydrogen carbonate (2 X), water (1 X), dried (Na_2SO_4) and evaporated to give an oil (0.42 g). Column chromatography on silica gel (10 g, petroleum ether to 60% CH_2Cl_2-petroleum ether as eluant) gave the title dithiane (225) as a colourless syrup which partially crystallised on standing (0.360 g, 94%) (Found: C, 64.23; H, 7.74. $C_{27}H_{38}O_3S_2Si$ requires C, 64.50; H, 7.62%); $[\alpha]_D^{20}$ - 19.4° (c 0.45 in $CHCl_3$); $\nu_{max.}$ (nujol) 2920, 2860, 1455, 1425, 1365, 1265, 1215, 1185, 1080, 1055, 995, 815, 700, and 690 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.77-7.70 and 7.44-7.36 (10H, m, 2 x Ph), 4.59 (1H, d, J 9 Hz, CHS), 4.05 (1H, d, J 9 Hz, CHO), 3.84 and 3.63 (2H, ABq, J 10 Hz, CH_2O Si), 2.94-2.65 (4H, m, 2 x CH_2S), 2.12-1.86 (2H, m, CH_2CH_2S), 1.46 (3H, s, CH_3), 1.40 (6H, s, 2 x CH_3), and 1.10 (9H, s, ^tBu); δ_H (60 MHz; $CDCl_3$) 7.70-7.10 (10H, m, 2 x Ph), 4.52 (1H, d, J 9 Hz, CHS), 3.97 (1H, d, J 9Hz, CHO), 3.81 and 3.55 (2H, ABq, J 10 Hz, CH_2O Si), 2.87-2.58 (4H, m, 2 x CH_2S), 2.10-1.75 (2H, m, CH_2CH_2S), 1.43 (3H, s, CH_3), 1.39 (6H, s, 2x CH_3), and 1.06 (9H, s, ^tBu); m/z 502 (M^+, weak), 487 (M - CH_3), 445 (M - ^tBu), 437, 386, 325, 281, 267, 255 ($Ph_2Si^tBuO^+$), 239, 199, 175, 119, 85, 83, 79, and 47; R.f. 0.7 (silica gel, CH_2Cl_2).

Attempted preparation of 2-[(4S, 5S)-5-(tert-butyldiphenylsilyloxymethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl]-2-cyano-1,3-dithiane (226)

a) With N-chlorosuccinimide - sodium cyanide

To a stirred solution of 2-[(4S, 5S)-5-(tert-butyldiphenylsilyloxymethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl]-1,3-dithiane (225) (90 mg, 0.18 mmol) in dry toluene was added N-chlorosuccinimide (25 mg, 0.19 mmol) at room temperature. After 2h at room temperature the solvent was decanted, evaporated and replaced with dry THF. Sodium cyanide (9 mg, 0.18 mmol) was added and the suspension

stirred under argon for 2 days at room temperature. T.l.c. analysis indicated a complex mixture.

b) With cyanogen bromide - triethylamine.

To a solution of dithiane (225) (94 mg, 0.19 mmol) in dry THF was added cyanogen bromide (0.19 mmol) in dry THF at 0°C. After 42h at room temperature no reaction had occurred (t.l.c., n.m.r., mass spectrometry).

c) With mercuric cyanide-iodine

Treatment of dithiane (225) with one equivalent of mercuric cyanide and iodine[139] in acetonitrile failed to totally consume starting materials (t.l.c.) and the products formed contained no nitrile components (i.r.).

2-Cyano-1,3-dithiane (227)

1,3-Dibromopropane was treated with sodium thiosulphate by the method of Hayashi[142] to give disodium trimethylenebisthiosulphate in 98% yield. Subsequent treatment with cyanoacetamide and sodium ethoxide in ethanol by the method of Hayashi[141] gave 2-cyano-1,3-dithiane (227) in 12% yield, m.p. 92-93°C (lit.,[141] 91°C); $\nu_{max.}$ (nujol) 2220 cm^{-1} (C ≡ N); δ_H ($CDCl_3$) 4.43 (1H, s, CHS) 3.7-2.6 (4H, m, 2 x CH_2S), and 2.4-2.0 (2H, m, CH_2CH_2S); R.f. 0.6 (silica gel, CH_2Cl_2).

1,3-Dithienium tetrafluoroborate (228)

1,3-Dithienium tetrafluoroborate (228) was prepared by a procedure based on methods outlined by Corey[143] and Paterson[144] as follows:- To a stirred

solution of 1,3-dithiane (1.20 g, 10 mmol) in dry dichloromethane (20 ml) was added triphenylcarbenium tetrafluoroborate (3.30 g, 10 mmol) at room temperature. An immediate brown solution resulted which was refluxed under nitrogen for 2 h. After cooling in ice under nitrogen for 20 min. the solvent was decanted and the residue washed with ice-cold diethyl ether (4X), dichloromethane (2X) and diethyl ether (1X). The beige coloured solid was dried in vacuo to give 1,3-dithienium tetrafluoroborate (228) (1.07 g, 52%) which was stored under nitrogen at -20°C; δ_H (CD_3NO_2) 11.10 (1H, br s, CH=S), 3.82-3.63 (4H, m, 2 x CH_2S), and 2.8-2.4 (2H, m, $C\underline{H}_2CH_2S$). The ^1H n.m.r. spectrum was unchanged after 3 days at room temperature.

Attempted preparation of 2-cyano-1,3-dithiane(227) from 1,3-dithienium tetrafluoroborate (228)

a) With Amberlite 1RA-400 (CN^-) resin[146]

A mixture of tetrafluoroborate (228) (0.206 g, 1 mmol) and Amberlite 1RA-400(CN^-) resin (1 g, approx 3.8 mmol) in dry nitromethane was stirred under nitrogen at room temperature for 3 days. No 2-cyano-1,3-dithiane was produced (t.l.c.).

b) With Amberlyst A-26 (CN^-) resin

Treatment of (228) as in procedure a) above except using Amberlyst A-26 (CN^-) resin and reaction for 5 days at room temperature and 1.5 days at 50°C gave only trace amounts of 2-cyano-1,3-dithiane (t.l.c.).

c) With potassium cyanide - 18 - crown - 6[147]

A mixture of tetrafluoroborate (228) (0.206 g, 1 mmol), potassium cyanide (0.098 g, 1.5 mmol) and 18-crown-6 (0.1 mmol) in dry acetonitrile (5 ml) was

stirred for 5 days at room temperature and 1.5 days at 50°C. Only trace amounts of 2-cyano-1,3-dithiane were detected (t.l.c.).

d) With sodium cyanide - DMF[148]

A mixture of tetrafluoroborate (228) (0.110g, 0.53 mmol) and sodium cyanide (31 mg, 0.64 mmol) in dry DMF (2 ml) was stirred under nitrogen for 3 days at room temperature and 1.5 days at 50°C. Only trace amounts of 2-cyano-1,3-dithiane were detected (t.l.c.).

e) With tetrabutylammonium cyanide[149]

To a stirred solution of tetrabutylammonium cyanide (0.281 g, 1.05 mmol) in dry nitromethane (5 ml) was added 1,3-dithienium tetrafluoroborate (228) (0.206 g, 1 mmol) at room temperature. The reaction was stirred under nitrogen for 1 day. The solvent was evaporated and the residue dissolved in dichloromethane, washed with water, dried (Na_2SO_4), filtered through a pad of silica gel, and evaporated to give a yellow oil (0.138 g). Column chromatography on silica gel (10 g, 50% petroleum ether - CH_2Cl_2) gave 2-cyano-1,3-dithiane (227) (13 mg, 9%) (R.f. 0.5 (silica gel, 50% CH_2Cl_2-petroleum ether)) and a product believed to be 2,2'-bis(1,3-dithianylidene) (230) (7 mg, 6%), m.p. 130-135°C (lit.,[161] 140-141°C) (Found: M^+, 235.9828. $C_8H_{12}S_4$ requires M, 235.9822); $\nu_{max.}$ (nujol) 2960, 2920, 1420, 1400, 1280, 1265, 1240, 910, 885, and 720 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 2.97-2.93 (8H, m, 4 x CH_2S) and 2.22-2.12 (4H, m, 2 x CH_2 CH_2S) (lit.,[161] 2.94 (8H, m) and 2.16 (4H, m)); m/z 238, 237, 236 (M^+, shows S_4 pattern), 195, 162, 149, 129, 119, 97, 88, 73, 69, 67, 57, 55, 41, and 40; R.f. 0.4 (silica gel, 50% CH_2Cl_2-petroleum ether).

1,3-Dithiane-1-oxide (229)

1,3-Dithiane was oxidised with sodium periodate in methanol according to the procedure of Carlson[145] to give 1,3-dithiane-1-oxide (229) (2.06 g, 91%) m.p. 86-87°C (from $CHCl_3$-cyclohexane) (lit.,[145] 86-87°C); δ_H ($CDCl_3$) 4.2-2.0 (complex multiplets); R.f. 0.1 (silica gel, EtOAc).

Attempted preparation of 2-cyano-1,3-dithiane (227) from 1,3-dithiane-1-oxide (229)

a) With trimethylsilyl cyanide.

Treatment of (229) with trimethylsilyl cyanide and ethyldiisopropylamine in dry dichloromethane at room temperature gave no reaction after 2 days (t.l.c.). Addition of imidazole or trimethylsilyl trifluoromethanesulphonate failed to produce significant reaction (t.l.c.).

b) With trifluoroacetic anhydride - tetrabutylammonium cyanide.

Treatment of (229) with tetrabutylammonium cyanide, ethyldiisopropylamine and trifluoroacetic anhydride in dry dichloromethane resulted in loss of starting material leading to a complex mixture (t.l.c.) containing no 2-cyano-1,3-dithiane (t.l.c., n.m.r.).

2-[(1S, 4S)-1-Hydroxy-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-methyl]-1,3-dithiane (231)

a) To a stirred solution of 2-[(1S, 2S)-2-methyl-1,2,3-trihydroxypropyl]-1,3-dithiane (221) (100 mg, 0.45 mmol) in dry acetone (2 ml) and 2,2-dimethoxypropane (5 ml) was added p-toluenesulphonic acid (10 mg) at room temperature.

After stirring under nitrogen for 18h the acetone was evaporated and the concentrated residue dissolved in chloroform, washed with dilute aqueous potassium hydrogen carbonate, dried (Na_2SO_4) and evaporated to give a yellow oil (0.144 g). Column chromatography on silica gel (10 g, 80% CH_2Cl_2-petroleum ether to CH_2Cl_2 to 6% Et_2O - CH_2Cl_2 as eluant) gave the title dithiane (231) as a colourless oil (109 mg, 92%) (Found: C,49.70; H, 7.74. $C_{11}H_{20}O_3S_2$ requires C, 49.97; H, 7.62%); $[\alpha]_D^{20}$ + 8.0° (c 0.63 in $CHCl_3$); $\nu_{max.}$ (film) 3460-3390 cm^{-1} (OH); δ_H (250 MHz; $CDCl_3$) 4.32 (1H, d, J 3.1 Hz, CHS), 4.23 (1H, d, J 7.5 Hz, CH of CH_2O), 3.74 (1H, d, J 7.5 Hz, CH of CH_2O), 3.88 (1H, t, J 3.1Hz, CHOH), 3.02-2.78 (5H, m, 2 x CH_2S, OH), 2.15-1.82(2H, m, CH_2 dithiane), 1.44 (3H, s, CH_3), 1.42 (3H, s, CH_3), and 1.39 (3H, s, CH_3); δ_H (60 MHz; $CDCl_3$) 4.30-3.59 (4H, m, CH_2O, CHOH, CHS), 2.98 - 2.72 (5H, m, 2 x CH_2S, OH), 2.13-1.66 (2H, m, CH_2 dithiane), 1.41 (6H, s, 2 x CH_3), and 1.37 (3H, s, CH_3); m/z 264 (M^+), 249 (M - CH_3), 246 (M - H_2O), 231 (M - CH_3 - H_2O), 175, 149, 148, 145, 119 (1,3-dithianyl 1^+, base), and 115; R.f. 0.6 (silica gel, 10% Et_2O - CH_2Cl_2).

b) To a solution of 2-[(1S, 2S) - 2-methyl-1,2,3-trihydroxypropyl]-1,3-dithiane (221) (0.122 g, 0.54 mmol) in dry acetone (4 ml) was added anhydrous copper (II) sulphate (0.282 g) at room temperature. After stirring under argon for 14h, filtration and evaporation yielded an oil (0.148 g). Column chromatography on silica gel (10 g, 70% CH_2Cl_2 - petroleum ether to CH_2Cl_2 to 6% Et_2O - CH_2Cl_2) gave dithiane (231) (82 mg, 57%).

Metalation of 2-[(1S, 2S) -3-tert-Butyldiphenylsilyloxy-1,2-dihydroxy-2-methylpropyl]-1,3-dithiane (224)

Dithiane (224) was reacted with various bases using dry solvents under nitrogen or argon in standard conditions. % deuterium incorporation were determined by ^1H n.m.r. spectroscopy. Results are tabulated below.

Base	No. Equivs.	Solvent	^{o}C	Time / h	Electro-phile	Result / % D
^{n}BuLi	3.1	THF	-78	2.5	CO_2	Starting material
^{n}BuLi	4	THF	-55	2	D_2O	30% D
^{n}BuLi	4	THF	0	2	D_2O	Decomposition (t.l.c.)
^{n}BuLi	4	THF	RT	2	D_2O	Decomposition (t.l.c.)
^{t}BuLi	4	DME	-78	0.6	AcOD	21% D
^{t}BuLi	5	DME	-55	3.5	AcOD	25% D
^{t}BuLi	5	THF	-60	6	AcOD	29% D
^{t}BuLi	5	THF	-60	7	D_2O	16% D
^{t}BuLi	5	THF	0	4	D_2O	<50% D - much decomposition (t.l.c.)
^{t}BuLi-TMEDA	4	THF	-25	5	AcOD	33% D
^{t}BuLi TMEDA	4	THF	-20	18.5	AcOD	34% D
^{t}BuLi	4	THF	-20	19	AcOD	16% D
$KN(SiMe_3)_2$	5	THF	-10	3	AcOD	< 10% D

Metalation of 2-[(1S, 2S)-2-methyl-1,2,3-trihydroxypropyl]-1,3-dithiane (221)

Reaction of dithiane (221) with 5 equivalents of t-butyllithium in THF at $-78^{o}C$ for 4h and quenching with deuterium oxide gave 0% D incorporation (n.m.r.) and considerable decomposition (t.l.c.).

Metalation of 2-[(1S, 4S)-1-hydroxy-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-methyl]-1,3-dithiane (231)

Dithiane (231) was treated with various bases under standard conditions as

summarised below. % D incorporations were determined by ^{1}H n.m.r. spectroscopy. % recovery referred to material after column chromatography.

Base	No. Equivs.	Solvent	°C	Time / h	Electro-phile	% Recovery	% D
^{n}BuLi	2.5	THF	-78	3.5	D_2O	-	0
^{n}BuLi-DABCO	2.5	THF	-78	4.5	AcOD	-	17
^{n}BuLi-DABCO	2.5	THF	-20	4	AcOD	37	38
^{n}BuLi-DABCO	3	THF	-45	4.5	AcOD	-	9
^{n}BuLi-TMEDA	3	THF	-45	5	AcOD	82	50
^{n}BuLi-TMEDA	4	THF	-20	21	AcOD	60	68

Metalation of 2-[(4S, 5S)-5-(tert-Butyldiphenylsilyloxymethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl]-1,3-dithiane (225) and decomposition to 2-[(2S)-3-tert-butyldiphenylsilyloxy-2-hydroxy-2-methyl-1-propenyl]-1,3-dithiane (238)

Dithiane (225) was reacted with n-butyllithium and TMEDA in THF under standard conditions as tabulated below. % D incorporations were determined by ^{1}H n.m.r. spectroscopy after quenching with 1-deuterioacetic acid.

No. Equivs. base	°C	Time/h	Result
4	-20	19	Decomposition (t.l.c.)
3	-78	2.5	Complete conversion to single component (t.l.c.) believed to be (238)
3	-100	2.5	Mixture approx. 1:1 of (238) and starting material (0% D)

Spectral data for (238):- δ_H ($CDCl_3$) 7.80-7.25 (10H, m, 2 x Ph), 6.03 (1H, s, CH = C), 3.65 (2H, s, CH_2O Si), and 3.2-0.8 (several m. complicated by butyl containing impurities); m/z 445 (M + 1), 427 (M - OH), 387 (M - ^{t}Bu), 368, 255 ($Ph_2Si\ ^tBu\ O^+$), and 175 (M - CH_2 OSi ^{t}BuPh$_2$, base). Purification of crude

(238) was not possible due to decomposition during column chromatography.

2-(Diphenylmethoxycarbonyl)-2[(1S, 4S)-1-hydroxy-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-methyl]-1,3-dithiane (239)

To a stirred solution of 2-[(1S, 4S)-1-hydroxy-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-methyl]-1,3-dithiane (231) (0.967 g, 3.7 mmol) in dry THF (20 ml) at -70°C was added dry TMEDA (2.2 ml, 14.8 mmol) and n-butyllithium (10.0 ml, 14.8 mmol) under argon. A pink colouration developed. After stirring for 2.5 days at -30→-35°C the pale yellow solution was cooled to -78°C and dry carbon dioxide gas passed through the solution for 0.5h at -78°C, 0.5h at -35°C, and 1h at 0°C. After warming to room temperature, the solvent was evaporated and the resulting yellow solid partitioned between dichloromethane and water. The aqueous phase was washed with dichloromethane (3 X), acidified with concentrated hydrochloric acid to pH 3, and extracted with ethyl acetate. The dried (Na_2SO_4) extracts were evaporated to give a compound believed to be crude 2-carboxy-2-[(1S, 4S)-1-hydroxy-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-methyl]-1,3-dithiane (0.85 g) (R.f. 0.4 (silica gel, 5% AcOH-EtOAc) as a yellow oil. The crude acid (0.85 g) was dissolved in dry dichloromethane and a solution of diphenyldiazomethane in dichloromethane was added at room temperature until the acid was consumed (t.l.c.). After stirring for 14h the solvent was evaporated and the residue (1.24 g) purified by column chromatography on silica gel (20 g, 80% CH_2Cl_2-petroleum ether to CH_2Cl_2 to 2-10% Et_2O - CH_2Cl_2 as eluant) to give the title ester (239) as an oil (0.62 g, 36%). Crystallisation from dichloromethane - petroleum ether at -20°C gave (239) as a white solid, m.p. 103.5-104.5°C (Found: C, 63.34; H, 6.36. $C_{25}H_{30}O_5S_2$ requires C, 63.26; H, 6.37%); $[\alpha]_D^{20}$ + 20.7° (c 0.16 in $CHCl_3$); $\nu_{max.}$ (film) 3460-3440 (OH) and 1725 cm^{-1} (CO); δ_H (250 MHz; $CDCl_3$) 7.47-7.27 (10H, m, 2x Ph), 6.93 (1H, s, C<u>H</u>Ph_2), 4.27 (1H, d, <u>J</u> 5.9 Hz, C<u>H</u>OH),

4.20 (1H, d, J 9.1 Hz, CH of CH_2O), 3.72 (1H, d, J 9.1 Hz, CH of CH_2O), 3.33 (1H, d, J 5.9 Hz, OH), 3.04-2.57 (4H, m, 2 x CH_2S), 1.96-1.78 (2H, m, CH_2CH_2S), 1.35 (3H, s, CH_3), 1.30 (3H, s, CH_3), and 1.26 (3H, s, CH_3); δ_H (60 MHz; $CDCl_3$) 7.45-7.26 (10H, m, 2 x Ph), 6.87 (1H, s, $CHPh_2$), 4.28-4.07 (2H, m, CHOH and CHOC superimposed), 3.62 (1H, d, J 9Hz, CHOC), 3.47-2.57 (4H, m, 2 x CH_2S), 2.07-1.62 (2H, m, CH_2CH_2S), 1.37 (3H, s, CH_3), 1.32 (3H, s, CH_3), and 1.28 (3H, s, CH_3); m/z 330 (Ph_2 CH OCOC (S CH_2CH_2 $CH_2S)^+$ + 1), 167 (Ph_2CH^+), 165, 152, 119, 115, and 58; R.f. 0.2 (silica gel, 5% Et_2O - CH_2Cl_2).

Attempted preparation of 2-(Diphenylmethoxycarbonyl)-2-[(1S, 4S)-1-tert-butyldiphenylsilyloxy-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-methyl]-1,3-dithiane (239, R = Si $^tBuPh_2$)

Treatment of 2-diphenylmethoxycarbonyl-2-[(1S, 4S)-1-hydroxy-1-(2,2, 4-trimethyl-1,3-dioxolan-4-yl)-methyl]-1,3-dithiane (239) with tert-butyldiphenyl-silyl chloride, imidazole and DMF under standard conditions[157] failed to produce any reaction (t.l.c.) at room temperature or 50°C for 2 days.

2-[(1S, 4S)-1-Acetoxy-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-methyl]-2-(diphenylmethoxycarbonyl)-1,3-dithiane (240)

A solution of-2 diphenylmethoxycarbonyl)-2[(1S, 4S)-1-hydroxy-1-(2,2, 4-trimethyldioxolan-4-yl)-methyl]-1,3-dithiane (239) (86 mg, 0.18 mmol), dry acetic anhydride (42 µl, 0.44 mmol), 4-dimethylaminopyridine (15 mg) in dry pyridine (2 ml) was stirred under nitrogen at room temperature for 1.5h. After the addition of water the solution was acidified to pH 3 with solid citric acid.

The mixture was extracted with dichloromethane (2 x), the extracts washed with water, dried (Na_2SO_4) and evaporated to give a pale yellow oil. Column chromatography on silica gel (1.5 g, 50% CH_2Cl_2 – petroleum ether to CH_2Cl_2 as eluant) yielded the title acetate (240) (75 mg, 80%) as a colourless syrup which could be crystallised from dichloromethane-petroleum ether, m.p. 109–110°C (Found: C, 62.69; H, 6.28. $C_{27}H_{32}O_6S_2$ requires C, 62.77; H, 6.24%); $[\alpha]_D^{20}$ + 21.3° (c 0.07 in $CHCl_3$); $\nu_{max.}$ (film) 1755 (CO) and 1725 cm^{-1} (CO); δ_H (250 MHz; $CDCl_3$) 7.49–7.26 (10H, m, 2 x Ph), 6.89 (1H, s, Ph_2 C<u>H</u>O), 6.01 (1H, s, C<u>H</u>OAc), 4.12 (1H, d, <u>J</u> 10Hz, CH of CH_2O) and 3.77 (1H, d, <u>J</u> 10Hz, CH of CH_2O), 3.37–3.24 and 2.70–2.57 (4H, m, 2 x CH_2S), 2.16 (3H, s, CH_3COO), 1.97–1.70 (2H, m, C<u>H</u>$_2CH_2S$), 1.33 (3H, s, CH_3), 1.21 (3H, s, CH_3), and 1.18 (3H, s, CH_3); δ_H (60 MHz, $CDCl_3$) 7.50–6.90 (10H, m, 2 x Ph), 6.77 (1H, s, Ph_2C<u>H</u>O), 5.90 (1H, s, C<u>H</u>OAc), 4.03 and 3.65 (2H, ABq, <u>J</u> 9Hz, CH_2O), 2.80–2.20 (4H, m, 2 x CH_2S), 2.09 (3H, s, CH_3COO), 1.93–1.46 (2H, m, C<u>H</u>$_2CH_2S$), 1.29 (3H, s, CH_3), 1.18 (3H, s, CH_3), and 1.15 (3H, s, CH_3); m/z 516 (M^+), 501 (M – CH_3), 469, 458 (M – $CH_3)_2CO$), 425, 401, 372, 359, 349, 342, 329, 305, (M – Ph_2CH OCO), 285, 262, 246, 231, 205, 167(Ph_2CH^+, base), 151, 115, 57, and 43; R.f. 0.6 (silica gel, 5% Et_2O – CH_2Cl_2).

2-Carboxy-1,3-dithiane (241)

The title compound was prepared according to the method of Bates[113]. Thus glyoxylic acid monohydrate (5.52 g, 60 mmol) gave dithiane-acid (241) (5.04 g, 51%), m.p. 113.5–114.5°C (lit.,[113] 115–116°C); δ_H ($CDCl_3$) 9.89 (1H, br s, CO_2H), 4.19 (1H, s, CHS), 3.62–1.74 (6H, m, 3 x CH_2); m/z 164 (M^+), 119, and 75; R.f. 0.7 (silica gel, 5% AcOH-EtOAc).

2-(1'-Acetoxyethyl)-2-carboxy-1,3-dithiane (242)

To a stirred solution of 1,3-dithiane-2-carboxylic acid (241) (0.164 g, 1 mmol) in dry THF (10 ml) was added n-butyllithium (1.49 ml, 2.2 mmol, total base 2.6 mmol) at 0°C under argon. During the addition a thick white precipitate formed which dissolved on addition of all the base. After 2h at 0°C and cooling to -78°C, freshly redistilled acetaldehyde (62 µl, 1.1 mmol) was added. After 30 min. at -78°C, acetic anhydride (acetic acid and hydrogen chloride free, 151 µl, 1.6 mmol) was added at -78°C. After 1h at -78°C a white precipitate had formed. On warming to room temperature the suspension was stirred for 30 min. and the reaction quenched with water. The organic solvent was evaporated and the residue dissolved in saturated aqueous sodium hydrogen carbonate. After washing with dichloromethane (3 x), the aqueous phase was acidified with concentrated hydrochloric acid, extracted with dichloromethane (until no further extraction of sulphur containing compounds - t.l.c. palladium(II)chloride spray) and the dried (Na_2SO_4) extracts evaporated to give dithiane-acid (242) (0.231 g, 92%) as a colourless oil (Found: M^+, 250.0325. $C_9H_{14}O_4S_2$ requires M, 250.0333); $\nu_{max.}$ (film) 3660-2140 (OH) and 1720 cm^{-1} (CO); δ_H ($CDCl_3$) 10.85 (1H, br s, CO_2H), 5.40 (1H, q, J 7Hz, $CHCH_3$), 3.60-2.5 (4H, m, 2 x SCH_2), 2.35-1.65 (2H, m, CH_2), 2.05 (3H, s, CH_3CO), and 1.50 (3H, d, J 7Hz, CH_3CH); m/z 250 (M^+), 206 (M - CO_2), 190 (M - AcOH), 164, 146, 118, and 92; R.f. 0.6 (silica gel, 5% AcOH-EtOAc).

Attempted acid hydrolysis of 5-tert-butyldiphenylsilyloxy-2-[N-(diphenylmethylene) amino]-3-methylpentanamide (198)

a) Treatment of (198) with methanolic hydrogen chloride (0.1N) gave a crude product containing no tert-butyldiphenylsilyloxy group (n.m.r.).

b) Treatment of (198) with 0.1N hydrochloric acid in diethyl ether[104] failed to consume starting material (t.l.c.).

c) Treatment of (198) with 15% aqueous acetic acid in THF for 6 days at room temperature failed to consume starting material (t.l.c.).

2-Amino-5-tert-butyldiphenylsilyloxy-3-methylpentanamide (243)

5-tert-Butyldiphenysilyloxy-2-[N-diphenylmethylene) amino]-3-methyl-pentanamide (198) (0.175 g, 0.32 mmol) in methanol (6 ml) was hydrogenated at atmospheric pressure over 5% palladium on carbon (20 mg) in the presence of trifluoroacetic acid (25 µl, 0.33 mmol). After 2.5 days starting material was consumed (t.l.c.). The mixture was filtered through Celite, the filtrate stirred with Amberlyst A-21 resin (1 ml) for 2h, filtered, evaporated, washed with petroleum ether (to remove diphenylmethane) and evaporated to give crude amino-amide (243) (134 mg); ^{1}H n.m.r. spectroscopy gave only very broad signals, δ_H ($CDCl_3$) 7.8-7.3 (10H, br m, Ph_2Si), 6.3-5.4 (2H, br s, $CONH_2$), 3.7 (2H, br s, CH_2O), 3.4 (1H, br s, $CHCONH_2$), 2.5-0.8 (13H, m, including $(CH_3)_3CSi$, CH_3CH, $CH\ CH_3$, and CH_2); m/z 436, 421, 384 (M^+), 340 (M - $CONH_2$), 337 (M - ^{t}Bu), 204, 198, 163, 141, 84, 69, and 45; R.f. 0.0 (alumina, EtOAc).

2-(1-Acetoxyethyl)-2-(chloroformyl)-1,3-dithiane (244)

A stirred solution of 2-(1-acetoxyethyl)-2-carboxy-1,3-dithiane (242) (0.125 g, 0.5 mmol) and thionyl chloride (73 µl, 1 mmol) in dry dichloromethane (2 ml) was refluxed under nitrogen for 2h. Evaporation of the solvent yielded crude acid chloride (244) as a brown oil, which was used directly for subsequent reactions; $\nu_{max.}$(film) 1780 (CO, acid chloride) and 1765 cm^{-1} (CO, acetate).

2-(1-Acetoxyethyl)-2-[N-(4-tert-butyldiphenylsilyloxy-1-carbamoyl-3-methylbutyl) carbamoyl]-1,3-dithiane (245)

To a stirred solution of crude acid chloride (244) (0.27 mmol) in dry dichloromethane (5 ml) under argon was added dry triethylamine (27 mg, 0.027 mmol) in dry dichloromethane at room temperature. A solution of crude amino-amide (243) (0.115 g, 0.27 mmol) in dry dichloromethane (5 ml) was added at room temperature. After 1.5h, the solution was washed with dilute aqueous sodium hydrogen carbonate, water, dried (Na_2SO_4), and evaporated to give a brown residue (158 mg). Column chromatography on silica gel (7 g, dichloromethane to 60% diethyl ether-dichloromethane as eluant) yielded pure pentanamide (245) as a foamy mixture of diastereomers (t.l.c.) (101 mg, 61% from imine (198)). Further purification by preparative layer chromatography (silica gel, 50% diethyl ether-ethyl acetate as eluant) gave an analytical sample (Found: C, 60.10; H, 7.33; N, 4.41. $C_{31}H_{44}N_2O_5S_2Si$ requires C, 60.36; H, 7.19; N, 4.54%); $\nu_{max.}$ (film) 3350 (NH), 3220 (NH), 3200 (NH), 1745 (CO ester), 1670 (CO amide), 1615 (CO amide), and 1505 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.98-7.35 (10H, m, Ph_2Si), 6.49 (1H, br s, NH), 5.88 and 5.79 (1H, 2 x br s, NH), 5.53 and 5.47 (1H, 2 x br s, NH), 5.45-5.31 (1H, m, CH OAc), 4.68-4.48 (1H, m, CH $CONH_2$), 3.94-3.70 (2H, m, CH_2OSi), 3.0-2.7 (4H, m, 2 x CH_2S), 2.4-1.65 (8H, m, CH_3CO, CH_3CHC, CH_2 and CH_2-CH_2 S), 1.45-1.38 (3H, m, CH_3 COAc), 1.05 (9H, s, $(CH_3)_3C$), and 0.97-0.92 (3H, m, CH_3 CH); m/z 559 (M - ^tBu), 499, 423, 275, 205, 163, and 145; R.f. 0.6 (silica gel, Et_2O-EtOAc,1:1) and 0.5 (silica gel, 10% MeOH-CH_2Cl_2). Pentanamide (245) has been prepared in 50% yield on a 1 mmol scale and in 44% yield on a 1.5 mmol scale from imine (198).

2-(1-Acetoxyethyl)-2-[N-(1-carbamoyl-4-hydroxy-3-methylbutyl)carbamoyl]-1,3-dithiane (246)

a) To a stirred solution of amide (245) (0.200 g, 0.32 mmol) in dry THF (1 ml) was added a THF solution of tetrabutylammonium fluoride (1M, 0.32 ml, 0.32 mmol) at 0°C under argon. After stirring for 2h at room temperature the solvent was evaporated and the residue purified by column chromatography on silica gel (10 g, dichloromethane to 6% methanol-dichloromethane as eluant) to give alcohol (246) (0.188 g, 96%) (Found: M^+, 378.1287. $C_{15}H_{26}N_2O_5S_2$ requires M, 378.1283); $\nu_{max.}$ (film) 3350-3280 (br, OH), 3190 (NH), 1735 (CO ester), 1660 (CO amide), and 1500 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 8.25, 8.11, and 8.04 (1H, 3 x br d, J 10Hz, CH NH CO), 7.40 and 7.15 (1H, 2 x br s, NH of $CONH_2$), 5.93 and 5.85 (1H, 2 x br s, NH of $CONH_2$), 5.42-5.32 (1H, 10 line m, CH_3CHOAc), 4.87-4.80 (1H, 6 line m, $CHCONH_2$), 3.96-3.65 (2H, m, CH_2OH), 3.08-2.80 (5H, m, 2 x CH_2S, OH), 2.35-1.50 (5H, m, CH_2, CH_2CH_2S, CH_3CH), 2.12-2.10 (3H, 4 x s, CH_3CO), 1.45 and 1.43 (3H, 2 x s, CH_3CHOAc), and 1.01, 0.98, 0.97, and 0.96 (3H, 4 x s, CH_3CH C); m/z 378 (M^+), 361 (M - OH), 334 (M - $CONH_2$), 318, 317 (M - $CONH_2$-OH), 301 (M - H_2O-$CONH_2$-CH_3), 292, 291, 275 (M - $CONH_2$-OAc), 246, 239, 229, 205, 162, 145, and 141; R.f. 0.2 (silica gel, 10% MeOH-CH_2Cl_2).

b) A reaction as in procedure a) but using two equivalents of tetrabutylammonium fluoride gave alcohol (246) (46%) along with significant amounts of an unidentified product. This product was derived from decomposition of alcohol (246) in the presence of excess tetrabutylammonium fluoride (t.l.c.), and showed loss of the CH_3CHOAc grouping (n.m.r.).

c) Reaction of amide (245) with 2 equivalents of tetrabutylammonium fluoride in THF at -78°C, or with 1 equivalent at -28°C gave no reaction (t.l.c.).

d) Reaction of amide (245) with 2 equivalents of potassium fluoride in methanol at room temperature failed to consume starting material (t.l.c.).

Attempted preparation of 1-(1-Acetoxyethyl)-8,10-diaza-5-methyl-2-oxabicyclo[4.2.2.]decan-7,9-dione (247)

1) From tert-butyldiphenylsilyloxy-amide (245)

To a mixture of silver(I)perchlorate[62] (0.062 g, 0.3 mmol) and phenylmercuric chloride (0.094 g, 0.3 mmol) under argon was added dry THF (0.5 ml) at room temperature. After stirring for 20 min. in the dark a solution of amide (245) (0.061 g, 0.1 mmol) in dry THF (0.5 ml) was added. After 19h at room temperature mainly starting material remained (t.l.c.).

2) From alcohol-amide (246)

a) With silver (I) trifluoromethanesulphonate[62]-dichloromethane

Treatment of alcohol (246) (9 mg, 0.02 mmol) with 3 equivalents of silver (I) trifluoromethanesulphonate in dry dichloromethane in the absence of light at room temperature for 2 days failed to consume starting material or show any detectable products (t.l.c.).

b) With silver (I) trifluoromethanesulphonate-diethyl ether

Treatment of alcohol (246) (3mg, 0.008 mmol) with 3 equivalents of silver (I) trifluoromethanesulphonate in diethyl ether in the absence of light, at room temperature for 2 days resulted in loss of starting material but no reaction products could be detected (t.l.c.).

c) With silver (I) perchlorate[62]-dichloromethane

Treatment of alcohol (246) (6 mg, 0.016 mmol) with 3 equivalents of silver (I) perchlorate in dry dichloromethane at room temperature in the absence of light for 11h gave no reaction (t.l.c.).

d) With silver(I) perchlorate-acetonitrile

A reaction as in procedure c) above but using acetonitrile as the solvent for 2 days led to partial consumption of starting material giving a less polar sulphur containing component and several other components (t.l.c.).

e) With mercuric oxide-trimethylsilyl trifluoromethanesulphonate - THF

To solid mercuric oxide (14 mg, 0.064 mmol) under argon was added trimethylsilyl trifluoromethanesulphonate (24µl, 0.128 mmol) at room temperature. An exothermic reaction converted the orange solid to a grey-white solid. After drying in vacuo the solid (presumed to be mercuric trifluoromethanesulphonate) was suspended in dry THF, and a solution of amide (246) (4 mg, 0.010 mmol) in dry THF was added at room temperature. After 18h no starting amide (246) remained (t.l.c.). A less polar sulphur containing component and numerous other components were formed (t.l.c.).

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