THE TOTAL SYNTHESIS OF MILBEMYCIN β_3

A thesis presented by

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in partial fulfilment of the requirements

for the award of the degree of

DOCTOR OF PHILOSOPHY

OF THE

UNIVERSITY OF LONDON

DEPARTMENT OF CHEMISTRY
IMPERIAL COLLEGE OF
SCIENCE AND TECHNOLOGY
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APRIL, 1983.

To my Parents

ACKNOWLEDGEMENTS

I am indebted to my supervisor, Dr. A. G. M. Barrett, for his friendly advice and encouragement throughout the duration of this research project.

I wish to thank my co-workers, Dr. J.-C. Florent, Dr. R. O. Jones, and Dr. G. Richardson, and all my colleagues, past and present, and specially Dr. G. W. Simpson, for helpful discussion.

Special thanks are due to the technical staff of Imperial College for their invaluable assistance over the years, in particular Mr. R. N. Sheppard and Miss S. Johnson for n.m.r. spectra.

I would also like to thank the Science Research Council for financial support and Pfizer Limited for additional funding of this project.

A very special thank you to Pamela Crace for making such a fine job of typing this manuscript.

I am grateful to Dr. Jim Irving, Dr. Thomas Buggy and Dr. Geoff Richardson for their invaluable proof reading.

Last, but not least, I would like to acknowledge the debt that I owe my parents.

ABSTRACT

Avermectin and milbemycin natural products are reviewed.

Milbemycin β_3 has been synthesized by two independent routes which are briefly discussed.

Studies towards the synthesis of milbemycin β_3 have been undertaken with the aim of developing a chiral route.

The milbemycin β_3 unit ethyl 2-acetyl-4-hydroxy-5-methylbenzoate was prepared from ethyl 2-(4-chlorobenzenesulphenyl)-4-oxo-2-pentenoate and (*E*)-1-methoxy-2-methyl-3-trimethylsilyloxy-1,3-butadiene *via* a Diels-Alder reaction.

Initial studies towards the preparation of the unsaturated *C*9-*C*14 unit, *via* 1,4-addition of phenylthioallyllithium to enone systems, were unsuccessful.

(4*S*,6*S*)-4-t-Butyldimethylsilyloxy-6-[(t-butyldimethylsilyloxy) methyl]tetrahydro-2*H*-pyran-2-one was prepared in six steps from D-(+)- ribonic acid-γ-lactone and should afford the required milbemycin β_3 spiro-acetal moiety by known methodology.

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REVIEW

AVERMECTIN AND MILBEMYCIN

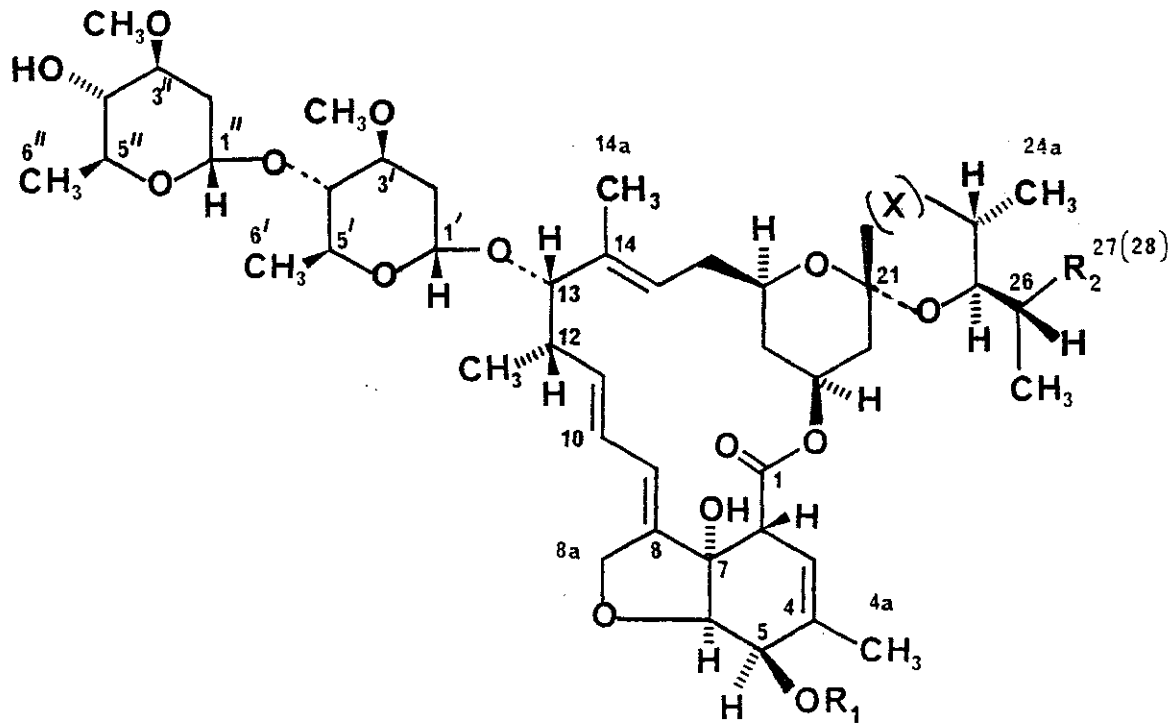
NATURAL PRODUCTS.

INTRODUCTION

Parasitic diseases of animals and man constitute serious problems in many countries of the world, and the need for new effective agents to treat these infections has been clearly stated.[1]

Since the days of the early antibiotics it has become more and more evident that micro-organisms may be a rich source of novel chemical structures. It was towards such microbial fermentation products that the Merck scientists turned in their search for new antiparasite agents.

In 1978, following a parasitology program at the Merck, Sharp and Dohme Research Laboratories, it was disclosed that a novel complex of chemically related agents, exhibiting extraordinarily potent anthelmintic[2] and insecticidal[3] activities, had been isolated from the culture broths of a new species of soil actinomycete, NRRL 8165, subsequently designated *Streptomyces avermitilis*.[4,5] Early tests indicated that whole broth was active against *Nematospiroides dubius* in mice,[4,6] an infection that is very hard to remove with some common anthelmintics. The active ingredient, as it occurred in nature and without chemical modification, was found to be active at one part per million of the diet, far more potent than other anthelmintics.[6] Subsequently, the anthelmintic activity was isolated[4] by solvent extraction of the mycelia and separated, by chromatography on silica, into 4 major (a) components. Mass spectral analysis revealed the presence, in each component, of 5-10% of a minor (b) homologue which were isolated by means of reverse-phase high-performance liquid chromatography. The eight compounds, designated A_{1a} through B_{2b}, were named collectively the "avermectins".[4] Mass spectral fragmentations and ^{13}C n.m.r. absorptions[7] suggested a



(1)

R_1 = Me : Component A

R_1 = H : Component B

R_2 = Et : Component a

R_2 = Me : Component b

X = -CH = CH- : Component 1

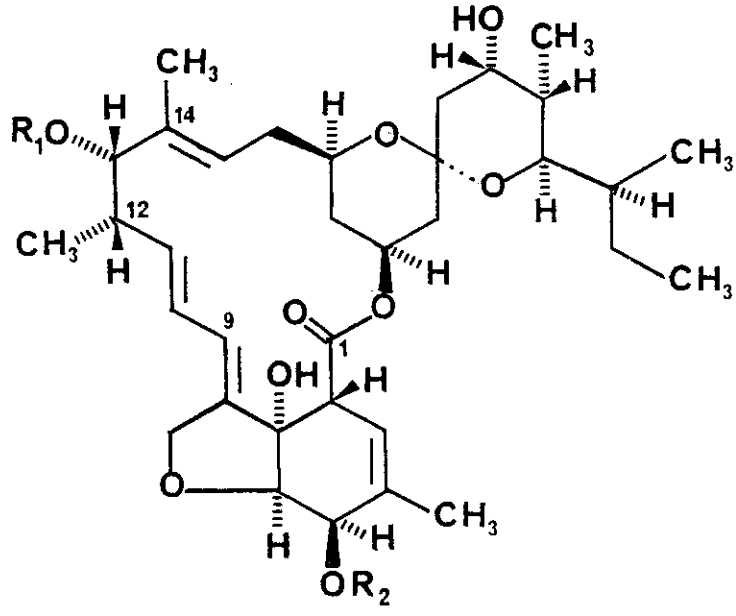
X = $-CH_2-\overset{OH}{\overset{|}{C}}H-$: Component 2

A_{1a} = (2) : A_{2a} = (3) : B_{1a} = (6) : B_{2a} = (7)

A_{1b} = (4) : A_{2b} = (5) : B_{1b} = (8) : B_{2b} = (9)

TABLE 1

relationship with the previously discovered milbemycins[8] and indicated the avermectins to be disaccharide derivatives of pentacyclic, 16-membered lactones. The eight compounds were subsequently designated the α-L-oleandrosyl-α-L-oleandroside structures (1) (TABLE 1). Single-crystal x-ray diffraction experiments of avermectin B_{1a} (6) and avermectin B_{2a} aglycon (10) (TABLE 2)



(3) $R_1 = C_{14} H_{25} O_6$; R_2 = Me

(7) $R_1 = C_{14} H_{25} O_6$; R_2 = H

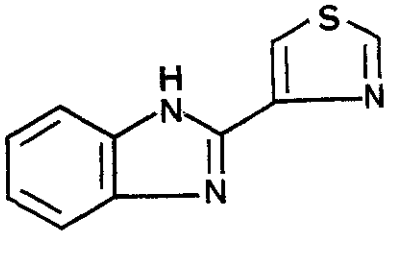
(10) R_1 = H ; R_2 = H

TABLE 2

confirmed the structures and established the remaining absolute stereochemical assignments. It was noted that branched butyl (a series) and propyl (b series) substituents at *C*-25 of the avermectins replace the methyl and ethyl substituents of the milbemycins. Biosynthetic experiments[10] have shown that these substituents derive from L-*iso*leucine and L-valine respectively. The virtually identical antiparasitic activities of these homologues eliminated the need for difficult separations for their biological evaluation.

Further testing revealed that this new family of compounds was active against a variety of parasitic helminths,[2,11] arachnids,[12] and ectoparasites.[3,13] They were found to be active when given orally or parenterally, at dosages of a fraction of a milligram per kilogram, against many immature and mature nematode and anthropod parasites of sheep, cattle, dogs, horses, and swine, yet were devoid of antibacterial and antifungal activity.[6] Chemical manipulation of the molecules revealed a substantial loss in anthelmintic efficacy on removal of one of the L-oleandrosyl sugar units; activity was further reduced by removal of the second sugar moiety.[6]

Avermectin B_{1a} (6) was subsequently shown to be about 1,000 times more potent than thiabendazole (11)[31,32] when tested in sheep.[2]



(11)

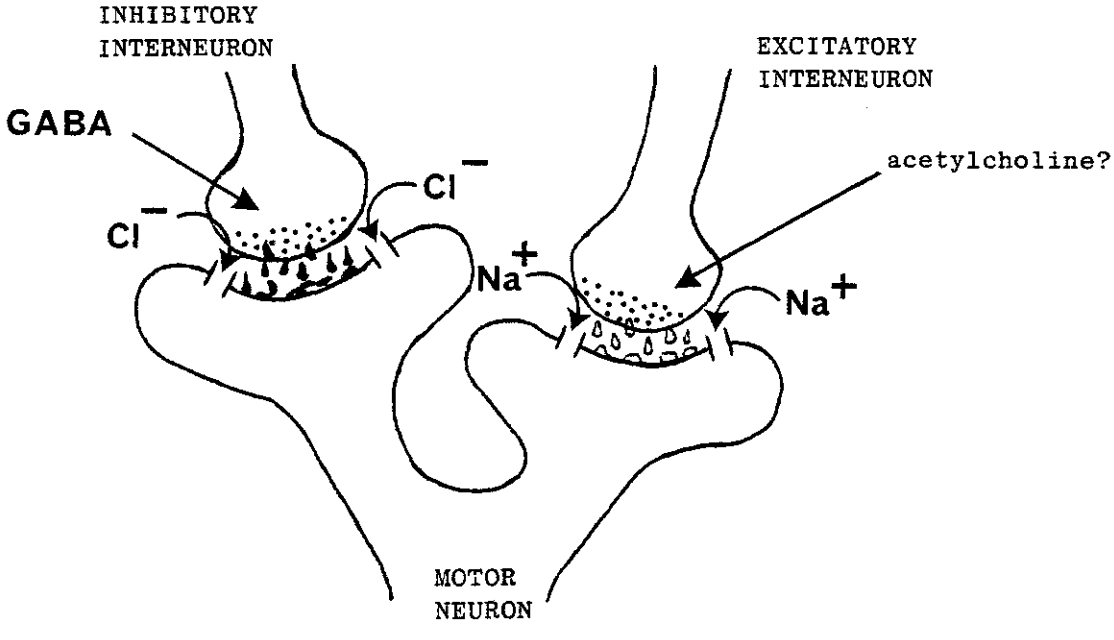
It was also shown to be very effective against two of the helminth

species (*Haemonchus contortus* and *Trichostrongylus colubriformis*) which are resistant to the benzimidazoles (TABLE 3).

Mode of Action

A series of efficacy studies[2,14] have shown that the avermectins paralyse worms, as do some other anthelmintics, but that they appear to do so in a unique way.

Nematodes (species *Ascaris*) have a central nervous system (CNS) based upon a ventral nerve cord. Between the CNS and the motor nerves are several connecting nerve cells (interneurons) which use γ-aminobutyric acid (GABA) as a neurotransmitter to pass inhibitory signals across the synaptic gap. A series of biochemical and electrophysiological studies[14,15,16,17] has shown that the avermectins act as GABA agonists stimulating the pre-synaptic release of GABA and enhancing its binding to the post-synaptic receptors (figure 1).

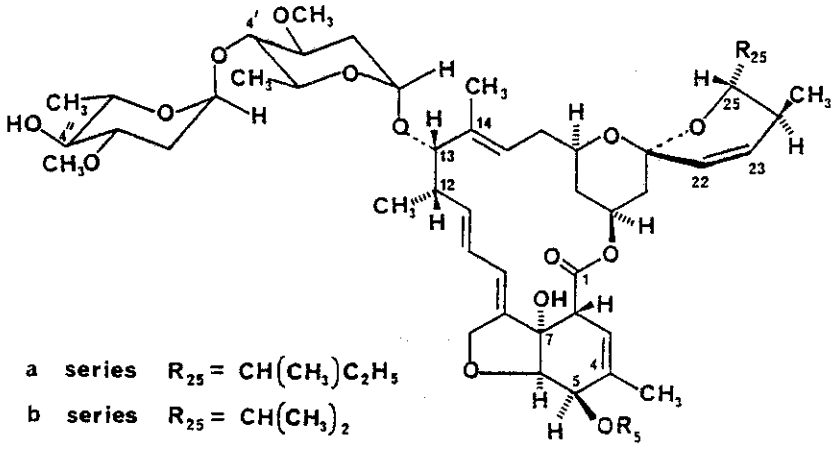


(fig. 1)

TABLE 3

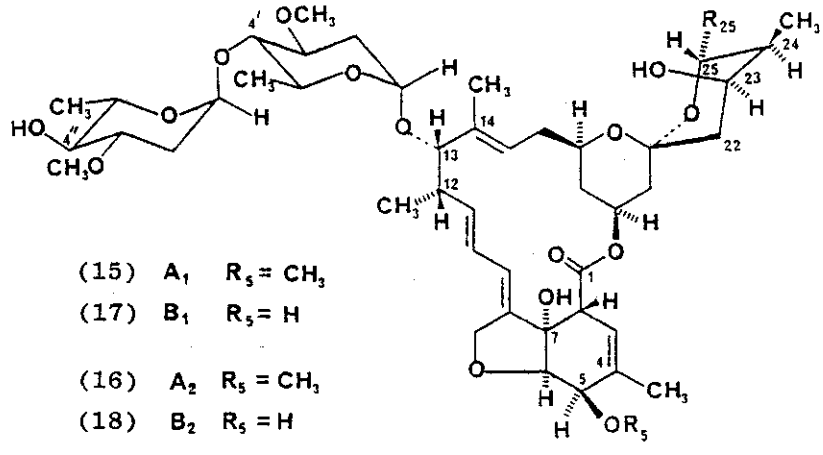
Comparative Activity of Four Naturally Occurring Avermectins:

(Nematode Infections of Sheep)



a series $R_{25} = CH(CH_3)C_2H_5$

b series $R_{25} = CH(CH_3)_2$



(15) A_1 $R_5 = CH_3$

(17) B_1 $R_5 = H$

(16) A_2 $R_5 = CH_3$

(18) B_2 $R_5 = H$

DOSE RATE 0.2 mg/kg	%Reduction in Worm Burden			
Avermectin Fractions	A_1	A_2	B_1	B_2
H. contortus (BZA-R)*				
Inhibited L_4	73	>96	>96	90
Adults	59	>99	98	0
O. circumcincta				
Inhibited L_4	17	9	95	99
Adults	58	99	98	>99
T. axei				
Adults	4	98	>99	>99
T. colubriformis (BZA-R)				
Adults	8	97	>99	>99
C. oncophora				
Inhibited L_4	0	36	97	>98
Adults	72	13	94	98
Oes. columbianum				
Adults	18	100	100	100

* Benzimidazole-resistant strain

(from Egerton J.R. - unpublished data)

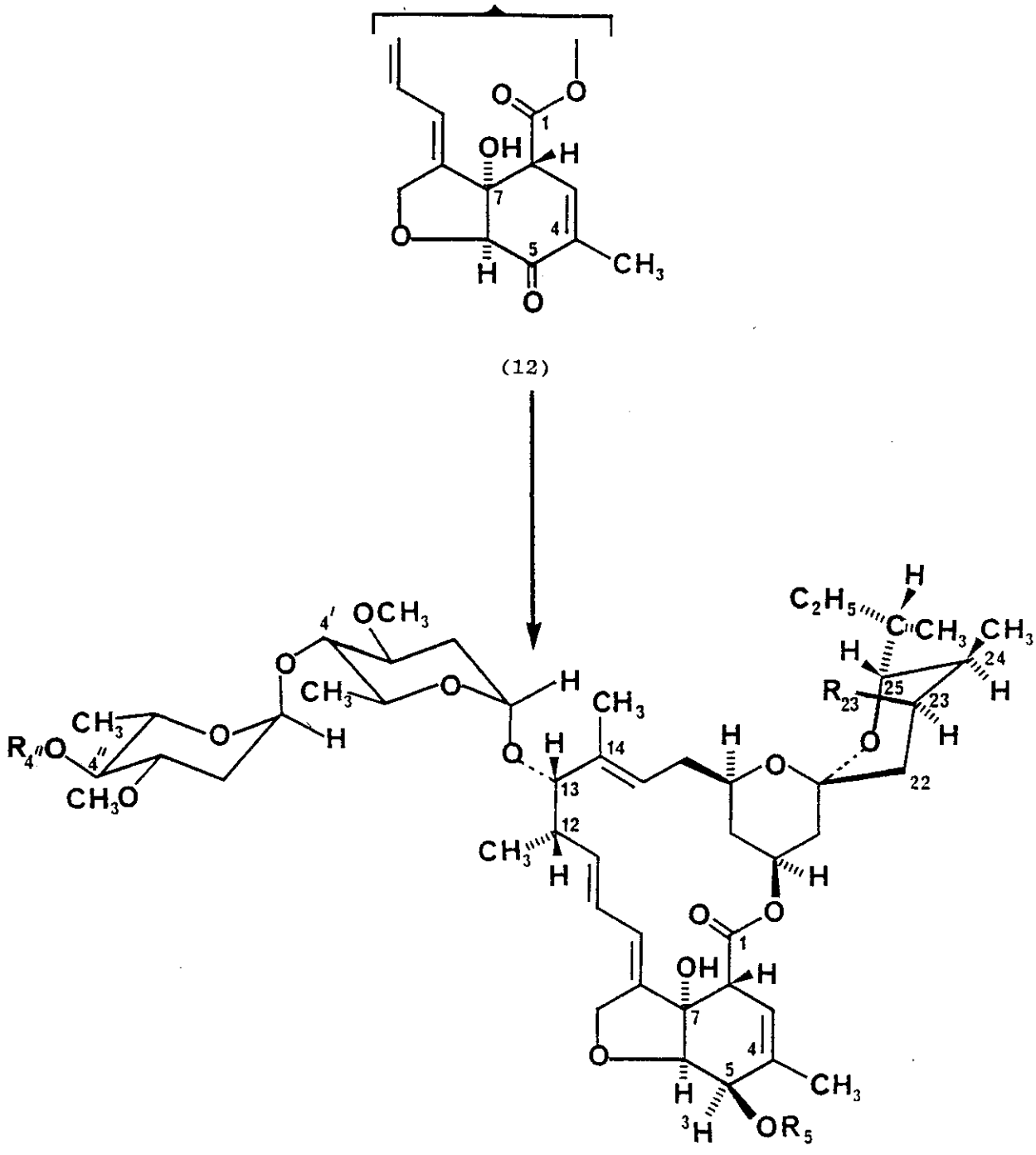
This inhibitory neurotransmitter is believed to open the chloride ion channels in the post-synaptic membrane, so allowing chloride ions to flow in and induce the "resting condition" in the motor neutron. Thus, the muscle cell does not function and for many parasites this paralysis results in death. Such activity is unprecedented among macrocyclic lactones.[4,18,19]

Since the mode of action of the avermectins in anthropods had been shown to be similar to that in nematodes much of the basic biochemical research was performed on the stretcher muscle of the walking-leg of the lobster.[15]

The postulated mode of action of the avermectins is consistent with their apparent lack of efficacy against trematodes and cestodes which are thought not to use GABA as a neurotransmitter.

A further study of the mode of action of the avermectins, as well as metabolic, pharmacokinetic, and tissue residue analyses required the synthesis of 5-[^{3}H] avermectins B_{1a} (13) and B_{2a} (14)[20] which were prepared *via* the stereoselective reduction of the corresponding 5-ketoavermectins using sodium borotritide (Scheme 1). The 5-ketoavermectins (12) were conveniently prepared, in 40-55% yields, by the manganese dioxide oxidation of the natural products.

All four of the major naturally-occurring avermectins were found to be active, to varying extents, against helminths in sheep (TABLE 3):[21] avermectins A_1 (15) and A_2 (16) were however clearly inferior. The efficacy of B_2 (18) was similar to that of B_1 (17) except in respect to *H.contortus*, against which B_1 (17) was highly active and B_2 (18) was totally inactive at all dosages tested.



(12)

(13) $R_{4''} = R_5 = H$, C_{22}-C_{23} = -CH = CH-

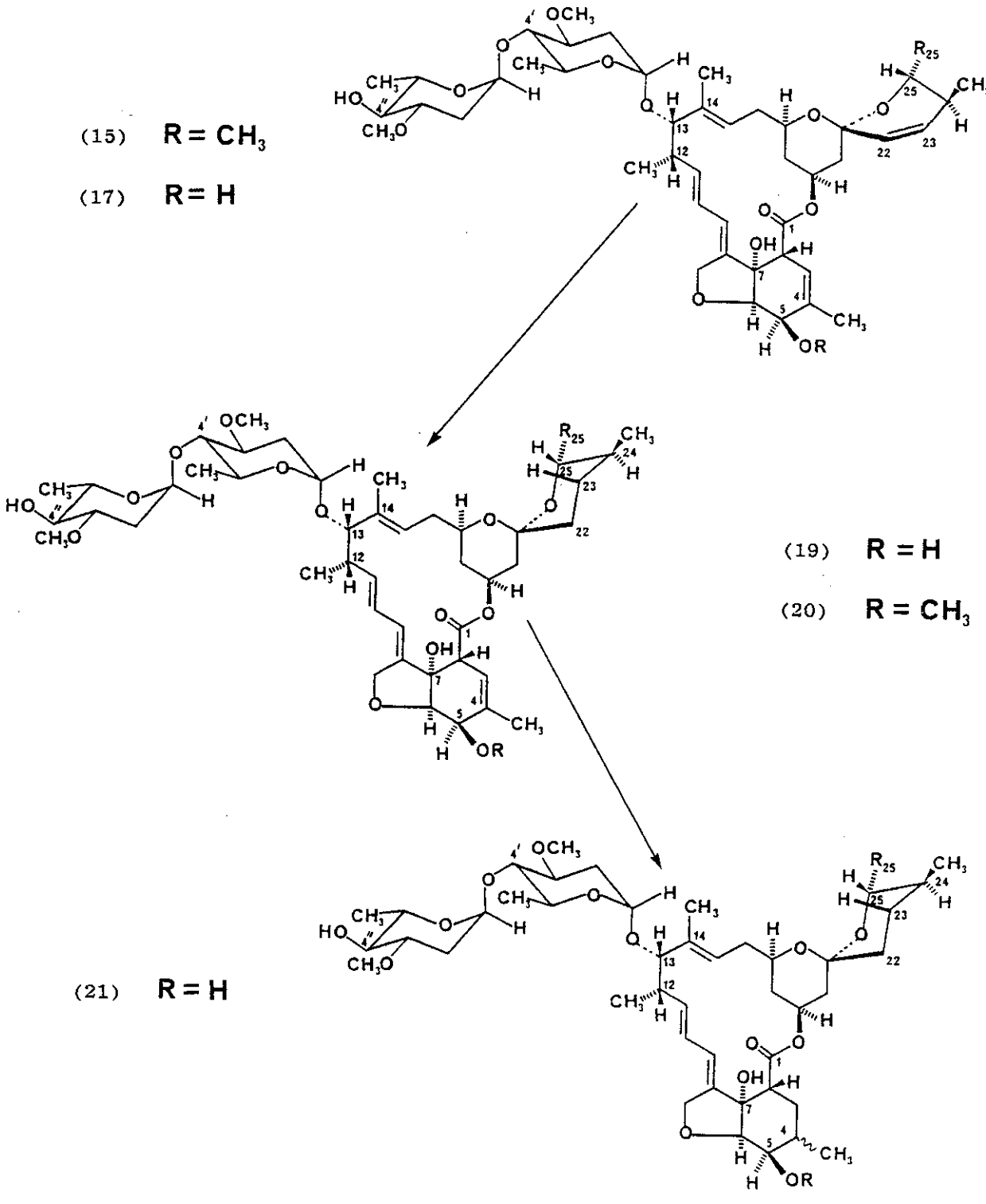
(14) $R_{4''} = R_5 = H$, $R_{23} = OH$.

Scheme 1

This peculiar differential efficacy was also found to apply to *Haemonchus placei* of cattle.[22] Further testing revealed that although avermectin B_1 (17) is more active than avermectin B_2 (18) upon oral administration, the converse is true when each is administered parenterally.[21,23]

Compounds of the avermectin 1 series possess an olefinic linkage between *C*-22 and *C*-23 while in the avermectin 2 series this linkage is hydrated.[7] Models have shown that this difference has a profound effect on the conformation of the spiro-acetal system which in turn causes subtle changes in bioactivity.[21] In their search for compounds with the conformation of the 2 series, but lacking the 23-hydroxyl substituent, the Merck scientists prepared the 22,23-dihydro analogues of the avermectin 1 series.[21] Thus, hydrogenation of avermectin B_1 (17) using chlorotris(triphenylphosphine)rhodium(I) (Wilkinson's) catalyst, provided 22,23-dihydroavermectin B_1 (19) (85%) together with 3,4,22,23-tetrahydroavermectin B_1 (21) (3%) (Scheme 2). Similar treatment of avermectin A_1 (15) provided 22,23-dihydroavermectin A_1 (20) (92%). All compounds were found to have broad spectrum activity (TABLE 4) but, in general, compounds of the B series (those containing a 5-hydroxy group) were found to be more potent than those of the A series (with a 5-methoxy group). Saturation of the 22,23-olefin had only a small effect on activity, while reduction of both the 3,4- and 22,23-olefins to form (21) considerably lowered activity. Sequential removal of the L-oleandrosyl moieties resulted in the expected lowering of anthelmintic activity.

In their search for biologically active analogues, the Merck scientists investigated the effect of selective acylation on the



a series $R_{25} = CH(CH_3)C_2H_5$

b series $R_{25} = CH(CH_3)_2$

Scheme 2

TABLE 4

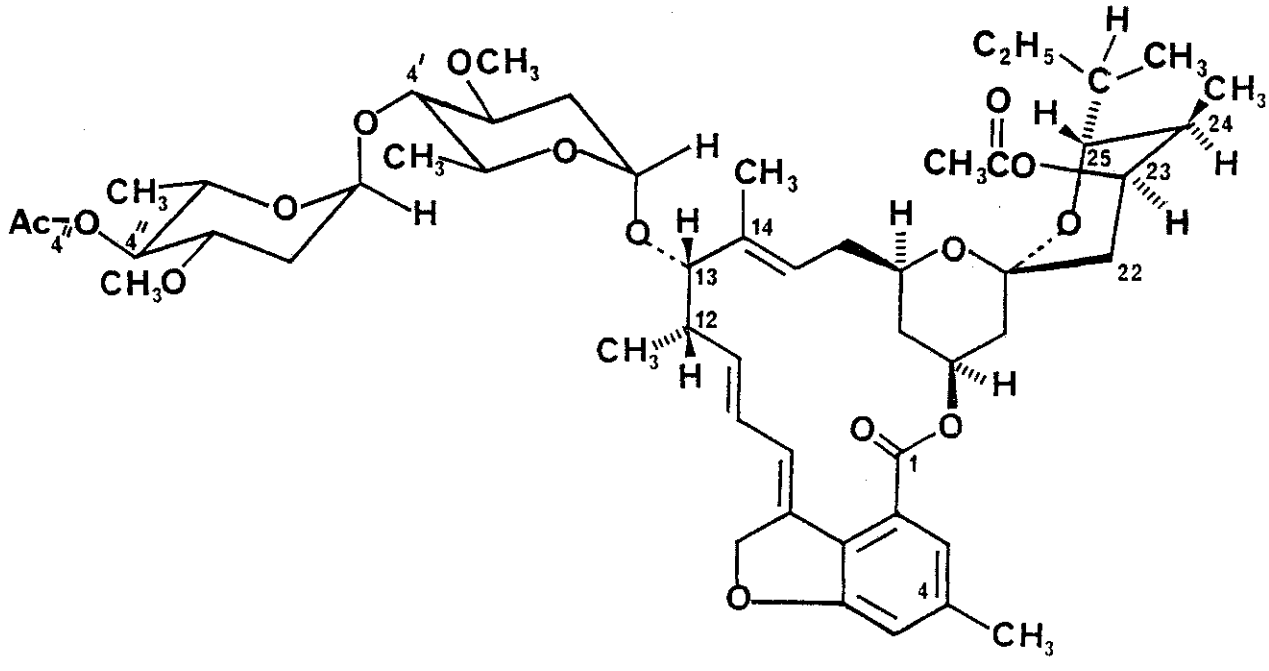
Activity of Avermectin Derivatives against Adult Gastrointestinal Helminths of Experimentally Infected Sheep on Oral Administration.

COMPOUND	structure[b]	dose, mg/kg	*efficacy*[a]					
			H.c.[c]	*O.c.*	*T.a.*	*T.c.*[c]	*C.spp.*	*O.c.*
15	A_1	0.1	2	2	0	0	2	0
16	A_2	0.1	3	3	3	3	0	3
17	B_1	0.05	3	3	3	3	3	3
18	B_2	0.1	0	3	3	3	3	3
22	H_2A_1	0.3	3	2	0	1	0	3
23	H_2B_1	0.1	3	3	3	3	3	3
24	B_1MS	0.15	2	2	3	3	3	0
25	B_2MS	0.2	1	1	3	3	3	3
26	H_2B_1MS	0.3	3	3	3	3	2	3
27	H_2B_1AG	3.0	1	2	3	3	1	3
28	H_4B_1	0.2	0	0	1	0	0	3

[a] 0 = <50%, 1 = 50-74%, 2 = 75-90%, 3 = >90% efficacy. Abbreviations used: *H.c., Harmonchus contortus; O.c., Ostertagio circumcinta; T.a., Trichostrongylus axei; T.c., Trichostrongylus colubriformis; C.spp., Cooperia spp; O.c., Oesophagostomum columbianum.*

[b] MS = monosaccharide, AG = aglycon, H_2 = 22,23-dihydro derivative, H_4 = 3,4,22,23-tetrahydro derivative. [c] Benzimidazole resistant.

anthelmintic activity of these polyhydroxy compounds (TABLE 5).[23] Notably, under forcing acetylation conditions the inactive aromatic diacetate (29) was generated from both avermectins A_{2a} (3) and B_{2a} (7).

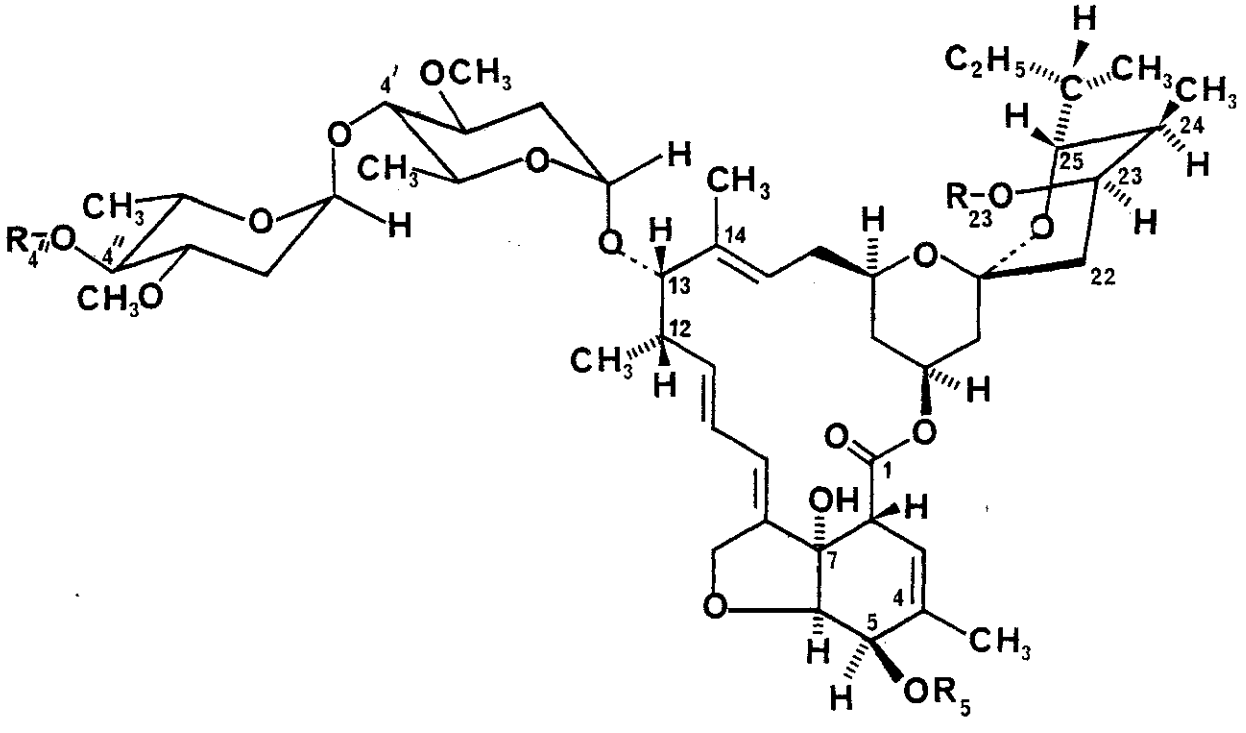


(29)

Preliminary tests of the acetyl derivatives against gastrointestinal nematode infections in sheep[25] indicated that the 4″-*O*-acetates, especially 4″-*O*-acetylavermectin B_{1a} (34) had the highest potency and widest spectrum of the analogues. Subsequently, the synthesis of a number of 4″-*O*-acylated derivatives of avermectin B_{1a} (6) was undertaken (TABLE 6). From the results of the biological assay[24] it appears

TABLE 5

Derivatives of Avermectin A_{2a} (3) and B_{2a} (7) and Anthelmintic Activity against *Trichostrongylus colubriformis* in Gerbils[a]



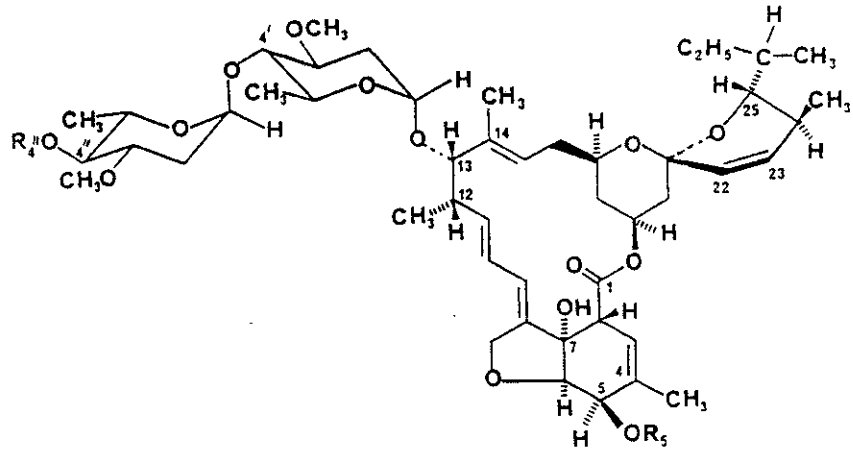
no.	$R_{4''}$	R_5	R_{23}	anthelmintic act.[b,c]
3	H	CH_3	H	0·05
7	H	H	H	0·0125
30	CH_3CO	CH_3	H	0·06
31	H	CH_3	CH_3CO	0·25
32	CH_3CO	CH_3	CH_3CO	0·5
33	CH_3CO	CH_3CO	CH_3CO	0·5

[a] Reference (24), [b] Minimal doses (mg/kg) needed to remove >83% of the worm burden.

[c] Compound 29: anthelmintic activity >2·5.

TABLE 6

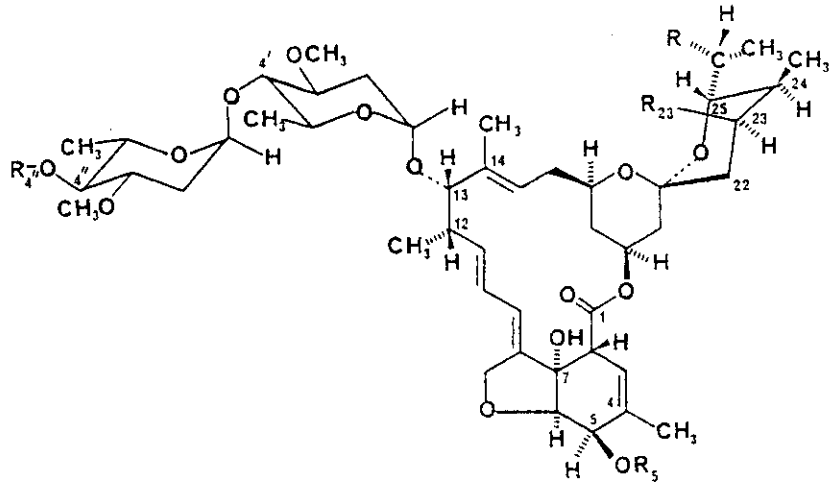
Derivatives of Avermectin B_{1a} and Anthelmintic Activity against *Trichostrongylus colubriformis* in Gerbils[a]



no.	$R_{4''}$	R_5	anthelmintic act.[b]
6	H	H	0.025
34	CH_3CO	H	0.031
35	H	CH_3CO	0.125
36	CH_3CO	CH_3CO	0.25
37	H	$Si(CH_3)_2C(CH_3)_3$	>2.5
38	$Si(CH_3)_2C(CH_3)_3$	$Si(CH_3)_2C(CH_3)_3$	>2.5
39	$(CH_3)_3CCO$	$Si(CH_3)_2C(CH_3)_3$	
40	$(CH_3)_3CCO$	H	0.5
41	$CH_3(CH_2)_6CO$	$Si(CH_3)_2C(CH_3)_3$	
42	$CH_3(CH_2)_6CO$	H	0.125
43	$CCl_3CH_2OOCCH_2CH_2CO$	$Si(CH_3)_2C(CH_3)_3$	
44	$CCl_3CH_2OOCCH_2CH_2CO$	H	
45	$HOOCCH_2CH_2CO$	H	0.03
46	$(4\text{-}NO_2C_6H_4O)CO$	$Si(CH_3)_2C(CH_3)_3$	
47	H_2NCO	$Si(CH_3)_2C(CH_3)_3$	
48	H_2NCO	H	0.025
49	$(CH_3)_2NCO$	$Si(CH_3)_2C(CH_3)_3$	
50	$(CH_3)_2NCO$	H	0.06
51	$CH_3CONHCH_2CO$	$Si(CH_3)_2C(CH_3)_3$	
52	$CH_3CONHCH_2CO$	H	0.025

[a] Reference (24), [b] Minimal doses (mg/kg) needed to remove >83% of the worm burden.

that, although acylation of the 5- or 23-hydroxy group results in a loss of anthelmintic activity, a free 4″-hydroxy group is not necessary for high potency. In particular, the 5-hydroxy group is essential, as shown by the lower activity of the natural product (3) which has a 5-methoxy substituent, and the total loss of activity in the cases of the 5-*O*-t-butyldimethylsilyl derivatives (37 and 38) and the aromatic analogue (29). This result is in agreement with the observation that chemical manipulation of the southern hemisphere of the milbemycins leads to a drastic reduction in their biological activity.[48] No advantage over the natural products was shown by any of the acylated derivatives. Eventually, 22,23-dihydroavermectin B_1 (19)[21] (consisting of at least 80% 22,23-dihydroavermectin B_{1a} (53) and not more than 20% 22,23-dihydroavermectin B_{1b} (54)) was selected as a new anthelmintic agent on the basis of its overall efficacy by oral and parenteral routes in sheep[25] and cattle,[26] and for its better safety profile. The mixture was assigned the non-proprietary name "ivermectin".



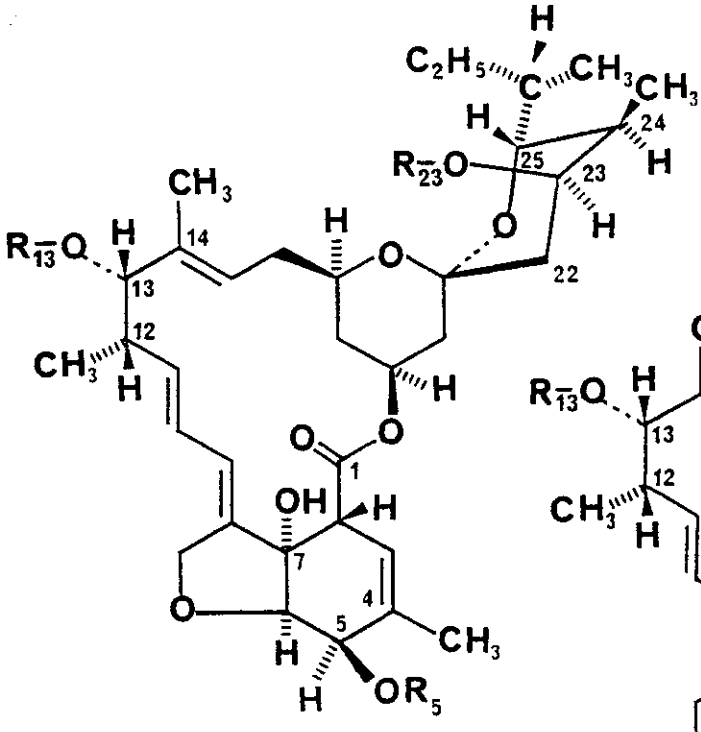
(53) R = Et, $R_{4''}$ = R_5 = H, R_{23} = H

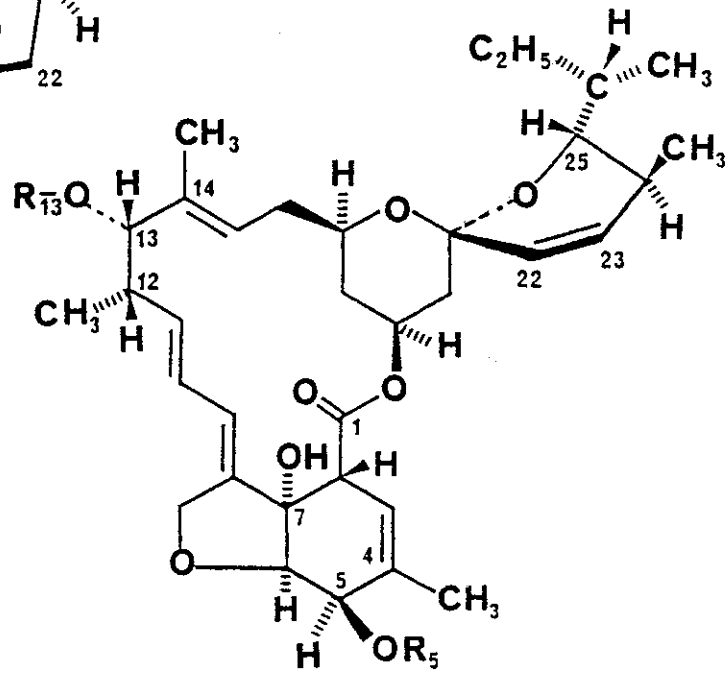
(54) R = Me, $R_{4''}$ = R_5 = H, R_{23} = H

Mrozik *et al.*[27] have since shown that both avermectin B_{1a} (6) and ivermectin (53) are readily available from avermectin B_{2a} (7) *via* the thermal *cis*-elimination of the *C*-23 hydroxy group.

As previously described the avermectins are structurally closely related to the milbemycins,[8] a group of macrolides lacking the *C*-13 hydroxy group and its disaccharide substituent. The aglycons of the avermectins A_{2a}, B_{2a}, and B_{1a} were prepared[28,29] in order to assess their biological activities and to utilize them as intermediates in the synthesis of 13-deoxyavermectin aglycons[30] for comparison with the milbemycins (TABLE 7). Reaction of avermectin A_{2a} (3) and B_{2a} (7) with methanol containing 1% concentrated sulphuric acid gave the corresponding aglycons (56 and 10); alcoholysis of the avermectins (3 and 7) in 2-propanol containing 1% concentrated sulphuric acid gave the monosaccharides (57) and (62). Acid-catalysed methanolysis of avermectin B_{1a} (6), however, gave a mixture of the aglycon (59) and the two epimeric 22,23-dihydro-23-methoxyaglycons (60 and 61). Hydrolysis of avermectin B_{1a} (6) in aqueous tetrahydrofuran containing 10% concentrated sulphuric acid gave a separable mixture of the monosaccharide (62) and the aglycon (59). The results of the biological assay of these compounds are yet to be published.

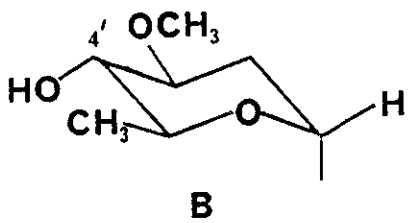
Prior to the discovery of the avermectins, Mishima and his co-workers[8] found that the metabolite produced in submerged cultures of the *Streptomyces B-41-146* strain was active against acarus, harmful agricultural and horticultural insects such as aphids and larvae of insects of the order *Lepidoptera*.[33] Notably, the metabolite showed no phytotoxicity towards many varieties of crops at effective dosages. The *Streptomyces* was found to be a new subspecies and was



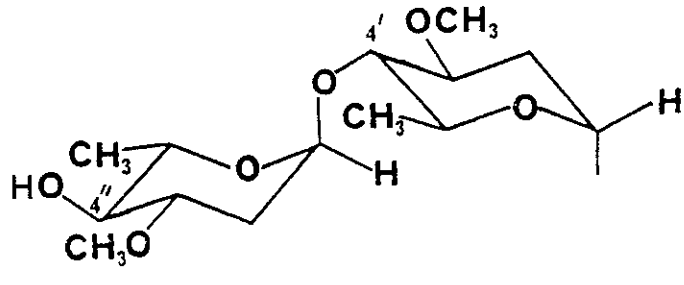


	R_5	R_{13}	R_{23}
3	CH_3	A	H
7	H	A	H
10	H	H	H
56	CH_3	H	H
57	CH_3	B	H
60	H	H	CH_3
62	H	B	H

	R_5	R_{13}
6	H	A
58	H	B
59	H	H



B



A

TABLE 7

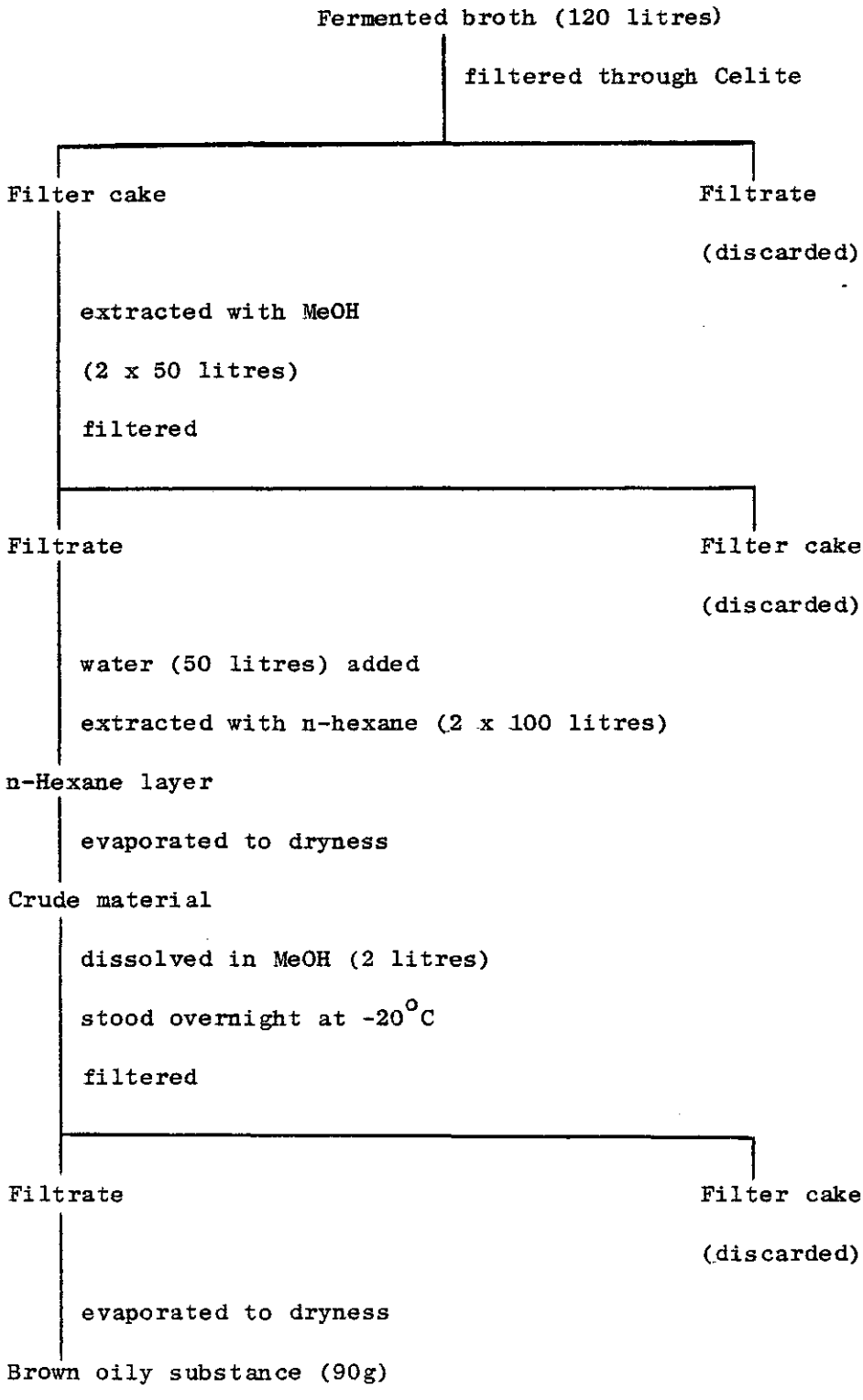
designated *Streptomyces hygroscopicus* subspecies *aureolacrimosus*. Subsequently, the metabolite was identified to be a mixture of thirteen macrolides, designated the "milbemycins", which were isolated from the culture broth and purified to homogeneity by column and thin-layer chromatography on silica-gel and alumina (Schemes 3 and 4).

Structure determination using n.m.r., i.r. and mass spectral analysis revealed the milbemycins to be 16-membered macrolides containing the spiro-acetal moiety. Ten of these compounds (milbemycins α_1 to α_{10}) were found to contain a tetrahydrofuran ring as a common structural component[34] (TABLE 8). Milbemycins β_1 (73), β_2 (74) and β_3 (75) were shown to have a similar macrocyclic structure[35] (TABLE 9). The crystallographic x-ray analysis of the *p*-bromophenylurethane derivative of milbemycin β_1 was used to define the absolute stereochemistry of the series.

The milbemycins, initially believed to consist of only 9 components (A_1, A_2, A_3, A_4, B_1, B_2, B_3, C_1, and C_2) (TABLES 8 and 9), were patented collectively as antibiotic B-41 by the Sankyo Company of Japan.[36]

In their search for biologically active analogues the Sankyo workers prepared a series of 13-hydroxymilbemycins.[37] Thus, allylic bromination of the milbemycins afforded the corresponding 13-bromo compounds (76) which were subsequently converted to the 13-hydroxymilbemycins (78) *via* hydrolysis of the acyl derivatives (77) (Scheme 5). The stereochemistry at the *C*-13 centre was undefined. The 13-hydroxymilbemycins were found to have significant parasiticidal activity as anthelmintics, insecticides, and acaricides, in human and animal health and in agriculture. Details of their full spectrum of

Extraction and Isolation of Milbemycins.



Scheme 3

Scheme 4

Separation of Milbemycins

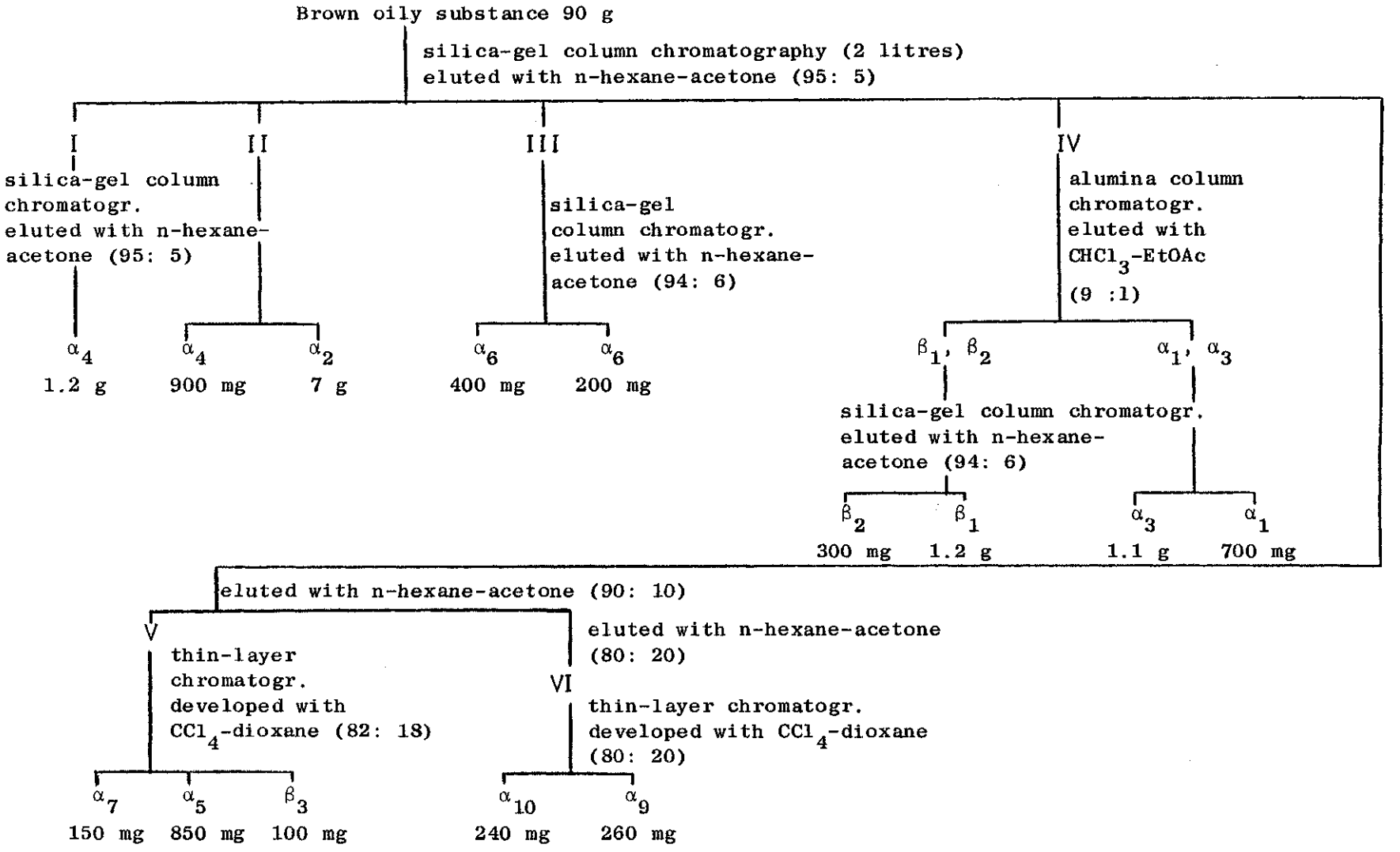
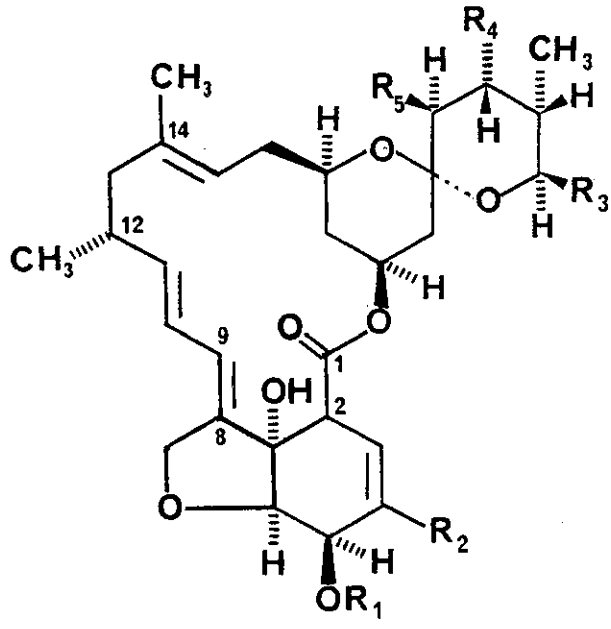


TABLE 8



Structures of Milbemycins.

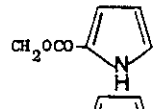
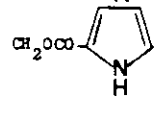
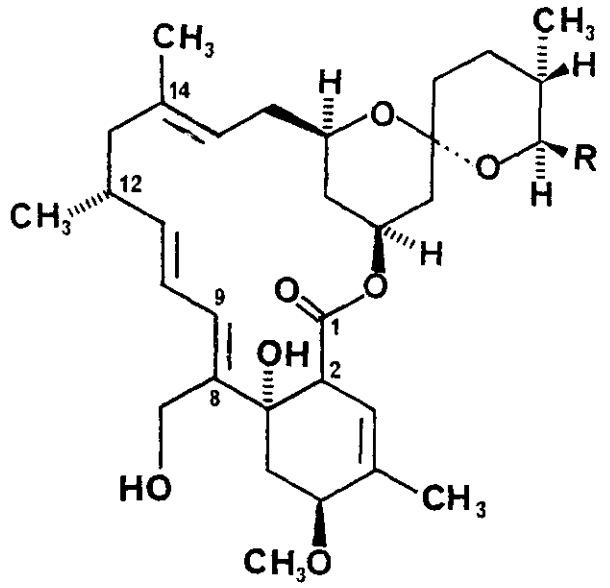
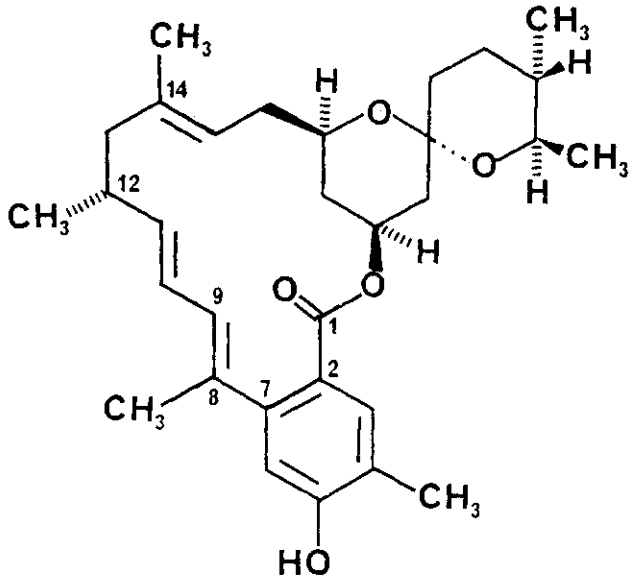
	Milbemycins (B-41)	R_1	R_2	R_3	R_4	R_5
63	α_1 (A_3)	OH	Me	Me	H	H
64	α_2 (B_2)	OMe	Me	Me	H	H
65	α_3 (A_4)	OH	Me	Et	H	H
66	α_4 (B_3)	OMe	Me	Et	H	H
67	α_5 (A_2)	OH	Me	Me	$OCOCH(CH_3)(CH_2)_3CH_3$	OH
68	α_6 (B_1)	OMe	Me	Me	$OCOCH(CH_3)(CH_2)_3CH_3$	OH
69	α_7	OH	Me	Et	$OCOCH(CH_3)(CH_2)_3CH_3$	OH
70	α_8	OMe	Me	Et	$OCOCH(CH_3)(CH_2)_3CH_3$	OH
71	α_9 (C_1)	OH		Me	H	H
72	α_{10} (C_2)	OH		Et	H	H

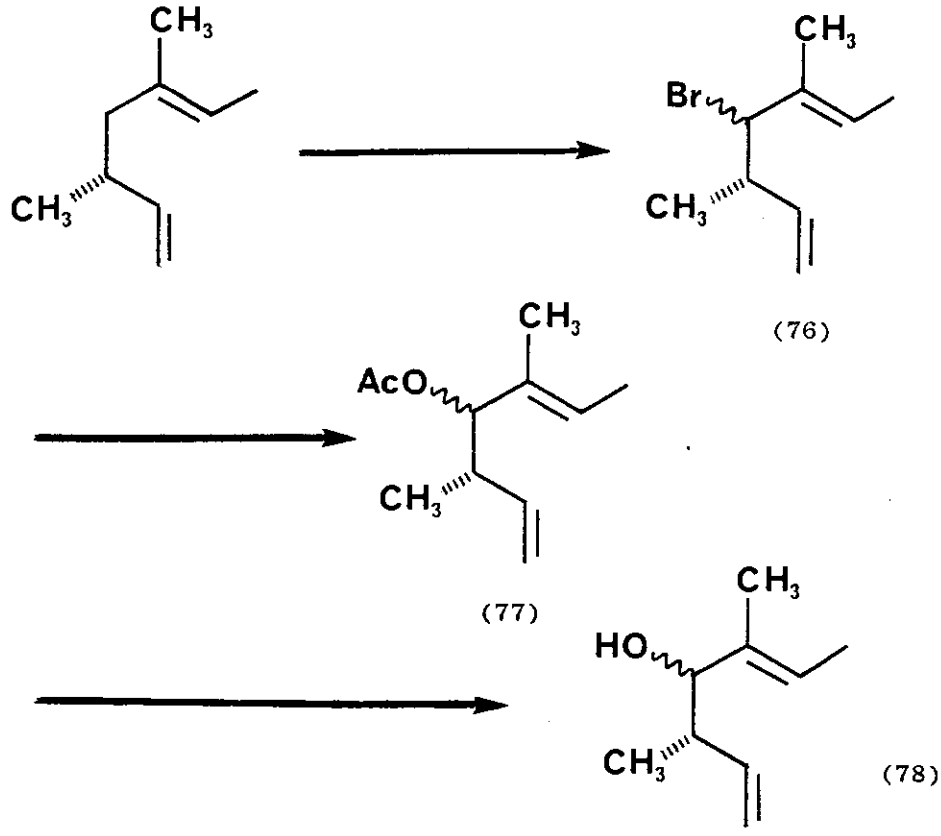
TABLE 9



			R
(73)	β_1	(A_1)	CH_3
(74)	β_2		C_2H_5



(75) β_3



Scheme 5

biological activity are given.[37]

Subsequently, carbohydrate derivatives of both the milbemycins and the 13-hydroxymilbemycins were prepared and their biological activity assessed.[38] Substitution of one or more of the free hydroxyl groups found in these molecules by a glycosyl group gave a series of compounds showing activity as anti-parasitic agents. The nature of the sugar moiety was found not to be critical; any sugars could be substituted onto the milbemycin substrates using known procedures.[38] Where there was more than one position bearing a reactive hydroxyl group selective substitution was obtained by careful ordering of the

reaction steps. The preferred sugar substituents were found to be mono- or disaccharides of glucopyranosyl, rhamnopyranosyl, oleandrosyl or daunosaminosyl sugars although the highest efficacy was noted for the glucopyranosyl and oleandrosyl derivatives (*cf.* the avermectins). The activity of compounds derived from sugars of both the D- and L-configuration were investigated.

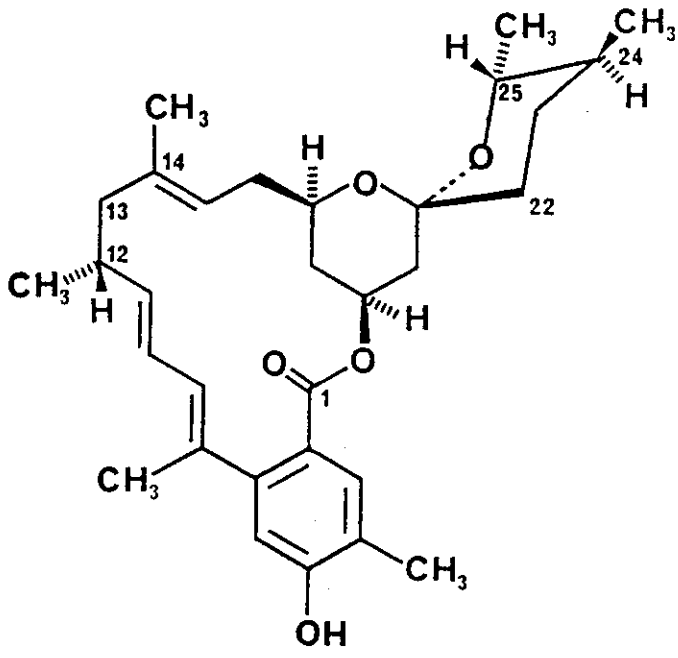
TOTAL SYNTHESIS OF MILBEMYCIN β_3

Total Synthesis of Milbemycin β_3

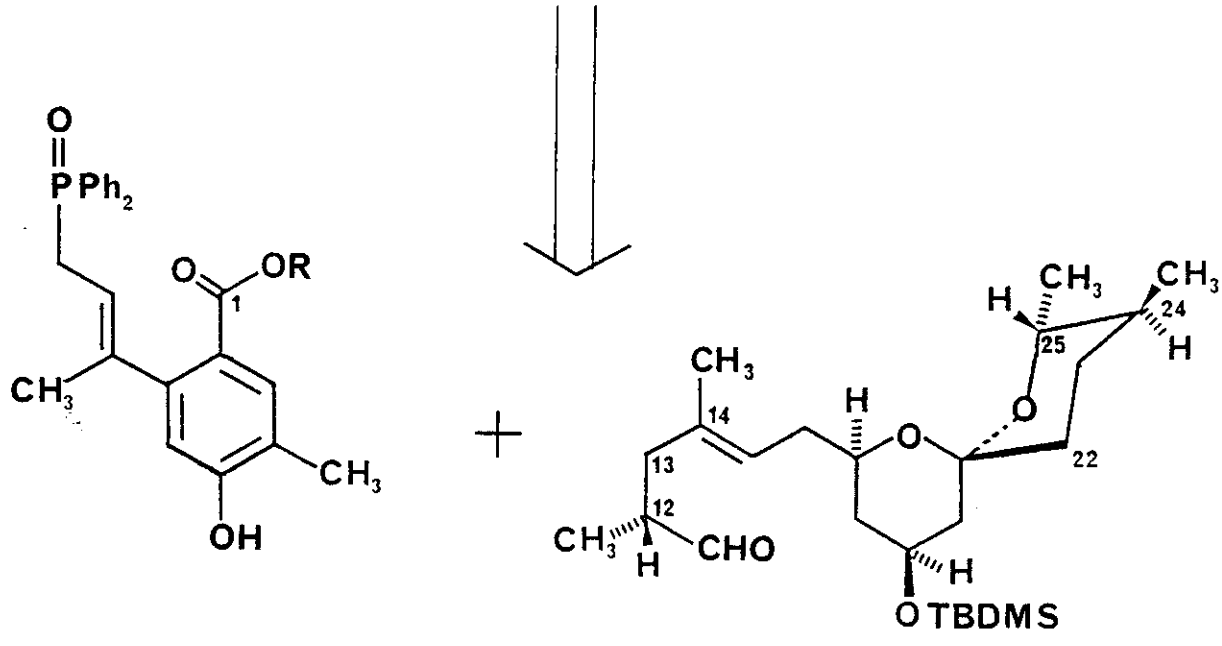
Within the last year two syntheses of the previously unsynthesized milbemycin β_3 molecule have been completed. The first synthesis, completed by Smith *et al.*,[39] employed a 16-step synthetic pathway to produce a racemic product; although slightly longer, the route of Williams and his co-workers[40] led to intermediates and a final product which were optically active. The overall synthetic approaches devised by the two competing research teams were generally similar, though they differed markedly in the details of synthetic pathways and intermediates. Conceptually, the target molecule was split into two or three major components, which were synthesized separately. These components were then assembled into the final product.

The approach taken by Smith's group was largely stereocontrolled though the goal was not to produce an optically pure product. The milbemycin β_3 molecule (75) was divided, at the diene and ester linkage, into two major fragments (Scheme 6); a "southern hemisphere" (80) containing the benzoic acid derivative (*C*-1 to *C*-10), and a "northern hemisphere" (79) containing the spiro-acetal and an aldehyde side chain (*C*-11 to *C*-25). Union of the two units was to take place *via* a Horner-Wittig coupling[41] followed by macrocyclic lactonization.[42]

Synthesis of the aromatic southern hemisphere (80) utilized a novel S_N2' displacement employing lithium diphenylphosphide[43] on the lactone (84), the latter prepared in seven steps from 3-methyl-*p*-anisic acid (81) in 33% overall yield (Scheme 7). Although the S_N2' reaction of the lactone (84) produced a separable 3:1 mixture of isomeric phoshine oxides (86 and 85, respectively), treatment with strong base afforded a more favourable 1:2 ratio of *Z* and *E* isomers. Treatment

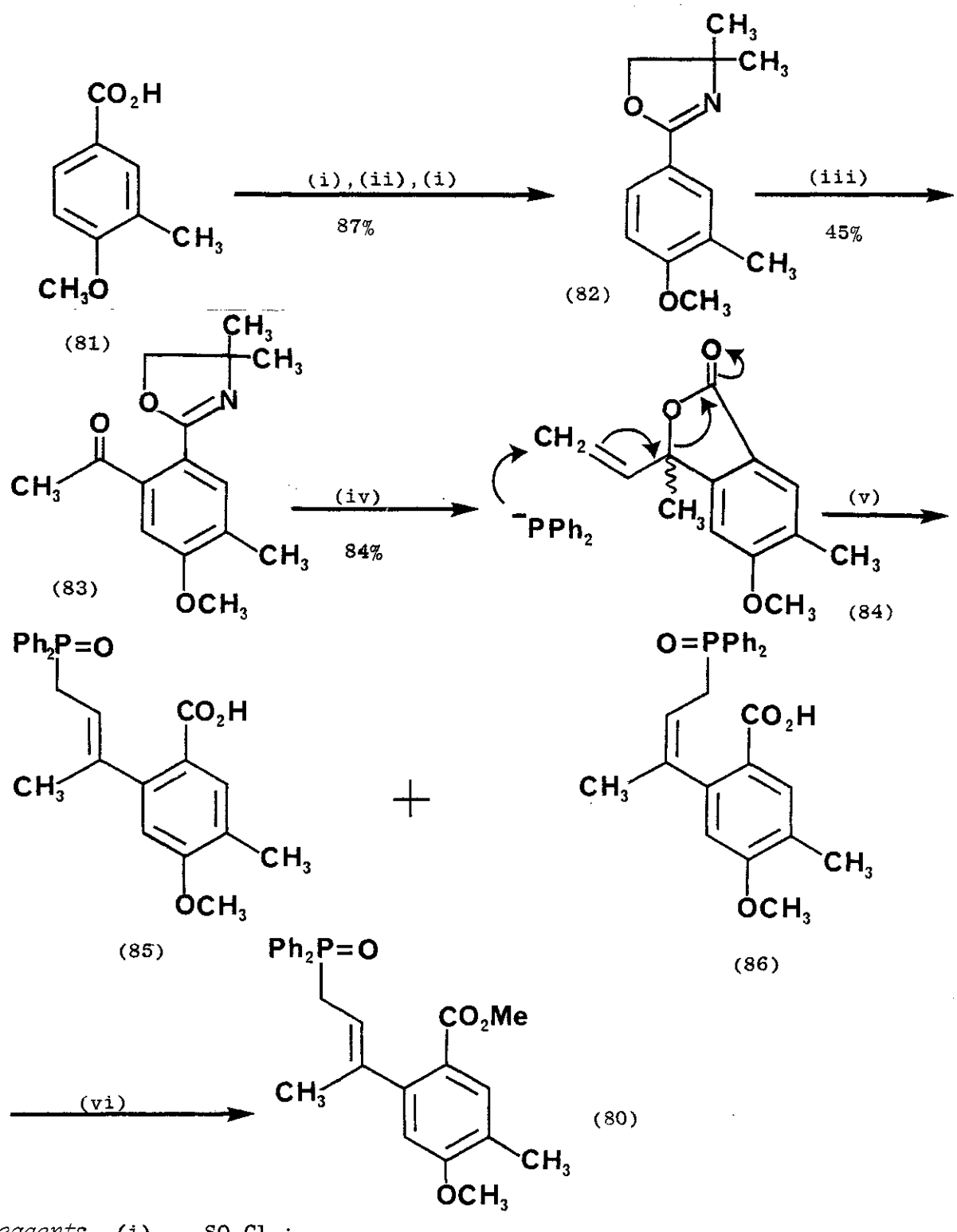


(75)



(80) (79)

Scheme 6



Reagents (i) SO_2Cl_2;

(ii) 2-amino-2-methyl-1-propanol/CH_2Cl_2;

(iii) a) *sec*-BuLi/0°C, 4 h, b) Ac_2O/-78°C;

(iv) a) CH_2=CHMgBr, b) 3M H_2SO_4/THF/25°C, 12 h;

(v) a) $LiPPh_2$ in THF/-22°→ 25°C, 3 h, b) [O] air;

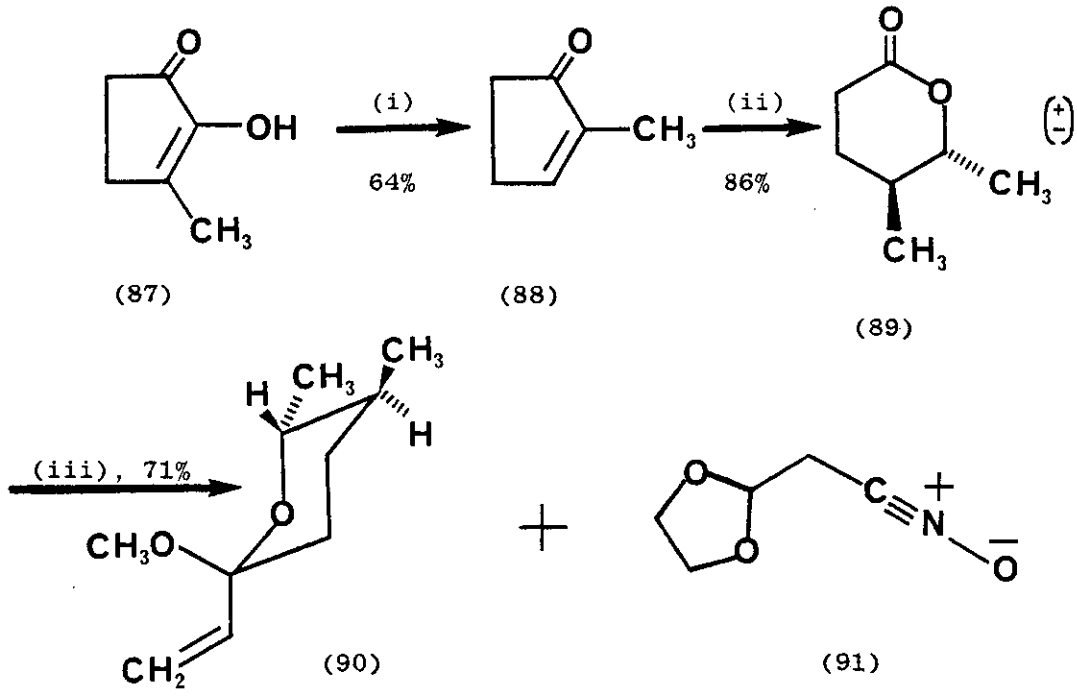
(vi) CH_2N_2.

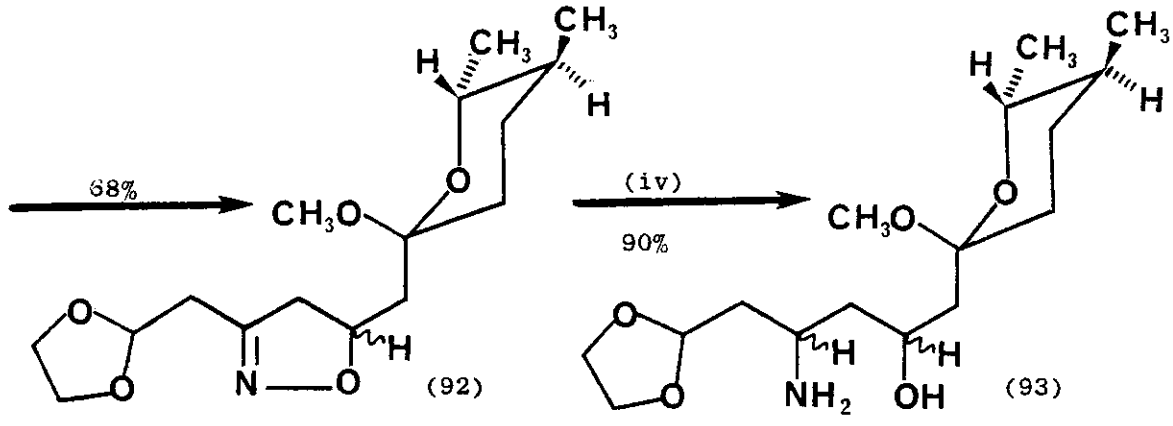
Scheme 7

of the separated phosphine oxide (85) with ethereal diazomethane then afforded the aromatic southern hemisphere.

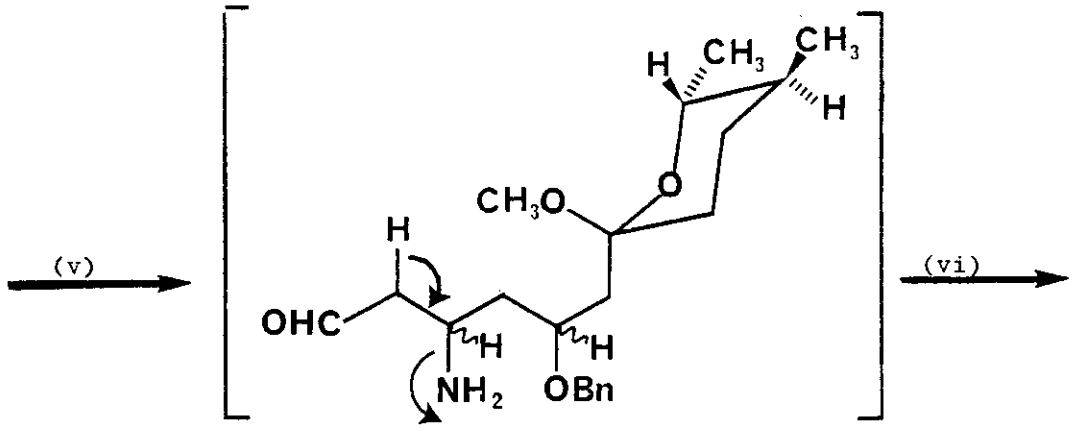
Smith's team experimented with building the spiro-acetal functionality from chiral citronellol (117), Williams' method.[40] Although this route has since been pursued[44] the initial synthesis was completed using a racemic approach beginning with cyclotene (87) (Scheme 8). Reduction of the 2:1 mixture of isoxazoline (92), the product of 1,3-dipolar addition of the nitrile oxide (91) to the mixed methyl ketal (90), afforded the aminol (93) as the expected mixture of diastereoisomers. Fortunately for Smith, this mixture could be converted to a single crystalline aldehyde (97) in 20-25% yield from isoxazoline (92) (Scheme 8). Seebach *et al.*[45] have recently shown that the 1,4-Michael addition of oxygen nucleophiles to α,β-unsaturated aldehydes is a reversible process thus accounting for the formation of the thermodynamically more stable equatorial aldehyde (97). In turn, Smith[46] proposes that serious 1,3-diaxial interactions may prevent the epimer of the benzyl ether (96) from attaining the necessary transition-state conformation to permit facile cyclization. Competitive elimination of benzyl alcohol and subsequent decomposition of this epimer (96) is put forward to explain the observation of an uncharacterized polyunsaturated product.

The spiro-acetal unit (97) thus far constructed had a short aldehyde side chain that was subsequently lengthened using the highly stereoselective Ireland-Claisen rearrangement[47] (Scheme 9). In this regard, the aldehyde (97) was treated with an isopropenyl Grignard reagent and the resulting alkoxide acylated to afford a separable 2:1 mixture of the propanoates (100) and (99). Subsequent application of the Ireland-Claisen rearrangement to each propanoate (99 and 100) generated the epimerically distinct acids (101) and (102), *via* the corresponding

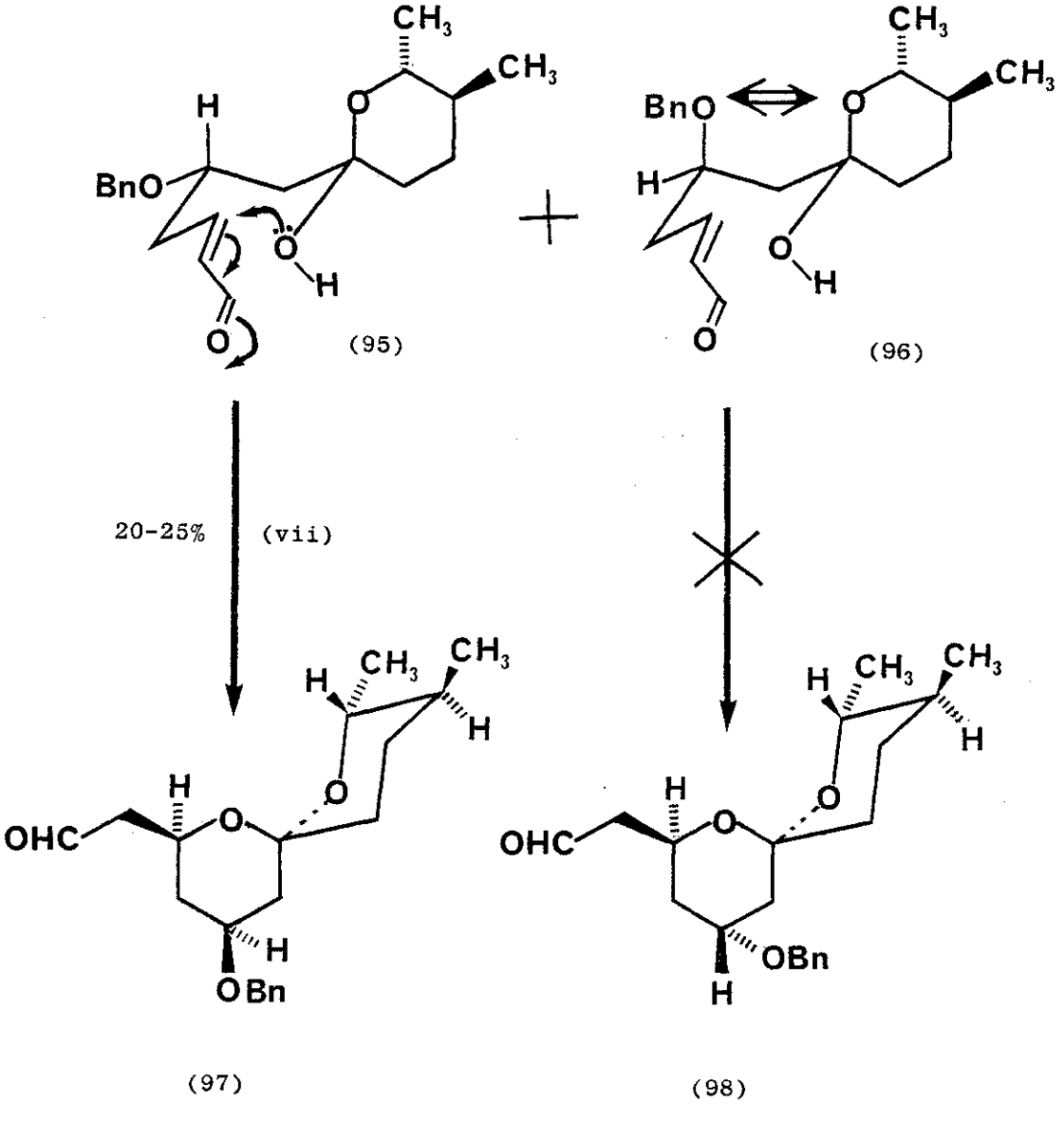




2:1 mixture of epimers



Scheme 8



Reagents (i) MeOH/HCl, LAH/Et_2O, H_2O;

(ii) Me_2CuLi/THF, HCl/Et_2O, m-CPBA;

(iii) CH_2=$CHCH_2MgBr$/THF, $CH(OMe)_3/CeCl_3 \cdot 7H_2O$;

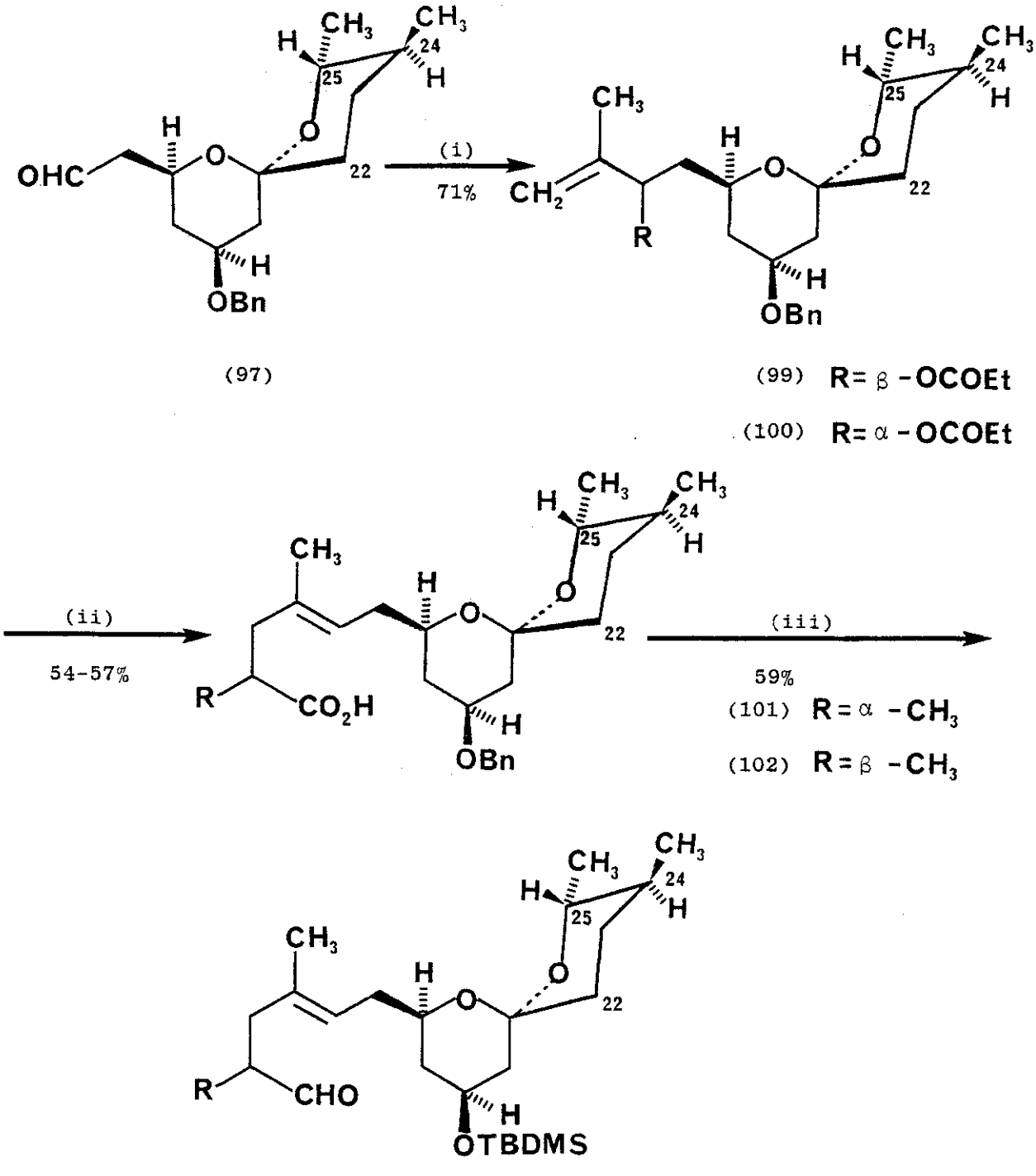
(iv) LAH/Et_2O;

(v) KH/$PhCH_2Cl$;

(vi) MeI;

(vii) TsOH/H_2O.

Scheme 8 cont.



Reagents (i) Isopropenyl Grignard/Et_2O, C_2H_5COCl

(ii) $KN(SiMe_3)_2$/TMS-Cl;

(iii) Li/liq. NH_3, TBDMS-Cl/DMF/imidazole/DMAP, LAH/Et_2O, Collins Oxidation.

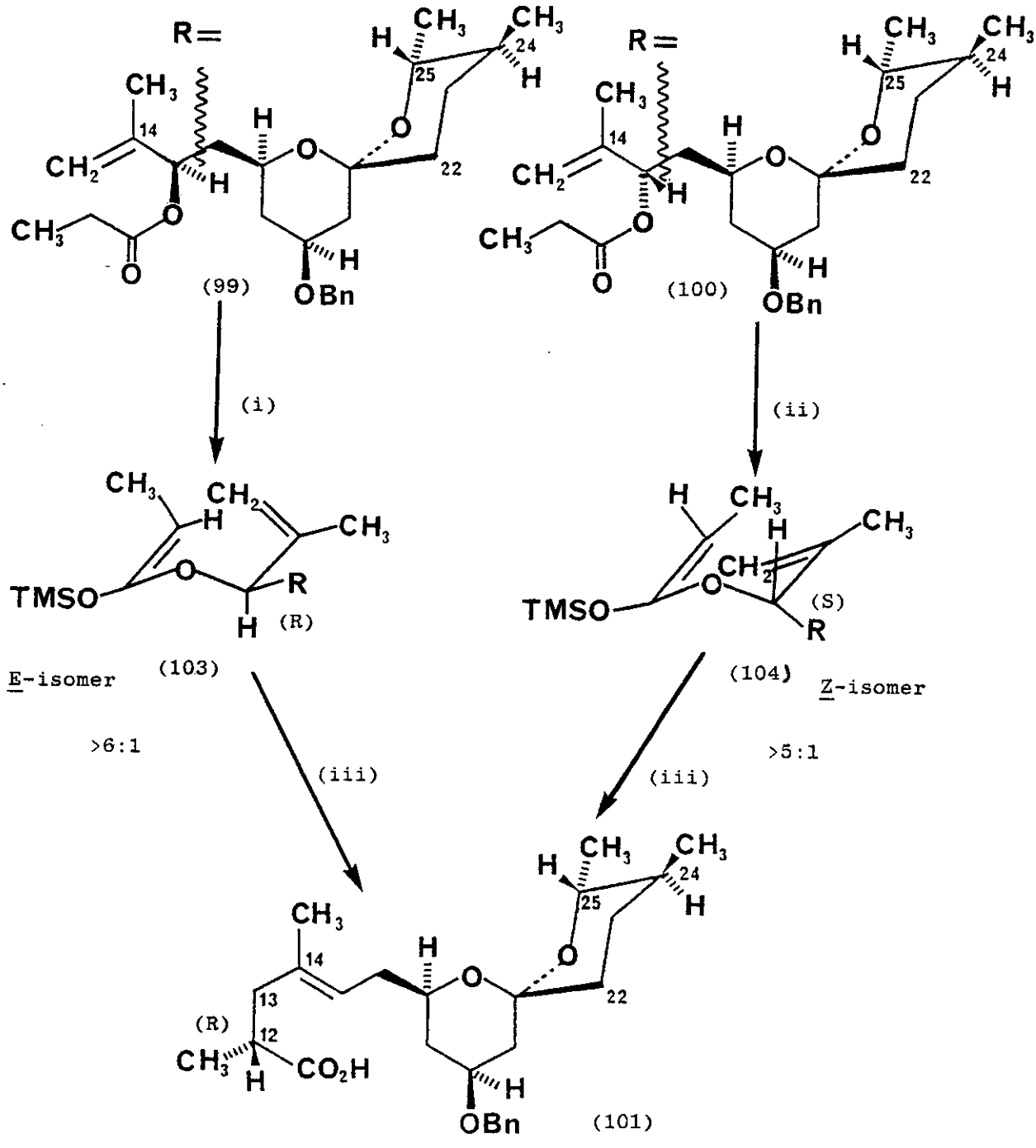
Scheme 9

E-enolates, with stereoselectivity in each case >6:1. Interestingly, no rearrangement was observed when the original Ireland-Claisen conditions[47] were employed. In their original synthesis, Smith and his co-workers[39] took both isomers (101 and 102) through to the final compound in order to establish, by spectral comparison with natural milbemycin β_3, the relative configurations of the two acids (101 and 102). Having confirmed the minor isomer (101) as that required for the synthesis of the natural product an unsuccessful attempt was made to increase the stereoselectivity of the Grignard reaction.[39,48] Fortunately, Smith found that the major propanoate (100) could be converted to the required acid (101) by modifying the conditions of the Ireland-Claisen rearrangement.[48] Thus, treatment of the propanoate (100) with LDA/DME/HMPA afforded the acid (101), *via* the *Z*-enolate, with a stereoselectivity of >5:1 (Scheme 10).

Finally, linkage of the northern and southern hemisphere, by the previously conceived method, afforded the macrolide ring (106) which was deprotected to give (±)-milbemycin β_3 (107). The epimeric acid (102) was in turn converted to (±)-epimilbemycin β_3 (108) (Scheme 11).

In the second of the syntheses[40] the Williams group assembled the milbemycin β_3 skeleton from three separate components; a substituted benzoic acid derivative (*C*-1 to *C*-8) (110), a carbon chain (*C*-9 to *C*-15) bearing a single chiral centre (*C*-12) (114), and a spiro-acetal moiety (*C*-16 to *C*-25) (130) (Schemes 15 and 16).

Conveniently, the two chiral fragments could be prepared from the same optically active starting material, the readily available terpene alcohol (-)-(3*S*)-citronellol (117). When considering their synthesis,

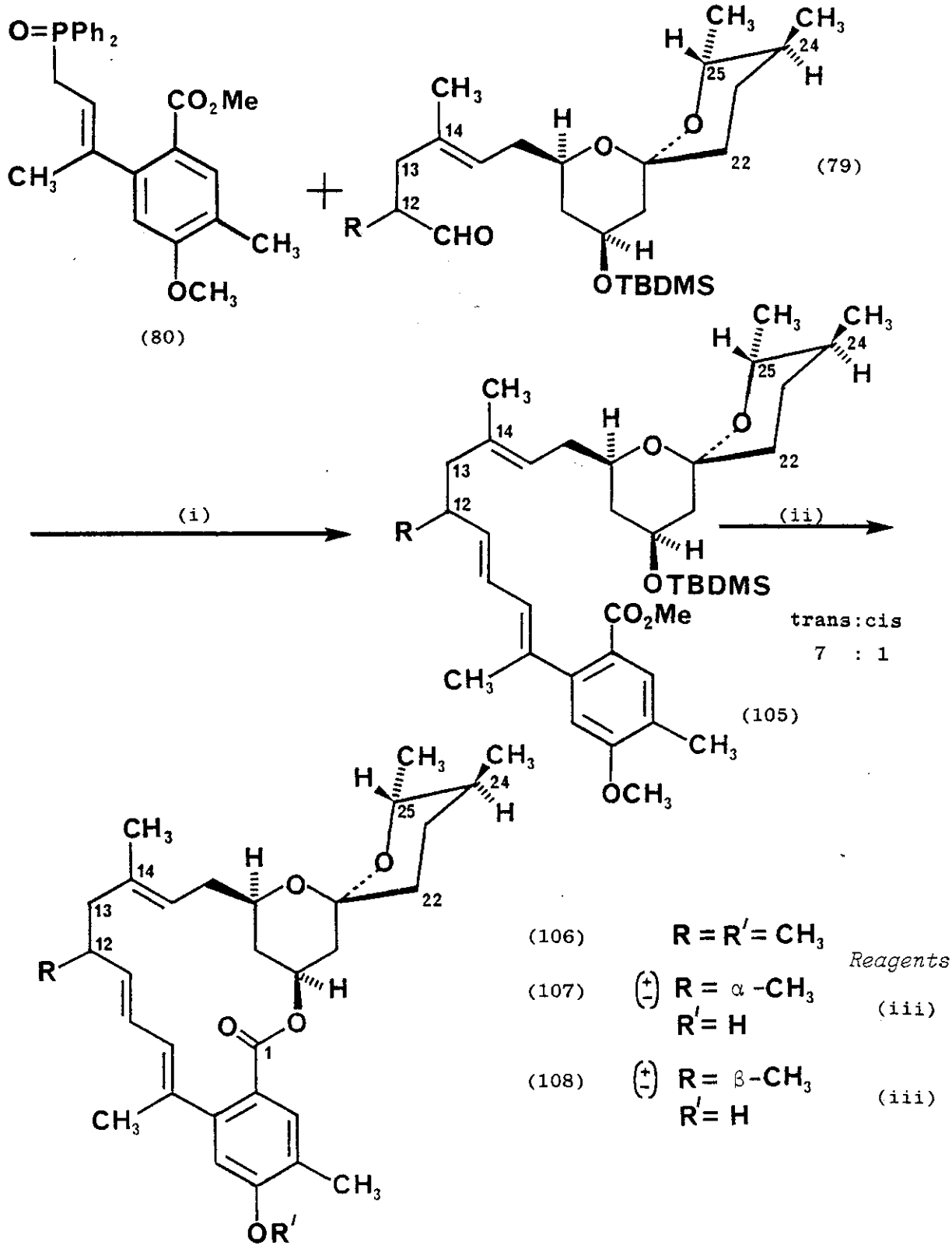


Reagents (i) $KN(SiMe_3)_2$/TMS-Cl;

(ii) LDA/DME/-78°C, HMPA/-78°C, TMS-Cl/-78°C, t-BuOH/-78°C;

(iii) -78° → 25°C.

Scheme 10



Reagents (i) $NaN(SiMe_3)_2$/THF;

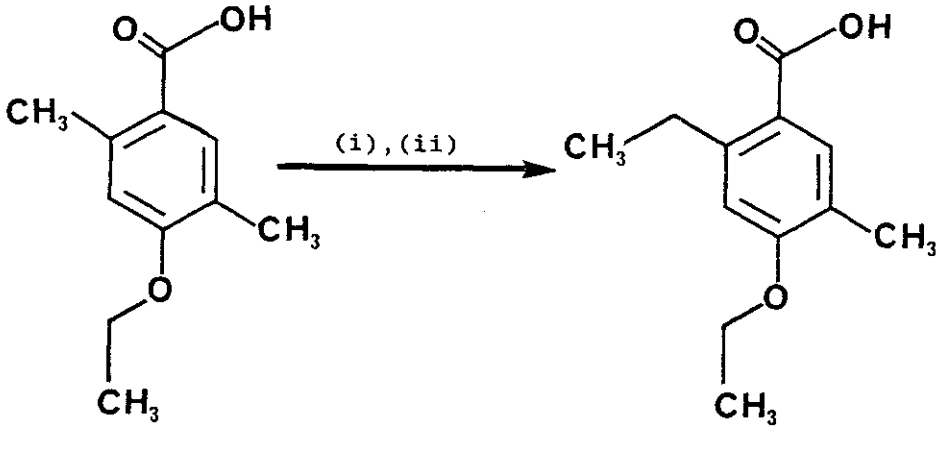
(ii) $(n\text{-}Bu)_4NF$, KH/THF;

(iii) NaSEt/DMF.

Scheme 11

the workers noted that the route avoided intermediates that might allow facile epimerization of established stereochemical features. Also, since molecular models seemed to indicate that both the *E*- and *Z*-configurations of carbon double bonds would afford 16-membered macrocycles much consideration was given to the method of construction of the olefin geometries.

The benzoic acid derivative (110) was conveniently prepared in 85% yield *via* methylation of the dianion of the aromatic acid (109) (Scheme 12).



(109) (110)

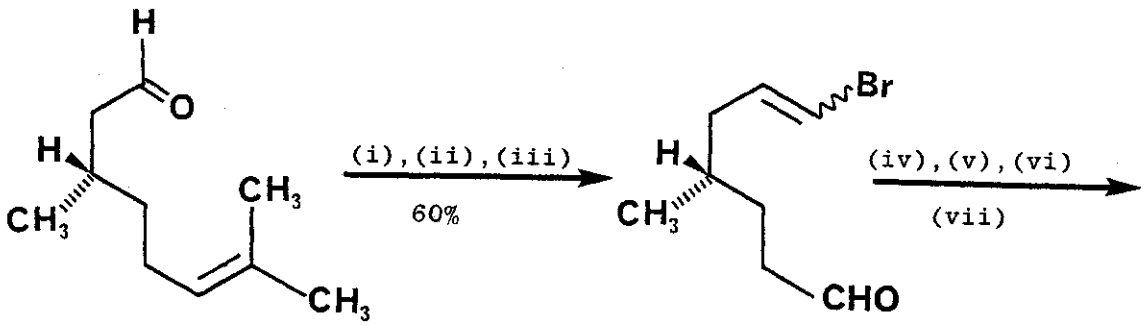
Reagents (i) NaH/THF, t-BuLi/-78°C;
(ii) Me_2SO_4/-78°→ -50°C.

Scheme 12

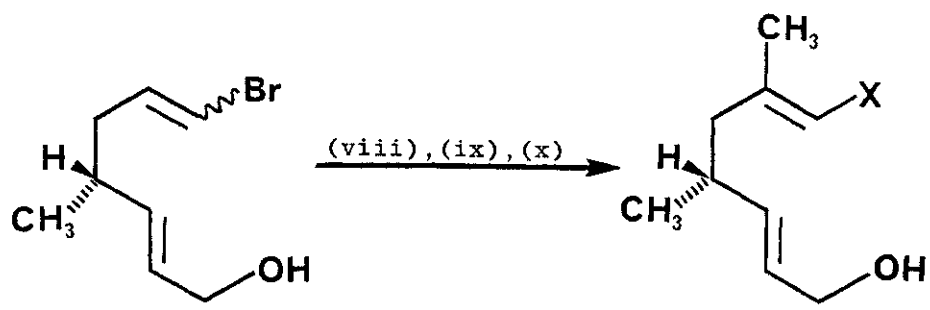
Construction of the chiral carbon chain (115) was completed in three steps from (-)-(3*S*)-citronellal (111) in 32% overall yield (Scheme 13). Formation of the trisubstituted alkene (114) in a stereospecific manner was best accomplished using the procedure described by Negishi and his co-workers.[49]

The chiral preparation of the spiro-acetal moiety (130) was successfully accomplished, *via* the lactone (119) obtained from (-)-(3*S*)-citronellol (117) in 40% overall yield (Scheme 14). Addition of the chiral α-lithiosulphinyl carbanion (120) to the lactone (119) led to the eventual isolation of the spiro-acetal (123). The stereochemistry of the spiro-junction was again that predicted from a consideration of the anomeric effect.[50,97] Additionally, epimerization occurred at the *C*-20 position to provide mainly the equatorial sulphoxide. Chlorohydrin formation from the derived alkene (124) proceeded rapidly to afford two separable products (125 and 126), in a 5:1 ratio. Thus, although the regio-control of this reaction was excellent the diaxial addition to the carbon double bond resulted in the formation of a major product (125) having the undesired configuration at the *C*-19 position. This stereochemical problem was resolved by inversion of the axial alcohol (127) *via* the stereospecific reduction of the ketone (129). The protected spiro-acetal (131) was subsequently transformed into two key intermediates; the aldehyde (133) and the bromide (132).

Initial attempts to link the spiro-acetal moiety (130) and the carbon chain unit (114), *via* alkylation of the vinyllithium reagent (135) with the bromide (132), were unsuccessful. The vinyllithium reagent (135) did however react with the aldehyde (133) to afford a



(111) (112)



(113) (114)

(115) X = I 71%

(116) X = Br

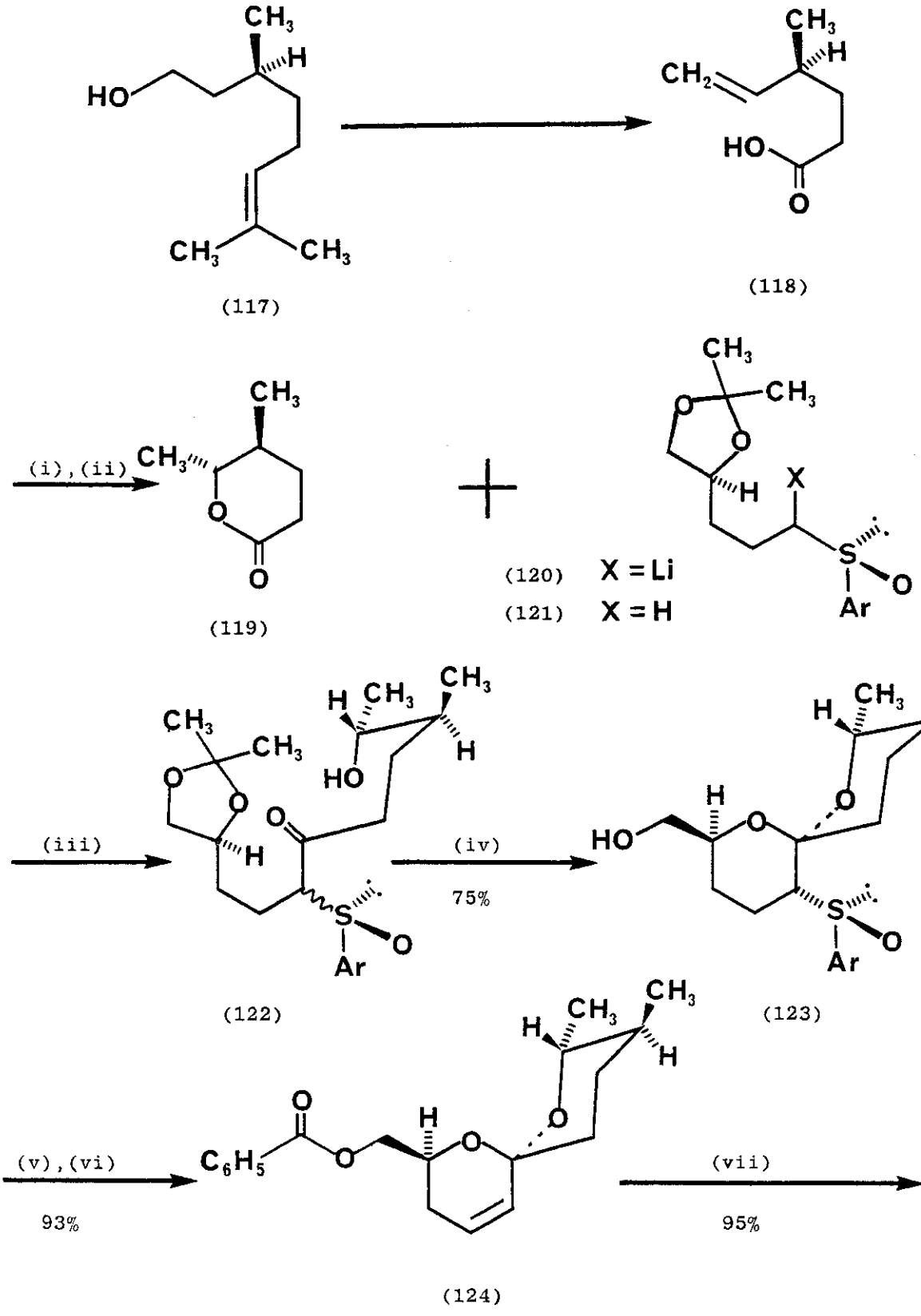
Reagents (i) $LiCHBr_2/-78^{\circ}C$; (ii) O_3; (iii) Zn/HOAc;

(iv) (v) $C_6H_5SeCl/-110^{\circ}C$;

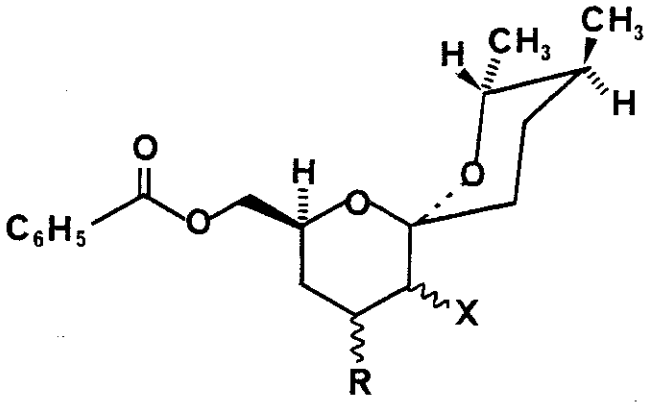
(vi) $LiAlH(O\text{-}t\text{-}Bu)_3$; (vii) m-CPBA; (viii) $MeLi/0^{\circ}C$;

(ix) $AlMe_3$, Cp_2ZrCl_2; (x) $I_2/THF/-30^{\circ}C$.

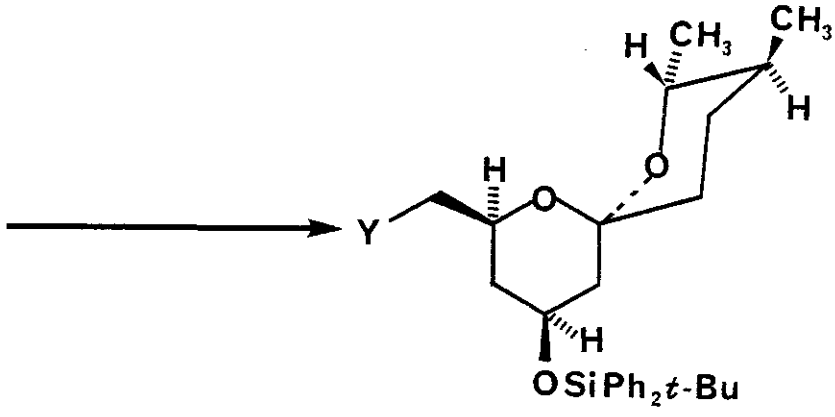
Scheme 13


CH3
H
HO
CH3
CH3
(117)
CH3
H
CH2
HO
O
(118)
(i),(ii)
CH3
CH3
O
O
(119)
CH3
CH3
O
O
H
X
S
O
Ar
(120) X = Li
(121) X = H
CH3
CH3
O
O
H
HO
CH3
H
O
(iii)
H
S
O
Ar
(122)
(iv)
75%
H
CH3
CH3
H
HO
O
O
S
O
Ar
(123)
(v),(vi)
93%
C6H5
O
O
H
O
H
CH3
CH3
H
O
(vii)
95%
(124)

Scheme 14



(125) R = α-OH ; X = β-Cl
(126) R = β-OH ; X = α-Cl
(127) R = α-OH ; X = H
(128) R = β-OH ; X = H
(129) R = O ; X = H



(130)

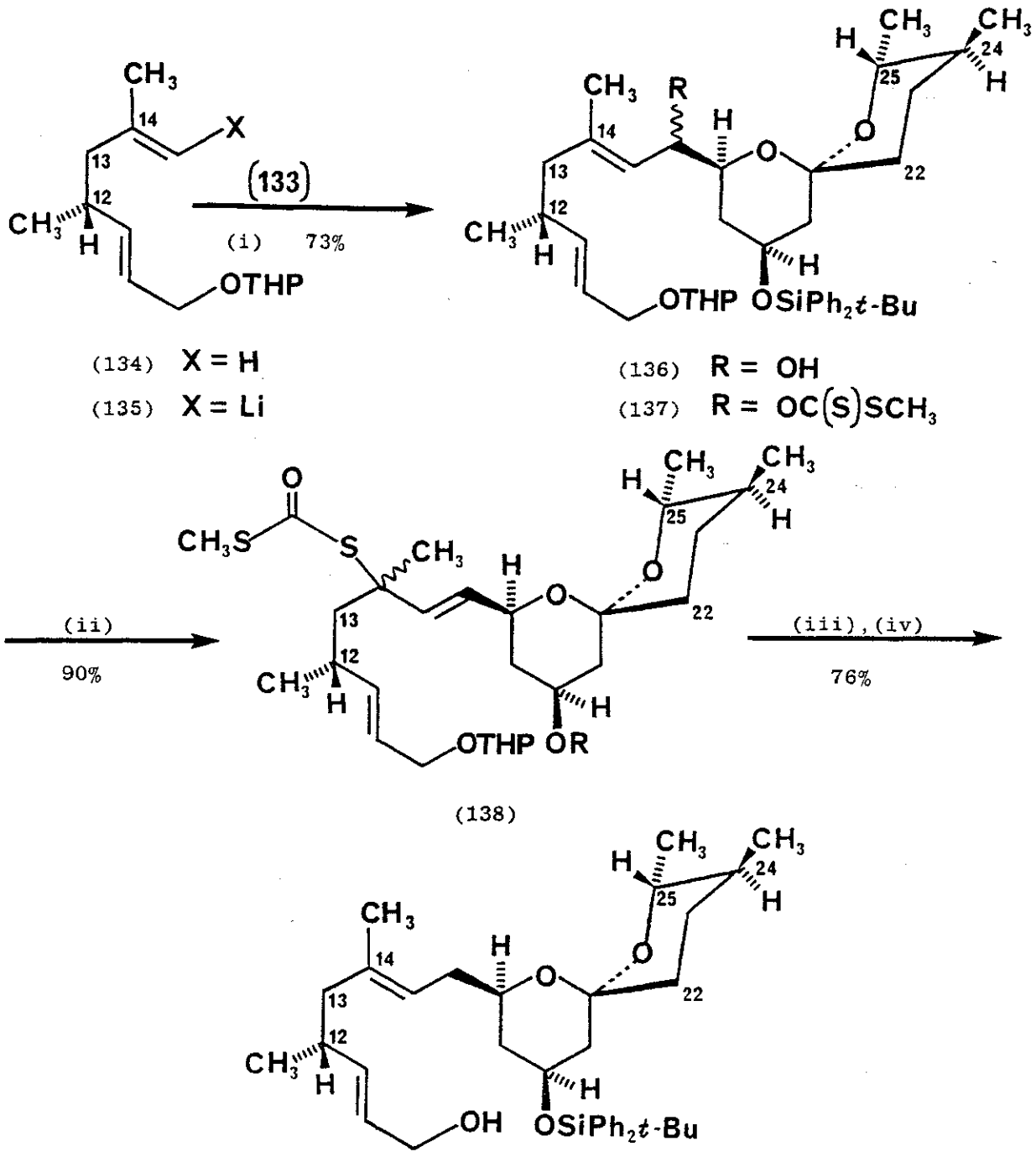
(131) Y = OH
(132) Y = Br
(133) Y = O

Reagents (i) I_2/CH_3CN;
(ii) $n\text{-}Bu_2SnH$;
(iii) LDA/THF/-78°C;
(iv) Cat. MsOH/H_2O/Benzene + 5°C;
(v) BzCl;
(vi) Toluene/$P(OMe)_3/\Delta$;
(vii) t-BuOCl, H_2O, Acetone.

Scheme 14 cont.

mixture of allylic alcohols (136). Removal of the extraneous hydroxyl group was eventually accomplished by S_N2' reduction of the dithiocarbonates (138), formed *via* the[3,3]-sigmatropic rearrangement of the xanthates (137) (Scheme 15).

Finally, addition of the dianion of the benzoic acid derivative (110) to the aldehyde (140) afforded a diastereomeric mixture of the 6-membered lactone (141) which was converted to (+)-milbemycin β_3 (75) in two steps (Scheme 16).



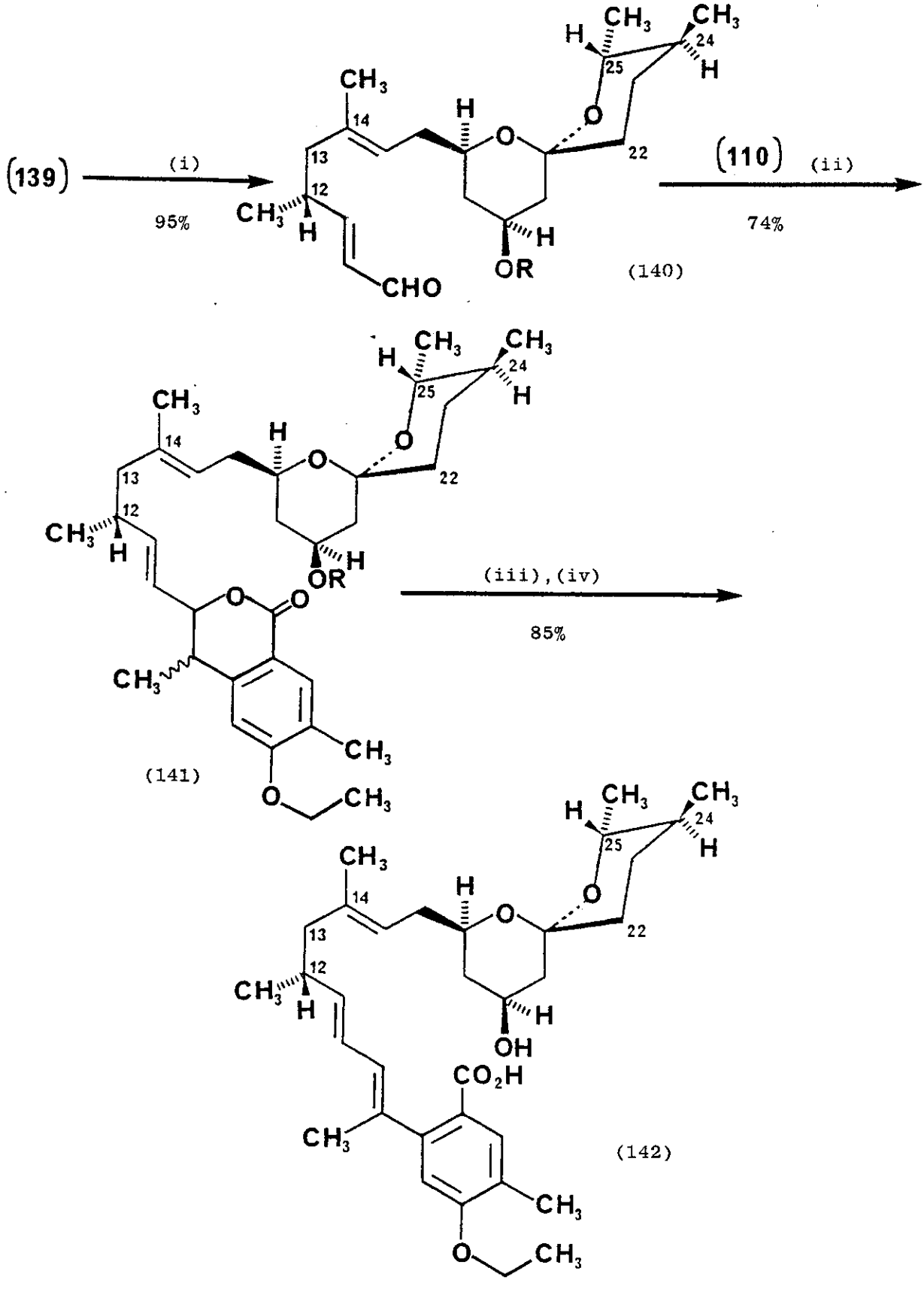
Reagents (i) t-BuLi/THF/-100°C;

(ii) CS_2/THF, NaH/CH_3I/55°C;

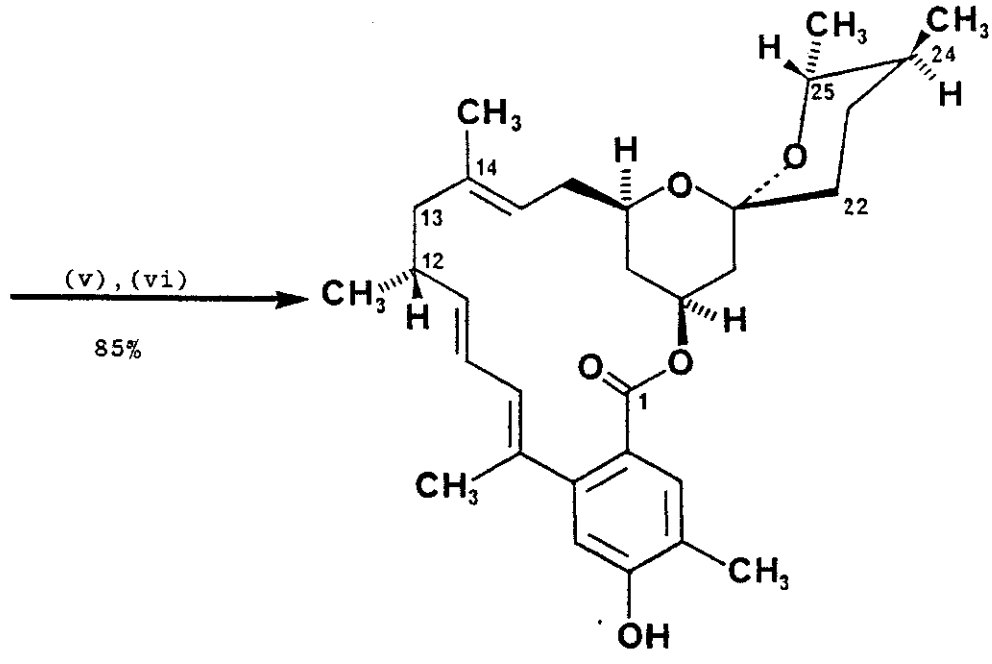
(iii) n-Bu_3SnH/80°C;

(iv) PPTS/MeOH.

Scheme 15



Scheme 16



(75)

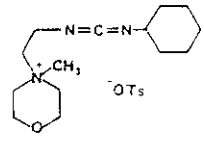
Reagents (i) Swern Oxidation;

(ii) NaH, THF, t-BuLi/-78°C;

(iii) $(n\text{-Bu})_4NF/40^{\circ}C$;

(iv) KH/THF/40°C;

(v)



(vi) NaI/acetone, cat. HCl/50°C.

Scheme 16 cont.

RESULTS AND DISCUSSION

INTRODUCTION

Since their recent discovery the avermectins and the structurally related milbemycins have, by virtue of their broad spectrum anthelmintic and antiparasitic activity and extreme potency, posed an important synthetic challenge to organic chemists. Prior to the commencement of this work none of these compounds had yielded to total synthesis. Our interest lay in studies towards the chiral synthesis of milbemycin β_3, the simplest member of the milbemycin family. This molecule has recently been synthesized by two independent groups.

Retrosynthetic analysis of the milbemycin β_3 molecule revealed a number of obvious strategic disconnections (Scheme 17) which led us to propose three major synthetic equivalents for the construction of the macrolide:-

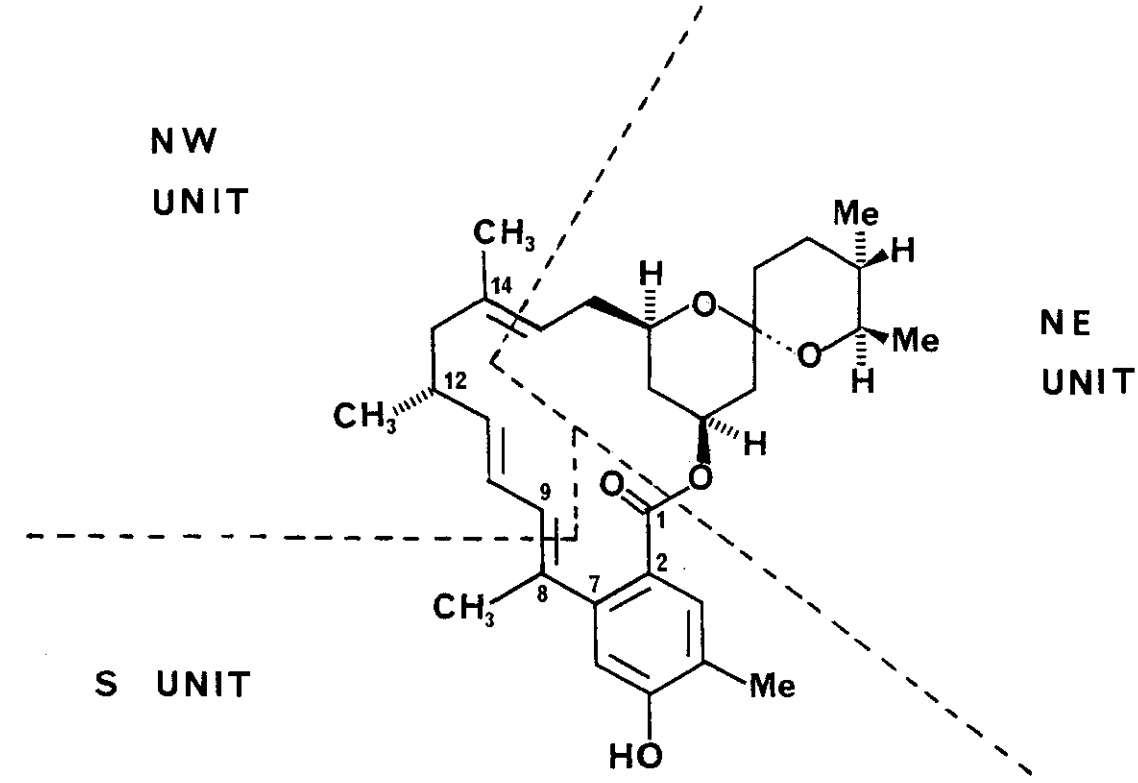
i) the aromatic southern (S) unit (143),

ii) the unsaturated north-western (NW) unit (144), and

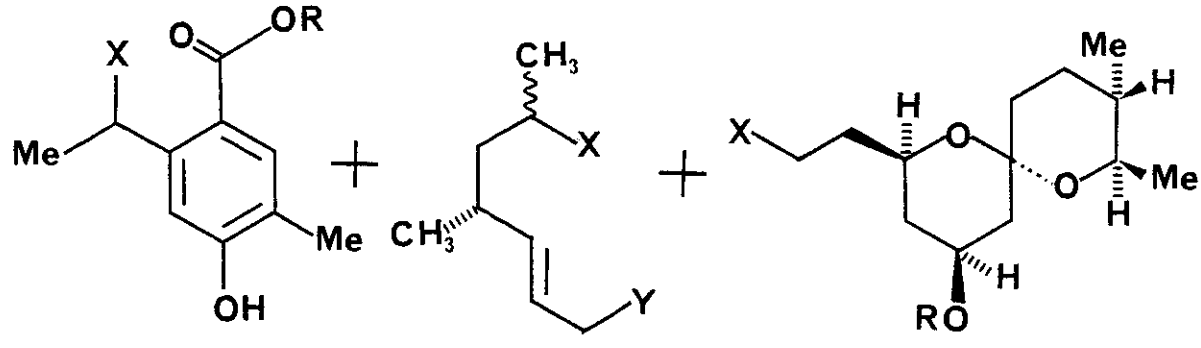
iii) the spiro-acetal north-eastern (NE) unit (145).

We envisaged that these three sub-units could be linked using the Julia[51] and / or Horner-Wittig[41] coupling reaction. The order of connection of these sub-units would be dependent on the outcome of later model reactions. One of the several well documented macrocyclic lactonization procedures[42] would then be used to complete the synthesis.

The synthesis of these three major units will be dealt with systematically and their linkage to form the milbemycin β_3 molecule discussed.



(75)

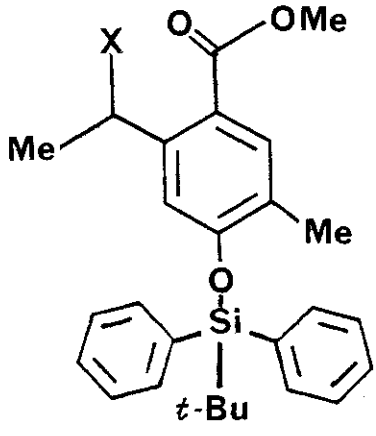


(143) (144) (145)

Scheme 17

i) The Aromatic Southern (S) Unit.

We envisaged that the aromatic southern (S) unit (143) of milbemycin β_3 should be a substituted benzoate ester of the type shown (146).



(147) X = O

(148) X = $S(O)_nPh$

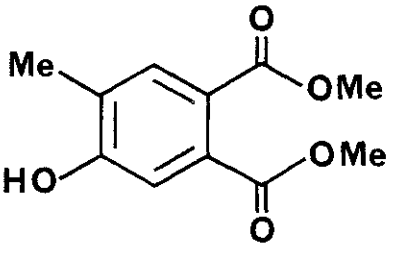
(149) X = $P(O)Ph_2$

(146)

This unit could be linked with the unsaturated north-western (NW) unit (144), to form the *C*-8 to *C*-9 double bond of the milbemycin β_3 molecule, in either an electrophilic or nucleophilic sense depending on the nature of group (X). Standard macrocyclic lactonization procedures[42] could be used to link the southern (S) unit (143) with the spiro-acetal moiety.

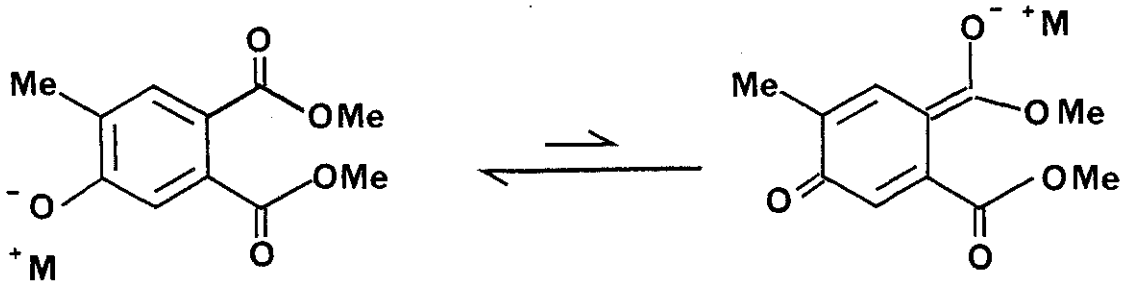
Our target molecule was to be the 2-acetylbenzoate ester (147) from which the other benzoate esters (148 and 149) would be available if required.

Danishefsky *et al.*[52] have conveniently prepared the dimethyl 4-hydroxy-5-methylphthalate (150) in good yield from dimethyl acetylenedicarboxylate (158) and the diene (157).



(150)

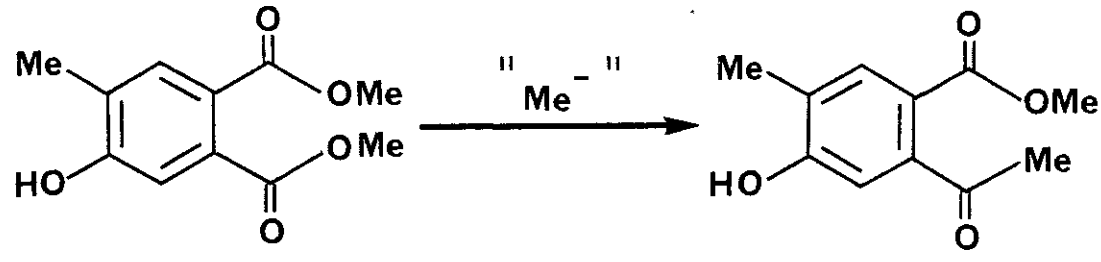
We reasoned that, due to the electron donating ability (R+) of the phenolic oxygen, the 1-methoxycarbonyl group of phthalate (150) would be less electrophilic, and thus less susceptible to nucleophilic attack, than the 2-methoxycarbonyl group. This differential reactivity would be greater in the case of the ionized phthalate (151) due to the contribution of the resonance form (152).



(151) (152)

Consequently, we initially believed that the 2-acetylbenzoate derivative (153) would be available *via* the nucleophilic attack of a suitable methylating agent at the more electrophilic 2-methoxycarbonyl group of

the phthalate derivative (150).

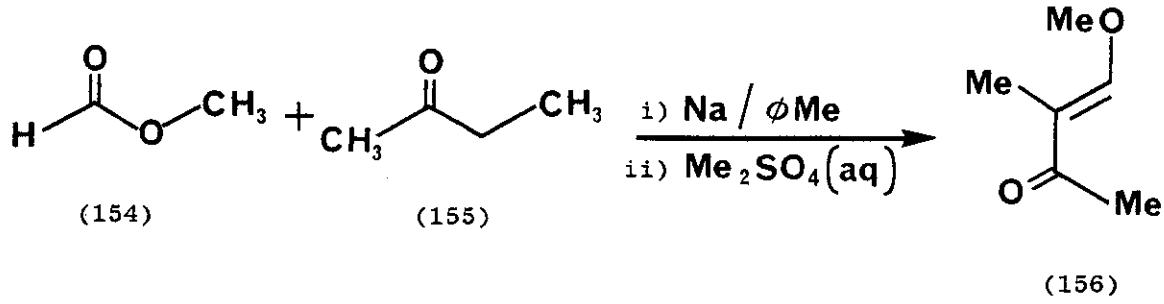


(150) (153)

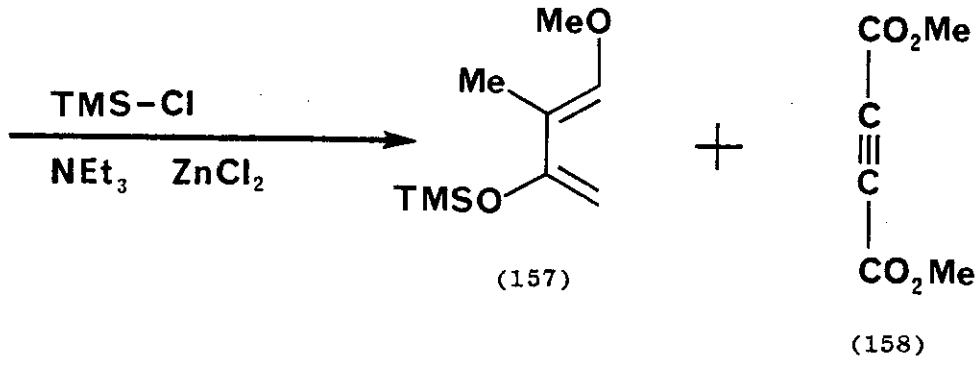
Scheme 18

Dimethyl 4-hydroxy-5-methylphthalate (150) was prepared according to the procedure of Danishefsky *et al.*[52] (Scheme 19). 1-Methoxy-2-methyl-1-buten-3-one (156) was prepared, in 22% yield, according to the modified procedure of Sugasawa *et al.*[53] Reaction of the methoxyenone (156) with chlorotrimethylsilane and triethylamine in the presence of anhydrous zinc chloride, according to Danishefsky's procedure,[52] afforded a mixture of the starting methoxy enone (156) and the required (*E*)-1-methoxy-2-methyl-3-trimethylsilyloxy-1,3-butadiene (157) (12:88). Using a modified work-up procedure the butadiene derivative (157) could be isolated as the sole product in 77% yield. The Diels-Alder reaction of the butadiene derivative (157) with dimethyl acetylenedicarboxylate (158), in dry benzene at the reflux, afforded the desired substituted dimethyl phthalate (150) (76 %). A slightly higher yield for this reaction (80%) was obtained when the hydrolytic work-up, as detailed in the literature,[52] was omitted and the crude material directly columned on silica.

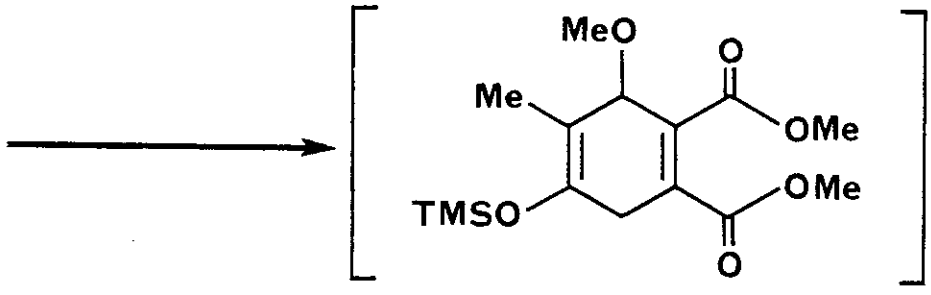
Initial attempts to prepare the benzoate (153) involved the addition of methyllithuim to the phthalate (150) in dry tetrahydrofuran (THF) at -78^{o}C. We hoped that, at sufficiently low temperature, the intermediate (159) would be slow to fragment affording

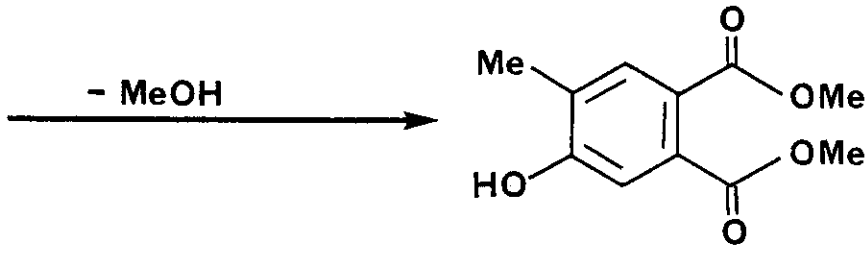


(154) (155) (156)



(157) (158)

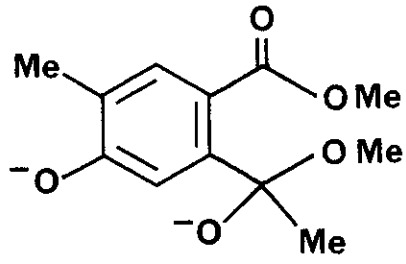




(150)

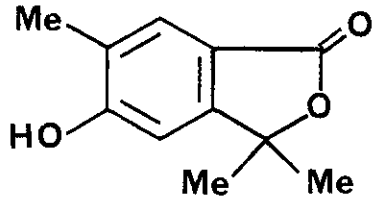
Scheme 19

the required product (153) only, on work-up.



(159)

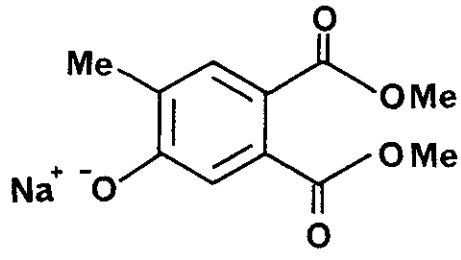
Addition of methyllithium to the second methoxycarbonyl group of intermediate (159) would then be discouraged by a combination of electrostatic and resonance effects. Unfortunately, treatment of the phthalate (150) with two mole equivalents of methyllithium, in dry tetrahydrofuran at -78°C, resulted in the isolation of a mixture of 5-hydroxy-3,3,6-trimethylphthalide (160) and the original phthalate (150) (1:1), as determined by n.m.r. spectral analysis of the crude reaction mixture. Formation of the phthalide (160) indicated the



(160)

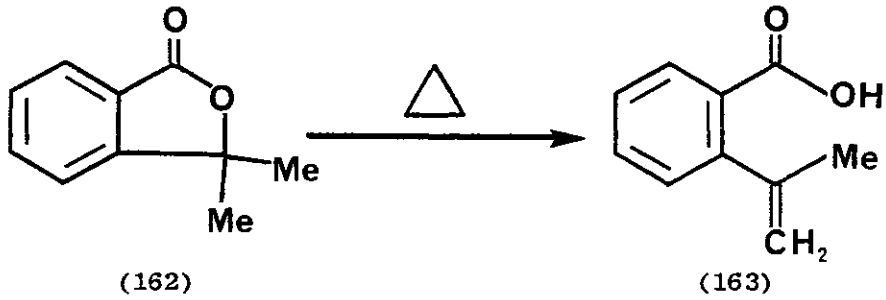
instability of the intermediate (159) under these reaction conditions. The reaction of methyllithium with the sodium derivative of phthalate (150) led to the recovery of the starting material, presumably due to the insolubility of the sodium salt (161) in tetrahydrofuran at low temperatures. Reaction of the phthalate (150) with three equivalents

of methyllithium, under the same reaction conditions, led to the isolation by column chromatography of the phthalide (160) in 35% yield.



(161)

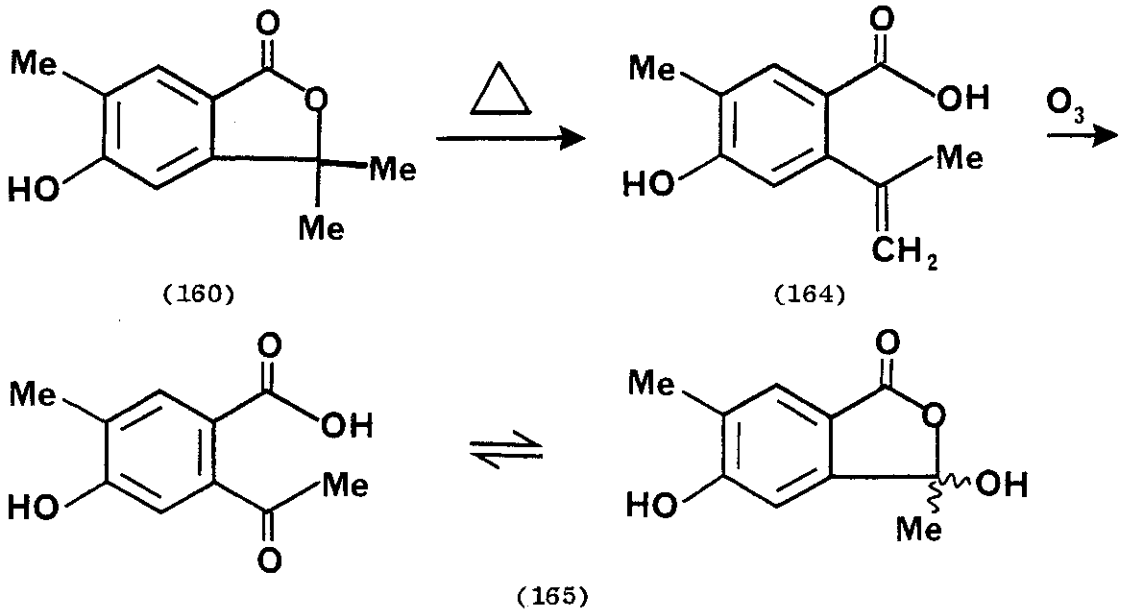
Berti *et al.*[54] have shown that 3,3-dimethylphthalide (162) undergoes pyrolysis to afford 2-(2-propenyl)benzoic acid (163) (Scheme 20).



(162) (163)

Scheme 20

Thus, the substituted phthalide (160) might be expected, on pyrolysis, to give the benzoic acid derivative (164) which should undergo



(160) (164)

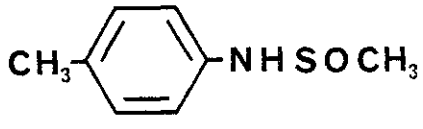
(165)

Scheme 21

ozonolysis to afford the 2-acetylbenzoic acid derivative (165). By analogy with 2-acetylbenzoic acid,[55] the compound (165) would probably exist as a mixture of open-chain and ring-closed forms (Scheme 21). Unfortunately, the attempted pyrolysis of the phthalide derivative (160), under a variety of reaction conditions, merely led to recovery of the starting material.

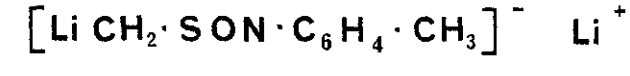
At this point we decided to investigate the possible use of some alternative nucleophilic methylating reagents for the conversion of the phthalate (150) to a suitable 2-acetylbenzoate derivative.

Corey and Durst[56] have successfully employed the dilithio derivative of *N*-methanesulphinyl-4-toluidine (166) in the conversion of esters to methyl ketones in good yield.



(166)

For example, the reaction of two mole equivalents of the dilithio derivative (167) with ethyl benzoate, ethyl cyclohexanecarboxylate, and ethyl pivaloate gave acetophenone, acetylcyclohexane, and pinacolone in 89, 84, and 93% yields respectively.

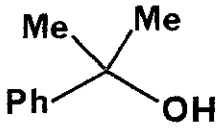


(167)

N-Methanesulphinyl-4-toluidine (166) was prepared according to the procedure of Corey and Durst.[56] In our hands the dilithio derivative

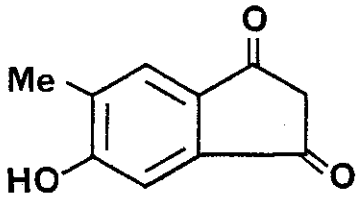
(167), prepared by the action of two mole equivalents of n-butyllithium at -78°C in dry tetrahydrofuran, reacted with methyl benzoate to afford acetophenone (47%) which was isolated and characterized as its 2,4-dinitrophenylhydrazone derivative. Under identical conditions the dilithio derivative (167) reacted with the phthalate (150) to afford a complex mixture of products from which the required 2-acetylbenzoate derivative (153) could not be isolated.

Lithium dimethylcuprate has been successfully used, by Schlessinger and his co-workers,[57] in the conversion of ethyl benzoate to acetophenone in 85% yield. Small amounts of dimethylphenylmethanol (168) (5-15%) were also produced. Accordingly, the phthalate (150) was treated with



(168)

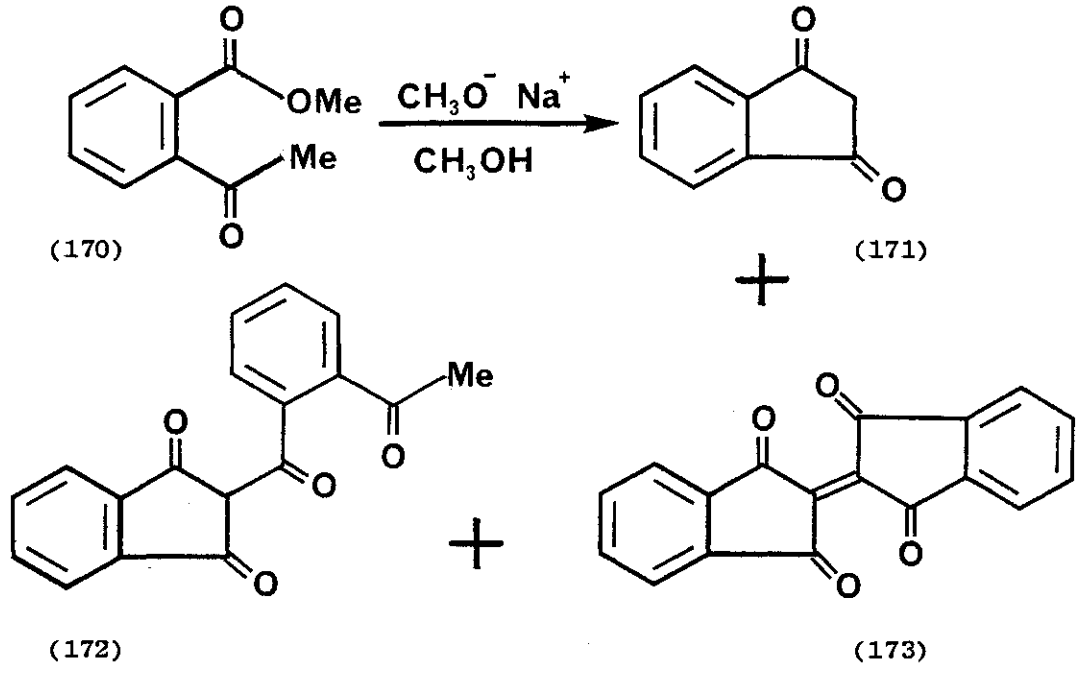
lithium dimethylcuprate, in dry diethyl ether at the reflux for 20 h. Work-up afforded a white crystalline solid which, although not fully characterized, was tentatively identified as the dione (169) on the basis of n.m.r. spectral analysis. In support of this assignment,



(169)

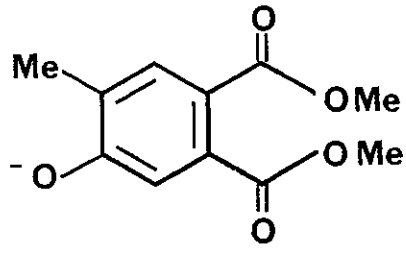
Briede *et al.*[58] have shown that methyl *O*-acetylbenzoate (170), on treatment with sodium methoxide in methanol at room temperature, affords

2-(*O*-acetylbenzoyl)-1,3-indandione (172) (14%) and bindone (173) (48%), presumably *via* further reaction of the initial condensation product 1,3-indandione (171) (Scheme 22).



Scheme 22

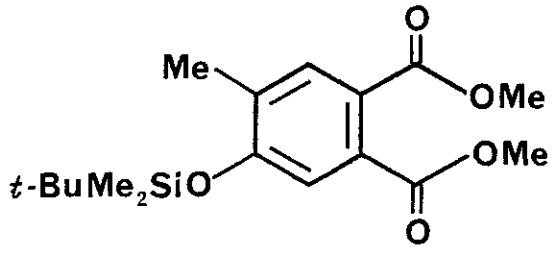
At this stage, we believed that the complex mixture of products obtained from the previous series of reactions may have been the result of side reactions involving the phenolic anion (174). Clearly, it was



(174)

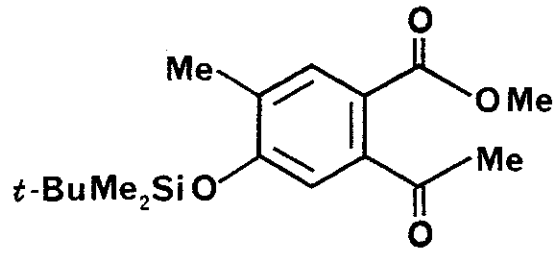
necessary to prepare a protected phenol derivative. Thus, the phthalate (150) was treated with one mole equivalent of

t-butylchlorodimethylsilane, in dry tetrahydrofuran containing sodium hydride, to give the novel silyl ether (175) in excellent yield (92%). Subsequent reaction of the silyl ether (175) with



(175)

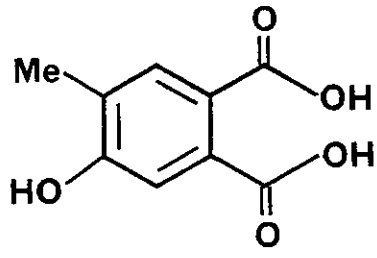
methyllithium, in tetrahydrofuran at -78°C, afforded a complex mixture of products which was found to contain no major 2,4-dinitrophenylhydrazine-active component, as judged by t.l.c. analysis. Reaction of the silyl ether (175) with the Corey reagent (167) produced a similar complex mixture of products, from which the required 2-acetylbenzoate derivative (176) could not be isolated.



(176)

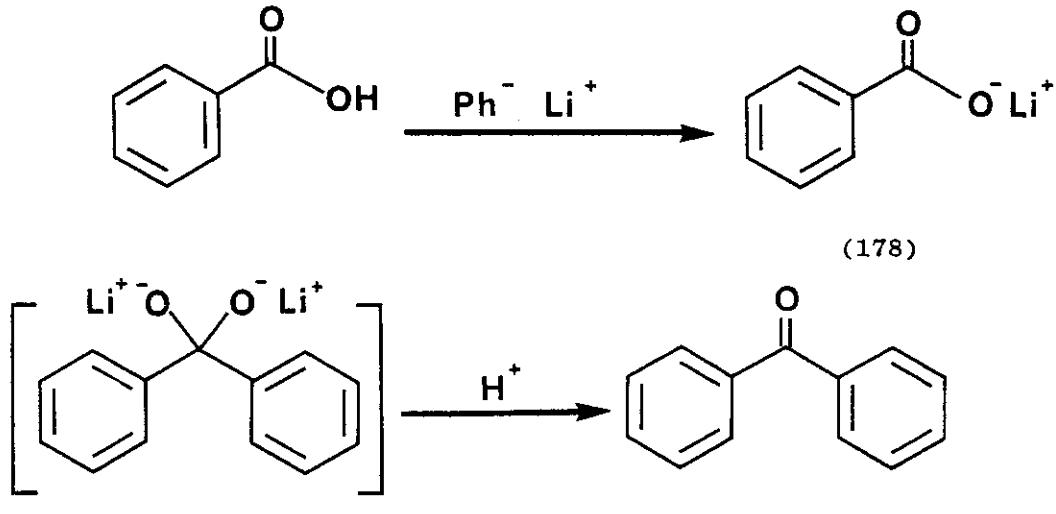
Thus, we concluded that our target compound (147) was not available from the direct methylation of the dimethyl phthalate derivative (150).

Several procedures are documented for the conversion of alkyl and aryl carboxylic acids[59,60,61] to their corresponding methyl esters. In order to investigate a number of these methods the dimethyl phthalate (150) was hydrolysed, with sodium hydroxide in a mixture of tetrahydrofuran and water at the reflux for 24 h, to afford the diacid (177) which was isolated and characterized as its monohydrate.



(177)

Gilman and Van Ess[59] have shown that benzoic acid may be converted to benzophenone (180) in high yield. Thus, treatment of lithium benzoate (178) with phenyllithium, at the reflux in diethyl ether-benzene solution for 5½ h, was found to yield the dilithium salt of the dihydroxymethane derivative (179). Hydrolysis of the salt (179) subsequently afforded benzophenone (180) in 70% yield (Scheme 23).



(178)

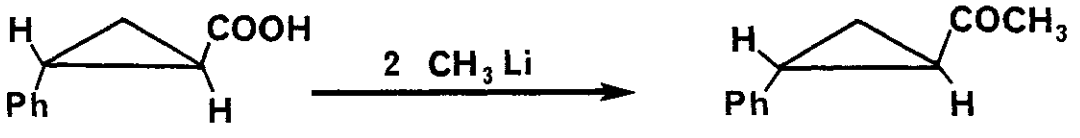
(179) (180)

Scheme 23

DePuy *et al.*[61] have prepared the *trans*-2-phenylcyclopropyl methyl ketone (182) in 75% yield by reaction of the acid (181) with two mole equivalents of methyllithium (Scheme 24).

Similarly, Tegnér[60] has shown that methyllithium may be used to convert several aryl and long-chain alkyl carboxylic acids directly to

their corresponding methyl ketones in good to excellent yield. Typically benzoic and n-hexanoic acids afforded the corresponding methyl ketones in 82 and 83% yield respectively.

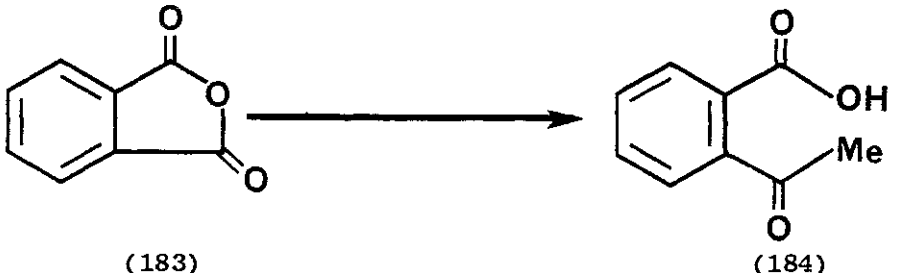


(181) (182)

Scheme 24

Unfortunately, reaction of the diacid (177) with 5 mole equivalents of methyllithium in diethyl ether led to the formation of a major unidentified dimeric material and a small amount of a gummy white solid tentatively identified as the required 2-acetylbenzoic acid derivative (165). Due to the extremely poor yield this reaction was clearly of no synthetic use.

Several methods for the conversion of acid anhydrides to methyl ketones are documented in the literature including the conversion of phthalic anhydride (183) to 2-acetylbenzoic acid (184) (Scheme 25).

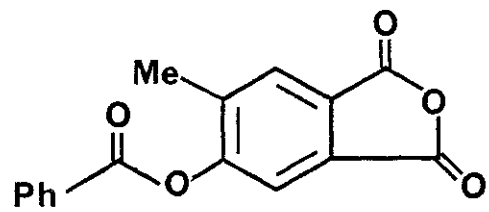


(183) (184)

Scheme 25

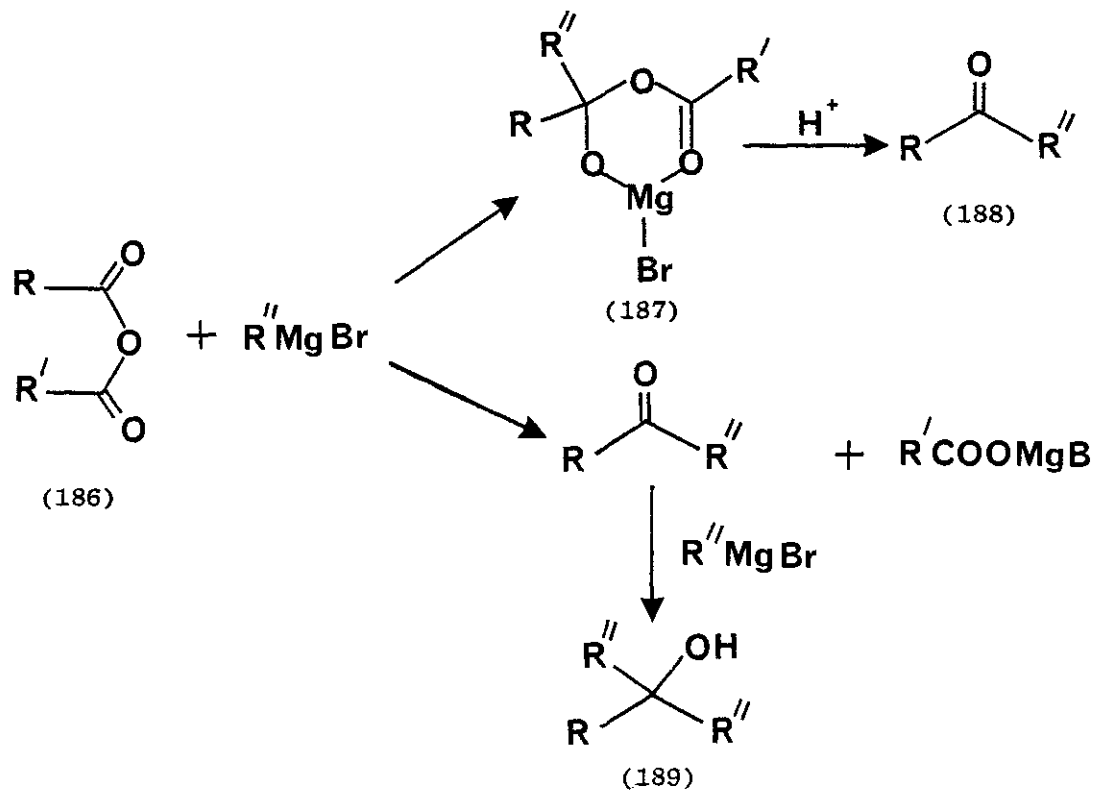
The reagents employed include Grignard reagents[62,63,64], organocopper reagents[65], and alkylcadmium reagents.[66,67] In order to investigate the possible application of this transformation to our synthesis the novel 3-benzoyl-4-methylphthalic anhydride (185) was prepared, in 85%

yield, by treatment of the diacid monohydrate (177) with benzoyl chloride and sodium hydride in dry tetrahydrofuran.



(185)

Newman and Smith[62] have shown that Grignard reagents may be successfully employed, at low temperature, to convert acid anhydrides (186) to ketones (188) in good yield. The absence of significant quantities of the carbinol compound (189)—resulting from the addition of a second equivalent of the Grignard reagent to the ketonic product (188)—is presented as an indication of the stability of the initial adduct (187) under the reaction conditions employed (Scheme 26).

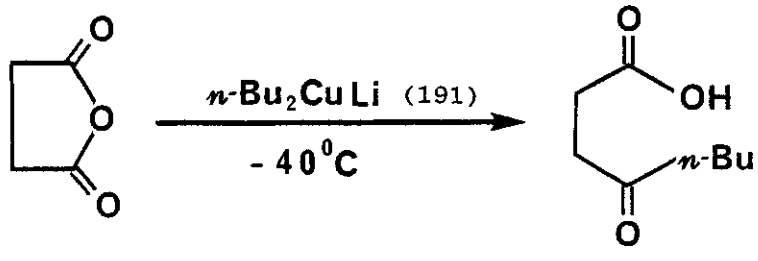


Scheme 26

This methodology was subsequently applied to our model system.

Thus, the anhydride (183) was reacted with methylmagnesium iodide in dry tetrahydrofuran at -78°C for 1 h. The standard work-up procedure, followed by chromatography on silica, afforded 2-acetylbenzoic acid (184) in 10% yield. This yield, however, was considered too low to be synthetically useful.

Anderson *et al.*[65] have shown that lithium alkylcuprates may be used for the conversion of cyclic acid anhydrides to keto-acids. Typically, succinic anhydride (190) with lithium di-n-butylcuprate (191), in diethyl ether-tetrahydrofuran (3:1) at -40°C, gave 4-oxo-octanoic acid (192) in 66% yield (Scheme 27).

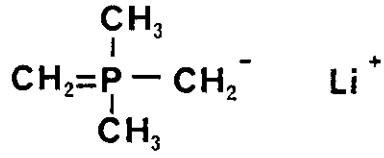


(190) (192)

Scheme 27

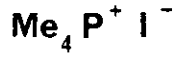
Accordingly, lithium dimethylcuprate, prepared by the procedure of Johnson and Dutra,[68] was reacted with phthalic anhydride (183) in diethyl ether-tetrahydrofuran (5:7), between -78°C and 10°C over 1 h. After the normal work-up procedure, chromatography on silica afforded trace amounts of 2-acetylbenzoic acid (184), as identified by mass spectral analysis. We concluded that there was little to be gained from attempting the reaction of this reagent with our substituted anhydride (185).

Our attention was next turned towards the reagent lithiomethyldimethylmethylenephosphorane (193) which has been used,



(193)

with some success, within this department as a methylating agent.[69] For example, benzoyl chloride, when treated with the reagent (193), afforded acetophenone in 81% yield. The phosphorane (193) was also found to react with acid anhydrides, typically acetic anhydride gave acetone, isolated as its 2,4-dinitrophenylhydrazone derivative in 8% unoptimized yield. In our hands, lithiomethyldimethylmethylenephosphorane (193), generated from tetramethylphosphonium iodide (194) with

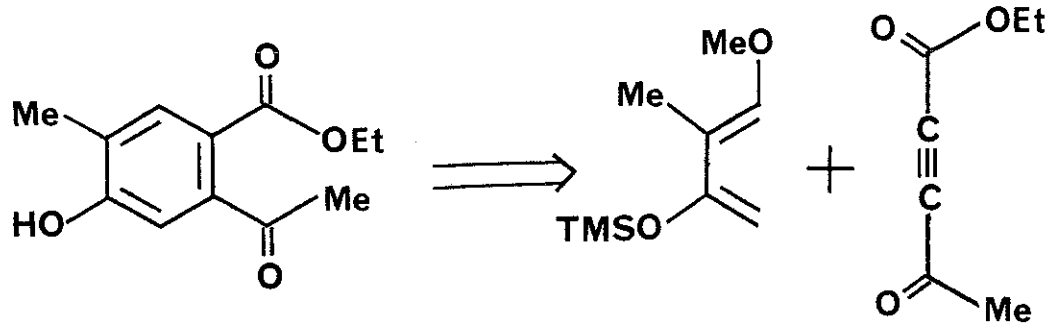


(194)

n-butyllithium at room temperature, reacted with phthalic anhydride (183) to afford 2-acetylbenzoic acid (184) (56%). Unfortunately, reaction of the phosphorane (193) with 3-benzoyl-4-methylphthalic anhydride (185) gave a complex mixture of products from which the required aromatic compound (165) could not be isolated.

Having been unsuccessful in our efforts to convert either the diacid (177), or its derivatives (150), (175), and (185), to the required substituted benzoic ester (147) we decided to consider a different approach towards the synthesis of the required aromatic southern (S) unit (143).

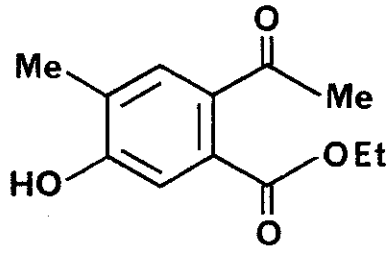
On initial inspection the most direct means of construction of the 2-acetylbenzoate derivative (195) would appear to be *via* a Diels-Alder reaction between the diene (157) and the dienophile (196) (Scheme 28).



(195) (157) (196)

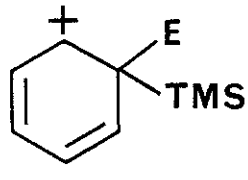
Scheme 28

However, a consideration of the molecular orbitals involved in this reaction leads us to predict the formation of the unwanted regioisomer (197).



(197)

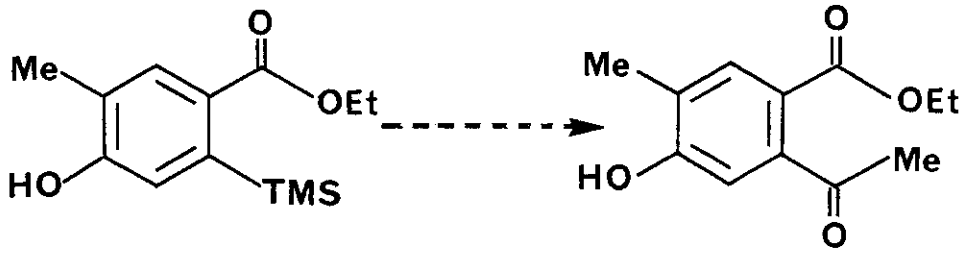
It has been shown that a trimethylsilyl group may be readily replaced in aromatic substitution reactions.[70,71] Eletrophilic attack normally takes place at the carbon atom carrying the silyl group. The intermediate (198) produced is thus stabilized by



(198)

hyperconjugative overlap of the orbitals of the carbon-silicon bond with the π-orbitals of the cyclohexadienyl cation system. We therefore might have expected that Friedel-Crafts acylation of the

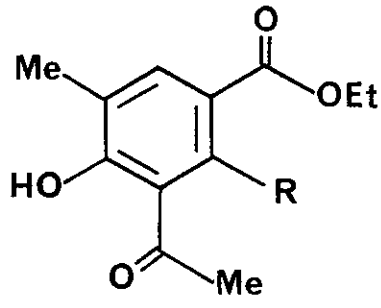
2-trimethylsilylbenzoate derivative (199) would afford the required



(199) (195)

Scheme 29

2-acetylbenzoate derivative (195) (Scheme 29). It was noted, however, that the presence of a phenolic hydroxy group in the molecule (199) could present a problem to this type of approach. For example, Eaborn and Webster[72] have shown that powerful *ortho/para*-directing groups, such as hydroxyl, are more effective in directing the electrophile to positions *ortho* and *para* to themselves than a *meta*-silyl group is in directing attack *ipso* to itself. Thus, Friedel-Crafts acylation of aromatic silyl compound (199) might be expected to yield a complex mixture of products, possibly including some of the pentasubstituted



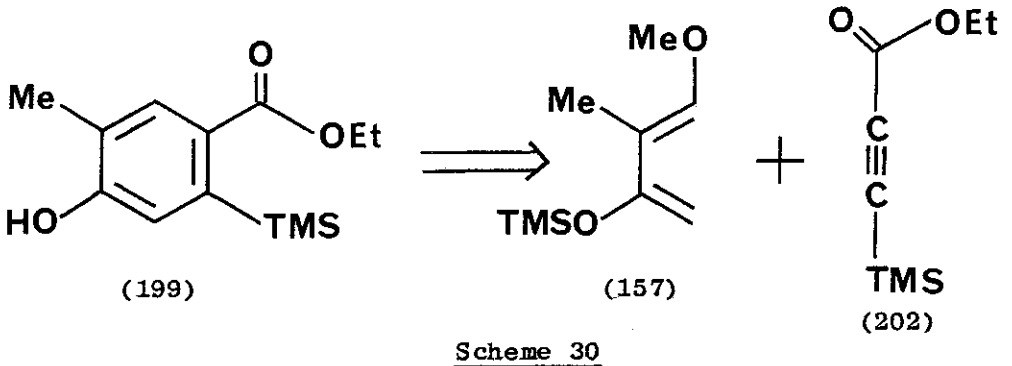
R = TMS or Ac

(201)

aromatic compound (201). It was hoped that protection of the hydroxyl group of the adduct (199), with a suitably bulky protecting group (ie: triisopropylsilyl), would block the adjacent *ortho* position and thus allow electrophilic substitution to take place cleanly at the carbon atom attached to the trimethylsilyl group.

Retrosynthetic analysis revealed that the silylbenzoate

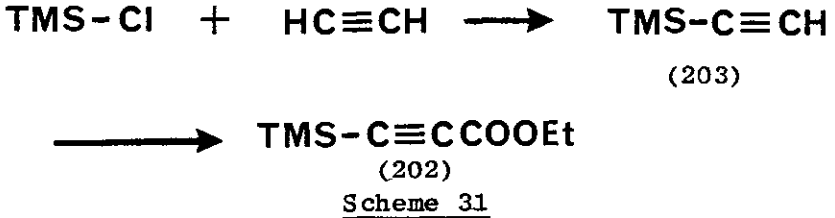
derivative (199) should be available *via* the Diels-Alder reaction of the diene (157) with ethyl 3-trimethylsilylpropynoate (202) (Scheme 30).



(199) (157) (202)

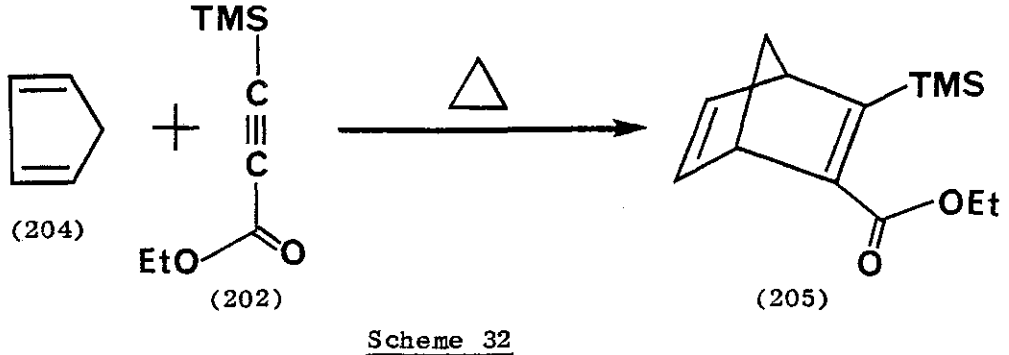
Scheme 30

Molecular orbital considerations led us to predict compound (199) to be the preferred regioisomer from the reaction. Accordingly, ethyl 3-trimethylsilylpropynoate (202) was prepared, using the literature procedures of Kraihanzel and Lossee,[73,74] in 38% overall yield (Scheme 31).



Scheme 31

Kraihanzel and Lossee[73] have shown that the reaction of the dienophile (202) with cyclopentadiene (204), in dry benzene at 190°C for 24 h proceeds to afford the expected heptadiene derivative (205) in



(204) (202) (205)

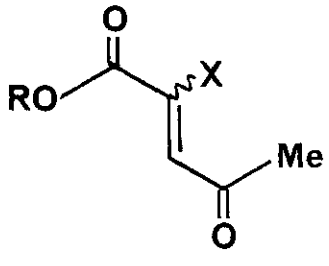
Scheme 32

66% yield (Scheme 32). Much to our displeasure, however, a solution of the diene (157) and the dienophile (202), heated at 110°C for one week, was found to contain none of the required adduct (199). Both

n.m.r. and t.l.c. analysis indicated that little reaction had occurred. Clearly, we needed to look for an alternative dienophile.

Danishefsky *et al.*[75] have elegantly shown that β-phenylsulphinyl-α,β-unsaturated carbonyl dienophiles (207) may be used in the Diels-Alder reaction. Thus, cycloaddition of a number of such dienophiles with suitable dienes, followed by the *syn*-elimination of the elements of phenylsulphenic acid from the adduct, was shown to provide a route directly into aromatic systems of the type (210) (Scheme 33).

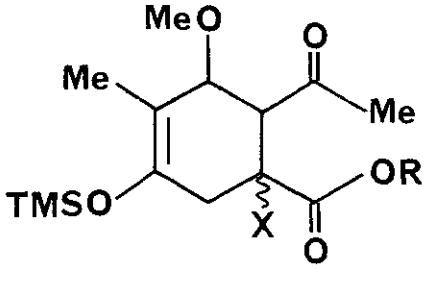
Danishefsky *et al.*[75] also showed that the phenylsulphinyl group does not significantly compete with the carbonyl functionality of these dienophiles for control of the regiochemical outcome of the cycloaddition step.



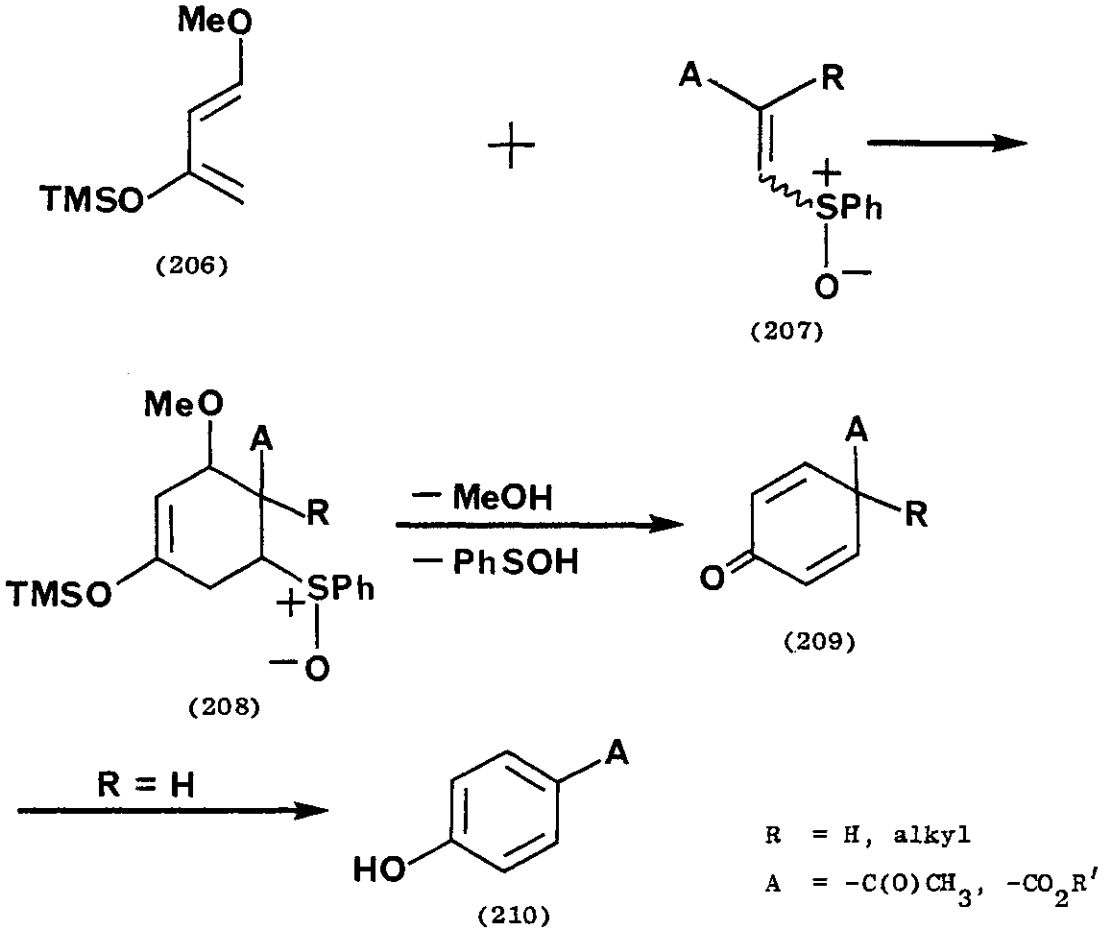
R = Me or Et

(211)

In the case of the dienophile (211) [X=H] we would predict that the ketonic carbonyl group should exert the dominant effect with respect to the regiochemistry of the cycloaddition; reaction with the diene (157) would therefore be expected to afford the adduct (212).

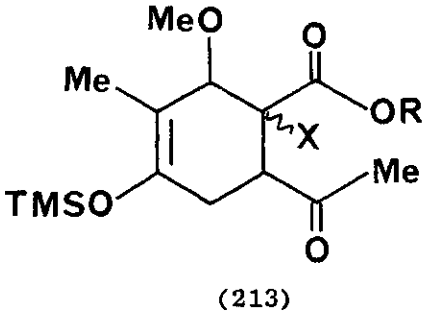


(212)



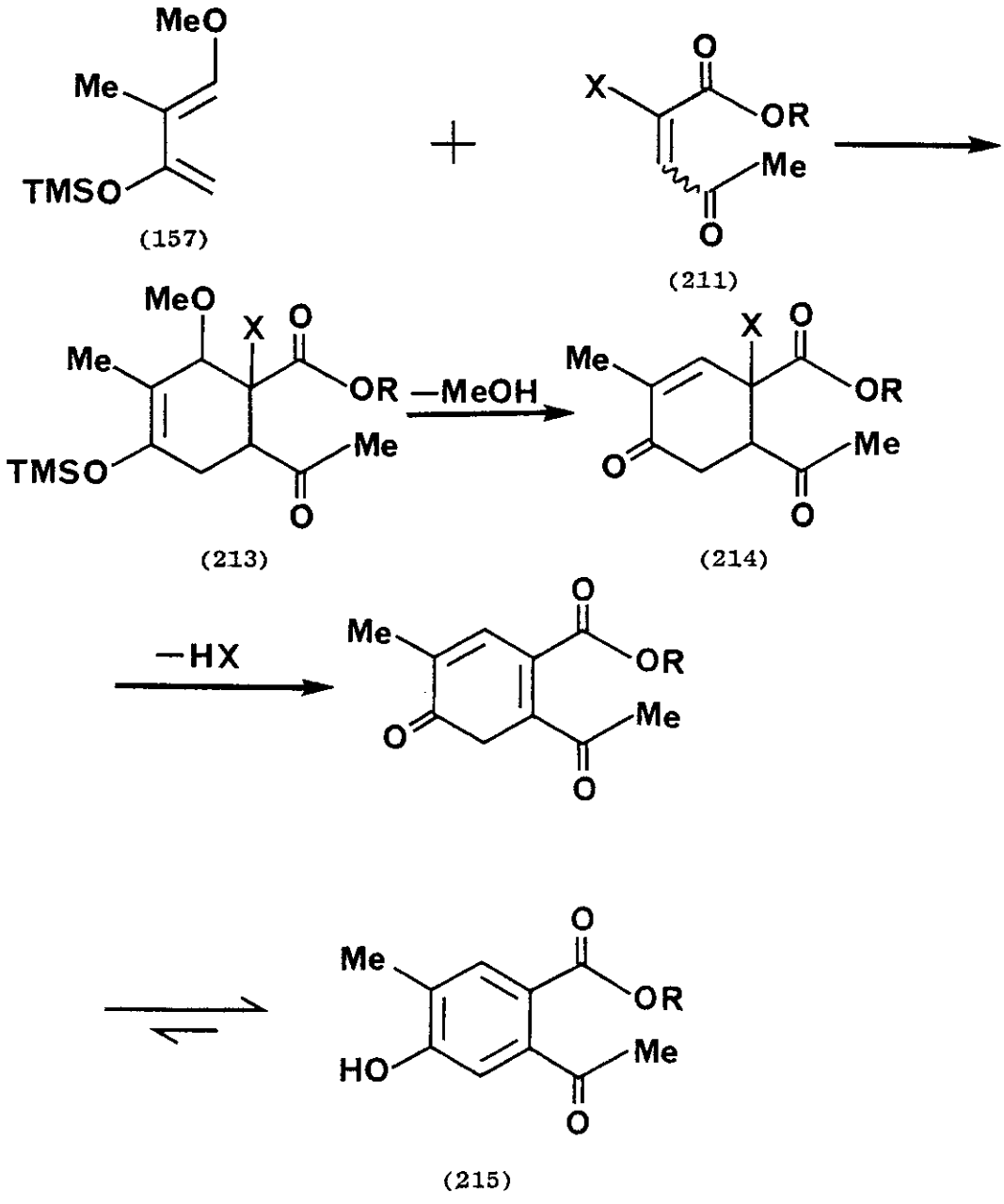
Scheme 33

It became apparent that we required a dienophile of the type (211) in which the choice of the group X was of prime importance. We acknowledged that a dienophile was required in which the alkoxycarbonyl substituent would overwhelm the affect of the ketonic carbonyl group, thus reversing the regiochemical outcome of the cycloaddition to yield an initial adduct of the type (213). After removal of the



(213)

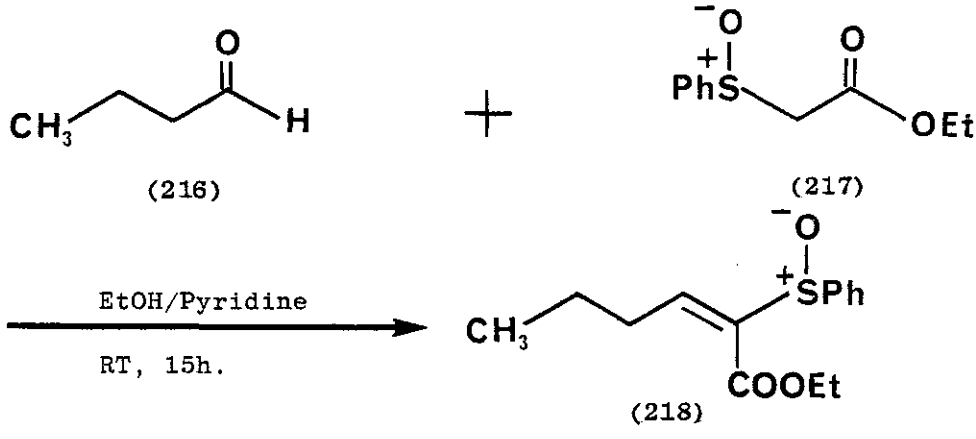
elements of methanol from adduct (213) we would require the facile elimination of a molecule of the type H-X to introduce the additional unit of unsaturation and so produce the required aromatic system (215) (Scheme 34).



Scheme 34

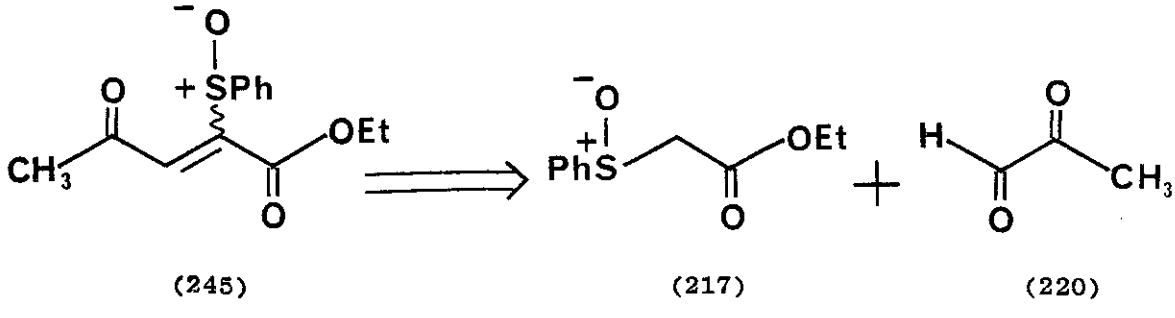
After a consideration of Danishefsky's work[75] we decided to investigate the Diels-Alder reactivity of the dienophile (211) [X= -S(O)Ph] as we felt that the phenylsulphinyl group would best fit the criteria we had set for the group X.

Tanikaga *et al.*[76] have shown that ethyl phenylsulphinylacetate (217) may be condensed with 1-butanone (216), over 15 h at room temperature in ethanol containing pyridine, to afford the α,β-unsaturated carbonyl compound (218) in 52% yield (Scheme 35).



Scheme 35

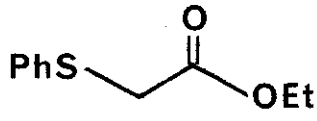
Retrosynthetic analysis of our required dienophile (219) revealed that this compound should be available from a similar condensation of ethyl phenylsulphinylacetate (217) with pyruvic aldehyde (220) (Scheme 36);



Scheme 36

as a consequence of the α-effect we expected pyruvic aldehyde (220) to react very readily with the sulphoxide (217) *via* the more reactive

aldehyde carbonyl group. Accordingly, ethyl phenylsulphinylacetate (217) was prepared, *via* ethyl phenylthioacetate[78] (222), using a procedure from the literature.[79]

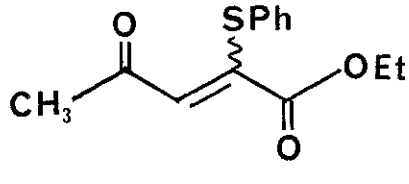


(222)

Unfortunately, using Tanikaga's procedure,[76] no trace of reaction between the sulphoxide (217) and pyruvic aldehyde (220) could be detected by t.l.c. analysis, even after 3 days.

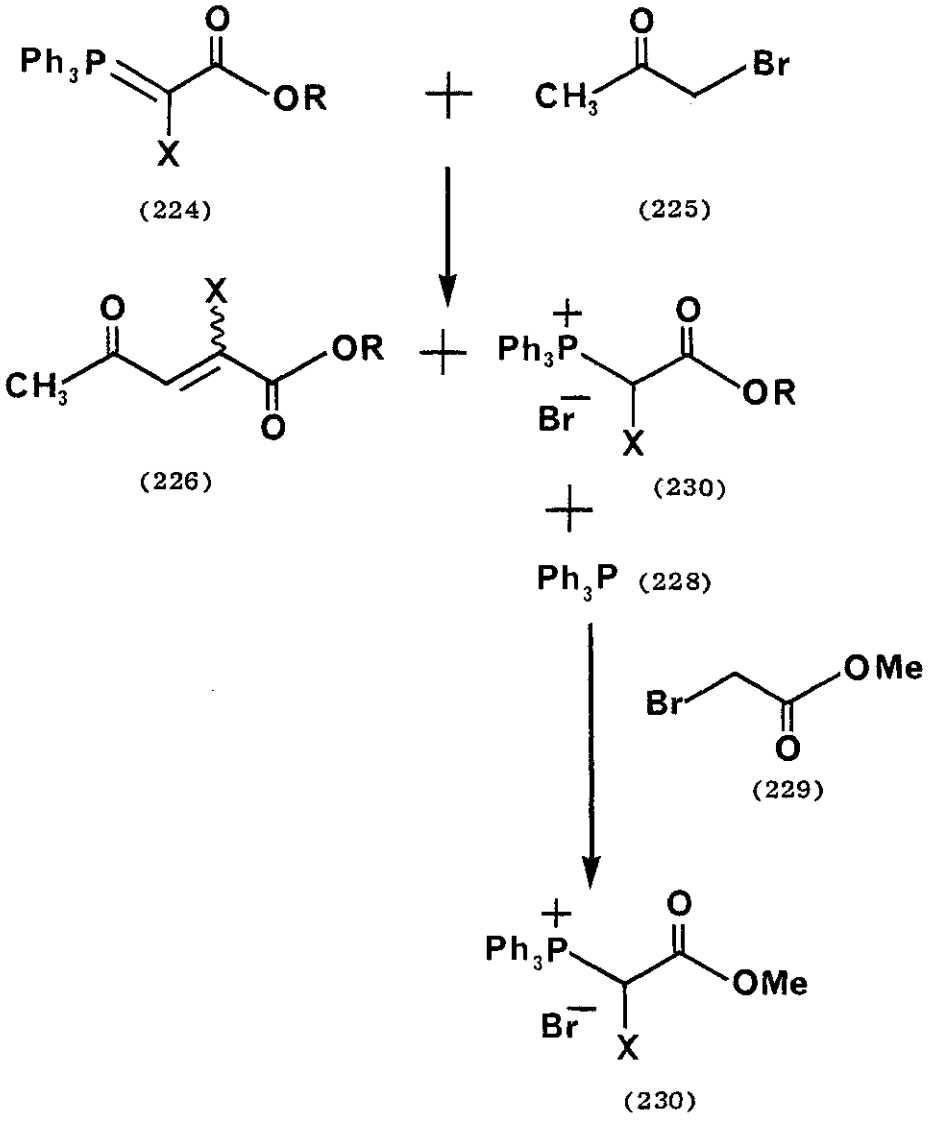
Due to our inability to isolate anhydrous pyruvic aldehyde (220) experiments involving the direct condensation of aldehyde (220) with the preformed anion of sulphoxide (217) could not be attempted.

Bestman *et al.*[80] have shown that the Wittig reagent (224) [R=Me, X=H] may be condensed with 1-bromopropanone (225), in benzene at the reflux, to afford an α,β-unsaturated ester (226) [R=Me, X=H]. Treatment of the reaction mixture, after reflux, with one mole equivalent of methyl bromoacetate (229) acted to precipitate the by-product, triphenylphosphine (228), as the starting ylide hydrobromide salt (230) (Scheme 37). Later work by Vig *et al.*[81] applied similar methodology to the synthesis of ethyl 4-oxo-2-pentenoate (226) [R=Et, X=H]. By analogy, the ylide (224) [R=Et, X=SPh] on reaction with 1-bromopropanone (225) might be expected to afford the sulphide (243) which we hoped could be



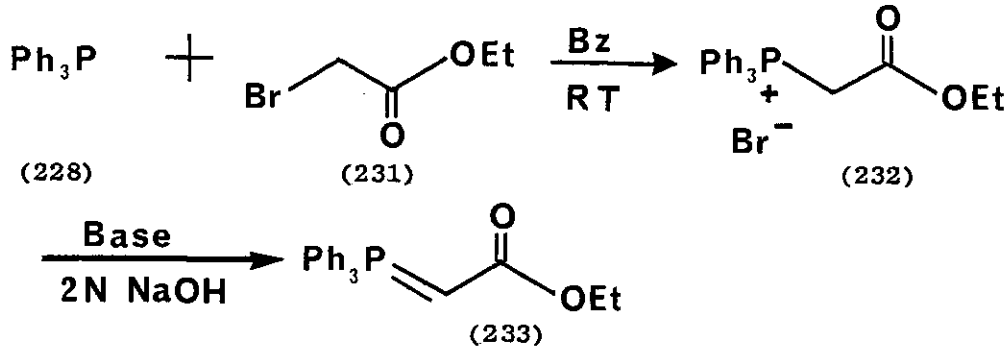
(243)

converted to the sulphoxide (245) by periodate oxidation. We decided to test this hypothesis.



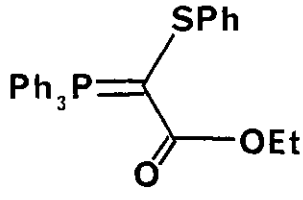
Scheme 37

[(Ethoxycarbonyl)methylene]triphenylphosphorane (233) was prepared in 86% yield according to the method of Denney and Ross[82] (Scheme 38). 1-Bromopropanone (225) was prepared, in 30% yield from acetone, using



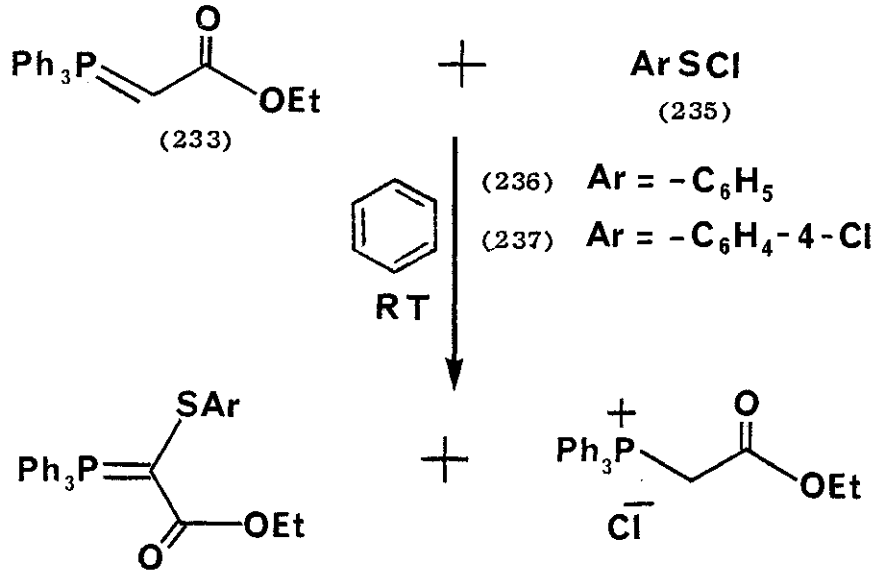
Scheme 38

the potassium chlorate/bromine procedure of Norris.[83] In our hands, the condensation of the ylide (233) with 1-bromopropanone (225), under the conditions of Vig *et al.*,[81] afforded ethyl 4-oxo-2-pentenoate (226) [R=Et, X=H] in 83% yield (Scheme 37). Satisfied that this reaction gave consistently high yields we directed our efforts towards the construction of the ylide (234).



(234)

Saikachi and Nakamura[84] have shown that ylides of the type (238) may be prepared *via* the addition of an arylsulphenyl chloride (235) to a solution of [(ethoxycarbonyl)methylene]triphenylphosphorane (233) in benzene at room temperature (Scheme 39). Fortunately, if two mole equivalents of the ylide (233) are employed the less basic product ylide (238) is formed *in situ* and can be isolated from the reaction mixture, after filtration to remove the starting ylide (233) as its hydrochloride salt (239) (Scheme 39).



(234) $Ar = -C_6H_5$

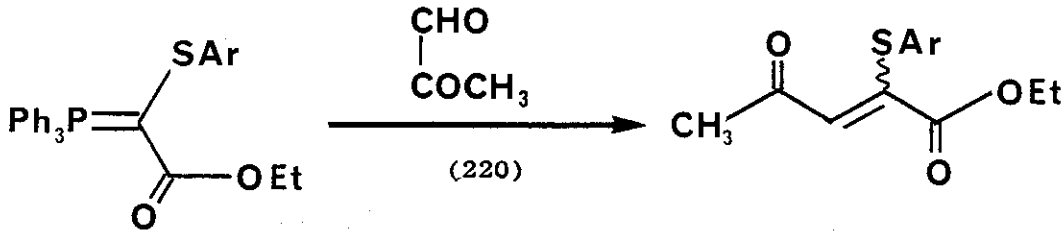
(242) $Ar = -C_6H_4\text{-}4\text{-}Cl$

Scheme 39

Benzenesulphenyl chloride (236) was prepared, according to a method in the literature,[85] and was reacted with [(ethoxycarbonyl)methlene]triphenylphosphorane (233) in dry benzene, according to the procedure of Saikachi and Nakamura,[84] to afford [(benzenesulphenyl)(ethoxycarbonyl)methlene]triphenylphosphorane (234) in 65% yield after recrystallization (Scheme 39). Unfortunately, the ylide (234) showed no sign of reaction with 1-bromopropanone (225), even after reflux in benzene for 74 h.

Since phosphoranes are well known to undergo the Wittig reaction with aldehydes we reasoned that the sulphur-containing ylide (234) might be expected to react with the activated aldehyde, pyruvic aldehyde (220), to afford the required adduct (243). Accordingly, a solution of the ylide (234) in benzene was heated with a 40% aqueous

pyruvic aldehyde solution, in two phases at the reflux for 48 h. Isolation of the major product, by chromatography on silica, afforded ethyl 2-benzenesulphenyl-4-oxo-2-pentenoate (243) in 87% yield (Scheme 40).



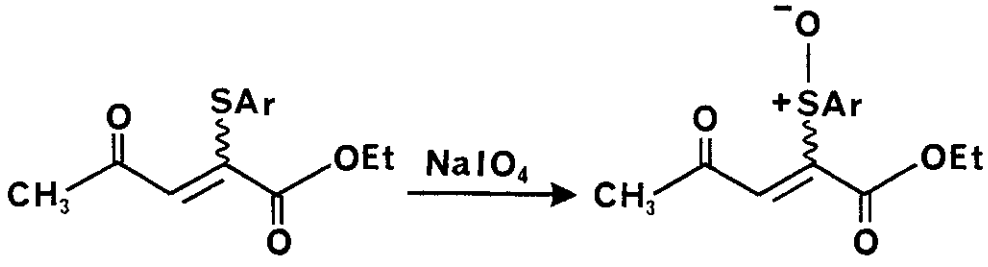
(234) Ar = $-C_6H_5$ (243) Ar = $-C_6H_5$

(242) Ar = $-C_6H_4-4-Cl$ (244) Ar = $-C_6H_4-4-Cl$

Scheme 40

In a separate series of reactions 4-chlorobenzenesulphenyl chloride (237) was prepared and converted to [(4-chlorobenzenesulphenyl)(ethoxycarbonyl)methylene]triphenylphosphorane (242) in 66% yield (Scheme 39). Reaction of this ylide (242) with pyruvic aldehyde (220) afforded ethyl 2-(4-chlorobenzenesulphenyl)-4-oxo-2-pentenoate (244) in 72% yield (Scheme 40). The spectral data for the novel α,β-unsaturated esters (243 and 244) were fully consistent with the proposed structures. Both compounds appeared to be single geometric isomers by n.m.r. analysis although the absolute stereochemistry was not defined.

Before investigating their oxidation to the corresponding sulphoxides (245 and 246) (Scheme 41), we decided to study the Diels-Alder reaction of the sulphides (243 and 244) with the Danishefsky diene (157).



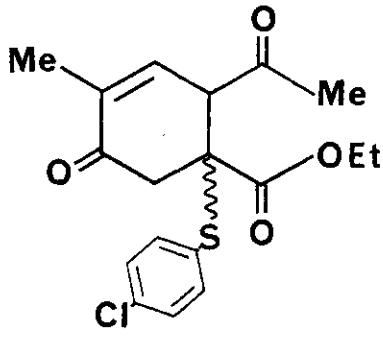
(243) Ar = $-C_6H_5$ (245) Ar = $-C_6H_5$

(244) Ar = $-C_6H_4$-4-Cl (246) Ar = $-C_6H_4$-4-Cl

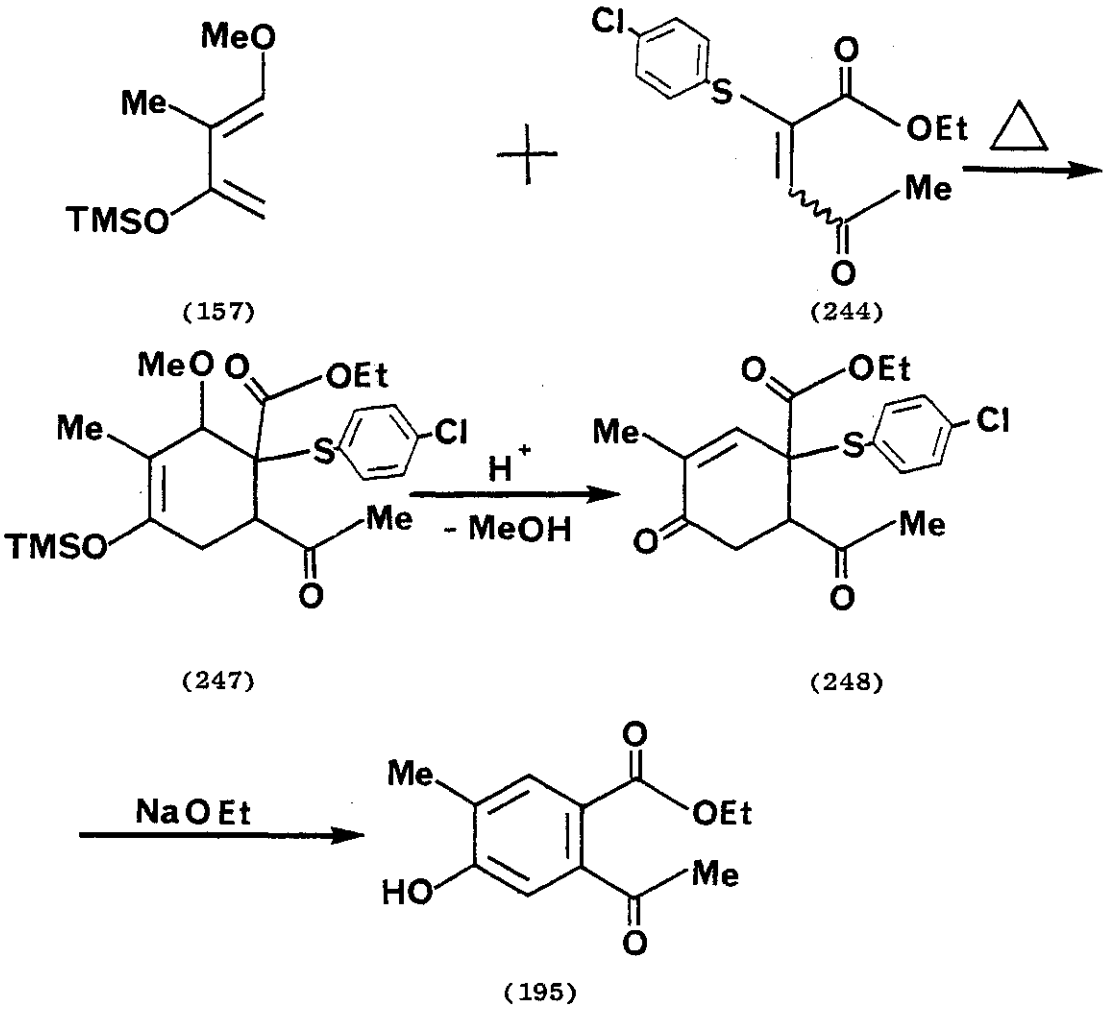
Scheme 41

Accordingly, the sulphide (244) was heated with the diene (157) in dry benzene at the reflux for 6 h. Hydrolytic work-up followed by chromatography on silica afforded the novel enone, 5-acetyl-4-(4-chlorobenzenesulphenyl)-4-ethoxycarbonyl-2-methylcyclohexa-2-enone (248) in 64% yield (Scheme 42). N.m.r. spectral data was fully consistent with the proposed structure thus confirming our prediction as to the regioselectivity of the cycloaddition.

Although this reaction was repeated on several occasions none of the regioisomer (249) was ever detected either by n.m.r. or t.l.c. analysis.



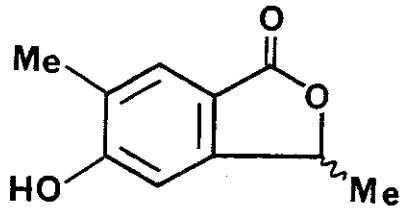
(249)



Scheme 42

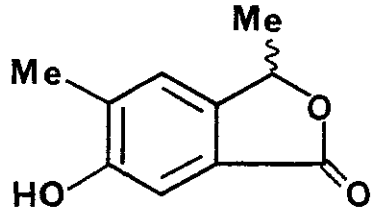
Treatment of the enone (248) with sodium ethoxide in ethanol at room temperature afforded, after chromatography on silica, the required aromatic compound (195) in 75% yield (Scheme 42). In a separate reaction the aromatic compound (195) was isolated, in 72% yield, by treatment of the crude cycloaddition reaction mixture with sodium ethoxide. Cycloaddition of the sulphide (243) with the diene (157) followed by treatment of the crude reaction mixture with sodium ethoxide also afforded the required aromatic compound (195), this time in 80% yield.

As a means of double-checking the regiospecificity of the cycloaddition the benzoate derivative (195) was treated with excess sodium borohydride in ethanol at 0°C to afford the novel phthalide 5-hydroxy-3,6-dimethyl-*iso*benzofuran-1(3*H*)-one (250), in a quantitative yield. U.v. spectral analysis revealed a shift to a



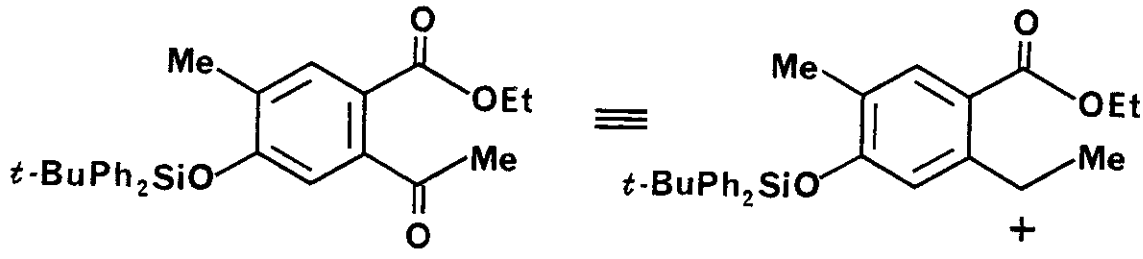
(250)

longer wavelength on treatment of a sample of the phthalide (250) with base. This bathochromic shift could be predicted, on removal of the phenolic proton from the compound (250), due to the increased conjugation of the aromatic system with the carbonyl group. The corresponding regioisomer (251) would not be expected to exhibit this effect.



(251)

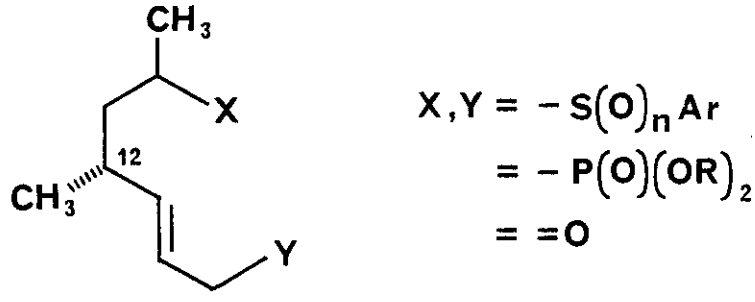
Finally, the benzoate derivative (195) was treated with t-butylchlorodiphenylsilane, in dry *N*,*N*-dimethylformamide containing imidazole, to afford ethyl 2-acetyl-4-t-butyldiphenylsilyloxy-5-methylbenzoate (252) (98%) which may be regarded as a synthetic equivalent of type (253).



(252) (253)

(ii) The Unsaturated North-Western (NW) Unit.

We envisaged that the unsaturated (NW) unit (144) of milbemycin β_3 would have the functionality shown (254).

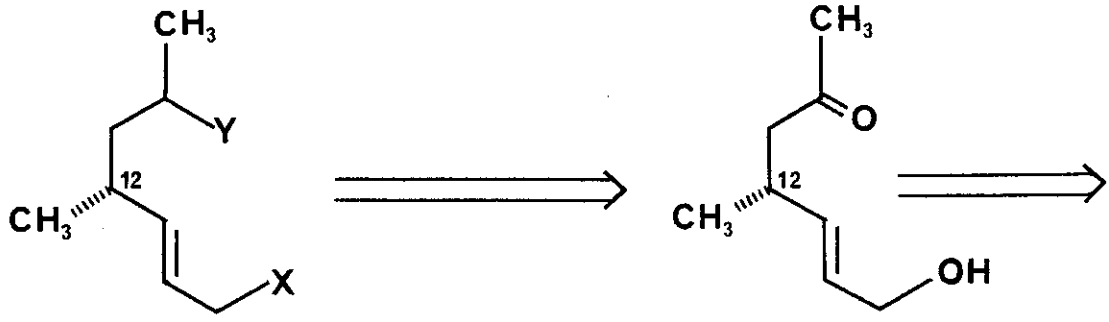


(254)

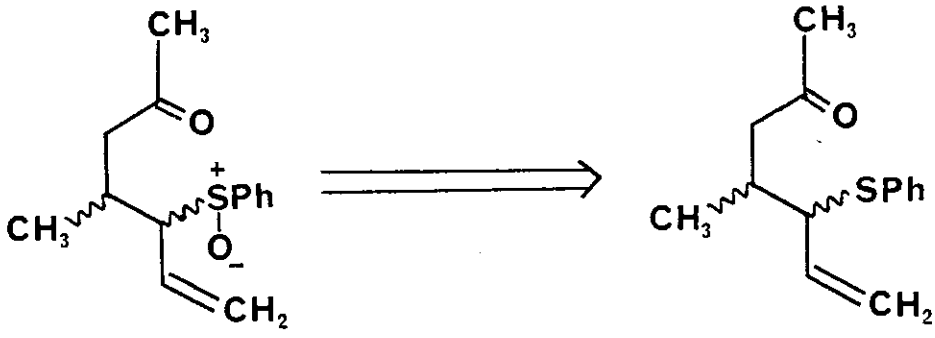
This unit should be linked with the other sub-units in either a nucleophilic or electrophilic sense, dependent on the outcome of later work, so as to give the correct *E*-geometry at the *C*-8 to *C*-9 and *C*-14 to *C*-15 olefinic linkages.

From a retrosynthetic viewpoint, the basic carbon skeleton of unit (254) would be available *via* the 1,4-addition of a metallated allylic sulphide (258) to an enone system (259). Subsequent oxidation of the initial adduct (257) to the sulphoxide (256) followed by a [2,3]-sigmatropic rearrangement should afford the allylic alcohol (255) (Scheme 43). Resolution, at this stage, would yield the required *C*-12 α-methyl enantiomer. Elaboration of this allylic alcohol (255) should then afford a series of synthetic equivalents of the type (254).

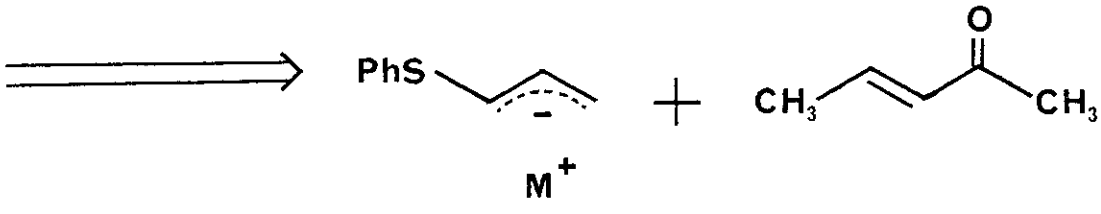
Brown and Yamaichi[87] have shown that the addition of



(254) (255)



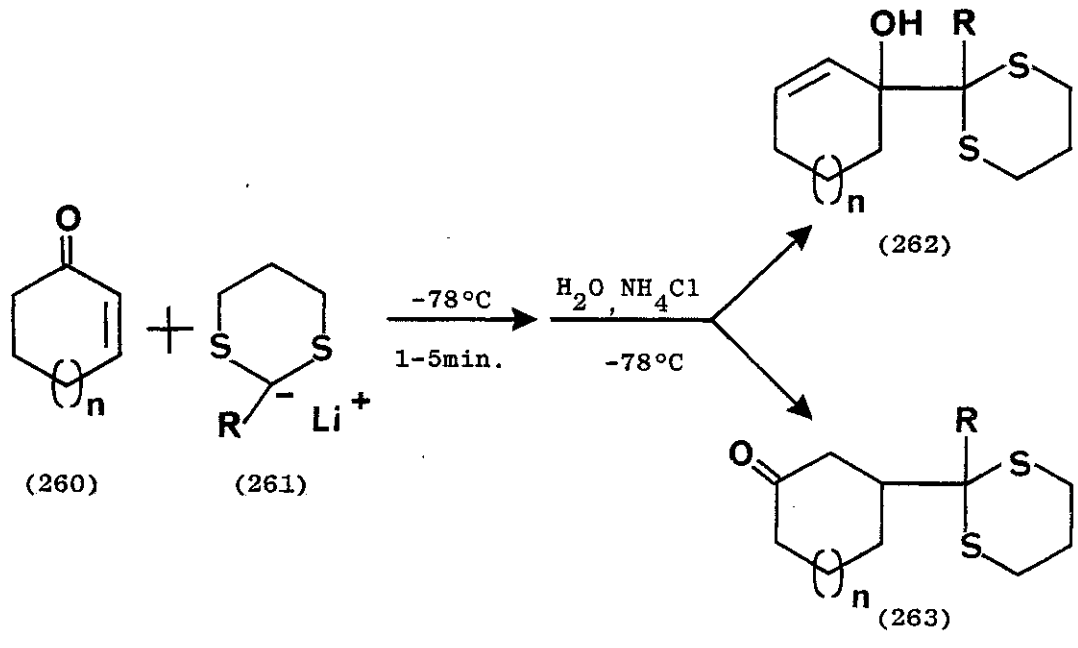
(256) (257)



(258) (259)

Scheme 43

2-lithio-1,3-dithians to cyclic α,β-unsaturated ketones (Scheme 44) could be directed from the normal 1,2-addition to 1,4-addition by the simple expedient of adding 1·0-2·0 mole equivalents of hexamethylphosphoramide to the reaction mixture (Table 10).



Scheme 44

TABLE 10

Addition of 2-Lithio-1,3-dithians to Cyclic Enones[a]

(260) n=	Additive[b] (mmol/mmol of dithian)	1,4-Addition[c] (263)%	1,2-Addition[c] (262)%
0	None	0	>99
0	HMPA(2·0)	98	2
1	None	0	>99
1	HMPA(2·0)	95	5
	HMPA(1·0)	88	12

a) Addition of 2·5 mmol of enone to 2·5 mmol of (261) in *ca.* 6 ml of THF-hexane (*ca.* 4:1) at -78°C followed by quenching after 1-5 min with saturated aq. NH_4Cl.

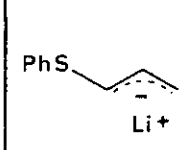
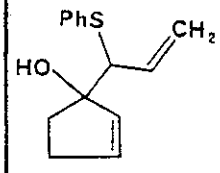
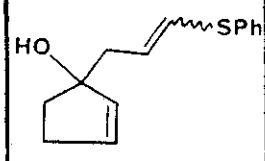
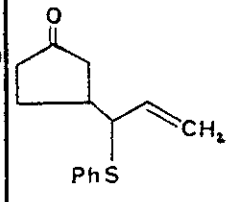
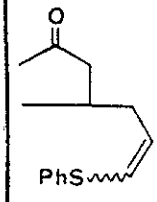
b) Additive mixed, at -78°C with (261) prior to addition of enone (260).

c) By g.l.c. analysis (after aqueous work-up) with carbowax or OV-17 columns. Yields were 50-80%.

The addition of hexamethylphosphoramide (HMPA) to solutions of the lithium salt of (262) produced no rearrangement to the conjugate-addition product (263), even after 24 h at room temperature, thus indicating the reaction to be a truly direct conjugate-addition. Haynes and his co-workers[88] have applied similar reaction conditions to effect the HMPA-mediated conjugate-addition of the phenylthioallyl anion (258) to cyclopentenone. Generation of the anion (258) in the presence of one equivalent of HMPA followed by addition of the cyclopentenone resulted in exclusive, and predominantly α-, 1,4-addition. The α- and γ-1,2 products were not formed in detectable amounts (Table 11).

TABLE 11

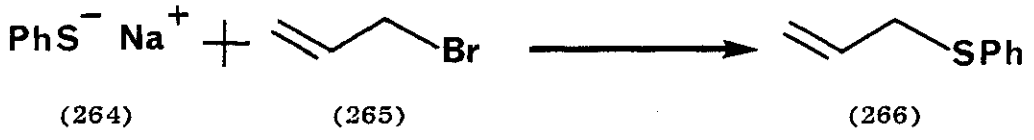
Reaction of Phenylthioallyllithium with Cyclopentenone:-

					
	α-1,2	γ-1,2(E:Z)	α-1,4	γ-1,4(E:Z)	Overall Yield
THF	60	18(1:1·1)	12	8(1:4·2)	85
+ 1eq. HMPA	0	0	95	4	89

These results are rationalized in terms of the efficient solvation of Li^+ by HMPA which enables frontier orbital control to operate in the 1,4-addition of the anion with conjugated enones.[88] Reactions involving t-butylthioallyllithium showed that replacement of the Li^+ by less electropositive counterions, in particular Cu^+, in the absence of HMPA, also results in predominantly α-addition to the enone system.

In order to test the feasibility of this reaction, as applied to our target molecule, we embarked upon the synthesis of the two starting

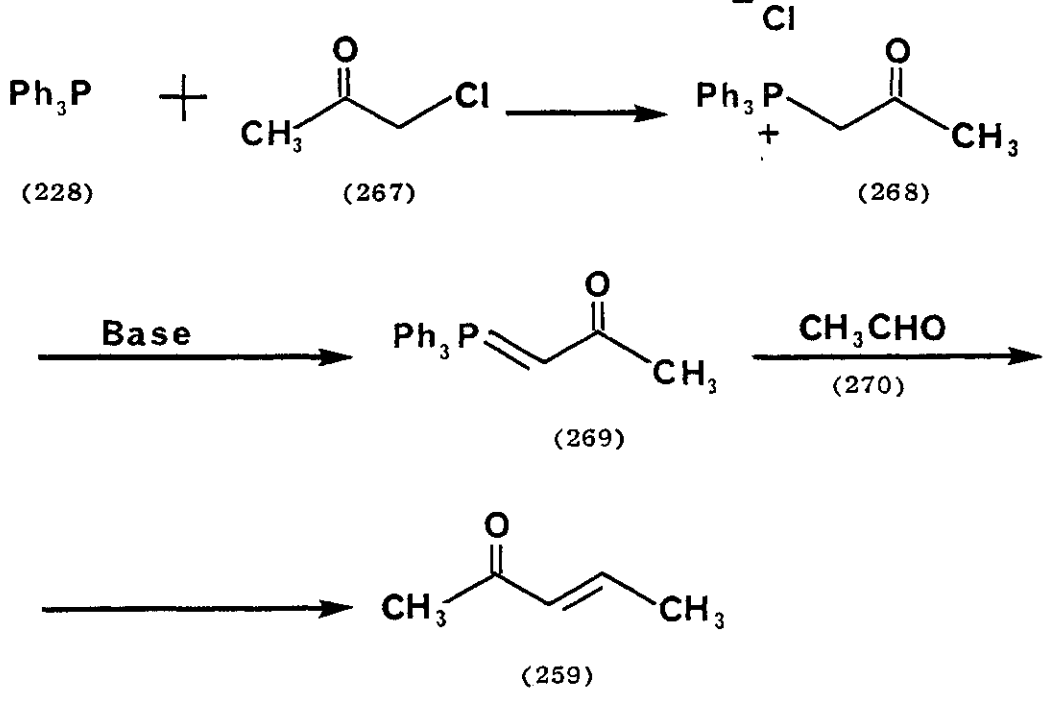
materials (266) and (259). Allylphenylsulphide (266) was conveniently prepared by reaction of the sodium salt of thiophenol (264) with allyl bromide (265) in tetrahydrofuran (Scheme 45).



(264) (265) (266)

Scheme 45

3-Penten-2-one (259) was synthesized, in a high yield (97%),[89] *via* the condensation of acetaldehyde (270) with the ylide (269),[90] the latter derived from chloroacetone (267) and triphenylphosphine (228) (Scheme 46).



(228) (267) (268)

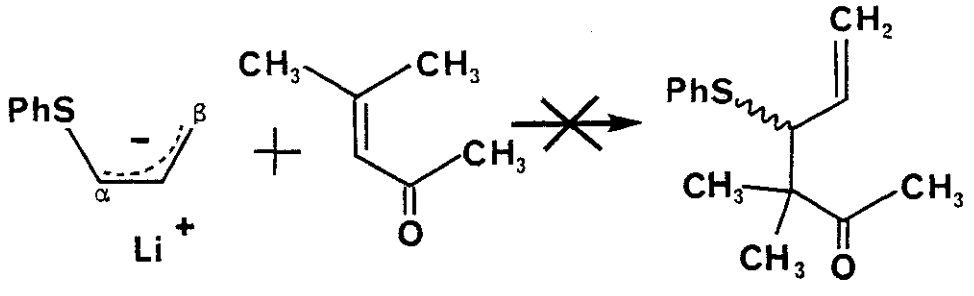
(269) (270)

(259)

Scheme 46

Phenylthioallyllithium (258) was prepared according to the procedure of Haynes and his co-workers.[88] Treatment of allylphenylsulphide (266) with

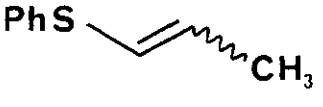
sec-butyllithium, in tetrahydrofuran containing one mole equivalent of HMPA at -78°C, resulted in the formation of the orange anion (258). Reaction of this anion with the model compound mesityl oxide (271) afforded none of the desired adduct (272) (Scheme 47).



(258) (271) (272)

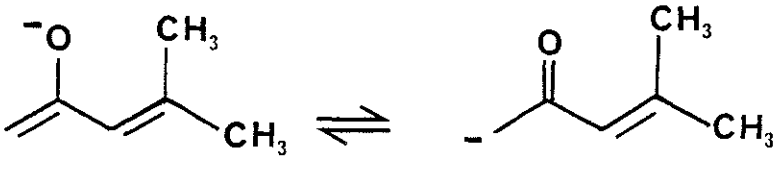
Scheme 47

The only compounds isolated on work-up were found to be allylphenylsulphide (266) and the isomeric sulphide (273)



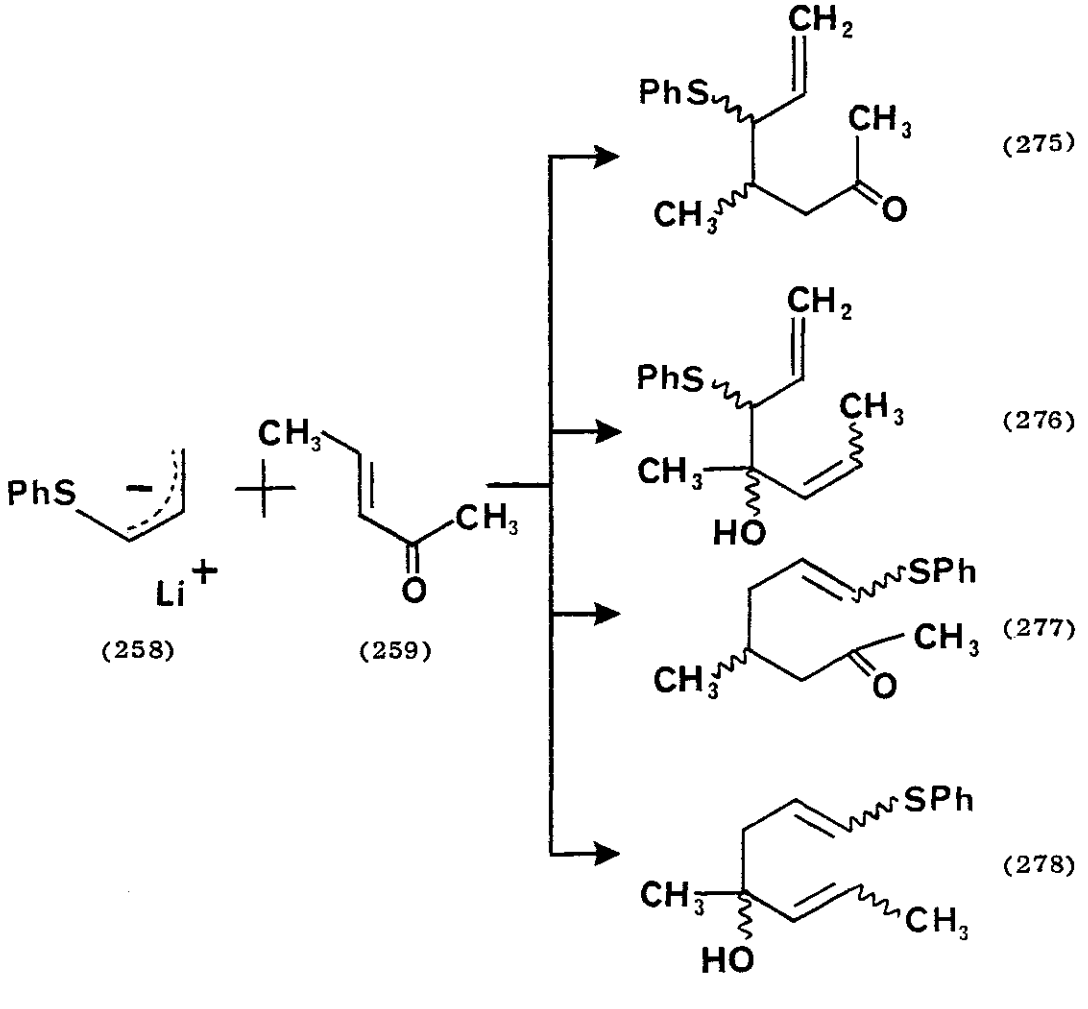
(273)

as identified by n.m.r. analysis. Presumably, the phenylthioallyllithium (258) had abstracted a proton from mesityl oxide (271), so producing the enolate anoin (274).



(274)

Alternatively, the anion (258) may have been unreactive towards the enone (271) and have simply undergone protonation on aqueous work-up. Protonation of phenylthioallyllithium (258) at either the α- or γ-position would afford the isomeric sulphides (266) and (273) respectively. Reaction of phenylthioallyllithium (258) with 3-penten-2-one (259), under the same conditions, afforded two main products as determined by t.l.c. analysis. Small quantities of allylphenylsulphide (266) and the vinyl sulphide (273) were also detected but these could be removed by distillation at reduced pressure. Column chromatography on silica then afforded the two major components which were identified as the γ-1,4-addition product (277) (4·5%) and an inseparable mixture of the α-1,2-addition product (276) and the required α-1,4-addition product (275) (55%) (*ca.* 1:8) (Scheme 48).



Scheme 48

The γ-1,2-addition product (278) was detected in the crude reaction mixture by high resolution ^{1}H n.m.r. analysis. However, no further characterization was undertaken.

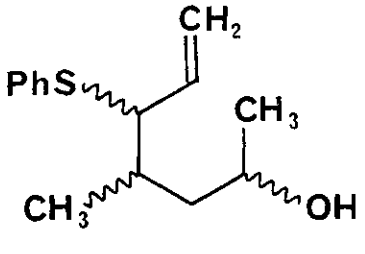
Copper is well known for its ability to promote 1,4-additions to α,β-unsaturated carbonyl systems.[88,91] Unfortunately, a reaction in which HMPA was replaced by one mole equivalent of phenylthiocopper (I) (279) resulted in the production of a higher percentage of the more

$$Cu^{+}\ ^{-}SPh$$

(279)

polar γ-1,4-addition product (277), as determined by t.l.c. analysis. Reactions mediated with both one and two mole equivalents of HMPA appeared to afford similar product ratios, as indicated by t.l.c. analysis. The reaction time between addition of the enone (259) and quenching with saturated aqueous anmonium chloride solution also appeared to have little or no effect on the product ratio; the reactions appeared complete after 10 min at -78°C.

Since it proved impossible to separate the α-1,4- and α-1,2-addition products (275 and 276, respectively) by chromatography or distillation, the mixture was treated with sodium borohydride in ethanol at 0°C. The α-1,2-addition product (276) was then separated by medium pressure



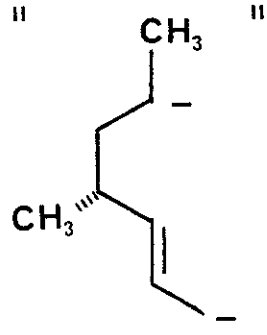
(280)

chromatography and the alcohol (280) isolated, as a mixture of diastereoisomers, in 42% overall yield from the enone (259).

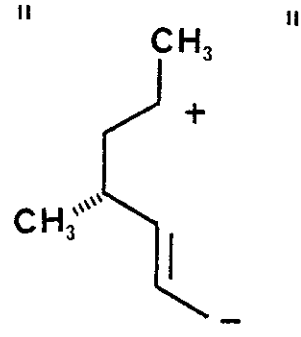
Since the degree of regioselectivity, and the overall yield, for the additions of phenylthioallyllithium (258) to the enone (259) were not as high as we had initially hoped, these initial studies towards the unsaturated (NW) unit (254) were suspended, and eventually abandoned, in favour of a more concise route.

Synthesis of the unsaturated north-western (NW) unit and model studies towards the formation of the C-8 to C-9 alkene linkage of milbemycin β_3

The synthesis of the unsaturated north-western (NW) *C*-9 to *C*-14 fragment of milbemycin β_3, in optically active form, was successfully completed by Dr. Geoff Richardson, one of our co-workers on the project. His work is briefly outlined here.

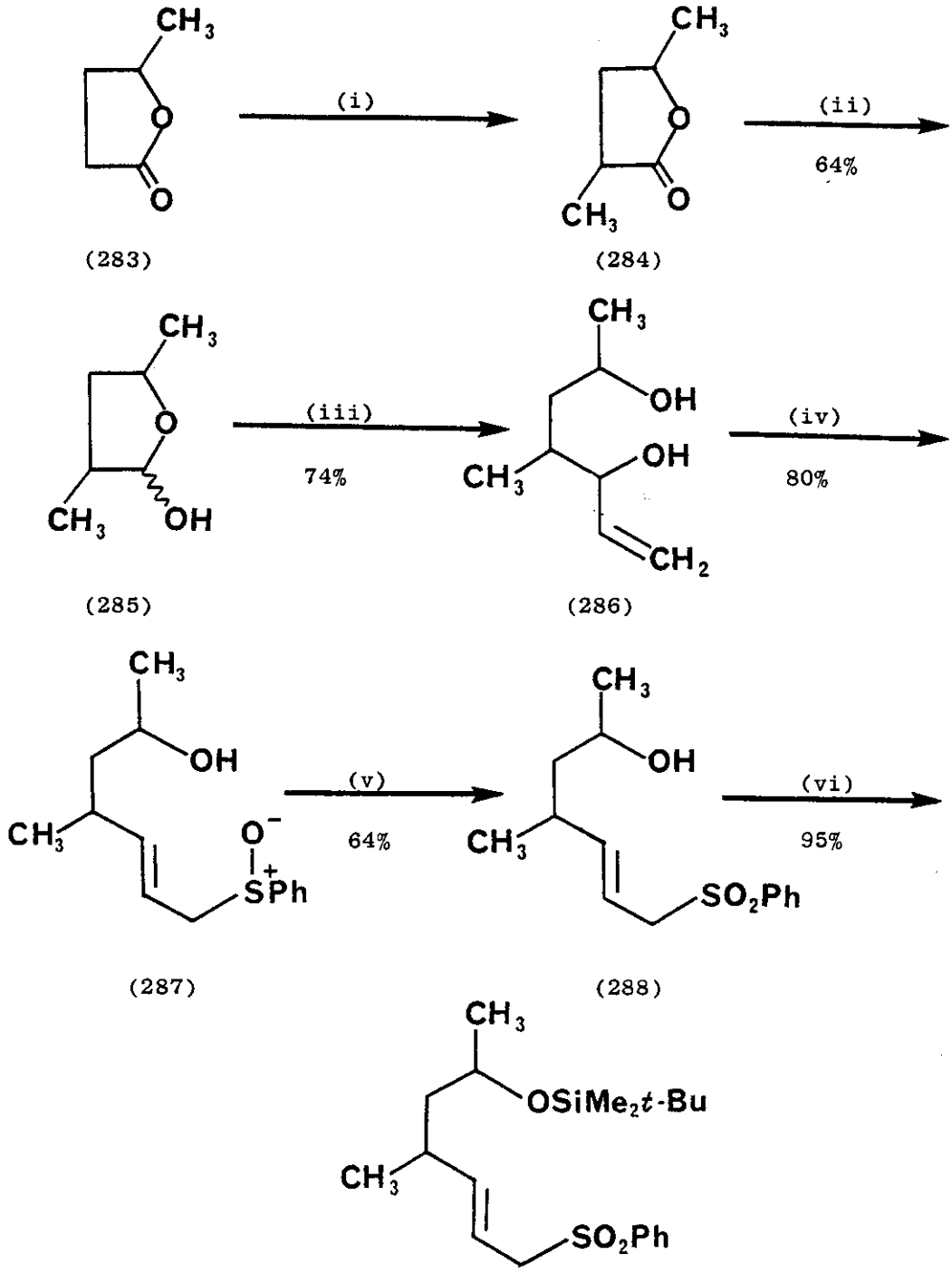


(281)



(282)

Initial approaches to the synthesis of the synthons (281) and (282) are outlined (Scheme 49).

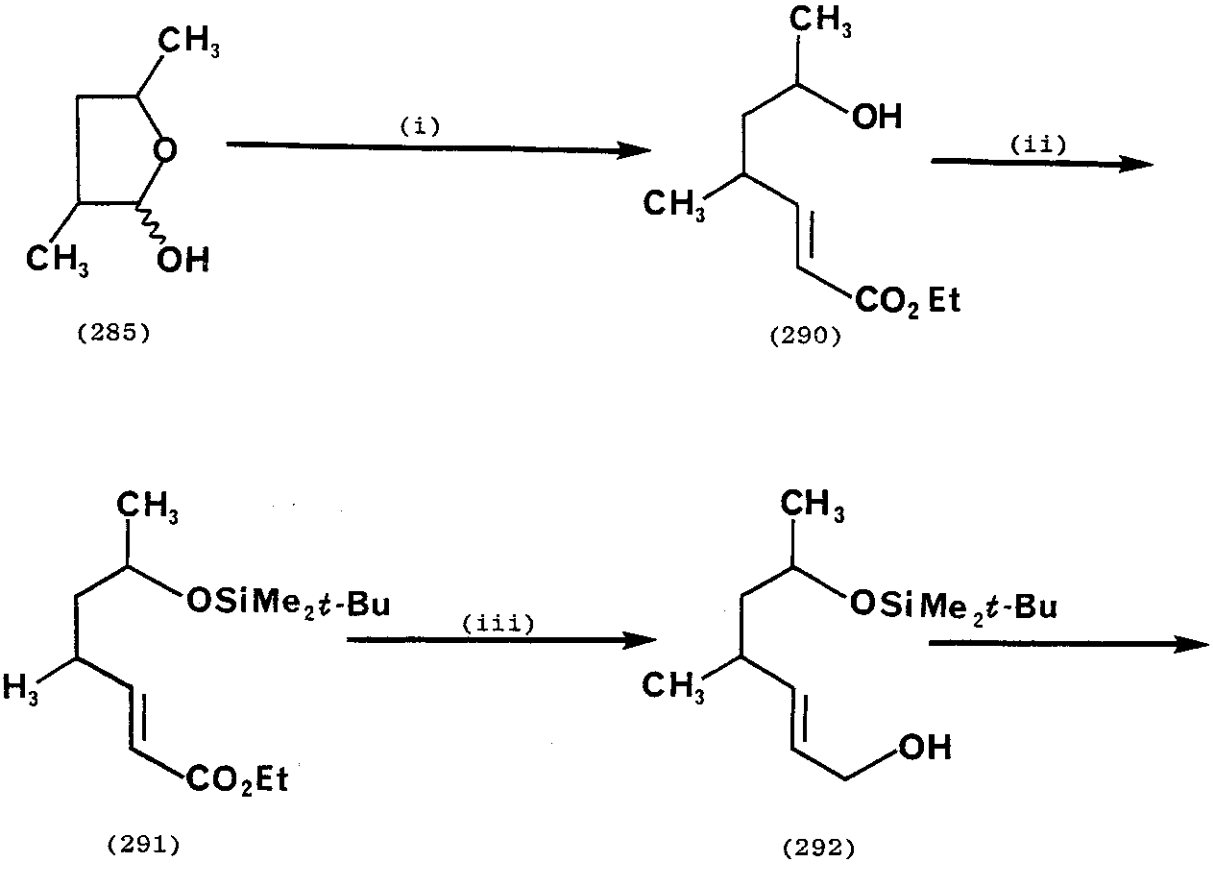


Reagents (i) LDA, MeI; (ii) DIBAL-H;

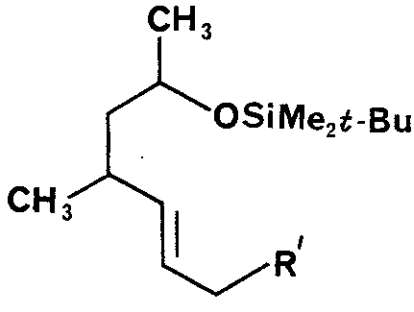
(iii) CH_2=CHMgBr; (iv) n-BuLi, PhSCl, $P(OEt)_3$;

(v) m-CPBA; (vi) t-$BuMe_2SiCl$, imidazole.

Scheme 49



(285) (290) (291) (292)



Reagents

(iv) (293) R' = OTs

(v) (294) R' = $P(O)Ph_2$ (27% from 292)

(vi) (295) R' = $S(isoC_3H_7)$ (47% from 292)

(ii) (296) R' = S(O)Ph (from 287)

(vii) (297) R' = SPh (70% from 296)

Reagents

(i) $Ph_3P = CHCO_2Et$;

(ii) t-$BuMe_2SiCl$, imidazole;

(iii) DIBAL-H;

(iv) n-BuLi, TsCl;

(v) Ph_2PLi, [O] air;

(vi) Me_2CHSLi;

(vii) $(CF_3CO)_2O$, NaI.

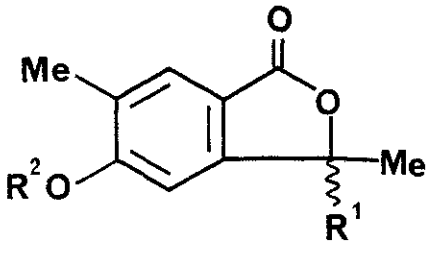
Scheme 50

The allylic sulphone (288) was prepared in 18% overall yield from racemic 5-methyl-tetrahydrofuran-2-one (283) in 5 steps. Notably, the reagent-approach controlled alkylation of the lactone (283) led to a 9:1 mixture of *trans* : *cis* isomers (284).

Attempted Julia coupling[51] of the lithiated derivatives of the sulphones (288) and (289) with the aromatic ketone (252) were unsuccessful.

The phosphine-oxide (294) was prepared, *via* the tosylate (293), in four steps from the lactol (285) in 10% overall yield (Scheme 50). However, Horner-Wittig condensation[41,96] of the lithiated derivative of (294) with the aromatic ketone (252) was not successful.

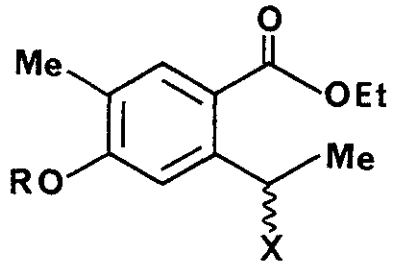
The sulphide (295) was prepared, in 47% yield from the allylic alcohol (292), *via* the unstable tosylate (293), and the sulphide (297) in 70% yield, by deoxygenation[92] of the sulphoxide (296) (Scheme 50). Unfortunately, under the conditions of Yamamoto *et al.*[93] the ate-complexes derived from the sulphides (295) and (297) failed to give addition products either with the aromatic ketone (252) or with acetophenone.

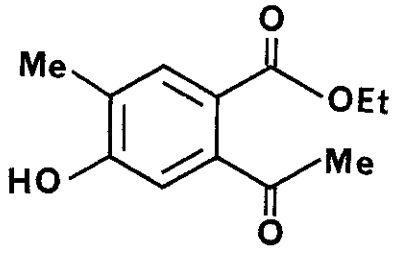


(298) R^1 = CH:CH_2, R^2 = $SiPh_2Bu^t$
(299) R^1 = H, R^2 = H
(300) R^1 = H, R^2 = $SiPh_2Bu^t$

TABLE 12

TABLE 12 cont.



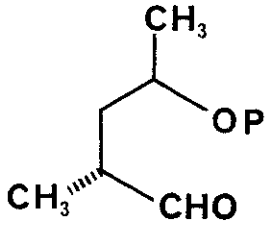


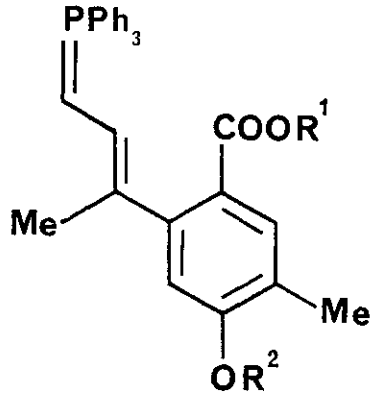
(195)

(302) X = OTs
(303) X = Br
(304) X = OH
(305) X = $P(O)Ph_2$
(306) X = SO_2Ph

R = H

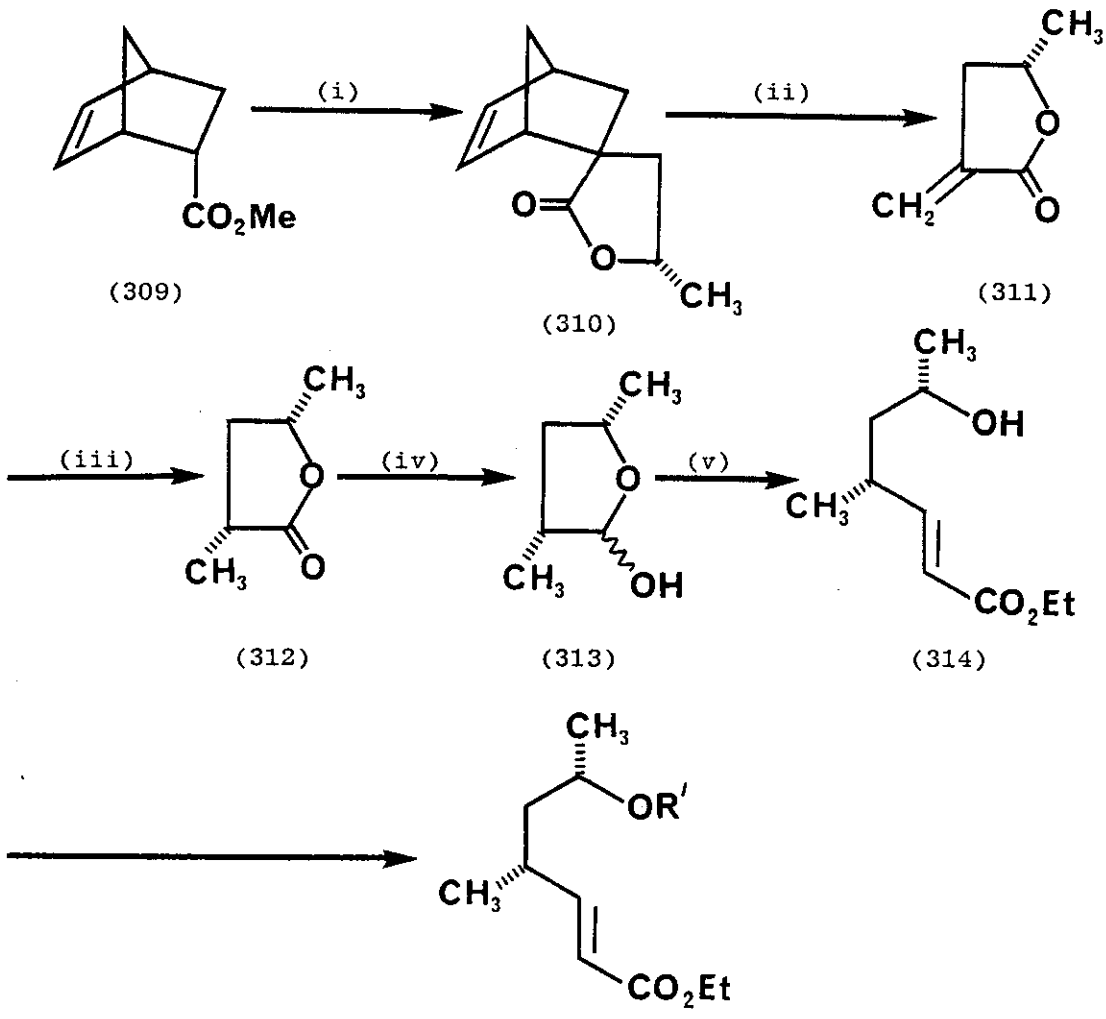
The synthesis of the *C*-9 to *C*-14 fragment has also been explored *via* a synthetic sequence which envisaged Horner-Wittig coupling of the phosphorane (308) with the chiral aldehyde (307). Unfortunately,





(307) (308)

the attempted preparation of the Wittig reagent (308), by an S_N2' displacement reaction on the vinyl phthalide (298) failed completely using Ph_3P-TMSI.



Reagents

(i) LDA, (S)-(-)-$CH_3\overset{O}{\overset{/}{C}}HCH_2$, HCl;

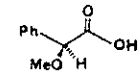
(ii) 660°C, 0.15 mm/Hg;

(iii) H_2/Pd;

(iv) DIBAL-H;

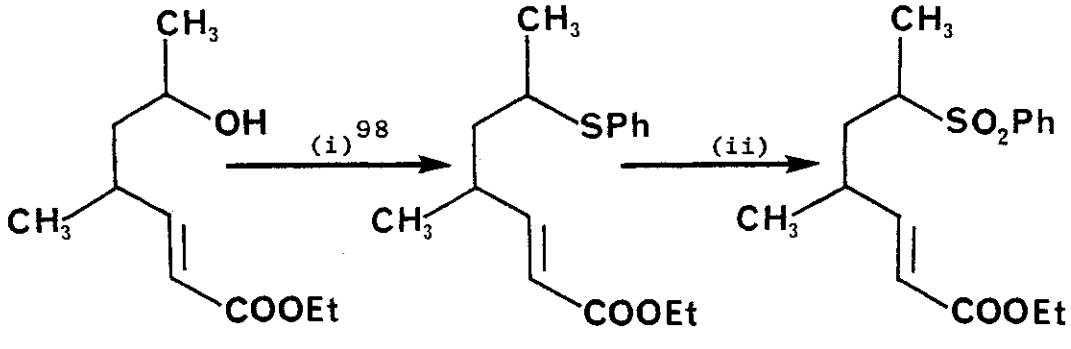
(v) $Ph_3P{=}CHCO_2Et$;

(vi) t-$BuMe_2SiCl$, imidazole;

(vii)  , DMAP, DCC.

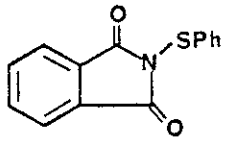
Scheme 51

The synthesis of the unsaturated north-western (NW) unit of milbemycin β_3 in optically active form has recently been completed (Scheme 51). The approach hinges on the ability of the 5-position methyl group of the α-methylene lactone (311) to direct the highly diastereoselective catalylic hydrogenation to the saturated lactone (312). The α-methylene lactone (311) has been synthesised, enantiomerically pure, from the norbornyl ester[97] (309) and (*S*)-(-)-propylene oxide[94] in 40% yield. The diastereoselection of the hydrogenation step was shown to be *ca.* 25:1 *cis-* : *trans*, thus setting the *C*-12 methyl group with the correct configuration. The stereochemical integrity of the α, β-unsaturated ester (314) was confirmed by n.m.r. spectral analysis of the t-butyldimethylsilyl ether (315) and the (*S*)-*O*-methylmandelate ester (316). Work carried out on the model system has shown that the sulphone (318) is readily available, from the alcohol (290) (Scheme 52).



(290) (317) (318)

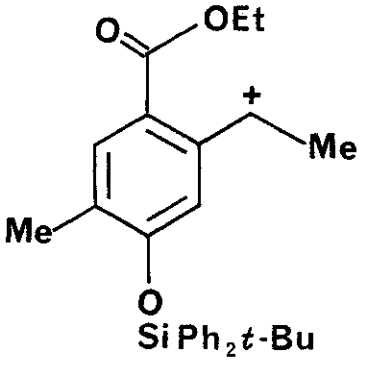
Reagents

(i)  , *n*-Bu_3P ;

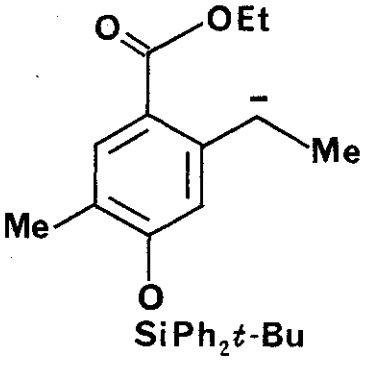
(ii) m - CPBA

Scheme 52

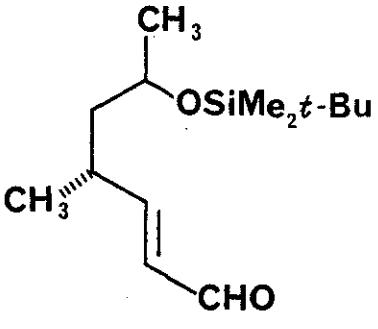
Failure to effect the *C*-8 to *C*-9 bond formation, using the synthons (281) and (253), led us to examine the possibility of using the aromatic residue as the nucleophilic partner (319), for coupling with the aldehyde (320). The conversion of the aromatic ketone (195) to



(253)



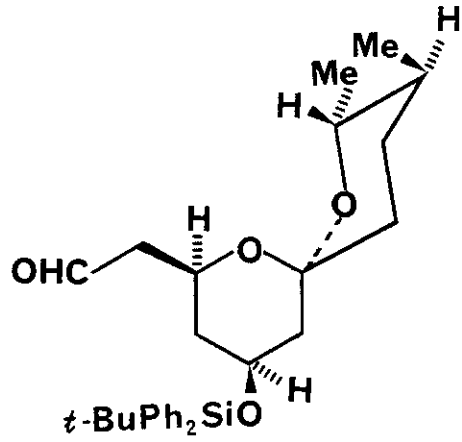
(319)



(320)

the benzylic sulphone (306) or the phosphine-oxide (305) was not possible *via* either the hydroxy derivative (304) or the tosyloxy derivative (302). All attempts at the reduction of the ketonic function of the aromatic ester (195) led to the isolation of the phthalide (299). Current work is aimed at the transformation of the phthalide (299) to both the sulphone (306) and the phosphine-oxide (305).

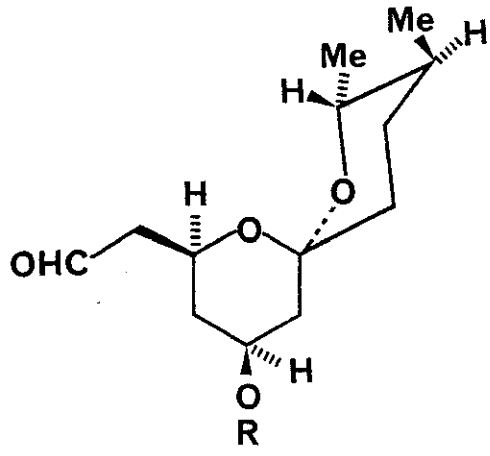
The rational behind our decision to use the unsaturated north-western (NW) unit as the nucleophilic partner in the coupling reaction with the spiro-acetal moeity (321) was based on the findings of Kocienski[95] who has shown that formation of trisubstituted carbon-carbon double bonds by coupling of tertiary carbon nucleophiles with aldehydes is feasible.



(321)

(iii) The Spiro-acetal North-Eastern (NE) Unit.

We envisaged that the spiro-acetal, north-eastern (NE) unit (145) of milbemycin β_3 would have the structure shown (322).

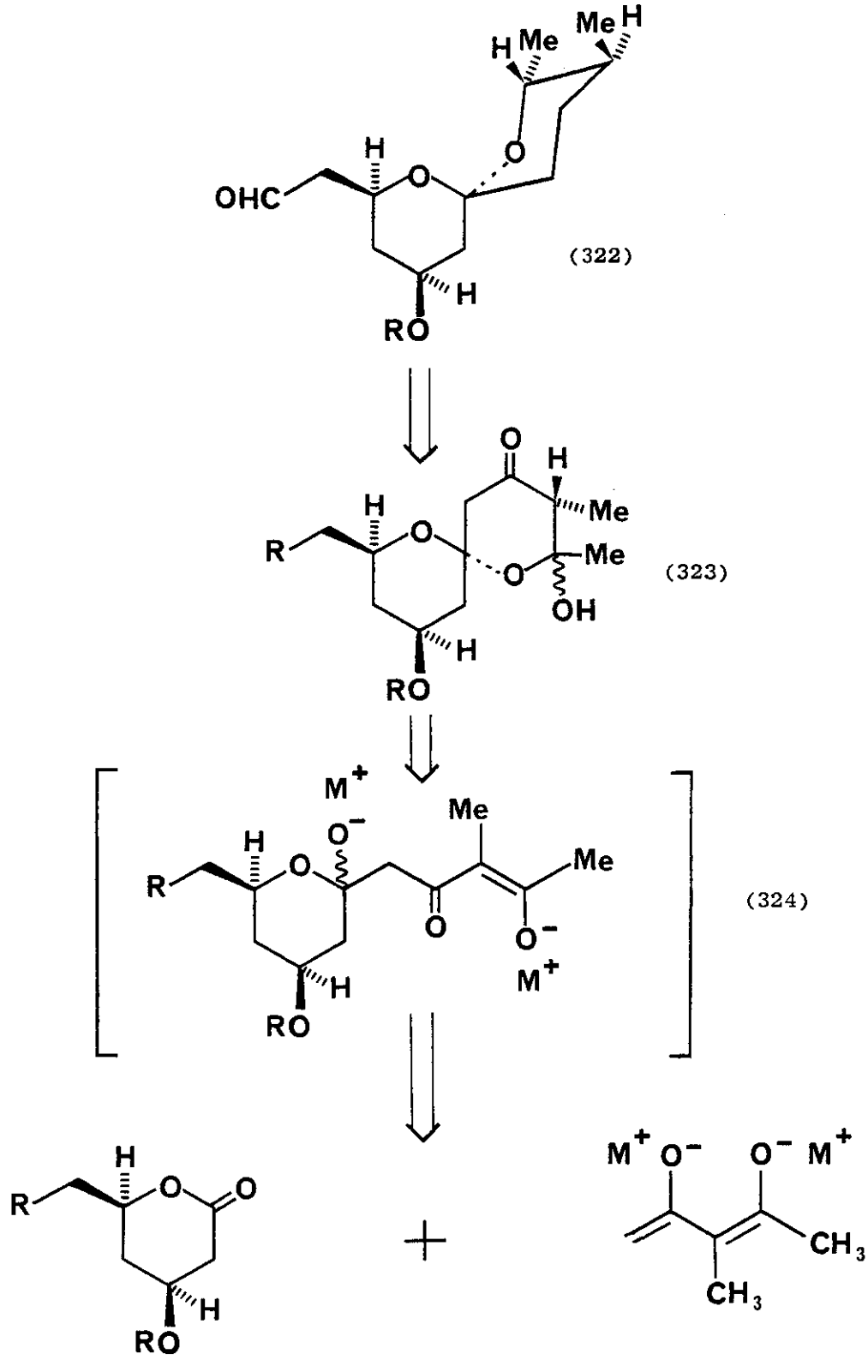


(321) R = Si Ph$_2$ *t*-Bu

(322)

This unit would be linked with the unsaturated north-western (NW) unit, *via* a Julia[51] or Horner-Wittig[41] condensation, to form the *C*-14 to *C*-15 double-bond of the milbemycin β_3 molecule with the correct *E*-geometry. Eventually, a standard macrocyclic lactonization procedure[42] could be used to complete the macrolide.

We initially considered that a concise novel route to the spiro-acetal unit (322) should be available *via* the condensation of the lactone (325) with the β-dione dianion (326) (Scheme 53). Spiro-ketalization of the initial adduct (324) should yield the spiro-cycle (323) with the stereochemistry of the ring junction, controlled by the anomeric effect,[50] such that both spiro-acetal oxygens would assume an axial configuration with respect to the adjacent ring. The stereochemistry of the spiro-cyclic centre should, in turn, control the stereochemistry of the required equatorial methyl group at


Me H
H Me
H
O
OHC
H
RO
(322)
O
H
Me
R
H
O
Me
O
OH
H
RO
(323)
M+
O−
Me
H
R
O
Me
O
O−
M+
H
RO
(324)
H
O
O
R
H
RO
(325)
M+ O−
O− M+
CH3
CH3
(326)

Scheme 53

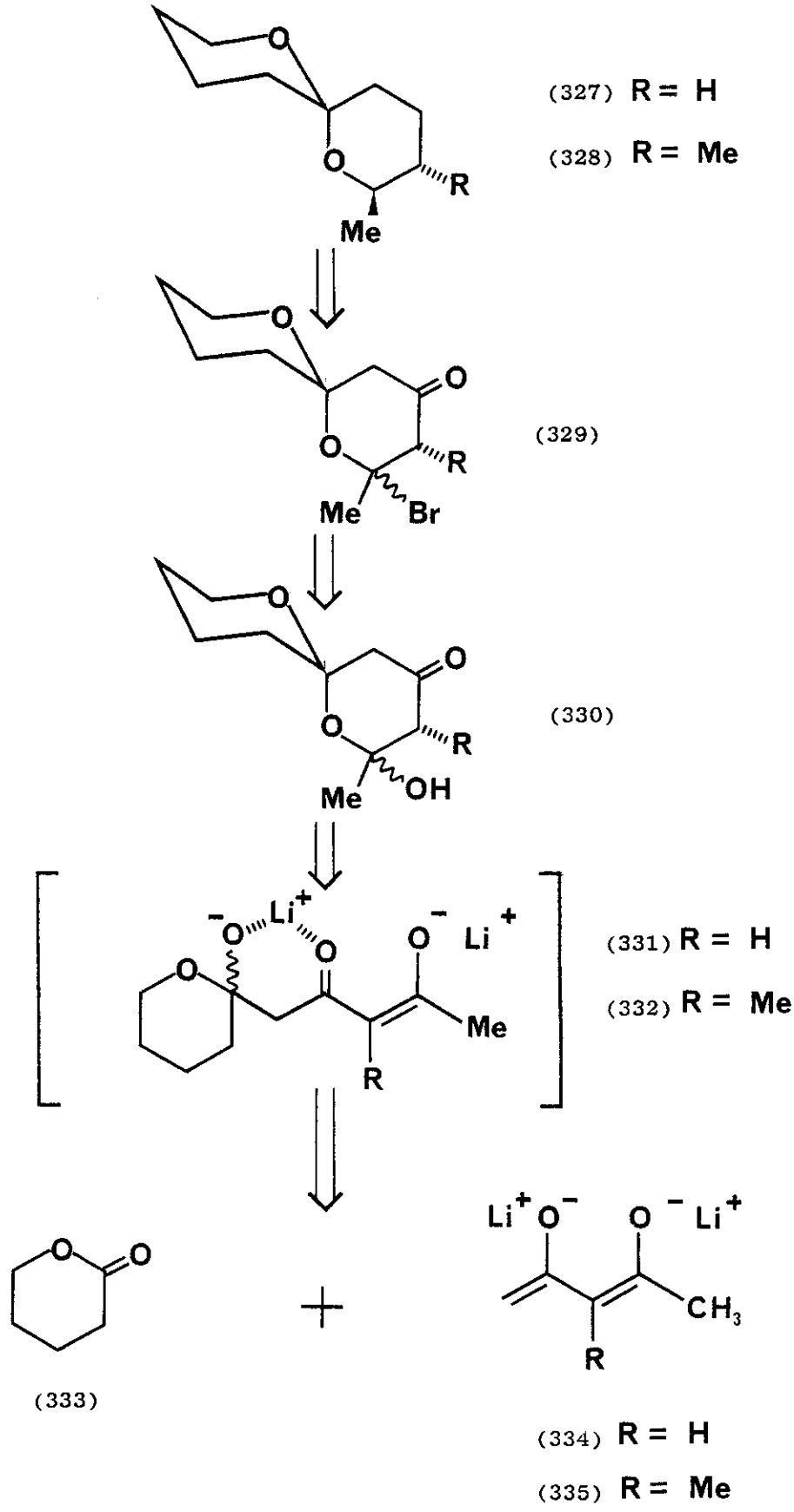
the epimerizable centre α to the carbonyl group. Controlled reduction of the spiro-cycle (323) should then afford the required spiro-acetal unit (322), with the correct orientation of the two methyl groups.

In order to investigate the feasibility of this route a series of model reactions were undertaken.

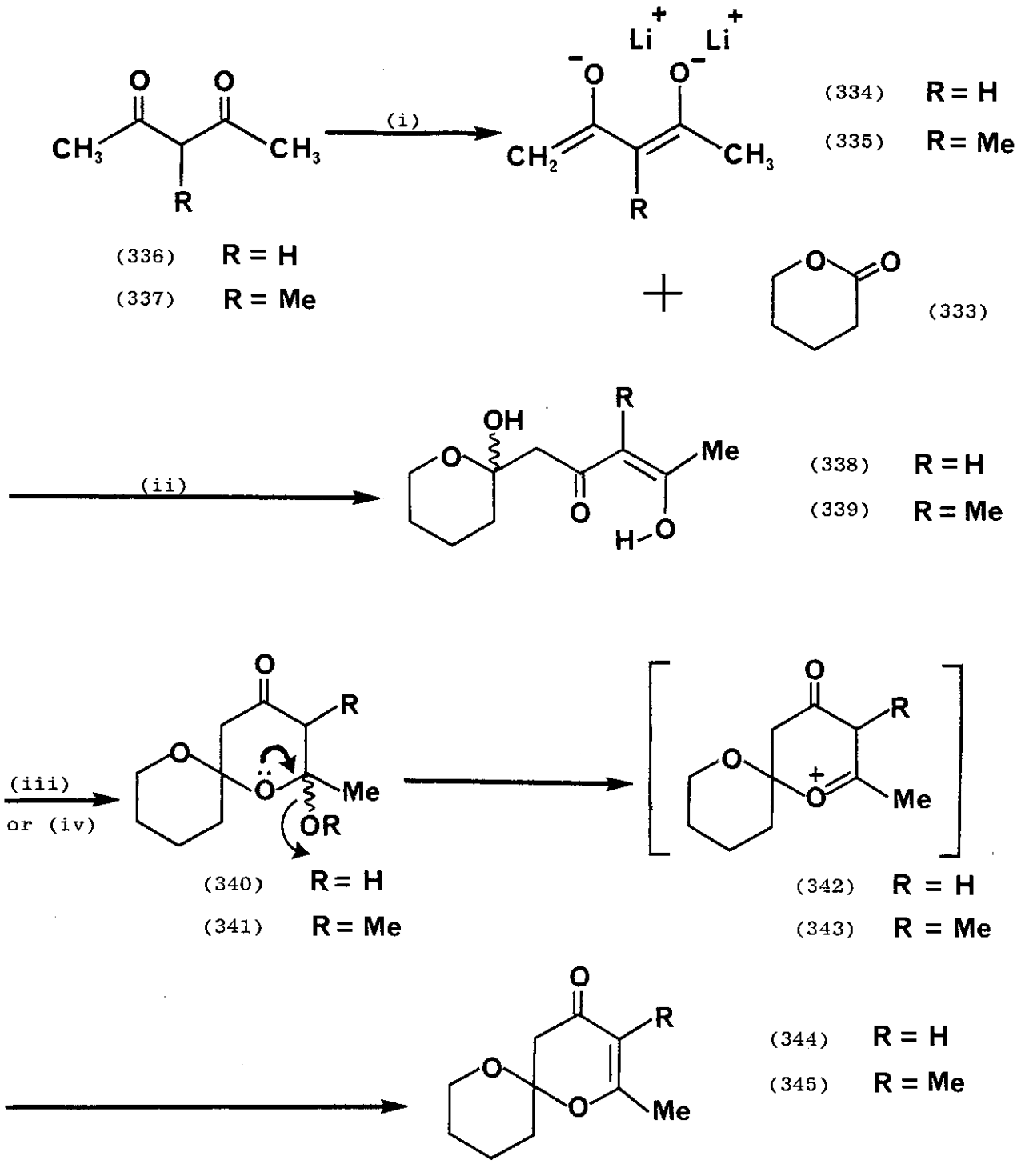
a) Model studies towards the synthesis of the spiro-acetal unit (322).[99]

The following model studies are the work of Dr. Jean-Claude Florent, one of our co-workers on the project, and are only briefly outlined here.

These studies involved the addition of the 2,4-pentandione dianion (334), and the 3-methyl-2,4-pentandione dianion (335), to tetrahydropyran-2-one (333). Subsequently attempts were made to effect the conversion of the resultant aldol products (331 and 332) to their respective saturated spiro-acetals (327 and 328) (Scheme 54). Accordingly, 2,4-di(lithio-oxy)penta-1,3-diene (334), prepared using lithium diisopropylamide, was condensed with tetrahydropyran-2-one (333) in tetrahydrofuran (THF) at -78°C to 0°C over 2 h. Quenching of the reaction at -78°C with an exact equivalent of acetic acid led to the isolation of the required aldol product (338) (95%). The spiro-dihydropyrone (344) (60%) was obtained by treatment of the aldol product (338) with toluene-4-sulphonic acid and 3A molecular sieve in benzene at the reflux. Obviously, the initial ring-closed spiro-acetal (340) was undergoing facile elimination of the elements of methanol, probably *via* the oxonium ion (342) (Scheme 55). The compound (344) was fully characterized and shown unambiguously to be spiro-cyclic.



Scheme 54



(i) 2 eq LDA/THF/0°C/1 h.

(ii) -78→0°C/-78°C HOAC.

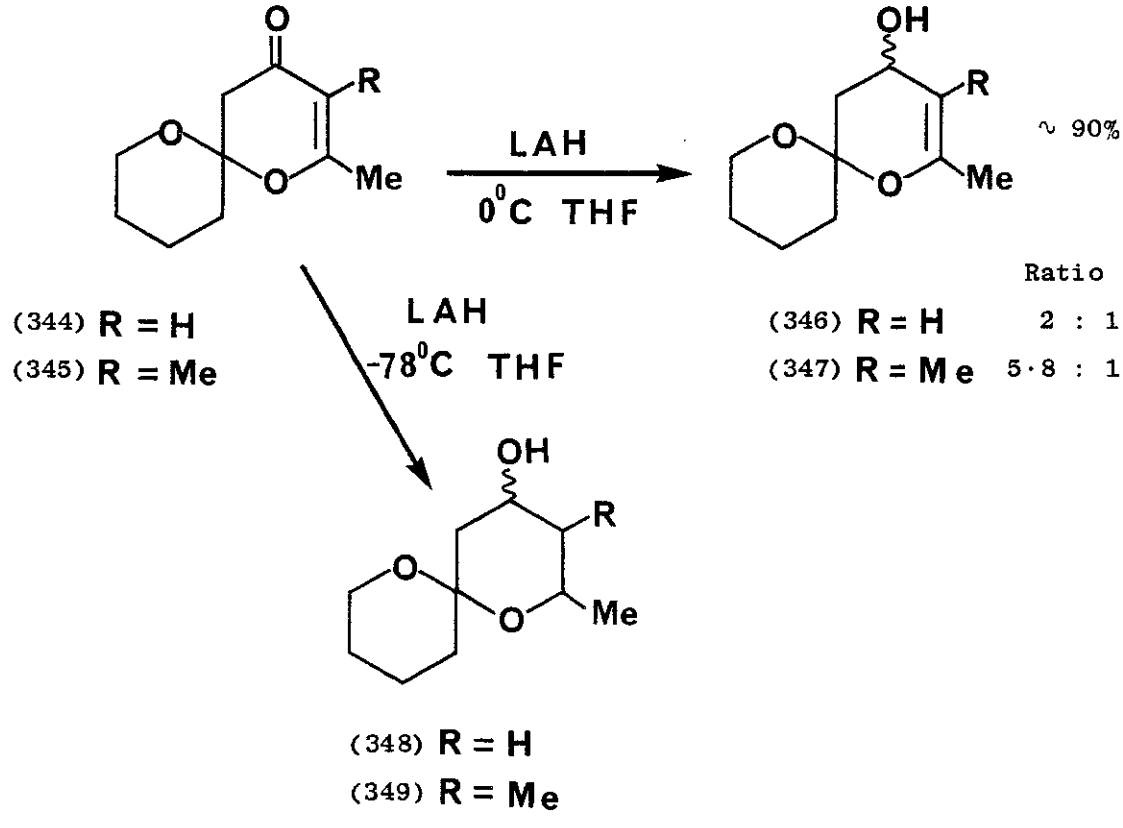
(iii) TsOH/3A molecular sieve/CH_2Cl_2.

(iv) TsOH/Benzene.Reflux.

Scheme 55

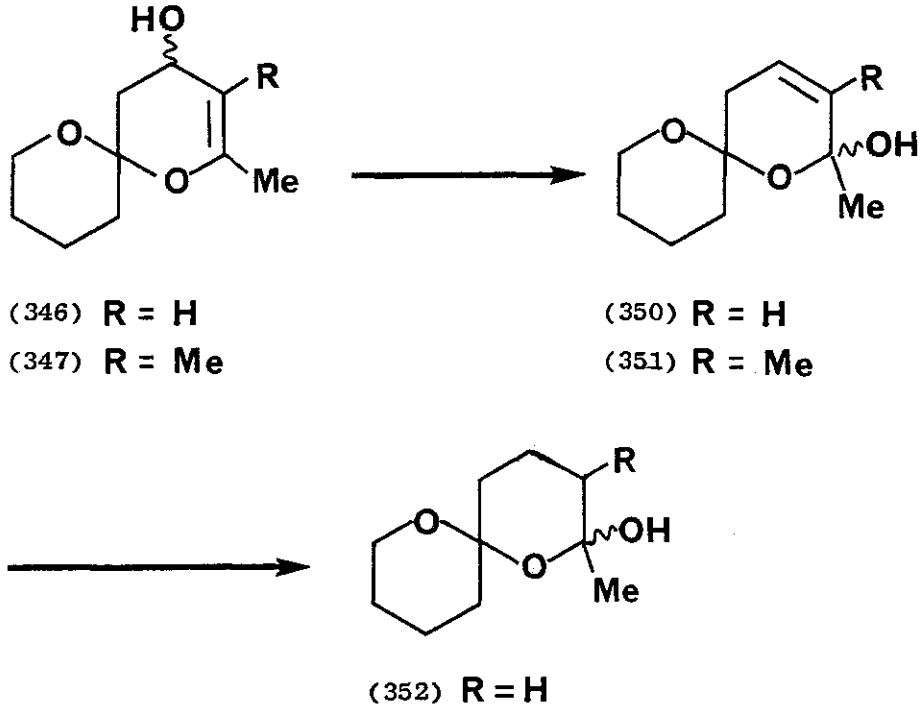
In a separate experiment, the crude aldol product (338) was directly cyclised using toluene-4-sulphonic acid and 3A molecular sieve in dichloromethane to afford the spiro-dihydropyrone (344) in 88% overall yield. Using the same sequence of reactions, the spiro-dihydropyran-2-one (345) (68%) was prepared from 3-methyl-2,4-pentadione (337) (Scheme 55).

The spiro-dihydropyrone (344) reacted with lithium aluminium hydride (LAH) in dry tetrahydrofuran at $0^{o}C$ to afford the 1,2-addition product (346) (90%) as a mixture of diastereoisomers (2:1) (Scheme 56) which could be separated by chromatography on alumina. Similar treatment of the dimethyl spiro-dihydropyrone (345) afforded the allylic alcohol (347) (88%) (Scheme 56) again as a separable mixture of diastereoisomers (5·8:1).



Scheme 56

Attempted isolation of the allylic alcohol (346) by column chromatography on silica gave the rearranged allylic alcohol (350) (64%) which existed as a mixture of ring open and closed forms. Hydrogenation of the spiro-cycle (350) over 5% rhodium on alumina gave the crystalline spiro-acetal (352) (Scheme 57).



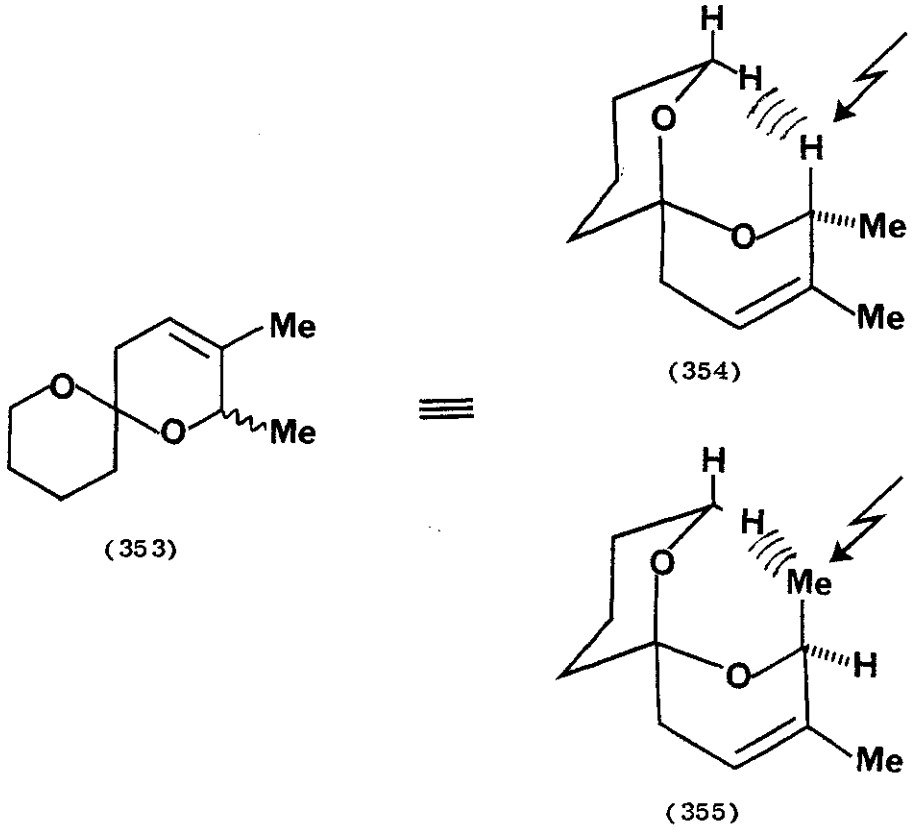
(346) R = H
(347) R = Me

(350) R = H
(351) R = Me

(352) R = H

Scheme 57

Treatment of the allylic alcohol (347) with lithium aluminium hydride and aluminium chloride (1:4) in tetrahydrofuran at $0^{o}C$, gave the transposed allylic alcohol (351) (50%) and two diastereoisomeric olefins (353). The two epimers (354 and 355) (Scheme 58) were readily distinguished by nuclear Overhauser effect (n.O.e.) experiments.



Scheme 58

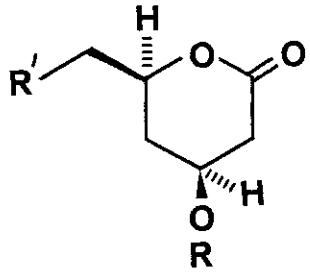
An attempt was made to reduce the spiro-dihyropyrone (345) directly, in a one-pot reaction, to the diastereoisomeric olefins (353). Thus, addition of the spiro-compound (345) to 1:1 mole equivalents of LAH in tetrahydrofuran at $0^{\circ}C$ followed by inverse addition to LAH and aluminium chloride (1:4) in tetrahydrofuran at -78° to $0^{\circ}C$ gave the spiro-acetals (355) (22%) and (354) (7%), and the isomeric allylic alcohol (351) (45%). Using boron trifluoride-diethyl ether and diborane (2:1), instead of lithium aluminium hydride-aluminium chloride, the same products (355 and 354) (40%) were obtained but with a less favourable ratio (1:1).

Unfortunately, due to the departure of Dr. Florent from the group, work on these systems was suspended. Since the overall yield of the olefin (355) was very poor this route to the spiro-acetal unit (322) was superceded by the acetylenic anion/lactone condensation procedure

of Deslongchamps *et al.*[100]

b) Preparation of the functionalized lactone (356).

Construction of the spiro-acetal, north-eastern (NE) unit (145) of milbemycin β_3 was envisaged to require the initial preparation of a functionalized lactone (356) of the type shown.



(356)

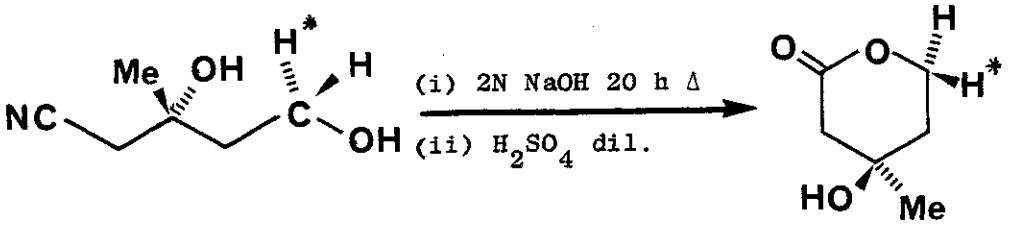
(357) $R' = COOH$, $R = H$

(358) $R' = OH$, $R = H$

(359) $R' = OSiMe_2t\text{-}Bu$, $R = -SiMe_2t\text{-}Bu$

A requisite of the lactone (356) was that it should contain a group R' which could be easily modified to afford an aldehyde function after formation of the spiro-cycle. We therefore chose to prepare the lactone (357) which, we felt, would be amenable to the construction of the spiro-acetal moiety *via* the initially conceived β-dione dianion route.

Cornforth *et al.*[101] have shown that the nitrile (360) may be readily hydrolysed to afford, on acidic work-up, mevalonic acid lactone (361) (Scheme 59);

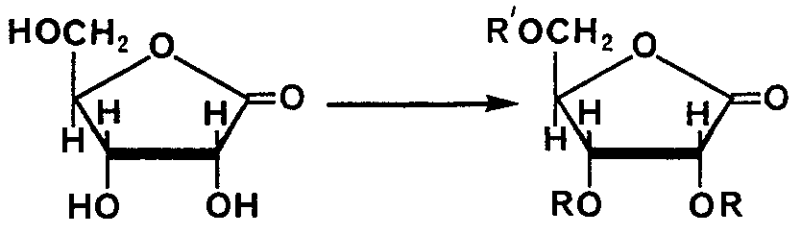


(360) (361)

Scheme 59

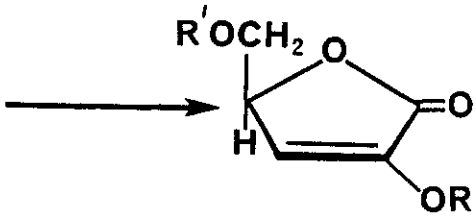
we believed that similar treatment of the dinitrile (376) would afford the lactone (357). A chiral synthesis of the dinitrile (376) was subsequently proposed starting from D-(+)-ribonic acid-γ-lactone (362) (Scheme 60). Notably, the presence of a sterically demanding substituent at the *C*-5 position of the enone (367) would direct the stereoselective reduction to the lactone (371), thus inducing the required *S*-configuration at the *C*-2 position.

Weidmann and his co-workers[102] have shown that 2,3,5-tri-*O*-benzyl-D-ribonic acid-γ-lactone (379) may be converted to the enone (380) (91%) by treatment with 1,5-diazobicyclo[5.4.0]undec-5-ene (DBU) in HMPA at 45°C (Scheme 61).



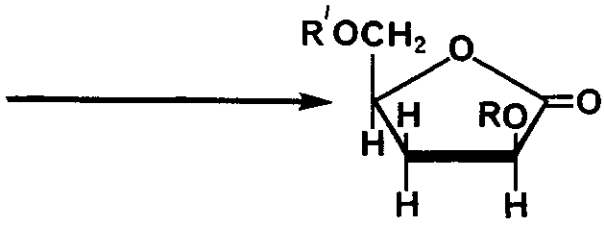
(362) (363)

(364) R = R′ = -SiMe$_2$*t*-Bu
(365) R = Ac ; R′ = -CPh$_3$
(366) R = R′ = Ac



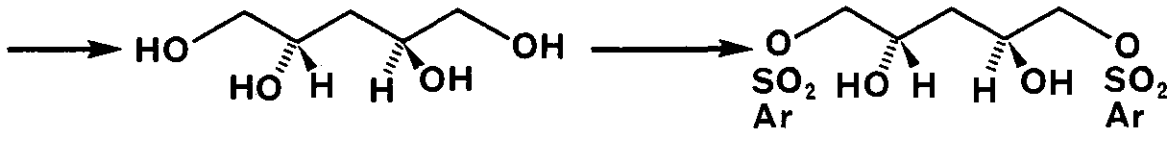
(367)

(368) R = R′ = -SiMe$_2$*t*-Bu
(369) R = Ac ; R′ = -CPh$_3$
(370) R = R′ = Ac



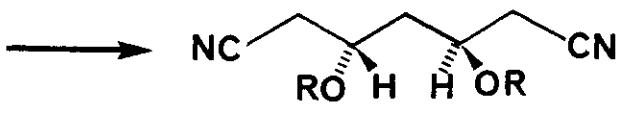
(371)

(372) R = R′ = Ac



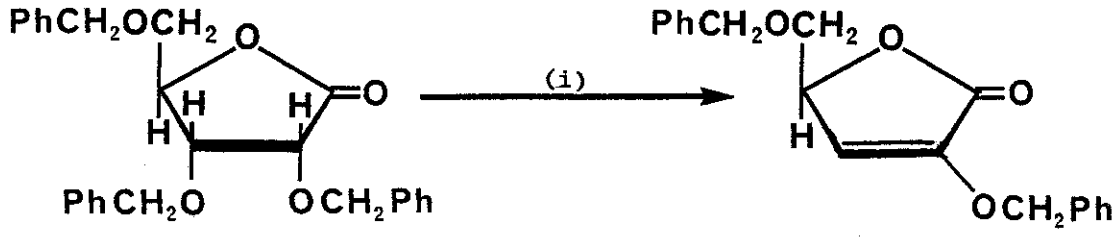
(373)

(374) Ar = -C$_6$H$_4$-4-CH$_3$
(375) Ar = -C$_6$H$_2$-2,4,6-*i*-Pr



(376) R = H
(377) R = -OCOPh
(378) R = -SiMe$_2$*t*-Bu

Scheme 60



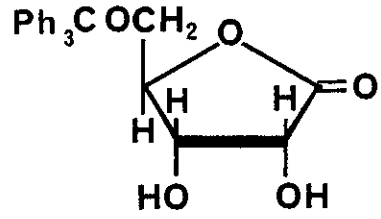
(379) (380)

Reagents (i) DBU/HMPA/45°C/5 min.

Scheme 61

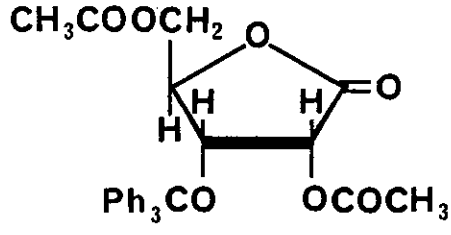
Initially, the tri-silyl ether (364) (96%) was prepared from D-(+)-ribonic acid-γ-lactone (362). Unfortunately, attempts to form the enone (368) from the protected lactone (364), by treatment with DBU in benzene at room temperature, and with lithium diisopropylamide in dry tetrahydrofuran at -78°C, led to the recovery of the starting material in virtually quantitative yield. Obviously, for facile elimination a better leaving-group was required at the *C*-3 position of the lactone (363); we believed that the acetate group would meet this requirement.

Treatment of D-(+)-ribonic acid-γ-lactone (362) with one mole equivalent of chlorotriphenylmethane gave predominately the expected primary protected hydroxy lactone (381) which was converted *in situ* to 2,3-Di-*O*-acetyl-5-*O*-triphenylmethyl-D-ribonic acid-γ-lactone (365) in 45% overall yield.



(381)

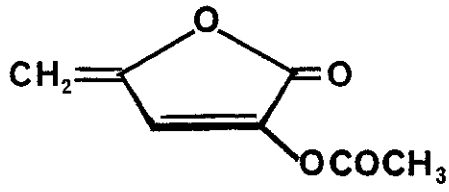
A quantity of 2,5-di-*O*-acetyl-3-*O*-triphenylmethyl-D-ribonic acid-γ-lactone (382) (10%) was also isolated.



(382)

Treatment of the lactone (365) with DBU in tetrahydrofuran at room temperature for 15 min led to the isolation of the required enone (369) (55%).

Concurrently with this work, 2,3,5-tri-*O*-acetyl-D-ribonic acid-γ-lactone (366) was prepared and treated with DBU in benzene at room temperature to afford 3-acetoxy-5-methylenefuran-2(5H)-one (383), the product of double elimination of the elements of acetic acid. Attempted conversion of the lactone (366) to the enone (370) by treatment with toluene-4-sulphonic acid monohydrate, in benzene at the reflux for two days, was unsuccessful.

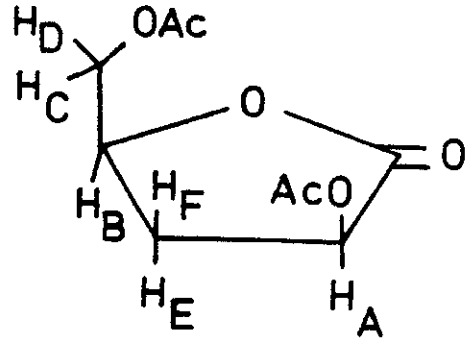


(383)

The furanone (383) was found to be a useful intermediate in the preparation of nonactic acid by another member of the research group.[103] During the course of this work it was found that the mono-eliminated lactone (370) could be prepared, by treatment of the lactone (366) with a suitable base at low temperature, but that this compound rapidly underwent a second elimination, to afford the unwanted furanone (383), on attempted purification by chromatography on silica. Consequently, a mixture of (5*S*)-3-acetoxy-5-[(acetoxy)methyl]furan-2(5*H*)-one (370) and the furanone (383) (2:1), prepared by treatment of the lactone (366) with 1 mole equivalent of DBU in tetrahydrofuran at -78°C, was hydrogenated directly over 10% palladium on carbon in ethanol. Chromatography on silica then afforded (3*S*, 5*S*)-3-acetoxy-5-[(acetoxy) methyl]dihydrofuran-2(3*H*)-one (372) in 46% yield from the lactone (366). The overall yield for these two combined steps was increased to 56% by the use of a modified procedure. Thus, the elimination reaction was quenched, at -78°C, by addition of water and the products extracted into diethyl ether. The combined extracts were concentrated to small volume, diluted with ethanol and the mixture hydrogenated over 10% palladium on carbon to afford the required lactone (372).

Nuclear Overhauser effect (n.O.e.) difference spectroscopy was used to confirm the *S*-configuration for the *C*-2 position of the

lactone (372). The n.O.e. difference spectrum of (3*S*,5*S*)-3-acetoxy -5-[(acetoxy)methyl]dihydrofuran-2(3*H*)-one (372) (fig. 2) was obtained using a

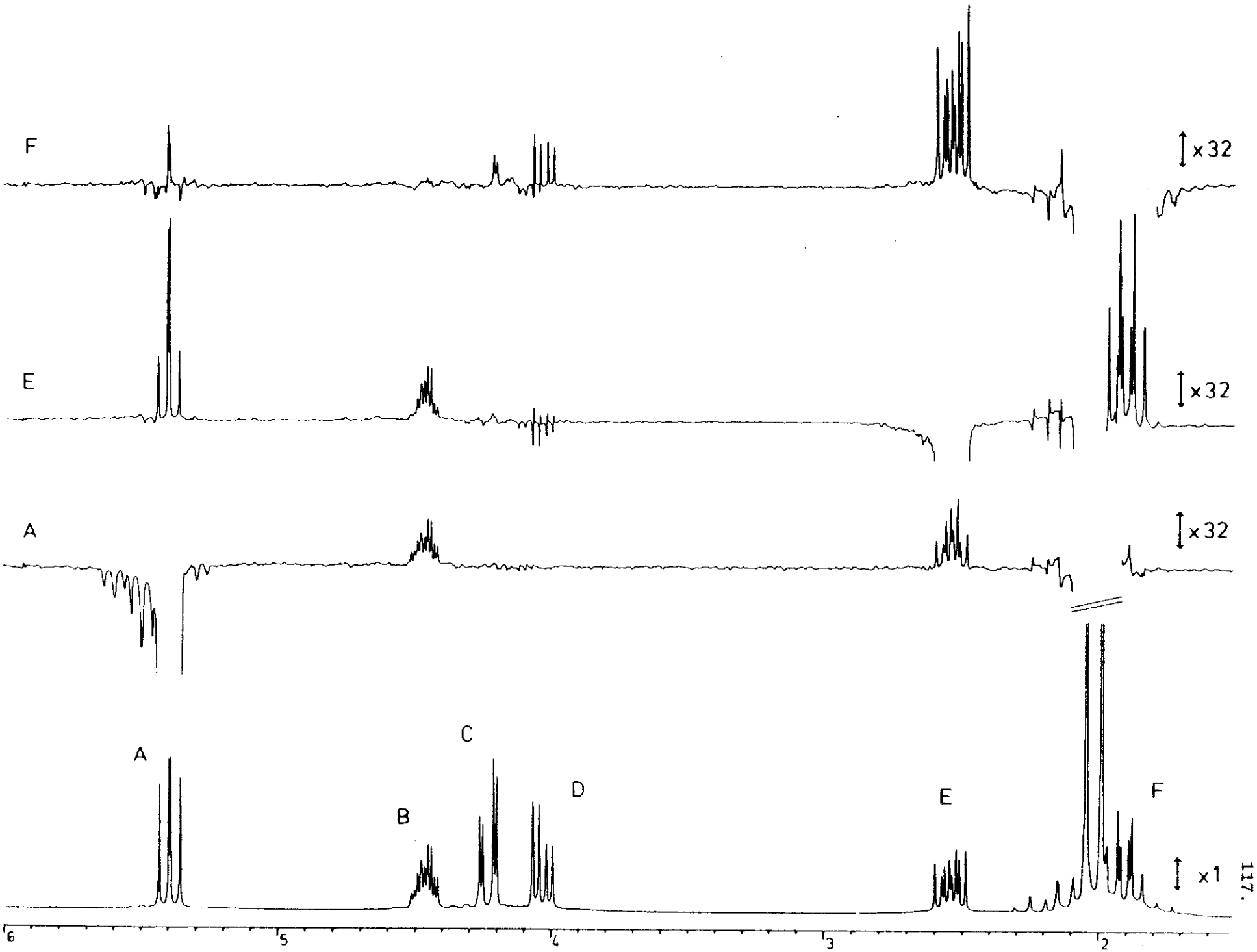


(fig. 2)

simple method for suppressing the unwanted complications produced by selective population transfer (S.P.T.).[104] The result is a difference spectrum in which only those multiplets enhanced by the n.O.e. appear (fig. 3); multiplets due to protons coupled to, but remote from, the pre-irradiated proton do not appear in the difference spectrum. Thus, pre-irradiation of the proton H_A led to the expected n.O.e. enhancement of the multiplets due to protons H_B and H_E; no effect was noted at the multiplet due to proton H_F. Pre-irradiation of the proton H_E led to n.O.e. enhancement of the multiplets due to protons H_A, H_B and H_F, plus a small enhancement of the multiplet due to proton H_D. Finally, pre-irradiation of the H_F proton led to the expected n.O.e. enhancements of the multiplets due to protons H_C, H_D and H_E, plus a small enhancement of the multiplet due to proton H_A.

With the successful preparation of lactone (372) the previous work on the triphenylmethyl protected lactone (365) was suspended.

In a series of small scale experiments, monitored by n.m.r. spectroscopy, the suitability of various other bases for use in the conversion of lactone (366) to enone (370) were investigated (TABLE 13).

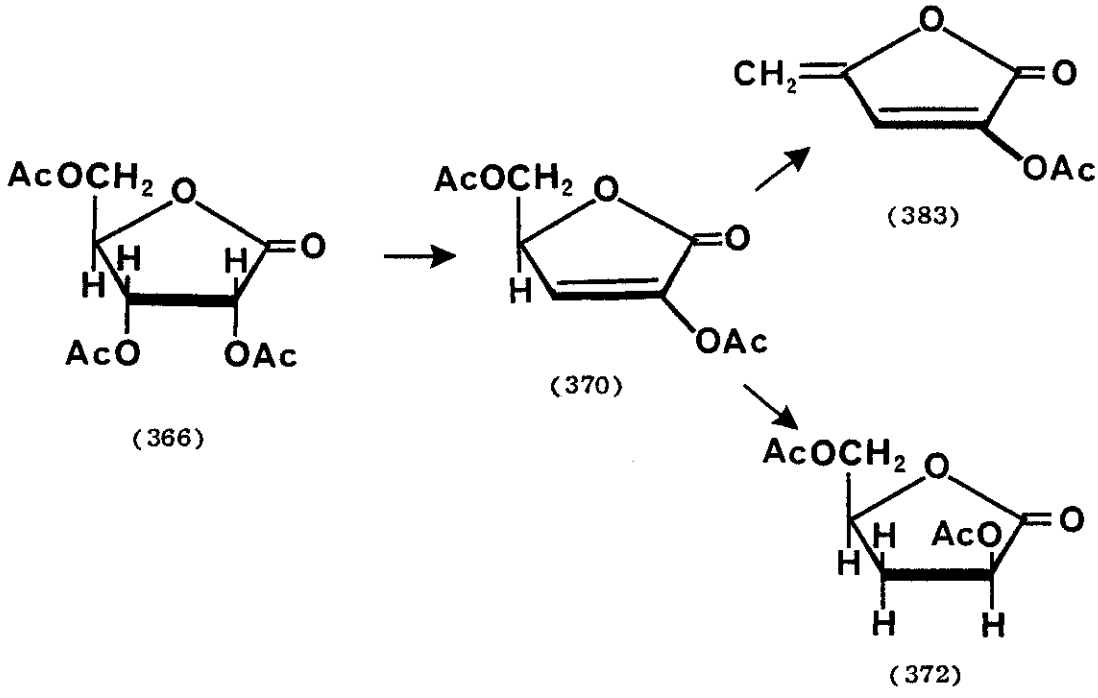


(fig. 3)

117.

TABLE 13

The Use of Alternative Bases in the Preparation of the Enone (370).



Base	Conditions	Product
KO^tBu	THF/-78°C/5 h	(366) / (383) 2:1[a]
NaH	THF/RT/20 h	(366) + (383) + Polymer[a,b]
Li $N(SiMe_3)_2$	THF/0°C/3 h	(372)[c] 11%
$HN[Pr^{ISO}]_2$	THF/-78°C/3 h	(366) / (383) 2:1[a]

a) As determined by n.m.r. spectral analysis.

b) As determined by t.l.c. analysis.

c) After hydrogenation over 10% Pd/C in ethanol at 1 atm.

Of the alternative bases tested none was found to be more effective than DBU which was therefore used in subsequent reactions.

Reduction of the saturated lactone (372) with sodium borohydride,

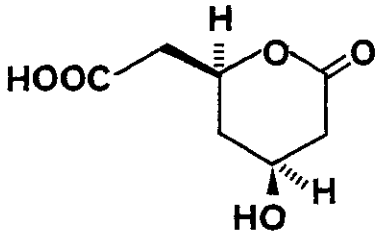
under conditions of controlled pH,[105] led to the isolation of (2*S*,4*S*)-1,2,4,5-pentanetetrol (373) in 86% yield.

Attempts at primary sulphonylation of the tetrol (373), with toluene-4-sulphonyl chloride in pyridine, resulted in the formation of at least two major products which were neither isolated nor characterized. Reactions in chloroform and acetonitrile containing pyridine were very slow and did not lead to the formation of a major product. However, sulphonylation with 2,4,6-triisopropylbenzenesulphonyl chloride in pyridine proceeded smoothly at room temperature to afford the disulphonate (375) in 88% yield.

Displacement of the sulphonate groups of the diol (375) with cyanide ion[106] was investigated in various solvents. Reaction of the disulphonate (375) with potassium cyanide in benzene containing 18-crown-6, at room temperature for 2 days, was unsuccessful as judged by n.m.r. spectral analysis. However, reactions using dimethyl sulphoxide and ethanol as solvents proceeded smoothly overnight to afford a single major product, as judged by t.l.c. analysis, which was later shown to be the required (3*S*,5*S*)-3,5-dihydroxyheptane-1,7-dinitrile (376). Methanol was eventually chosen as the most effective and convenient solvent for this reaction. Due to some initial difficulty in the isolation of the dinitrile (376) the reaction mixture was concentrated *in vacuo* and treated with excess benzoyl chloride in pyridine at room temperature overnight to afford, on work-up, the dibenzoate (377) in 34% overall yield.

Attempts to convert the dibenzoate (377) to the diol (376), using the strong base ion-exchange resin procedure of Reed *et al.*[107] led to the recovery of starting material (87%). Attempted methanolysis of the

dibenzoate (377) using the standard Zemplén procedure[108] resulted in the formation of a complex mixture of polar products. Hydrolysis of the dibenzoate (377) with sodium hydroxide in methanol followed by acidification in an attempt to obtain the lactone (357) directly was



(357)

also unsuccessful resulting in the isolation of a complex mixture of polymeric products.

Eventually, the dinitrile (376) (69%) was isolated directly from the reaction mixture by treatment sequentially with Amberlyte IR $120H^+$ and Amberlyst A-21(OH^-) resins followed by chromatography on silica. In a separate experiment the dinitrile (376) was isolated, in 59% yield from the concentrated reaction mixture, by medium pressure chromatography on silica.

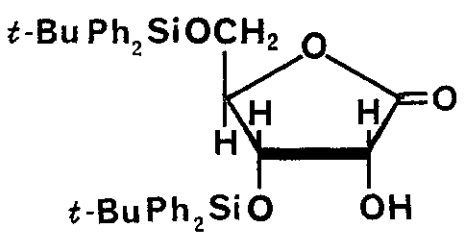
Unfortunately, attempts to hydrolyse the dinitrile (376) and effect ring-closure to afford the lactone (357) under various conditions were unsuccessful. Reaction of the dinitrile (376) with sodium hydroxide in water at room temperature followed by acidification with Amberlyte IR $120H^+$ resin resulted in the isolation of a complex mixture of ultra-violet active compounds; a similar mixture was obtained using acidic hydrolysis conditions (H_2SO_4). Attempted hydrolyses using both strong acid (Amberlyte IR $120H^+$) and strong base [Amberlyst A-26(OH^-)] resins were unsuccessful, with little reaction occurring over 6 days at

room temperature as detected by t.l.c. analysis.

Finally, the dinitrile (376) was converted to its silyl ether derivative (378) (96%), by treatment with t-butylchlorodimethylsilane and imidazole in dry *N*,*N*-dimethylformamide, and was fully characterized at this stage.

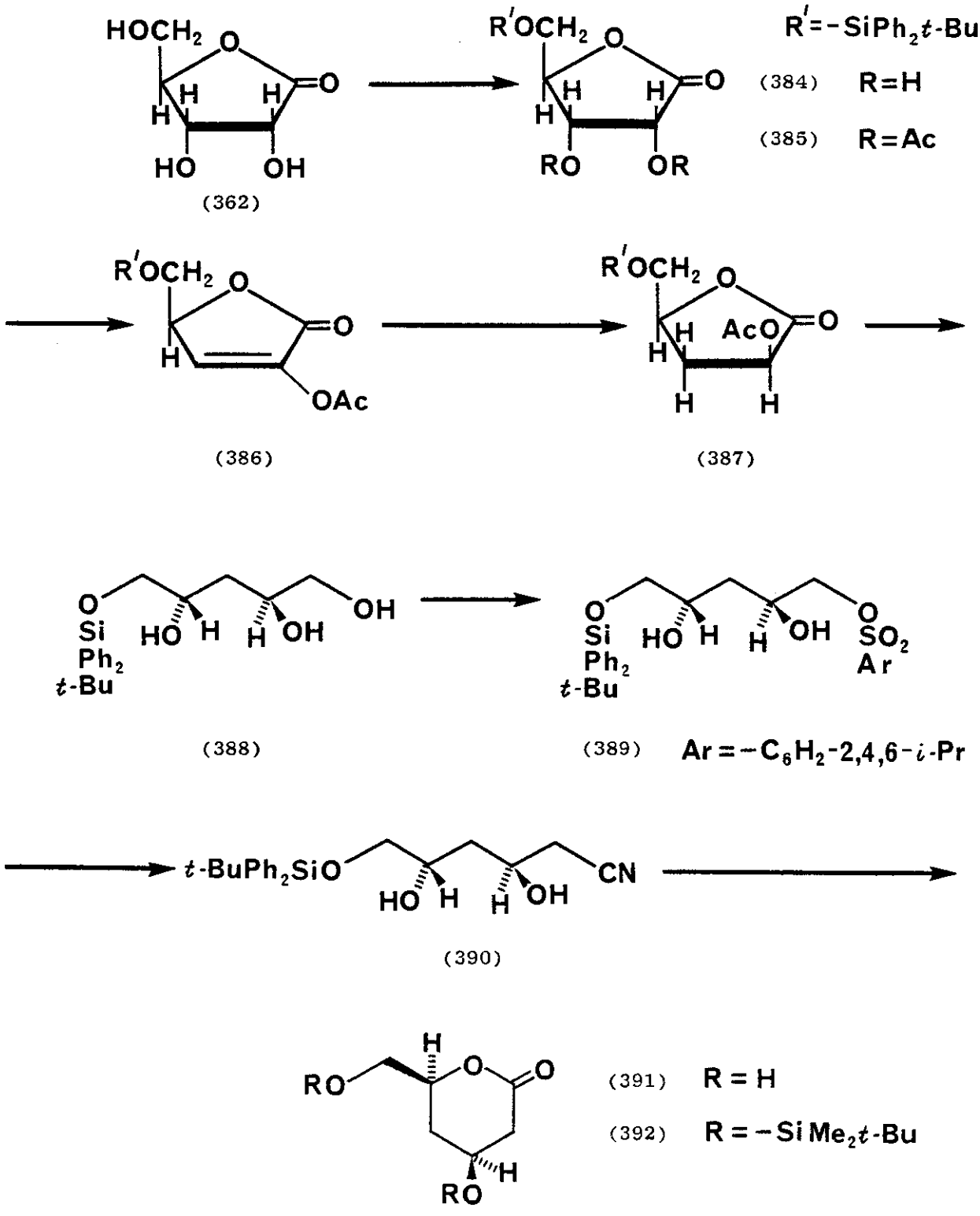
Believing that our attempts to form the lactone (357) may have been complicated by the presence of the second latent carboxyl group in the dinitrile (376), we decided to investigate another possible synthetic route to the required lactone moiety (356) (Scheme 62).

Treatment of D-(+)-ribonic acid-γ-lactone (362) with t-butylchlorodimethylsilane and imidazole in *N*,*N*-dimethylformamide, at room temperature, gave predominantly the expected primary hydroxyl protected silyl ether (384) (85%) together with a small amount of the di-silylated lactone (393) (9%). Structural assignment was based on n.m.r. spectral analysis.



(393)

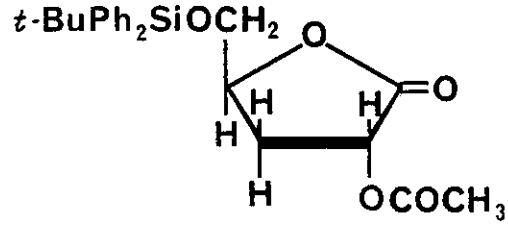
The silylated lactone (384) was acetylated by stirring with acetic anhydride and pyridine at room temperature, to afford 2,3-di-*O*-acetyl-5-*O*-t-butyldiphenylsilyl-D-ribonic acid-γ-lactone (385) in 94% yield.


HOCH2
O
H
H
H
HO
OH
O
(362)
R'OCH2
RO
OR
R'=-SiPh2t-Bu
(384) R=H
(385) R=Ac
OAc
(386)
AcO
(387)
Si
Ph2
t-Bu
HO
OH
(388)
SO2
Ar
(389) Ar=-C6H2-2,4,6-i-Pr
t-BuPh2SiO
CN
(390)
(391) R=H
(392) R=-SiMe2t-Bu

Scheme 62

In a separate experiment the one-pot preparation of the lactone (385) was carried out in 61% overall yield.

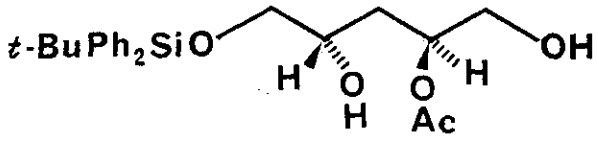
An initial attempt to convert the diacetyl lactone (385) to the enone (386), under identical conditions to those used successfully for the triacetyl analogue (366), led to a 92% recovery of the starting lactone (385). However, reaction of the lactone (385) with DBU in tetrahydrofuran at $0^{\circ}C$ for $\frac{3}{4}$ h led to the isolation of the required (5*S*)-3-acetoxy-5-[(t-butyldiphenylsilyloxy)methyl]furan 2(5H)-one (386) (89%) as a stable colourless oil which could be easily purified by chromatography on silica. In subsequent reactions the enone (386) was not isolated but, after quenching the elimination by addition of saturated aqueous ammonium chloride, was extracted into diethyl ether. The extracts were then concentrated *in vacuo*, diluted with ethanol, and directly hydrogenated, over 10% palladium on carbon, to afford the saturated lactone (387) in 84% overall yield. The stereoselectivity of this hydrogenation was checked by carrying out a second n.O.e. experiment. None of the epimeric lactone (394) was ever observed during the course of these reactions.



(394)

Initial attempts to reduce the lactone (387) to the triol (388), using the conditions used in the preparation of the tetrol (373), resulted in low yields of the required product. The recovery of large

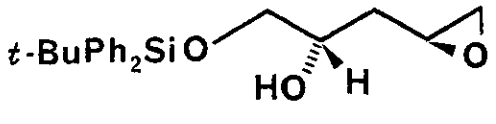
amounts of t-butyldiphenylsilanol indicated cleavage of the silyl ether linkage under the basic reaction conditions. Employing a shorter reaction time ($2\frac{1}{2}$ h) for this reduction led to the isolation of the required triol (388) in higher yield. This material, however, was shown to contain a trace amount of a second compound, of similar polarity, which was tentatively identified as the acetate (395) on the basis



(395)

of i.r. spectral analysis of the mixture ($\nu_{max.}$ 1725 cm^{-1}). Treatment of the crude triol (388) with potassium carbonate in methanol ensured the complete methanolysis of the acetate (395) and led to the isolation of the triol (388) in 89% yield after chromatography. In a separate series of reactions D-(+)-ribonic acid-γ-lactone (362) was converted to the triol (388) in 48% overall yield without isolation of any of the intermediates.

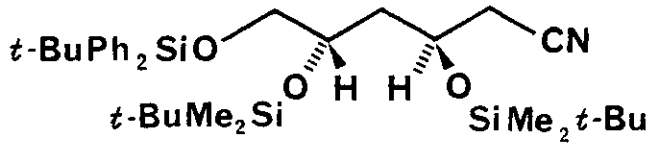
Treatment of the triol (388) with 2,4,6-triisopropylbenzenesulphonyl chloride, in pyridine at room temperature, afforded the primary sulphonylated compound (389), as a yellow oil in 84% yield. This material was found to be particularly unstable, forming the epoxide (396) and a number of unidentified products on prolonged storage.



(396)

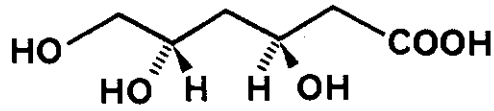
Reaction of the sulphonate (389) with potassium cyanide in ethanol at room temperature for 4 days, afforded the expected mononitrile (390) in 69% yield. In a separate experiment, in which dimethyl sulphoxide was used as a solvent, a higher yield (83%) was obtained after reaction, at room temperature, for 7 days. The intermediacy of the epoxide (396) was confirmed by its isolation from the reaction mixture after shorter reaction times. Thus, treatment of the sulphonate (389) with potassium cyanide in ethanol, at room temperature for 2 days, afforded the epoxide (396) (42%) and the mononitrile (390) (55%). The epoxide (396) was shown to undergo regioselective ring opening on treatment with potassium cyanide in ethanol, to afford the required mononitrile (390) in virtually quantitative yield as judged by t.l.c. analysis.

A sample of the mononitrile (390) was converted, by the usual method,[114] to its silyl ether derivative (397) which was fully characterized.



(397)

The base hydrolysis of the mononitrile (390) and subsequent ring-closure was successfully accomplished; the lactone (391) was isolated as its di-t-butyldimethylsilyl ether derivative (392). The yield (40%) for this final step requires optimization. Notably, ^{1}H n.m.r. spectral analysis seemed to indicate that lactonization of the intermediate δ-hydroxy acid (398) was not spontaneous but was best effected by



(398)

heating this compound at 65-70°C *in vacuo* for *ca.* 24 h.

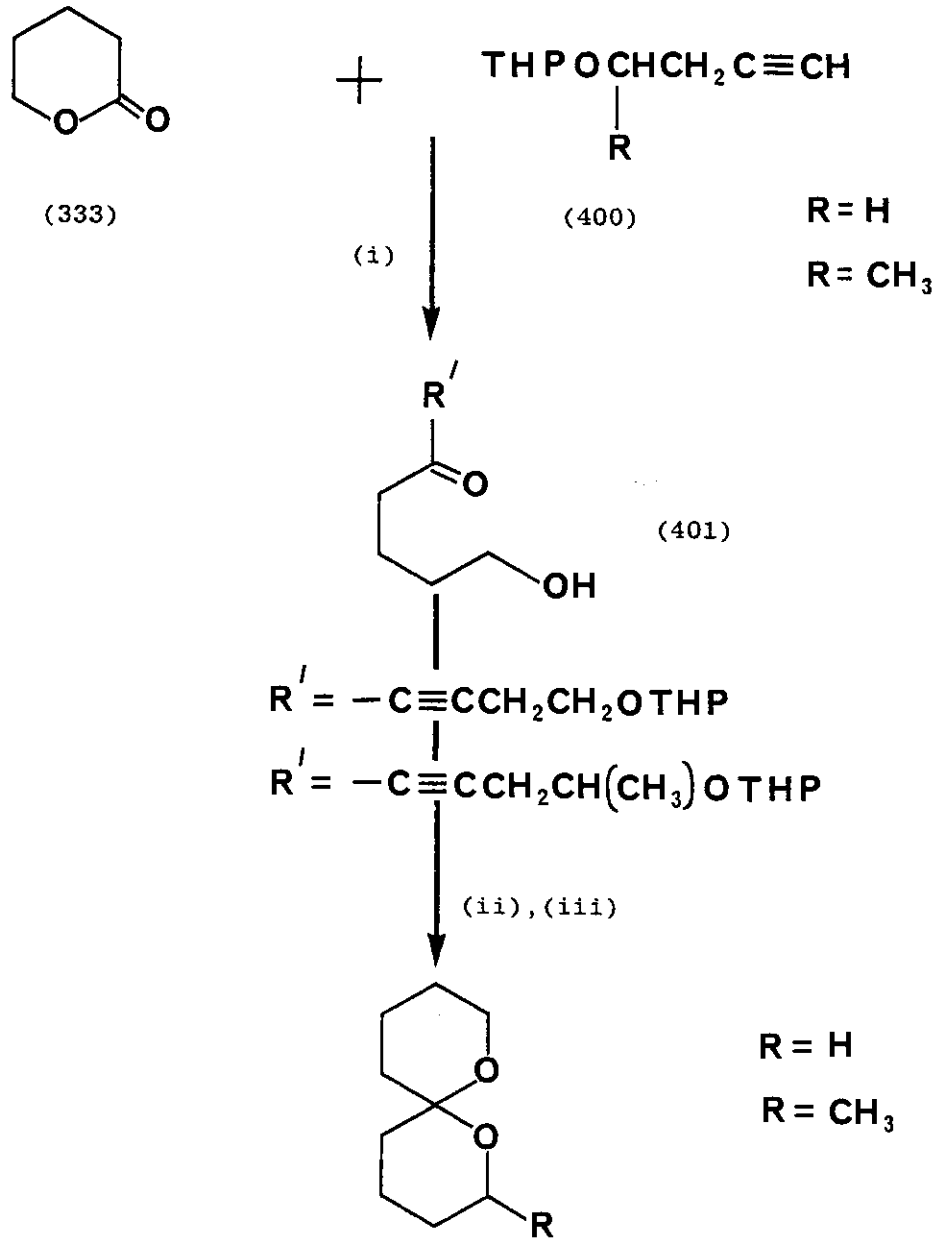
c) Further studies towards the synthesis of the spiro-acetal unit (322).

With the failure of the initially proposed β-dione dianion/lactone condensation route we required a new synthetic pathway to the spiro-acetal north-eastern (NE) unit (322).

Several methods for the production of spiro-acetals have been documented in the literature,[100,109] including the recent use of the organoselenium cyclisation process[109] which has been used to prepare several natural products.

Addition of acetylenic anions to lactones to yield hemi-acetals has been used in several syntheses including that of the 12-membered macrolide neomethynolide by Yamaguchi and his co-workers.[110] Deslongchamps *et al.*[100] have extended this reaction to prepare several 1,7-dioxospiro[5·5]undecanes (402) (Scheme 63). More recently Baker and his co-workers[111] have used this method to prepare two novel hydroxyspiro-acetals (403 and 404) originaly isolated from the rectal gland of the female olive fly (*Dacus oleae*) (Scheme 64). Similar methodology has also been applied to prepare a series of 5,5- and 5,6-spiro-acetals.[112]

We reasoned that a route to the spiro-acetal (405) would be available *via* the condensation of (2*R*,3*S*)-3-methyl-4-pentyn-2-ol

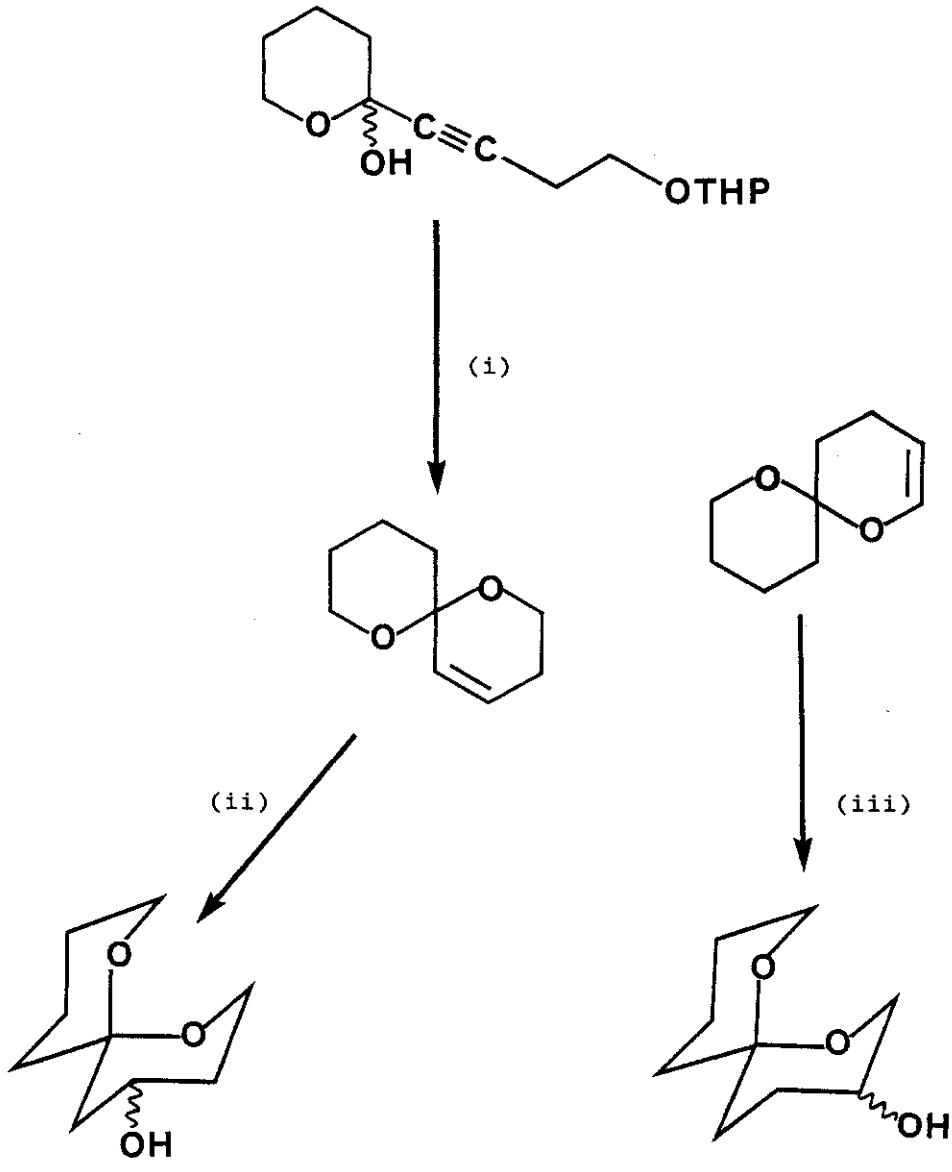


Reagents (i) n-BuLi/THF/-78°C/30 min

(ii) H_2/PtO_2/40psi

(iii) HCl/MeOH

Scheme 63



(403) (4S,6S)[a] : 20 (3S,6S)[a]

(404) (4R,6S) : 1 (3R,6S)

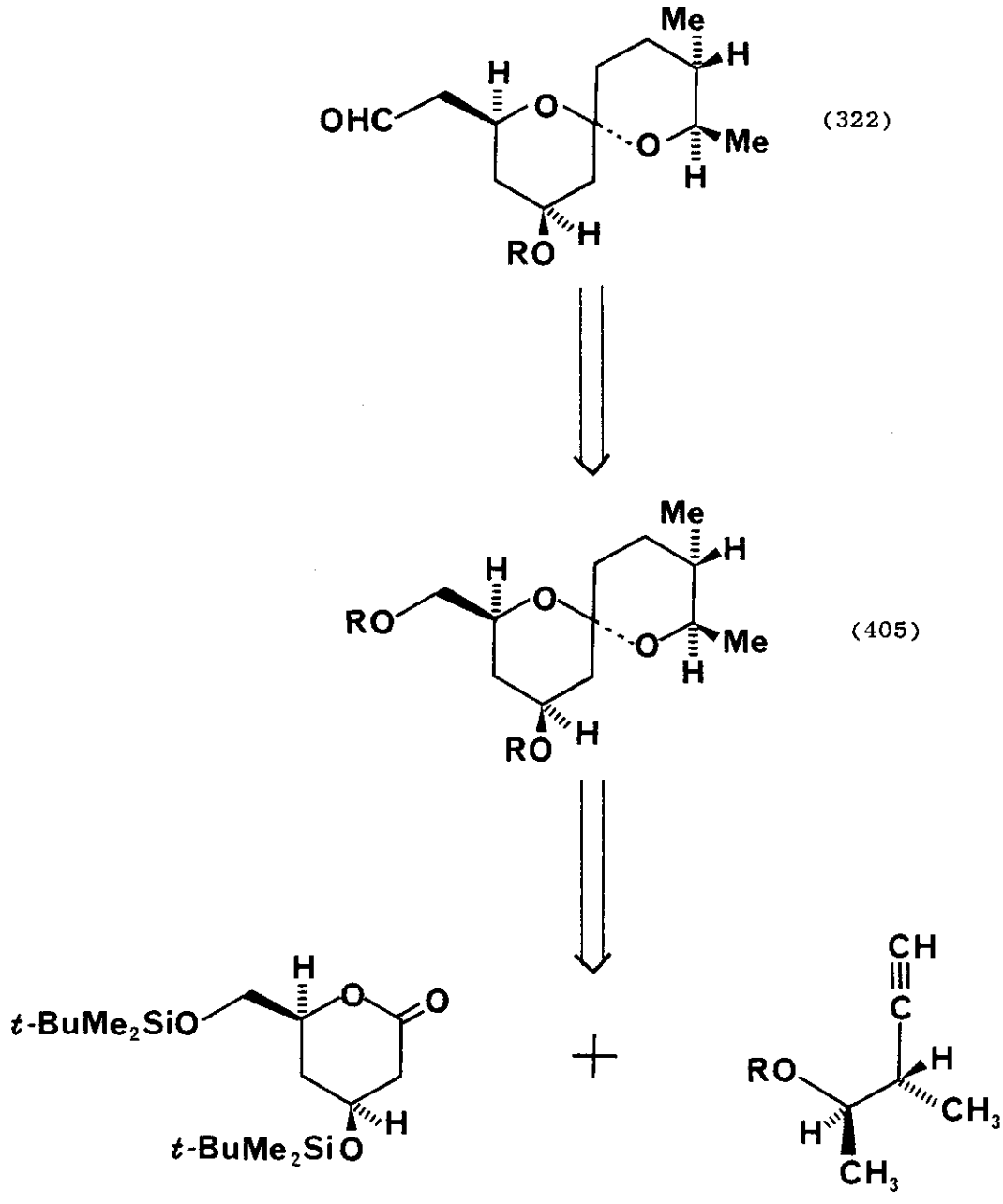
Reagents (i) H_2/5% Pd-$BaSO_4$-quinoline/MeOH

(ii) HCl-H_2O-THF (1:5:20)

(iii) BH_3-THF/H_2O_2-OH^-

Scheme 64

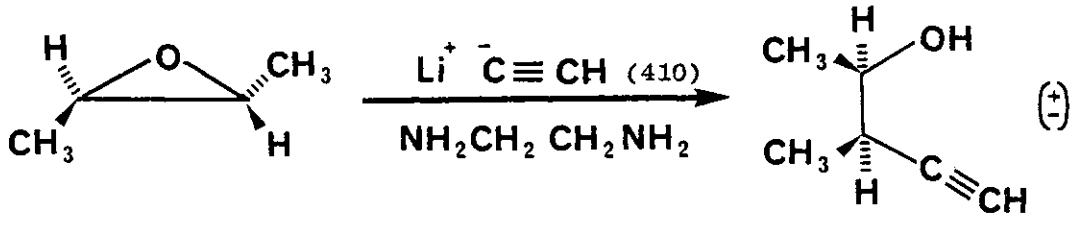
(a) Only one enantiomer shown for each racemic pair.


Me
H
OHC
H
O
O
Me
H
RO
H
(322)
Me
H
RO
H
O
O
Me
H
RO
H
(405)
H
t-BuMe2SiO
O
O
H
t-BuMe2SiO
(359)
CH
C
H
RO
CH3
H
CH3
(427) R = H
(428) R = -SiMe2t-Bu
(429) R = -SiPh2t-Bu

Scheme 65

(427), or one of its silyl ether derivatives (428) or (429), with the lactone (359) or possibly with one of the previously prepared nitriles (376) (378) (390) or (397). The spiro-acetal north-eastern (NE) unit (322) would then be available *via* chain extension of the spiro-acetal (405) (Scheme 65).

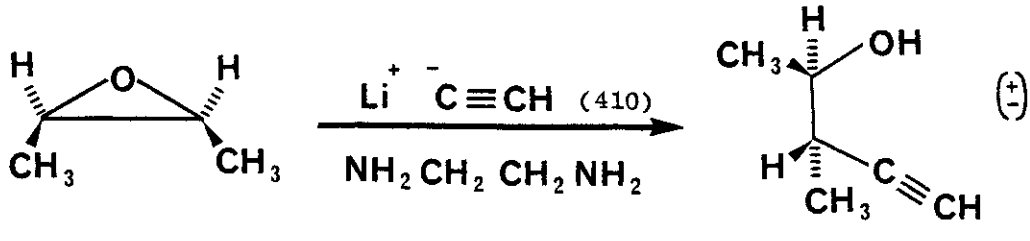
Meinwald and his co-workers,[113] in their synthesis of (±)-pederamide, have shown that *trans*-2,3-dimethyloxirane (409) may be ring-opened, by treatment with the lithium acetylide-ethylene diamine complex (410) in dimethyl sulphoxide, to afford the acetylene-alcohol (411) (55%) (Scheme 66).



(409) (411)

Scheme 66

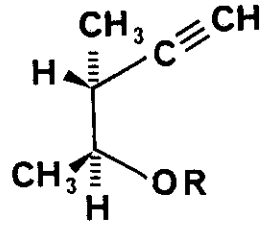
Under similar reaction conditions *cis*-2,3-dimethyloxirane (412) afforded (2*SR*,3*RS*)-3-methyl-4-pentyn-2-ol (406) in 51% yield (Scheme 67).



(412) (406)

Scheme 67

Samples of the acetylene-alcohol (406) were successfully converted to the t-butyldimethylsilyl ether (407) (95%) and t-butyldiphenylsilyl ether (408) (96%) derivatives using the standard procedures.[114]



(±)

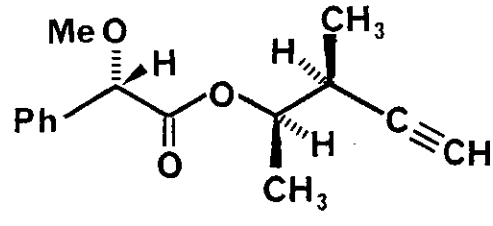
(407) R = Si Me$_2$ *t*-Bu

(408) R = Si Ph$_2$ *t*-Bu

Prior to the successful preparation of the lactone (391), a series of model reactions involving the attempted addition of the racemic acetylene-alcohol dianion (413) to various nitriles were investigated (TABLE 14). Clearly, preparation of the spiro-acetal moiety (322) *via* this type of condensation was not possible.

A number of reviews exist which deal with the resolution of optically active compounds.[115,116] Several syntheses involve the resolution of optically active acetylene alcohols, *via* their corresponding diastereoisomeric (*S*)-*O*-methylmandelate esters, notable amongst these are Corey's total synthesis of erythronolide A[117] and Yamaguchi's neomethynolide synthesis.[110]

In order to resolve the acetylene alcohol (406) we chose to convert the compound to its (*S*)-*O*-methylmandelate ester (414).

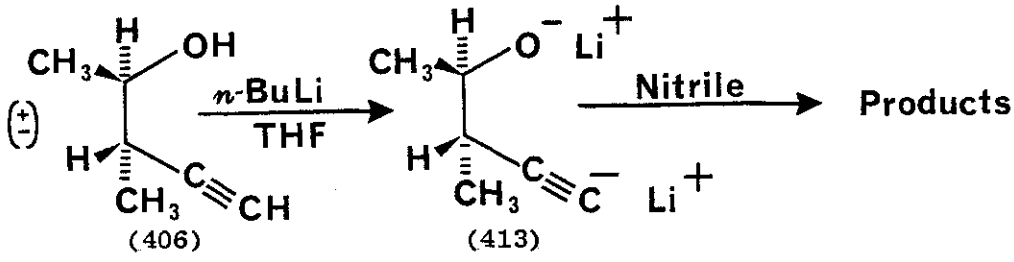


(±) alcohol

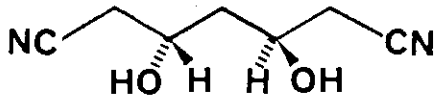
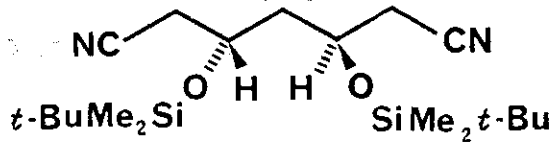
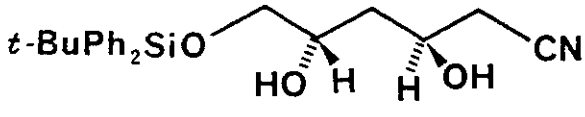
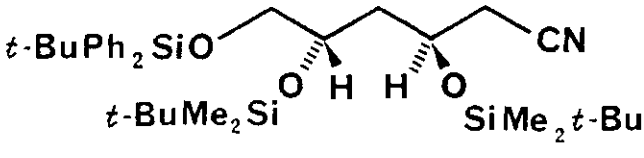
(414)

TABLE 14

Attempted addition of the Acetylene Alcohol Dianion (413) to Nitriles.

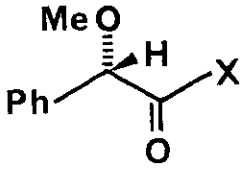


(406) (413)

Nitrile	Products [a]
	Mainly starting material (376)
	Mainly starting material (378)
	Complex mixture of products
	Mainly starting material (397)
CH_3CN	Intracible mixture of products

(a) Based on t.l.c. and n.m.r. spectral analysis.

Initial attempts at esterification *via* formation of the acid chloride (415), according to the procedure of Corey,[117] were unsuccessful leading to the isolation of a complex mixture of products.



(415) X = Cl

(416) X = OH

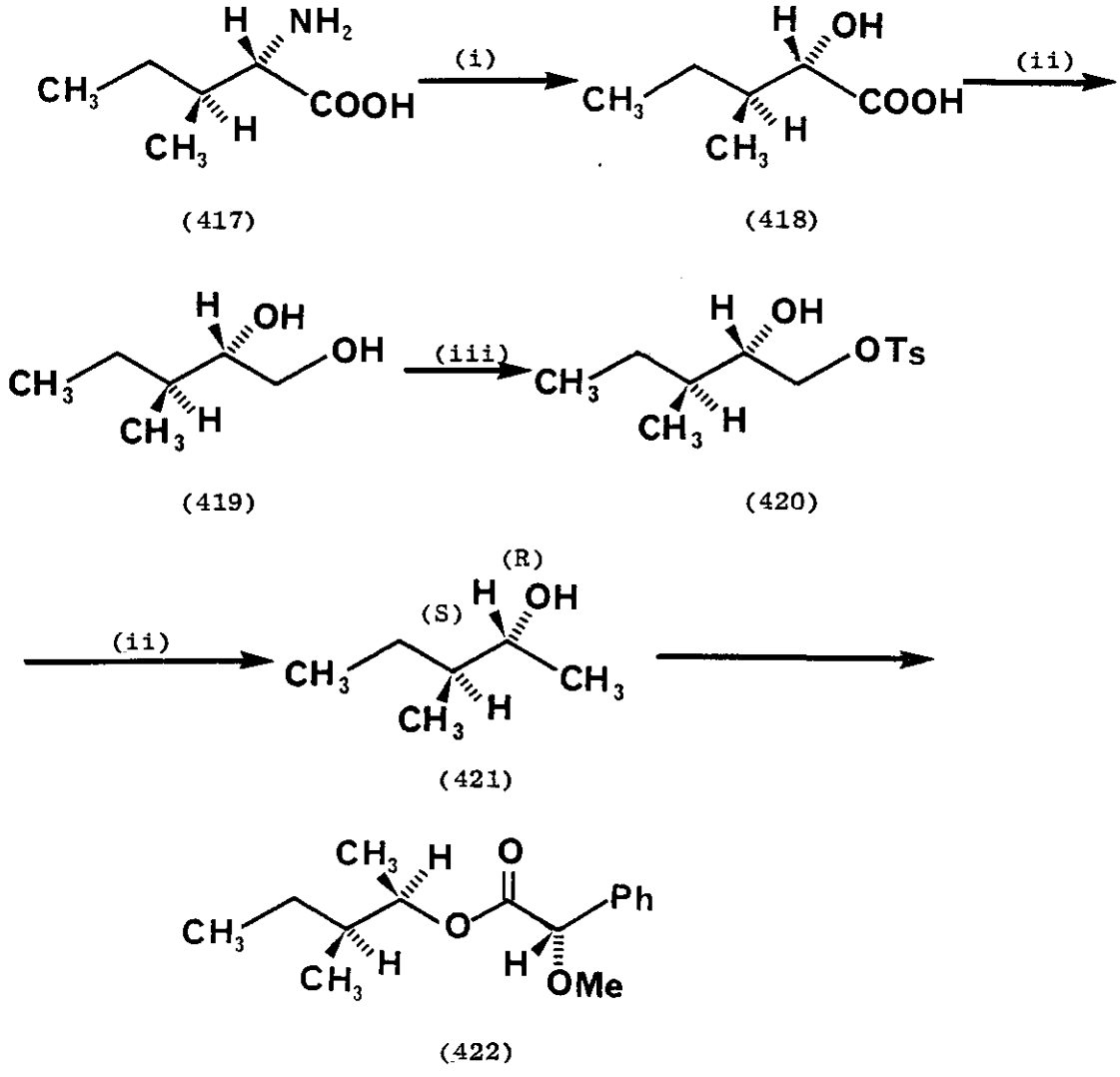
However, reaction of the free acid (416) [118] with the acetylene alcohol (406) in dichloromethane, in the presence of dicyclohexylcarbodiimide (DCC) and 4-*N*,*N*-dimethylaminopyridine (DMAP),[110,119] afforded the required ester (414) in consistently high yields (>90%). ^{1}H n.m.r. spectral analysis of the ester (414) showed a discrete set of signals of each of the two diastereoisomers; integration of the acetylenic proton region (δ 1·90-2·10) was later to prove useful in determining the diastereomeric excess (d.e.) of the separated diastereoisomers.

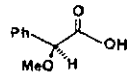
Cleavage of the ester (414) was accomplished using lithium hydroxide in wet tetrahydrofuran. Although t.l.c. analysis indicated quantitative regeneration of the volatile alcohol (406), problems of isolation resulted in its recovery in only poor yield (43%). Fortunately, methanolysis of the ester (414) with potassium hydroxide in methanol[117] was found to be more rapid and enabled isolation of the alcohol in higher yield (65%).

Correlation Experiment:-

Clearly prior to the separation of the two diastereoisomeric esters (414), a means of identifying the required [(2*R*,3*S*)-3-methyl-4-pentyn-2-yl] (*S*)-*O*-methylmandelate (423) was needed.

Kirmse and Prolingheuer[134] have shown that L-*iso*leucine (417) may be converted, with overall retention of configuration, to (2*R*, 3*S*)-3-methyl-2-pentanol (421) of high enantiomeric purity (Scheme 68).



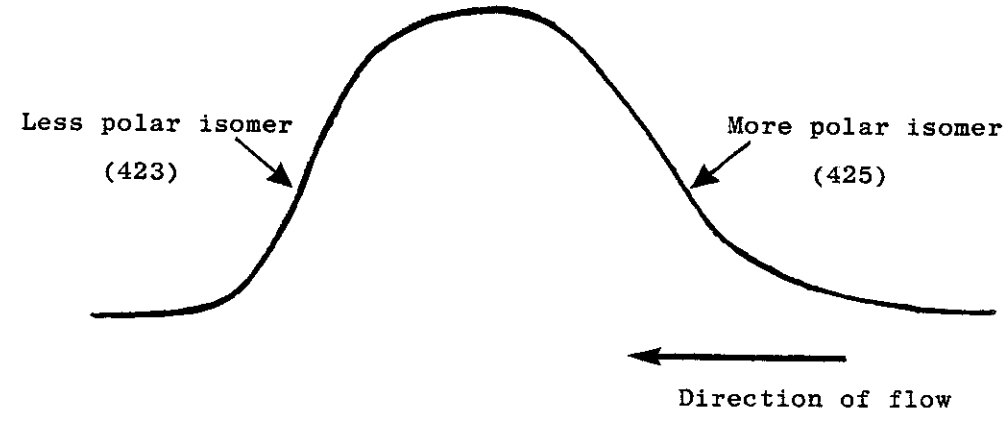
Reagents (i) HNO_2;
(ii) LAH/Et_2O;
(iii) TsCl/Pyridine;
(iv)  /DCC/DMAP/CH_2Cl_2.

Scheme 68

We reasoned that the (*S*)-*O*-methylmandelate ester (422), formed from the alcohol (421), and the product of hydrogenation of the required ester (423) would have the same absolute stereochemistry; ^{1}H n.m.r. spectral analysis could then be used to unambiguously define the stereochemistry in each of the diastereoisomers (423 and 425).

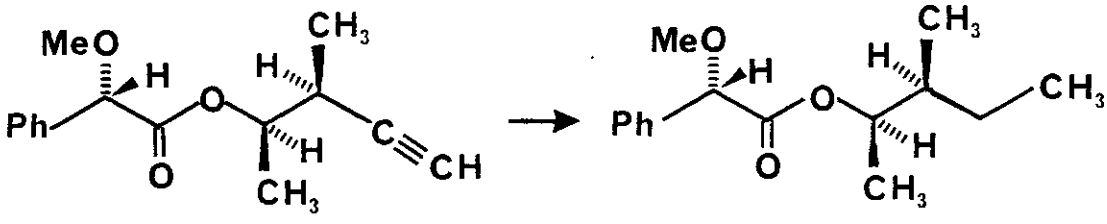
Accordingly, the enantiomerically pure alcohol (421) was prepared by a series of modified literature procedures,[120,121] in 35% overall yield. Treatment of the alcohol (421) with (*S*)-*O*-methylmandelic acid (416) afforded the expected saturated ester (422) in 82% yield after chromatography (Scheme 68).

Although the diastereoisomers of the ester (414) were readily distinguished by 250 MHz ^{1}H n.m.r. spectroscopy, both normal and reverse phase h.p.l.c. analysis of the mixture indicated a single homogeneous material. Fortunately, using a Walters Prepak 500 silica column and the recycle facility of the Walters Associates 500 h.p.l.c. machine, some degree of separation could be obtained by repeated "peak-shaving" of the material. Thus, a small sample of the diastereoisomeric mixture of esters (414) was subjected to h.p.l.c. separation. Collection of the material indicated by the rising slope of the trace peak (fig. 4) gave mainly the less-polar isomeric ester (414) (90% d.e.). Hydrogenation of this material afforded the saturated ester (424) (fig. 5) (Scheme 69) which was shown unambiguously to have the (2*R*, 3*S*) configuration by ^{1}H n.m.r. spectral comparison with the ester (422) (fig. 6) derived from L-*iso*leucine. The less-polar isomeric ester (414) was thus identified as the required (2*R*, 3*S*)-mandelate ester (423).

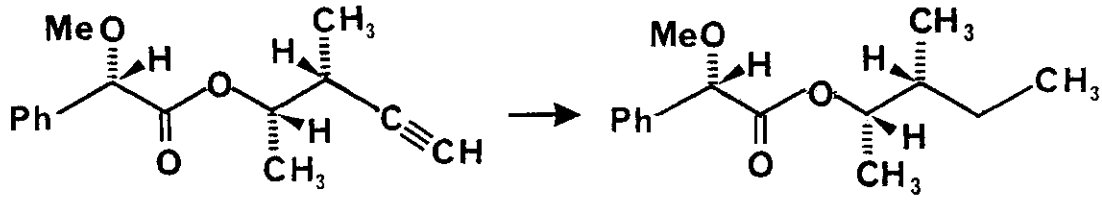


(fig. 4)

Similarly, the more-polar isomer (414) (84% d.e.), indicated by the trailing slope of the trace peak was isolated and hydrogenated to afford the saturated ester (426) (fig. 7) (Scheme 69) which was shown to be substantially different from the L-*iso*leucine derived ester (422) (fig. 6) by ^{1}H n.m.r. spectral analysis.



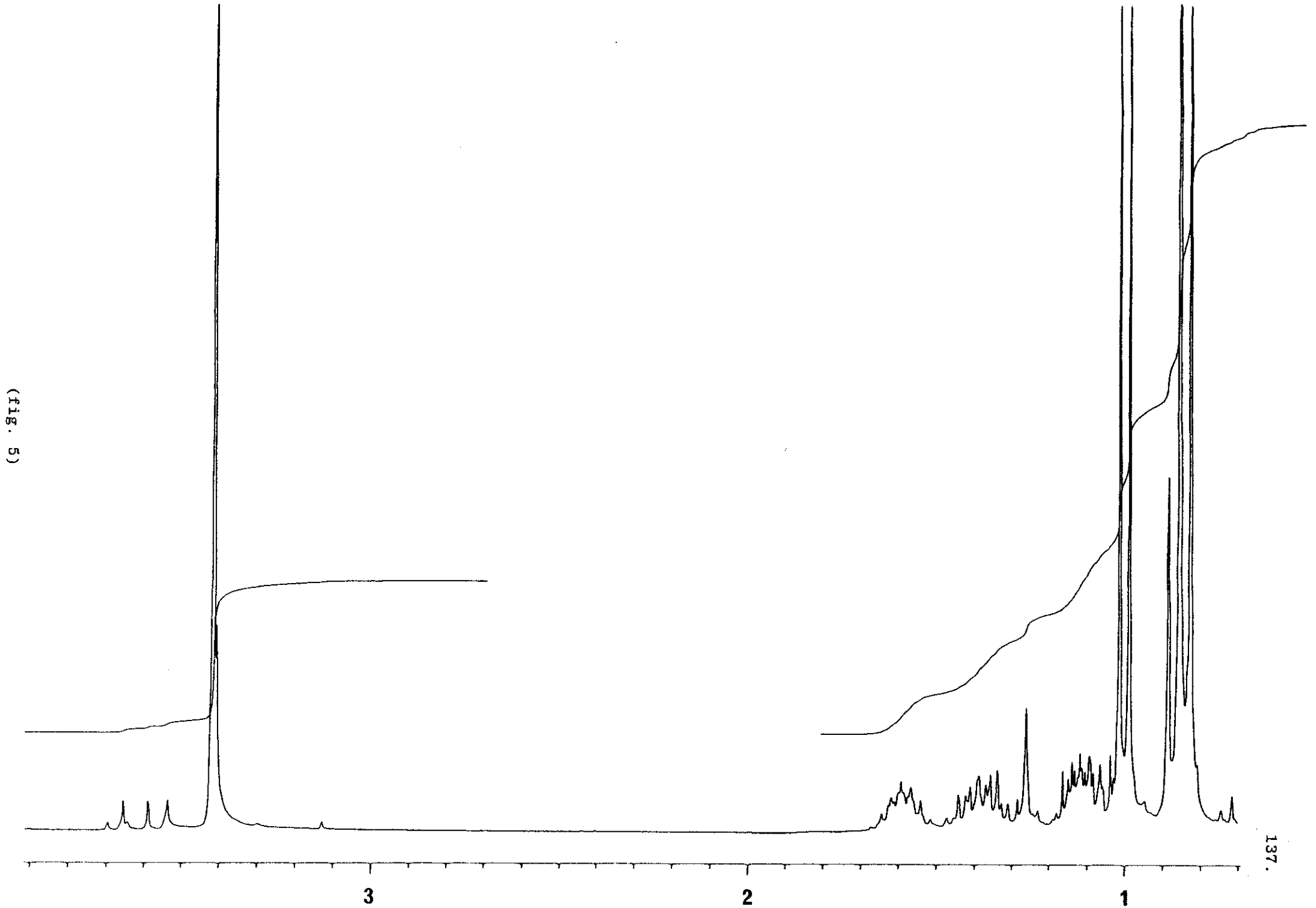
(423) (424)



(425) (426)

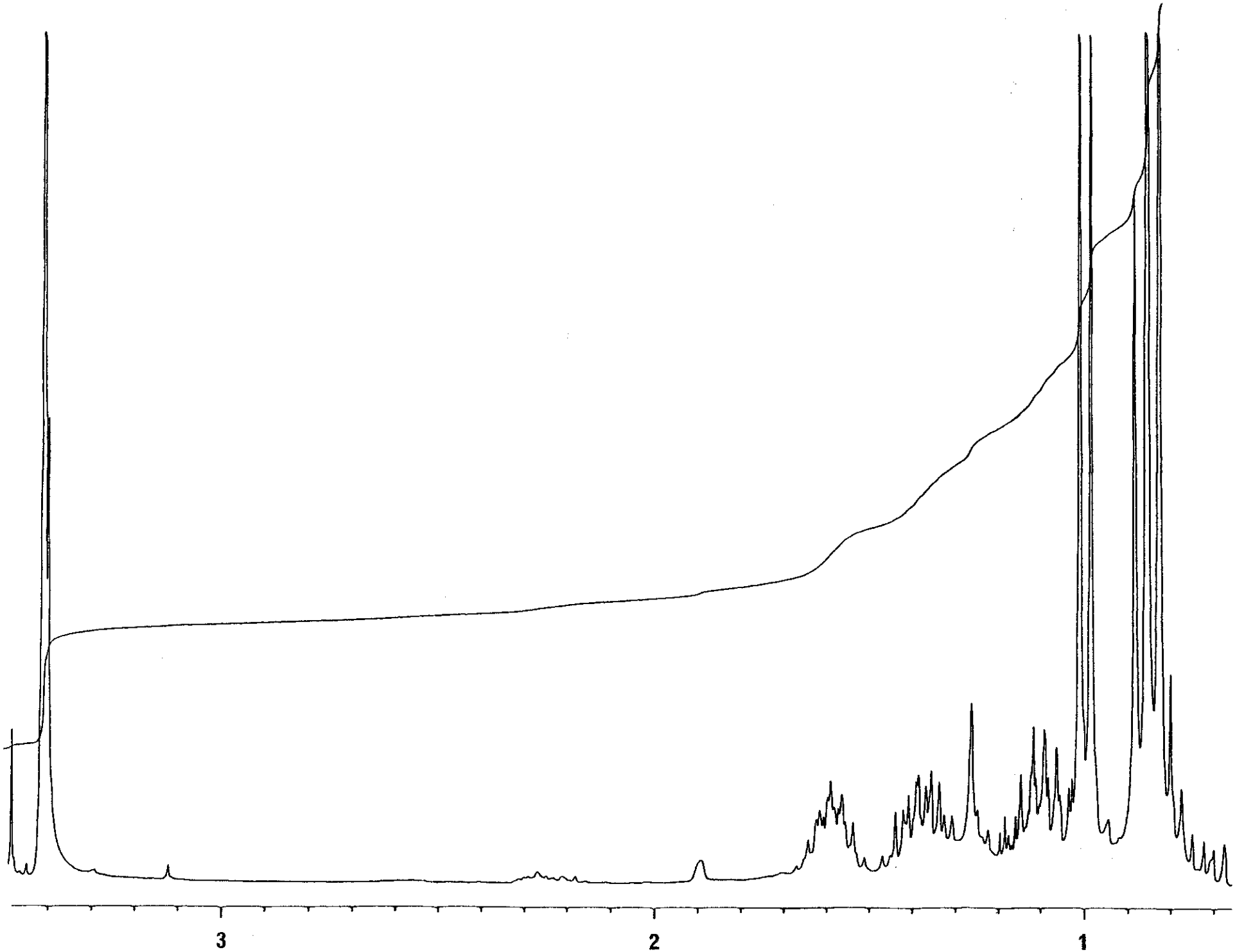
Scheme 69

The more-polar isomeric ester (414) was therefore identified as the unwanted (2*S*, 3*R*)-mandelate ester (425).

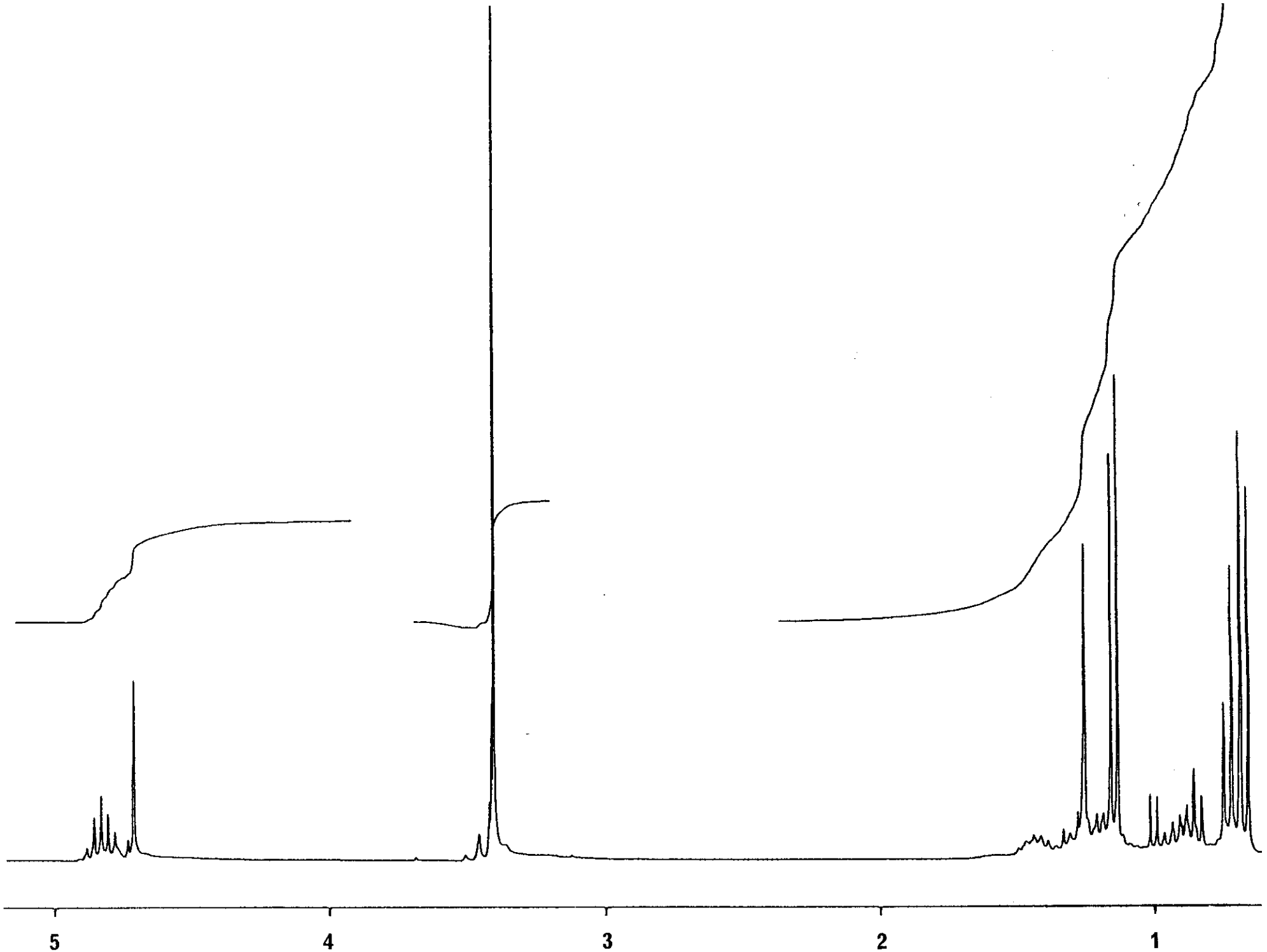


(fig. 5)

137.



(fig. 6)

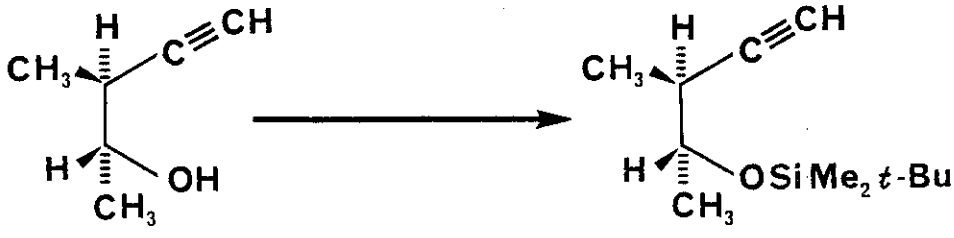


(fig. 7)

139.

Resolution of synthetically useful quantities of the ester (423) proved to be extremely difficult. After several weeks work the ester (414) (87 g) had been partially resolved to afford the (2*R*, 3*S*)-mandelate ester (423) (12 g) (*ca.* 80% d.e.). Due to the poor efficiency of this separation further purification was not attempted; material with this degree of enantiomeric purity was used in subsequent experiments.

Finally, (2*R*, 3*S*)-3-methyl-4-pentyn-2-ol (427) (80% e.e., 69%), generated by the methanolysis of the ester (423), was converted, by the standard procedure,[114] to its t-butyldimethylsilyl ether derivative (428) in 95% yield (Scheme 70).



(427) (428)

Scheme 70

EXPERIMENTAL

EXPERIMENTAL

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Ultraviolet spectra were recorded on a Unicam SP 800A ultraviolet spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer 157G, 257 or 298 grating infrared spectrophotometer. ^{1}H N.m.r. spectra were recorded on a Varian 360A or a Perkin-Elmer R32 spectrometer, at 60 MHz and 90 MHz respectively, and on a Bruker WM250 machine at 250 MHz. Signal allocations in n.m.r. spectra were established by carrying out the appropriate spin-decoupling experiments. ^{13}C N.m.r. spectra were recorded on a Bruker WM250 machine at 62.9 MHz. Tetramethylsilane was used as an internal reference for n.m.r. spectra unless otherwise stated. Optical rotations were determined using a Perkin-Elmer 141 polarimeter. Microanalysis and mass spectral measurements were carried out by the appropriate laboratories at Imperial College.

Analytical thin layer chromatography (t.l.c.) was performed on Merck precoated GF_{254} silica or F_{254} (Type E) alumina plates. Preparative layer chromatography (p.l.c.) was performed on GF_{254} silica plates. Medium pressure chromatography was carried out on Merck Kieselgel H (type 60) silica as described by Still *et al.*[132] High-pressure liquid chromatography (h.p.l.c.) was performed on a Waters Associates 500 machine using Waters Prepak 500 silica columns.

Solvents were purified as follows:- benzene and toluene were redistilled and sodium dried; dichloromethane, ethyl acetate and light petroleum (b.p. 40-60^{o}C) were redistilled; diethyl ether (ether) was redistilled and dried when required over sodium wire. Tetrahydrofuran (THF) was redistilled from potassium benzophenone ketyl.

N,N-Dimethylformamide (DMF) was distilled from calcium hydride onto 4A molecular sieves. Pyridine was redistilled from potassium hydroxide and stored over 4A molecular sieves. Ethanol and Methanol were AnalaR reagents and were dried, when required, over 3A molecular sieves. Hexamethylphosphoramide (HMPA) was distilled from calcium hydride and stored over 4A molecular sieves. Reagents were purified according to standard procedures.[121] Organic solutions were routinely dried over anhydrous sodium or magnesium sulphate. Solvents were evaporated at reduced pressure using a rotary evaporator at, or below, 40°C unless otherwise stated.

Preparation of 1-*Methoxy*-2-*methyl*-1-*buten*-3-*one* (156)

The methoxy enone (156) was prepared according to the modified procedure of Sugasawa *et al.*[53] A mixture of methyl formate (154) (120 g, 2·0 mol) and butanone (155) (144 g, 2·0 mol) was added to preformed sodium sand (46 g, 2·0 mol) in dry toluene (800 ml), with external cooling, at such a rate as to maintain the reaction temperature below 40°C. The reaction mixture was stirred for 12 h at room temperature and treated with water (500 ml). The aqueous layer was extracted with benzene (2 x 100 ml) and the combined organic phases back-extracted with water (2 x 200 ml). The combined aqueous fractions were stirred with dimethyl sulphate (190 g, 1·5 mol) for 12 h and the reaction mixture was then heated to 60-70°C for 5 h. After cooling the mixture was extracted with benzene (4 x 200 ml) and the combined organic layers dried (anhydrous $CaCl_2$) and evaporated to afford a red oil. Fractional distillation at reduced pressure resulted in the isolation of the title compound (156) (50·7 g, 22%) as a colourless oil, b.p. 48°C/2 mmHg (lit.,[53] b.p. 62-4°C/4 mmHg), n_D^{23} 1·4800, $\nu_{max.}$ (liq. film) 2950 m, 1640 s (C=O str.), 1370 m, 1310 s, 1250 s,

1150 s (C-O str.), 980 s, and 790 m cm^{-1}, δ_H (90 MHz) ($CDCl_3$) 1·32 (3H, d, *J* 1Hz, -C*H*$_3$), 1·85 (3H, s, -COC*H*$_3$), 3·54 (3H, s, -OC*H*$_3$), and 7·00 [1H, m, -C=C(OMe)*H*].

Preparation of (E)-1-*Methoxy*-2-*methyl*-3-*trimethylsilyloxy*-1,3-*butadiene* (157)

(i) (*E*)-1-Methoxy-2-methyl-3-trimethylsilyloxy-1,3-butadiene (157) was prepared from the methoxy enone (156) (50·72 g) according to the procedure of Danishefskey *et al.*[52] The crude title compound (157) (66·64 g) was isolated as a colourless oil, b.p. 52-56°C/6 mmHg (lit.,[52] b.p. 45-49°C/5 mmHg). N.m.r. analysis indicated this to be an 88 : 12 mixture of (157) : (156). Compound (157) (74%) (lit.,[52] 69%) was used in this form in subsequent reactions, δ_H (90 MHz) ($CDCl_3$) 0·20 (9H, s), 1·70 (3H, s), 3·67 (3H, s), 4·17 (1H, s), 4·28 (1H, s), 6·50 (1H, br.s).

(ii) Anhydrous zinc chloride (0·75 g, 5·5 mmol) was stirred with triethylamine (58·5 ml) at room temperature for 1 h. The reaction mixture was then treated with chlorotrimethylsilane (39 g, 0·36 mol) and a solution of the methoxy enone (156) in dry benzene (45 ml), and the system stirred vigorously at room temperature for 72 h. The solution was then poured into diethyl ether (500 ml), filtered at the pump to remove triethylammonium chloride and the filtrate concentrated *in vacuo* to afford a brown oil. Further trituration with diethyl ether resulted in the isolation of a further quantity of a white solid. This process was repeated until no further white solid could be isolated. Distillation at reduced pressure, from base washed glassware, afforded the title compound (157) (25·0 g, 77%) as a

colourless liquid, b.p. 66°C/10 mmHg (lit.,[52] 69% b.p. 45-59°C/5 mmHg). N.m.r. analysis indicated the complete absence of the methoxy enone (156) from the distilled product.

Preparation of Dimethyl 4-Hydroxy-5-methylphthalate (150)

(i) Dimethyl 4-hydroxy-5-methylphthalate (150) (12·0 g, 76%) was prepared from the butadiene derivative (157) (14·5 g) according to the procedure of Danishefsky *et al*,[52] m.p. 144-146°C (methanol-toluene) (lit.,[52] 87%, m.p. 147-148°C), $\nu_{max.}$ (Nujol) 3350 s (O-H str.), 1730 s (C=O str.), 1710 s (C=O str.), and 1290 s cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 2·25 (3H, s, $-CH_3$), 3·86 (3H, s, $-OCH_3$), 3·88 (3H, s, $-OCH_3$), 6·70 (1H, br.s, D_2O exch.), 7·03 (1H, s, aryl-*H*), and 7·59 (1H, s, aryl-*H*).

(ii) A solution of (*E*)-1-methoxy-2-methyl-3-trimethylsilyloxy-1,3-butadiene (157) (1·0 g, 5·37 mmol) and freshly distilled dimethyl acetylenedicarboxylate (1·53 g, 10·74 mmol) in dry benzene (5·4 ml) was heated at the reflux, under an atmosphere of nitrogen, for 12 h and then allowed to stand at room temperature for 2 days. After removal of the solvent the reaction mixture was subjected to medium pressure chromatography on silica (Kieselgel H, 20 g, eluant 10% diethyl ether/toluene) to afford dimethyl 4-hydroxy-5-methylphthalate (150) (0·87 g, 80%) as a white crystalline solid, m.p. 144-146°C (methanol-toluene).

Attempted preparation of Methyl 2-Acetyl-4-hydroxy-5-methylbenzoate (153)

(i) Dimethyl 4-hydroxy-5-methylphthalate (150) (0·45 g, 2·0 mmol) was dissolved in dry tetrahydrofuran (10 ml) and cooled to -78°C under an atmosphere of nitrogen. The solution was treated with 0·87 M

methyllithium-lithium bromide complex in diethyl ether (2·5 ml, 2·1 mmol) and the mixture stirred for 1 h. The resultant pale yellow solution was treated with a further quantity of the methyllithium-lithium bromide complex (2·5 ml, 2·1 mmol) to yield a peach coloured precipitate. After a further 2 h at -78°C the reaction was quenched, by the addition of glacial acetic acid (0·4 ml), and immediately partitioned between diethyl ether (50 ml) and water (30 ml). The aqueous phase was extracted with diethyl ether (3 x 50 ml) and the combined extracts dried and concentrated *in vacuo* to afford a slightly pink white solid (381 mg). T.l.c. analysis (silica, diethyl ether) indicated the solid to be a two component mixture — identified as the diester (150) and 5-hydroxy-3,3,6-trimethylphthalide (160) (1:1) by n.m.r. spectral analysis.

(ii) A solution of dimethyl 4-hydroxy-5-methylphthalate (150) (0·45 g, 2·0 mmol) in dry tetrahydrofuran (10 ml) was treated with 100% sodium hydride (50 mg, 2·1 mmol) and the mixture stirred at room temperature, under an atmosphere of dry nitrogen, for 2 h. The solution was cooled to -78°C and treated with 0·87 M methyllithium-lithium bromide complex in diethyl ether (2·3 ml, 2·0 mmol). After stirring for 2 h the reaction was quenched, by the addition of saturated ammonium chloride solution, and partitioned between diethyl ether (50 ml) and water (30 ml). The aqueous phase was extracted with diethyl ether (3 x 50 ml) and the combined extracts dried and concentrated *in vacuo* to afford a red solid (398 mg). T.l.c. and n.m.r. analysis indicated the solid to be mainly the unreacted diester (150).

Preparation of Methanesulphinyl Chloride

Methanesulphinyl chloride (19·05 g, 91%) was prepared from dimethyl

disulphide (10 g) according to the procedure of Corey and Durst,[56] b.p. 51°C/40 mmHg (lit.,[56] 86%, b.p. 55-59°C/40 mmHg), n_D^{22} 1·5078 (lit.,[122] n_D^{25} 1·500-1·501), δ_H (60 MHz) (CCl_4) 3·37 (s).

Preparation of N-Methanesulphinyl-4-toluidine (166)

N-Methanesulphinyl-4-toluidine (166) (11·2 g, 70%) was prepared from methanesulphinyl chloride (9·5 g) and *p*-toluidine (10·0 g) according to the procedure of Corey and Durst,[56] m.p. 112-114°C (lit.,[122] 86%, m.p. 109-111°C), δ_H (90 MHz) ($CDCl_3$) 2·25 (3H, s, aryl-C*H*$_3$), 2·78 (3H, s, -NHC*H*$_3$), 6·96 (4H, s, aryl-*H*), and 7·65 (1H, br.s); m/e 169 ($M^{+\cdot}$), 154 and 106.

Preparation of Acetophenone from Methyl Benzoate

A solution of 1·35M n-butyllithium in hexane (6·60 ml, 9 mmol) was added to a stirred solution of *N*-methanesulphinyl-4-toluidine (166) (0·74 g, 4·4 mmol) in dry tetrahydrofuran (80 ml) at -78°C, under an atmosphere of nitrogen, over 2 min. The reaction mixture was stirred at -78°C for 3½ h and treated with methyl benzoate (0·272 g, 2 mmol). After a further 30 min the reaction was quenched, by the addition of water at -78°C, and extracted with diethyl ether (x 3). The combined extracts were dried and concentrated *in vacuo* to afford a yellow semi-crystalline oil which was washed with light petroleum at the pump. Acetophenone was isolated from the filtrate as its 2,4-dinitrophenylhydrazone derivative (284 mg, 47%), m.p. 238-241°C (lit.,[123] m.p. 238-240°C), m/e 300 ($M^{+\cdot}$) with spectral data identical with an authentic sample.

Attempted preparation of Methyl 2-Acetyl-4-hydroxy-5-methylbenzoate (153)

To a rapidly stirred solution of *N*-methanesulphinyl-4-toluidine (166) (0·74 g, 4·4 mmol) in dry tetrahydrofuran (80 ml), at -78°C under an atmosphere of nitrogen, was added 1·35M n-butyllithium in pentane (6·66 ml, 9·0 mmol). The solution became yellow rapidly and was stirred, at low temperature, for a further 3 h. Dimethyl 5-hydroxy-5-methylphthalate (150) (0·28 g, 1·25 mmol) in dry tetrahydrofuran (10 ml) was added and the solution stirred for 30 min at which time t.l.c. analysis indicated total disappearance of the starting diester (150). The reaction mixture was partitioned between diethyl ether (200 ml) and water (100 ml) and the aqueous phase extracted with diethyl ether (3 x 100 ml). The combined extracts were dried and concentrated *in vacuo* to afford a sticky white solid (720 mg). T.l.c. analysis (silica, diethyl ether) revealed this to be a complex mixture of products from which the title compound could not be isolated.

Reaction of Dimethyl 4-Hydroxy-5-methylphthalate (150) *with Lithium Dimethylcuprate*

A solution of lithium dimethylcuprate (6 mmol) in dry diethyl ether (20 ml) was prepared according to the procedure of Johnson and Dutra.[68] The phthalate (150) (0·41 g, 1·8 mmol) in dry diethyl ether (20 ml) was added to the solution of the cuprate and the resultant yellow precipitate heated, at the reflux, for 20 h under an atmosphere of argon. The cooled reaction mixture was treated with saturated aqueous ammonium chloride, acidified with 2N hydrochloric acid and extracted into diethyl ether (3 x 50 ml). After drying, the combined extracts were concentrated *in vacuo* to afford a white solid (298 mg). T.l.c.

analysis (silica, diethyl ether) indicated the presence of one major compound (Rf 0·60; 2,4-dinitrophenylhydrazine active). Medium pressure chromatography on silica [Kieselgel H, eluant diethyl ether : light petroleum (1:1)] afforded a white crystalline solid (108 mg), m.p. which, although unidentified, was not regarded to be the required product on the basis of the available spectral data, $\nu_{max.}$ (Nujol) 3350 s (OH str. phenolic), 1740 m (C=O str.), 1690 s (C=C str.), 1580 s, 1495 w, 1320 m, 1285 s, 1215 w, 1175 w, 1160 w, 1110 m, 1010 w, 925 w, 880 w, 870 w, 800 w, 730 w, 715 w, 685 w, and 670 w cm^{-1}; δ_H (100 MHz) (d^6 - acetone) 2·38 (3H, s, aryl-CH_3), 3·16 (2H, s), 7·29 (1H, s, aryl-*H*), and 7·76 (1H, s, aryl-*H*).

Preparation of 5-*Hydroxy*-3,3,6-*trimethylphthalide* (160)

Dimethyl 4-hydroxy-5-methylphthalate (150) (0·45 g, 2 mmol) was dissolved in tetrahydrofuran (10 ml) and the solution cooled to -78°C under a nitrogen atmosphere. Methyllithium-lithium bromide complex in diethyl ether (0·87 M, 2·3 ml, 2·0 mmol) was added and the reaction mixture stirred at -78°C for 1 h before the addition of a second equivalent of the methyllithium-lithium bromide complex (2·3 ml, 2 mmol). After a further 2 h a third equivalent of 0·87 M methyllithium-lithium bromide complex in diethyl ether (2·3 ml, 2·0 mmol) was added and, after ½ h, the reaction was quenched at -78°C with glacial acetic acid (0·36 ml, 6 mmol). The mixture was partitioned between diethyl ether (100 ml) and water (50 ml) and the organic phase washed with aqueous sodium hydrogencarbonate (25 ml) and water (25 ml) and dried. Concentration of the organic phase *in vacuo* afforded an off-white solid. Medium pressure chromatography on silica (Kieselgel H, eluant diethyl ether) afforded the *title compound* (160) (130 mg, 35%) as a white

crystalline solid, m.p. 197-199°C (methanol - toluene); $\nu_{max.}$ (Nujol) 3295 s (-OH str.), 1725 s (C=O str.), 1610 m, 1340 m, and 1030 w cm^{-1}; $\lambda_{max.}$ (EtOH) 254 nm (ε 8640), (EtOH + NaOH) 305 nm; δ_H (250 MHz) ($CDCl_3$) 1·60 (6H, s, -C*H*$_3$), 2·30 (3H, s, aryl-C*H*$_3$), 6·95 (1H, s, aryl-*H*), 7·68 (1H, s, aryl-*H*), and 9·50 (1H, br.s, D_2O exch.); m/e 192 ($M^{+\cdot}$) and 177 ($M^{+\cdot}$ -C*H*$_3$) (Found: C, 68·91; H, 6·26. $C_{11}H_{12}O_3$ requires C, 68·73; H, 6·29%).

Attempted preparation of 4-*Hydroxy*-5-*methyl*-2-(2-*propenyl*)*benzoic Acid* (164)

5-Hydroxy-3,3,6-trimethylphthalide (160) was subjected to various pyrolysis conditions according to the modified procedure of Berti *et al.*[54] Several attempted pyrolysis reactions:- i) 150°C/4 mmHg, ii) 180°C/0·5 mmHg, iii) 200°C/760 mmHg (under an atmosphere of nitrogen) - resulted in the recovery of the starting phthalide (160), based on t.l.c. and n.m.r. analysis.

Preparation of Dimethyl 3-*t*-*Butyldimethylsilyloxy*-4-*methylphthalate* (175)

Sodium hydride (100%) (0·12 g, 5 mmol) was added to a solution of the diester (150) (1·0 g, 4·5 mmol) in dry tetrahydrofuran (20 ml) at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred for 2 h and a solution of t-butylchlorodimethylsilane (0·75 g, 5 mmol) in dry tetrahydrofuran (5 ml) was added to the resulting white suspension. Stirring was continued, at 50°C for 1 h, and the reaction mixture filtered, partitioned between diethyl ether (50 ml) and water (30 ml) and the aqueous phase extracted with diethyl ether (3 x 20 ml). The combined organic layers were dried and

concentrated *in vacuo* to yield a yellow oil. Medium pressure chromatography on silica (Kieselgel H, 20 g, eluant light petroleum) afforded the *title compound* (175) (1·39 g, 92%) as a colourless oil, homogeneous by t.l.c. [silica, diethyl ether : light petroleum (1:1); Rf 0·75]; $\nu_{max.}$ (thin film) 2960 s, 2940 s, 2900 s, 2865 s, 1725 s, (C=O str.), 1610 s (C=C str.), 1565 s, 1505 m, 1465 m, 1440 s, 1400 m, 1380 w, 1370 w, 1315 s, 1265 s, 1245 s, 1195 s, 1170 s, 1130 s, 1055 s, 1010 m, 980 m, 950 s, 880 s, 835 s, 810 s, 790 s, 720 m, and 680 m cm^{-1}; δ_H (90 MHz) ($CDCl_3$) 0·23 (6H, s, -SiC*H*$_3$), 0·95 (9H, s, -Si^t*Bu*), 2·14 (3H, s, aryl-C*H*$_3$), 3·75 (3H, s, -OC*H*$_3$), 3·78 (3H, s, -OC*H*$_3$), 6·92 (1H, s, aryl-*H*), and 7·48 (1H, s, aryl-*H*); m/e 338 ($M^{+\cdot}$), 307 ($M^{+\cdot}$ -31), 281 ($M^{+\cdot}$ -57), 250, 221, 193, 163, 149, 131, 89, 75, 47, and 45 (Found: C, 60·30; H, 7·85, $C_{17}H_{26}O_5Si$ requires C, 60·32; H, 7·74%).

Attempted preparation of Methyl 2-Acetyl-4-t-butyldimethylsilyloxy-5-methylbenzoate (176)

(i) Dimethyl 3-t-butyldimethylsilyloxy-4-methylphthalate (175) (0·338 g, 1 mmol) was dissolved in dry tetrahydrofuran (30 ml) and the solution cooled to -78°C under an atmosphere of nitrogen. Methyllithium-lithium bromide complex in diethyl ether (0·87 M, 4 x 1·15 ml, 4 x 1·0 mmol) was added in portions over 4 h, at which time no starting material could be detected by t.l.c. analysis. The reaction was quenched by the addition of water (15 ml) and the mixture extracted with diethyl ether (3 x 20 ml). The combined extracts were dried and evaporated to give a colourless oil (111 mg) which rapidly turned brown. T.l.c. analysis [silica, diethyl ether : light petroleum (1:1)] indicated a complex mixture of products from which the title compound could not be isolated.

(ii) To a rapidly stirred solution of *N*-methanesulphinyl-4-toluidine (166) (0·74 g, 4·4 mmol) in dry tetrahydrofuran (80 ml), at -78°C under an atmosphere of nitrogen, was added dropwise 1·35 M n-butyllithium in hexane (6·66 ml, 9·0 mmol) over a 2 min period. The solution became yellow and was stirred at low temperature for ½ h. The protected diester (175) (0·338 g, 1 mmol) was added to the solution which was stirred for a further ½ h and treated at low temperature with water (100 ml). The reaction mixture was extracted with diethyl ether (3 x 150 ml) and the combined extracts dried and concentrated *in vacuo* to yield a yellow oil (454 mg) which turned rapidly brown. T.l.c. analysis [silica, diethyl ether : light petroleum (1:1)] indicated this to be a complex mixture of products.

Preparation of 3-*Hydroxy*-4-*methylphthalic Acid Monohydrate* (177)

A solution of dimethyl 4-hydroxy-5-methylphthalate (150) (2·0 g, 9·0 mmol) in tetrahydrofuran (35 ml) and water (35 ml) was heated, at the reflux, with sodium hydroxide (3·6 g, 90·0 mmol) under an atmosphere of argon for 24 h. After cooling, the reaction mixture was washed with diethyl ether (20 ml) and the aqueous phase acidified with 2N hydrochloric acid and extracted with diethyl ether (3 x 70 ml). The combined extracts were dried and concentrated *in vacuo* to afford a white solid. Recrystallization from water yielded the *title compound* (177) (1·83 g, 96%) as a white microcrystalline solid, m.p. 190-191°C, $\nu_{max.}$ (Nujol) 3495 s (-OH str.), 3080 s (-OH str.), 1905 s, 1690 s (C=O str.), 1565 s, 1495 s, 1290 s, 1265 s, 1180 m, 1145 w, 1025 s, 920 w, 850 w, 840 w, 800 w, 785 m, and 765 s cm^{-1}; δ_H (d^6 DMSO) 2·14 (3H, s, aryl-CH_3), 6·92 (1H, s, aryl-*H*), 7·48 (1H, s, aryl-*H*), 10·23 (1H, s, D_2O exch.), 12·60 (2H, br.s, D_2O exch.); m/e 196 ($M^{+\cdot}$), 178 ($M^{+\cdot}$ -H_2O), 134 (100%), and 106 (Found: C, 50·15, H, 4·62. $C_9H_8O_5 \cdot H_2O$ requires C, 50·47; H, 4·71%).

Attempted preparation of 2-Acetyl-4-hydroxy-5-methylbenzoic Acid (165)

3-Hydroxy-4-methylphthalic acid monohydrate (177) (0·75 g, 3·5 mmol) was dissolved in dry diethyl ether (60 ml) at 0°C, with stirring under an atmosphere of dry nitrogen. Methyllithium-lithium bromide complex in diethyl ether (0·87 M, 20·0 ml, 17·4 mmol) was added dropwise and the reaction stirred at 0°C for 3 h and at room temperature for a further 24 h. T.l.c. analysis (silica, ethyl acetate) indicated the presence of the unreacted diacid (177). An additional quantity of the methyllithium-lithium bromide complex (5·2 ml, 4·5 mmol) was added and stirring continued for 26 h. The reaction mixture was partitioned between diethyl ether (100 ml) and water (100 ml). The aqueous phase was acidified with glacial acetic acid and extracted with diethyl ether (3 x 100 ml). The combined extracts were dried and concentrated *in vacuo* to afford a white solid (464 mg). T.l.c. analysis (silica, ethyl acetate) revealed the solid to be a mixture of two components. Separation by medium pressure chromatography on silica (Kieselgel H, ethyl acetate-diethyl ether) and p.l.c. afforded a white solid (111 mg) of unknown structure, m.p. 174-177°C, $\nu_{max.}$ (Nujol) 3335 s (OH str. phenolic), 3200 br.s (OH str.), 1675 s (C=O str.), 1600 s, 1505 w, 1320 m, 1300 s, 1240 w, 1220 w, 1175 m, 1150 s, 1125 w, 1055 m, 1005 m, 985 w, 955 w, 900 w, 880 s, 865 s, 785 m, 740 m, 730 m, 705 m, and 660 m cm^{-1}; δ (250 MHz) (d^6 DMSO) 1·66 (s), 2·04 (s, only on D_2O exch.), 2·12 (s), 2·15 (s), 2·26-2·45 (br.s, D_2O exch.), 3·35 (s, D_2O exch.), 6·67 (br.s, D_2O exch.), 6·85 (s), 6·99 (s), 7·36 (s), 7·47 (s), 7·55 (s, D_2O exch.), 10·18 (br.s, D_2O exch.), 10·66 (br.s, D_2O exch.), and 12·77 (br.s, D_2O exch.) (Found: C, 61·23; H, 5·12. $(C_5H_5O_2)_n$ requires C, 61·85; H, 5·19%), and a hygroscopic white solid (46 mg, 7%) [2,4-dinitrophenylhydrazine active] tentatively identified as the title compound (165) on the basis of n.m.r. and i.r. spectral data,

$\nu_{max.}$ (Nujol) 3360 s, 3200 s, 1755 m, 1675 s, 1595 s, 1320 s, 1305 s, 1200 w, 1130 w, 1080 w, 945 w, 890 m, and 870 m cm^{-1}, the n.m.r. spectrum seemed to indicate the mixture of chain and ring forms[55] (1:2) (165), δ_H (250 MHz) (d^6 DMSO) 2·17 (3H, s, -aryl CH_3), 2·62 (3H, s, -$COCH_3$), 3·31 (1H, s, D_2O exch.), 7·03 (1H, s, aryl-*H*), 7·38 (1H, s, aryl-*H*), and 10·51 (1H, s, D_2O exch.) (chain); 1·46 [3H, s, -C(OH)CH_3], 2·14 (3H, s, -$COCH_3$), 3·31 (1H, s, D_2O exch.), 5·40 (1H, s, D_2O exch.), 6·98 (1H, s, aryl-*H*), and 7·30 (1H, s, aryl-*H*) (ring).

Preparation of 4-*Benzoyl*-5-*methylphthalic Anhydride* (185)

4-Hydroxy-5-methylphthalic acid monohydrate (177) (0·60 g, 2·80 mmol) was dissolved in dry tetrahydrofuran (30 ml) and treated with 100% sodium hydride (0·37 g, 15·3 mmol) at the reflux for 1½ h. The mixture was allowed to cool to room temperature over 2 h and was treated with benzoyl chloride (1·07 g, 7·65 mmol). After heating at the reflux overnight, a further quantity of benzoyl chloride (1·07 g, 7·65 mmol) was added and the reflux maintained for 2 h. After cooling the mixture was diluted with diethyl ether and filtered. Concentration of the filtrate *in vacuo* yielded an off-white solid which was triturated with light petroleum and recrystallized from acetone to afford the *title compound* (185) (670 mg, 85%), as a white crystalline solid, m.p. 161-164°C, $\nu_{max.}$ (Nujol) 2860 s, 1850 s (C=O str. anhyd.), 1770 s, (C=O str. anhyd.), 1740 s, 1738 s (C=O str. ester), 1600 w (C=C str.), 1585 w (C=C str.), 1480 w, 1465 s, 1350 s, 1265 s, 1210 m, 1185 s, 1110 m, 1090 s, 1070 m, 1045 m, 1030 s, 1005 m, 930 w, 905 s, 760 w, 740 s, 705 s, and 680 w cm^{-1}; δ_H (60 MHz) ($CDCl_3$) 2·46 (3H, s, aryl-CH_3), 7·42-8·48 (5H, m, aryl-*H*), 8·68 (1H, s, aryl-*H*), and 8·88 (1H, s, aryl-*H*); m/e 283 ($M^{\cdot+}$ + 1), 282 ($M^{\cdot+}$), 238 ($M^{\cdot+}$ -CO_2), 177 ($M^{\cdot+}$ -PhCO) and 105 (Found: C, 68·29; H, 3·59. $C_{16}H_{10}O_5$ requires C, 68·09;

H, 3·57%).

Reaction of Phthalic Anhydride (183) *with Methylmagnesium Iodide*

A solution of methylmagnesium iodide (8 mmol) in dry diethyl ether (15 ml) was prepared according to a procedure in the literature.[124] Phthalic anhydride (183) (1·18 g, 8 mmol) in dry tetrahydrofuran (30 ml) was added to the solution of Grignard reagent, at -78°C under an atmosphere of argon. After 1 h the reaction was quenched, by the rapid addition of methanol (10 ml) at -78°C and the mixture partitioned between diethyl ether (100 ml) and water (70 ml). The aqueous phase was acidified with concentrated hydrochloric acid and extracted with diethyl ether (3 x 100 ml). The combined extracts were dried and concentrated *in vacuo* to afford a white solid (471 mg). T.l.c. analysis (silica, diethyl ether) indicated the presence of two main products. Medium pressure chromatography on silica (Kieselgel H, dichloromethane-diethyl ether) led to the isolation of 2-acetylbenzoic acid (184) (134 mg, 10%), t.l.c. analysis (silica, diethyl ether; Rf 0·70). The spectral data were identical with an authentic sample.

Reaction of Phthalic Anhydride (183) *with Lithium Dimethylcuprate*

A solution of lithium dimethylcuprate (1·1 mmol) in dry diethyl ether (10 ml) was prepared according to the procedure of Johnson and Dutra.[68] Phthalic anhydride (183) (0·296 g, 2·00 mmol) in dry diethyl ether (5 ml) and dry tetrahydrofuran (7 ml) was added to the cuprate solution at -78°C and the mixture was allowed to warm up to -10°C over 1 h. The reaction was quenched, by the addition of chilled dilute hydrochloric acid, and the products extracted into diethyl ether (3 x 50 ml).

The combined extracts were dried and concentrated *in vacuo* to afford a gummy solid (310 mg). T.l.c. analysis (silica, diethyl ether) indicated a complex mixture of products; only one compound appeared to be active to 2,4-dinitrophenylhydrazine spray reagent. Medium pressure chromatography on silica [Kieselgel H, 10 g, eluant diethyl ether : light petroleum (1:1)] afforded 2-acetylbenzoic acid (184), in trace amounts, as identified by spectral analysis (m/s).

Reaction of Lithiomethyldimethylmethylenephosphorane (193) *with Phthalic Anhydride* (183)

To a stirred solution of tetramethylphosphonium iodide (194) (0·622 g, 2·85 mmol) in dry tetrahydrofuran (10 ml), at room temperature under an atmosphere of argon, was added a solution of 1·4 M n-butyllithium in hexane (4·08 ml, 5·71 mmol). The resulting pale yellow solution was cooled to -78°C and treated with phthalic anhydride (183) (0·422 g, 2·85 mmol) in dry tetrahydrofuran (5 ml). The resulting thick pale-orange precipitate was stirred for a further 10 min, and the reaction quenched by addition of water. The mixture was partitioned between diethyl ether (50 ml) and water (50 ml). The aqueous phase was acidified with concentrated hydrochloric acid and extracted with diethyl ether (3 x 50 ml). The combined ether extracts were dried and concentrated *in vacuo* to afford a white solid (349 mg). Medium pressure chromatography on silica (Kieselgel H, eluant diethyl ether -light petroleum) afforded 2-acetylbenzoic acid (184) (263 mg, 56%) as a white crystalline solid, m.p. 116-118°C (lit.,[125] m.p. 114-115°C), $\nu_{max.}$ (Nujol) 3270 s (O-H str.), 2860 s (C-H str.), 1730 s (C=O str.), 1620 w, 1605 w (C=C str.), 1495 w, 1415 w, 1135 w, 1295 s, 1255 s, 1235 m, 1215 s, 1195 m, 1165 w, 1145 s, 1115 m, 1070 s, 1035 s, 960 s,

875 s, 795 s, 765 s, 705 s, 650 w, and 625 w cm^{-1}; δ_H (90 MHz) ($CDCl_3$) 1·89 (3H, s) , 5·35 (1H, br.s, D_2O exch.), and 7·32-7·87 (4H, m); m/e 164 ($M^{+\cdot}$), 149 ($M^{+\cdot} - CH_3$), and 105 ($M^{+\cdot}$ -Ac).

Reaction of Lithiomethyldimethylmethylenephosphorane (193) *with* 4-*Benzoyl*-5-*methylphthalic Anhydride* (185)

4-Benzoyl-5-methylphthalic anhydride (185) (0·143 g, 0·507 mmol) in dry tetrahydrofuran (5 ml) was added to a solution of lithiomethyldimethylmethylenephosphorane (193) (1·42 mmol) in dry tetrahydrofuran (10 ml) [prepared as previously described], at -78°C under an atmosphere of argon, to yield an orange precipitate which rapidly turned yellow. After stirring at -78°C for 10 min the reaction was quenched by the addition of water and partitioned between diethyl ether (50 ml) and water (30 ml). The aqueous phase was acidified with concentrated hydrochloric acid and extracted with diethyl ether (3 x 50 ml). The combined extracts were dried and concentrated *in vacuo* to afford a dark oil (99 mg). T.l.c. analysis (silica-diethyl ether) indicated a complex mixture of products, containing at least two 2,4-dinitrophenylhydrazine active compounds. The required product could not be isolated.

Preparation of Ethynyltrimethylsilane (203)

Ethynyltrimethylsilane (203) (78·4 g, 57%) was prepared according to the procedure of Kraihanzel and Losee,[74] b.p. 52-54°C (lit.,[74] 70%, b.p. 52·5-53·5°C), $\nu_{max.}$ (CCl_4) 3290 s (C-H str.), 2970 s, 2910 m, 2035 s, 1410 s, 1335 s, 1250 s, 1170 m, 855 (br.s) 765 s, 700 s, 675 s, and 650 s cm^{-1}; δ_H (60 MHz) ($CDCl_3$) 0·18 (9H, s) and 2·21 (1H, s); m/e 98 ($M^{+\cdot}$) and 83 ($M^{+\cdot} - CH_3$).

Preparation of Ethyl 3-Trimethylsilylpropynoate (202)

Ethyl 3-trimethylsilylpropynoate (202) (16·40 g, 67%) was prepared from ethynyltrimethylsilane (203) (14 g) according to the procedure of Kraihanzel and Losee,[73] b.p. 78°C/13 mmHg (lit.,[73] 53%; b.p. 83-85°C/16 mmHg, 92-96°C/28 mmHg), $\nu_{max.}$ (liq. film) 3410 w, 2975 s, 2915 m (C-H str.), 2195 s (C≡C str.), 1710 s (C=O str.), 1470 s, 1450 s, 1395 m, 1370 s, 1305 s, 1215 s (C-O str.), 1135 m, 1120 w, 1100 w, 1030 s, 960 s, 940 s, 845 s, 800 w, 770 s, 710 s, and 630 s cm^{-1}; δ_H (90 MHz) ($CDCl_3$) 0·24 (9H, s), 1·31 (3H, t, *J* 7 Hz), and 4·20 (2H, q, *J* 7 Hz).

Attempted reaction of (E)-1-*Methoxy*-2-*methyl*-3-*trimethylsilyloxy*-1,3-*butadiene* (157) *with Ethyl* 3-*Trimethylsilylpropynoate* (202)

The diene (157) (0·93 g, 0·5 mmol) and the dienophile (202) (0·85 g, 0·5 mmol) were heated together, under an atmosphere of nitrogen, at 110°C for 1 week. T.l.c. and n.m.r. analysis of the resultant dark solution showed that little reaction had occurred.

Preparation of Ethyl Phenylthioacetate (222)

Ethyl phenylthioacetate (222) was prepared according to the procedure of Dressler and Graham,[78] $\nu_{max.}$ (liq. film) 3060 m, 2980 s, 1725 s, (C=O str.), 1585 s, 1480 s, 1440 s, 1370 s, 1265 s, 1025 s, 740 m, and 690 s cm^{-1}; δ_H (90 MHz) ($CDCl_3$) 1·17 (3H, t, *J* 8 Hz), 3·58 (2H, s), 4·11 (2H, q, *J* 8 Hz), and 7·10-7·50 (5H, m); m/e 196 ($M^{+\cdot}$), 123, 86, 84, and 72.

Preparation of Ethyl Phenylsulphinylacetate (217)

Ethyl phenylsulphinylacetate (217) was prepared according to the procedure of Leonard and Johnson,[79] $\nu_{max.}$ (liq. film) 3065 m, 2995 s, 2945 m, 1740 s (C=O str.), 1480 s, 1450 s, 1395 s, 1370 s, 1270 s (C-O str.), 1120 m, 1090 m, 1055 s, 910 m, 850 m, 750 s, and 690 s cm^{-1}; δ_H (90 MHz) ($CDCl_3$) 1·20 (3H, t, J 8 Hz), 3·52 and 3·77 (2H, AB q J_{AB} 14 Hz), 4·10 (2H, q, J 8 Hz), and 7·34-7·77 (5H, m); m/e 212 ($M^{+\cdot}$), 125 (100%), and 77. A sample of material was purified by medium pressure chromatography on silica (Kieselgel H, eluant diethyl ether-light petroleum) (Found: C, 56·77; H, 5·77. Calc. for $C_{10}H_{12}O_3S$ C, 56·59; H, 5·70%).

Attempted preparation of Ethyl 2-Benzenesulphinyl-4-oxo-2-pentenoate (245)

Ethyl phenylsulphinylacetate (217) was stirred with 40% aqueous pyruvic aldehyde (220) in ethanol containing pyridine according to the procedure of Tanikaga *et al.*[76] After 3 days at room temperature no appreciable reaction had occurred as judged by t.l.c. analysis (silica, diethyl ether).

Preparation of [(Ethoxycarbonyl)methylene]triphenylphosphorane (233)

[(Ethoxycarbonyl)methylene]triphenylphosphorane (233) (35·8 g, 86%) was prepared from triphenylphosphine (228) (31·4 g) and ethyl bromoacetate (231) (20 g) according to the method of Denney and Ross,[82] m.p. 125-127°C (lit.,[82] 76%, m.p. 125-127·5°C), $\nu_{max.}$ (Nujol) 1610 s (C=O str.), 1485 m, 1435 s, 1370 s, 1330 s, 1120 s, 1100 s, 890 s, 750 s, 725 m, 715 m, and 695 m cm^{-1}; δH (90 MHz) ($CDCl_3$) 1·03

(3H, t, J 8 Hz), 2·90 (1H, br.s), 4·00 (2H, q, J 8 Hz), and 7·27-7·83 (15H, m).

Preparation of 1-*Bromopropanone* (225)

1-Bromopropanone (225) (20 g, 30%) was prepared according to the method of Norris,[83] b.p. 64-66°C/53 mmHg (lit.,[124] b.p. 31·5°C/8 mmHg), δ_H (90 MHz) ($CDCl_3$) 2·32 (3H, s), and 3·90 (2H, s).

Preparation of Ethyl 4-*Oxo*-2-*pentenoate* (226) [R=Et, X=H]

Ethyl 4-oxo-2-pentenoate (226) [R=Et, X=H] (1·20 g, 83%) was prepared by the procedure of Vig *et al*,[81] b.p. 82-84°C/0·5 mmHg (lit.,[81] 75%, b.p. 115-117°C/6 mmHg), δ_H (90 MHz) ($CDCl_3$) 1·28 (3H, t, J 8 Hz), 2·33 (3H, s), 4·23 (2H, q, J 8 Hz), and 6·59 and 6·95 (2H, AB q, J_{AB} 16 Hz).

Preparation of Benzenesulphenyl Chloride (236)

Benzenesulphenyl chloride (236) (44·7 g, 86%) was prepared from thiophenol (39·6 g) by the method of Fieser and Fieser,[85] b.p. 76°C/10 mmHg (lit.,[86] 80%, b.p.[127] 58°C/3 mmHg, 73-75°C/9 mmHg). When the title compound was prepared from the action of chlorine gas on thiophenol, according to the procedure of Lecher and Holschneider,[128] the product was found to be contaminated with 4-chlorobenzenesulphenyl chloride (237).

Preparation of [(*Benzenesulphenyl*)(*ethoxycarbonyl*)*methylene*] *triphenylphosphorane* (234)

[(Benzenesulphenyl)(ethoxycarbonyl)methylene]triphenylphosphorane

(234) (14·7 g, 65%) was prepared from benzenesulphenyl chloride (236) (7·3 g) and the phosphorane (233) (34·7 g) according to the procedure of Saikachi and Nakamura,[84] m.p. 198-200°C (lit.,[84] m.p. 199°C), δ_H (250 MHz) ($CDCl_3$) 0·42-1·37 (3H, br.s, $-OCH_2CH_3$), 3·80-4·20 (2H, br.s, $-OCH_2CH_3$), 6·92-7·28 (5H, m, -S-aryl-*H*), and 7·33-7·64 (15H, m, aryl-*H*). This compound was found to be light sensitive turning pink on exposure to visible light.

Attempted preparation of Ethyl 2-Benzenesulphenyl-4-oxo-2-pentenoate (243)

The phosphorane (234) and 1-bromopropanone (225) were heated together using the procedure of Bestman *et al.*[80] After heating the mixture at the reflux for 74 h, t.l.c. analysis (silica, dichloromethane) indicated that no reaction had occurred.

Preparation of Ethyl 2-Benzenesulphenyl-4-oxo-2-pentenoate (243)

The phosphorane (234) (48·0 g, 0·105 mol) in benzene (1 l) was treated with 40% aqueous pyruvic aldehyde (220) (11·52 g, 0·16 mol) at the reflux for 48 h. After cooling, the mixture was concentrated *in vacuo* to yield a yellow semi-crystalline oil which was filtered and washed, at the pump, with diethyl ether-light petroleum (1:1). Concentration of the filtrate *in vacuo* followed by medium pressure chromatography on silica (Kieselgel H, eluant 10% diethyl ether/light petroleum) afforded the *title compound* (243) (17·9 g, 87%) as a yellow oil which crystallized on standing, m.p. 50-53°C (diethyl ether-light petroleum) $\nu_{max.}$ (liq. film) 2990 m, 1720 s (C=O str.), 1665 s (C=O str.), 1545 s, 1475 m, 1390 w, 1365 m, 1360 m, 1240 s, 1190 m, 1095 m, 1050 m, 1015 m,

965 w, 825 s, and 755 s cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 0·88 (3H, t, *J* 7 Hz), 2·35 (3H, s), 3·76 (2H, q, *J* 7 Hz), 6·73 (1H, s), and 7·26-7·54 (5H, m); m/e 250 ($M^{+\cdot}$), 207, 204, 179, 177, 161, 135, 134, 91, 85, 83, and 43 (100%) (Found: C, 62·35; H, 5·64; S $C_{13}H_{14}O_3S$ requires C, 62·38; H, 5·64; S, 12·81%).

Preparation of 4-*Chlorobenzenesulphenyl Chloride* (237)

4-Chlorothiophenol (30 g, 0·21 mol) in carbon tetrachloride (300 ml) was treated with chlorine gas, at room temperature for 4 h. Removal of the solvent *in vacuo* followed by distillation at reduced pressure afforded the title compound (237) (34·8 g, 93%) as a red liquid, b.p. 104-105°C/8 mmHg (lit.,[129] b.p. 33-34°C/0·22 mmHg, δ_H (60 MHz) ($CDCl_3$) 7·52 and 7·30 (4H, AB q, J_{AB} 8 Hz).

Preparation of [*(4-Chlorobenzenesulphenyl)(ethoxycarbonyl)methylene*] *triphenylphosphorane* (242)

[(4-Chlorobenzenesulphenyl)(ethoxycarbonyl)methylene]triphenylphosphorane (242) (61·8 g, 66%) was prepared from [(ethoxycarbonyl)methylene] triphenylphosphorane (233) (132·0 g) and 4-chlorobenzenesulphenyl chloride (237) (34·78 g) according to the procedure of Saikachi and Nakamura,[84] m.p. 198-201°C (lit.,[84] m.p. 199°C), $\nu_{max.}$ (Nujol) 1720 m (C=O str.), 1605 s (C=C str.), 1480 s, 1440 s, 1410 w, 1365 w, 1275 s (C-O str.), 1195 w, 1105 s, 1070 s, 1010 w, 845 w, 825 s, 770 m, 755 s, 745 w, 720 s, and 695 s cm^{-1}; δ_H (60 MHz) ($CDCl_3$) 0·90 (3H, t, *J* 8 Hz), 4·00 (2H, q, *J* 8 Hz), 7·07 (4H, s, aryl-*H*), and 7·23-7·83 (15H, m, aryl-*H*); m/e 490 ($M^{+\cdot}$), 277 (100%), 201, 199, 183, 152, 77, and 51 (Found: C, 68·72; H, 4·92. Calc. for $C_{28}H_{24}ClO_2PS$ C, 68·50; H, 4·93%).

This compound was found to be light sensitive turning green on exposure to visible light.

Preparation of Ethyl 2-(4-*Chlorobenzenesulphenyl*)-4-*oxo*-2-*pentenoate* (244)

The phosphorane (242) (8·0 g, 16·3 mmol) in dry benzene (200 ml) was treated with 40% aqueous pyruvic aldehyde (220) (1·84 g, 25·5 mmol , 4·4 ml) at the reflux for 20 h. After cooling, the mixture was concentrated *in vacuo* to yield a yellow semi-crystalline oil which was filtered and washed at the pump with diethyl ether-light petroleum (1:1). Concentration of the filtrate *in vacuo* followed by medium pressure chromatography on silica (Kieselgel H, eluant dichloromethane-light petroleum) afforded the *title compound* (244) (3·33 g, 72%) as a yellow oil, $\nu_{max.}$ (liq. film) 3090 w, 2995 w, 1730 s (C=O str.), 1675 s (C=O str.), 1575 m, 1555 s, 1480 s, 1395 m, 1370 m, 1245 s, 1195 m, 1100 s, 1055 m, 1015 s, 970 w, 865 w, 830 s, and 755 s cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 0·95 (3H, t, *J* 7 Hz, $-OCH_2CH_3$), 2·34 (3H, s, $-COCH_3$), 3·84 (2H, q, *J* 7 Hz, $-OCH_2CH_3$), 6·76 (1H, s), and 7·30 and 7·39 (4H, AB q, J_{AB} 8·5 Hz); m/e 284 ($M^{+\cdot}$), 279, 255, 241, 213, 197, 108, and 43 (100%) (Found: C, 55·06; H, 4·63; S, 10·96; $M^{+\cdot}$ 284·0274. $C_{13}H_{13}ClO_3S$ requires C, 54·83; H, 4·60; S, 11·26%; $M^{+\cdot}$ 284·0274).

Preparation of 5-*Acetyl*-4-(4-*chlorobenzenesulphenyl*)-4-*ethoxycarbonyl*-2-*methylcyclohexa*-2-*enone* (248)[99]

A solution of (*E*)-1-Methoxy-2-methyl-3-trimethylsilyloxy-1,3-butadiene (157) (0·78 g, 4·16 mmol) and the dienophile (244) (0·80 g, 2·77 mmol) in dry benzene (2 ml) was heated, under an atmosphere of nitrogen, at the reflux for 6 h. The cooled reaction mixture was treated with ethanolic hydrogen chloride and concentrated *in vacuo* to afford a dark

oil. Trituration with diethyl ether yielded the *title compound* (248) (0·64 g, 64%) as a white crystalline solid, m.p. 116·5-119·5°C (sublim.), $\nu_{max.}$ (Nujol) 1745 s (C=O str.), 1720 s (C=O str.), 1675 s (C=O str.), 1635 w, 1575 w, 1480 m, 1410 m, 1395 w, 1360 m, 1350 w, 1280 s, 1240 s, 1190 m, 1160 w, 1110 w, 1095 m, 1080 w, 1035 w, 1020 w, 1015 m, 970 w, 930 w, 835 w, 820 m, 750 m, and 710 w cm^{-1}; $\lambda_{max.}$ (EtOH) 234 nm (sh.) (4·15); δ_H (250 MHz) ($CDCl_3$) 1·32 (3H, t, *J* 7 Hz, $-OCH_2CH_3$), 1·69 [3H, d, *J* 1·5 Hz, $-CH=C(CH_3)-$], 2·30 (3H, s, $-COCH_3$), 2·68 and 2·75 (1H, dd, *J* 4 Hz, $-COCH_2-$), 3·05 and 3·10 (1H, dd, *J* 17 Hz, $-COCH_2-$), 3·77 and 3·82 (1H, dd, *J* 4 Hz, $-COCH_2-CH-$), 4·26 (2H, q, *J* 7 Hz, $-OCH_2CH_3$), 6·12 [1H, q, *J* 1·5 Hz, $-CH=C(CH_3)-$], and 7·29 and 7·42 (4H, AB q, J_{AB} 8·5 Hz, aryl-*H*); δ_C ($CDCl_3$) 13·9 (q, $-CH_3$ ester), 15·3 (q, $-CH_3$ ring), 29·8 (q, $-CH_3$ ketone), 36·8 (t, $-CH_2-$ ring), 52·3 (d, *C*H ring), 56·1 (s, *C* ring), 62·7 (t, $-CH_2-$ ester), 128·3 (s, *C* sp^2), 128·7 (d, 2 x *C*H aryl), 135·7 (s, *C* sp^2), 136·6 (s, *C* sp^2), 139·5 (d, 2 x *C*H aryl), 142·0 (d, *C*H sp^2), 170·9 (s, *C*=O ester), 195·6 (s, *C*=O enone), and 205·1 (s, *C*=O ketone); m/e 366 ($M^{+\cdot}$), 251, 223, 181, 153, 144, 137, 109, (100%), 91, 77, and 43 (Found: C, 59·09; H, 5·23. $C_{18}H_{19}ClO_4S$ requires C, 58·93; H, 5·22%).

Preparation of Ethyl 2-Acetyl-4-hydroxy-5-methylbenzoate (195)[99] (I)

A solution of the enone (248) (0·18 g, 0·5 mmol) in dry benzene (5 ml) and ethanol (5 ml) was treated, at room temperature, with a solution of sodium (13 mg, 0·55 mmol) in ethanol (5 ml). The resultant yellow solution was concentrated *in vacuo* and the residue was subjected to medium pressure chromatography on silica (Kieselgel H, 5g, eluant dichloromethane) to afford the *title compound* (195) (83 mg, 75%) as a white crystalline solid, m.p.128·5-129·5°C, $\nu_{max.}$ (Nujol) 3170 s (-OH str.), 1695 s (C=O str.), 1615 m, 1585 m (C=C str.), 1415 w,

1365 m, 1325 m, 1285 s (C-O str.), 1235 m, 1165 s, 1125 w, 1110 w, 1015 m, 965 w, 890 w, 870 w, and 780 w cm^{-1}; $\lambda_{max.}$ (EtOH) 264 (3·87); (EtOH + 1 drop 2N NaOH) 236 and 310 nm; δ_H (250 MHz) ($CDCl_3$) 1·36 (3H, t, *J* 7 Hz, $-OCH_2CH_3$), 2·23 (3H, s, aryl-CH_3), 2·49 (3H, s, $-COCH_3$), 4·32 (2H, q, *J* 7 Hz, $-OCH_2CH_3$), 6·67 (1H, s, aryl-*H*), 7·50 (1H, br.s, D_2O exch.), and 7·69 (1H, s, aryl-*H*); δ_C ($CDCl_3$) 14·1 (q, $-OCH_2CH_3$), 15·5 (q, aryl-CH_3), 30·7 (q, $-COCH_3$), 61·4 (t, $-OCH_2CH_3$), 112·7 (d, *C*H aryl), 119·7 (s, $-CCH_3$ aryl), 126·1 (s, $-CCO_2Et$ aryl), 133·1 (d, *C*H aryl), 143·4 (s, $-CCOCH_3$ aryl), 157·9 (s, *C*-OH aryl), 166·4 (s, *C*=O ester), and 205·3 (s, *C*=O ketone); m/e 222 ($M^{+\cdot}$), 207 ($M^{+\cdot} - CH_3$), 179 ($M^{+\cdot}$ -Ac) (100%), 177, 135, 109, 77, and 43 (Found: C, 64·78; H, 6·35. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%). In a separate experiment the butadiene derivative (157) and the dienophile (244) were converted directly to the title compound (195) (72%) without isolation of the intermediate enone (248).

Preparation of Ethyl 2-Acetyl-4-hydroxy-5-methylbenzoate (195)[99]
(II)

A solution of (E)-1-methoxy-2-methyl-3-trimethylsilyloxy-1,3-butadiene (157) (1·35 g, 7·26 mmol) and ethyl 2-benzenesulphenyl-4-oxo -2-pentenoate (243) (1·25 g, 5·0 mmol) in dry benzene (5 ml) was heated, under an atmosphere of nitrogen, at the reflux for 18 h. After cooling the reaction mixture was treated, at room temperature, with a solution of sodium (0·17 g, 7·5 mmol) in ethanol (50 ml). The resultant dark solution was evaporated *in vacuo* and the residue subjected to medium pressure chromatography on silica (Kieselgel H, 25 g, eluant dichloromethane) to afford the *title compound* (195) (0·88 g, 80%) as a white crystalline solid, m.p. 129-129·5°C. Spectral data were identical to that obtained from the previously characterized sample.

Preparation of 5-*Hydroxy*-3,6-*dimethyl*-isobenzofuran-1(3H)-*one* (250)[99]

The benzoate (195) (50 mg, 0·23 mmol) in ethanol (5 ml) was treated with sodium borohydride (55 mg, 1·47 mmol) at 0°C for 1 h. The reaction was stirred, at room temperature, overnight and quenched by addition of dilute hydrochloric acid. Extraction of the reaction mixture with diethyl ether (x 3), followed by concentration of the dried extracts *in vacuo* afforded the *title compound* (250) (38 mg, 95%) as a white crystalline solid, m.p. 182·5-184°C, $\nu_{max.}$ (Nujol) 3175 br.s (-OH str.), 1725 s (C=O str.), 1620 m, 1600 m, 1330 s, 1280 s, 1195 w, 1135 s, 1075 w, 1045 s, 995 w, 975 w, 925 w, 890 w, 865 w, 805 w, 785 w, 750 w, 720 w, and 675 w cm^{-1}; $\lambda_{max.}$ (EtOH) 254 (4·09), 281 (3·79), 288 (3·79); (EtOH + 1 drop 2N NaOH) 307, and 228 (sh) nm.; δ_H (250 MHz) ($CDCl_3$) 1·58 (3H, d, *J* 7 Hz), 2·33 (3H, s), 5·46 (1H, q, *J* 7 Hz), 6·80 (1H, s), 7·51 (1H, br.s, D_2O exch.), and 7·55 (1H, s); m/e 178 ($M^{+\cdot}$), 163 ($M^{+\cdot} - CH_3$), and 135 (100%) (Found: C, 67·41; H, 5·67. $C_{10}H_{10}O_3$ requires C, 67·41; H, 5·66%).

Preparation of Ethyl 2-*Acetyl*-4-*t*-*butyldiphenylsilyloxy*-5-*methylbenzoate* (252)

Ethyl 2-acetyl-4-hydroxy-5-methylbenzoate (195) (1·0 g, 4·50 mmol) and t-butylchlorodiphenylsilane (1·36 g, 4·95 mmol) were stirred in dry *N*,*N*-dimethylformamide (10 ml) containing imidazole (0·67 g, 9·91 mmol) at room temperature for 24 h. The reaction mixture was partitioned between diethyl ether (50 ml) and water (50 ml) and the aqueous phase extracted with diethyl ether (3 x 50 ml). The combined extracts were dried and concentrated *in vacuo* to afford a yellow oil. Medium pressure chromatography on silica [Kieselgel H, eluant dichloromethane : light petroleum (1:1)] yielded the *title compound*

(252) (2·02 g, 98%) as a white crystalline solid, m.p. 73-75°C, $\nu_{max.}$ (Nujol) 1715 s (C=O str.), 1605 m, 1555 m, 1550 m, 1315 m, 1285 m, 1275 m, 1255 w, 1225 m, 1165 s, 1110 s, 1010 m, 965 w, 905 s, 825 w, 805 w, 785 w, 745 w, 735 w, 720 w, 715 w, 695 m, 685 w, 675 w, and 665 w cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 1·14 (9H, s, -^tBu), 1·30 (3H, t, *J* 7 H, $-OCH_2CH_3$), 2·03 (3H, s, aryl-CH_3), 2·43 (3H, s, $-COCH_3$), 4·27 (2H, q, *J* 7 Hz, $-OCH_2CH_3$), 6·33 (1H, s, aryl-*H*), and 7·32-7·73 (11H, m, aryl), δ_C ($CDCl_3$) 14·0 (q, $-OCH_2CH_3$), 16·8 (q, aryl-CH_3), 19·6 [s, $-SiC(CH_3)_3$], 26·6 (q, $-SiCH_3$), 29·5 (q, $-COCH_3$), 61·1 (t, $-OCH_2CH_3$), 116·6 (d, *C*H aryl), 121·5 (s, *C* aryl), 128·1 (d), 130·4 (d), 130·4 (s), 132·1 (s), 132·6 (d), 135·4 (d), 141·8 (s), 156·7 (s), 166·8 (s, *C*=O ester), and 201·6 (s, *C*=O ketone); m/e 460 ($M^{+\cdot}$), 415, 403, 358, 256, 199 (100%), 77 and 45 (Found: C, 73·03; H, 6·96. $C_{28}H_{32}O_4Si$ requires C, 73·01; H, 7·00%).

Preparation of Allylphenylsulphide (266)

A solution of thiophenol (22 g, 0·2 mol) in dry tetrahydrofuran (100 ml) containing 100% sodium hydride (5·2 g, 0·22 mol) was heated, at the reflux, for 2 h and then stirred at room temperature overnight. Allyl bromide (265) (24·2 g, 0·2 mol) was added and the reaction stirred for a further 2½ h. After filtration the reaction mixture was concentrated *in vacuo* and distilled at reduced pressure to afford the title compound (266) (25·0 g, 83%) as a colourless liquid, b.p. 100°C/15 mmHg, n_D^{22} 1·5760 (lit.,[130] b.p. 104-106°C/25 mmHg, $n_D^{20·5}$ 1·4772), δ_H (60 MHz) ($CDCl_3$) 3·40 (2H, d), 4·92-5·16 (2H, m), 5·62-6·06 (1H, m), and 7·00-7·40 (5H, m); m/e 150 ($M^{+\cdot}$) (100%), 135, 117, 109, 91, 85, 65, and 41. A literature procedure[130] using ethanol as a solvent and sodium ethoxide as the base afforded the title compound in quantitative yield.

Preparation of Acetonyltriphenylphosphonium Chloride (268)

Acetonyltriphenylphosphonium chloride (268) (135·7 g, 72%) was prepared from triphenylphosphine (228) (150 g) and chloroacetone (267) (49 g) according to the method of Ramirez and Dershowitz,[90] m.p. 233-235°C (lit.,[90] 90%, m.p. 237-238°C), $\nu_{max.}$ (Nujol) 2930 s (C-H str.), 1705 s (C=O str.), 1465 s, 1110 s, 760 s, 720 s, and 695 s cm^{-1}; δ_H (90 MHz) ($CDCl_3$) 2·52 (3H, s), 6·10 (2H, d, *J* 13 Hz), and 7·40-8·02 (15H, m).

Preparation of Acetylmethylenetriphenylphosphorane (269)

Acetylmethylenetriphenylphosphorane (269) (103·8 g, 88%) was prepared from acetonyltriphenylphosphonium chloride (268) (133·0 g) according to the method of Ramirez and Dershowitz,[90] m.p. 205-206°C (lit.,[90] 92%, m.p. 205-206°C), $\nu_{max.}$ (Nujol) 2930 s (C-H str.), 1540 s (C=O str.),

1390 s, 1110 s, 875 m, 770 m, 760 m, 725 m, and 700 s cm^{-1}; δ_H (90 MHz) ($CDCl_3$) 2·08 (3H, s), 3·70 (1H, d, *J* 27 Hz), and 7·30-7·80 (15H, m).

Preparation of (E)-3-*Penten*-2-*one* (259)

(*E*)-3-Penten-2-one (259) (18·8 g, 97%) was prepared from acetylmethylenetriphenylphosphorane (269) (91·5 g, 0·23 mol) according to the procedure of House *et al*,[89] b.p. 25°C/22 mmHg; n_D^{23} 1·4355 (lit.,[89] 75·5%; b.p. 113-119°C; n_D^{21} 1·4352); $\nu_{max.}$ (liq. film) 3040 m, 2920 m, 1770 s, (C=O str.), 1630 s, 1440 s (C-O str.), 1360 s, 1255 s, 1180 s, and 970 s cm^{-1}; δ_H (100 MHz) ($CDCl_3$) 1·48 and 1·54 (3H, 2d, *J* 1·5 Hz, -CH=CHC*H*$_3$), 1·82 (3H, s, -COC*H*$_3$), 5·60 and 5·76 (1H, 2q, *J* 1·5 Hz, -C*H*=CHCH$_3$) and 6·28-6·64 (1H, m, -CH=C*H*CH$_3$).

Attempted preparation of 4,4-*Dimethyl*-3-*phenylthio*-1-*hepten*-6-*one* (272)

A solution of phenylthioallyllithium (258) (5·0 mmol) in dry tetrahydrofuran (20 ml) containing hexamethylphosphoramide (5·0 mmol) was prepared according to the procedure of Haynes and his co-workers.[88] The resulting orange solution was stirred at -78°C and treated with mesityl oxide (271) (0·49 g, 5·0 mmol). The orange colouration was immediately discharged and the resulting yellow solution was stirred, at -78°C, for 30 mins. The reaction was quenched by the addition of a saturated aqueous ammonium chloride solution and extracted with diethyl ether (3 x 20 ml). The combined extracts were dried and concentrated *in vacuo* to afford a yellow oil. N.m.r. and i.r. spectral analysis indicated this oil to contain mainly allylphenylsulphide (266) and the vinylsulphide (273). The title compound (272) was not detected.

Preparation of 4-*Methyl*-3-*phenylthio*-1-*hepten*-6-*one* (275)

A solution of phenylthioallyllithium (258) (50 mmol) in dry tetrahydrofuran (200 ml) containing hexamethylphosphoramide (50 mmol) was prepared according to the procedure of Haynes and his co-workers.[88] The orange solution was maintained at -30°C for 2 h and then cooled to -78°C and treated with 3-penten-2-one (259) (4·2 g, 50 mmol). The colouration of the mixture was slowly discharged to afford a pink solution. The reaction was stirred at -78°C for 1 h, quenched by the addition of a saturated aqueous ammonium chloride solution and extracted with diethyl ether (3 x 150 ml). The combined extracts were dried and concentrated *in vacuo* to afford an amber oil (12·83 g). Medium pressure chromatography on silica (Kieselgel H, 150 g, eluant light petroleum) afforded a yellow oil (6·42 g, 55%), b.p. 100-136°C/0·2 mmHg; $\nu_{max.}$ (liq. film) 1710 s (C=O str.) cm^{-1}. T.l.c. analysis silica, (20% diethyl ether/light petroleum; Rf 0·5) indicated a single product, however, n.m.r. spectral analysis revealed a diastereoisomeric mixture of the title compound (275) and 4-methyl -3-phenylthio-1,5-heptadien-4-ol (276) (*ca.*8 : 1). The title compound was used in this form in the subsequent reaction. $\nu_{max.}$ (liq. film) 1710 s (C=O str.) cm^{-1}; δ_H (90 MHz) ($CDCl_3$) 1·05 (3H, d, $-CHCH_3$) 2·07 (3H, s, $-COCH_3$), 2·20-3·00 [3H, m, $-CH(CH_3)CH_2COCH_3$], 3·45-3·75 [1H, m, -CH(SPh)], 4·75-5·25 (2H, m, $-CH=CH_2$), 5·60-5·90 (1H, m, $-CH=CH_2$), and 7·15-7·55 (5H, m, -SPh).

Preparation of 4-*Methyl*-3-*phenylthio*-1-*hepten*-6-*ol* (280)

A solution of 4-Methyl-3-phenylthio-1-hepten-6-one (275) (5 g, 21·4 mmol) [contaminated with the alcohol (276)] in absolute ethanol (25 ml) was treated with sodium borohydride (0·20 g, 5·34 mmol) at 0°C for 1½ h,

and then quenched by addition of glacial acetic acid. After removal of the solvent *in vacuo* the material was partitioned between diethyl ether (100 ml) and water (50 ml). The organic phase was washed with aqueous sodium hydrogen carbonate and dried. Concentration of the organic solution *in vacuo* yielded a yellow oil which was subjected to medium pressure chromatography on silica (Kieselgel H, 100 g, light petroleum-diethyl ether) to afford a diastereoisomeric mixture of the *title compound* (280) [3·84 g, 42% overall yield from the enone (259)] as a colourless oil. $\nu_{max.}$ (liq. film) 3365 br.s (OH str.), 3075 w, 3060 w, 2970 s, 2930 s, 1705 w, 1630 w (C=C str.), 1580 m (C=C str. aryl), 1485 m, 1440 m, 1380 m, 910 s, 840 m, 740 s, 705 w, and 695 w cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 1·04-1·10 (3H, m, $-CHCH_3$), 1·16-1·25 [3H, m, $-CH(OH)CH_3$], 1·38-1·90 (3H, m, $-CH_2-$ and $-CHCH_3$), 1·90-2·30 (1H, br.s, D_2O exch.), 3·47-3·74 [1H, m, $-CH(OH)CH_3$], 3·78-4·05 [1H, m, -CH(SPh)-], 4·80-5·04 (2H, m, $-CH=CH_2$), 5·64-5·88 (1H, m, $-CH=CH_2$), and 7·14-7·48 (5H, m, -Ph); m/e 236 ($M^{+\cdot}$), 196, 178, 149 (100%), 127, 110, 109, 87, 83, 82, and 45 (Found: C, 71·05; H, 8·80. $C_{14}H_{20}OS$ requires C, 71.14; H, 8·53%).

Preparation of 2,3,5-*Tri*-O-*t-butyldimethylsilyl-D-ribonic Acid-γ-lactone* (364)

A solution of D-(+)- ribonic acid-γ-lactone (362) (4·12 g, 0·028 mol) and imidazole (16·20 g, 0·238 mol) in dry *N*,*N*-dimethylformamide (80 ml) was stirred together with a solution of t-butylchorodimethylsilane (14·80 g, 0·098 mol) in dry *N*,*N*-dimethylformamide (25 ml) under an atmosphere of argon. The reaction mixture was maintained at 65-70°C for 5 h, allowed to cool and stored at room temperature overnight. The resultant solid was partitioned between diethyl ether (150 ml) and water (150 ml) and the aqueous phase was extracted with diethyl ether (2 x 100 ml). The combined extracts were dried and concentrated *in vacuo* to yield a white crystalline solid which was recrystallized from methanol (150 ml) to afford the *title compound* (364) (13·1 g, 96%) as colourless needles, m.p. 119-120°C, $[\alpha]_D^{22}$ + 28·2° (*c* 0·99, $CHCl_3$), $\nu_{max.}$ (Nujol) 2900 s, 1790 s (C=O str.), 1170 s, 1110 s, and 840 s cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 0·06 (3H, s, -SiC*H*$_3$), 0·08 (3H, s, -SiC*H*$_3$), 0·09 (3H, s, -SiC*H*$_3$), 0·10 (3H, s, -SiC*H*$_3$), 0·14 (3H, s, -SiC*H*$_3$), 0·18 (3H, s, -SiC*H*$_3$), 0·88 (9H, s, -Si^t*Bu*), 0·89 (9H, s, -Si^t*Bu*), 0·94 (9H, s, -Si^t*Bu*), 3·78 (1H, dd, J_{gem} 11·7, $J_{4,5}$ 2·1 Hz, C5-*H*), 3·86 (1H, dd, J_{gem} 11·7, $J_{4,5'}$ 3·0 Hz, C5-*H'*), 4·25-4·30 (2H, m, C4-*H* and C3-*H*), and 4·57 (1H, d, $J_{2,3}$ 5·0 Hz, C2-*H*); m/e 490 ($M^{+\cdot}$), 489, 475 ($M^{+\cdot}$ -15), 474, 433 ($M^{+\cdot}$ -57), 432, 404, 301, 300, 273, 272, 146, 116, 114, and 73 (Found: C, 56·50; H, 10·42. $C_{23}H_{50}O_5Si_3$ requires C, 56·27; H, 10·27%).

Attempted preparation of (5S)-3-*t-Butyldimethylsilyloxy*-5-[(*t-butyldimethylsilyloxy*)*methyl*]*furan*-2-(5H)-*one* (368)

(i) 2,3,5-Tri-*O*-t-butyldimethylsilyl-D-ribonic acid-γ-lactone (364)

(2·94 g, 6·0 mmol) in dry benzene (10 ml) was treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (0·9 g, 6·0 mmol) at room temperature.[102] After 30 mins no elimination product could be detected by n.m.r. spectral analysis.

(ii) The protected lactone (364) (1·47 g, 3·0 mmol) in dry tetrahydrofuran (10 ml) was added to a solution of lithium diisopropylamide (2·96 mmol) in dry tetrahydrofuran (30 ml) at -78°C. After 30 mins the reaction was quenched by the addition of water and the mixture partitioned between diethyl ether and water. The aqueous phase was extracted with diethyl ether (x 2) and the combined extracts were dried and concentrated *in vacuo* to afford a white crystalline solid (1·20 g), identified as mainly the starting lactone (364) by n.m.r. spectral analysis.

Preparation of 2,3-*Di*-O-*acetyl*-5-O-*triphenylmethyl*-D-*ribonic Acid* -γ-*lactone* (365)

D-(+)-Ribonic acid-γ-lactone (362) (5·92 g, 40 mmol) was treated with chlorotriphenylmethane (11·65 g, 42 mmol) in dry pyridine (25 ml). Warming the mixture produced a clear solution which rapidly converted to a gelatinous solid. The reaction was allowed to stand at room temperature overnight and was treated with acetic anhydride (10 ml). The mixture was stirred at room temperature for 5 h, partitioned between diethyl ether (150 ml) and water (200 ml) and quenched by the addition of solid sodium hydrogencarbonate. The aqueous layer was extracted with diethyl ether (3 x 100 ml) and the combined extracts dried and concentrated to yield a white solid. Medium pressure chromatography on silica [Kieselgel H, eluant dichloromethane : light petroleum

(1:1)] afforded the *title compound* (365) (8·60 g, 45%) as a white crystalline solid, m.p. 109-110°C, (dichloromethane-light petroleum) $[\alpha]_D^{22}$ + 18·6° (*c* 1·59, $CHCl_3$), $\nu_{max.}$ (Nujol) 1800 s (C=O str. lactone), 1755 br.s (C=O str.), 1600 w (C=C str.), 1245 s, 1215 s, 1180 m, 1125 m, 1090 s, 1035 m, 1000 s, 955 m, 940 m, 905 m, 875 w, 855 w, 795 w, 770 s, 750 s, 715 s, 705 s, and 640 m cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 2·03 (3H, s, $-COCH_3$), 2·11 (3H, s, $-COCH_3$), 3·29 (1H, dd, J_{gem} 11·0, $J_{4,5}$ 2·2 Hz, C5-*H*), 3·65 (1H, dd, J_{gem} 11·0, $J_{4,5'}$ 2·6 Hz, C5'-*H*), 4·49 (1H, distorted t, C4-*H*), 5·37 (1H, dd⇒d, *J* 6·2 Hz, C3-*H*), 6·14 (1H, d, $J_{2,3}$ 5·8 Hz, C2-*H*), and 7·17-7·46 (15H, m, aryl-*H*); m/e 474 ($M^{+\cdot}$), 397, 260, 243, 183, 165, 154, 105, 77 (100%), 51, and 43 (Found: C, 70·91; H, 5·51. $C_{28}H_{26}O_7$ requires C, 70·87; H, 5·52%), and the regioisomer 2,5-*di*-O-*acetyl*-3-O-*triphenylmethyl*-D-*ribonic acid*-γ-*lactone* (382) (1·76 g, 10%) as a white crystalline solid, m.p. 165-166°C (dichloromethane-light petroleum), $[\alpha]_D^{22}$ + 42·9° (*c* 1·26, $CHCl_3$), $\nu_{max.}$ (Nujol) 1800 s (C=O str.), 1755 s, (C=O str.), 1750 s (C=O str.), 1600 w (C=C str.), 1490 m, 1230 br.s (C-O str.), 1175 m, 1140 s, 1060 s, 1020 m, 1000 m, 965 w, 950 w, 930 w, 900 w, 835 w, 770 m, 750 m, 710 s, 700 s, 665 w, and 645 w cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 1·76 (3H, s, $-COCH_3$), 1·93 (3H, s, $-COCH_3$), 3·35 (1H, dd⇒d, *J* 5·9 Hz, C3-*H*), 3·98 (1H, dd, J_{gem} 12·5, $J_{4,5}$ 3·3 Hz, C5-*H*), 4·10 (1H, dd, J_{gem} 12·5, $J_{4,5'}$ 3·3 Hz, C5-*H'*), 4·29 (1H, distorted t, C4-*H*), 4·64 (1H, d, $J_{2,3}$ 5·9 Hz, C2-*H*), 7·23-7·39 (10H, m, aryl-*H*), and 7·57-7·67 (10H, m, aryl-*H*); m/e 474 ($M^{+\cdot}$), 397, 259, 243 (100%), 228, 215, 183, 165, 105, 77, and 43 (Found: C, 70·87; H, 5·49. $C_{28}H_{26}O_7$ requires C, 70·87; H, 5·52%).

Preparation of (5S)-3-*Acetoxy*-5-[(*triphenylmethoxy*)*methyl*]*furan*-2(5H)-*one* (369)

2,3-Di-*O*-acetyl-5-*O*-triphenylmethyl-D-ribonic acid-γ-lactone (365)

(0·5 g, 1·05 mmol) in dry tetrahydrofuran (5 ml) was treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (0·17 g, 1·11 mmol) for 15 min at room temperature. The solution rapidly turned very dark. The mixture was partitioned between diethyl ether and water, and the highly coloured aqueous phase extracted several times with diethyl ether (x 3). The combined extracts were dried and concentrated *in vacuo* to yield a dark solid (0·38 g). Medium pressure chromatography on silica [Kieselgel H, eluant dichloromethane : light petroleum (1:1)] afforded the *title compound* (369) (240 mg, 55%) as a white solid, m.p. 148-152°C (decomp.) (dichloromethene-light petroleum), $[\alpha]_D$ $\nu_{max.}$ (CCl_4) 3070 w, 3030 w, 2940 w (C-H str.), 1785 s (C=O str.), 1650 m (C=C str.), 1490 m, 1450 m, 1370 m, 1195 s (C-O str.), 1155 w, 1110 s, 1080 s, 1035 w, 900 w, 705 s, and 635 m cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 2·27 (3H, s, $-COCH_3$), 3·38 (2H, ddd⇒septet, $-OCH_2-$), 5·02 (1H, ddd⇒sextet, 5-*H*), and 7·12-7·47 (15H, m, 4-*H* and aryl-*H*); m/e 414 ($M^{+\cdot}$), 371 ($M^{+\cdot}$ -Ac), 337, 243 (100%), 183, 165, 105, and 43 (Found: C, 75·41; H, 5·39. $C_{26}H_{22}O_5$ requires C, 75·35; H, 5·35%).

Preparation of 2,3,5-*Tri*-O-*acetyl*-*D*-*ribonic Acid*-γ-*lactone* (366)

D-(+)-Ribonic acid-γ-lactone (362) (25 g, 0·17 mol) dissolved in acetic anhydride (200 ml) containing dry pyridine (6 drops) was stirred, after initial cooling at room temperature, overnight. The solvent was removed *in vacuo* and the reaction mixture partitioned between diethyl ether (750 ml) and water (500 ml), and basified by the addition of solid sodium hydrogencarbonate. The aqueous phase was extracted with diethyl ether (3 x 500 ml) and the combined extracts dried and concentrated *in vacuo* to yield the title compound (366) (44·3 g, 95%) as a white crystalline solid, m.p. 54-55°C (acetic acid-water),

$[\alpha]_D^{22}$ + 14·5° (*c* 1·44, $CHCl_3$), [lit.,[133] m.p. 54-56°C, $[\alpha]_D^{25}$ + 27° ($CDCl_3$)], $\nu_{max.}$ (Nujol) 1785 s (C=O str.), 1760 s (C=O str.), 1745 s (C=O str.), 1385 s, 1235 s, 1200 s, 1175 s, 1135 m, 1065 s, 1030 m, 975 w, 965 m, 945 m, 920 w, 885 m, 835 m, 765 w, 720 w, 685 w, 665 w, and 635 w cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 2·13 (6H, s, 2 x $-COCH_3$); 2·16 (3H, s, $-COCH_3$), 4·38 (2H, ddd, J_{gem} 18, $J_{4,5}$ 13·5 $J_{4,5'}$ 3·3 Hz, C5-*HH'*), 4·75 (1H, distorted t, C4-*H*), 5·47 (1H, dd⇒d, *J* 6·3 Hz, C3-*H*), and 5·73 (1H, d, $J_{2,3}$ 6·3 Hz, C2-*H*); m/e 317 ($M^{+\cdot}$ + 43), 275 ($M^{+\cdot}$ + 1), 232, 214, 201, 172, 170, 157, 153, 128, 115, 103, 100, 86, and 43 (100%).

Attempted preparation of (5S)-3-*Acetoxy*-5-[(*acetoxy*)*methyl*]*furan*-2(5H)-*one* (370)

(i) 2,3,5-Tri-*O*-acetyl-D-ribonic acid-γ-lactone (366) (1·64 g, 6 mmol) in dry benzene (10 ml) was treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) (0·9 g, 6 mmol) at room temperature. The reaction mixture, which turned rapidly black, was stirred for 15 min and partitioned between diethyl ether and water. The aqueous phase was extracted with diethyl ether (x 3) and the combined extracts dried and concentrated, *in vacuo* to afford a yellow oil. Purification by medium pressure chromatography on silica (Kieselgel H, eluant dichloromethane) yielded 3-*acetoxy*-5-*methylenefuran*-2(5H)-*one* (383) (631 mg, 68%), as a white crystalline solid, m.p. 75-76°C (chloroform), $\nu_{max.}$ (Nujol) 3040 m, 1785 s (C=O str. lactone), 1740 br.m (C=O str.), 1645 m (C=C str.), 1230 s, 760 s, 680 w, cm^{-1}; δ_H (250 MHz) ($CDCl_3$), 2·32 (3H, s, $-COCH_3$), 4·95 (1H, d, J_{gem} 3 Hz), 5·25 (1H, d, J_{gem} 3 Hz), and 7·30 (1H, s); m/e 154 ($M^{+\cdot}$), 112, 88, 85, 83, 70, 69, 67, 61, 60, and 43 (100%) (Found: C, 54·27; H, 3·92; $M^{+\cdot}$ 154·0267. Calc. for $C_7H_6O_4$ C, 54·55; H, 3·92%; $M^{+\cdot}$ 154·0266).

(ii) 2,3,5-Tri-*O*-acetyl-D-ribonic acid -γ-lactone (366) (1·0 g, 3·65 mmol) was heated, at the reflux for 2 days, in dry benzene (10 ml) containing a catalytic amount of toluene-4-sulphonic acid. At this time none of the required product could be detected by n.m.r. spectral analysis.

(iii) 2,3,5-Tri-*O*-acetyl-D-ribonic acid-γ-lactone (366) (10·0 g, 36·5 mmol) in dry tetrahydrofuran (100 ml) was cooled to -78°C and treated with 1,5-diazabicyclo[5.4.0.]undec-5-ene (DBU) (5·56 g, 36·5 mmol). The reaction mixture was stirred at -78°C for 4 hr; the appearance of a flocculent white precipitate was noted after 3 hr. The mixture was partitioned between diethyl ether and water, and the highly coloured aqueous phase was extracted with diethyl ether (x 3). The combined extracts were concentrated, *in vacuo* at low temperature, to afford a yellow crystalline solid (6·14 g) which was shown to be a > 2:1 mixture of the title compound (370), δ_H (60 MHz) ($CDCl_3$) 2·07 (3H, s, $-COCH_3$), 2·29 (3H, s, $-COCH_3$), 4·20-4·40 (2H, m, 6-*H*,*H'*), 5·05 -5·34 (1H, m, 5-*H*), and 7·12 (1H, d, *J* 2 Hz, 4-*H*); m/e 215 (M^+ + 1), and the previously characterized 3-acetoxy-5-methylenefuran-2(5*H*)-one (383). Compound (370) was used in this form in the subsequent reaction. Similar reactions employing either aqueous hydrochloric acid or aqueous sodium hydrogencarbonate work-up resulted in the isolation of a more highly coloured mixture of crude products.

Preparation of (3S,5S)-3-*Acetoxy*-5-[(*acetoxy*)*methyl*]*dihydrofuran* -2(3H)-*one* (372)

The previously prepared mixture of (5*S*)-3-acetoxy-5-[(acetoxy)methyl]furan -2(5*H*)-one (370) and 3-acetoxy-5-methylenefuran-2(5*H*)-one (383) (5·79 g) in ethanol (60 ml) was hydrogenated at atmospheric pressure over 10%

palladium on carbon. The catalyst was removed, by filtration through Celite, and the solvent removed *in vacuo* to afford a dark oil (4·41 g). Medium pressure chromatography on silica (Kieselgel H, eluant dichloromethane) afforded the *title compound* (372) [3·63 g, 46% from the triacetate (366)] as a white crystalline solid, m.p. 71-72°C (dichloromethane-diethyl ether), $[\alpha]_D^{22}$ + 51·1° (*c* 1·09, $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 2955 w (C-H str.), 1795 s (C=O str. lactone), 1745 s (C=O str.), 1450 m (sh.), 1380 s, 1250 s (sh.), 1170 s, 1110 s, 1015 m, 970 w, and 940 w cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 2·11 (3H, s, -COC*H*$_3$), 2·17 (3H, s, -COC*H*$_3$), 2·12 (1H, ddd⇒sextet, $J_{4\alpha,4\beta}$ 12·5, $J_{3,4\alpha}$=$J_{4\alpha,5}$ 10·3 Hz, 4α-*H*), 2·79 (1H, ddd, $J_{4\alpha,4\beta}$ 12·5, $J_{4\beta,5}$ 5·9, $J_{3,4\beta}$ 8·8 Hz, 4β-*H*), 4·18 (1H, dd, $J_{6,6'}$ 12·5, $J_{5,6}$ 5·8 Hz, 6-*H*), 4·39 (1H, dd, $J_{6,6'}$ 12·5, $J_{5,6'}$ 2·9 Hz, 6'-*H*), 4·72 (1H, 10 line m, 5-*H*), and 5·54 (1H, dd, $J_{3,4\alpha}$ 10·3, $J_{3,4\beta}$ 8·8 Hz, 3-*H*); δ_C ($CDCl_3$) 20·2 (q, -CO*C*H$_3$), 20·3 (q, -CO*C*H$_3$) 30·3 (t, -*C*H$_2$-), 64·0 (t, -O*C*H$_2$-), 67·8 (d, -O*C*H- ring), 73·9 (d, -O*C*HCO-), 169·3 (s, *C*=O), 170·1 (s, *C*=O), and 171·4 (s, *C*=O); m/e 259 (M^+ + Ac), 217 (M^+ + 1), 175, 143, 115 (100%), and 103 (Found: C, 49·99; H, 5·56. $C_9H_{12}O_6$ requires C, 50·00; H, 5·59%).

Preparation of (3S,5S)-3-*Acetoxy*-5-[(*acetoxy*)*methyl*]*dihydrofuran*-2(3*H*)-*one* (372)

2,3,5-Tri-*O*-acetyl-D-ribonic acid-γ-lactone (366) (15 g, 54·8 mmol) in dry tetrahydrofuran (150 ml) was treated with 1,5-diazabicyclo [5.4.0] undec-5-ene (DBU) (9·13 g, 60 mmol) at -78°C dropwise over 15 min. The reaction mixture was stirred at -78°C for 1½ h at which time a white solid was observed and the reaction quenched by addition of water (200 ml). The highly coloured aqueous phase was extracted with

diethyl ether (3 x 150 ml) and the volume of the combined organic phases reduced *in vacuo*. After dilution with ethanol (100 ml) the crude material was hydrogenated over 10% palladium on carbon overnight. The catalyst was removed by filtration through Celite and the solvent evaporated *in vacuo* to afford a dark oil (12·3 g). Medium pressure chromatography on silica (Kieselgel H, eluant dichloromethane) removed some highly polar base-line material and afforded a yellow oil (10·64 g) which crystallized on standing to an oily solid. Trituration with diethyl ether afforded the title compound (372) (6·6 g, 56%) as a white crystalline solid, m.p. 71-72°C (dichloromethane-diethyl ether) with spectral data identical to that of an authentic sample.

Investigation of the possible use of alternative bases in the preparation of (5S)-3-*Acetoxy*-5-[*(acetoxy)methyl*]*furan*-2(5H)-*one* (370)

The course of these reactions was monitored by n.m.r. spectroscopy. Samples from each reaction mixture were quenched with water and extracted with deuteriochloroform. The organic phases were then dried (Na_2SO_4) and submitted to n.m.r. spectral analysis.

(i) A solution of the lactone (366) (2·0 g, 7·30 mmol) in dry tetrahydrofuran (20 ml) was treated with potassium t-butoxide [preformed from potassium (285 mg, 7·30 mmol) and t-butanol (2 ml)] at -78°C. After 5 h n.m.r. spectral analysis indicated a 2:1 mixture of the starting lactone (366) and 3-acetoxy-5-methylenefuran-2(5H)-one (383).

(ii) A solution of the lactone (366) (2·0 g, 7·30 mmol) in dry tetrahydrofuran (20 ml) was treated with 100% sodium hydride (175 mg, 7·30 mmol) at room temperature. After 20 h n.m.r. spectral and t.l.c.

analysis indicated a mixture of the starting lactone (366) and 3-acetoxy-5-methylenefuran-2(5H)-one (383) plus some polymeric material.

(iii) A solution of the lactone (366) (2·74 g, 10·0 mmol) in dry tetrahydrofuran (40 ml) at -78°C, was treated with a solution of lithium hexamethyldisilazide [preformed from 1,1,1,3,3,3 -hexamethyldisilazane (1·77 g, 11·0 mmol) in dry tetrahydrofuran (20 ml) treated with 1·5 M n-butyllithium in hexane (11·0 mmol, 7·10 ml) at 0°C for 45 min]. After 3 h n.m.r. spectral analysis indicated no further change in the product ratio. The reaction was quenched by the addition of water and extracted several times with diethyl ether (x 3). The combined extracts were concentrated *in vacuo* to small volume, diluted with ethanol (50 ml) and hydrogenated over 10% palladium on carbon (200 mg) for 12 h. The catalyst was removed, by filtration through Celite, and the solvent evaporated *in vacuo* to yield a yellow semi-crystalline solid. Medium pressure chromatography on silica [Kieselgel H, 40 g, eluant dichloromethane : light petroleum (1:1)] afforded (3*S*, 5*S*)-3-acetoxy-5-[(acetoxy)methyl]dihydrofuran -2(3H)-one (372) (242 mg, 11%) with spectral data identical with that of an authentic sample.

(iv) A solution of the lactone (366) (1·0 g, 3·65 mmol) in dry tetrahydrofuran (10 ml) was treated with *N*,*N*-diisopropylethylamine (0·52 g, 4·01 mmol) at -78°C. After 3 h n.m.r. spectral analysis indicated a 2:1 mixture of the starting lactone (366) and 3-acetoxy-5-methylenefuran-2(5H)-one (383).

Preparation of (2S,4S)-1,2,4,5-*Pentanetetrol* (373)

The lactone (372) (3 g, 13·9 mmol) in water (20 ml) containing boric

acid (0·83 g) and Amberlyte IR 120H$^+$ resin (10·5 ml) was treated with sodium borohydride (5·80 g, 0·15 mol) over 1½ h at 0°C.[105] The reaction was stirred at room temperature overnight and quenched to pH 7 by addition of Amberlyte IR 120H$^+$ resin. The mixture was filtered and the resin washed with water and methanol. Concentration of the combined filtrate and washings *in vacuo* afforded a gummy white solid which was dissolved in methanol and concentrated by heating on a steam bath. This procedure was repeated several times to ensure the complete removal of boron residues. The resulting solid was recrystallized from ethanol to afford the *title compound* (373) (1·62 g, 86%) as colourless platelets, m.p. 106-107°C, $[\alpha]_D^{22}$ - 46·0° (*c* 1·03, EtOH), δ_H (250 MHz) (D_2O + ref. ^{t}BuOH) 1·54 (2H, distorted t, -C*H*$_2$-), 2·43-2·70 (4H, m, 2 x -OC*H*$_2$-), and 2·83-3·00 (2H, distorted ddd, 2 x -OC*H*-); δ_C (D_2O + ref. ^{t}BuOH), 38·3 (t, -*C*H$_2$-), 68·5 (t, 2 x -O*C*H$_2$-), and 70·8 (d, 2 x-O*C*H-); m/e 137 (M^+ + 1), 119, 106, 105 (M^+ -31), 88, 87, 69, 61, 57, 45, 43, 41, 31 and 29 (Found: C, 44·18; H, 8·95. $C_5H_{12}O_4$ requires C, 44·11; 8·88%).

Attempted preparation of (2S,4S)-2,4-*Dihydroxy*-1,5-*pentanediylbis* (*toluene*-4-*sulphonate*) (374)

(2*S*,4*S*)-1,2,4,5-pentanetetrol (373) (0·5 g, 3·73 mmol) was dissolved in dry pyridine (1 ml) and treated with toluene-4-sulphonyl chloride (1·43 g, 7·45 mmol). The reaction mixture was stirred at 4°C for 3 days and partitioned between diethyl ether and dilute hydrochloric acid. T.l.c. analysis [silica, dichloromethane : diethyl ether (1:1)] of the organic phase indicated a mixture of at least two major products. Further characterization was not attempted. In separate experiments,

in which chloroform and acetonitrile were used as solvents, reaction rates were found to be very slow and none of the required product could be isolated.

Preparation of (2S,4S)-2,4-*Dihydroxy*-1,5-*pentanediylbis*(2,4,6-*triisopropylbenzenesulphonate*) (375)

(2*S*,4*S*)-1,2,4,5-pentanetetrol (373) (1 g, 7·35 mmol) was dissolved, with warming, in dry pyridine (6 ml) and the resulting solution cooled to 0°C and treated with 2,4,6-triisopropylbenzenesulphonyl chloride (5 g, 16·53 mmol). The reaction mixture was stirred at 5°C overnight and the solvent removed *in vacuo* at room temperature. The resulting white solid was triturated with dichloromethane and filtered. The filtrate was concentrated *in vacuo* and the residue columned on silica (Kieselgel H, 30 g, eluant dichloromethane). Recrystallization from dichloromethane-light petroleum afforded the *title compound* (375) (4·31 g, 88%) as white crystals m.p. 154-155°C; t.l.c. analysis (silica, 10% diether ether/dichloromethane; Rf 0·5) indicated a single homogeneous compound, $[\alpha]_D^{22}$ - 8·8° (*c* 0·2, EtOH), $\nu_{max.}$ (Nujol) 3300 br.s (OH str.), 1600 *s*, 1565 m, 1425 *s*, 1345 s, 1315 w, 1305 w, 1260 m, 1240 w, 1195 m, 1175 s, 1155 m, 1135 w, 1105 m, 1075 w, 1060 w, 1040 m, 1025 m, 975 s, 965 s, 935 s, 910 s, 895 s, 880 s, 845 s, 835 s, 810 s, 755 w, 720 s, 680 w, 665 s, and 650 w cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 1·25 [24H, d, *J* 6·8 Hz 4 x $-CH(CH_3)_2$], 1·26 [12H, d, *J* 6·8 Hz, 2 x $-CH(CH_3)_2$], 1·63 (2H, dd, *J* 2·6 and 6·6 Hz, $-CH_2-$), 2·92 [2H, septet, *J* 6·8 Hz, 2 x $-CH(CH_3)_2$], 3·93-4·29 (10H, m), and 7·19 (4H, s, aryl-*H*); δ_C ($CDCl_3$) 23·5 (q, 4 x $-CH_3$), 24·7 (q, 8 x $-CH_3$), 29·7 [d, 4 x $-CH(CH_3)_2$], 34·3 [d, 2 x $-CH(CH_3)_2$], 35·3 (t, $-CH_2-$), 66·5 (d, 2 x -OCH-), 72·7 (t, 2 x $-OCH_2-$), 123·9 (d, 2 x *C* aryl), 129·0 (s, *C* aryl), 150·9 (s, 2 x *C* aryl), and 154·0 (s, *C* aryl);

m/e No M^{+} peak, 384 (M^{+} - 284), 284 ($C_{15}H_{24}O_3S$), 269, 267, 266, 251, 218, 203, 202, 188, 187, 161, 159, 145, 131, 129, 128, 117, 115, 105, 101, 91, 87, 83, 69, 55, 43, and 41 (Found: C, 63·00; H, 8·46. $C_{35}H_{56}O_8S_2$ requires C, 62·84; H, 8·44%).

Attempted preparation of (3S,5S)-3,5-*Dihydroxyheptane*-1,7-*dinitrile* (376)

A series of experiments were carried out in order to investigate the suitability of various solvents for use in this reaction.

(i) The disulphonate (375) (50 mg, 7·48 x 10^{-2} mmol) in d^6-benzene (0·5 ml) containing 18-Crown-6 (5 mg) and d^6-dimethyl sulphoxide (1-2 drops) was treated with potassium cyanide (15 mg, 23·0 x 10^{-2} mmol) at room temperature. After 2 days n.m.r. analysis indicated that no reaction had occurred.

(ii) The disulphonate (375) (50 mg, 7·48 x 10^{-2} mmol) in d^6-dimethyl sulphoxide (0·5 ml) was treated with potassium cyanide (15 mg, 23·0 x 10^{-2} mmol) at room temperature overnight. N.m.r. analysis showed a shift in the low field aromatic signals when compared with the starting material (375), and t.l.c. analysis (silica, 10% diethyl ether/ dichloromethane) indicated the complete disappearance of the disulphonate (375). The reaction mixture was partitioned between diethyl ether and water and the aqueous phase was extracted with diethyl ether (x 3). The combined extracts were dried and concentrated *in vacuo* to afford a brown semi-crystalline solid (10 mg), which was shown to be mainly a single compound by t.l.c. analysis (silica, ethyl acetate). This product was tentatively assigned as the title compound (376), $\nu_{max.}$ 2240 m cm^{-1}; m/e 154 (M^{+}).

(iii) The disulphonate (375) (50 mg, $7{\cdot}48 \times 10^{-2}$ mmol) in ethanol (3 ml) was treated with potassium cyanide (15 mg, $23{\cdot}0 \times 10^{-2}$ mmol) at room temperature overnight. T.l.c. analysis indicated the absence of starting material (375). The solvent was removed *in vacuo* to afford a white solid $\nu_{max.}$ (Nujol) 2240 m cm^{-1}. T.l.c. analysis (silica, ethyl acetate) showed the presence of a single ulta-violet inactive material (Rf 0·5) which was tentatively assigned as the title compound (376).

Preparation of (3S,5S)-3,5-*Di*(*benzoyloxy*)*heptane*-1,7-*dinitrile* (377)

A solution of the disulphonate (375) (1·33 g, 2·0 mmol) in methanol (10 ml) was treated with potassium cyanide (0·39 g, 6 mmol) for 3 h at the reflux. T.l.c. analysis (silica, 10% diethyl ether/dichloromethane) indicated the absence of starting material (375). The solvent was removed *in vacuo* to yield a light brown solid which was treated with dry pyridine (5 ml) and benzoyl chloride (0·70 g, 5 mmol) at room temperature overnight. The mixture was concentrated *in vacuo* and the residue partitioned between diethyl ether and aqueous sodium hydrogencarbonate. The aqueous phase was extracted with diethyl ether (x 3) and the combined extracts dried and concentrated *in vacuo* to yield a crystalline white solid (674 mg). Preparative layer chromatography on silica (Merck $GF_{254}H$, eluant dichloromethane) afforded the *title compound* (377) (244 mg, 34%) as a white crystalline solid m.p. 94-95°C (dichloromethane-light petroleum). T.l.c. analysis (silica, 10% diethyl ether/dichloromethane; Rf 0·80) indicated a homogeneous material, $[\alpha]_D^{22}$ - 148·3° (*c* 1·19, $CHCl_3$), $\nu_{max.}$ (Nujol) 2260 m (C≡N str.), 1740 s, 1730 s (C=O str.), 1610 m, 1590 m (C=C str.),

1430 m, 1355 m, 1320 m, 1280 s (C-O str.), 1235 w, 1220 w, 1180 m, 1155 w, 1120 s, 1110 s, 1100 s, 1090 w, 1070 s, 1040 s, 1030 s, 1010 m, 960 m, 890 w, 875 w, 860 w, 820 w, 810 w, 720 s, 690 m, and 670 m cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 2·49 (2H, dd, *J* 7·3 and 5·7 Hz, $-CH_2-$), 2·82 (2H, dd, J_{gem} 17·0, *J* 4·0 Hz, 2 x $-CHH'CN$), 3·02 (2H, dd, J_{gem} 17·0, *J* 5·5 Hz, 2 x $-CHH'CN$), 5·37-5·47 (2H, m, 2 x -OC*H*-), and 7·40-8·03 (10H, m, aryl-*H*); δ_C ($CDCl_3$) 23·5 (t, $-CH_2CN$), 37·2 (t, $-CH_2-$), 65·6 (d, -O*C*H-), 115·8 (s), 128·6 (d, 4 x *C*H aryl), 128·9 (s), 129·8 (d, 4 x *C*H aryl), 133·7 (d, 2 x *C*H aryl), and 165·4 (s, *C*=O); m/e 362 ($M^{+\cdot}$), 322, 257, 240, 200, 123, 122, 106, 105, 91, 84, 77, 69, and 51 (Found: C, 69·33; H, 4·98; N, 7·89. $C_{21}H_{18}N_2O_4$ requires C, 69·60; H, 5·01; N, 7·73%).

Attempted methanolysis of (3S,5S)-3,5-*Di(benzoyloxy)heptane* -1,7-*dinitrile* (377)

(i) A solution of the dibenzoate (377) (206 mg, 0·57 mmol) in dry methanol (10 ml) was stirred with Amberlyst A-26(OH^-) resin (50 mg). The resin rapidly darkened in colour. After stirring at room temperature for 16 h, t.l.c. analysis (silica, 10% diethyl ether/ dichloromethane) showed that no reaction had occurred. An additional quantity of Amberlyst A-26(OH^-) resin (50 mg) was added and the solution stirred, at room temperature, for a further 2 days. T.l.c. analysis still showed that no reaction had occurred; no trace of methyl benzoate could be detected. The reaction mixture was filtered and the solvent removed *in vacuo* to afford the starting diester (377) (179 mg, 87%).

(ii) The dibenzoate (377) (179 mg, 0·49 mmol) in dry methanol (3 ml) was treated, at room temperature, with a solution of sodium methoxide [preformed from sodium metal (10 mg) and methanol (2 ml)]. The reaction

mixture rapidly turned deep purple; t.l.c. analysis (silica, 10% diethyl ether/dichloromethane) indicated mainly starting diester (377) and polymeric base-line material. The solution was stirred at room temperature for 16 h at which time t.l.c. analysis indicated the absence of the starting diester (377); methyl benzoate was not detected. The solvent was removed *in vacuo* to afford a highly-coloured oil from which the required product (376) could not be isolated.

Attempted preparation of (2S,4S)-*Tetrahydro*-4-*hydroxy*-6-*oxo*-2H-*pyran*-2-*acetic Acid* (357)

The dibenzoate (377) (135 mg, 0·373 mmol) was treated with sodium hydroxide (45 mg, 1·122 mmol) in methanol (2 ml) and water (4 ml) at the reflux. The solution turned rapidly dark-red; t.l.c. analysis (silica, dichloromethane) showed the absence of starting material after 2 h. The reaction mixture was allowed to cool and was acidified by the addition of 1N hydrochloric acid. Removal of the solvent *in vacuo* afforded a highly-coloured oil from which the title compound (357) could not be isolated.

Preparation of (3S,5S)-3,5-*Dihydroxyheptane*-1,7-*dinitrile* (376)

(i) A solution of the disulphonate (375) (3·20 g, 4·79 mmol) in methanol (50 ml) was treated with potassium cyanide (1·17 g, 17·97 mmol) with stirring at room temperature. A homogeneous solution was produced after 4 h. After 2½ days the reaction mixture was diluted with water, passed through a column of Amberlyte IR $120H^+$ resin and then stirred with Amberlyst A-21(OH^-) resin overnight. After filtration the resin

was washed with water and the combined filtrate and washings concentrated *in vacuo* to yield a yellowish brown oil (743 mg). Medium pressure chromatography on silica (Kieselgel H, 15 g, eluant diethyl ether-ethyl acetate) afforded the *title compound* (376) (510 mg, 69%) as a pale yellow oil. T.l.c. analysis (silica, ethyl acetate; Rf 0·5) indicated a homogeneous material, $[\alpha]_D$ (*c* $CHCl_3$), $\nu_{max.}$ (liq. film) 3420 br.s (OH str.), 2940 s (C-H str.), 2250 s (C≡N str.), 1670 s (H_2O overtone), 1415 s, 1300 s, 1215 s, 1080 s, 1040 m, 1010 m, 965 s, 940 m, 885 m, 855 m, and 830 m cm^{-1}; δ_H (250 MHz) (D_2O + ref. ^tBuOH) 1·64 (2H, dd, *J* 5·8 and 7·2 Hz, $-CH_2-$), 2·56 (2H, dd, J_{gem} 12·8, *J* 6·3 Hz, 2 x $-CHH'CN$), 2·65 (2H, dd, J_{gem} 12·8, *J* 4·6 Hz, 2 x $-CHH'CN$), and 3·97-4·13 (2H, m, 2 x $-OCH-$); δ_C (D_2O + ref. ^tBuOH), 28·5 (t, $-CH_2CN$), 44·2 (t, $-CH_2-$), 66·1 (d, $-OCH-$), and 122·0 (s, $-CN$); m/e 154 ($M^{+\cdot}$), 136, 126, 118, 113, 95, 69, 67, 45, 42 (100%), and 41 (Found: C, ; H, ; N, . $C_7H_{10}N_2O_2$ requires C, 54·54; H, 6·54; N, 18·17%).

(ii) A solution of the disulphonate (375) (3·82 g, 5·72 mmol) in methanol (50 ml) was treated with potassium cyanide (1·11 g, 17·15 mmol) with stirring at room temperature. A homogeneous solution was produced after 5 h. After 2 days the solvent was removed *in vacuo* to yield a white solid. Medium pressure chromatography on silica (Kieselgel H, 15 g, eluant diethyl ether-ethyl acetate) afforded the title compound (376) (517 mg, 59%) as a pale yellow oil. Spectral data were in full agreement with that of an authentic sample.

Attempted preparation of (2S,4S)-*Tetrahydro*-4-*hydroxy*-6-*oxo*-2H-*pyran*-2-*acetic Acid* (357)

The selective mono-hydrolysis and subsequent lactonization of

(3*S*,5*S*)-3,5-dihydroxyheptane-1,7-dinitrile (376) was attempted using a variety of reaction conditions.

(i) A solution of the dinitrile (376) (76 mg, 0·49 mmol) in deuterium oxide (1 ml) was treated with sodium deuteroxide (20 mg, 0·50 mmol) at 70°C for 16 h. N.m.r. spectral data at this time was found to be too complicated to interpret. The reaction mixture was acidified by passage through a column of Amberlyte IR $120H^+$ resin (10 ml) and the solvent removed *in vacuo* to afford a brown oil (56 mg). T.l.c. analysis (silica, ethyl acetate) showed this material to be a complex mixture of ultra-violet active compounds from which the title compound (357) could not be isolated.

(ii) A solution of the dinitrile (376) (11 mg, 0·071 mmol) in water (2 ml) was stirred with Amberlyte IR $120H^+$ resin (41 mg) at room temperature. After 6 days t.l.c. analysis (silica, ethyl acetate) showed that no detectable reaction had occurred.

(iii) A solution of the dinitrile (376) (15·4 mg, 0·1 mmol) in water (3 ml) was stirred with sodium hydroxide (4 mg, 0·1 mmol) at room temperature. After 6 days some starting material was still present as detected by t.l.c. analysis. The reaction mixture was acidified with Amberlyte IR $120H^+$ resin (2 ml) and the solvent removed *in vacuo* to afford a brown oil. T.l.c. analysis (silica, ethyl acetate) indicated a complex mixture of polar products from which the required compound (357) could not be isolated.

(iv) A solution of the dinitrile (376) (15·4 mg, 0·1 mmol) in water (3 ml) was stirred with Amberlyst A-26(OH^-) resin (30 mg) at room temperature. After 6 days no significant reaction had occurred as detected by t.l.c. analysis (silica, ethyl acetate).

(v) A solution of the dinitrile (376) (35 mg, 0·23 mmol) in water (3 ml) containing concentrated sulphuric acid (5 drops) was heated, at the reflux, for 16 h. T.l.c. analysis (silica, ethyl acetate) indicated a complex mixture of ultra-violet active compounds from which the required product (357) could not be isolated.

Preparation of (3S,5S)-3,5-*Di*(*t-butyldimethylsilyloxy*)*heptane* -1,7-*dinitrile* (378)

The dinitrile (376) (0·52 g, 3·36 mmol) in dry *N*,*N*-dimethylformamide (5 ml) was treated with t-butylchlorodimethylsilane (1·11 g, 7·39 mmol) and imidazole (1·01 g, 14·78 mmol). The reaction mixture was stirred at room temperature for 2 days and partitioned between diethyl ether (50 ml) and water (50 ml). The aqueous phase was extracted with ether (3 x 50 ml) and the combined extracts, dried and evaporated *in vacuo* to yield a pale oil (2·05 g). Medium pressure chromatography on silica (Kieselgel H, eluant dichloromethane-light petroleum) afforded the *title compound* (378) (1·23 g, 96%) as a white crystalline solid m.p. 43-45·5°C. T.l.c. analysis (silica, dichloromethane; Rf 0·75) indicated a single homogeneous product, $[\alpha]_D^{22}$ - 30·2° (*c* 1·61, $CHCl_3$), $\nu_{max.}$ (Nujol) 2245 (C≡N str.), 1440 w, 1425 w, 1410 w, 1375 m, 1360 m, 1310 w, 1280 w, 1255 s (C-O str.), 1225 w, 1200 w, 1180 w, 1110 s, 1100 s (C-O str.), 1065 m, 1040 w, 1010 w, 990 m, 975 m, 940 w, 925 m, 905 w, 840 s, 810 s, 780 s, 730 m, and 670 m cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 0·13 (6H, s, 2 x -SiC*H*$_3$), 0·16 (6H, s, 2 x -SiC*H*$_3$), 0·92 (18H, s, 2 x -Si^t*Bu*), 1·90 (2H, dd⇒t, *J* 5·7 Hz, -C*H*$_2$-), 2·52 (2H, dd, J_{gem} 16·7, *J* 5·0 Hz, 2 x -C*H*H′CN), 2·62 (2H, dd, J_{gem} 16·7, *J* 5·5 Hz, 2 x -CH*H*′CN), and 4·05-4·11 (2H, m, 2 x -C*H*O-); δ_C ($CDCl_3$) -4·4 (q, -Si*C*H$_3$), -4·3 (q, -Si*C*H$_3$), 17·9 [s, -*C*(CH$_3$)$_3$], 25·7 [q, -C(*C*H$_3$)$_3$], 27·1 (t, -*C*H$_2$CN),

44·9 (t, -*C*H_2-), 66·2 (d, -*C*HO-), and 116·9 (s, -*C*N); m/e No $M^{+\cdot}$ peak, 367 ($M^{+\cdot}$ -CH_3), 325 ($M^{+\cdot}$ -^{t}Bu), 299, 285, 231, 224, 189, 184, 147, 129, 115, 101, 89, 75 (100%), 73, 59, 57, and 55 (Found: C, 59·82; H, 10·03; N, 7·13. $C_{19}H_{38}N_2O_2Si$ requires C, 59·63; H, 10·00; N, 7·32%).

Preparation of 5-O-*t-Butyldiphenylsilyl-D-ribonic acid-γ-lactone* (384)

D-(+)-Ribonic acid-γ-lactone (362) (3·0 g, 20·30 mmol) was stirred with t-butylchlorodiphenylsilane (6·13 g, 22·30 mmol) and imidazole (3·0 g, 44·60 mmol) in dry *N*,*N*-dimethylformamide (20 ml) at room temperature for 20 h. The reaction mixture was partitioned between diethyl ether (150 ml) and water (150 ml) and the aqueous phase extracted with diethyl ether (3 x 100 ml). The combined extracts were dried and concentrated *in vacuo* to yield a white solid (9·51 g). T.l.c. analysis (silica, dichloromethane) showed a mixture of two major products. Medium pressure chromatography on silica (Kieselgel H, 250 g, eluant dichloromethane-diethyl ether) afforded the *title compound* (384) (6·62 g, 85%) as a microcrystalline solid, m.p. 65-70°C (dichloromethane-light petroleum), t.l.c. analysis (silica, diethyl ether; Rf 0·3) indicated a single homogeneous compound, $[\alpha]_D^{22}$ + 46·3° (*c* 0·84. $CHCl_3$), $\nu_{max.}$ (Nujol) 3300 br.s (OH str.), 3070 w, 3045 w (C-H str.), 1790 s (C=O str.), 1590 m (C=C str.), 1430 s, 1365 m, 1310 w, 1265 w, 1235 w, 1180 s, 1135 s, 1110 s, 1080 s, 1015 m, 995 w, 970 s, 940 s, 855 s, 820 s, 765 s, 740 m, 725 s, 700 s, 690 m, 630 m, and 620 m cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 1·03 (9H, s, -Si^t*Bu*), 3·78 (1H, dd, $J_{5,5'}$ 12·0, $J_{4,5}$ 2·5 Hz, C5-*H*), 3·87 (1H, dd, $J_{5,5'}$ 12·0, $J_{4,5'}$ 2·5 Hz, C5'-*H*), 4·03 (1H, br.s, D_2O exch.), 4·49 (1H, m distorted t, C4-*H*), 4·54 (1H, dd⇒d, *J* 5·5 Hz, C3-*H*), 4·62 (1H, br.s, D_2O exch.), and 4·87 (1H, d, $J_{2,3}$ 4·0 Hz, C2-*H*). m/e No $M^{+\cdot}$ peak, 329 ($M^{+\cdot}$ -^{t}Bu), 283, 242, 241, 224, 223, 199, 183, 181, 164, 163,

145, 139, 135, 105, 91, 87, 77, 57, 50, 49, 48, 47, and 35 (Found: C, 65·11; H, 6·80. $C_{21}H_{26}O_5Si$ requires C, 65·26; H, 6·78%), and 3,5-*di*-O-*t*-*butyldiphenylsilyl*-D-*ribonic acid*-γ-*lactone* (393) (1·15 g, 9%) as a white crystalline solid, m.p. 143-146°C (dichloromethane-light petroleum), t.l.c. analysis (silica, dichloromethane; Rf 0·7) indicated a single homogeneous compound, $[\alpha]_D^{22}$ + 44·2° (*c* 0·56, $CHCl_3$), $\nu_{max.}$ (Nujol) 3480 s (OH str.), 3070 w, 3055 w (C-H str.), 1755 s (C=O str.), 1590 m (C=C str.), 1430 s, 1390 m, 1310 w, 1340 m, 1300 w, 1260 m, 1215 s, 1200 s, 1190 m, 1165 s, 1110 s, 1100 s, 1075 m, 1015 m, 990 w, 980 w, 940 s, 920 w, 870 m, 860 m, 820 s, 800 s, 760 s, 740 s, 725 m, 700 s, 685 w, 665 w, 620 m, and 610 m cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 0·73 (9H, s, $-Si^tBu$), 1·17 (9H, s, $-Si^tBu$), 3·07 (1H, s, D_2O exch.), 3·55 (1H, dd, J_{gem} 11·7, $J_{4,5}$ 1·5 Hz, C5-*H*), 3·75 (1H, dd, J_{gem} 11·7, $J_{4,5'}$ 2·5 Hz, C5-*H'*), 3·94 (1H, dd, $J_{2,3}$ 5·5, $J_{3,4}$ 1·2 Hz, C3-*H*), 4·38 (1H, m, C4-*H*), 4·86 (1H, d, $J_{2,3}$ 5·5 Hz, C2-*H*), and 7·20-7·90 (20H, m, aryl-*H*); m/e No $M^{+\cdot}$ peak, 568 ($M^{+\cdot} - {}^tBu$), 551, 550, 523, 522, 491, 490, 463, 462, 384, 320, 260, 243, 223, 205, 183, 163, and 77 (Found: C, 71·10; H, 7·17. $C_{37}H_{44}O_5Si_2$ requires C, 71·11; H, 7·10%).

Preparation of 2,3-*Di*-O-*Acetyl*-5-O-*t*-*butyldiphenylsilyl*-D-*ribonic acid*-γ-*lactone* (385)

(I)

5-*O*-t-Butyldiphenylsilyl-D-ribonic acid-γ-lactone (384) (2·0 g, 5·18 mmol) was dissolved in acetic anhydride (50 ml) at 0°C and the solution treated with pyridine (2 drops). The reaction mixture was stirred at room temperature overnight and the solvent removed *in vacuo*. The residue was partitioned between diethyl ether and aqueous sodium hydrogencarbonate solution and the aqueous phase was extracted with diethyl ether (x 3). The combined extracts were dried and concentrated

in vacuo to afford the *title compound* (385) (2·28 g, 94%) as a colourless oil. T.l.c. analysis (silica, dichloromethane; Rf 0·5) indicated the oil to be a single homogeneous compound, $[\alpha]_D^{22}$ + 4·9° (*c* 1·51, $CHCl_3$), $\nu_{max.}$ (liq. film) 3075 w, 3050 w, 3020 w, 3000 w, 2960 s, 2935 s, 2860 s (C-H str.), 1805 s (C=O str. lactone), 1755 s (C=O str.), 1590 m (C=C str.), 1490 w, 1470 m, 1465 w, 1430 s, 1375 s, 1330 w, 1310 w, 1240 s (C-O str.), 1210 s, 1180 s, 1110 s, 1090 m, 1065 m, 1020 w, 990 m, 975 m, 935 m, 910 m, 880 m, 860 w, 825 s, 770 w, 730 s, 705 s, 690 m, 650 w, and 625 m cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 1·07 (9H, s, -Si^tBu), 2·12 (3H, s, -COCH_3), 2·18 (3H, s, -COCH_3), 3·85 (1H, dd, $J_{5,5'}$ 11·8, $J_{4,5}$ 1·8 Hz, C5-*H*), 3·92 (1H, dd, $J_{5,5'}$ 11·8, $J_{4,5'}$ 2·3 Hz, C5'-*H*), 4·52 (1H, distorted t, C4-*H*), 5·58 (1H, dd⇒d, *J* 6·1 Hz, 3-*H*), 6·06 (1H, d, $J_{2,3}$ 6·1 Hz, 2-*H*), and 7·36-7·50 and 7·60-7·73 (10H, m, aryl-*H*); m/e 471 (M^+ + 1), 413 (M^+ - ^tBu), 371, 311, 283, 241, 223, 199, 181, 163, and 43 (100%) (Found: C, 63·98; H, 6·46. $C_{25}H_{30}SiO_7$ requires C, 63·81; H, 6·42%).

Preparation of 2,3-*Di*-O-*Acetyl*-5-O-*t-butyldiphenylsilyl*-D-*ribonic acid*-γ-*lactone* (385)

(II)

D-(+)-Ribonic acid-γ-lactone (362) (2·11 g, 14·23 mmol) was treated with t-butylchlorodiphenylsilane (3·91 g, 14·23 mmol) and imidazole (1·94 g, 28·45 mmol) in dry *N*,*N*-dimethylformamide (16 ml) at room temperature overnight. The reaction mixture was partitioned between diethyl ether (100 ml) and water (100 ml) and the aqueous phase was extracted with diethyl ether (3 x 100 ml). The combined extracts were dried and concentrated *in vacuo* to yield a colourless oil (6·72 g). The oil was dissolved in acetic anhydride (25 ml) containing pyridine (3 drops) and the solution stirred at room temperature overnight.

The solvent was removed *in vacuo* and the reaction mixture partitioned between diethyl ether and aqueous sodium hydrogencarbonate. The aqueous phase was extracted with diethyl ether (x 3) and the combined extracts dried and concentrated *in vacuo* to afford a colourless oil (5·85 g). Medium pressure chromatography on silica [Kieselgel H, 100 g, eluant dichloromethane : light petroleum (1:1)] afforded the title compound (385) (4·08 g, 61%), with spectral data identical with that of an authentic sample.

Attempted preparation of (5S)-3-*Acetoxy*-5-[(*t-butyldiphenylsilyloxy*)*methyl*]*furan*-2(5H)-*one* (386)

A solution of 2,3-di-*O*-acetyl-5-*O*-t-butyldiphenylsilyl-D-ribonic acid -γ-lactone (385) (1 g, 2·13 mmol) in dry tetrahydrofuran (30 ml) at -78°C was treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (0·324 g, 2·13 mmol) with stirring for 3 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution and was partitioned between diethyl ether (100 ml) and water (100 ml). The aqueous phase was extracted with diethyl ether (3 x 100 ml) and the combined extracts dried and concentrated *in vacuo*. Medium pressure chromatography on silica (Kieselgel H, eluant dichloromethane) led to the recovery of the starting lactone (385) (0·92 g, 92%).

Preparation of (5S)-3-*Acetoxy*-5-[(*t-butyldiphenylsilyloxy*)*methyl*]*furan* -2(5H)-*one* (386)

A solution of 2,3-di-*O*-acetyl-5-*O*-t-butyldiphenylsilyl- D-ribonic acid-γ-lactone (385) (1·99 g, 4·23 mmol) in dry tetrahydrofuran (40 ml) was treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (0·64 g, 4·23 mmol) with stirring at 0°C for ¾ h. The reaction was quenched by the

addition of Amberlyte IR 120H$^+$ resin, filtered and evaporated *in vacuo* to dryness. Medium pressure chromatography on silica (Kieselgel H, eluant dichloromethane) afforded the *title compound* (386) (1·54 g, 89%) as a colourless oil. T.l.c. analysis (silica, dichloromethane; Rf 0·75) indicated a single homogeneous material, $[\alpha]_D^{22}$ (c $CHCl_3$), $\nu_{max.}$ (thin film) 3065 w, 3040 w, 2960 m, 2930 m, 2890 m, 2860 m (C-H str.), 1775 s, (C=O str.), 1645 m (C=C str.), 1590 w (C=C str. aromatic), 1465 w, 1425 m, 1365 m, 1330 w, 1300 w, 1190 s, 1105 s, 1000 m, 940 w, 910 w, 855 w, 820 m, 765 w, 730 m, 700 s, and 600 s cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 1·02 (9H, s, -Si^t*Bu*), 2·29 (3H, s, -COC*H*$_3$), 3·84 and 3·88 (3H, ddd, J_{gem} 16·0, $J_{5,6}$ 4·5, $J_{5,6'}$ 4·6 Hz, 6-*H*,*H'*), 5·02-5·09 (1H, m, 5-*H*), 7·18 (1H, d, $J_{4,5}$ 1·9 Hz, 4-*H*), 7·33 -7·48 and 7·58-7·68 (10H, m, aryl-*H*); m/e 412 ($M^{+\cdot}$ + 2), 410 ($M^{+\cdot}$), 377, 353 ($M^{+\cdot}$ -57), 311, 256, 199 (100%), 181, 77, and 43 (Found: C, 67·22; H, 6·59; $M^{+\cdot}$ 410·1557. $C_{23}H_{26}O_5Si$ requires C, 67·29; H, 6·38%; $M^{+\cdot}$ 410·1549).

Preparation of (3S,5S)-3-*Acetoxy*-5-[(*t-butyldiphenylsilyloxy*)*methyl*]*furan*-2(3H)-*one* (387)

The lactone (385) (5·17 g, 11·0 mmol) in dry tetrahydrofuran (150 ml) was treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (2·01 g, 13·2 mmol) with stirring at 0°C for 20 min. The reaction was quenched, by the addition of saturated aqueous ammonium chloride solution, and partitioned between diethyl ether (150 ml) and water (150 ml). The aqueous phase was extracted with ether (3 x 100 ml) and the combined extracts were concentrated *in vacuo* to small bulk, diluted with ethanol (100 ml) and hydrogenated over 10% palladium on carbon (200 mg), at atmospheric pressure overnight. After filtration through Celite the

solvent was removed *in vacuo* to yield a yellow oil (4·37 g). Medium pressure chromatography on silica (Kieselgel H, eluant dichloromethane) afforded the *title compound* (387) (3·80 g, 84%) as a yellow oil. T.l.c. analysis (silica, dichloromethane; Rf 0·7) indicated a single homogeneous material, $[\alpha]_D$ (*c* $CHCl_3$), $\nu_{max.}$ (liq. film) 3075 w, 3060 w, 2960 m, 2940 s, 2900 w, 2860 s (C-H str.), 1800 s (C=O str. lactone), 1750 s (C=O str. acetate), 1590 w (C=C str.), 1490 w, 1475 m, 1465 m, 1430 s, 1390 m, 1375 s, 1365 m, 1340 w, 1310 w, 1230 s, 1200 m, 1115 s (C-O str.), 1050 w, 1030 w, 1000 w, 940 m, 910 w, 890 w, 860 w, 825 s, 805 m, 745 s, 705 s, 695 w, 665 w, and 610 m cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 1·06 (9H, s, -Si^{t}*Bu*), 2·16 (3H, s, -COC*H*$_3$), 2·27 (1H, ddd⇒sextet, $J_{4\alpha,4\beta}$ 12·8, $J_{4\alpha,5}$= $J_{3,4\alpha}$ 10·0 Hz, 4α-*H*), 2·69 (1H, ddd, $J_{4\alpha,4\beta}$ 12·8, $J_{3,4\beta}$ 9·1, $J_{4\beta,5}$ 6·1 Hz, 4β-*H*), 3·74 (1H, dd, $J_{6,6'}$ 11·6, $J_{5,6}$ 3·9 Hz, 6-*H*), 3·92 (1H, dd, $J_{6,6'}$ 11·6, $J_{5,6'}$ 3·4 Hz, 6-*H'*), 4·53 (1H, 10 line m, 5-*H*), 5·52 (1H, dd, $J_{3,4\alpha}$ 10·0 Hz, $J_{3,4\beta}$ 9·1 Hz, 3-*H*), and 7·34-7·73 (10H, m, aryl-*H*); m/e 455 ($M^{\ddagger}$ + 43), 413 ($M^{\ddagger}$ + 1), 355 (M^{+} -57), 313, 297, 267, 241, 207, 199 (100%), 181, 77, and 43 (Found: C, 66·97; H, 6·85. $C_{23}H_{28}O_5Si$ requires C, 66·96; H, 6·84%).

Preparation of (2S,4S)-1-(*t-Butyldiphenylsilyloxy*)-2,4,5 *-pentanetriol* (388)

A solution of the lactone (387) (12·41 g, 26·40 mmol) in tetrahydrofuran (190 ml) and water (60 ml) containing boric acid (1·70 g, 27·50 mmol) and Amberlyte IR 120H^{+} resin (26 ml) was treated with sodium borohydride (11·0 g, 291·0 mmol), over 30 min. The temperature of the reaction mixture was maintained between 20-30^{o}C with the aid of external ice-cooling. T.l.c. analysis (silica, dichloromethane) indicated an absence of starting material after 2 h. The reaction was quenched

after 2½ h by addition of glacial acetic acid. The solvent was removed *in vacuo* and the residue partitioned between diethyl ether (200 ml) and water (200 ml). The aqueous phase was extracted with ether (3 x 150 ml) and the combined extracts concentrated *in vacuo* to afford a colourless oil which was dissolved in methanol (100 ml) and stirred with potassium carbonate (0·75 g, 5·43 mmol) for 2 h. The solvent was removed *in vacuo* to yield an amber oil. Medium pressure chromatography on silica (Kieselgel H, eluant diethyl ether-dichloro methane) afforded the *title compound* (388) (8·82 g, 89%) as a colourless oil which solidified on standing to yield a waxy white solid, m.p. 35-40°C. T.l.c. analysis (silica, diethyl ether; Rf 0·35) indicated a single homogeneous material, $[\alpha]_D^{22}$ - 3·0° (*c* 4·07, $CHCl_3$), $\nu_{max.}$ (Nujol) 3360 br.s (O-H str.), 3065 w, 3025 w (C-H str.), 1590 w (C=C str.), 1430 s, 1365 m, 1305 w, 1265 w, 1185 w, 1110 s (C-O str.), 1080 s, 935 w, 890 w, 875 w, 825 m, 800 m, 740 s, 700 s, and 610 s cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 1·06 (9H, s, -Si^tBu), 1·47 (2H, distorted t, -C*H*$_2$-), 3·40-4·10 (9H, m), and 7·30-7·45 and 7·57-7·75 (10H, m, aryl-*H*); m/e No $M^{+\cdot}$ peak, 343 (M^+ -31), 299, 281, 241, 221, 199 (100%), 181, 143, 139, 135, 101, 83, 77, 57, and 43 (Found: C, 67·17; H, 8·09. $C_{21}H_{30}O_4Si$ requires C, 67·34; H, 8·07%),

In a separate series of reactions D-(+)-ribonic acid-γ-lactone (362) (22·2 g) was converted to the alcohol (388) in 48% overall yield without isolation of the intermediates.

Preparation of (2S,4S)-5-*t-Butyldiphenylsilyloxy*-2,4-*dihydroxypentyl* (2,4,6-*triisopropylbenzenesulphonate*) (389)

A solution of the triol (388) (8·68 g, 23·21 mmol) in dry pyridine (90 ml) was cooled to 0°C and treated with 2,4,6-triisopropylbenzenesulphonyl

chloride (11·13 g, 36·78 mmol). The reaction mixture was allowed to warm up to room temperature and stirred for 40 h. The solvent was removed *in vacuo* and the residue partitioned between diethyl ether (300 ml) and dilute hydrochloric acid (200 ml). The aqueous phase was extracted with diethyl ether (3 x 100 ml) and the combined extracts dried and concentrated *in vacuo*. The residue was subjected to medium pressure chromatography on silica (Kieselgel H, eluant dichloromethane-light petroleum) to afford the title compound (389) (12·48 g, 84%) as a yellow oil. $[\alpha]_D$ $\nu_{max.}$ (thin film) 3380 br.s (OH str.), 3070 w, 3050 w, 2960 s, 2930 s, 2890 s, 2860 s (C-H str.), 1600 (C=C str. aromatic), 1565 m, 1460 s, 1430 s, 1385 s, 1365 s, 1350 s, 1260 m, 1195 m, 1180 s, 1155 m, 1110 s, 1070 m, 1040 w, 1010 w, 1000 w, 975 m, 940 m, 910 m, 880 m, 845 m, 820 s, 740 s, 700 s, 690 m, 665 m, 650 w, and 610 m cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 1·05 (9H, s, -Si^tBu), 1·10-1·40 [19H, m, 3 x -CH(CH_3)$_2$+ C3-*H*], 1·50-1·65 (1H, m, C3-*H'*), 2·80-3·00 [1H, m, -C*H*(CH_3)$_2$], 3·42-3·75 (2H, m), 3·87-4·30 [6H, m, 2 x -C*H*(CH_3)$_2$], 4·55-4·90 (2H, m), 7·19 (2H, s, aryl-*H*), 7·30-7·47 and 7·55-7·76 (10H, m, aryl-*H*) (Found: C, H, S, $C_{36}H_{52}O_6SSi$ requires C, 67·46; H, 8·18; S, 5·00%).

Preparation of (3S,5S)-6-*t-Butyldiphenylsilyloxy*-3,5-*dihydroxyhexanenitrile* (390)

A solution of the sulphonate (389) (1·49 g, 2·33 mmol) in ethanol (20 ml) was treated with potassium cyanide (0·22 g, 3·28 mmol) at room temperature with stirring for 48 h. T.l.c. analysis (silica, 10% diethyl ether/dichloromethane) indicated the presence of two non-polar ultra-violet active materials. The solvent was removed *in vacuo* to yield a brown oil. Medium pressure chromatography on silica (Kieselgel

H, eluant 10% diethyl ether/dichloromethane) afforded the *title compound* (390) (486 mg, 55%) as a colourless oil. T.l.c. analysis (silica, 10% diethyl ether/dichloromethane; Rf 0·3), $[\alpha]_D$ (*c* $CHCl_3$), $\nu_{max.}$ (Nujol) 3460 s (OH str.), 3075 m, 3050 m, (C-H str.), 2250 m (C≡N str.), 1590 m (C=C str.), 1430 s, 1390 m, 1260 m, 1210 w, 1190 w, 1105 s (C-O str.), 960 w, 940 m, 910 s, 860 w, 850 m, 815 s, 800 m, 735 s, 700 s, 650 w, and 615 m cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 1·07 (9H, s, -Si^tBu), 1·66 (2H, ddd⇒t, C4-*H*,*H'*), 2·52 (1H, d, $J_{2,3}$ 1·5 Hz, C2-*H*), 2·55 (1H, d, $J_{2',3}$ 1·2 Hz, C2-*H'*), 2·91 (1H, br.s, D_2O exch.), 3·56 (1H, dd, $J_{6,6'}$ 10·2, $J_{5,6}$ 7·3 Hz, C6-*H*), 3·66 (1H, dd, $J_{6,6'}$ 10·2, $J_{5,6'}$ 4·0 Hz, C6-*H'*), 3·94-4·10 (1H, m, C5-*H*), 4·14-4·30 (2H, m, C3-*H* and D_2O exch.), and 7·30-7·77 (10H, m, aryl-*H*); m/e No $M^{+\cdot}$ peak, 326 ($M^{+\cdot}$ -57), 299, 281, 246, 228, 226, 199 (100%), 181, 163, 143, 139, 135, 117, 105, 57, 43, and 41 (Found: C, ; H, $C_{22}H_{29}NO_3Si$ requires C, 68·89; H, 7·62; N, 3·65%); and (2S,4S)-5-(*t-Butyldiphenylsilyloxy*)-4-*hydroxy*-1,2-*epoxypentane* (396) (345 mg, 42%) as a colourless oil. [T.l.c. analysis (silica, 10% diethyl ether/dichloromethane); Rf 0·6], $[\alpha]_D^{22}$ - 9·4° (*c* 2·24, $CHCl_3$), $\nu_{max.}$ (liq. film) 3450 br.s (OH str.), 3065 m, 3045 m, 3000 m, 2925 s, 2860 s (C-H str.), 1590 m (C=C str.), 1470 s, 1460 s, 1425 s, 1390 m, 1360 m, 1310 w, 1260 m, 1210 w, 1190 w, 1100 s, 1090 s (C-O str.), 1000 m, 940 m, 910 w, 840 w, 820 s, 800 s, 740 s, 700 s, and 610 s; δ_H (250 MHz) ($CDCl_3$) 1·09 (9H, s, -Si^tBu), 1·42-1·52 (1H, ddd, $J_{3,3'}$ 14·3, $J_{2,3}$ 7·1, $J_{3,4}$ 3·9 Hz, C3-*H*), 1·74 and 1·85 (1H, ddd, $J_{3,3'}$ 14·3, $J_{3',4}$ 8·8, $J_{2,3'}$ 4·2 Hz, C3-*H'*), 2·48 (1H, dd, $J_{1,1'}$ 5·0, $J_{1,2}$ 2·7 Hz, C1-*H*), 2·75 (1H, dd, $J_{1,1'}$ 5·0, $J_{1',2}$ 4·1 Hz, C1-*H'*), 2·80 (1H, br.s, D_2O exch.), 3·05-3·13 (1H, m, C2-*H*), 3·55 (1H, dd, $J_{5,5'}$ 10·2, $J_{4,5}$ 7·0 Hz, C5-*H*), 3·69 (1H, dd, $J_{5,5'}$ 10·2, $J_{4,5'}$ 4·0 Hz, C5-*H'*), 3·90-4·04 (1H, br.m, C4-*H*), and 7·32-7·50 and 7·60-7·78 (10H, m, aryl-*H*);

δ_C ($CDCl_3$) 19·3 [s, -Si*C*$(CH_3)_3$], 27·0 [q, -SiC(*C*$H_3)_3$], 36·1 (t, central -*C*H_2-), 47·2 (t, -*C*H_2OSi-), 49·7 [d, -*C*H(OH)-], 68·0 (t, -*C*H_2CH-), 69·9 (d, -CH_2*C*H-), 127·9 (d, *C*H aryl), 129·9 (d, *C*H aryl), 133·3 (s, aryl), and 135·6 (d, *C*H aryl); m/e No M^+ peak, 341 (M^+ -15), 299 (M^+ -57), 281, 241, 220, 199 (100%), 181, 163, 139, 135, 116, 105, 91, 77, 57, and 41 (Found: C, 70·54; H, 8·08. $C_{21}H_{28}O_3Si$ requires C, 70·74; H, 7·91%).

Preparation of (3S,5S)-6-*t-Butyldiphenylsilyloxy*-3,5-*dihydroxyhexanenitrile* (390) *via cyanide ion opening of the epoxide* (396)

A solution of the epoxide (396) (10 mg, 0·028 mmol) in ethanol (5 ml) was treated with potassium cyanide (50 mg, 0·77 mmol) at room temperature with stirring for 12 h. T.l.c. analysis (silica, 20% diethyl ether/dichloromethane) showed mainly the nitrile (390) (Rf 0·50) plus a trace (<10%) of an unidentified more polar material (Rf 0·35).

Preparation of (3S,5S)-6-*t-Butyldiphenylsilyloxy*-3,5-*dihydroxyhexanenitrile* (390)

(i) A solution of the sulphonate (389) (1·0 g, 1·56 mmol) in ethanol (20 ml) was stirred with potassium cyanide (0·35 g, 5·35 mmol) at room temperature for 2 days. T.l.c. analysis (silica, 10% diethyl ether/dichloromethane) indicated the presence of a quantity of the epoxide (396) (Rf 0·5). Potassium cyanide (0·2 g, 3·08 mmol) was added to the reaction mixture and stirring continued for 2 days. The solvent was removed, *in vacuo*, to yield a brown oil. Medium pressure chromatography on silica (Kieselgel H, eluant diethyl ether/dichloromethane) afforded

the title compound (390) (413 mg, 69%) as a colourless oil. Spectral data were identical with that of an authentic sample.

(ii) A solution of the sulphonate (389) (0·61 g, 0·95 mmol) in dry dimethyl sulphoxide (3 ml) was stirred with potassium cyanide (0·12 g, 1·89 mmol) at room temperature for 7 days. The solvent was removed *in vacuo* to yield a dark oil (387 mg). Preparative layer chromatography on silica [GF_{254}, eluant diethyl ether : dichloromethane (1:1)] afforded the title compound (390) (301 mg, 83%) as a colourless oil. Spectral data were identical with that of an authentic sample.

Preparation of (3S,5S)-3,5-*Di*(*t-butyldimethylsilyloxy*)-6-(*t-butyldiphenylsilyloxy*)*hexanenitrile* (397)

A solution of the nitrile (390) (0·77 g, 2·0 mmol) in dry *N,N*-dimethylformamide (6 ml) was stirred with imidazole (0·75 g, 11·0 mmol) and t-butylchlorodimethylsilane (0·66 g, 4·40 mmol) at room temperature for 2 days. The solvent was removed *in vacuo* and the residue partitioned between diethyl ether (50 ml) and water (50 ml). The aqueous phase was extracted with diethyl ether (3 x 50 ml) and the combined extracts dried and concentrated *in vacuo* to yield a colourless oil. Purification by medium pressure chromatography on silica [Kieselgel H, eluant dichloromethane : light petroleum (1:2)], afforded the *title compound* (397) (1·03 g, 84·5%) as a colourless oil. T.l.c. analysis [silica, dichloromethane : light petroleum (1:1); Rf 0·75] indicated a single homogeneous compound, $\nu_{max.}$ (thin film) 3075 m, 3050 m, 2950 s, 2925 s, 2890 s, 2855 s (C-H str.), 2250 w (C≡N str.), 1590 w (C=C str. aromatic), 1465 s, 1430 s, 1390 m, 1360 m, 1325 w, 1305 w, 1255 s, 1185 m, 1100 br.s (C-O str.), 1005 m, 940 m, 830 s,

805 m, 775 s, 740 s, 705 s, 655 m, and 610 s cm^{-1}; δ_H (250 MHz) ($CDCl_3$) - 0·11 (3H, s, -SiC*H*$_3$), - 0·01 (3H, s, -SiC*H*$_3$), 0·12 (3H, s, -SiC*H*$_3$), 0·14 (3H, s, -SiC*H*$_3$), 0·82 (9H, s, -Si^t*Bu*), 0·93 (9H, s, -Si^t*Bu*), 1·06 (9H, s, -Si^t*Bu*), 1·55-1·73 (1H, ddd, $J_{4,4'}$ 14·1, $J_{4,5}$ 8·2, $J_{3,4}$ 6·1 Hz, C4-*H*), 2·03-2·16 (1H, ddd, $J_{4,4'}$ 14·1, $J_{3,4'}$ 5·7, $J_{4',5}$ 3·7 Hz, C4-*H'*), 2·47 (1H, dd, $J_{2,2'}$ 16·6, $J_{2,3}$ 6·0 Hz, C2-*H*), 2·61 (1H, dd, $J_{2,2'}$ 16·6, $J_{2',3}$ 4·5 Hz, C2-*H'*), 3·38 (1H, dd, $J_{6,6'}$ 10·0, $J_{6,5}$ 7·8 Hz, C6-*H*), 3·58 (1H, dd, $J_{6,6'}$ 10·0, $J_{6',5}$ 4·6 Hz, C6-*H'*), 3·70-3·86 (1H, m, C5-*H*), and 4·04-4·16 (1H, m, C3-*H*) (Found: C, 67·04; H, 9·43; N, 2·03. $C_{34}H_{57}NO_3Si_3$ requires C, 66·72; H, 9·38; N, 2·29%).

Preparation of (4S,6S)-4-*t-Butyldimethylsilyloxy*-6-[(*t-butyldimethylsilyloxy*)*methyl*]*tetrahydro*-2H-*pyran*-2-*one* (392)

A solution of the nitrile (390) (9·38 g, 24·5 mmol) in 1N sodium hydroxide solution (90 ml) was heated at 60-70°C for 44 h; the reaction mixture was stirred by passage of a constant stream of nitrogen gas. After cooling the mixture was washed with diethyl ether (2 x 50 ml) and acidified by the addition of Amberlyte IR 120H$^+$ resin. The aqueous phase was filtered and the solvent removed *in vacuo* to afford a white solid. The solid was heated at reduced pressure, 65-70°C/1 mmHg, for 17 h and the residue stirred with t-butylchlorodimethylsilane (22·14 g, 0·15 mol) and imidazole (24·98 g, 0·37 mol) in dry *N*,*N*-dimethylformamide (50 ml) at room temperature for 2 days. The solvent and the excess chlorosilane were removed *in vacuo* and the residue partitioned between diethyl ether (200 ml) and water (200 ml). The aqueous phase was extracted with diethyl ether (3 x 100 ml) and the combined extracts dried and concentrated *in vacuo* to afford a white crystalline solid. Medium pressure chromatography on silica (Kieselgel H, eluant

dichloromethane) yielded an amber oil (6·76 g), which was subjected to bulb-to-bulb distillation to afford the *title compound* (392) (3·70 g, 40%) as a pale yellow oil, b.p. 150°C/0·4 mmHg, $[\alpha]_D^{22}$ + 0·5° (*c* 1·07, $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 2920 s, 2850 s (C-H str.), 1730 s (C=O str.), 1460 m, 1420 w, 1375 w, 1360 w, 1230 m, 1085 s, 1005 m, 900 w, 885 w, and 830 s cm^{-1}, (thin film) 2950 s, 2850 s (C-H str.), 1745 s (C=O str.), 1465 s, 1390 m, 1360 m, 1250 s, 1135 s, 1090 s, 1005 w, 940 w, 915 w, 885 w, 840 s, 780 s, 740 s, and 670 cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 0·07 [6H, s, $-Si(CH_3)_2$], 0·08 [6H, s, $-Si(CH_3)_2$], 0·87 (18H, s, 2 x $-Si^tBu$), 1·71-1·78 (1H, ddd, $J_{5,5'}$ 13·6, $J_{5,6}$ 11·3, $J_{4,5}$ 9·7 Hz, 5-*H*), 2·13-2·17 (1H, 16 line m, 5*H'*), 2·42 (1H, dd, $J_{3,3'}$ 17·2, $J_{3,4}$ 8·5 Hz, 3-*H*), 2·74-2·85 (1H, ddd, $J_{3,3'}$ 17·2, $J_{3',4}$ 5·6, $J_{3',5'}$ 1·6 Hz, 3-*H'*), 3·76-3·77 (2H, ddd, $J_{\alpha,\alpha'}$ 10·9, $J_{\alpha,6}$ 4·9, $J_{\alpha',6}$ 4·3 Hz, C_α-*H*,*H'*), 4·07-4·23 (1H, m, 4-*H*), and 4·17-4·33 (1H, m, 6-*H*); m/e 375 (M^+ + 1), 358, 318, 316, 289, 243, 236, 211, 146, 116, 73, and 75 (Found: C, 57·73; H, 10·30. $C_{18}H_{38}O_4Si_2$ requires C, 57·70; H, 10·22%).

Preparation of cis-2,3-*Dimethyloxirane* (412)

Cis-2,3-Dimethyloxirane (412) was prepared according to the modified procedure of Parto and Cumbo.[131] Anhydrous sodium acetate (14·3 g,) in dry diglyme (360 ml) containing a 37% W/V peracetic acid solution (115 ml, 0·91 mol) was cooled to -40°C and treated with *cis*-butene (44 g, 0·79 mol). The reaction mixture was allowed to warm up to room temperature and was stirred for an additional 4½ h. Distillation at reduced pressure yielded a colourless distillate which was redistilled to afford the title compound (412) (38·8 g, 69%) as a colourless liquid, b.p. 63-64°C (lit.,[131] 55%, b.p. 58-59°C), δ_H (250 MHz) ($CDCl_3$) 1·22-1·29 (6H, m), and 2·97-3·10 (2H, m).

Preparation of (2SR,3RS)-3-*Methyl*-4-*pentyn*-2-*ol* (406)

(2*SR*,3*RS*)-3-Methyl-4-pentyn-2-ol (406) was prepared according to the modified procedure of Meinwald and his co-workers.[113] *Cis*-2,3 dimethyloxirane (11·6 g, 0·16 mol) (412) in dry dimethyl sulphoxide (100 ml) was treated with lithium acetylide-ethylene diamine complex (29·65 g, 0·32 mol) with external cooling. The reaction mixture was allowed to warm to room temperature and stirred under an atmosphere of nitrogen for 290 h. The mixture was poured into aqueous saturated ammonium chloride (400 ml) and the solution continuously extracted with light petroleum for 2 days. Removal of the solvent *in vacuo* followed by distillation at atmospheric pressure afforded the *title compound* (406) (9·30 g, 51%) as a colourless liquid, b.p. 121-123°C, $\nu_{max.}$ (liq. film) 3410 br.s (OH str.), 3300 s (C≡CH str.), 2980 s, 2930 s, 2900 s, 2880 s (C-H str.), 2110 w (C≡C str.), 1450 s, 1380 s, 1345 w, 1300 m, 1265 m, 1160 m, 1100 s, 1075 m, 1040 m, 1015 w, 1000 w, 990 m, 920 s, 870 m, 740 w, 635 s, and 625 s; δ_H (250 MHz) ($CDCl_3$) 1·21 (3H, d, *J* 7·0 Hz, $-CH_3$), 1·25 (3H, d, *J* 6·2 Hz, $-CH_3$), 2·16 (1H, d, *J* 2·4 Hz, $-C\equiv CH$), 2·25 (1H, br.s, D_2O exch.), 2·41-2·55 [1H, m, $-CH(CH_3)-$], and 3·62-3·75 [1H, br.m, $-CH(OH)-$]; m/e 98 ($M^{+\cdot}$), 97, 83 ($M^{+\cdot}$ -15), 69, 54 (100%), 53, 45, 43, and 39 (Found: C, 72·92; H, 10·45; $M^{+\cdot}$ 98·0731. $C_6H_{10}O$ requires C, 73·43; H, 10·27%; $M^{+\cdot}$ 98·0731).

Attempted addition of the dilithio- derivative of (2SR,3RS)-3-*Methyl*-4-*pentyn*-2-*ol* (406) *to* (3S,5S)-3,5-*Dihydroxyheptane*-1,7-*dinitrile* (376)

A solution of the acetylene alcohol (406) (393 mg, 4·01 mmol) in dry tetrahydrofuran (3 ml) was treated with 1·5 M n-butyllithium in hexane (5·88 ml, 8·82 mmol), at -78°C under an atmosphere of dry nitrogen.

The reaction mixture was allowed to warm up to 0°C and stirred for 1 h. The pale yellow solution was recooled to -78°C and added to a solution of the dinitrile (376) (0·154 g, 1·00 mmol) in dry tetrahydrofuran (5 ml), also at -78°C. The solution was allowed to warm up to 0°C and stirred for 1 h. T.l.c. analysis (silica, 10% diethyl ether/dichloromethane) indicated that no reaction had occurred. The reaction was quenched by the addition of glacial acetic acid (1 ml) and the solvent was removed *in vacuo* to afford a yellow oil (170 mg). Both t.l.c. and n.m.r. spectral analysis indicated this material to be predominantly the starting dinitrile (376).

Attempted addition of the dilithio- derivative of (2SR,3RS)-3-*Methyl*-4-*pentyn*-2-*ol* (406) *to* (3S,5S)-3,5-*Di*(*t*-*Butyldimethylsilyloxy*)*heptane*-1,7-*dinitrile* (378)

A solution of the acetylene alcohol (406) (80 mg, 0·82 mmol) in dry tetrahydrofuran (1 ml) was treated with 1·5 M n-butyllithium in hexane (1·26 ml, 1·89 mmol), at -78°C under an atmosphere of dry nitrogen, and the reaction mixture stirred for 1 h. The resultant yellow solution was then added to a solution of the dinitrile (378) (200 mg, 0·52 mmol) in dry tetrahydrofuran (4 ml) at -78°C. The reaction mixture, which rapidly darkened in colour, was stirred at -78°C for 2¾ h. T.l.c. analysis (silica, dichloromethane) indicated the appearance of an ultra-violet active material (Rf 0·6). The reaction was quenched by the addition of glacial acetic acid (2 ml) and the solvent was removed *in vacuo* to afford a yellow oil (159 mg) which rapidly darkened in colour on exposure to air. T.l.c. analysis indicated this material to be a complex mixture of products containing predominantly the starting dinitrile (378).

In a separate experiment the reaction was quenched by addition of saturated aqueous ammonium chloride solution, diluted with ethanol, and hydrogenated at atmospheric pressure over 10% palladium on carbon for 16 h. Removal of the solvent *in vacuo* followed by medium pressure chromatography on silica (Kieselgel H, eluant dichloromethane-diethyl ether) afforded mainly the starting dinitrile (378), as identified by n.m.r. spectral analysis.

Attempted addition of the dilithio- derivative of (2SR,3RS)-3-*Methyl*-4-*pentyn*-2-*ol* (406) *to* (3S,5S)-6-*t*-*Butyldiphenylsilyloxy*-3,5-*dihydroxyhexanenitrile* (390)

A solution of the acetylene-alcohol (406) (445 mg, 4·54 mmol) in dry tetrahydrofuran (2 ml) was treated with 1·5 M n-butyllithium in hexane (6·66 ml, 9·99 mmol), at -78°C under an atmosphere of dry nitrogen. The reaction mixture was allowed to warm up to 0°C and stirred for 1 h. The yellow solution was recooled to -78°C and treated with a solution of the nitrile (390) (290 mg, 0·76 mmol) in dry tetrahydrofuran (4 ml). The reaction mixture was stirred at -78°C for 2¾ h, allowed to warm up to 0°C and the reaction quenched by the addition of glacial acetic acid (0·7 g, 11·66 mmol). The solvent was removed *in vacuo* and the residue subjected to medium pressure chromatography on silica (Kieselgel H, 10 g, eluant diethyl ether) to afford a yellow oil (271 mg). T.l.c. analysis (silica, 10% diethyl ether/dichloromethane) showed this material to be a complex mixture of polar compounds, some producing a positive result with 2,4-dinitrophenylhydrazine spray-reagent. N.m.r. spectral analysis indicated the presence of a large amount of butylated material. Attempts to isolate the required addition product, by chromatography or *via* hydrogenation of the crude material, were unsuccessful.

Attempted addition of the dilithio- derivative of (2SR,3RS)-3-*Methyl*-4-*pentyn*-2-*ol* (406) *to* (3S,5S)-3,5-*Di*(*t-butyldimethylsilyloxy*)-6-(*t-butyldiphenylsilyloxy*)*hexanenitrile* (397)

A solution of the acetylene alcohol (406) (163 mg, 1·66 mmol) in dry tetrahydrofuran (2 ml) was treated with 1·5 M n-butyllithium in hexane (2·44 ml, 3·66 mmol) at -78°C under an atmosphere of dry nitrogen. The reaction mixture was allowed to warm up to 0°C and was stirred for 45 min. The yellow solution was recooled to -78°C and added to a solution of the nitrile (397) (490 mg, 0·802 mmol) in dry tetrahydrofuran (4 ml) also at -78°C. The reaction mixture was allowed to warm up to 0°C and was stirred for 1 h. T.l.c. analysis [silica, diethyl ether : dichloromethane, (1:1)] indicated the presence of trace amounts of two new compounds (Rf 0·6-0·7, u.v. and 2,4-dinitrophenylhydrazine active). The reaction mixture was stirred at -20°C for 16 h; no change was noted by t.l.c. analysis. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution and the aqueous phase extracted with diethyl ether (x 3). The combined extracts were dried and concentrated *in vacuo* to afford a yellow oil (486 mg) which was shown to be mainly the starting nitrile (397) by t.l.c. and n.m.r. spectral analysis. Attempts to isolate the ultraviolet active compounds were unsuccessful.

Attempted addition of the dilithio- derivative of (2SR,3RS)-3-*Methyl*-4-*pentyn*-2-*ol* (406) *to Acetonitrile*

A solution of the acetylene alcohol (406) (100 mg, 1·02 mmol) in dry tetrahydrofuran (2 ml) was treated with 1·5 M n-butyllithium in hexane (1·5 ml, 2·25 mmol), at -78°C under an atmosphere of dry nitrogen, and the mixture stirred at -70°C for 1¼ h. The solution was treated with

acetonitrile (0·5 ml) and stirring continued at -70°C for 3½ h. T.l.c. analysis (silica, dichloromethane) indicated the presence of a major ultra-violet active material (Rf 0·6). The reaction was quenched by the addition of trifluoroacetic acid (0·5 ml) and the solvent removed *in vacuo* to afford a highly coloured oil (200 mg). T.l.c. analysis showed this material to be an intractible mixture of products.

In a separate experiment the reaction was quenched by the addition of saturated aqueous ammonium chloride solution, diluted with ethanol and hydrogenated at atmospheric pressure over 10% palladium on carbon for 16 h. Filtration through Celite and removal of the solvent *in vacuo* afforded a white solid (100 mg) (mainly NH_4Cl) from which no major product could be isolated.

Preparation of (3RS,4SR)-4-*t-Butyldimethylsilyloxy*-3-*methyl*-1-*pentyne* (407)

A solution of the acetylene alcohol (406) (333 mg, 3·40 mmol) in dry *N*,*N*-dimethylformamide (5 ml) was treated with t-butylchlorodimethylsilane (640 mg, 4·25 mmol) and imidazole (1·08 g, 15·95 mmol). The reaction mixture was stirred at room temperature for 2 days and partitioned between diethyl ether (30 ml) and water (30 ml). The aqueous phase was extracted with diethyl ether (2 x 30 ml) and the combined extracts dried and concentrated *in vacuo* to yield a colourless oil. Medium pressure chromatography on silica (Kieselgel H, eluant light petroleum) afforded the *title compound* (407) (721 mg, 95%) as a colourless liquid, t.l.c. analysis (silica, light petroleum; Rf 0·7) $\nu_{max.}$ (liq. film) 3310 s (C≡C*H* str.), 2120 w (C≡C str.), 1460 s, 1410 w, 1375 s, 1360 m, 1335 m, 1290 m, 1255 s, 1160 s, 1105 s, 1070 s, 1030 s, 1005 m, 980 w,

950 s, 940 m, 890 m, 830 s, 820 m, 770 s, 665 m, and 630 s; δ_H (250 MHz) ($CDCl_3$) 0·06 [6H, s, $-Si(CH_3)_2$], 0·89 (9H, s, $-Si^tBu$), 1·15 (3H, d, *J* 7·1 Hz, $-CH_3$), 1·17 (3H, d, *J* 6·2 Hz, $-CH_3$), 2·03 (1H, d, *J* 2·5 Hz, $-C\equiv CH$), 2·43-2·58 [1H, m, $-CH(CH_3)-$], and 3·80-3·94 [1H, m, $-CH(OH)-$]; m/e No M^+ peak, 197 ($M^+ - CH_3$), 159, 155 ($M^+ - {}^tBu$), 147, 111, and 73 (Found: C, 67·68; H, 11·10. $C_{12}H_{24}OSi$ requires C, 67·85; H, 11·39%).

Preparation of (3RS,4SR)-4-*t*-*Butyldiphenylsilyloxy*-3-*methyl*-1-*pentyne* (408)

A solution of the acetylene alcohol (406) (100 mg, 1·02 mmol) in dry *N*,*N*-dimethylformamide (5 ml) was treated with t-butylchlorodiphenylsilane (420 mg, 1·53 mmol) and imidazole (173 mg, 2·55 mmol). The reaction mixture was stirred, at room temperature for 2 days, and partitioned between diethyl ether (30 ml) and water (30 ml). The aqueous phase was extracted with diethyl ether (2 x 30 ml) and the combined extracts dried and concentrated *in vacuo* to yield a colourless oil. Medium pressure chromatography on silica [Kieselgel H, eluant dichloromethane : light petroleum, (1:1)] afforded the *title compound* (408) (330 mg, 96%) as a colourless oil, t.l.c. analysis (silica, light petroleum; Rf 0·4), $\nu_{max.}$ (liq. film) 3300 s (C≡CH str.), 3065 m, 3045 m, 1590 m (C=C str.), 1480 m, 1470 s, 1460 s, 1425 s, 1375 s, 1360 m, 1290 m, 1260 m, 1190 w, 1160 s, 1100 s, 1070 s, 1025 s, 1005 m, 950 s, 890 m, 820 s, 770 s, 740 s, 700 s, 690 s, and 630 s; δ_H (250 MHz) ($CDCl_3$) 1·06 (9H, s, $-Si^tBu$), 1·10 (3H, d, *J* 6·2 Hz, $-CH_3$), 1·20 (3H, d, *J* 7·0 Hz, $-CH_3$), 2·00 (1H, d, *J* 2·5 Hz, $-C\equiv CH$), 2·48-2·64 [1H, m, $-CH(CH_3)-$], 3·90-4·04 [1H, m, $-CH(OH)-$], and 7·30-7·47 and 7·63-7·75 (10H, m, aryl-*H*); m/e 336 (M^+), 321 ($M^+ - CH_3$), 279 ($M^+ - {}^tBu$), 235, 207, 201, 181, 135, 105, and 77 (Found: C, 78·42; H, 8·66. $C_{22}H_{28}OSi$ requires C, 78·51; H, 8·38%).

Preparation of (S)-O-*Methylmandelic acid* (416)

(*S*)-(+)-Mandelic acid (67·45 g, 0·44 mol) was converted, according to the procedure of Bonner,[118] to the title compound (416) (57·36 g, 78%) which was obtained as a white crystalline solid, m.p. 64-65°C (light petroleum), $[\alpha]_D^{22}$ + 148·8° (*c* 1·305, EtOH), [lit.,[118] m.p. 64-65°C, $[\alpha]_D^{25}$ + 149·4° (*c* 0·964, EtOH)], δ_H (250 MHz) ($CDCl_3$) 3·40 (3H, s, $-OCH_3$), 4·77 [1H, s, $-CH(OCH_3)$], and 7·28-7·50 (5H, m, aryl-*H*).

Attempted preparation of [(2SR,3RS)-3-*Methyl*-4-*pentyn*-2-*yl*] (S)-O-*methylmandelate* (414)

(i) This attempted esterification was carried out according to the procedure of Corey *et al.*[117]

(*S*)-*O*-Methylmandelic acid (416) (440 mg, 2·65 mmol) was heated in thionyl chloride (5 ml) at the reflux for 30 min. The solvent was removed *in vacuo* and the residue was added to a solution of (2*SR*,3*RS*)--3-methyl-4-pentyn-2-ol (406) (0·280 g, 2·65 mmol) in dry dichloromethane (10 ml) containing 4-*N*,*N*-dimethylaminopyridine (DMAP) (20 mg, 0·16 mmol). The reaction mixture was stirred at room temperature overnight and partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (x 2) and the combined extracts dried and concentrated *in vacuo* to yield a dark oil. Medium pressure chromatography on silica (Kieselgel H, eluant dichloromethane) afforded a colourless oil (0·37 g). T.l.c. analysis (silica, dichloromethane) showed this oil to be a complex mixture of ulta-violet active and inactive compounds. No attempt at further purification was made.

(ii) (*S*)-*O*-Methylmandelic acid (416) (440 mg, 2·65 mmol) in thionyl chloride (5 ml) containing *N*,*N*-dimethylformamide (1 drop) was heated,

at the reflux, for 2 h. I.r. analysis indicated mainly acid chloride [$\nu_{max.}$ (liq. film) 1790 s cm^{-1}] with some starting acid [$\nu_{max.}$ (liq. film) 1700 s cm^{-1}]. The solvent was removed *in vacuo* and the residue was added to (2*SR*,3*RS*)-3-methyl-4-pentyn-2-ol (406) (100 mg, 1·02 mmol) and 4-*N*,*N*-dimethylaminopyridine (0·16 g, 1·33 mmol) in dry dichloromethane (5 ml). The solvent was removed *in vacuo* to yield a dark oil. T.l.c. analysis (silica, dichloromethane) indicated a complex mixture of products similar to that obtained previously. No attempt at further purification was made.

Preparation of [(2SR,3RS)-3-*Methyl*-4-*pentyn*-2-*yl*] (S)-O-*methylmandelate* (414)

(2*SR*,3*RS*)-3-Methyl-4-pentyn-2-ol (406) (1·52 g, 15·51 mmol) and (*S*)-*O*-methylmandelic acid (416) (3·32 g, 20·0 mmol) in dry dichloromethane (120 ml) containing 4-*N*,*N*-dimethylaminopyridine (0·25 g, 2·03 mmol) were stirred together at 0°C. The solution was treated with dicyclohexylcarbodiimide (DCC) (4·16 g, 20·33 mmol) and the reaction mixture allowed to warm up to room temperature and stirred overnight. The mixture was filtered and concentrated *in vacuo* to yield a yellow oil. The oil was treated with a small volume of dichloromethane and filtered to remove a further quantity of white solid. Evaporation *in vacuo* followed by medium pressure chromatography on silica [Kieselgel H, 40 g, eluant dichloromethane : light petroleum (1:1)] afforded the *title compound* (414) (3·43 g, 90%) as a yellow oil, t.l.c. analysis (silica, dichloromethane; Rf 0·55). A sample was further purified by bulb-to-bulb distillation to afford a colourless oil, b.p. 150°/0·5 mmHg, $\nu_{max.}$ (liq. film) 3280 s (C-H str. acetylene) 3040 m, 3020 m, 2980 s, 2920 s, 2820 s (C-H str.), 2100 w, (C≡C str.), 1745 s, (C=O str.),

1590 w (C=C str. aromatic), 1470 s, 1440 s, 1370 s, 1350 w, 1330 w, 1250 s, 1190 m, 1175 s, 1145 m, 1100 s, 1065 m, 1020 s, 990 s, 960 w, 940 w, 910 s, 850 m, 720 s, 690 s, and 620 m cm^{-1}. The two diastereoisomers were readily distinguishable by ^{1}H n.m.r. δ_H (250 MHz) ($CDCl_3$) 0·85 (3H, d, *J* 7·1 Hz, $-CH_3$), 1·14 (3H, d, *J* 6·0 Hz, $-CH_3$), 1·14 (3H, d, *J* 7·3 Hz, $-CH_3$), 1·31 (3H, d, *J* 6·3 Hz, $-CH_3$), 1·95 (1H, d, *J* 2·5 Hz, -C≡C*H*), 2·05 (1H, d, *J* 2·5 Hz, -C≡C*H*), 2·47-2·60 (1H, m, -C*H*C≡CH), 2·60-2·77 (1H, m, -C*H*C≡CH), 3·42 (6H, s, 2 x $-OCH_3$), 4·77 [1H, s, $-CH(OCH_3)-$], 4·78 [1H, s, $-CH(OCH_3)-$], 4·87-5·08 [2H, m, 2 x $-CH(CH_3)O-$], and 7·29-7·53 (10H, m, aryl-H); m/e 246 ($M^{+\cdot}$), 231 ($M^{+\cdot}$ -15), 121, 105, 91, 77, 57, and 43 (Found: C, 72·87; H, 7·44; $M^{+\cdot}$, 246·1250. $C_{15}H_{18}O_2$ requires C, 73·15; H, 7·37%; $M^{+\cdot}$, 246·1256).

Resolution of the diastereoisomers of [(2SR,3RS)-3-*Methyl*-4-*pentyn*-2-*yl*] (S)-O-*Methylmandelate* (414)

A sample of the (2*SR*,3*RS*)-mandelate ester (414) (1·70 g) was subjected to High Performance Liquid Chromatography (H.P.L.C.) on a Walters Associates H.P.L.C. machine equipped with re-cycle facility. Two Walters Prepak 500 silica columns were used for the separation in which 10% ethyl acetate/light petroleum (b.p. 60-80°) was the preferred eluant. The sample was re-cycled through the columns a total of 6 x. Separation was affected by repeated "peak-shaving" of the material which appeared to be a single component as indicated by a single symmetrical peak in the refractive index (R.I.) detector trace. The various fractions were concentrated *in vacuo* and analysed by n.m.r. spectroscopy; those fractions having similar diastereomeric purity were combined to afford:-

i) the less polar [(2*SR*,3*RS*)-3-methyl-4-pentyn-2-yl] (*S*)-*O*-methylmandelate diastereoisomer of (414) (387 mg, 80% d.e.) as a pale

yellow oil. $\nu_{max.}$ (liq. film) 3260 s (C≡CH str.) 3240 m, 3210 m, 2960 s, 2910 s, 2800 s (C-H str.), 2100 w (C≡C str.), 1735 s (C=O str.), 1590 s (C=C str. aromatic), 1480 m, 1440 s, 1365 m, 1335 w, 1315 w, 1245 s, 1190 m, 1160 s, 1140 m, 1090 s, 1010 s, 980 s, 900 m, 840 m, 715 s, 680 s, and 625 s cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 1·14 (3H, d, *J* 6·0 Hz, -C*H*$_3$), 1·14 (3H, d, *J* 7·3 Hz, -C*H*$_3$), 2·05 (1H, d, *J* 2·5 Hz, -C≡C*H*), 2·60-2·77 (1H, m, -C*H*C≡CH), 3·42 (3H, s, -OC*H*$_3$), 4·78 [1H, s, -C*H*(OCH_3)-], 4·87-5·08 [1H, m, -C*H*(CH_3)O-], and 7·29-7·53 (5H, m, aryl-*H*) (Found: C, 73·08; H, 7·39. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·37%). This material was subsequently shown to be the required (2*R*,3*S*)-mandelate ester (423).

ii) the more polar [(2*SR*,3*RS*)-3-methyl-4-pentyn-2-yl] (*S*)-*O*-methylmandelate diastereoisomer of (414) (515 mg, 70% d.e.) as a pale yellow oil. $\nu_{max.}$ (liq. film) 3280 s (C≡CH str.), 3040 m, 3020 m, 2980 s, 2920 s, 2820 s (C-H str.), 2100 w (C≡C str.), 1745 s (C=O str.), 1590 w (C=C str. aromatic), 1470 s, 1440 s, 1370 s, 1350 w, 1330 w, 1250 s, 1190 m, 1175 s, 1145 m, 1100 s, 1065 m, 1020 s, 990 s, 960 w, 940 w, 910 s, 850 m, 720 s, 690 s, and 620 m cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 0·85 (3H, d, *J* 7·1 Hz, -C*H*$_3$), 1·31 (3H, d, *J* 6·3 Hz, -C*H*$_3$), 1·95 (1H, d, *J* 2·5 Hz, -C≡C*H*), 2·47-2·60 (1H, m, -C*H*C≡CH), 3·42 (3H, s, -OC*H*$_3$), 4·77 [1H, s, -C*H*(OCH_3)-], 4·87-5·08 [1H, m, -C*H*(CH_3)O-], and 7·29-7·53 (5H, m, aryl-*H*) (Found: C, 72·87; H, 7·44. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·37%). This material was subsequently shown to be the unwanted (2*S*,3*R*)-mandelate ester (425).

The purest fractions of each diastereoisomer were retained for use in the correlation experiment.

Hydrogenation of the resolved O-*methylmandelate diastereoisomers of* (414)

(i) The less polar [(2*SR*,3*RS*)-3-methyl-4-pentyn-2-yl] (*S*)-*O*-methyl mandelate diastereoisomer of (414) (90% d.e.) (93 mg, 0·38 mmol) in tetrahydrofuran (5 ml) was hydrogenated over 10% palladium on carbon (30 mg) for 7 h. The mixture was filtered through Celite and the solvent removed *in vacuo* to afford the required product (424) (88 mg, 93%) as a colourless oil. $\nu_{max.}$ (liq. film) 3040 m, 3010 m, 2950 s, 2910 s, 2860 s, 2800 m (C-H str.), 1725 s (C=O str.), 1590 w (C=C str. aromatic), 1480 m, 1440 s, 1360 s, 1340 w, 1310 w, 1260 s, 1240 s, 1190 s, 1170 s, 1090 s, 1030 w, 1020 w, 990 s, 950 w, 905 m, 885 w, 835 m, 720 s, and 690 s cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 0·84 (3H, d, *J* 7·1 Hz, $-CH_3$), 0·85 (3H, t, *J* 7·6 Hz, $-CH_2CH_3$), 1·00 (3H, d, *J* 6·4 Hz, $-CH_3$), 1·02-1·20 (1H, m), 1·27-1·50 (1H, m), 1·50-1·68 (1H, m), 3·41 (3H, s, $-OCH_3$), 4·74 [1H, s, $-CH(OCH_3)-$], 4·80-4·94 [1H, m 5 lines, $-OCH(CH_3)-$], and 7·25-7·50 (5H, m, aryl-*H*), see fig. 5; m/e 250 ($M^{+\cdot}$), 121 (100%), 105, 91, 85, 77, 57, 51, and 43 (Found: $M^{+\cdot}$ 250·1576. $C_{15}H_{22}O_3$ requires $M^{+\cdot}$ 250·1569). This material was subsequently shown to be identical to the mandelate ester (422) derived from L-*iso*leucine.

(ii) The more polar [(2*SR*,3*RS*)-3-methyl-4-pentyn-2-yl] (*S*)-*O*-methylmandelate diastereoisomer of (414) (90% d.e.) (87 mg, 0·35 mmol) in tetrahydrofuran (5 ml) was hydrogenated over 10% palladium on carbon (33 mg) overnight. The mixture was filtered through Celite and the solvent removed *in vacuo* to afford the required product (426) (82 mg, 93%) as a colourless oil. $\nu_{max.}$ (liq. film) 3040 m, 3010 m, 2950 s, 2910 s, 2860 s, 2800 m (C-H str.), 1725 s (C=O str.), 1590 w (C=C str. aromatic), 1480 m, 1440 s, 1360 s, 1340 w, 1310 w, 1260 s, 1240 s, 1190 s, 1170 s, 1090 s, 1030 w, 1020 w, 990 s, 950 w, 905 m, 885 w,

835 m, 720 s, and 690 s cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 0·67 (3H, d, *J* 6·9 Hz, $-CH_3$), 0·72 (3H, d, *J* 7·4 Hz, $-CH_2CH_3$), 0·80-1·00 (1H, m), 1·11-1·30 (1H, m), 1·15 (3H, d, *J* 6·4 Hz, $-CH_3$), 1·36-1·55 (1H, m), 3·40 (3H, s, $-OCH_3$), 4·72 [1H, s, $-CH(OCH_3)$], 4·74-5·00 [1H, m, $-CH(CH_3)-$], and 7·25-7·50 (5H, m, aryl-*H*), see fig. 7; m/e 250 ($M^{\cdot+}$), 121, 105, 87, 85, 83 (100%), 77, 48, 47, and 43 (Found: $M^{\cdot+}$ 250·1576. $C_{15}H_{22}O_3$ requires $M^{\cdot+}$ 250·1569).

Preparation of (2S,3S)-3-*Methyl*-1,2-*pentanediol* (419)

(2*S*,3*S*)-3-Methyl-1,2-pentanediol (419) was prepared by a combination of modified procedures from the literature.[120,134] L-*Iso*leucine (417) (6·5 g, 0·05 mol) in a solution of 1N hydrochloric acid (50 ml), water 200 ml) and acetic acid (100 ml) was cooled to 5°C and treated dropwise with a solution of sodium nitrite (35 g, 0·51 mol) in water (60 ml). The reaction mixture was maintained at 10°C during the addition and for a further 1 h. The solution was stirred at room temperature overnight and was quenched by addition of concentrated hydrochloric acid (50 ml). Removal of the solvent, at reduced pressure, afforded a white solid which was thoroughly dried *in vacuo*. The solid was slurried with dry diethyl ether (50 ml) and treated with lithium aluminium hydride (5·04 g, 0·133 mol), at room temperature with stirring for 20 h. The reaction was quenched by the addition of saturated aqueous sodium sulphate. Removal of the solvent *in vacuo* afforded a white solid which was continuously extracted with diethyl ether for 2 days. Concentration of the extract *in vacuo* afforded the crude title compound (419) (3·7 g, 73%) as an amber oil, t.l.c. analysis (silica, diethyl ether; Rf 0·4), δ_H (250 MHz) ($CDCl_3$) 0·86 [3H, d, *J* 6·8 Hz, $-CH(CH_3)-$], 0·90 (3H, t, *J* 7·2 Hz, $-CH_2CH_3$), 1·07-1·30 (1H, m), 1·38-1·70 (2H, m), 3·40-3·56 (2H, m),

3·59-3·78 (1H, m), and 3·67-4·00 (2H, br.s, D_2O exch.). The material was not further purified but was used, in this form, in the subsequent reaction.

Preparation of (2S,3S)-1-(*Toluene-4-sulphonyloxy*)-3-*methyl*-2-*pentanol* (420)

(2*S*,3*S*)-1-(Toluene-4-sulphonyloxy)-3-methyl-2-pentanol (420) was prepared by the modified procedure of Kirmse and Prolingheuer.[134] Crude (2*S*,3*S*)-3-methyl-1,2-pentanediol (419) (3·7 g, 0·031 mol) in dry pyridine (40 ml) at -15°C was treated portionwise with toluene-4-sulphonyl chloride (5·95 g, 0·312 mol) and the mixture stirred at -15°C for 5 h. The solvent was removed *in vacuo* and the residue was partitioned between diethyl ether (200 ml) and water (200 ml). The aqueous phase was extracted with further quantities of diethyl ether (3 x 100 ml). The combined extracts were dried and concentrated *in vacuo* to afford the crude title compound (420) (7·57 g, 89%) as an amber oil. The material was not further purified but was used directly in the subsequent reaction.

Preparation of (2R,3S)-3-*Methyl*-2-*pentanol* (421)

(2*R*,3*S*)-3-Methyl-2-pentanol (421) was prepared by a modified procedure of Kirmse and Prolingheuer.[134] Crude (2*S*,3*S*)-1-(toluene-4-sulphonyloxy)-3-methyl-2-pentanol (420) (7·57 g, 0·028 mol) in dry diethyl ether (45 ml) was stirred with lithium aluminium hydride (2·7 g, 0·071 mol) at room temperature for 14 h. The reaction was quenched by the addition of saturated sodium sulphate solution and diluted with water (250 ml). The mixture was continuously extracted with diethyl ether for 2 days. Removal of the solvent *in vacuo* followed by distillation

at reduced pressure afforded the title compound (421) [1·8 g, 35% from L-*iso*leucine (417)] as a colourless liquid, b.p. 68-70°C/53 mmHg, α_D^{22} -10·44°(Neat), [lit.,[134] b.p. 66°C/50 mmHg, α_D^{22} -11·99° (Neat)]; $\nu_{max.}$ (liq. film) 3330 s (OH str.), 2930 s, 2890 s, 2850 s (C-H str.), 1435 s, 1355 s, 1280 s, 1125 w, 1070 s, 1040 m, 990 m, 960 w, 940 m, 890 s, and 830 m cm^{-1}; δ_H (250 MHz) ($CDCl_3$) 0·86 [3H, d, *J* 7 Hz, -CH(CH_3)-], 0·90 (3H, t, *J* 7 Hz, -CH_2CH_3), 1·02-1·23 [1H, m, -CH(CH_3)-], 1·10 [3H, *J* 7 Hz, -CH(OH)CH_3], 1·28-1·62 (2H, m, -CH_2CH_3), 3·03 (1H, br.s, D_2O exch.), and 3·54-3·70 [1H, m, -CH(OH)-]; m/e 102 ($M^{+\cdot}$), 101, 87 ($M^{+\cdot}$ -15), 73, 69, 57, 56, 55, and 45 (100%) (Found: $M^{+\cdot}$ 102·1043. $C_6H_{14}O$ requires $M^{+\cdot}$ 102·1045).

Preparation of [(2R,3S)-3-*Methyl*-2-*pentanyl*] (S)-O-*methylmandelate* (422)

(2*R*,3*S*)-3-Methyl-2-pentanol (421) (0·46 g, 4·49 mmol) and (*S*)-*O*-methyl mandelic acid (416) (0·75 g, 4·49 mmol) in dry dichloromethane (20 ml) containing 4-*N*,*N*-dimethylaminopyridine (0·147 g, 1·20 mmol) was cooled to 0°C. The solution was treated with dicyclohexylcarbodiimide (DCC) (1·05 g, 5·13 mmol) and was allowed to warm to room temperature and stirred overnight. The reaction mixture was filtered and concentrated *in vacuo* to yield a pale yellow oil. Medium pressure chromatography on silica [Kieselgel H, eluant dichloromethane : light petroleum (1:1)] afforded the *title compound* (422) (0·92 g, 82%) as a pale yellow oil. A sample was further purified by bulb-to-bulb distillation to afford a colourless oil, b.p. 180°C/10 mmHg, $[\alpha]_D^{22}$ + 46·0° (*c* 1·34, $CHCl_3$) $\nu_{max.}$ (liq. film) 3040 m, 3010 m, 2950 s, 2910 s, 2860 s, 2800 m (C-H str.), 1725 s (C=O str.), 1590 w (C=C str. aromatic), 1480 m, 1440 s, 1360 s, 1340 w, 1310 w, 1260 s, 1240 s, 1190 s, 1170 s, 1090 s, 1030 w, 1020 w, 990 s, 950 w, 905 m, 885 w, 835 m, 720 s, and 690 s cm^{-1}; δ_H

(250 MHz) ($CDCl_3$) 0·84 (3H, d, *J* 7·1 Hz, -C*H*$_3$), 0·85 (3H, t, *J* 7·6 Hz, -C*H*$_3$), 1·00 (3H, d, *J* 6·4 Hz, -C*H*$_3$), 1·02-1·20 (1H, m), 1·27-1·50 (1H, m), 1·50-1·68 (1H, m), 3·41 (3H, s, -OC*H*$_3$), 4·74 [1H, s, -C*H*(OCH_3)-], 4·80-4·94 [1H, m 5 lines, -OC*H*(CH_3)-], and 7·25-7·50 (5H, m, aryl-*H*), see fig. 6; m/e 250 ($M^{+\cdot}$), 136, 121, 105, 91, 85, 77, and 43 (Found: C, 71·94; H, 9·11. $C_{15}H_{22}O_3$ requires C, 71·97; H, 8·86%).

Ester cleavage of [(2SR,3RS)-3-*Methyl*-4-*pentyn*-2-*yl*] (S)-O-*methylmandelate* (414)

(i) A solution of the ester (414) (1·23 g, 0·5 mmol) in tetrahydrofuran (10 ml) containing water (0·5 ml) and lithium hydroxide (100 mg, 4·2 mmol) was stirred at room temperature for 3 days. T.l.c. analysis (silica, dichloromethane) indicated the complete absence of the starting ester (414). Removal of the solvent *in vacuo* followed by distillation at reduced pressure afforded (2*SR*,3*RS*)-3-methyl-4-pentyn-2-ol (406) (212 mg, 43%) with spectral data fully consistent with that of an authentic sample.

(ii) A solution of the ester (414) (0·372 g, 1·51 mmol) in dry methanol (5 ml) containing potassium hydroxide (8·5 mg, 0·15 mmol) was stirred at room temperature for 30 mins. T.l.c. analysis (silica, dichloromethene) indicated the complete absence of the starting ester (414). Removal of the solvent *in vacuo* followed by distillation at atmospheric pressure afforded (2*SR*,3*RS*)-3-methyl-4-pentyn-2-ol (406) (96 mg, 65%) with spectral data fully consistent with that of an authentic sample.

Cleavage of [(2R,3S)-3-*Methyl*-4-*pentyn*-2-*yl*] (S)-O-*methylmandelate* (423)

A solution of the ester (423) (80% d.e.) (2·46 g, 10·00 mmol) in dry

methanol (40 ml) containing potassium hydroxide (28 mg, 0·50 mmol) was stirred at room temperature for 3½ h. The solvent was removed by fractional distillation and the residue distilled at atmospheric pressure to afford (2*R*,3*S*)-3-methyl-4-pentyn-2-ol (427) (80% e.e.) (0·68 g, 69%) as a colourless liquid, b.p. 121-123°C, $[\alpha]_D^{22}$ + 2·1° (*c* 6·11, EtOH). Spectral data were found to be fully consistent with that obtained from the racemic alcohol (406).

Preparation of (3S,4R)-4-*t*-*Butyldimethylsilyloxy*-3-*methyl*-1-*pentyne* (428)

(2*R*,3*S*)-3-Methyl-4-pentyn-2-ol (427) (80% e.e.) (333 mg, 3·40 mmol) was converted to the *title compound* (428) (720 mg, 95%) using the procedure previously described for the racemic alcohol (406), $[\alpha]_D^{22}$ - 1·9° (*c* 1·80, $CHCl_3$), α_D^{22} - 2·0° (Neat). Spectral data were found to be fully consistent with that obtained from the racemic silyl ether (407).

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Model Studies on the Synthesis of Milbemycin β_3

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Reprinted from the Journal of The Chemical Society
Chemical Communications 1981

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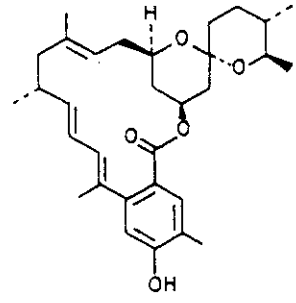
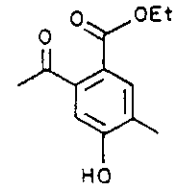
Summary 2,4-Di(lithio-oxy)penta-1,3-diene and 2,4-di(lithio-oxy)-3-methylpenta-1,3-diene condensed with tetrahydropyran-2-one to give 2-methyl- and 2,3-dimethyl-1,7-dioxaspiro[5.5]undec-2-en-4-one; subsequent reduction gave the derived alcohols ($LiAlH_4$) and 2,3-dimethyl-1,7-dioxaspiro[5.5]undec-3-ene ($LiAlH_4$–$AlCl_3$); the milbemycin β_3 unit ethyl 2-acetyl-4-hydroxy-5-methylbenzoate was prepared from ethyl 2-(4-chlorophenylthio)-4-oxopent-2-enoate and (*E*)-1-methoxy-2-methyl-3-trimethylsilyloxy-buta-1,3-diene *via* a Diels–Alder reaction.

THE avermectins[1] are noted for their most potent anthelmintic properties. The milbemycins,[2] including milbemycin β_3 (**1**) are structurally related pesticidal antibacterials. Herein we report model studies directed towards the construction of the spiro-acetal system and the synthesis of the milbemycin β_3 unit (**2**).

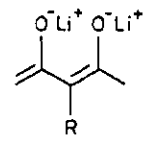
We considered that a concise novel route to the spiro-acetal unit should be available by the condensation of a lactone and β-dione dianion. As a model study, tetrahydropyran-2-one was condensed with the dianion (**3a**)[3] in tetrahydrofuran (THF) at − 78 to 0 °C to give the β-dione (**5**)† (95%) or the spiro-dihydropyrone (**4a**) (88%), m.p. 56—57 °C, on acetic or toluene-4-sulphonic acid work-up respectively. In the same way, tetrahydropyran-2-one and the dianion (**3b**) gave the spiro-dihydropyrone (**4b**) (68%). Both adducts (**4a** and **b**)† were unambiguously spiro-cyclic; for example, (**4a**) exhibited ν_{max} (film) 1720w, 1670s, and 1620s cm^{-1}, λ_{max} (MeOH) 260 nm (ϵ 11,000) [2,3-dihydro-2,2,6-trimethylpyran-4-one 266 nm (11,800)[4]]. δ (^1H) ($CDCl_3$) 5·37 (1H, s, 3-H), 3·72 (2H, m, 8-CH_2), 2·6 and 2·5 (2H, ABq, J 15 Hz, 5-CH_2), and 2·03 (3H, s, 2-Me), *m/e* 182 (M^+), 167, and 98 (retro-Diels–Alder).



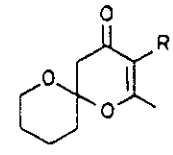
(1)



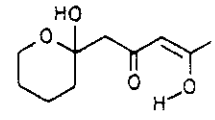
(2)



(3)
a; R = H
b; R = Me



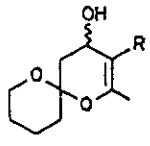
(4)
a; R = H
b; R = Me

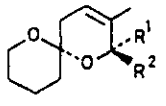


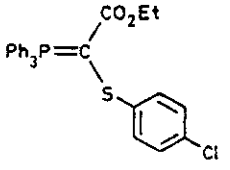
(5)

Both spiro-compounds (**4a** and **b**) were reduced with lithium aluminium hydride in THF at 0 °C to give the expected alcohols (**6a**, 2:1 mixture of epimers) (90%) and (**6b**, 5·8:1 mixture of epimers) (88%). Alternatively, addition of the spiro-compound (**4b**) to lithium aluminium hydride in THF at 0 °C followed by inverse addition to lithium aluminium hydride and aluminium chloride (1:4)

† All new compounds were fully characterised by spectral data and microanalyses. The alcohol (**6b**) and olefin (**7b**) were not obtained microanalytically pure although all other data were consistent with the structural assignments.


(6)
a; R = H
b; R = Me


(7)
a; R^1 = H, R^2 = Me
b; R^1 = Me, R^2 = H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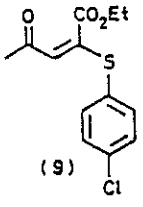
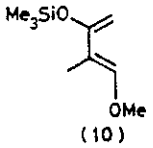

(9)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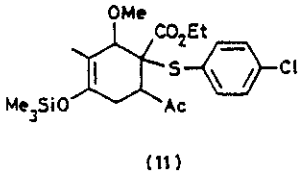
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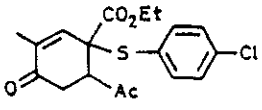
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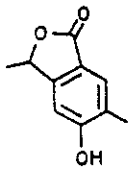
(13)

in THF at − 78 to 0 °C gave the spiro-acetals (**7a**) (22%) and (**7b**) (7%) (yields unoptimised). Using boron trifluoride–diethyl ether and diborane (2 : 1), instead of lithium aluminium hydride–aluminium chloride, the same products (**7a** and **b**) (40%, 1 : 1) were obtained. The two epimers were readily distinguished by nuclear Overhauser effect experiments. Clearly spiro-acetals are now readily available from the highly versatile β-diones.

The milbemycin β_3 unit (**2**) was prepared *via* a Diels–Alder reaction. Condensation of the ylide (**8**), m.p. 198—201 °C, with pyruvaldehyde in refluxing benzene for 24 h gave the enone (**9**)‡ (72%). This reacted with the Danishefsky diene (**10**)[5] in refluxing benzene for 6 h to give the adduct (**11**). Although not characterized, the crude product (**11**) gave the enone (**12**) (64%), m.p. 116·5—119·5 °C, with ethanolic hydrogen chloride and, subsequently, unit (**2**) (75%), m.p. 128·5—129·5 °C, with ethanolic sodium ethoxide. The regioselectivity of the Diels–Alder reaction was unequivocal since unit (**2**) was formed *via* (**12**). In addition, sodium borohydride reduction of (**2**) gave the derived phthalide (**13**) (100%), m.p. 182·5—184 °C, with the expected bathochromic shift in the u.v. spectrum on deprotonation.

We thank the S.R.C. and the Royal Society for generous support, and Dr. M. R. G. Leeming and Dr. N. D. Walsh for helpful discussion and generosity.

(*Received, 27th February* 1981; *Com.* 226.)

‡ Compounds (**9**) and (**12**) [and presumably (**11**)] were single isomers.

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