APPROACHES TO CLERODANE NATURAL PRODUCTS

a thesis presented by

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Abstract.

The review section of this thesis describes the isolation and structural elucidation of over 450 clerodane natural products discovered in the period 1961 to 1986, together with the taxanomic trends of the various genera involved. Also briefly considered are natural compounds structurally related to the clerodane series, and the biological activity demonstrated by certain clerodane natural products.

This thesis describes the development of a novel synthetic approach to the class of clerodane diterpenes typified by those isolated from the *Teucrium* genus (Labiatae).

In model studies, the use of a Diels-Alder approach to the clerodane structures was investigated, and the stability of the dienophile to various reaction conditions determined. The use of catalysis in the cycloaddition reaction was also examined. The introduction of an α-ethylidene group onto γ-lactones in a stereospecific manner is described.

The preparation of spiro[4α-methyl-6β-[4,4,0]-1,10-decen-2-one-5,3'-5'-(3''-furyl)tetrahydrofuran-2'-one], the key intermediate in the synthetic strategy, is described, and the determination of its relative stereochemistry by spectroscopic means is discussed. This compound marks the first successful approach to clerodanes containing a 5-(3'-furyl)-spiro-γ-lactone C_9 substituent. An enantiospecific approach to the total synthesis is also outlined.

Further model studies towards the introduction of the C_4-C_6 substituents of the natural compounds are described.

An approach towards the bis-tetrahydrofuranyl unit, as found in compounds isolated from the *Clerodendron* and *Caryopteris* genera (Verbenaceae) is also described.

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To all of you,

Thanks.

For my Parents,
and Andrea.

Abbreviations.

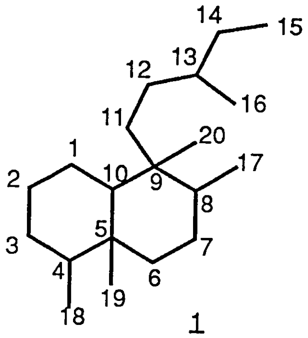
acac	acetoacetonate
DABCO	1,4-Diazabicyclo[2,2,2]octane
DBN	1,5-Diazabicyclo[4,3,0]non-5-ene
DET	Diethyl Tartrate
DHP	Dihydropyran
DIBAL	Di-isobutylaluminium Hydride
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethyl Formamide
DMS	Dimethylsulphide
eq.	equivalents
HMPA	Hexamethylphosphoric Triamide
KDA	Potassium Di-isopropylamide
LDA	Lithium Di-isopropylamide
mCPBA	*meta*-Chloroperoxybenzoic Acid
NBS	N-Bromosuccinamide
NPSP	N-Phenylselenyl Phthalamide
pTSA	*para*-Toluene Sulphonic Acid
RT	Room Temperature
TBDMS	t-Butyldimethylsilyl
TBDPS	t-Butyldiphenylsilyl
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin Layer Chromatography
TMA	Trimethylaluminium
TMS	Trimethylsilyl
TosMIC	(*para*-tolylsulphonyl)methyl Isocyanide

REVIEW.

Isolations of Clerodane Natural Products.

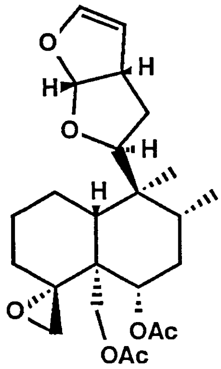
1. Introduction.

During the last twenty-five years, over four hundred and fifty diterpenoids and nor-diterpenoids with the clerodane carbon skeleton (1) have been isolated.



1

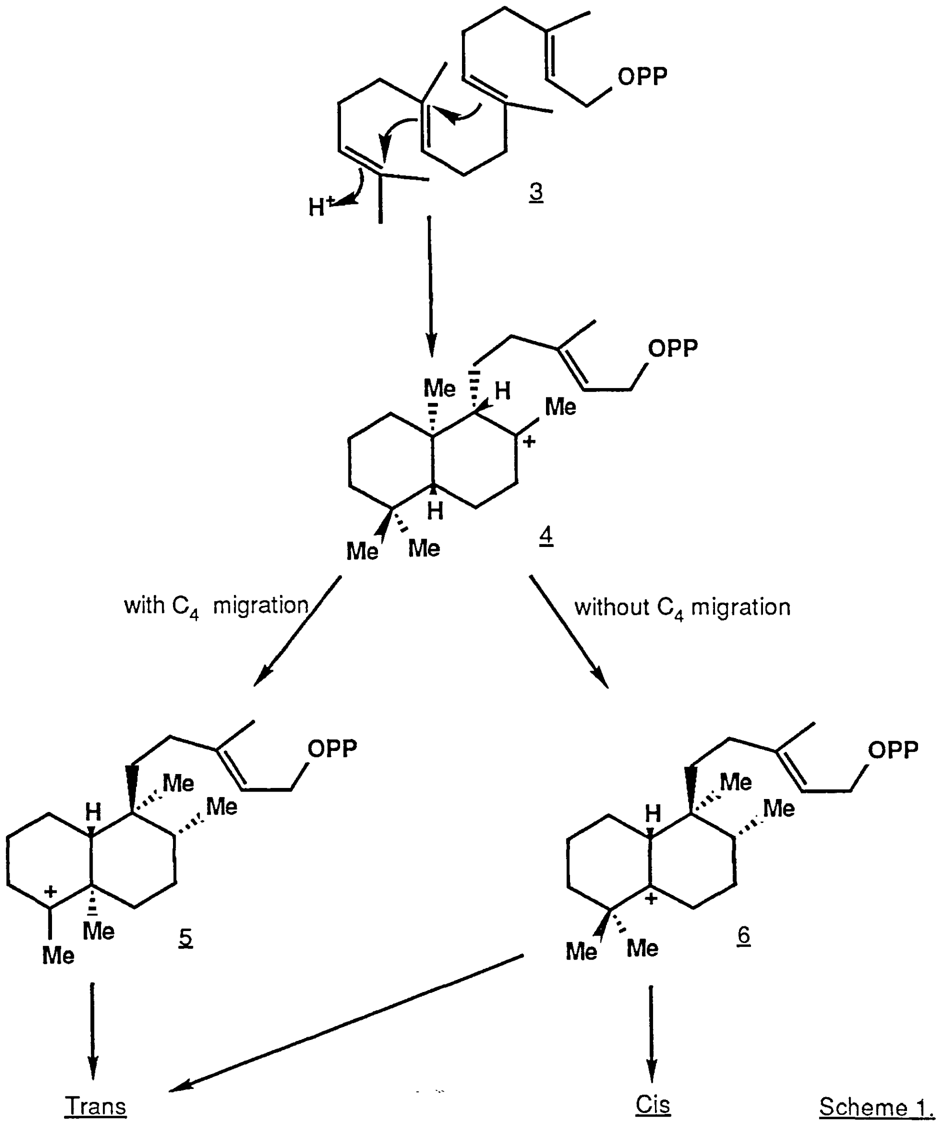
Confusion has arisen in the literature over the absolute stereochemistry of the various clerodanes isolated. The revision of the absolute stereochemistry of clerodin (2),[1] the first member of the clerodane series,[2] has led to those compounds with the same absolute stereochemistry as clerodin being termed _neo_-clerodanes, with those structures enantiomeric to clerodin being termed _ent_-_neo_-clerodanes.



2

A further division of the clerodanes has been to _cis_ and _trans_ compounds, dependant upon the stereochemistry of the decalin ring junction.

Biosynthetically, the clerodanes appear to be related to the labdanes, _via_ a series of methyl and hydride shifts. The labdane skeleton (4) is itself derived from geranylgeranylpyrophosphate (3) (scheme 1).[3]

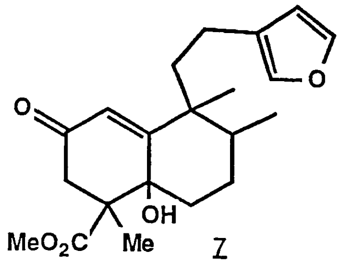

OPP
3
H+
Me
H
Me
+
H
Me
Me
4
with C_4 migration
without C_4 migration
OPP
Me
Me
H
+
Me
Me
5
OPP
Me
Me
H
+
Me
Me
6
Trans
Cis

Scheme 1.

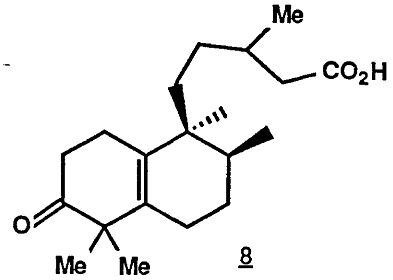
The trans clerodanes can arise via a concerted migration process to intermediate (5), whilst the cis compounds require a step-wise process, with a 'pause' at intermediate (6). This can then lead to either cis or trans compounds depending on which of the C_4 methyl groups migrates.[4]

This proposed biosynthetic pathway is supported by the isolation of the partially rearranged labdane compounds chettaphanin (7) from Adenochlaena siamensis (Compositae)[5] and salmantic acid (8) from

Cistus laurifolius (Cistaceae).[6]



7



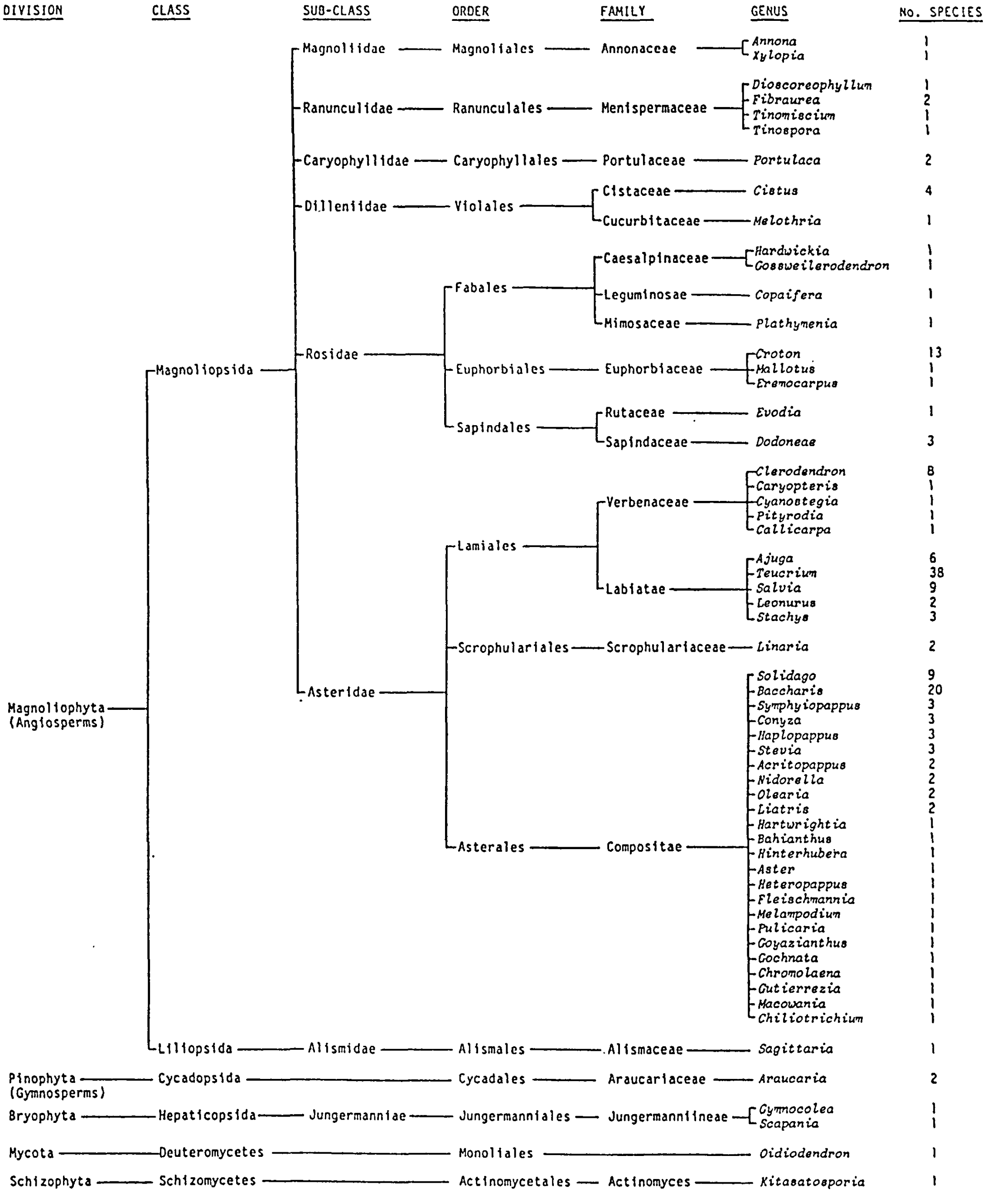
8

Several synthetic approaches to the clerodanes have appeared in the literature, but these have been extensively reviewed,[7] and will not be covered in this section. This review will consider the isolation, structural elucidation, and reported biological activity of the large number of clerodanes reported in the literature up to the present day.

2. Taxonomy.

The taxonomic relationships of the clerodane producing plants are shown in scheme 2, to the rank of genera. The scheme is based on the system of Cronquist,[8] extended beyond the angiosperms by the systems of Holmes.[9] The vast majority of clerodanes have been isolated from dicotyledonous plants (the Magnoliopsida), with examples from all but one of the relevant sub-classes. Below sub-class however, a greater degree of specificity occurs, with only a small fraction of orders and families apparently producing clerodanes. This appears to go against normal taxanomic trends, where one would expect a pyramidal relationship leading down from sub-class to genus. It is possible that the various genera/families developed independantly the capacity to biosynthesize the clerodanes, or simply that there are a large number of families which produce clerodanes that have not yet been isolated.

The independant developement of synthetic ability is supported by the occurrance of the non-dicotyledonous producers, with a single



DIVISION	CLASS	SUB-CLASS	ORDER	FAMILY	GENUS	No. SPECIES
Magnoliophyta (Angiosperms)	Magnoliopsida	Magnoliidae	Magnoliales	Annonaceae	*Annona*	1
					Xylopia	1
		Ranunculidae	Ranunculales	Menispermaceae	*Dioscoreophyllum*	1
					Fibraurea	2
					Tinomiscium	1
					Tinospora	1
		Caryophyllidae	Caryophyllales	Portulaceae	*Portulaca*	2
		Dilleniidae	Violales	Cistaceae	*Cistus*	4
				Cucurbitaceae	*Melothria*	1
		Rosidae	Fabales	Caesalpinaceae	*Hardwickia*	1
					Gossweilerodendron	1
				Leguminosae	*Copaifera*	1
				Mimosaceae	*Plathymenia*	1
			Euphorbiales	Euphorbiaceae	*Croton*	13
					Mallotus	1
					Eremocarpus	1
			Sapindales	Rutaceae	*Evodia*	1
				Sapindaceae	*Dodoneae*	3
		Asteridae	Lamiales	Verbenaceae	*Clerodendron*	8
					Caryopteris	1
					Cyanostegia	1
					Pityrodia	1
					Callicarpa	1
				Labiatae	*Ajuga*	6
					Teucrium	38
					Salvia	9
					Leonurus	2
					Stachys	3
			Scrophulariales	Scrophulariaceae	*Linaria*	2
			Asterales	Compositae	*Solidago*	9
					Baccharis	20
					Symphyiopappus	3
					Conyza	3
					Haplopappus	3
					Stevia	3
					Acritopappus	2
					Nidorella	2
					Olearia	2
					Liatris	2
					Hartwrightia	1
					Bahianthus	1
					Hinterhubera	1
					Aster	1
					Heteropappus	1
					Fleischmannia	1
					Melampodium	1
					Pulicaria	1
					Goyazianthus	1
					Gochnata	1
					Chromolaena	1
					Gutierrezia	1
					Macowania	1
					Chiliotrichium	1
	Liliopsida	Alismidae	Alismales	Alismaceae	*Sagittaria*	1
Pinophyta (Gymnosperms)	Cycadopsida		Cycadales	Araucariaceae	*Araucaria*	2
Bryophyta	Hepaticopsida	Jungermanniae	Jungermanniales	Jungermannineae	*Gymnocolea*	1
					Scapania	1
Mycota	Deuteromycetes		Monoliales		*Oidiodendron*	1
Schizophyta	Schizomycetes		Actinomycetales	Actinomyces	*Kitasatosporia*	1

Scheme 2.

genus of a monocotyledonous species (class Liliopsida), one genus of a gymnosperm, two genera of liverworts (Bryophyta), one genus of fungi (Mycota) and one genus of bacteria (Schizophyta). Although these plants/organisms have been shown to produce only a limited number of clerodanes, their ability to do so, considered alongside the large taxanomic differences, lends strong support to an independant synthetic developement.

In the following sections, the individual families will be discussed, with reference to any family or genera related trends, and they will be considered in the evolutionary order for the Magnoliopsida, as proposed by Cronquist,[8] reading top to bottom of scheme 2.

3. Isolation and Elucidation.

The elucidation of the clerodane structures, and specifically the stereochemical relationship of substituents, has not been consistent in the literature. Several of the compounds have proved suitable for X-ray structural analysis, whilst others have been assigned by extensive spectral and correlation techniques. Many compounds, however, have been presented with only a minimal amount of spectral data to support the structural assignments. Only in the former cases has the relevant technique been indicated in the following texts.

3.1. Family Annonaceae.

Two genera have been shown to give clerodanes, with only trans compounds produced.

Genus - Annona. A. coriacea is the only clerodane producing species, giving the furyl compound (9), also produced by the Compositae family, and the furyl acid (10).[10]

Genus - Xylopia. X. aethiopica produces the 2-oxo compound (11), as the only isolated compound from this genus.[11]

3.2. Family Menispermaceae.

Four genera are of interest here, giving twelve clerodanes. Eleven of these have been shown, by chemical and spectral methods, to be *cis*-clerodanes, whereas the other compound remains unassigned. All the compounds contain an unusual fused δ-lactone ring at C_8-C_9, containing the C_{11}-C_{16} side chain.

Genus - Dioscoreophyllum. *D. cumminsii* produces four clerodanes, the dilactone columbin (12), and jateorin (13), chasmanthin (14), and palmarin (15),[12] all 2,3-epoxycolumbins with varying stereochemistry at the C_8-C_9 δ-lactone.

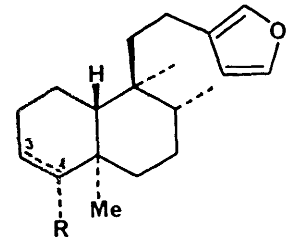
Genus - Fibraurea. *F. chloroleuca* produces fibleucin (16),[13] fibraurin (17), and 6-hydroxyfibraurin (18),[14] assigned as enantiomers of (13)-(15), with a C_7-C_8 double bond. *F. tinctoria* also gives fibleucin (16) and fibraurin (17), along with their respective C_4-glycosides fibleucinoside (19) and fibraurinoside (20). Tinophylloside (21), a C_2-glycoside with no C_1-C_4 lactone linkage has also been found.[15]

Genus - Tinomiscium. *T. philippinense* produces the oxidised aglycone of (21), tinophyllone (22).[16] Although stereochemically unassigned, this would appear to be structurally related to (21).

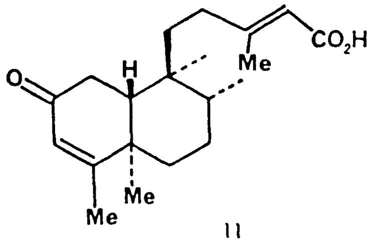
Genus - Tinospora. *T. cordifolia* produces the unnamed C_4-C_6 hydroxy γ-lactone compound (23), as the only isolated clerodane from this genus.[17]

3.3. Family Portulacaceae.

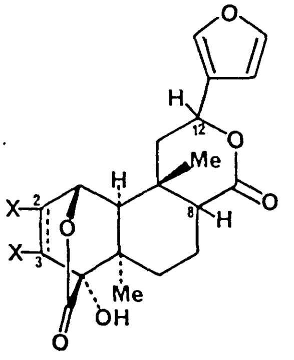
Genus - Portulaca. *P. cv* Jewel has been shown to produce four *trans* clerodanes with a C_4-C_5 γ-lactone and dihydroxyl functionality, portulides A-D, (24)-(27),[18] with portulides A and D having an unusual



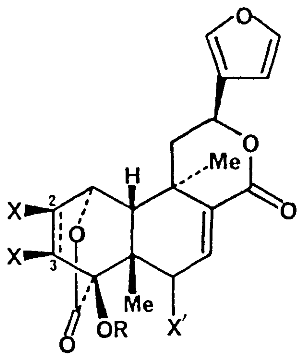
R		3-4
9	Me	Double
10	CO_2H	Single


O
H
Me
CO_2H
Me
Me

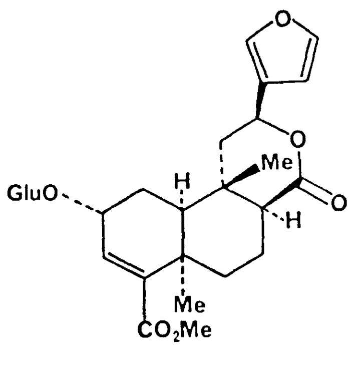
11


H
12
O
Me
H
O
X
2
8
H
X
3
O
Me
OH
O

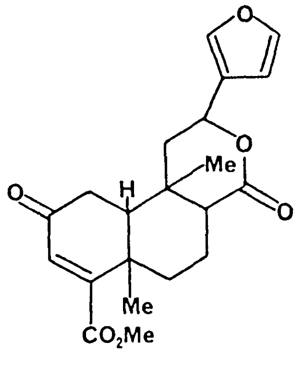
	X	2-3	C_8-H	C_{12}-H
12	H	Double	β	α
13	/O\	Single	β	α
14	/O\	Single	β	β
15	/O\	Single	α	β


O
O
Me
H
X
2
O
X
3
Me
O
OR
X'

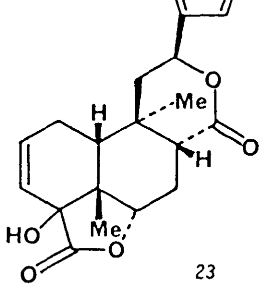
	R	X	X'	2-3
16	H	H	H	Double
17	H	/O\	H	Single
18	H	/O\	OH	Single
19	Gluc	H	H	Double
20	Gluc	/O\	H	Single


O
Me
H
GluO
O
H
Me
CO_2Me

21


O
Me
H
O
O
Me
CO_2Me

22


O
H
Me
O
H
HO
Me
O
O

23

site of oxidation at C_{17}. Portulide A, also known as just portulide, had previously been isolated from P. grandiflora Hook.[19]

3.4. Family Cistaceae.

Genus - Cistus. This is the only genus of interest, with four species producing both cis and trans clerodanes. All are of the C_{11}-C_{16} open chain variety, with this chain being fully saturated. Various levels of oxidation occur at C_2, C_{15} and C_{18}, whilst C_{16} and C_{19} remain as methyl groupings, and C_3-C_4 is consistently an unsaturated bond. C. monspeliensis gives the diol cistidiol (28) and the equivalent diacid cistidioic acid (29), as cis compounds.[20,21] (28) and (29) are also given by C. laurifolius, along with the cis compounds (30)-(37).[22] C. palinhae gives the 2-oxo cis compound (38).[23] C. populifolius gives the trans diastereomer of the acid (29), populifolic acid (39), also produced by the Compositae family, trans compounds (40)-(46),[24,25,26] and 2-oxopopulifolic acid (47),[27] with all compounds assigned by spectral interpretation.

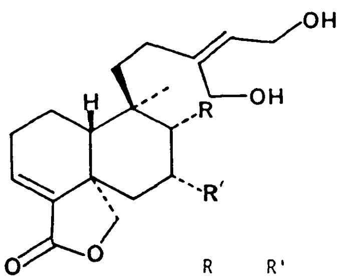
3.5. Family Cucurbitaceae.

Genus - Melothria. M. maderospatuna produces columbin (12),[12] chemically identical to that produced by Dioscoreophyllum cumminsii (Menispermaceae), as the only clerodane isolated from this family. This is surprising, as (12) is a highly functionalized clerodane derivative, and the two plants are unrelated below class level.

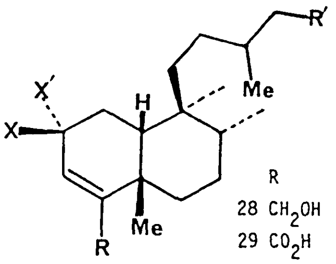
3.6. Family Caesalpinaceae.

Two genera of this family produce trans clerodanes, all with either a C_{11}-C_{16} open chain, or a C_{12} furan substituent, and with varying oxidation levels of C_2-C_4.

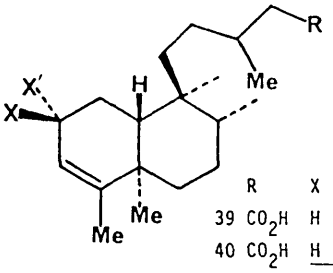
Genus - Hardwickia. H. pinnata gives the C_{11}-C_{16} open chain alcohol



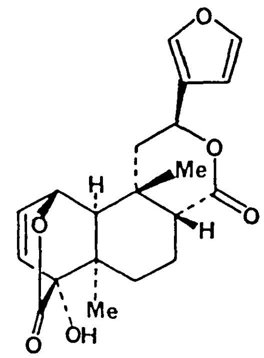
	R	R'
24	CH_2OH	H
25	Me	H
26	Me	OH
27	CHO	H



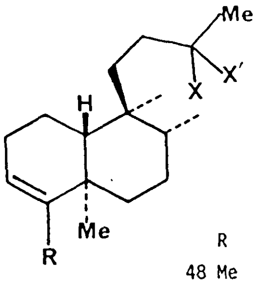
	R	R'	X	X'
28	CH_2OH	CH_2OH	H	H
29	CO_2H	CO_2H	H	H
30	CH_2OAc	CO_2H	H	H
31	CO_2H	CH_2OAc	H	H
32	CO_2H	CH_2OH	H	H
33	CH_2OH	CO_2H	H	H
34	CH_2OAc	CO_2Me	OH	H
35	CH_2OAc	CO_2Me	OMe	H
36	CH_2OAc	CO_2Me	=O	
37	CHO	CO_2Me	=O	
38	Me	CO_2Me	=O	


R
X′
H
Me
X
Me
Me

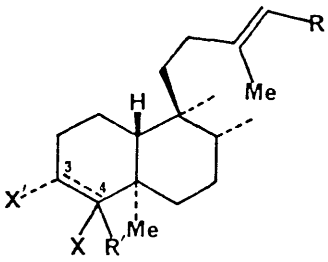
	R	X	X'
39	CO_2H	H	H
40	CO_2H	H	OAc
41	CH_2OH	=O	
42	CH_2OH	H	OH
43	CO_2H	H	OH
44	CO_2H	OH	H
45	CO_2H	OMe	H
46	CO_2H	H	OMe
47	CO_2H	=O	


O
O
H
Me
O
H
O
Me
O
OH

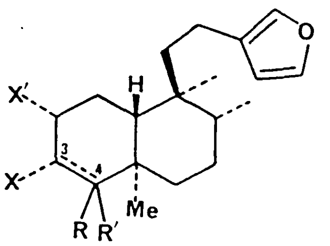
12



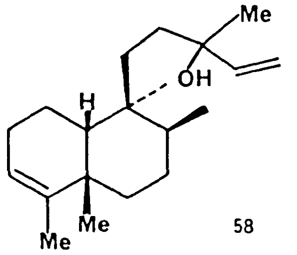
	R	X	X'
48	Me	OH	Vinyl
49	CO_2H	=O	


R
H
Me
3
X′
4
Me
X
R′

	R	R'	X	X'	3-4
50	CH_2OH	Me	-	H	Double
51	CO_2Me	Me	-	H	Double
52	CO_2H	Me	OH	H	Single
53	CO_2H	CO_2H	-	H	Double
55	CH_2OH	$=CH_2$		OH	Single


O
H
X′
3
X
4
Me
R
R′

	R	R'	X	X'	3-4
54	CO_2H	-	H	H	Double
56	$=CH_2$		OH	OH	Single
57	$=CH_2$		OH	H	Single



58

kolavelool (48), the bis-norditerpene kolavonic acid (49), the alcohol kolavenol (50), the related kolavenic acid (51), and three other acids, kolavenolic acid (52), kolavic acid (53), and the furyl hardwickiic acid (54).[28,29,30]

Genus - Gossweilerodendron. *G. balsiferum* also produces kolavic and hardwickiic acids (53), (54), along with the C_4-methylene substituted agbanindiols A and B (55), (56) and agbaninol (57).[31]

3.7. Family Leguminosae.

Genus - Copaifera. Of the same order as the Caesalpinaceae (Fabales), the only species of this family shown to produce clerodanes, *C. officinales*, gives hardwickiic acid (54),[32] identical to that from the Caesalpinaceae.

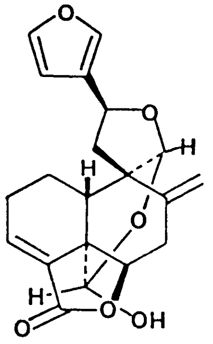
3.8. Family Mimosaceae.

Genus - Plathymenia. Also of the same order as the Caesalpinaceae (Fabales), the only species of this genus to produce clerodanes, *P. reticulata*, gives the *cis* alcohol plathyterpol (58),[33,34] diastereomeric to kolavelool (48) from the Caesalpinaceae.

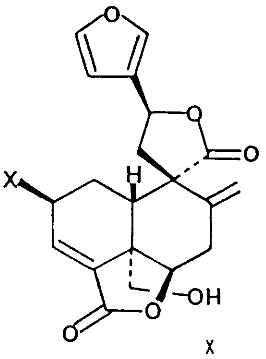
3.9. Family Euphorbiaceae.

Three genera of this family produce clerodanes, with the genus *Croton* the most prolific. All but two compounds isolated are of the *trans* variety, with a strong family trend to produce structures with a C_{12}-furan substituted C_9 spiro-γ-lactone, or compounds arising from rearrangements of this structure.

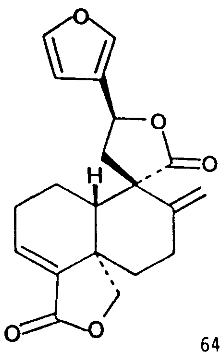
Genus - Croton. Thirteen species have so far been shown to produce clerodanes. The Thai folk drug Plau-noi, *C. sublyratus* Kurz, produces the plaunols A-E (59)-(63), all with a C_4-C_6 γ-lactone and a C_8-methylene substituent,[35,36,37] and plaunolide (64), with a C_4-C_5



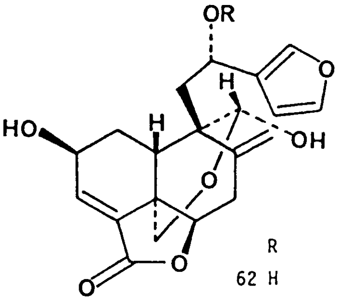
59



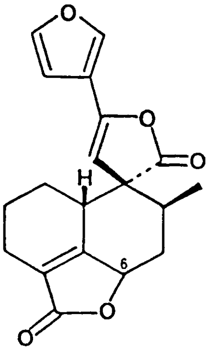
	X
60	H
61	OH



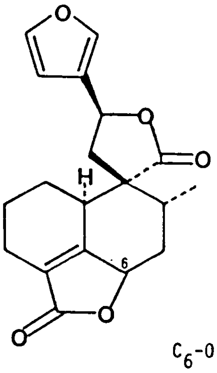
64



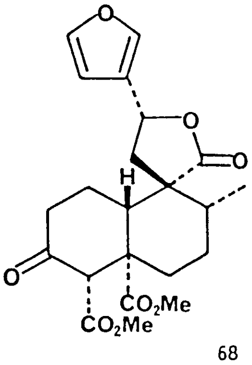
	R
62	H
63	Ac



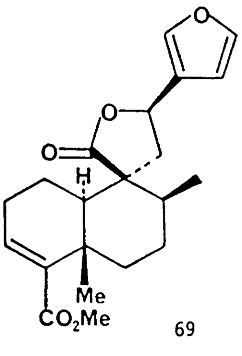
	C_6-O
65	β
66	α



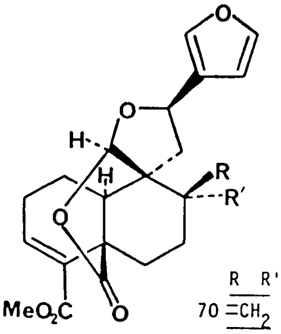
	C_6-O
67	β
81	α



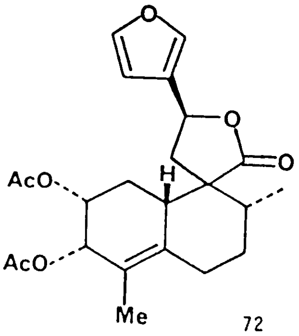
68



69



	R	R'
70	$=CH_2$	
71	Me	H



72

γ-lactone,[38] with structures determined by X-ray analysis.[39,40,41] C. ioufra has also been shown to produce plaunol D (62),[37] and swassin, identical to plaunolide (64).[42] C. caudatus gives the di-unsaturated-γ-lactones crotocaudin (65) and isocrotocaudin (66), along with the congener of (65), teucvidin (67),[43,44] also isolated from several Teucrium species (Labiatae). C. corylifolius Lam gives the diester corylifuran (68) structurally assigned by X-ray analysis,[45] whilst the ester sonderianin (69), with an ent-neo-clerodane skeleton, has been isolated from C. sonderianus, also assigned by X-ray analysis.[46] C. verreauxii Baill gives the C_8-methylene C_5-C_{11} δ-lactone linked croverin (70), and the C_8-C_{17} dihydro derivative dihydrocroverin (71). Croverin was assigned by X-ray determination, with (71) tentatively assigned as the β-C_{17}-methyl compound on spectral analysis.[47] C. pyramidalis gives the C_2,C_3 diacetoxy compound (72),[48] whilst the C_5-C_{10} unsaturated compound penduliflaworosin (73) has been isolated from C. penduliflorus, assigned from spectral data.[49] Dehydrocrotonin, a nor-diterpene isolated from C. ajucara, has been tentatively assigned as the des-C_{19}-methyl clerodane (74),[50] whilst C. californicus gives the C_8-C_9 δ-lactone compound methyl barbascoate (75),[3] and hardwickiic acid (54),[51] previously shown in the Caesalpinaceae family. Hardwickiic acid has also been detected in extracts from C. oblongifolus, along with the C_{11}-C_{12} unsaturated dehydrohardwickiic acid (76).[52] C. eleuteria gives the C_{12}-hydroxy-C_{20}-oxo triol cascarillin (77), and the related C_3-C_4 epoxy lactol cascarillin A (78),[53] and the cis assigned 3-oxo compound cascarillone (79),[54] whilst C. lucidus gives the 2-oxo compound crotonin (80),[55,56] assigned by X-ray analysis as cis,[57] thus throwing doubt on the assignment of dehydrocrotonin (74) as trans.

Genus - Mallotus. M. repandus is the only species shown to produce clerodanes, giving the C_4-C_5 unsaturated mallotucin A (81), and the

C_5-C_{10} unsaturated compounds mallotucins B, C, and D (82)-(84),[58,59] with mallotucin A chemically identical to teucvin (also known as eugarzasadine) isolated from various Teucrium species (Labiatae).

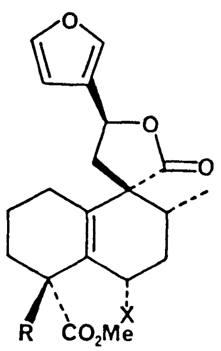
Genus - Eremocarpus. E. setigerus is the only species of interest, giving hautriwaic acid (85), found also in the Compositae family, and the diketone eremone (86).[60]

3.10. Family Rutaceae.

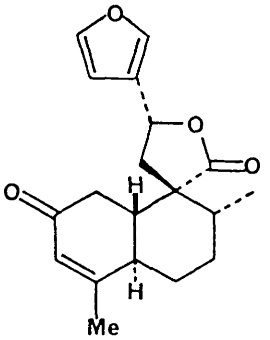
Genus - Evodia. E. floribunda Baker is the only clerodane producing species of this family reported, giving cis structures with the ent-neo-clerodane stereochemistry. Floridolides A and B (87), (88) are C_{12}-butenolide substituted acids differing in oxidation at C_{17}, whilst the C_8-C_9 δ-lactone (89) has a hydroxylated butenolide at C_{12}.[61] Floribundic acid (90), a C_{12}-furyl equivalent of (89), has also been isolated,[62] along with the dihydroxy floridiolic acid (91),[63] the structure of which being confirmed by X-ray analysis of the corresponding methyl ester.[64]

3.11. Family Sapindaceae.

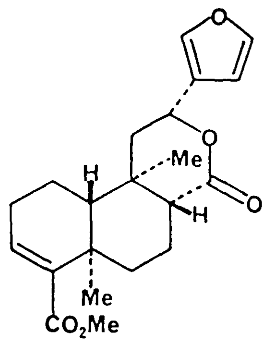
Genus - Dodoneae. Three species of this genus have been shown to produce clerodanes, with all the compounds possessing the trans arrangement, and the C_{11}-C_{16} chain existing as a furyl-ethyl substituent. Oxidation at C_{18}, witha C_3-C_4 double bond is also a family trait. D. boroniaefolia produces the alcohol (92), and the 2-hydroxylated form (93), along with the 2-hydroxy acid (94) and C_1-C_2-dehydro equivalent (95).[65] D. attenuata also gives (95), with the 17-acetoxy compound (96), and the C_4-C_5 γ-lactone (97).[66,67] D. viscosa gives hautriwaic acid (85),[68] also found in the Euphorbiaceae and Compositae families.


O
O
O
X
R
CO2Me

	R	X
73	Me	H
82	CO_2Me	OAc

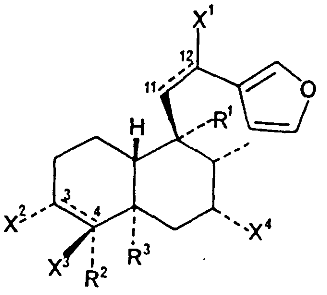


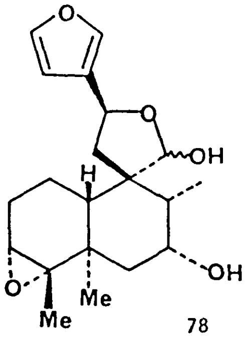
74


O
O
Me
H
O
H
Me
CO2Me

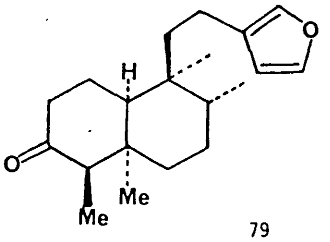
75

	R^1	R^2	R^3	X^1	X^2	X^3	X^4	3-4	11-12
54	Me	CO_2H	Me	H	H	-	H	Double	Single
76	Me	CO_2H	Me	H	H	-	H	Double	Double
77	CHO	Me	Me	OH	OH	OH	OAc	Single	Single
85	Me	CO_2H	CH_2OH	H	H	-	H	Double	Single

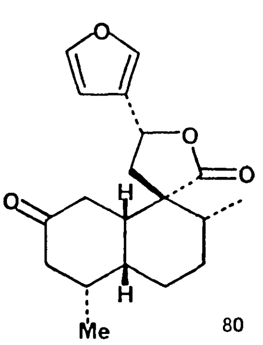

X1
12
11
O
H
R1
3
4
X2
X4
X3
R2
R3


O
O
OH
H
OH
O
Me
Me

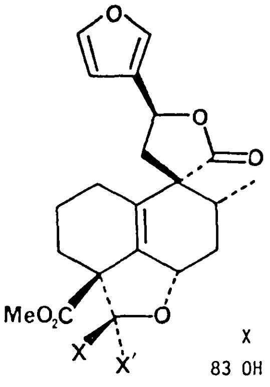
78



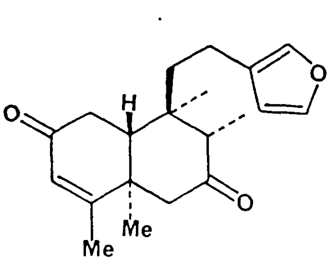
79



80


O
O
O
MeO2C
O
X
X'

	X	X'
83	OH	H
84	H	OH



86

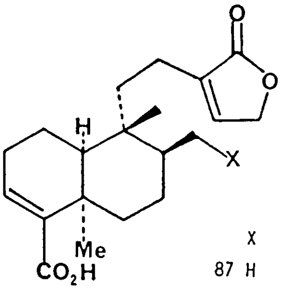
3.12. Family Verbenaceae.

Five genera of this family have thus far been shown to produce clerodanes, with the Clerodendron and Caryopteris genera the most prolific.[69] The compounds isolated from these two genera all possess a bis-tetrahydrofuranyl C_{11}-C_{16} sidechain, with varying levels of oxidation at C_{14}-C_{15}, and a common arrangement of 6α-acetoxy, 19-acetoxy, C_4-C_{18} α-epoxide on the southern portion of the decalin.

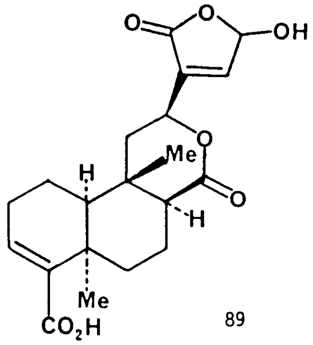
Genus - Clerodendron. Clerodin (2) was the first isolated compound of the clerodane family, thus lending its name to the whole series, with its structure assigned by X-ray analysis.[1,70] Initially isolated from C. infortunatum,[2] it has also been found as the only clerodane isolated from C. colebrookium.[71] C. phlamoides also gives clerodin, along with the C_2,C_3 oxygenated C_7-C_8 unsaturated clerodendrin A (98),[71] whilst C. tricotomum Thumb gives clerodendrin A and the dihydro form clerodendrin B (99),[72,73] with the structure of clerodendrin A being confirmed by X-ray analysis.[74,75,76] C. cryptophyllum also gives clerodendron A,[69] whilst C. fragrans, C. calamitosum, and C. inerme have all been shown to produce the 3-acetoxy compound 3-epicaryoptin (100), with structural assignment confirmed by X-ray analysis.[1,69,77]

Genus - Caryopteris. C. divaricata Maxim has been shown to produce clerodin (2), along with the clerodin hemiacetal (101), and dihydroclerodin (102), 3-epicaryoptin (100) and its 3-epimer caryoptin (103), caryoptin hemiacetal (104), dihydrocaryoptin (105), the deacetyl form of caryoptin, caryoptinol (106) and dihydrocaryoptinol (107). All of these structures have been assigned by chemical correlation to the proven structures of clerodin and 3-epicaryoptin.[78,79,80,81,82]

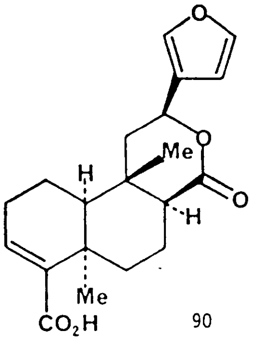
Genus - Cyanostegia. C. angustifolia is the only species of this genus shown to produce clerodanes, giving the trans diacid (108), assigned by correlation to clerodanes from Dodoneae boroniaefolia


O
O
H
X
Me
CO₂H

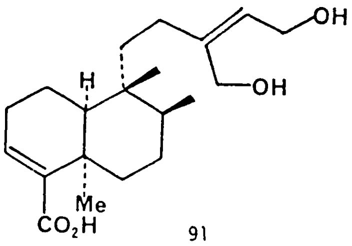
	X
87	H
88	OH


O
O
OH
O
Me
H
O
H
Me
CO₂H

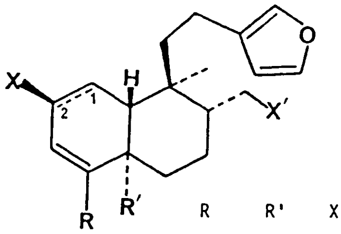
89


O
O
Me
H
O
H
Me
CO₂H

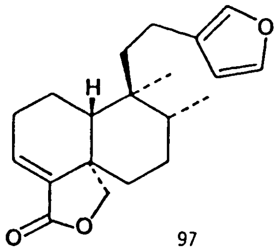
90


OH
OH
H
Me
CO₂H

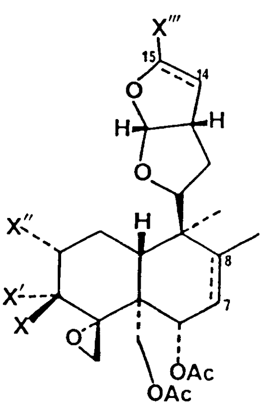
91



	R	R'	X	X'	1-2
85	CO_2H	CH_2OH	H	H	Single
92	CH_2OH	Me	H	H	Single
93	CH_2OH	Me	OH	H	Single
94	CO_2H	Me	OH	H	Single
95	CO_2H	CH_2OH	H	H	Double
96	CO_2H	CH_2OH	H	OAc	Single

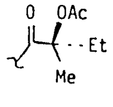


97


X‴
15
14
O
H
H
O
H
X″
X′
X
O
8
7
OAc
OAc

	X	X'	X"	X"'	7-8	14-15	C_8-Me
2	H	H	H	H	Single	Double	α
98	OR	H	OH	H	Double	Double	-
99	OR	H	OH	H	Single	Double	α
100	H	OAc	H	H	Single	Double	α
101	H	H	H	OH	Single	Single	α
102	H	H	H	H	Single	Single	α
103	OAc	H	H	H	Single	Double	α
104	OAc	H	H	OH	Single	Single	α
105	OAc	H	H	H	Single	Single	α
106	OH	H	H	H	Single	Double	α
107	OH	H	H	H	Single	Single	α

R=



(Sapindaceae).[65]

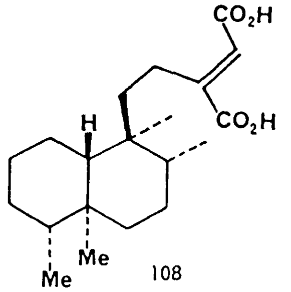
Genus - Pityrodia. The only clerodane producing member of this genus, P. lepidota, gives two trans ent-neo compounds, dihydroxy ester (109), and the corresponding diacetate (110), with structures determined by X-ray analysis.[83]

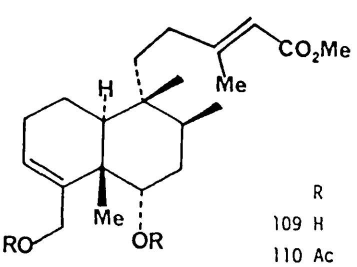
Genus - Callicarpa. C. maingayii gives the trans furyl acid maingayic acid (111), as the only isolated clerodane from this genus.[84]

3.13. Family Labiatae.

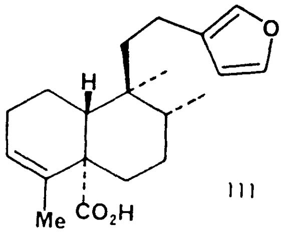
Five genera of this family have been shown to produce clerodanes. The genus Ajuga produces compounds closely related, structurally, to those from the Clerodendron and Caryopteris genera, with similar southern substitution patterns. This may be due to the Labiatae and the Verbenaceae families belonging to the same order (Lamiales). The Teucrium genus is the most prolific of all the clerodane producing genera, accounting for over one hundred of the reported clerodanes, though this apparent productivity may, in part, be due to the extremely extensive investigation of this genus by Piozzi, Savona, Malakov, and Papanov, with previous reviews of the clerodanes isolated from this genus having been published by Piozzi[85] and Fujita.[86] The Teucria, and the less prolific genera of the Labiatae, show a strong tendancy to give compounds with a 3-furyl substituted spiro-γ-lactone at the C_9 position, and give almost exclusively trans, or non-definable, compounds. The Teucrium generated compounds also all show oxidation at the C_6 position.

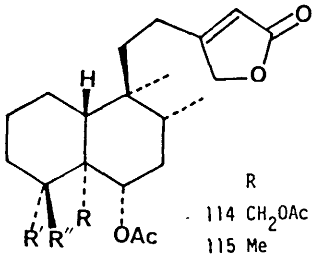
Genus - Ajuga. A. remota gives the C_{12}-butenolide compounds ajugarins I, II, III, IV, and V (112)-(116),[87,88,89,90] with X-ray determination of the 12-bromo derivative of ajugarin I.[91] A. nipponensis gives the C_1, C_{12} oxygenated compound ajugamarin (117), the dihydro derivative (118), and the corresponding chlorohydrin of ajugamarin, assigned not


108

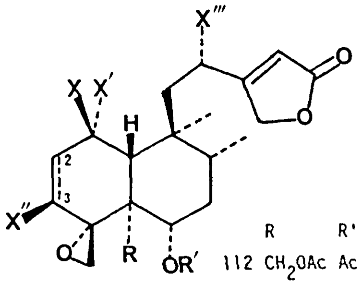


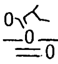
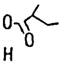
	R
109	H
110	Ac

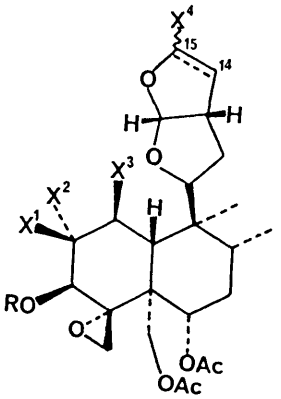

111



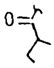
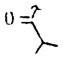
	R	R'	R"
114	CH_2OAc	OH	CH_2OH
115	Me	CO_2Me	H



	R	R'	X	X'	X"	X'''	2-3
112	CH_2OAc	Ac	H	H	H	H	Single
113	CH_2OAc	H	H	H	H	H	Single
116	Me	Ac	H	H	H	H	Single
117	CH_2OAc	Ac	OTig	H	H	OH	Single
118	CH_2OAc	Ac		H	H	OH	Single
120	CH_2OAc	Ac	—O— =O			H	Single
121	CH_2OAc	Ac	=O		H	H	Double
184	CH_2OH	H	H	H	H	H	Single

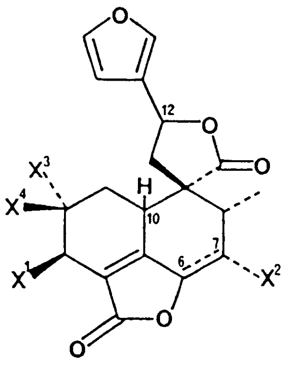


	R	X^1	X^2	X^3	X^4	14-15
119	H	H	H	OR^1	H	Single
122	R^2	OH	H	H	H	Single
123	R^2	H	H	H	H	Single
124	R^2	OH	H	H	OEt	Single
125	R^1	OH	H	H	H	Single
126	R^1	H	OH	H	H	Double
127	R^1	H	OH	H	H	Single
128	R^1	H	OH	H	OEt	Single
129	R^1	H	OH	H	OH	Single
130	R^2	OAc	H	H	H	Single

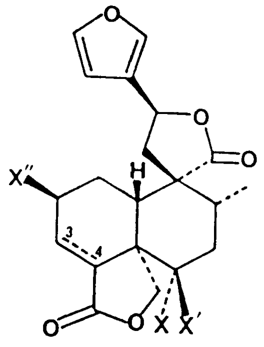
R^1 =  R^2 = 

as a natural product, but a product of the isolation of (117), which included the use of hydrochloric acid.[92,93,94] A. reptans has been shown to produce the C_9-bis-tetrahydrofuranyl compound ajugareptansin (119), the 1-oxo butenolide ajugareptansone A (120), and the 2,3-dehydro derivative ajugareptansone B (121), with X-ray structural determination of ajugareptansin and ajugareptansone B.[95,96,97] A.iva produces the bis-tetrahydrofuranyl 2-hydroxy, 3-oxygenated compound ivain I (122), and the derived compounds ivains II, III, and IV (123)-(125), with X-ray determination of the structure of the 2-oxo derivative of ivain I.[98] A. chamaepitys gives ajugapitin (126), a dehydro C_2-epimeric derivative of ivain IV, dihydrajugapitin (127), the C_2-epimer of ivain IV,[99] and the corresponding hemiacetal derivatives (128) and (129).[100] A. pseudoiva has been shown to give 2-acetylivain I (130), along with dihydroajugapitin (127).[101]

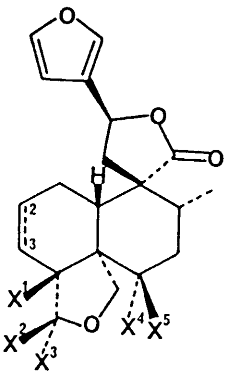
Genus - Teucrium. T. chamaedrys has been shown to produce the C_4-C_6 unsaturated γ-lactone compound teucrin A (131), the dihydroxy C_4-C_5 γ-lactone teucrin B (132), originally assigned as the C_7 hydroxyl, but later revised to the C_6 compound dihydroteugin,[102,103] teucrins C and D (133), (134), reported with no structural details, the monohydroxyl form of (132), teucrin E (135), the hydroxylated and unsaturated teucrin F (136), and the corresponding epoxide of teucrin F (136), teucrin G (137).[104,105,106,107,108,109] This species also gives teuchamaedryn A (81), a dehydroxylated form of teucrin A also known as teucvin, and previously shown isolated as mallotucin A from Mallotus repandus (Euphorbiaceae), teuchamaedryn B (138), the C_6 epimer of teucrin E also known as teucrin H_2,[110] and the C_5-C_9 δ-lactone compound teuchamaedryn C (139),[111] along with 6-epiteucrin A (140), 6-epiteucvin (141), also known as teuflin, teugin (142), a dehydro-teucrin B compound also known as dihydroxyteuscordin, 6α-hydroxy-teuscordin (143), a dehydro form of teucrin E, and teucvidin (67), the


12
X3
X4
H
10
7
6
X1
X2

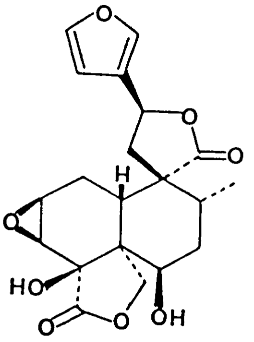
	X^1	X^2	X^3	X^4	6-7	C_6-O	C_{10}-H	C_{12}-Fur
67	H	H	H	H	Single	β	α	β
81	H	H	H	H	Single	α	β	β
131	H	OH	H	H	Single	α	β	β
140	H	H	H	H	Single	β	β	β
141	H	H	H	H	Single	β	β	α
144	OH	H	H	H	Single	β	α	β
145	OH	H	H	H	Single	α	β	β
148	H	H	H	OH	Single	β	α	β
180	H	H	H	H	Double	-	β	β
181	H	H	OH	H	Double	-	β	β
205	H	H	H	H	Single	α	β	α
216	H	H	OH	H	Single	β	β	β



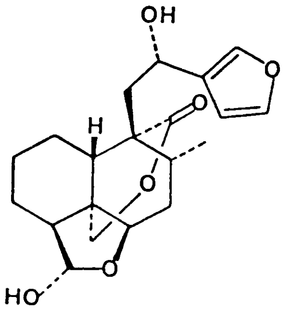
	X	X'	X"	3-4	C_4-H
132	H	OH	OH	Single	β
135	OH	H	H	Single	β
138	H	OH	H	Single	β
142	H	OH	OH	Double	-
143	OH	H	H	Double	-
210	H	OH	H	Double	-
211	OH	H	OH	Double	-
212	=O		H	Double	-
213	=O		OH	Double	-
214	=O		H	Single	β


H
2
3
X1
X2
X3
X4
X5

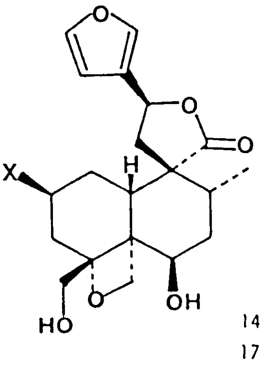
	X^1	X^2	X^3	X^4	X^5	2-3
136	OH	=O		H	OH	Double
179	H	OH	H	=O		Single
209	H	=O		OH	H	Double



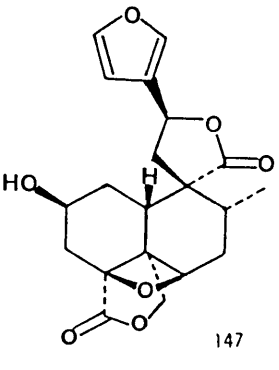
137



139

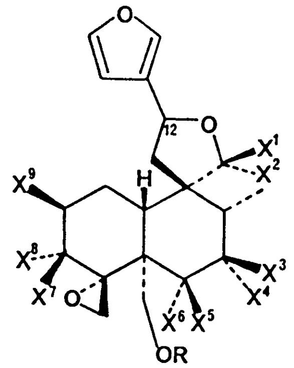


	X
146	OH
174	H

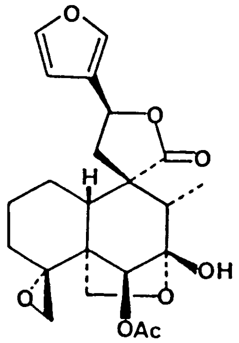


147

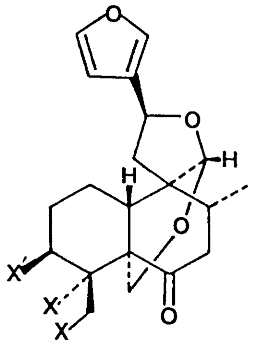
C_{10} epimer of teuflin already detailed as isolated from Croton caudatus (Euphorbiaceae).[112] Teuflidin (144), a 3-hydroxylated form of teucvidin, the C_6 epimeric isoteuflidin (145),[113] and two novel oxetane ring containing compounds, teucroxide (146), with a C_4-C_5 oxetane ring[114] and chamaedroxide (147), with a C_4-C_6 oxetane ring determined from X-ray analysis,[115] have also been isolated from T. chamaedrys. T. lucidum has been shown to produce teucrins F and G (136), (137), teucvidin (67), teuflin (141) and 6α-hydroxyteuscordin (143),[116] whilst T. barbeyanum also gives teucrins A, F, and G, (131), (136), (137).[116] T. subspinosum has been shown to give teuchamaedryns A (teucvin) and B (teucrin H_2) (81), (138), teuflin (141) and 6α-hydroxyteuscordin (143),[117] whilst T. webbianum yields teucrin A (131), teuflidin (144), and the novel 2β-hydroxyteucvidin (148).[118] T. viscidum subsp. miquelianum yields teucvin (81),[119,120] teucvidin (67),[121,122] and teuflin (141),[123,124] with all structures confirmed by X-ray analysis, whilst both T. intricatum[116] and T. cubense give only teucvin (81), in the latter case named eugarzasadine.[125,126,127] T. fragile gives teugin (142),[128] whilst T. heterophyllum gives only teucvidin (67).[118] T. polium gives picropolin (149),[129] with a C_4-C_{18} epoxy 19-acetoxy-6-hydroxyl structure similar to that found in the compounds isolated from the Ajuga, 6-acetylpicropolin (150), and the rearranged isopicropolin (151),[130] along with the acetal compound teucrin P_1 (152).[131] T. polium subsp. capitatum also yields picropolin (149)[132] and the corresponding C_6,C_7 dione, enol ether form, picropolinone (153),[133] capitatin (154), a 6-oxo-7-acetoxy isomer of picropolin, a reduced form, teucapitatin (155)[134] with structures confirmed by X-ray analysis, 7-deacetylcapitatin (156), and the epoxide hydrolysed 6-epimeric form of picropolin, picropolinol (157).[132] This subspecies also produces 7-deacetoxycapitatin (158), also known both as teucrin H_3 and 19-acetyl-gnaphalin, the diacetyl tetraol lolin (159),[135] the structure of which having been confirmed by X-ray techniques, teucjaponin B (160), a reduced form of teucrin H_3, and 20-epi-isoeriocephalin (161), a 6-epimeric acetal form of picropolin.[132] T. polium subsp. polium also produces teucrin P_1 (152) and 19-acetylgnaphalin (158), along with the novel compounds teupolin I (162), originally assigned as teucjaponin B, but later reassigned to the C_{12} epimer,[136] teupolin II (163), a 6-acetyl-19-deacetyl isomer of teucjaponin B,[137] teupolin III (164), an epoxide opened form of teucrin P_1,[138] teupolin IV (165), a 7-acetoxy-19-deacetyl form of teucrin H_3 , and teupolin V (166), a rearranged form of teupolin III.[139] Montanin B (167), a simple C_6,C_{18} diol,[137] and montanin E (168), an epoxide opened deacetyl form of teupolin II[139] have also been isolated from this subspecies. T. polium subsp. aureum also produces teucrin P_1 (152) and 19-acetyl-gnaphalin (158), plus gnaphalidin (169),[85] a C_{20}-acetoxy derivative of (158), and auropolin (170), a rearranged form of capitatin, structurally determined by X-ray analysis,[140] whilst T. polium subsp. pilosum produces the novel 19-acetylteupolin IV (171).[141] T. montanum subsp. skorpilii has been shown to produce, along with montanins B[142] and E[146] (167), (168), montanin A (172), a C_4-C_6 fused furan compound,[142] montanin C (173), an acetylated form of teupolin I[143] similarly reassigned at the C_{12} position,[136] montanin D (174), a 2-dehydroxy form of teucroxide,[144,145] and montanin F (175), also known as teucjaponin A, a C_6-epimer of teucjaponin B.[146] T. japonicum yields teucjaponin A (175) (montanin F), teucjaponin B (160), and teucvin (81).[147] T. scorodonia subsp. scorodonia has been shown to produce the 19-acetyl triol teuscorodol (176), and the corresponding C_{18}-oxo compound teuscorodal (177).[148] Also produced by this subspecies are the 19-hydroxy C_4-C_6 γ-lactone teuscorodonin (178), the 6-oxo C_4-C_5 γ-lactol teuscorodin (179),[149] the C_4-C_5, C_6-C_7 diene lactone


O
12
O
X1
X2
X9
H
X8
X7
O
X3
X4
X6
X5
OR

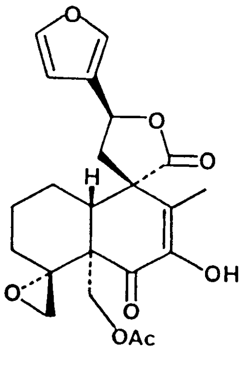
	R	X1	X2	X3	X4	X5	X6	X7	X8	X9	C12-Fur
149	Ac	=O		=O		OH	H	H	H	H	β
150	Ac	=O		=O		OAc	H	H	H	H	β
154	Ac	=O		H	OAc	=O		H	H	H	β
155	Ac	=O		H	OH	H	OAc	H	H	H	β
156	Ac	=O		H	OH	=O		H	H	H	β
158	Ac	=O		H	H	=O		H	H	H	β
160	Ac	=O		H	H	H	OH	H	H	H	β
161	Ac	H	OAc	=O		H	OH	H	H	H	β
162	Ac	=O		H	H	H	OH	H	H	H	α
163	H	=O		H	H	H	OAc	H	H	H	β
165	H	=O		OAc	H	=O		H	H	H	β
169	Ac	OAc	H	H	H	=O		H	H	H	β
171	Ac	=O		OAc	H	=O		H	H	H	β
173	Ac	=O		H	H	H	OAc	H	H	H	α
175	Ac	=O		H	H	OH	H	H	H	H	β
188	H	=O		H	H	=O		H	H	H	β
191	Ac	OAc	H	H	OH	=O		H	H	H	β
192	Ac	OH	H	H	OH	=O		H	H	H	β
194	Ac	OAc	H	=O		H	OH	H	H	H	β
195	Ac	H	OAc	H	H	=O		OAc	H	H	β
196	Ac	OAc	H	H	H	=O		OAc	H	H	β
201	Ac	=O		H	H	H	OAc	OAc	H	H	α
202	Ac	H	OAc	H	H	H	OAc	OAc	H	H	β
207	Ac	H	OH	H	H	OH	H	=O		H	β
208	Ac	=O		H	H	OH	H	H	H	OH	β
217	Ac	=O		H	H	H	OAc	H	H	H	β
218	Ac	H	OAc	H	H	H	OH	OAc	H	H	β
219	Ac	H	OH	H	H	H	OH	OAc	H	H	β
233	H	=O		H	H	=O		OH	H	H	β
234	Ac	=O		H	H	=O		OH	H	H	β


O
O
O
H
OH
O
O
OAc

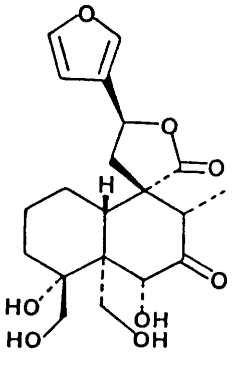
151



	X	X'
152	ˏOˎ	H
164	OH	H
200	ˏOˎ	OAc

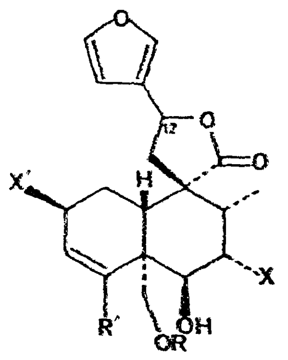

O
O
O
H
OH
O
O
OAc

153

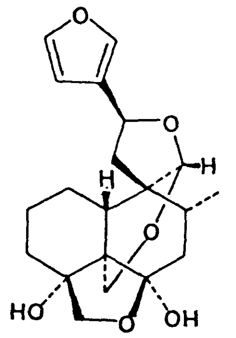

O
O
O
H
O
HO
HO
OH
OH

157

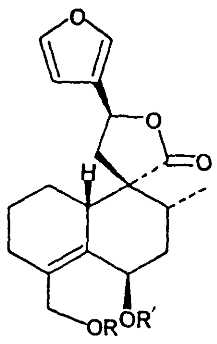
teuscorolide (180),[148] and the 2-hydroxyteuscorolide derivative (181),[149] along with teupolin I (162), and teuflin (141),[116] also produced by *T. scorodonia* subsp. *euganeum*.[116] *T. massiliense* yields montanins C and F (173), (175), along with the novel compounds teumassilin (182), with a 12-hydroxyl furan-ethyl substituent at C_9 and the epoxy diol southern portion, 6,19-diacetylteumassilin (183), and deacetylajugarin II (184), possibly indicating the taxanomic connection of the *Teucrium* and *Ajuga* species.[150] *T. fruticans* also produces compounds with a furyl-ethyl C_9 substituent, the 1-hydroxy-6-oxo compound fruticolone (185), the 6-hydroxy-1-oxo isofruticolone (186),[151] and also 8β-hydroxyfruticolone (187),[152] with X-ray determination of the triacetate of fruticolone. *T. gnaphalodes* produces the 19-hydroxy-6-oxo epoxide gnaphalin (188), along with the 19-acetyl derivative (158), and gnaphalidin (169).[153] This species also produces the novel dihydroxy compound teugnaphalodin (189),[154] as well as teucrins P_1 (152), and P_2 (190), reported but with no structural information provided.[155] *T. eriocephalin* produces eriocephalin (191), a C_{20} acetoxy derivative of deacetylcapitatin (156),[156] also produced by *T. chartaginense* subsp. *homotrichum*, along with teucrin H_3 (19-acetylgnaphalin) (158).[116] *T. lanigerum* also produces eriocephalin (191), along with 20-deacetyleriocephalin (192),[157] 7,8-dehydroeriocephalin (193),[158] and isoeriocephalin (194).[157] This species also gives teupolin I (162),[136] teulanigin (195), a 3-hydroxyl isomer of eriocephalin, 20-epiteulanigin (196), and the novel C_{20}-oxo opened acetal of (194), teulanigeral (197), along with teulanigerin (198), related to teupolin V, and teulanigeridin (199).[158] *T. pyrenaicum* produces teupyrenone (200), the 3-acetoxy derivative of teucrin P_1, teupyreinin (201), originally assigned as the 3-acetoxy-19-acetyl form of teupolin II,[159] but reassigned as the C_{12} epimer by nOe investigation,[160] teupyreinidin


12
X'
H
X
R'
OH
OR

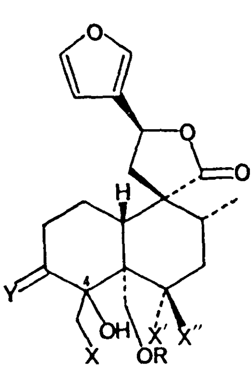
	R	R'	X	X'	C_{12}-Fur
159	Ac	CH_2OH	OH	H	β
176	Ac	CH_2OH	H	H	β
177	Ac	CHO	H	H	β
222	H	CH_2OH	H	H	β
228	H	CH_2OH	H	H	α
229	H	CH_2OH	H	OH	β



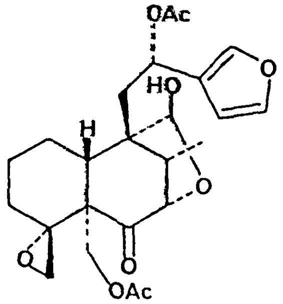
166



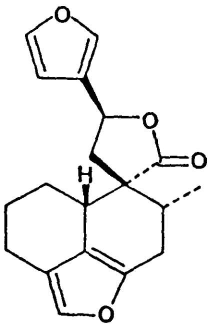
	R	R'
167	H	H
206	Ac	Gluc


H
Y
4
OH
X
X'
X"
OR

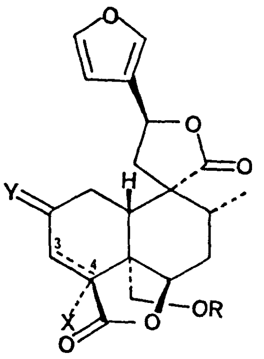
	R	X	X'	X"	Y	C_4-OH
168	H	OH	H	OH	H_2	β
224	Ac	Cl	=0		0	α
225	Ac	Cl	OAc	H	0	α



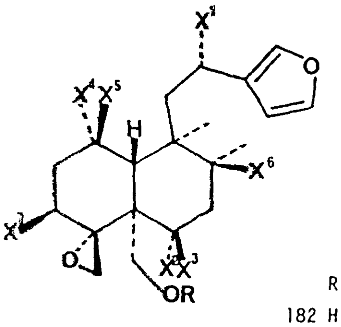
170



172

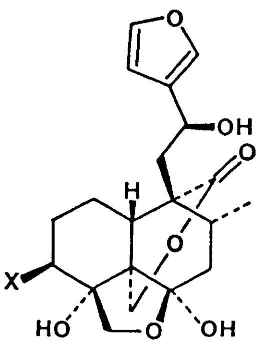


	R	X	Y	3-4
178	H	-	H_2	Double
215	H	H	0	Single
220	H	OH	H_2	Single
221	Ac	OH	H_2	Single

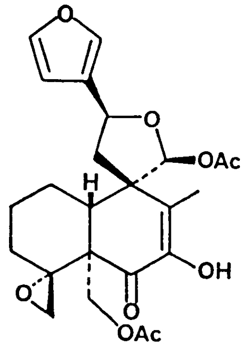

X¹
X⁴
X⁵
H
X⁶
X²
X³
OR

	R	X^1	X^2	X^3	X^4	X^5	X^6	X^7
182	H	OH	OH	H	H	H	H	H
183	Ac	OH	OAc	H	H	H	H	H
185	Ac	H	=0		OH	H	H	H
186	Ac	H	H	OH	=0		H	H
187	Ac	H	=0		OH	H	OH	H
204	H	OH	OAc	H	H	H	H	OH

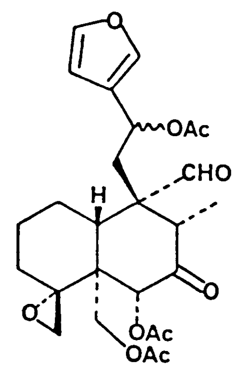
(202), the C_{20} acetoxy derivative of (201),[159] and teupyrins A and B (203), (204), rearranged and reduced forms of (202).[117] T. flavum subsp. flavum produces teuflidin (144),[161] and teuflin (141),[162] structurally confirmed by X-ray analysis, and also found in T. flavum subsp. glaucum, along with 12-epiteucvin (205), isomeric with (81),[136] a glycoside derivative of montanin B, teuflavoside (206), and teuflavin (207), a 3-oxo hemi-acetal derivative of montanin F.[160,163] T. carolipaui subsp. carolipaui has been reported as producing picropolinone (153) and 19-acetylgnaphalin (158),[118] whilst teumarin (208), a 2-hydroxy derivative of montanin F, has been reported from T. marum.[164] T. scordium has been shown to produce teucroxide (146),[165] montanin E (168),[146] teucrin E (135), the novel dehydroteucrin E (209), teugin (142), dihydroteugin (132),[165] and 6α-hydroxyteuscordin (143),[166] along with several novel teuscordin derivatives, 6β-hydroxyteuscordin (210),[167] 2β,6α-dihydroxyteuscordin (211),[165] the 6-keto derivative teuscordinon (212),[168] 2β-hydroxyteuscordinon (213),[165] the C_3-C_4 saturated 6-ketoteuscordin (214),[166] and 2-keto-19-hydroxy-teuscordin (215).[169] T. scordium has also been shown to produce a 2-hydroxy derivative of teuflin, teucrin H_4 (216),[169] the 6-acetyl derivative of teucjaponin B (217), and two derivatives of teupyreinidin, 6-deacetylteupyreinidin (218) and 6,20-bisdeacetyl-teupyreinidin (219).[165] T. hyrcanicum produces teucrin H_1 (teuflidin) (144), teucrin H_2 (teuchamaedryn B) (138),[170,171] teucrin H_3 (19-acetylgnaphalin) (158), and teucrin H_4 (216),[172,173,174,175] whilst T. spinosum also gives teucrin H_3, along with teuspinin (220), a C_2-deoxy hydroxylated form of (215), and the 19-acetyl derivative (221),[176] structurally confirmed by X-ray analysis.[177] T. botrys has been shown to produce teucvidin (67), teuchamaedryn C (139), montanin D (174), and 6β-hydroxyteuscordin (210), along with the novel 19-deacetyl-teuscorodol (222), and teubotrin (223), a C_{19}-C_9 δ-lactone form of


O
OH
O
H
X
O
HO
O
OH

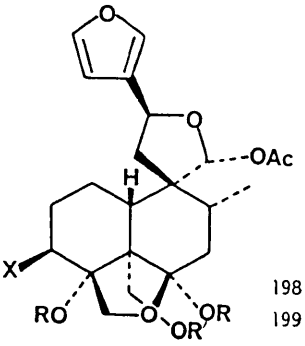
	X
189	H
232	OH


O
O
OAc
H
OH
O
O
OAc

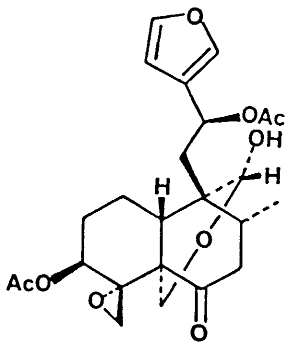
193


O
OAc
CHO
H
O
O
OAc
OAc

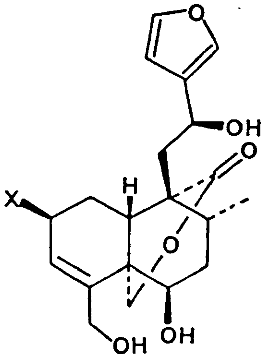
197


O
O
OAc
H
X
RO
O
OR
OR'

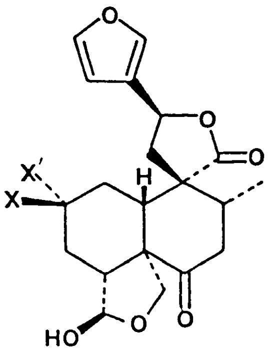
	R	R'	X
198	H	Ac	H
199	$\overline{CH_3C<}$		OH


O
OAc
OH
H
H
O
AcO
O
O

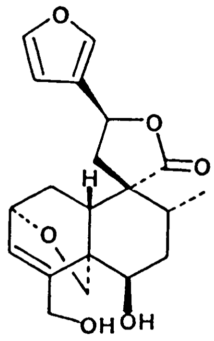
203


O
OH
O
H
X
O
OH
OH

	X
223	H
230	OH


O
O
O
X'
X
H
HO
O
O

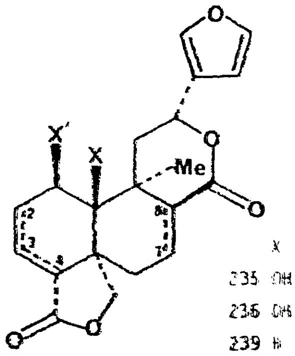
	X	X'
226	$\overline{=O}$	
227	OH	H



231

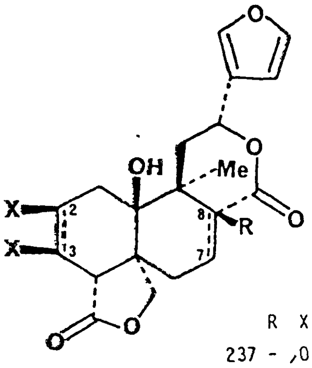
(222)[178] whilst _T. africanum_ yields tafricanins A and B, (224), (225), notable for the chloride opened epoxide at C_4-C_{18}. No chloride ion was used in the isolation of these compounds, thus confirming them as naturally halogen substituted clerodanes.[179] _T. salviastrum_ gives the known teucvidin (67), and teucroxide (146), along with teusalvins A and B, (226), (227), C_2-oxidised forms of teuscorodin (179), teusalvin C (228), the C_{12} epimer of (222), teusalvin D (229), also known as 2-hydroxy-19-deacetylteuscorodol, teusalvin E (230), a 2-hydroxyl form of teubotryn (223), and teusalvin F (231), containing a novel C_2-C_{18} ether linkage.[180] _T. lepicephalum_ yields teulepicephin (232), a 3-hydroxylated form of teugnaphalodin (189), teulepicin (233), a 3-hydroxylated form of gnaphalin, and 19-acetylteulepicin (234), with (234) also isolated from _T. buxifolium_, along with the corresponding 3-dehydroxyl compound 19-acetylgnaphalin (teucrin H_3) (158).[118]

Genus - Salvia. This genus shows a strong tendancy towards either _trans_ compounds with a fused C_8-C_9 δ-lactone, or _cis_ compounds with an unusual C_7-C_{20} ether linkage, with nearly all the compounds having a C_4-C_5 γ-lactone substituent. _S. rubescens_ has been reported as yielding the 10-hydroxylated compound (235), with no stereochemical assignement,[181] whilst _S. coccinea_ yields the _trans_ 10-hydroxylated diene compound salviacoccin (236).[182] (236) has also been isolated from _S. plebeia_, along with a monoepoxide form, epoxysalviacoccin (237).[183] 7,8β-dihydrosalviacoccin (238) has been isolated from _S. greggii_,[184] whilst _S. splendens_ yields the C_8 epimer of (238), salviarin (239), and 1,11-diacetoxysalviarin, splendidin (240).[185] _S. lineata_ yields a 1,10-dehydro form of salviarin, compound (241), the 1,10α-epoxy derivative (242), and the C_1-C_4 diene _trans_ rearranged form of (241), compound (243).[186] _S. divinorum_ has been shown to produce salvinorin (244),[187] also known as divinorin A, with a _trans_ structure containing the fused δ-lactone, but epimeric at C_{12} to the



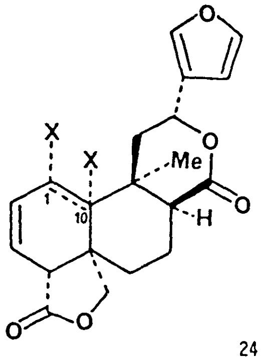
X'
X
Me
2
3
4
8a
7a

	X	X'	2-3	3-4	7-8
235	OH	H	Single	Double	Single (no assigned stereochem.)
236	OH	H	Double	Single	Double
239	H	H	Double	Single	Single
240	H	OAc	Double	Single	Single

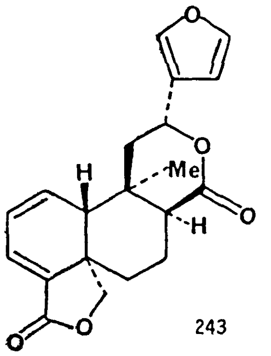


OH
Me
X
X
2
3
8
7
R

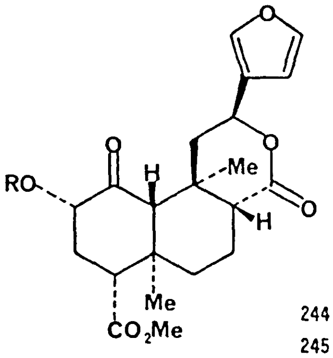
	R	X	2-3	7-8
237	-	,O,	Single	Double
238	H	H	Double	Single



	X	1-10
241	H	Double
242	,O,	Single

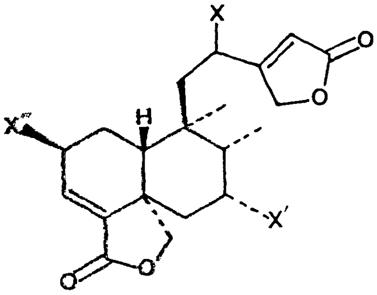


243

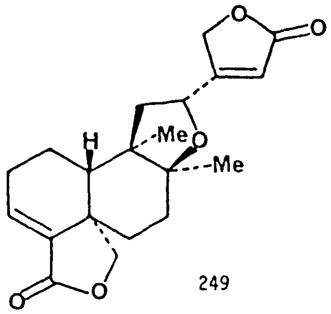


RO
H
Me
H
Me
CO2Me

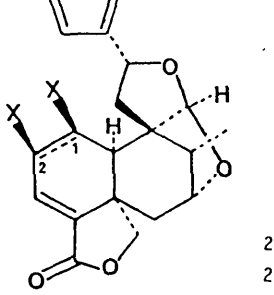
	R
244	Ac
245	H



	X	X'	X''
246	OH	H	OH
247	H	OH	H
248	OH	OAc	H



249



	X	1-2
250	H	Double
251	,O,	Single

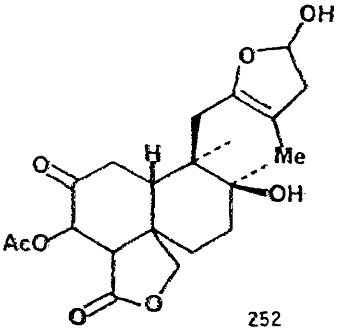
previous Salvia generated compounds detailed, and without the southern γ-lactone, structurally proven by X-ray analysis, and the corresponding 2-deacetyl compound divinorin B (245).[188] S. semiatratha yields two C_{12} butenolide substituted trans compounds, the 2,12-dihydroxy compound semiatrin (246), and the 7-hydroxy compound (247), also isolated from the Compositae family,[189] whilst S. keerlii yields a 7-acetyl-12-hydroxy derivative of (247), kerlinolide (248), and kerlin (249), structurally assigned by X-ray analysis as possessing an unusual C_8-C_{12} ether linkage.[190] S. farinacea produces the C_7-C_{11} ether linked compounds salvifaricin (250), and the corresponding epoxide salvifarin (251), initially assigned as trans compounds,[191] but later reassigned as cis by X-ray structural determination.[192,193]

Genus - Leonurus. Only two species of this genus have been shown to produce clerodanes, with L. cardiaca yielding the C_2, C_3, C_8 oxygenated trans compound (252), with a novel rearranged C_{12}-C_{16} section,[194] and L. marrubiastrum yielding two cis C_{12}-butenolide compounds, the glucopyranosyl marrubiaside (253), and the C_4-C_5 γ-lactone 17-hydroxylated marrubialactone (254).[195]

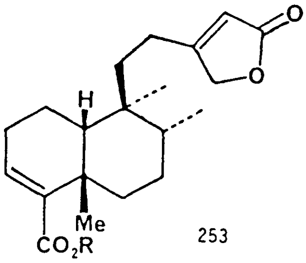
Genus - Stachys. S. annua yields the trans 7-hydroxyl enone stachysolone (255),[196,197] also known as annuanone,[198] with an open chain C_{11}-C_{16} arrangement, the 3,4-dihydro derivative stachylone (256), and the tetrahydro stachone (257).[199] S. recta gives three stachysolone derivatives, the 7-acetyl compound (258), the 13-acetyl compound (259), and the corresponding diacetyl compound (260).[200,201]

3.14. Family Scrophulariaceae.

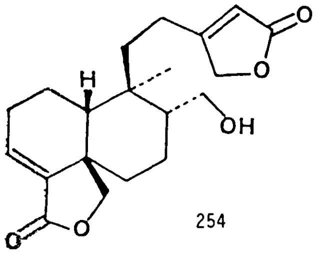
Genus - Linaria. Two species of this genus produce clerodane natural products. L. japonica Miq produces two cis compounds, with an open chain C_{11}-C_{16} arrangement, the dialdehyde linaridial (261),[202,203] and


OH
O
Me
OH
H
O
AcO
O
O

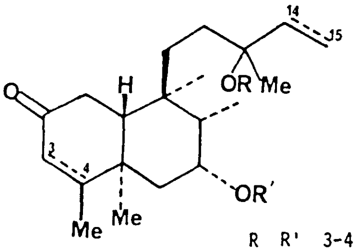
252



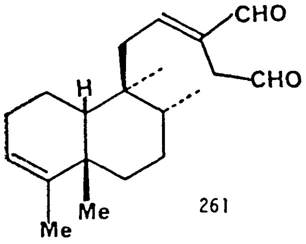
253



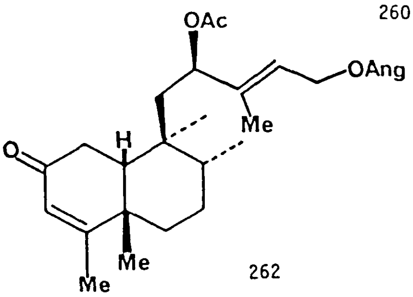
254


14
15
OR
Me
O
H
3
4
OR'
Me
Me

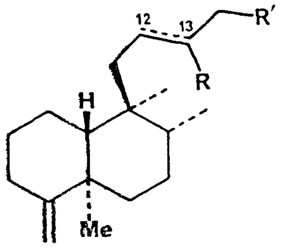
	R	R'	3-4	14-15
255	H	H	Double	Double
256	H	H	Single	Double
257	H	H	Single	Single
258	H	Ac	Double	Double
259	Ac	H	Double	Double
260	Ac	Ac	Double	Double


CHO
CHO
H
Me
Me

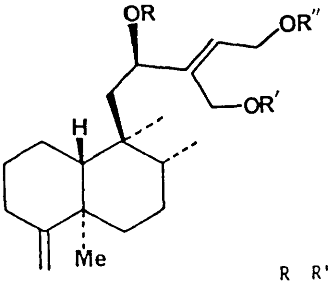
261


OAc
OAng
Me
O
H
Me
Me

262



	R	R'	12-13
263	CHO	CHO	Double
264	Me	CHO	Double
265	Me	CHO	Single
266	CH_2OAc	CH_2OAc	Double



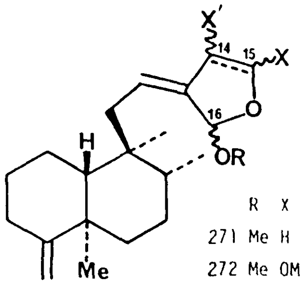
	R	R'	R"
267	Ac	Ac	Ac
268	H	Ac	Ac
269	Ac	H	Ac
270	Ac	Ac	H

the 12-acetoxy-15-angeloyloxy compound linarienone (262),[204,205] with correlation studies cis to trans confirming the structure of (261).[206] L. saxitalis has been shown to produce twenty trans compounds, all with a simple 4-exo methylene 5α-methyl decalin unit. Isolinaridial (263), a trans isomer of linaridial, the corresponding 16-deoxy compound (264), a corresponding reduced form (265), and the 15,16-diacetoxy compound (266) all share the same basic C_{11}-C_{16} unit. C_{13}-C_{14} unsaturated compounds have also been isolated, the 12,13,15-triacetoxy compound (267), and the three corresponding monodeacetates (268), (269), and (270). Also found have been several C_{12}-C_{13} unsaturated cyclic ethers, the 16-methoxy dihydrofuran (271), two epimeric forms of the corresponding 15,16-dimethoxy tetrahydrofuran (272), (273), the 15,16-diacetoxy compounds (274), (275), the 15-acetoxy-16-methoxy compounds (276), (277), and the corresponding 14-hydroxy compounds (278), (279). L. saxitalis also yields the unsaturated δ-lactone (280), the corresponding acetal (281), and the novel (282), a combination product of compounds (270) and (274).[207,208,209]

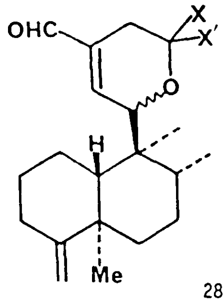
3.15. Family Compositae.

As the largest family of angiosperms, with an estimated 19,000 species,[8] it is not surprising that twenty-four genera have been shown to produce clerodanes. The natural products isolated comprise both cis and trans compounds, though mainly trans clerodanes, and with a large variety of structures, though a tendancy towards simple C_{11}-C_{16} open chain substitution is evident. The presence of clerodane natural products in the Compositae has been partially covered during a symposium of the biology and chemistry of the Compositae.[210]

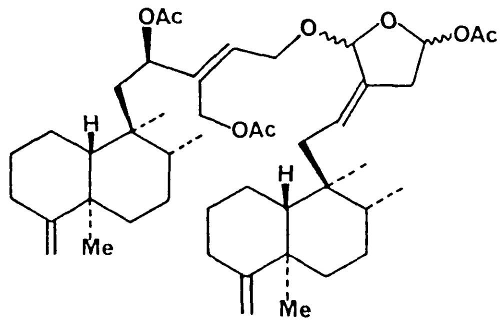
Genus - Solidago. S. altissima gives the trans compounds kolavenol (50) and kolavenic acid (51),[211,212,213] already shown from Hardwickia pinnata (Caesalpinaceae), and six derivatives of kolavenic acid, the 6-angeloyloxy and tigloyloxy derivatives (283), (284), the corresponding methyl esters (285), (286), the 6-keto ester (287) and methyl dehydro-kolavenate (288).[214,215,216] Also isolated has been the 7-acetoxy-kolavenic acid, solidagonic acid (289),[211,217] and the 16-oxidised butenolide compound equivalent to kolavenic acid, solidagolactone I (290). Also produced are the 6-angeloyloxy, tigloyloxy and hydroxy compounds solidagolactones II, III, and IV respectively (291), (292), and (293), the 6-keto compound solidagolactone V (294), and the 6-acetoxy-3,4-epoxy substituted solidagolactone VI (295).[218] All these compounds were originally assigned trans, but lactones II-VI have been reassigned cis, with a β-C_9-methyl, along with the novel solidagolactone VII (296), the C_3,C_4 epoxide of lactone II, and solidagolactone VIII (297), the corresponding epoxide of lactone III.[219] In a seperate study on S. altissima, elongatolides A-E were described, with only elongatolide B (298) a novel compound, the 6-acetyl form of lactone IV. Elongatolide A was shown to be solidagolactone IV, elongatolide C was shown to be lactone II, elongatolide D was shown to be lactone VI, and elongatolide E was shown identical to lactone VII.[220] S. elongata Nutt gives elongatolides A-D, the trans epimers of elongatolides B-E (299), (300), (301), and (302), methyl kolavenate (303), and the corresponding 6-acetoxy compound (304), kolavelool (48), previously shown in Hardwickia pinnata (Caesalpinaceae), and the 6-angeloyloxy-kolavelool derivative (305).[221] S. vigaurea yields solidagolactones II, III, V, VII, and VIII, along with the 2β-hydroxyl forms of lactones II, III, and V, (306), (307), and (308), the epoxide opened diol forms of lactones VII and VIII, (309) and (310), and the 3-keto forms of lactones VII and VIII, (311) and (312).[222] S. gigantea subsp. serotina yields eleven cis compounds with a furyl-ethyl



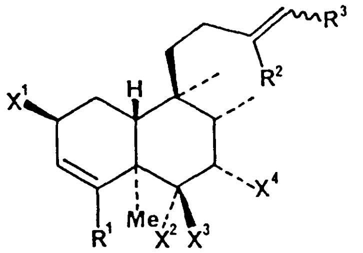
	R	X	X'	14-15	15/16
271	Me	H	H	Double	-
272	Me	OMe	H	Single	*cis*
273	Me	OMe	H	Single	*trans*
274	Ac	OAc	H	Single	*cis*
275	Ac	OAc	H	Single	*trans*
276	Me	OAc	H	Single	*cis*
277	Me	OAc	H	Single	*trans*
278	Me	OAc	OH	Single	*cis*
279	Me	OAc	OH	Single	*trans*



	X	X'
280	$=$O	
281	OAc	H



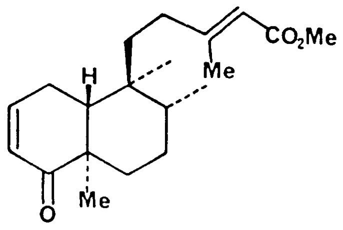
282



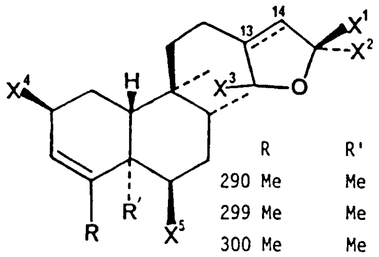
	R^1	R^2	R^3	X^1	X^2	X^3	X^4	R^2/R^3
50	Me	Me	CH_2OH	H	H	H	H	*cis*
51	Me	Me	CO_2H	H	H	H	H	*cis*
283	Me	Me	CO_2H	H	H	OAng	H	*cis*
284	Me	Me	CO_2H	H	H	OTig	H	*cis*
285	Me	Me	CO_2Me	H	H	OAng	H	*cis*
286	Me	Me	CO_2Me	H	H	OTig	H	*cis*
287	Me	Me	CO_2Me	H	$=$O		H	*cis*
289	Me	Me	CO_2H	H	H	H	OAc	*cis*
303	Me	Me	CO_2Me	H	H	H	H	*cis*
304	Me	Me	CO_2Me	H	H	OAc	H	*cis*
352	CH_2OH	CH_2OH	CH_2OH	H	H	H	H	*cis*
378	Me	CH_2OH	CHO	H	H	H	H	*cis*
379	Me	CH_2OH	CHO	H	H	H	H	*trans*
380	Me	CO_2H	CHO	H	H	H	H	*cis*
381	Me	CO_2H	CHO	H	H	H	H	*trans*
382	Me	CH_2OH	CH_2OH	H	H	H	H	*trans*
383	Me	CH_2OH	$CH_2O\overset{O}{C}(CH_2)_{18}Me$	H	H	H	H	*trans*
384	Me	CH_2OH	$CH_2O\underset{O}{C}(CH_2)_{20}Me$	H	H	H	H	*trans*
410	Me	Me	CO_2Me	OAc	H	H	H	*trans*
411	CH_2OH	CH_2OH	CO_2H	H	H	H	H	*cis*
412	CHO	CH_2OH	CO_2H	H	H	H	H	*cis*
413	CH_2OH	CH_2OAc	CO_2H	H	H	H	H	*cis*
414	CHO	CH_2OAc	CO_2H	H	H	H	H	*cis*
418	Me	CH_2OH	CO_2H	H	H	H	H	*cis*

substituent at C_9 and a β-C_9 methyl, solidagonic acid A (313), the corresponding 18-angeloyloxy acid solidagonic acid B (314),[223] the aldehydic reduced form of acid A, (315), and dialdehyde (316), the 19-hydroxy reduced form (317), and the isomeric 18-hydroxy compound (318), an 18,19-diol (319), a C_4-C_5 γ-lactone (320), a corresponding lactol (321), an epoxy form of lactol (321), (322) and the epoxide opened dihydroxylactol (323).[224] S. arguta Ait yields a C_5, C_9, C_{10} epimer of (318), the cis compound (324), the corresponding acetate (325), and dehydroxylated (326), the 6-hydroxyl (327) and the 18-monoacetylated (328), and a C_4-C_6 γ-lactone (329) structurally confirmed by X-ray analysis.[225,226,227,228,229] S. serotina Ait yields the trans isomer of (326), compound (9), already shown isolated from the Annonaceae family, a C_3-C_4 epoxide derivative (330), the corresponding butenolide (331), the epoxide opened form (332), and the 3-keto butenolide (333). Also shown in this species are the E and Z isomers of the C_{13}-C_{14} unsaturated epoxy aldehyde (334), (335), and the corresponding 3-keto derivatives (336) and (337).[229,230,231] S. shortii produces (338), originally assigned identical to (331), but later reassigned by X-ray studies to the cis compound, and the corresponding 7-angeloyloxy compound (339).[225,232] S. juncea Ait. produces the C_{20} oxidised derivative of (9), junceic acid (340), and the corresponding epoxide (341),[233] while S. chilensis also produces junceic acid (340),[234] and S. canadensis gives the trans aldehyde rugosolide (342).[235]

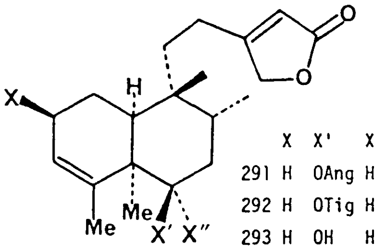
Genus - Baccharis. B. tricuneata has been shown to produce four novel trans clerodanes, bacchotricuneatin A (343), a C_8-C_9 δ-lactone ent-neo-clerodane, bacchotricuneatin B (344), with a C_9 spiro γ-lactone and a neo-clerodane structure,[236] both structurally confirmed by X-ray analysis, bacchotricuneatin C (345), with a novel acetal arrangement at C_{17}, and bacchotricuneatin D (346), a 7,18-dihydroxy form of


CO₂Me
H
Me
O
Me

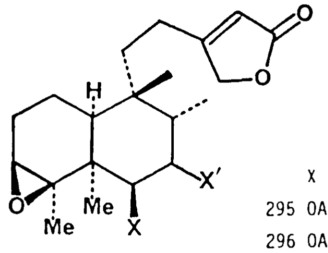
288


14
13
X^1
X^2
X^3
X^4
H
O
R
R'
X^5

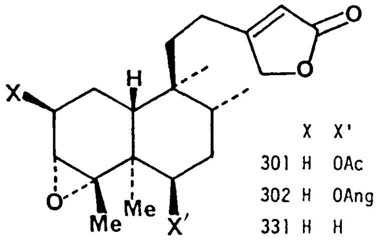
	R	R'	X^1 X^2	X^3	X^4	X^5	13-14
290	Me	Me	=O	H	H	H	Double
299	Me	Me	=O	H	H	OAc	Double
300	Me	Me	=O	H	H	OAng	Double
364	CH_2OMal	Me	H OH	H	H	H	Single
365	CH_2OMal	Me	OH H	H	H	H	Single
368	CH_2OAc	Me	H,OMe	H	H	H	Single
369	CH_2OH	Me	H,OMe	H	H	H	Single
370	CH_2OH	CH_2OH	H,OMe	H	H	H	Single
371	CH_2OAc	CH_2OAc	H,OMe	H	H	H	Single
389	Me	Me	=O	H	OH	H	Double
417	Me	Me	=O	OH	H	H	Double
427	Me	Me	=O	H	H	H	Single
428	Me	Me	=O	OH	H	H	Single


O
O
X
H
Me
Me
X'
X"

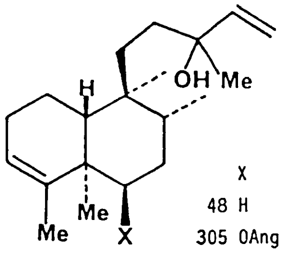
	X	X'	X"
291	H	OAng	H
292	H	OTig	H
293	H	OH	H
294	H	=O	
298	H	OAc	H
306	OH	OAng	H
307	OH	OTig	H
308	OH	=O	


O
O
H
X'
O
Me
Me
X

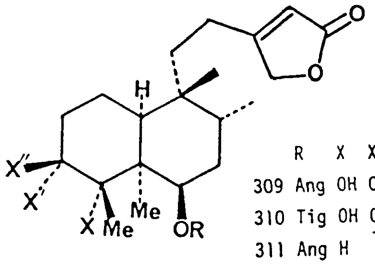
	X	X'
295	OAc	H
296	OAng	H
297	OTig	H
338	H	H
339	H	OAng


O
O
X
H
O
Me
Me
X'

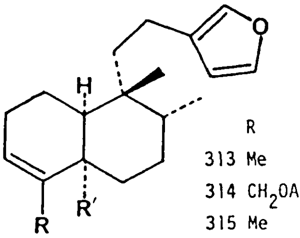
	X	X'
301	H	OAc
302	H	OAng
331	H	H
390	OH	H


H
OH
Me
Me
Me
X

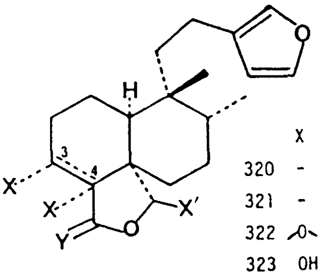
	X
48	H
305	OAng


O
O
H
X"
X'
X
Me
Me
OR

	R	X	X'	X"
309	Ang	OH	OH	H
310	Tig	OH	OH	H
311	Ang	H	=O	
312	Tig	H	=O	

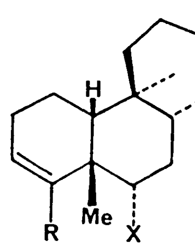


	R	R'
313	Me	CO_2H
314	CH_2OAng	CO_2H
315	Me	CHO
316	CHO	CHO
317	Me	CH_2OH
318	CH_2OH	Me
319	CH_2OH	CH_2OH

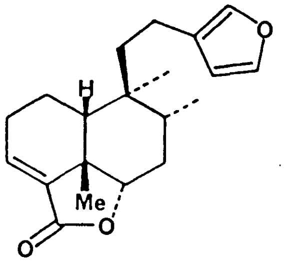


	X	X'	Y	3-4
320	-	H	O	Double
321	-	OH	H_2	Double
322	⟋O⟍	OH	H_2	Single
323	OH	OH	H_2	Single

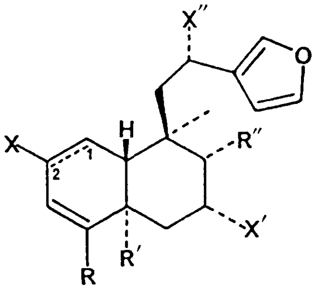
(9),[237] whilst B. cassinaefolia D.C. yields two 2-hydroxy derivatives of bacchotricuneatin B, (347) and (348).[238] B. nitida gives the angeloyl form of (347), (349),[239] whilst B. kingii yields kingidiol (350), an 18,19-dihydroxy compound isomeric with bacchotricuneatin D.[240] B. incarum yields the diacetyl derivative of kingidiol, (351), renamed as barticulidiol, the 19-dehydroxy derivative of kingidiol, bacchalineol (92), previously shown from Dodoneae boroniaefolia (Sapindaceae), and the furan opened triol derivative bincatriol (352).[241] B. articulata also yields a diester derivative of barticulidiol (353), along with bacchotricuneatin A,[242] whilst B. calvescens,[238] B. chilko HBK,[239] B. vaccinoides,[243] and B. macraei[244] have been shown to yield hautriwaic acid (85), a C_{18} oxidised form of kingidiol previously shown isolated from the Euphorbiaceae and Sapindaceae families. B. macraei also yields the 19-dehydroxyl compound hardwickiic acid (54), previously shown in the Caesalpinaceae, Leguminosae, and Euphorbiaceae families, and two novel 7-oxo-γ-lactones, bacchasmacranone (354) and the 2-hydroxy derivative (355).[244] B. sarothroides has also been shown to give hautriwaic acid, along with the 2β-hydroxy derivatives (356),[243] whilst B. scoparia yields the 7-oxo C_8-C_9 pyranyl compound (357), and the dihydro derivative (358), and B. hutchinsonii yields (9), previously described from the Solidago genus, and the 17-oxo derivative (359).[239] B. trimera Less has been shown to produce a 7-hydroxy butenolide form of bacchasmacranone, (247), previously shown isolated from Salvia semiatratha (Labiatae), the corresponding dihydro dilactone (360), and the 7-dehydroxy compound (361), all structurally confirmed by X-ray analysis,[245] whilst B. genistelloides also produces (247) and (360), along with the corresponding 7-oxo compound (362), and a tetranorclerodane (363).[246,247] B. microcephala also produces (362), whilst B. alerternoides yields two epimeric compounds (364), (365), hemi-



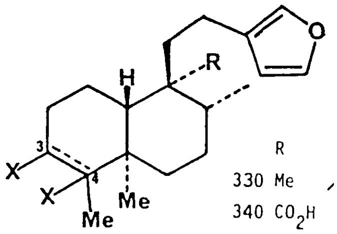
	R	X
324	CH_2OH	H
325	CH_2OAc	H
326	Me	H
327	CH_2OH	OH
328	CH_2OAc	OH



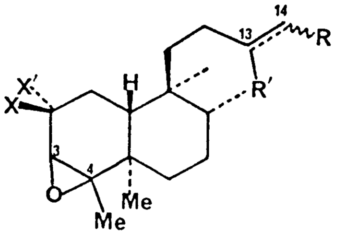
329



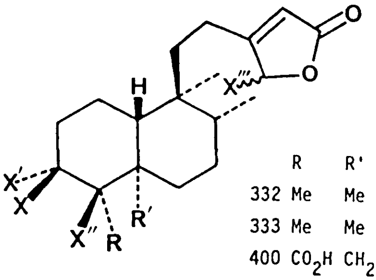
	R	R'	R"	X	X'	X"	1-2
9	Me	Me	Me	H	H	H	Single
54	CO_2H	Me	Me	H	H	H	Single
85	CO_2H	CH_2OH	Me	H	H	H	Single
92	CH_2OH	Me	Me	H	H	H	Single
346	CH_2OH	Me	Me	H	OH	H	Single
350	CH_2OH	CH_2OH	Me	H	H	H	Single
351	CH_2OAc	CH_2OAc	Me	H	H	H	Single
353	CH_2OMal	CH_2OAc	Me	H	H	H	Single
356	CO_2H	CH_2OH	Me	βOH	H	H	Single
359	Me	Me	CHO	H	H	H	Single
392	CO_2H	CH_2Oac	Me	H	H	H	Single
393	CO_2H	CH_2OAng	Me	H	H	H	Single
394	CO_2H	CH_2OVal	Me	H	H	H	Single
395	CO_2H	CH_2OMe	Me	H	H	H	Single
396	CO_2H	CH_2OAc	Me	H	H	H	Double
397	CO_2H	CHO	Me	H	H	H	Single
422	CO_2H	CH_2OH	Me	OH	H	H	Single
434	CO_2H	Me	Me	H	H	OMeBu	Single



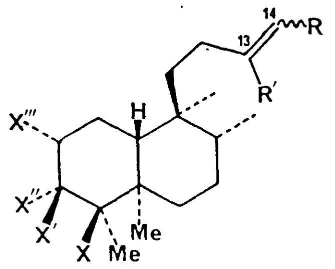
	R	X	3-4	C_3/C_4-X
330	Me	/O\	Single	α
340	CO_2H	-	Double	-
341	CO_2H	/O\	Single	β



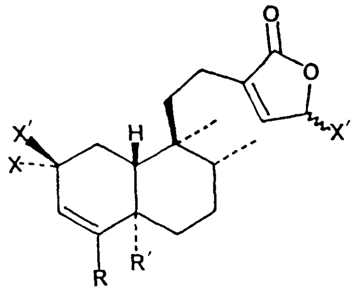
	R	R'	X	X'	13-14	C_3/C_4-O
334	CHO	Me	H	H	Double(E)	α
335	CHO	Me	H	H	Double(Z)	α
391	CH_2OH	Me	OH	H	Single	α
426	CO_2H	Me	=O		Single	β
438	CH_2OAc	Me	H	OH	Double(E)	β
439	CH_2OAc	Me	H	OAc	Double(E)	β
440	CH_2OAc	CH_2OH	H	OH	Double(Z)	β
441	CH_2OAc	CH_2OAc	H	OAc	Double(Z)	β



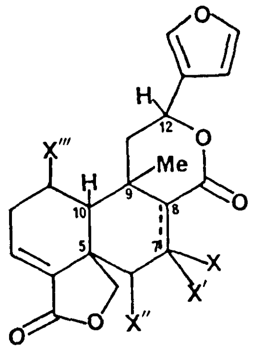
	R	R'	X	X'	X"	X"'
332	Me	Me	H	OH	OH	H
333	Me	Me	=O		H	H
400	CO_2H	CH_2OH	H	H	H	αOH
401	CO_2H	CH_2OH	H	H	H	βOH


14
13
R
R′
X‴
H
X″
X′
X
Me
Me

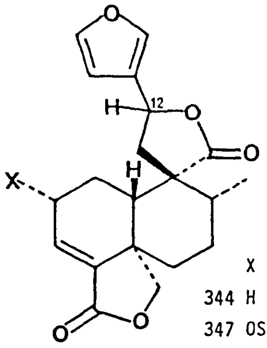
	R	R'	X	X'	X"	X"'	R/R'
336	CHO	Me	H	=O		H	cis
337	CHO	Me	H	=O		H	trans
375	CO_2H	Me	OH	H	OH	OH	trans
442	CH_2OAc	Me	OH	H	OAc	OAc	cis
443	CH_2OAc	CH_2OAc	OH	H	OAc	Oac	cis



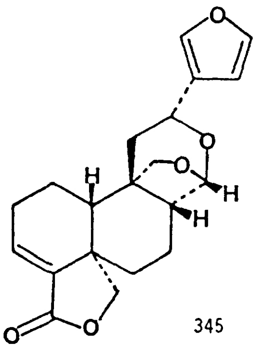
	R	R'	X	X'	X"
342	Me	Me	H	H	H
398	CO_2H	CH_2OH	H	H	αOH
399	CO_2H	CH_2OH	H	H	βOH
415	Me	Me	H	OH	H
416	Me	Me	=O		H


O
H
12
O
X‴
Me
H
9
10
8
O
5
7
X
X′
O
O
X″

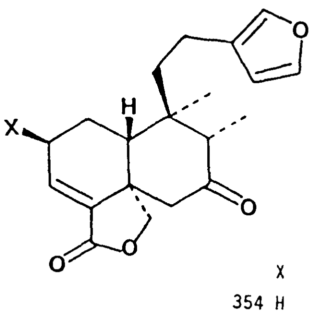
	X	X'	X"	X"'	7-8	C_8-H	C_{10}-H	C_{12}-H	C_9-Me	C_5-CH_2
343	H	H	H	H	Single	α	α	α	β	β
404	OH	-	H	H	Double	-	β	α	α	α
425	H	-	βOH	H	Double	-	β	β	α	α
433	H	H	H	OH	Single	α	α	α	β	β


O
H
12
O
O
X
H
O
O

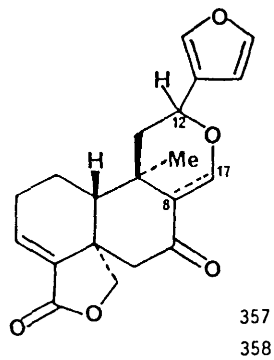
	X	C_{12}-H
344	H	β
347	OSen	β
348	OMeBu	β
349	OAng	α



345



	X
354	H
355	OH


O
H
12
O
H
Me
17
8
O
O
O

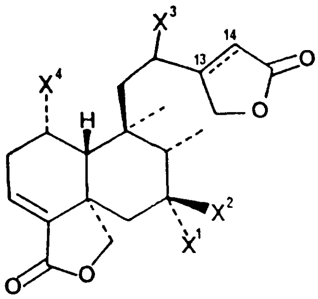
	8-17	C_8-H	C_{12}-H
357	Double	-	β
358	Single	β	β
405	Double	-	α

acetal derivatives of bacchalineol, and two epimeric reduced forms of bincatriol (366), (367).[248] B. grandicapitata has been shown to produce the 18-acetyl methyl acetal of (364), compound (368),[239] whilst the deacetyl compound (369), the corresponding 18,19-dihydroxy (370), and the diacetate (371) have been isolated from B. rhomboidalis, along with dihydrobincatriol triacetate (372), the corresponding 16-deacetyloxy compound (373), and a novel 1-hydroxy butenolide (374).[249] Finally B. tucumanensis has been shown to yield the trihydroxy acid tucumanoic acid (375).[250]

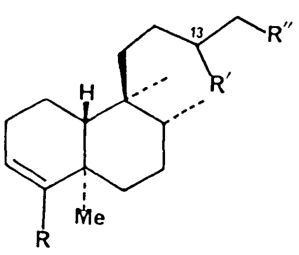
Genus - Symphiopappus. S. itatiagensis yields two cis clerodanes, the C_4-C_6 γ-lactone butenolide (376), and the corresponding 2-hydroxy dihydro compound (377),[251] whilst S. reticulatus produces eleven trans compounds, with an open chain C_{11}-C_{16} structure, the C_{13}-C_{14} unsaturated hydroxy aldehydes (378), (379), oxo acids (380), (381), diol (382), and monoester derivatives (383) and (384), along with the C_{13}-C_{14} saturated acetylated equivalents (385) and (386), hydroxy-aldehyde (387), and aldehyde (388). S. compressus has been shown to produce the 2-hydroxy butenolide (389), the corresponding C_3-C_4 epoxide (390), and diol (391).[252]

Genus - Conyza. Hautriwaic acid (85), previously shown in the Baccharis genus, and the Euphorbiaceae and Sapindaceae families, has been isolated from C. ivaefolia Less.,[253] and from C. scabrida D.C., along with the three ester derivatives (392), (393), and (394), and 19-methyl hautriwaic acid (395), a dehydrohautriwaic acid derivative (396), the corresponding 19-oxo (397), four hydroxy butenolide derivatives of hautriwaic acid (398)-(401), and epoxy derivatives (402) and (403).[254] C. podacephala has been shown to produce the C_{12}-epimer of (357), from Baccharis scoparia, (404), and the corresponding δ-lactone fused enol compound (405).[255]

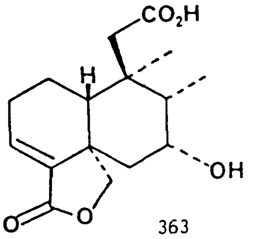
Genus - Haplopappus. H. foliosus and H. angustifolia have both been


X⁴
X³
14
13
O
H
X²
X¹
O
O

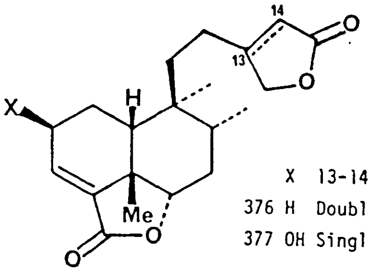
	X^1	X^2	X^3	X^4	13-14
247	OH	H	H	H	Double
360	OH	H	H	H	Single
361	H	H	H	H	Single
362	=O		H	H	Single
374	H	H	H	OH	Double
423	H	H	OH	H	Double



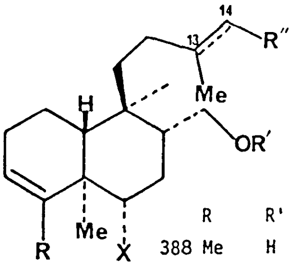
	R	R'	R"	C_{13}-R'
39	Me	Me	CO_2H	-
366	CH_2OMal	Me	CH_2OH	α
367	CH_2OMal	Me	CH_2OH	β
372	CH_2OAc	CH_2OAc	CH_2OAc	-
373	CH_2OAc	Me	CH_2OAc	-
385	Me	CH_2OAc	$CH_2OC(=O)(CH_2)_{18}Me$	-
386	Me	CH_2OAc	$CH_2OC(=O)(CH_2)_{20}Me$	-
387	Me	CHO	CH_2OH	-
407	CO_2H	Me	CO_2H	β
424	CH_2OAc		CO_2H	-



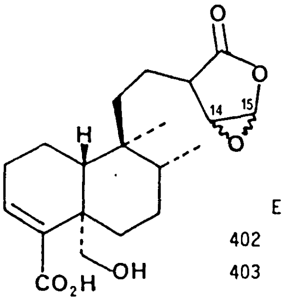
363


14
O
13
O
X
H
Me
O
O

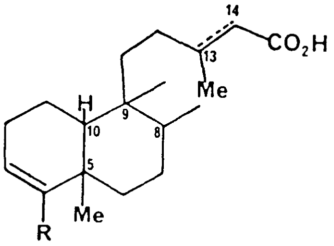
	X	13-14
376	H	Double
377	OH	Single


14
13
R″
Me
H
OR′
Me
R
X

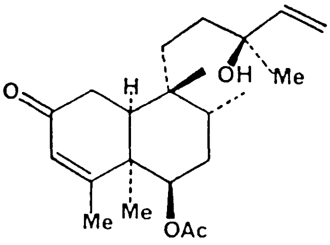
	R	R'	R"	X	13-14
388	Me	H	CHO	H	Single
444	CHO	Ac	CH_2OH	OH	Single
445	CH_2OH	Bz	CH_2OH	OH	Single
446	CH_2OH	Ac	CO_2H	OH	Double
447	CH_2OH	Bz	CO_2H	OH	Double


O
O
14
15
O
H
OH
CO₂H

	Epoxide
402	α
403	β


14
CO₂H
13
Me
H
9
10
8
5
Me
R

	R	13-14	C_8-Me	C_9-Me	C_5-Me	C_{10}-H
406	CO_2H	Double	α	α	β	β
456	Me	Single	β	β	α	α


O
H
OH
Me
Me
Me
OAc

408

shown to produce haplopappic acid (406), a cis 5-epimer of kolavic acid (53),[256] whilst haplociliatic acid (407), a dihydro form of kolavic acid is produced by H. ciliatus,[257,258] structurally confirmed as trans by X-ray analysis.[259]

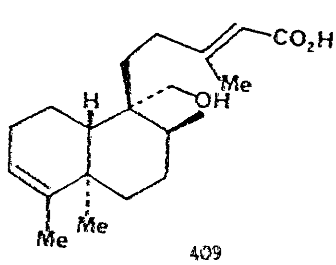
Genus - Stevia. S. salicifolia gives (408), a 7-acetoxy-2-oxo cis isomer of kolavelool (48).[260] S. polycephala has been shown to produce the trans stephalic acid (409), a 20-hydroxy isomer of kolavenic acid (51) assigned by X-ray analysis,[261] whilst S. myriadenia yields a 2-acetoxy isomer of (51), (410).[262]

Genus - Acritopappus. A. hagei K. & R. has been shown to give four trans compounds related to kolavenic acid (51), the 16,18-dihydroxy derivative (411), the corresponding 18-oxo compound (412), and the two 16-acetyl derivatives (413) and (414), along with the 2-hydroxy and 2-oxo butenolides (415) and (416).[263] A. longifolius has been shown to yield the known solidagolactone I (290), and two novel compounds (417), a 16-hydroxy form of solidagolactone I, and 16-hydroxykolavenic acid (418).[264]

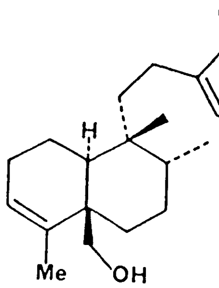
Genus - Nidorella. Two species of this genus have been shown to produce clerodanes, with N. agria yielding two isomeric trans butenolides with an 8α-methyl ent-neo structure, nidorellalactone (419) and isonidorellalactone (420), whilst N. residifolia yields the furyl dienoic acid ester, methyl nidoresedate (421), with the same stereochemical arrangement as (419) and (420).[265]

Genus - Olearia. Two species are of relevance here, with O. muelleri yielding the 19-hydroxy form of furyl acid (95), (422),[266] possibly identical to (356), but with no assignement of C_2 stereochemistry, and O. heterocarpa producing olearin (423), a butenolide γ-lactone compound isomeric with the Baccharis produced (247).[267]

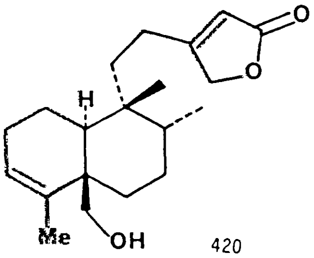
Genus - Liatris. L. scariosa has been shown to give the trans compound (424), a C_{11}-C_{16} open chain acid acetoxy derivative of



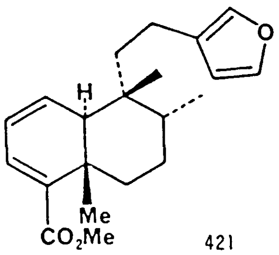
409



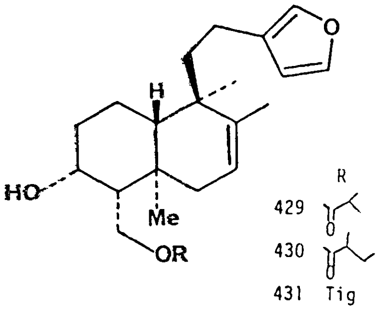
419

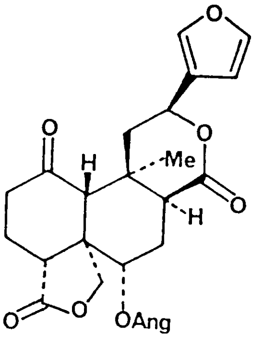


420

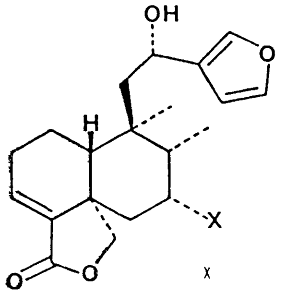


421

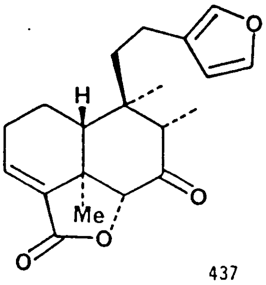




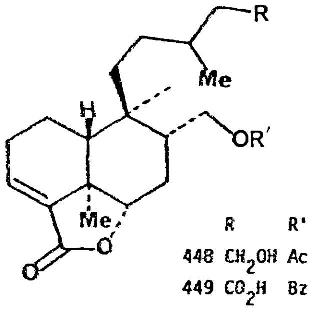
432



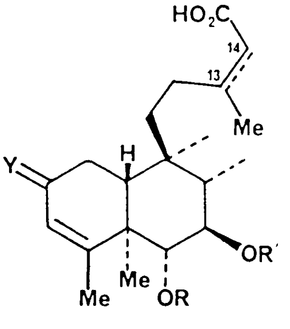
X
435 H
436 OH



437



	R	R'
448	CH_2OH	Ac
449	CO_2H	Bz



	R	R'	Y	13-14
450	Ac	Ac	H_2	Double
451	Ang	Ac	H_2	Double
452	^{i}Bu	Ac	H_2	Double
453	H	H	O	Double
454	^{i}Bu	Ang	H_2	Single

populifolic acid (39),[268] whilst L. spicata gives bacchotricuneatin A, (343), and the 1-hydroxy derivative (425).[269]

Genus - Hartwrightia. H. floridana is the only member of this genus to produce clerodanes, yielding populifolic acid (39), and the 2-oxo epoxide derivative (426).[270]

Genus - Bahianthus. B. viscidus has been shown to give two trans clerodanes, yielding the dihydro derivative of solidagolactone I (290), (427), and the corresponding 16-hydroxy butenolide (428).[271]

Genus - Hinterhubera. H. imbricata Cuatr. yields three ester derivatives of a trans furyl 7,8-dehydro-4,18-dihydroxy clerodane, (429), (430), and (431).[272]

Genus - Aster. A. alpinus yields two trans clerodanes with fused C_8-C_9 δ-lactone rings related to bacchotricuneatin A (343), the 1-oxo-6-angeloyloxy-3,4-dihydro compound (432), and the 7,8-dehydro-6-hydroxy derivative (433), both assigned with enantiomeric stereochemistry to bacchotricuneatin A.[273]

Genus - Heteropappus. H. altaicus has been shown to produce three trans clerodanes, the 12-hydroxylated derivative of hardwickiic acid (54), (434), the corresponding C_4-C_5 γ-lactone (435), and the 7-hydroxy lactone (436).[274]

Genus - Fleischmannia. F. sinclairii has been shown to produce kolavenic acid (51) and populifolic acid (39), with both compounds shown to be identical to those products isolated from other sources.[275]

Genus - Melampodium. The sole product from this genus has been identified as kolavenol (50), isolated from M. divaricatum, identical to the samples isolated from Hardwickia pinnata (Caesalpinaceae) and the Solidago.[276]

Genus - Pulicaria. P. gnaphalodes has been shown to produce the furyl C_4-C_6 γ-lactone compound (437) as the sole product from this genus.[277]

Genus - Goyazianthus. G. tetrastichus has been shown to yield several derivatives of kolavenol (50), the 15-acetyl-3,4-epoxy-2-hydroxy compound (438) and corresponding diacetate (439), the corresponding 16-hydroxy and acetoxy compounds (440) and (441), and two corresponding epoxide hydrolysed compounds, triacetate (442) and tetraacetate (443).[278]

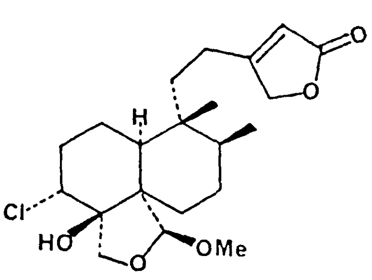
Genus - Gochnata. G. paniculata is the only species of this genus yielding clerodanes, giving six C_{11}-C_{16} open chain trans compounds with either an acetoxy or benzyloxy substituent at C_{17}, hydroxy-aldehyde (444), the corresponding benzyl diol (445), the two C_{13}-C_{14} dehydro acids (446) and (447), and two C_4-C_6 γ-lactones, alcohol (448) and acid (449), all assigned by high field nmr.[279]

Genus - Chromolaena. C. laevigata has been shown to yield four Z-olefin derivatives of kolavenic acid (51), 6,7-diacetoxy (450), the corresponding 6-angeloyloxy and isobutyloxy compounds (451) and (452), and the 2-oxo diol (453), along with a 7-angeloyloxy-6-isobutyloxy derivative of populifolic acid (39), (454).[280]

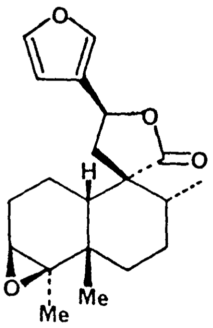
Genus - Gutierrezia. G. dracunculoides has been shown to yield the cis ent-neo-clerodane gutierolide (455), a 12-butenolide acetal compound with a novel 3-chloro substituent. No chloride ion was used during the isolation of this product, nor could any equivalent epoxide compounds be isolated.[281]

Genus - Macowania. M. glandulosa has been shown to produce (456), a cis ent-neo isomer of populifolic acid (39), as the only isolated clerodane natural product from this genus.[282]

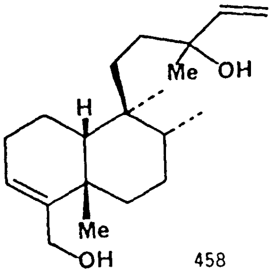
Genus - Chiliotrichium. C. rosmarinifolium has been shown to produce chiliomarin (457), a cis neo-clerodane with a C_3-C_4 epoxide and a furyl substituted C_9 spiro γ-lactone substituent.[283]


H
Cl
HO
O
OMe
O
O

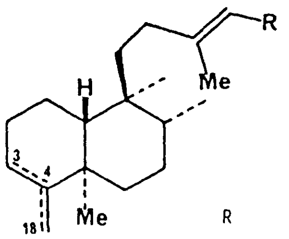
455



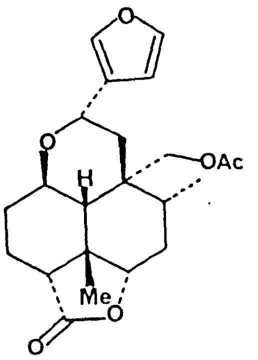
457



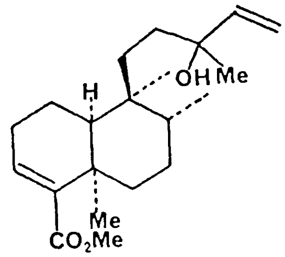
458


R
H
Me
3
4
18
Me

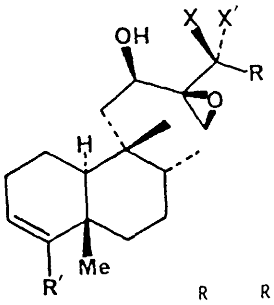
	R	3-4	4-18
303	CO_2Me	Double	Single
459	CO_2Me	Single	Double
460	CH_2OH	Single	Double


O
O
H
OAc
Me
O
O

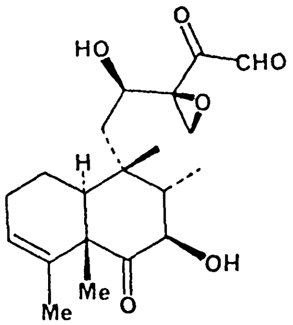
461


H
OH Me
Me
CO₂Me

462


OH
X
X′
R
O
H
R′
Me

	R	R'	X	X'
463	CH_2OH	CHO	OH	H
464	CH_2OH	CH_2OH	OH	H
465	CH_2OH	CH_2OH	H	OH
466	CHO	CHO	=O	


O
HO
CHO
O
H
OH
Me
Me
O

467

3.16. Family Alismaceae.

Genus - Sagittaria. S. sagittifolia is the only monocotyledonous (class Liliopsida) species shown to produce clerodanes, giving the cis 18-hydroxy epimer of kolavelool (48), sagittariol (458), assigned cis by ^{13}C nmr comparison with other clerodanes.[284]

3.17. Family Araucariaceae.

Genus - Araucaria. The only genus of the gymnosperms shown to produce clerodanes, A. bidwilli gives the known compound methyl kolavenate (303), previously shown in the Solidago genus (Compositae), and the C_4-C_{18} dehydro isomer (459),[285,286] whilst A. hunsteinii yields the corresponding alcohol (460).[287]

3.18. Family Jungermanniineae.

These are the liverworts, with two genera shown to yield clerodanes.

Genus - Gymnocolea. G. inflata yields the cis compound gymnocolin (461), with a novel C_1-C_9 fused tetrahydropyran ring giving a tetracyclic structure.[288]

Genus - Scapania. S. bolanderi yields an 18-oxidised form of kolavelool (48), (462), though with no assignement of stereochemistry.[289]

3.19. Order Moniliales.

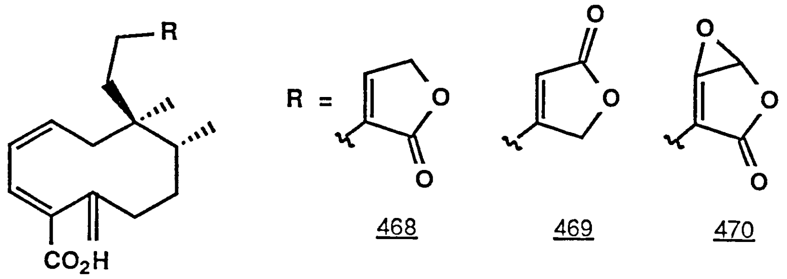
Genus - Oidiodendron. O. truncatum is the only member of the fungi to give clerodane natural products, yielding four trans compounds (463), (464), (465) and clerocidin (466), all containing a novel 12,14,15-oxidised, 13-14-epoxide substituent at C_9.[290,291]

3.20. Family Actinomyces.

Genus - Kitasatosporia. This genus of bacteria has been shown to yield terpentecin (467), a 6-oxo isomeric form of clerocidin (466) from Oidiodendron truncatum (Moniliales), from the MF-730-N6 strain of actinomyces.[292,293]

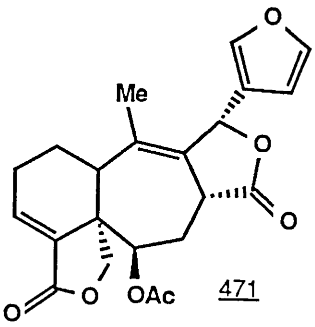
4. Clerodane Derived Diterpenes.

Several examples of diterpenes apparently related to the clerodanes have also been isolated. Some may arise by seperate biosynthetic routes, but in two cases these related compounds have been found in the same species as clerodane natural products. Pulicaria angustifolia (Compositae), already shown to produce (437), yields a series of diterpenes with the decalin system opened to give a 5-exo methylene carbocyclic system as in structures (468)-(470).[294]



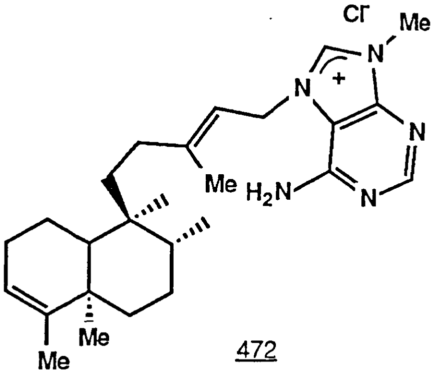
468 469 470

The Salvia genus (Labiatae) has been shown to produce several clerodanes (235-250), and S. fulgens produces the ring expanded compound salvigenolide (471).[295]



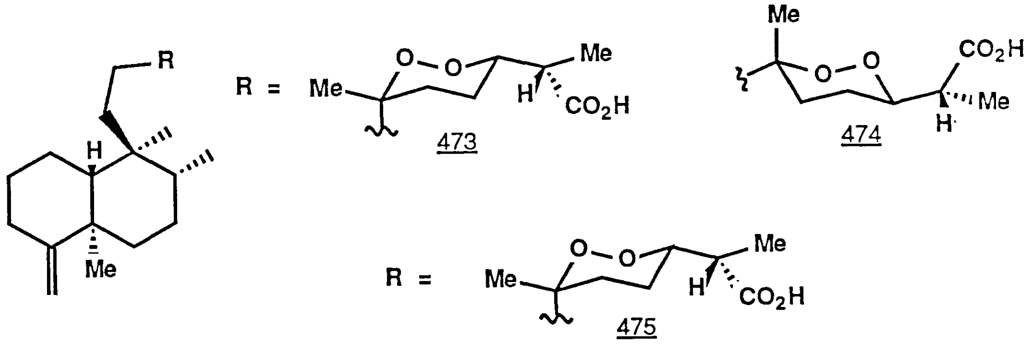
471

Several sea sponges have been shown to produce novel clerodane related compounds. The Agelas sponges produce agelasin B (472), containing a heterocyclic C_{15} substituent, shown to be an inhibitor of sodium and potassium ATP-ases.[296]



472

Sigmosceptrella laevis has been shown to produce the ichthyotoxic compounds sigmosceptrellins A (473),[297] B (474), and C (475), all containing a novel peroxide linkage.[298]

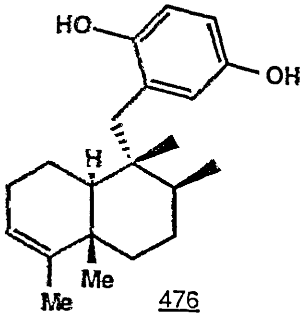


473

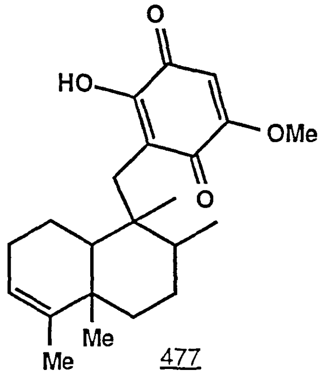
474

475

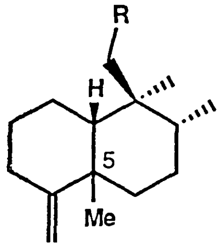
Other sea sponges have been shown to produce quinone, or hydroquinone substituted decalin systems with the clerodane structure. Averol (476) has been isolated from Disidia avara,[299] whilst the stereochemically unassigned quinone isospongiaquinone (477) has been found in Stelospongia conulata.[300] Hippiospongia metachromia yields the quinone ilimaquinone (478), isomeric with (477),[301] whilst the cis derivatives arenarol (479) and arenarone (480) have been found in the pacific sponge Dysidea arenaria.[302] Finally, palauolide (481) has been isolated from an unidentified sponge source.[303]



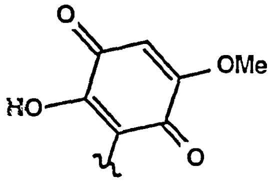
476

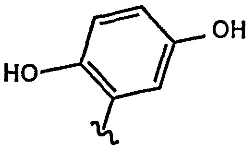

O
HO
OMe
O
Me
Me

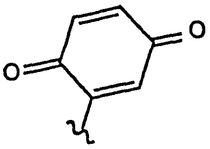
477



R =



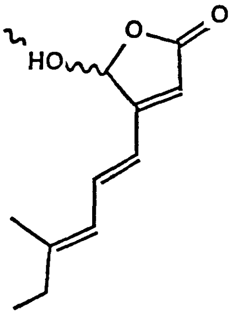




C_5 - Me = β α α

478 479 480

R =



C_5 - Me = β

481

5. Biological Activity.

Only forty-four of the clerodanes listed in section 3 have been shown to exhibit any biological activity. Although apparently a small number, only a further four compounds hace been reported as having no activity in the tests carried out, thus leaving the large majority as simply untested or unreported.

The clerodanes are best known for their insect antifeedant properties, and related insecticidal properties, with emphasis placed on the safety aspects of natural insect antifeedants in relation to mammalian and piscial life.[304,305] All of the compounds isolated from the Clerodendron and Caryopteris genera (Verbenaceae) (2,98-107) have proved active against certain plant pests, notably the tobacco cut worm (Spodoptera litura) and the african army worm (Spodoptera exempta), but not effective as general antifeedants.[72,73,306,307] Of the compounds obtained from the Ajuga genus (Labiatae), ajugarins I-III (112-114) showed antifeedant activity towards the african army worm and african desert locust (Schistocerea gregaria)[308] whilst ajugarin IV (115) has been shown to act as an insecticide against Bombyx mori,[88] though ajugarin V (116) appears inactive.[308,309] The ivains I-IV (122-125) have demonstrated antifeedant activity in a crude mixture form,[98] whilst ajugareptansin (119), ajugapitin (126), dihydroajugapitin (127) and 2-acetylivain I (130) have all shown activity against the egyptian cotton leafworm (Spodoptera litteralis), along with purified fractions of the ivains I-IV.[310] Ajugareptansone A (120), however, proved inactive in the same study. Finally, four compounds from the Teucrium genus (Labiatae) have shown antifeedant activity, tafricanins A and B (224,225) against Locusta migratoria,[179] montanin F (175) against Prodenia litura,[147] and 6,19-diacetylteumassilin (183), shown by our studies to be active against Spodoptera litteralis.

Antiviral and antitumour properties have been demonstrated by a crude extract of Baccharis tricuneata (Compositae) containing bacchotricuneatins A-D (343-346),[237] whilst antibiotic and antitumour properties have been reported for terpentecin (467) from Kitasatosporia MF-730-N6 (Actinomyces),[292,293] and clerocidin (466) from Oidiodendron truncatum (Moniliales) has shown antibiotic potential.[290,291] Kolavenic acid (51), isolated from several sources, has been reported as antimicrobial,[212,213] whilst teucvin (81), isolated from the Teucrium (Labiatae) and Mallotus (Euphorbiaceae) genera, has been shown to be amoebocidal, and act as a root development inhibitor,[127] though showing no antitumour potential, also the case with the related teucvidin (67).[311]

The plaunols B-E (60-63), isolated from the Thai folk drug Plau-noi Croton sublyratus (Euphorbiaceae) have all shown antipeptic ulcer properties,[35] though plaunol A (59) shows no activity.[36] Divinorin A (salvinorin, 244), from the hallucinogenic mexican mint Salvia divinorum (Labiatae), has shown psychotropic activity.[188] Finally, solidagolactones IV-VI and VIII (293-295, 297) from various Solidago species (Compositae) are the only cis compounds with reported activity, as piscicidal agents.[219,312]

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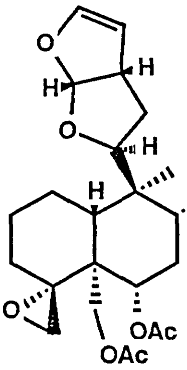
RESULTS AND DISCUSSION.

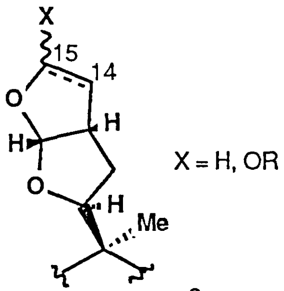
1. Approaches to the Clerodin bis-Hydrofuranyl Unit.

1.1. Introduction.

Clerodin (1), and related clerodanes isolated from the Verbenaceae family,[1] share a common bis-hydrofuranyl unit, varying only in oxidation level at the C_{14} and C_{15} positions, as shown in (2).‡



1



2

Two synthetic approaches have appeared in the literature towards this bis-furanyl arrangement. Kojima and Kato[2] have developed a method *via* the attack of a 3-furanyl organometallic reagent on an epoxide system (3), followed by treatment sequentially with bromine in methanol in the presence of potassium acetate, hydrogenation over Raney nickel, and treatment with perchloric acid, to yield a diastereomeric mixture of hemiacetals (5) in high yield (scheme 1).

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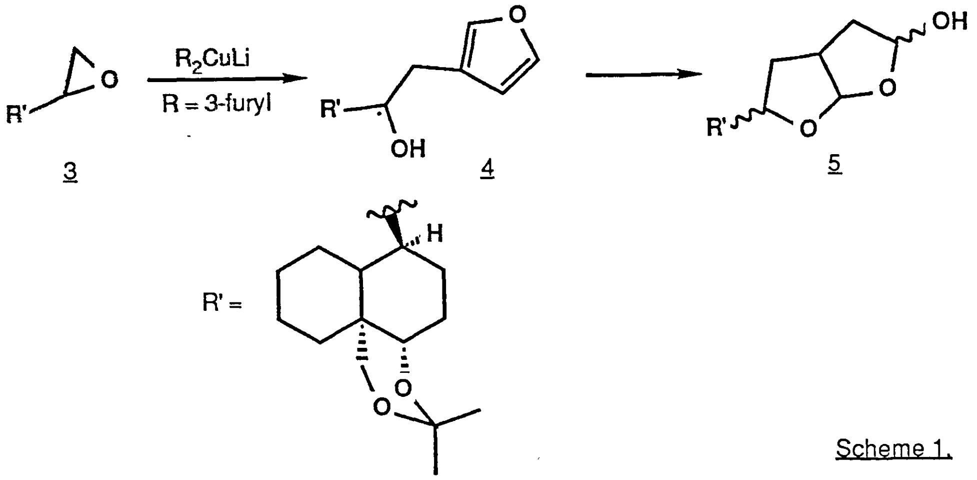
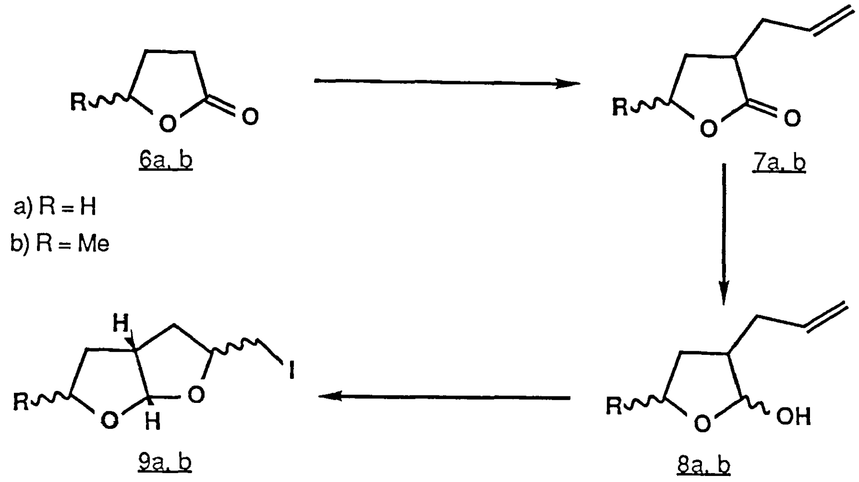
‡Throughout this results and discussion section the numbering of decalin systems corresponds to that of the clerodane skeleton, as shown in the review section (structure 1). In the experimental section, the correct IUPAC numbering system is deployed. Also, all structures shown represent racemates, with the enantiomer bearing a direct relationship to the natural compounds shown for convenience, apart from those structures representing natural compounds, and those in section 3.2. 'Approaches to Chiral 5-(3'-Furyl)butyrolactone.'



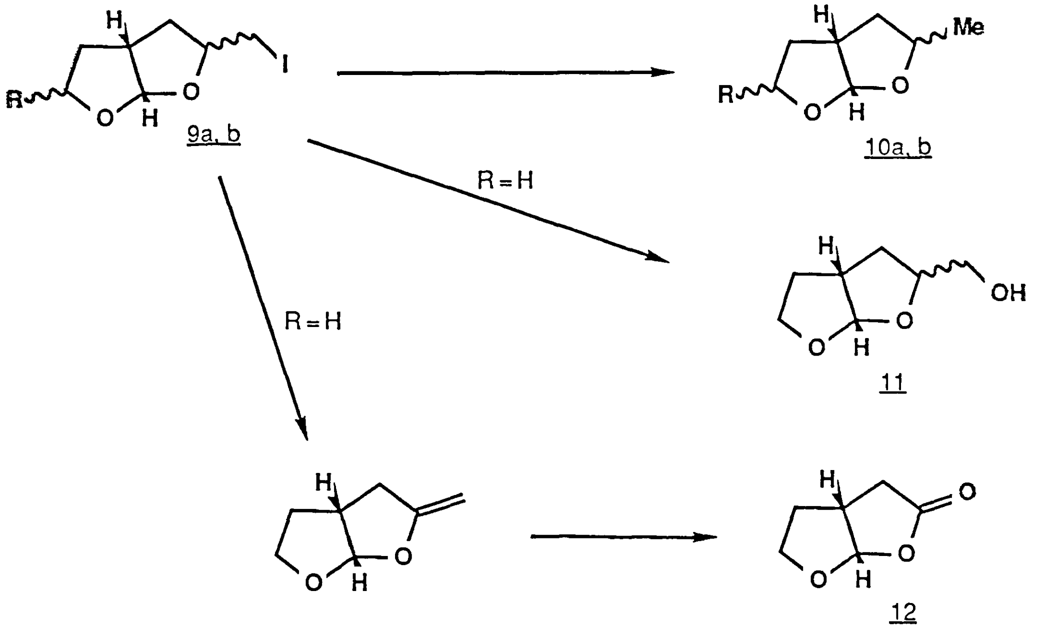
Scheme 1.

Lallemand[3] used an iodolactonisation approach to bis-furanyl derivatives starting from γ-lactone substrates (6a) and (6b). Standard alkylation techniques gave the allyl lactones (7a), (7b), and reduction with di-isobutylaluminium hydride (DIBAL) gave the corresponding hemiacetals (8a), (8b). These hemiacetals were cyclised without further purification in 60% yield with iodine and solid sodium bicarbonate in acetonitrile to yield iodides (9a) and (9b) (scheme 2).



Scheme 2.

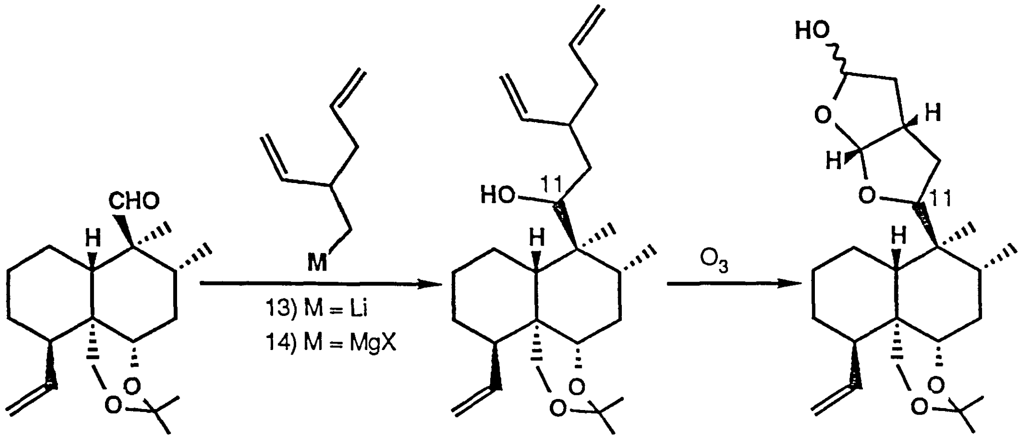
In the case of (9a) (R=H), two isomers were produced, whose ratio could only be improved to 75 : 25 by modification of the reaction conditions both by lowering the reaction temperature and increasing the reaction times. Spectroscopic studies established the major isomer as the compound with a trans relationship between the iodomethyl substituent and the tetrahydrofuranyl ring. Transformations of (9a) to the corresponding de-iodo compound (10a), alcohol (11), and oxo compound (12) were also reported, along with the formation of a mixture of three isomers of (10b) from the corresponding (9b) (scheme 3).



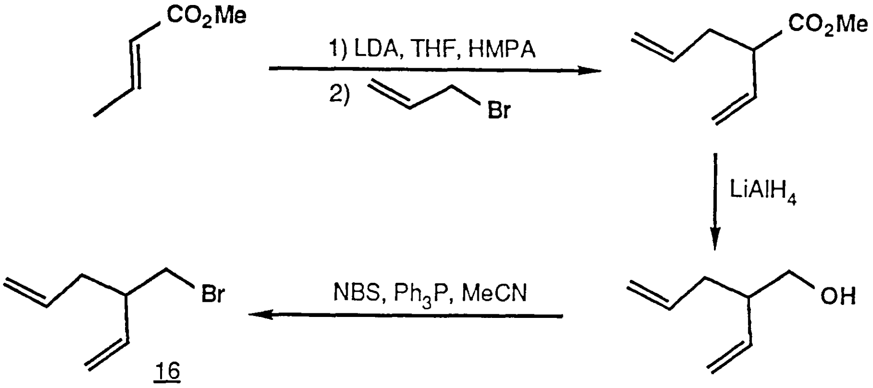
Scheme 3.

1.2. Synthetic Approaches.

In the studies towards the synthesis of ajugarin 1, we had prepared the aldehyde intermediate (13),[4] and hoped that attack by an organometallic species such as (14) or (15), followed by subsequent ozonolysis may lead to the desired bis-furanyl system (scheme 4). Although the formation of the required isomer at C_{11} could not be guaranteed by this reaction, the simplicity of this approach was attractive. The bromide (16) was prepared readily from methyl crotonate in 65% overall yield, as in scheme 5.


CHO
H
M
13) M = Li
14) M = MgX
HO
11
H
O
O
O_3
HO
O
H
H
O
11
H
O
O

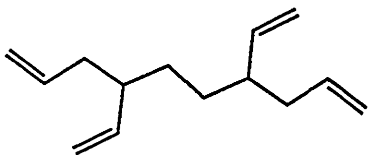
Scheme 4.


CO_2Me
1) LDA, THF, HMPA
2)
Br
CO_2Me
$LiAlH_4$
Br
NBS, Ph_3P, MeCN
OH

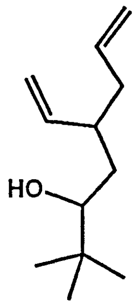
16

Scheme 5.

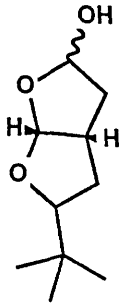
However, extensive attempts to form the Grignard or lithio species from this bromide were disappointing. Using a lithium dispersion, only the coupled dimeric species (17) was detected, whilst at reflux with freshly cleaned dry magnesium in THF with trimethylacetaldehyde, the reaction gave a small amount of the required adduct (18), although compound (19) could not be isolated upon subsequent ozonolysis.



17

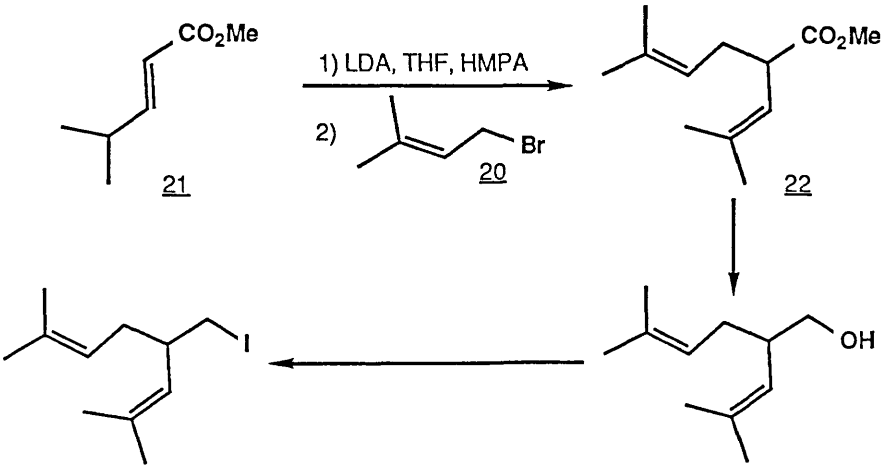


18



19

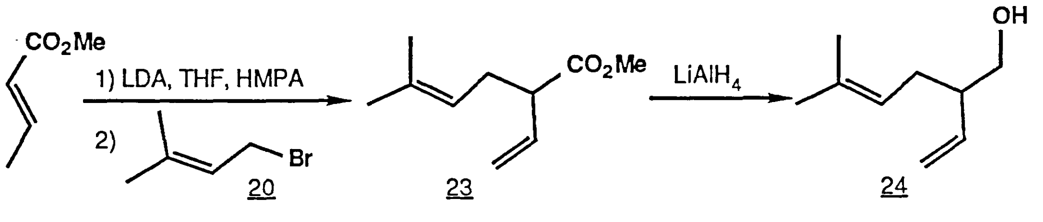
In order to overcome these early problems, we felt that two separate modifications of the original idea would be beneficial. Firstly, the use of 3,3-dimethylallyl bromide (20) and methyl 4-methyl-pent-2-enoate (21) should lead, after subsequent modification, to a halide diene with dimethyl substituted alkenes, and thus would undoubtedly facilitate the final ozonolytic cleavage of the process. Secondly, the use of iodide rather than the bromide was also proposed, in the hope that the formation of the corresponding organometallic species would be more facile, thus allowing for milder reaction conditions, and hopefully suppressing any Wurtz coupling side reaction (scheme 6).



Scheme 6.

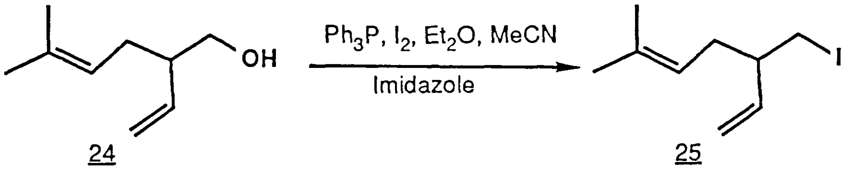
However, treatment of ester (21) with standard lithium di-isopropylamide (LDA) deprotonation conditions, followed by bromide

(20), did not yield the desired ester (22), but rather gave an unidentifiable adduct apparently from reaction between the ester and di-isopropylamine, possibly by conjugate addition. When potassium di-isopropylamide (KDA), a less nucleophilic base than LDA, was used to effect the deprotonation, no product of alkylation of the ester anion with the bromide could be detected. The mixture contained only starting ester and a small amount of the corresponding pent-3-enoate, indicating that the desired deprotonation had occurred to some extent, but that steric crowding was possibly preventing any quenching of the anion by the bromide. It was therefore decided to use the bromide (20) with the less sterically demanding crotonate ester. Treatment of methyl crotonate with LDA, followed by bromide (20), smoothly led to the desired ester (23) in good yield. Subsequent reduction with lithium aluminium hydride gave the required alcohol (24) (scheme 7).



Scheme 7.

Treatment of the alcohol with iodine, triphenyl phosphine, and imidazole in ether/acetonitrile (3 : 1)[5] gave the iodide (25) in 64% yield (scheme 8).

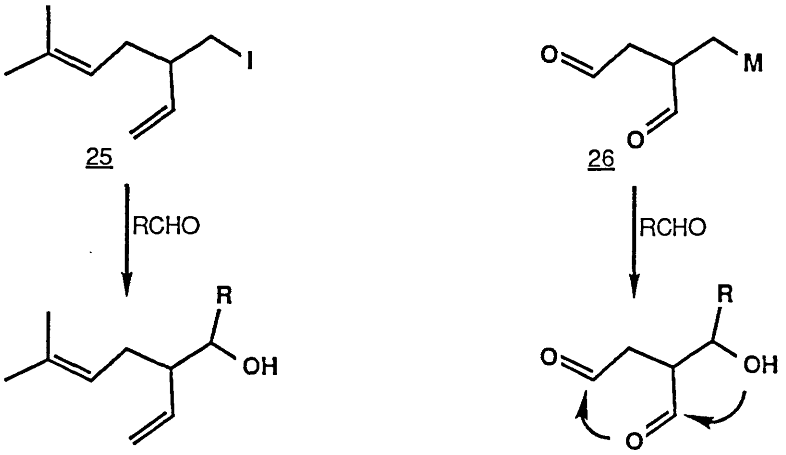


Scheme 8.

However, repeated attempts to form either the Grignard reagent or the lithio species from the iodide (25), with conditions including

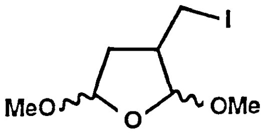
Mg/Et$_2$O, Mg/THF/reflux, Mg/THF/ultrasound, tBuLi/THF, Li dispersion/Et$_2$O, all led to no reaction, or to the formation of only small amounts of the organometallic species, which could not be trapped, either by dimethylacetaldehyde or adamantylaldehyde.

At this point, it was felt a different approach to the bis-hydrofuranyl system was needed. The previous approach had been based on an equivalent for a di-aldehyde (26), capable of being used in addition reactions into carbonyl systems (scheme 9).



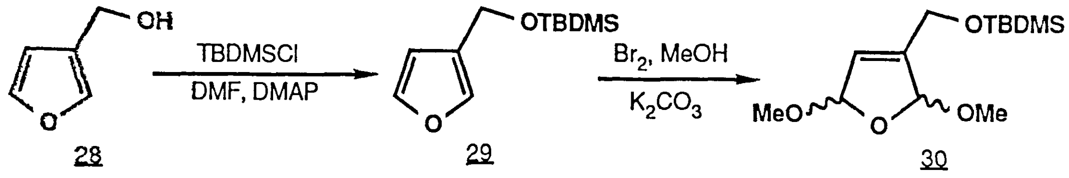
Scheme 9.

An alternative equivalent for the di-aldehyde was therefore considered, this being the iodo diacetal compound (27).



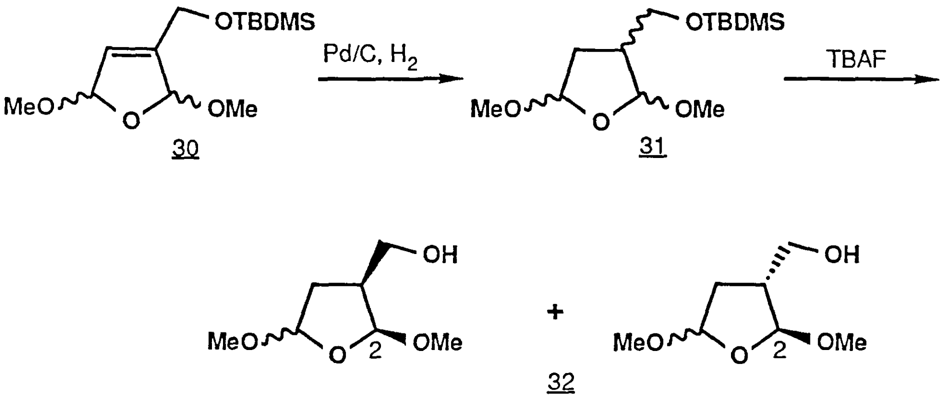
27

The synthesis of this compound was envisaged as starting from the readily available 3-furanmethanol (28). Thus, treatment of the alcohol (28) with t-butyldimethylsilyl chloride cleanly led to the protected species (29), which was treated with methanol and bromine, in the presence of potassium carbonate, by the method of Levisalle,[6] to yield the dihydrofuran (30) (scheme 10).


OH
TBDMSCl
DMF, DMAP
OTBDMS
Br_2, MeOH
K_2CO_3
OTBDMS
MeO
OMe
O
28
29
30

Scheme 10.

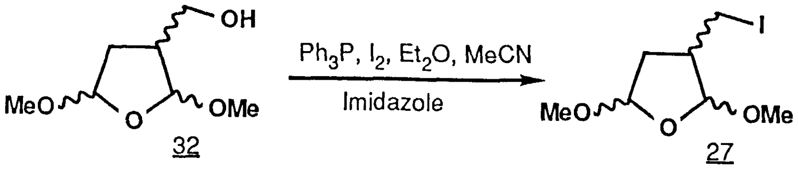
Hydrogenation of (30) over palladium on carbon proceeded smoothly in high yield on a small scale, to give the corresponding tetrahydrofuran (31) as the expected mixture of diastereoisomers. Any attempt to increase the scale of this reaction, however, led to problems, with concurrent removal of the protecting group and loss of material. Deprotection of (31) with tetrabutylammonium fluoride (TBAF) gave the corresponding alcohol (32) as two separable diastereoisomers in good yield, as a 1.3 : 1 ratio of compounds, tentatively assigned as those compounds with cis and trans relationships respectively of the hydroxymethyl and 2-methoxy substituents (scheme 11).


OTBDMS
MeO
OMe
O
30
Pd/C, H_2
OTBDMS
31
TBAF
OH
2
+
32

C_2- H nmr data δ 5.02, d, J 5.0 Hz δ 5.05, d, J 2.0 Hz

Scheme 11.

Subsequent formation of the iodide (27) by the previously shown method proceeded smoothly and in good yield (scheme 12).



32

27

Scheme 12.

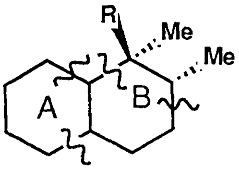
Once again, however, attempts to form the organometallic species from this iodide gave no success. This was considered due to the highly oxygenated nature of the substrate, thus leading to complexation problems and no formation of the organometallic species.

It was therefore decided to temporarily abandon this problem, and concentrate our efforts on the synthesis of clerodane natural products typified by those isolated from the Teucrium genus (Labiatae).

2. Diels-Alder Approaches to Clerodane Natural Products.

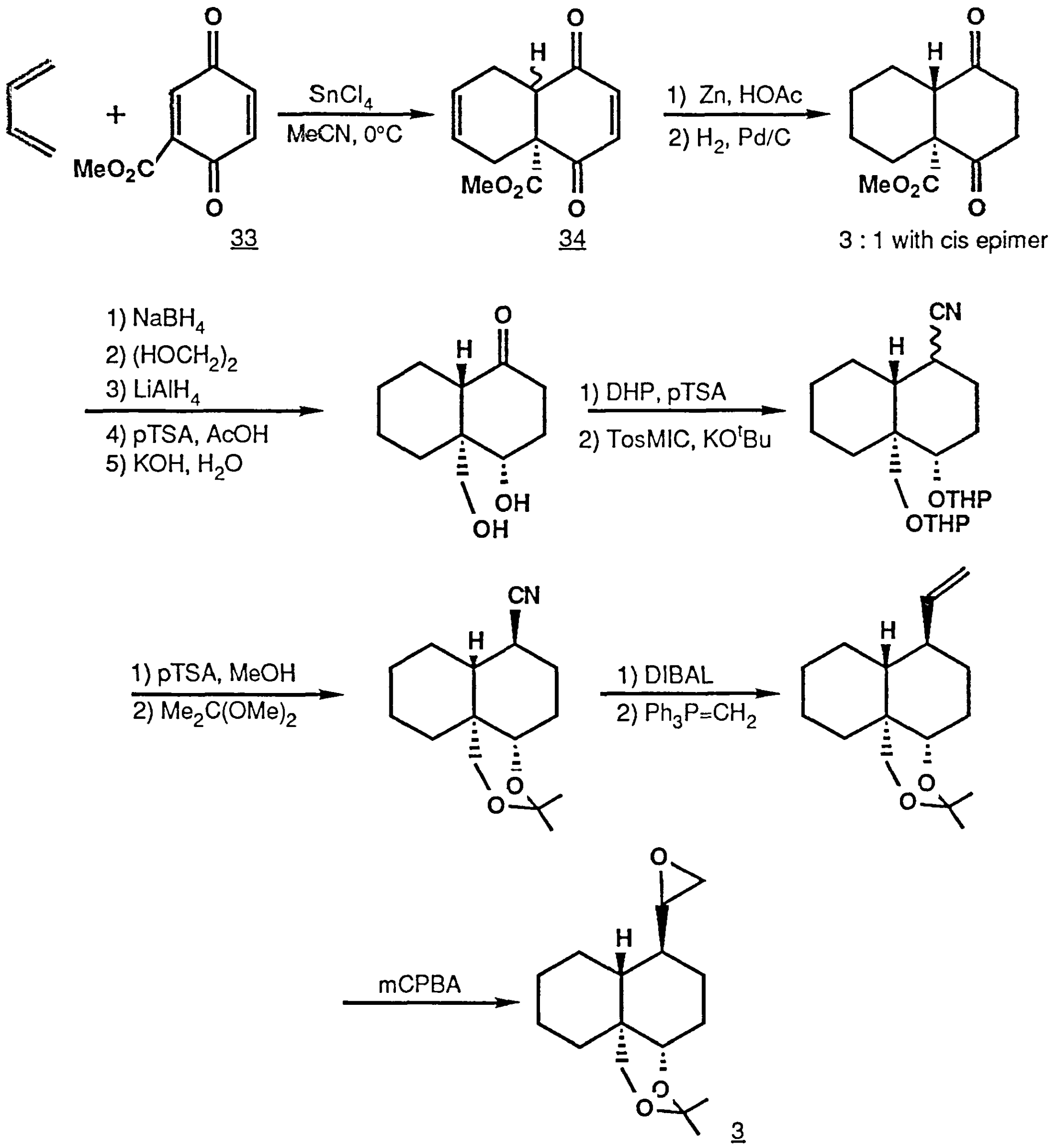
2.1. Introduction.

The Diels-Alder reaction has been used in syntheses of clerodane diterpenes, either to construct the C_1-C_4 ring of the decalin system as shown in disection A (scheme 13) , or to introduce the C_8-C_9 functionality as shown in disection B of scheme 13.



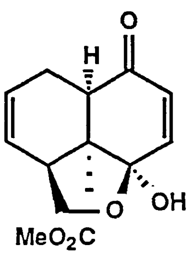
Scheme 13.

The construction of the decalin unit (disection A) was used both by Kato[7] and Goldsmith.[8] Kato, in the preparation of the epoxide (3), used in his studies of structure-activity relationships of the bis-tetrahydrofuranyl units already detailed in section 1.1, used the reaction between butadiene and a benzoquinone (33), catalysed by tin tetrachloride, to form the bicyclic system (34), with subsequent modification to yield the model decalin unit (3) (scheme 14).

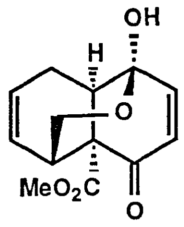

33
SnCl$_4$
MeCN, 0°C
34
1) Zn, HOAc
2) H$_2$, Pd/C
3 : 1 with cis epimer
1) NaBH$_4$
2) (HOCH$_2$)$_2$
3) LiAlH$_4$
4) pTSA, AcOH
5) KOH, H$_2$O
1) DHP, pTSA
2) TosMIC, KO^{t}Bu
1) pTSA, MeOH
2) Me$_2$C(OMe)$_2$
1) DIBAL
2) Ph$_3$P=CH$_2$
mCPBA
3

Scheme 14.

Goldsmith used a similar Diels-Alder approach between benzoquinone (33) and 1-hydroxymethylbutadiene to give the isomeric hemiacetals (35) and (36).

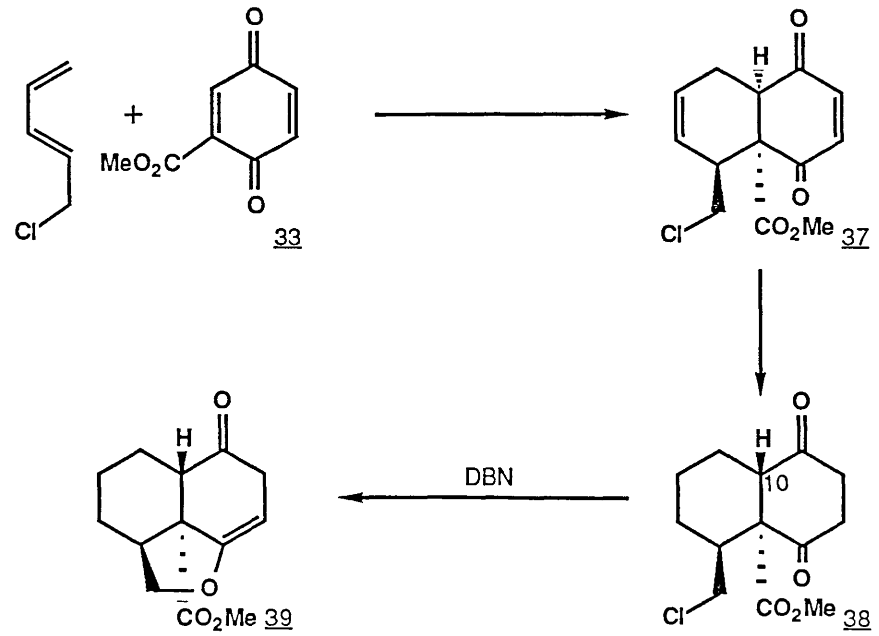


35



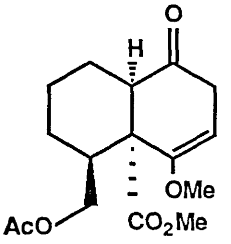
36

Problems with the opening of the hemiacetal functionality in both (35) and (36) led Goldsmith to divert his attention to the corresponding 1-chloromethylbutadiene adduct (37). Reduction of (37) occurred with concomitant epimerisation at C_{10} to give the chloro compound (38). However, treatment with 1,5-diazabicyclo[4,3,0]non-5-ene (DBN) did not lead to the desired exo-methylene compound, but gave exclusively the enol ether (39) (scheme 15).



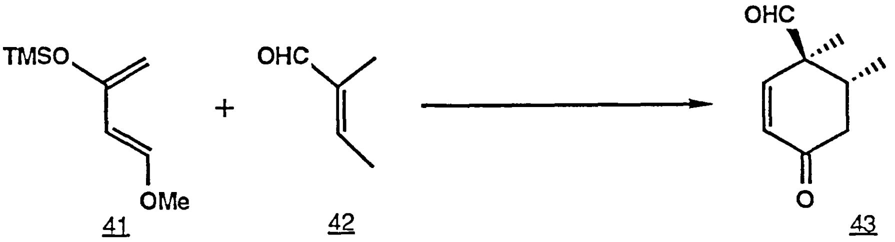
Scheme 15.

On returning to his original route, Goldsmith finally succeeded in converting the trans isomer of hemiacetal (35) into a cis decalin (40), involving Zn/AcOH reduction as a key step. Further work included the introduction of a C_8 methyl group, and conditions for cis trans epimerisation, but this approach now appears, not too surprisingly, to have been abandoned.



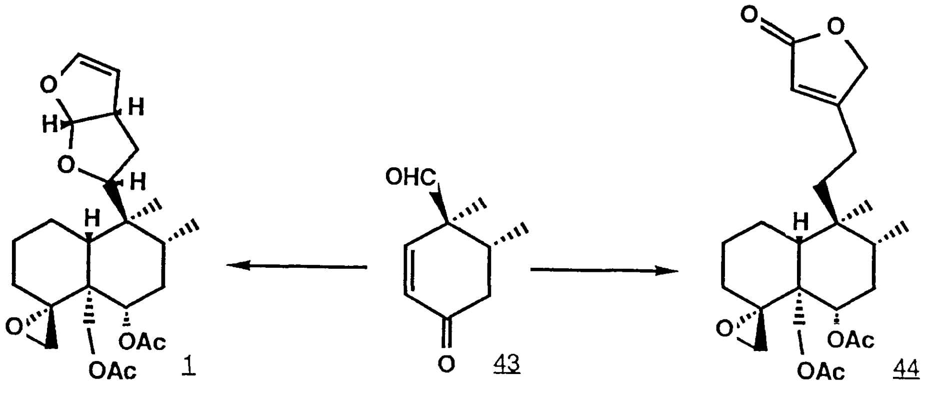
40

The construction of the substitution pattern at C_7-C_8 by a cycloaddition reaction between 1-methoxy-3-trimethylsilyloxybutadiene (Danishefsky's diene) (41)[10] and tiglic aldehyde (42) to yield the cyclohexenone (43) was used as the first stage of the total synthesis of ajugarin 1 by Ley[9] (scheme 16).



Scheme 16.

Cyclohexenone (43) contained the required dimethyl substitution, and allowed for the introduction of the second ring of the decalin by cuprate addition to the enone system, sterically controlled by a bulky dithiolane unit. The aldehyde group served as a site of introduction for the C_{11}-C_{16} unit of ajugarin 1 (44), and also for alternative clerodane side chains, notably that of clerodin (1) (see section 1.2) (scheme 17).

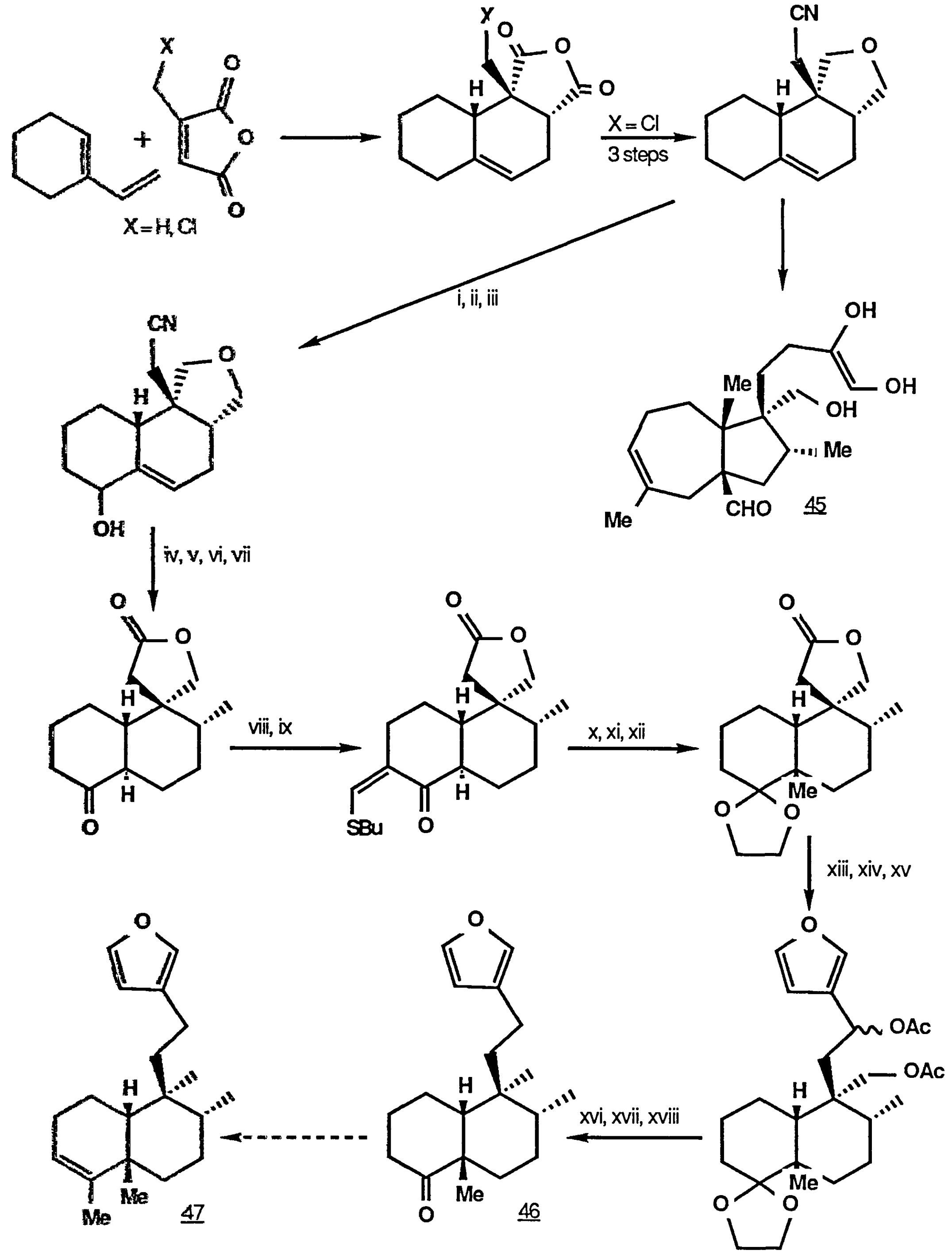


Scheme 17.

Tokoroyama[11] used a Diels-Alder addition between 1-vinylcyclohexene and substituted maleic anhydrides to yield intermediates for clerodane syntheses. The adduct from chloromethylmaleic anhydride has subsequently been transformed both into the unusual perhydroazulenoid portulal (45)[12] and into a key intermediate (46) for the synthesis of the cis clerodane (47),[13] though by a long, multistep process (scheme 18).

2.2. A New Approach.

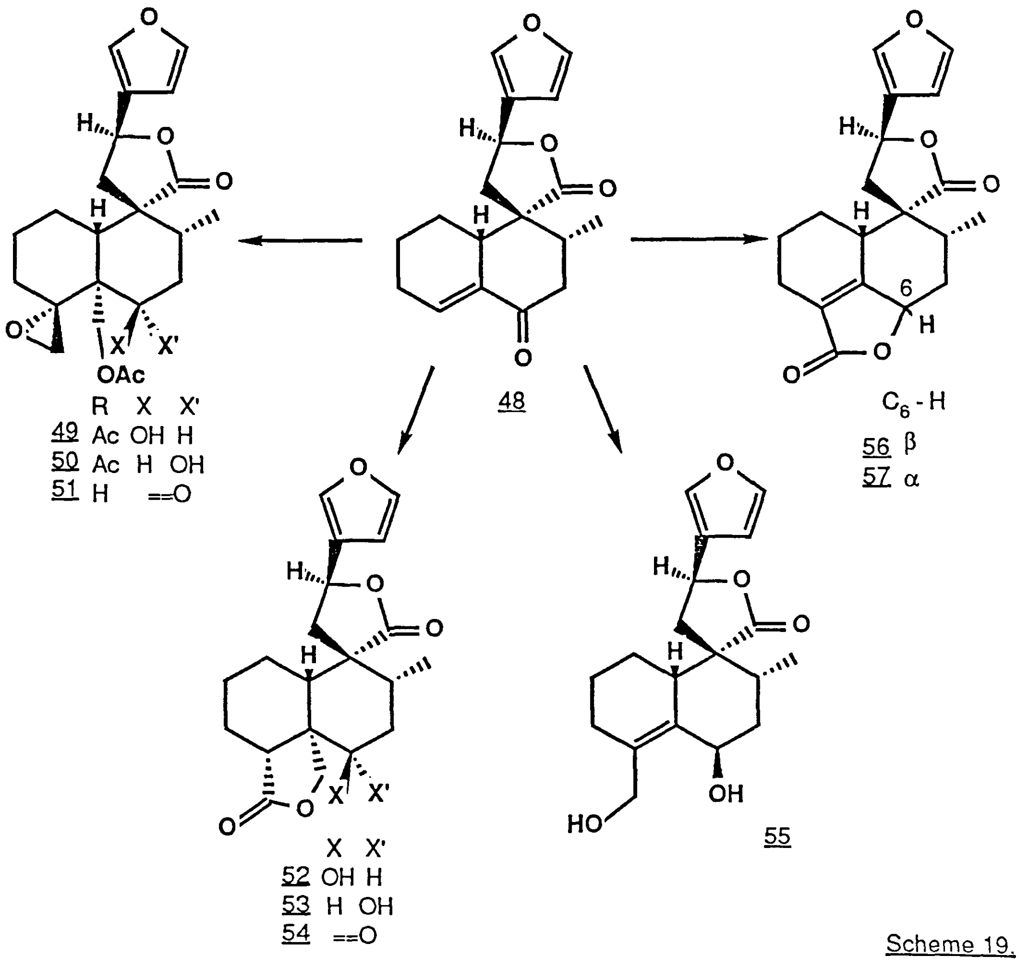
We felt that the Diels-Alder strategy to the clerodane system could be improved to give much more versatile and chemically advanced structures than previous attempts. The construction of the decalin ring via bonds C_7-C_8 and C_9-C_{10} (disection B, scheme 13) appealed to us, because of its ability to introduce the C_8-methyl and C_9-substituents in a stereoselective manner. However, unlike the approach of Tokoroyama, suitable choice of a substituted diene, and of a dienophile already containing substituent arrangements allowing for facile further transformations, would lead to a short, more convergent, synthetic approach to clerodane natural products. The


X
X=H, Cl
X=Cl
3 steps
CN
i, ii, iii
OH
45
iv, v, vi, vii
viii, ix
SBu
x, xi, xii
xiii, xiv, xv
OAc
OAc
xvi, xvii, xviii
46
47
Me

i. SeO_2 ii. AcOH iii. OH^- iv. MnO_2 v. H_2, Pd vi. HI, AcOH vii. Zn, AcOH
viii. HCO_2Et, Na ix. n-BuSH x. MeI, ${}^tBuOK$ xi. KOH xii. $(HOCH_2)_2$ xiii. 3-furyl-Li
xiv. Red^n xv. Ac_2O, py. xvi. Li, NH_3 xvii. CrO_3, py. xviii. Huang-Minlon

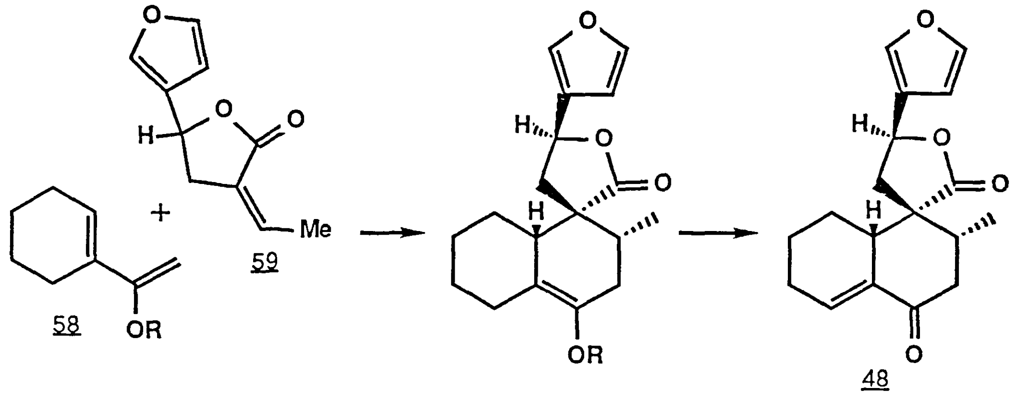
Scheme 18.

teucrium clerodanes[14] were chosen as our initial targets, as these provided a wide range of structural features within the decalin portion, but contain a common spiro 5-(3'-furyl)-γ-lactone unit. The enone (48) was designed as a pivotal intermediate which could lead to several compounds, notably teucjaponins A and B (49 and 50),[15] gnaphalin (51),[16] teuchamaedryn B (52),[17] teucrin E (53),[18] 6-keto-teuscordin (54),[19] montanin B (55),[20] teucvin (56),[15] and teuflin (57)[21] (scheme 19).



Scheme 19.

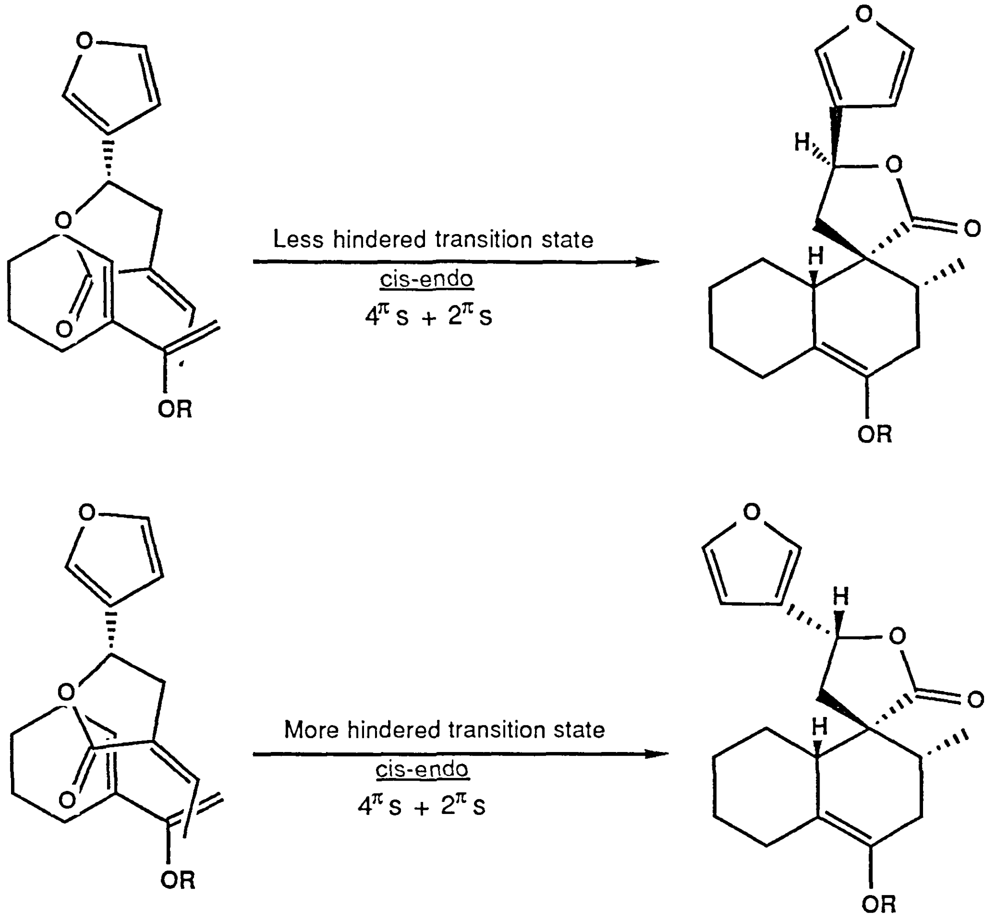
In principle, the enone (48) could be readily obtained in a short synthetic sequence (scheme 20), starting from a simple substituted vinylcyclohexene (58) and a dienophile (59), already containing the required furyl-lactone arrangement.



Scheme 20.

It was hoped that the proposed Diels-Alder would control both the regiochemistry of addition, and the relative stereochemistry at three centres, C_9, C_{10}, and C_{12}. The presence of the electron donating oxygen on the diene, and the electron withdrawing effect of the lactone of the dienophile should assure the desired regiochemistry of addition. If a cis-endo transition state was to occur in the addition, then the required stereochemical arrangement between C_9 and C_{10} would be achieved, leading to two possible adducts (60) and (61). However, steric interaction between the furan ring and the incoming diene should disfavour the adduct (61), leading to the desired diastereoisomer (60) (scheme 21, only one enantiomer of the lactone shown for clarity).

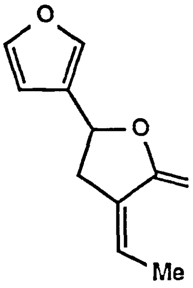
Furthermore, this steric effect of the furan ring on the outcome of the cycloaddition reaction was important, as an enantiospecific synthesis of intermediate (48) might be possible by use of the relevant (S)-lactone in an optically pure form.


Less hindered transition state
cis-endo
$4^{\pi}s + 2^{\pi}s$
More hindered transition state
cis-endo
$4^{\pi}s + 2^{\pi}s$
O
H
OR

Scheme 21.

2.3. Model Dienophiles.

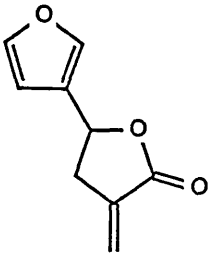
The required furano-dienophile for the proposed synthetic route above was compound (59).



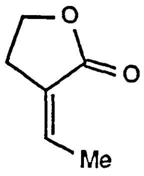
59

Three potential problems concerned us in the use of this dienophile. Firstly, the stability of the furan ring, both to the conditions required for the Diels-Alder reaction, and particularly to subsequent reagents proposed for the later transformations, was an unknown quantity. Secondly, the steric requirement of the bulky trisubstituted olefin in the Diels-Alder reaction was a natural concern, since forcing conditions for the cycloaddition could cause other problems. Finally, the need to introduce the ethylidene group into the molecule in a stereospecific manner, yielding only the required _Z_-isomer, could also be problematical. Many methods have been reported for the introduction of a methylene group in the α position of γ-lactones,[22] however the introduction of an ethylidene grouping normally yields the _E_-isomer, due to steric interaction between the methyl group and the carbonyl oxygen.

For these reasons, we initially chose to study two model dienophiles. The first of these was the α-methylene-γ-furyl-γ-lactone (62) which would provide stability information, and indicate the ease of the cycloaddition and the relative stereochemical outcome. Secondly, the introduction of an ethylidene unit onto γ-butyrolactone would provide a suitable model system (63) to investigate the stereochemical outcome of such a reaction, and also yield a trisubstituted dienophile substrate for assessment of steric inhibition factors in the cycloaddition reaction.

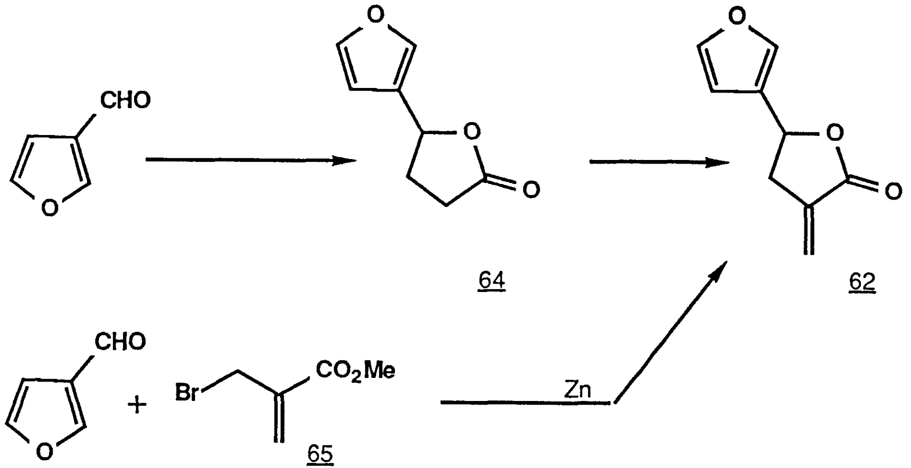


62



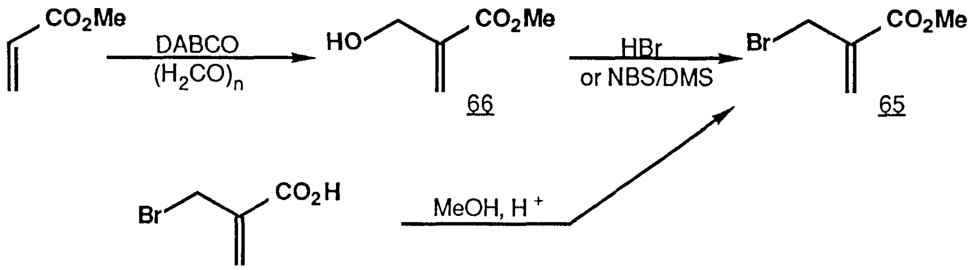
63

For the preparation of the furyl lactone (62), it was felt that although a synthetic route _via_ the lactone (64) would be most useful when compared to the real system, a much simpler route was possible _via_ the methods of Schmidt,[23] using a Reformatsky style process, as shown in scheme 22.



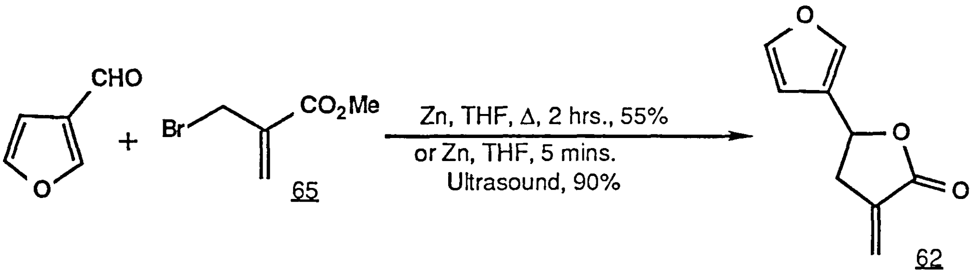
Scheme 22.

Initially, methyl α-bromomethylacrylate (65) was prepared from methyl acrylate in a two step process. This involved treatment of the acrylate with excess paraformaldehyde in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO),[24] followed by bromination of the product hydroxymethylacrylate (66) either by treatment with aqueous 48% hydrobromic acid in the presence of sulphuric acid, or by treatment with an N-bromosuccinamide dimethylsulphide complex.[25] However, although both these processes could be carried out on a large scale, neither were completely satisfactory, as the bromination step achieved only a 25% conversion using either route. Later preparation of the required bromomethyl acrylate was carried out by simple esterification of the commercially available acid, in 85% yield (scheme 23).[26]



Scheme 23.

Treatment of a mixture of the acrylate (65) with furan-3-carboxaldehyde in the presence of zinc in THF at reflux initially gave no reaction. However, the use of freshly acid washed zinc powder led to the required adduct (62) in a respectable 55% yield after two hours. Although satisfactory, we felt that an improvement in this yield was possible. The use of ultrasound in organometallic reactions has been well documented,[27] and has found considerable application within our laboratories.[28] Thus, a mixture of the acrylate (65) and furan-3-carboxaldehyde over freshly acid washed zinc in THF was subjected to sonication. After only two minutes, conversion to the desired adduct had occured, to yield, after purification, 90% of the required furyl lactone (62) (scheme 24).



Scheme 24.

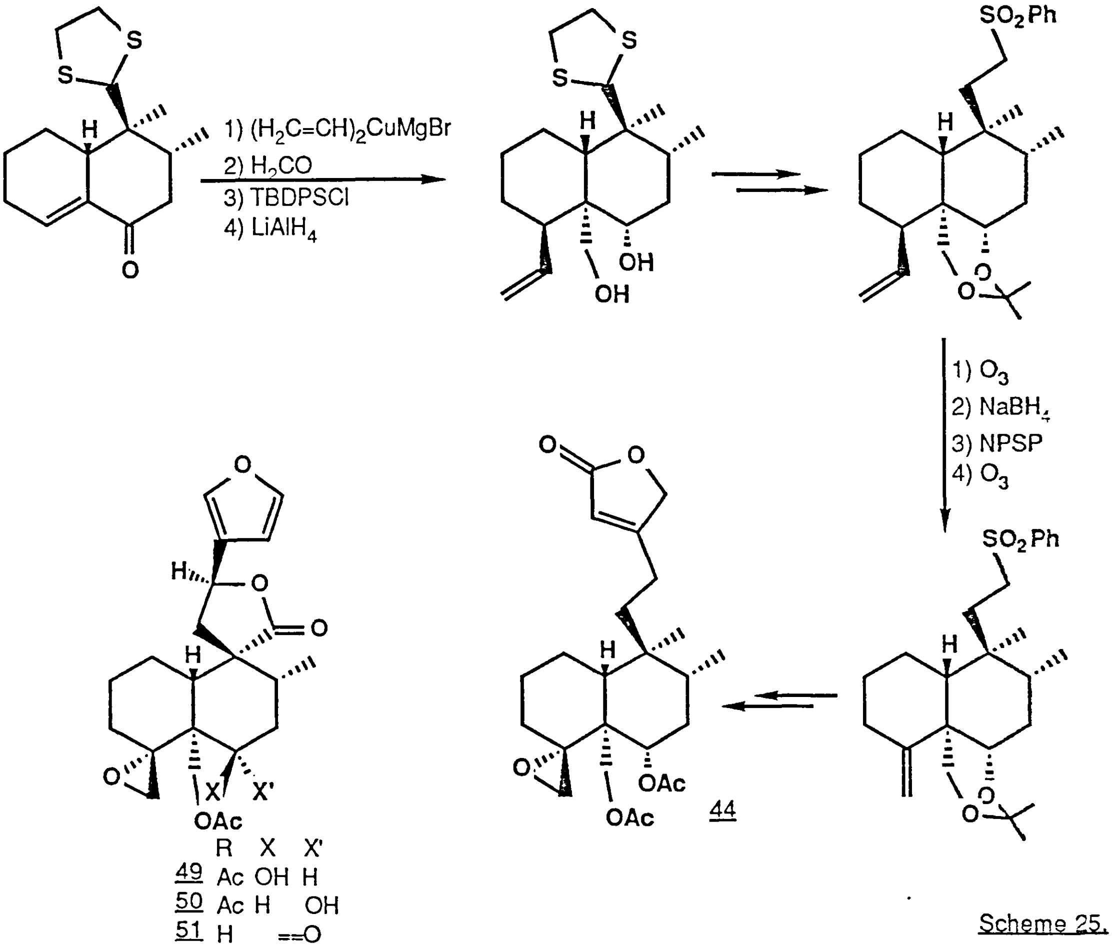
Having obtained the model compound (62), the stability to various conditions was evaluated. During the synthesis of ajugarin 1 (44) in our laboratories,[9] it was found that the Diels-Alder reaction between tiglic aldehyde (42) and 1-methoxy-3-trimethylsilyloxybutadiene (Danishefsky's diene) (41)[10] needed conditions of high temperature (130°C) in a sealed tube system, with neat reagents (vide supra), which led to loss of reactants, and only a 55% yield. It was hoped that the cycloaddition reaction in our system could be catalysed by the addition of Lewis acids, thus allowing a decrease in reaction temperature. Accordingly, the model compound (62) was exposed to a series of Lewis acids, both at low temperatures and at ambient temperature, for periods of 14 hours. The recovery of the furyl lactone in each case is indicated in table 1, with results based on isolated material, before further purification.

Lewis Acid	Recovered material (%)		
	-78°C	-10 - 0°C	RT
$TiCl_4$	95+	15	0
$SnCl_4$	95+	25	0
$ZnCl_2$	95+	95+	95+
$BF_3.OEt_2$	95+	85	50
$EtAlCl_2$	95+	95+	85
Et_2AlCl	95+	95+	85
Me_3Al	95+	90	50

Table 1

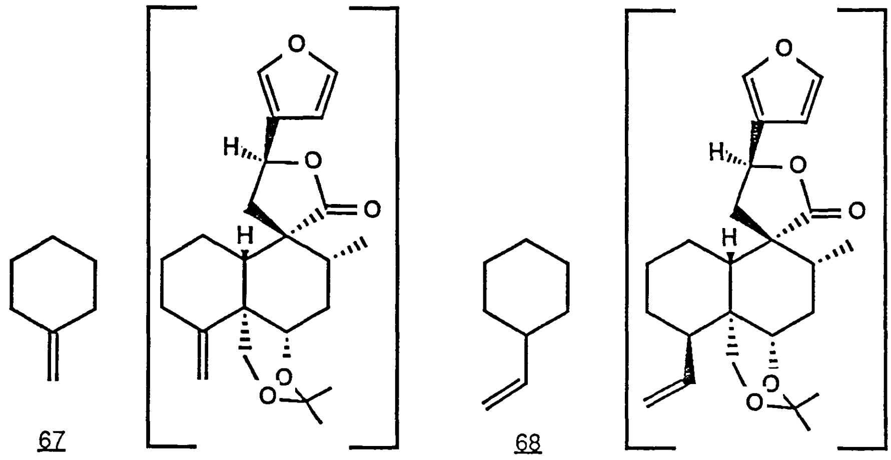
The apparent stability of the furan group to these acids was a pleasant surprise. For the Diels-Alder reaction, the stability to titanium tetrachloride at low temperature, and the relative stability to the alkyl aluminium reagents was most pleasing, as these would be our reagents of choice, owing to excellent literature precedence.[29,30] The stability to boron trifluoride diethyl etherate was also welcome, as it was envisaged that this reagent may be necessary during the introduction of the ethylidene unit, and for possible further transformations (vide infra).

A related series of stability studies was also carried out with reference to further possible synthetic transformations. In the synthesis of ajugarin 1 (44), which shares the same C_4-C_6 substitution as teucjaponins A and B (49,50), and gnaphalin (51), the C_{18} carbon was introduced as a vinyl unit, with subsequent ozonolysis and elimination to allow for the introduction of the epoxide grouping (scheme 25).[9]


1) $(H_2C{=}CH)_2CuMgBr$
2) H_2CO
3) TBDPSCl
4) $LiAlH_4$
SO_2Ph
1) O_3
2) $NaBH_4$
3) NPSP
4) O_3
SO_2Ph
44
R X X'
49 Ac OH H
50 Ac H OH
51 H =O

Scheme 25.

We felt that the furan ring would be incompatable with ozonolytic conditions, thus requiring other means of double bond cleavage, if a similar route was to be followed. A selenide oxidation elimination step, and a final epoxidation stage, were also considered as likely necessities for the synthesis. The furyl lactone (62) was thus submitted to both epoxidising and cis hydroxylating reagents, to assess the furan stability. These examinations were carried out both with and without the presence of alternative substrates, to investigate any possible relative reactivities. For the epoxidising reagents, exo-methylenecyclohexane (67) was chosen, to mimic a C_4-C_{18} methylene unit, and for the cis hydroxylation, vinylcyclohexane (68) was the alternative substrate, mimicking a vinyl addition compound (scheme 26).



67

68

Scheme 26.

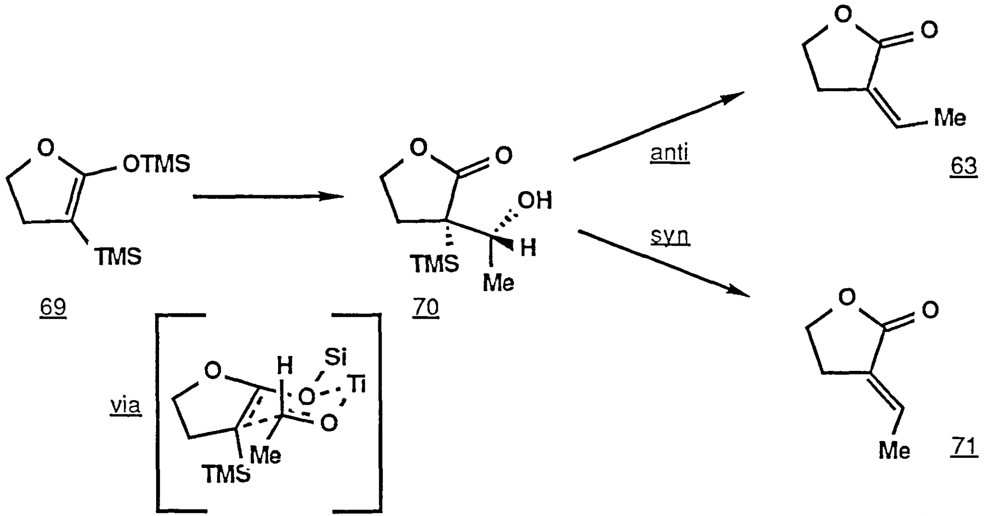
The results of these studies are shown in table 2, with the recovered yields based on purified isolated material, and also with the aid of nmr integration ratios.

Reagent	Conditions	(62)	(62)+(67)	(62)+(68)
$VO(acac)_2$, ^tBuOOH	RT, 14 hr.	50	65	-
$VO(acac)_2$, ^tBuOOH	RT, 3 hr.	95+	95+	-
mCPBA	0≡C, 14 hr.	25	40	-
mCPBA	0≡C, 3 hr.	95	95+	-
OsO_4, H_2O_2	0≡C, 3 hr.	0	-	0
$NaIO_4$	0≡C, 14 hr.	95	-	95+

Table 2

Although the stabiliity of the furyl lactone (62) appeared to be only moderate over longer reaction periods, the high recovery based on the shorter reaction times appeared hopeful. However, the apparent stability to the vanadyl epoxidation conditions over the shorter period may be somewhat spurious, as this system normally requires a directing hydroxyl group, and in the presence of such a group adjacent to the furan, the result may well be altered.

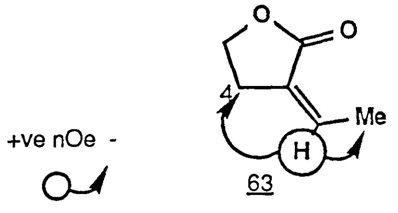
The synthesis of the other model dienophile (63) was originally approached using the work of Yamamoto.[31] Unlike the majority of syntheses to introduce an α-ethylidene, which yield the *E* geometry, Yamamoto developed a route to either *E* or *Z* dependant upon the reagents chosen to effect the final elimination. Thus, treatment of the silyl enol ether (69) with titanium tetrachloride and acetaldehyde should result in a directed aldol condensation to yield the diastereomerically pure alcohol (70), followed by *anti* elimination of trimethylsilyl alcohol to give the desired *Z* product (63). An alternative *syn* elimination would yield the *E* isomer (71) (scheme 27).



Scheme 27

The silyl enol ether (69) was readily prepared from γ-butyrolactone and excess trimethylsilyltriflate. Initially (69) was distilled immediately prior to use, but it was later found that a higher overall yield of the aldol product (68% compared to 56%), based on starting γ-butyrolactone, was obtained by reaction of the enol ether directly after preparation, without distillation. Either with, or without, distillation of (69), it was found that the aldol product (70) was obtained essentially as one diastereoisomer, as only one methyl doublet ($\delta 1.26$) was evident in the high field nmr, rather than a further doublet at δ1.36 reported for the undesired diastereoisomer.31 The anti-elimination was carried out using boron trifluoride etherate at -20°C, as this reagent is documented as giving purely anti-elimination products from α-hydroxyalkylsilanes.[32] The reaction, however, proceeded only very slowly, and even after treatment of the reaction mixture with a large excess of the Lewis acid, unreacted starting (70) remained, although an apparent clean conversion of around 80% of the alcohol had occurred. The major product was isolated by column chromatography, yielding (63) in only a 60% yield, (based on recovered starting material), although apparently purely one isomer. The loss of material in the above reaction was of concern, however overnight treatment with boron trifluoride etherate was found to remove all the starting alcohol (70), and on purification, the required ethylidene lactone (63) was isolated in 55% yield, along with a 40% yield of the E isomer (71), readily separable by column chromatography.

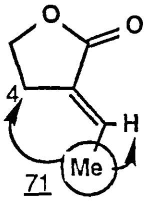
The correct stereo geometry of these products was confirmed by nmr techniques, using nuclear Overhauser effects, as shown in figures 1 and 2.



63

nmr data (δ)

Me	2.15,	dt,	J 7.0 2.5 Hz
C4-H	2.88,	tquint,	J 7.3 2.5 Hz
C=CH	6.30,	qt,	J 7.0 2.5 Hz



71

nmr data (δ)

Me	1.83,	dt,	J 7.0 2.0 Hz
C4-H	2.84,	tdq,	J 7.3 3.0 2.0 Hz
C=CH	6.77,	qt,	J 7.0 3.0 Hz

For the Z isomer (63) (figure 1), irradiation at the vinylic proton signal leads to enhancement at the β position, and also the methyl signal. The signal occurring at the γ position occurs due to a long range coupling effect, via the β position. For the E isomer (71)

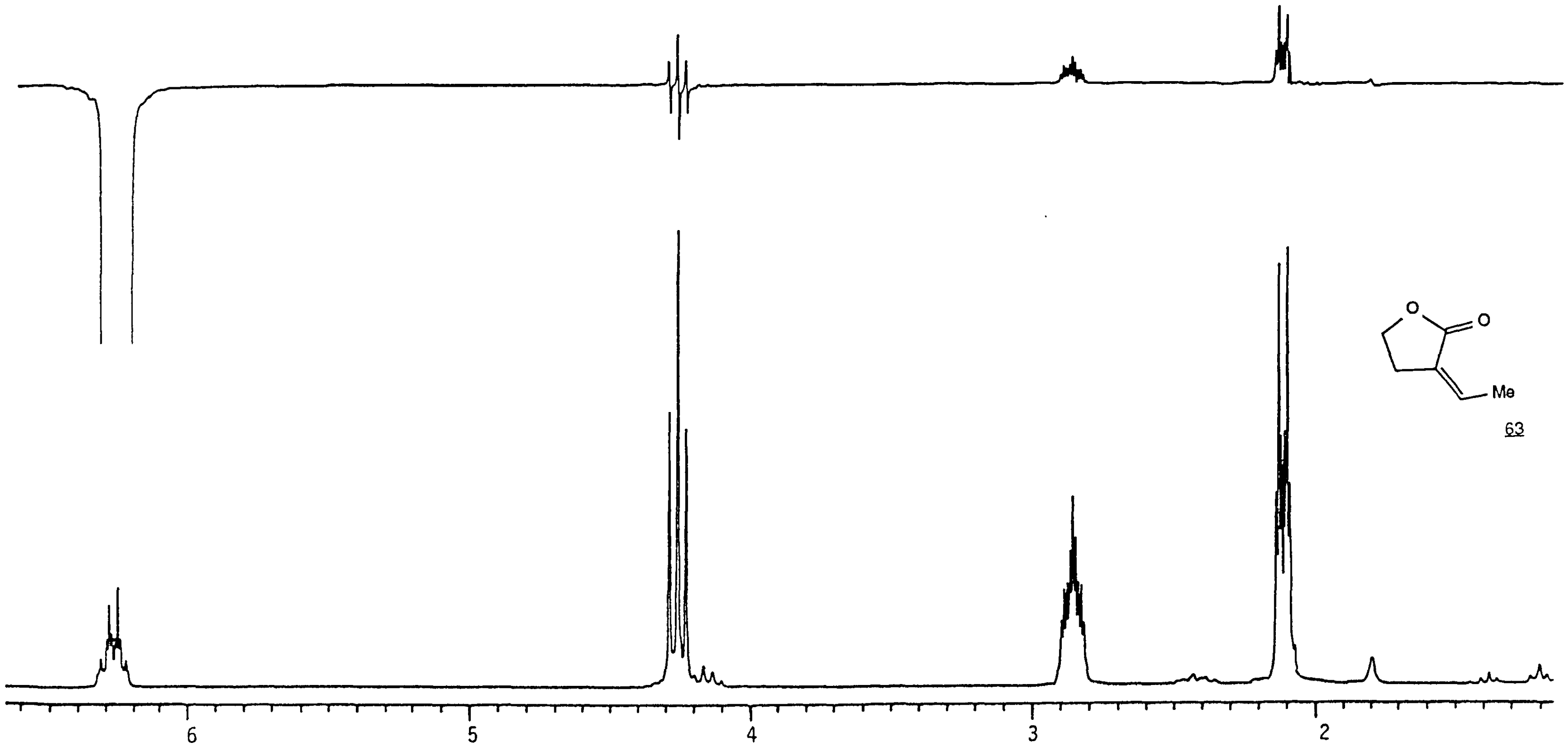


Figure 1.

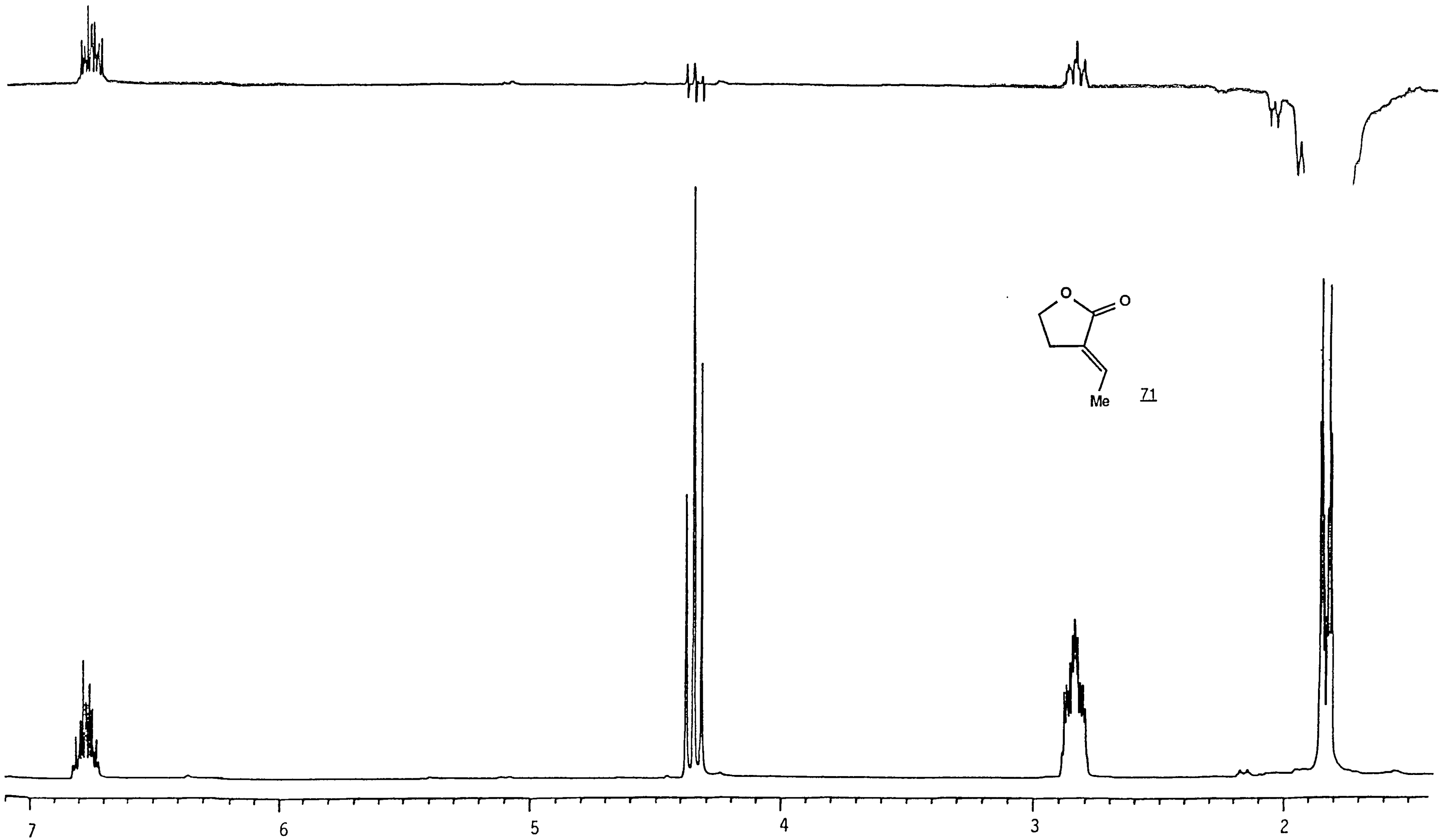
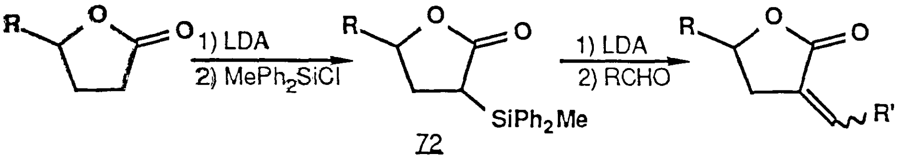


Figure 2.

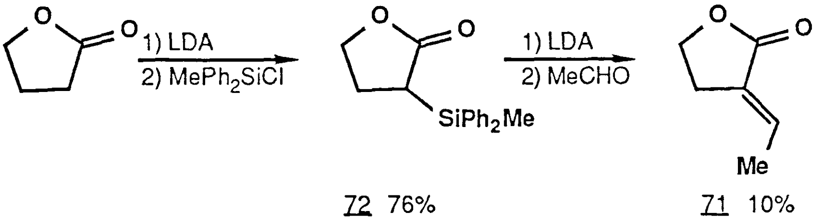
(figure 2), irradiation at the methyl signal leads to enhancement at the β position, and the vinylic signal, with long range coupling effects also observed to the γ position.

Further investigation of this reaction failed to achieve any large improvement in the Z : E ratio, with 70 : 30 the optimum result, as monitored by gas chromatography. Although the two isomers were readily separable by column chromatography, and there was hope that substituted butyrolactones may undergo a more selective elimination, we felt that a better ratio would be beneficial. Larson[33] published a route through to alkylidene γ-lactones using a deprotonation of an α-silyl lactone (72) (scheme 28).



Scheme 28.

Although the majority of the reactions carried out yielded the E isomer as the major, or only, product, consistent with results obtained by Yamamoto,[30] the reaction starting from γ-butyrolactone and using acetaldehyde was apparently reported to yield exclusively the Z isomer. This result appeared to be in direct contrast to the work of Grieco,[34] who, in using the same conditions with trimethylsilyl α-substituted lactones, obtained only the E geometry. No explanation for this apparent reversal in stereoselectivity was given, though the Z isomer was obtained in a relatively low yield (25%, contaminated with γ-butyrolactone). Accordingly, we found that treatment of γ-butyrolactone with diphenylmethylsilyl chloride under standard alkylating conditions (LDA,THF) gave the required α-silyl adduct (72, R=H) in 76% yield. Pleasingly, no O-silylation product could be detected, a problem found by Larson, though more especially when using γ-valerolactone. Treatment of the silyl adduct with LDA followed by addition of redistilled acetaldehyde, and subsequent heating for fifteen minutes, gave mainly γ-butyrolactone, along with a 10% yield of an eliminated ethylidene lactone, shown by gas chromatography and nmr comparison to the previous samples to be purely the E isomer (71) (scheme 29).

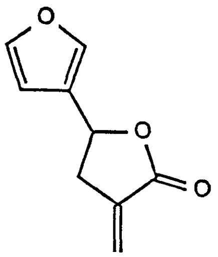


Scheme 29.

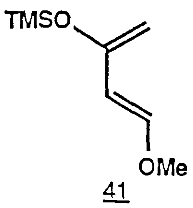
This result confirmed that of Grieco, and although attempts were made to alter reaction conditions, only the E geometrical isomer could be obtained. Thus it was necessary to rely on the original route to the Z isomer (63).

2.4. Model Cycloaddition Reactions.

It was decided, for the sake of convenience, to carry out the initial attempts at the Diels-Alder reaction on the furyl lactone (62) with Danishefsky's diene (1-methoxy-3-trimethylsilyloxybutadiene) (41).

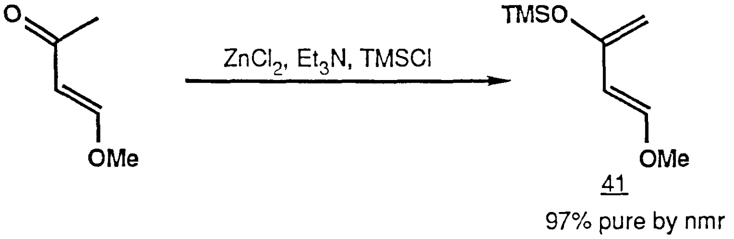


62



41

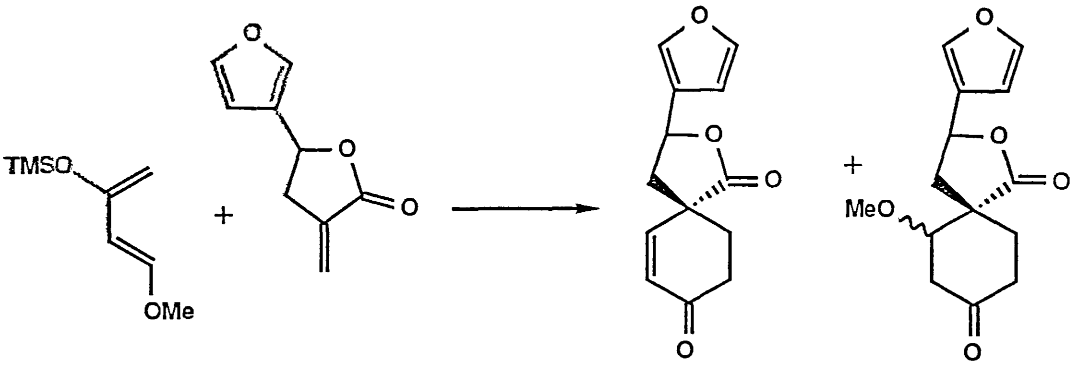
The diene was readily available in large quantities from 4-methoxy-3-buten-2-one, using a modified procedure of the original Danishefsky preparation.[35] By this route, after distillation, a high purity diene could be prepared, with the purity higher than any commercially available material, as indicated by nmr peak ratios (scheme 30).



Scheme 30

Initial attempts to obtain a cycloaddition reaction between diene (41) and dienophile (62) in either refluxing benzene or toluene failed, leading to only a quantitative recovery of lactone (62). Attempts to catalyse the reaction with various Lewis acids were next considered. Titanium and tin tetrachlorides gave no reaction at -78°C, however warming to -30°C gave some apparent loss of dienophile, along with total consumption of the diene. The use of anhydrous zinc dichloride gave no reaction between the substrates at elevated temperature over an extended period of time, whilst boron trifluoride etherate gave no reaction below 0°C, and at room temperature caused decomposition of both substrates, with no cycloaddition products isolable. The reactants also gave no reaction with alkyl aluminium species, diethylaluminium chloride, ethylaluminium dichloride, and trimethylaluminium, except for decomposition of the diene in the latter case on warming to room temperature.

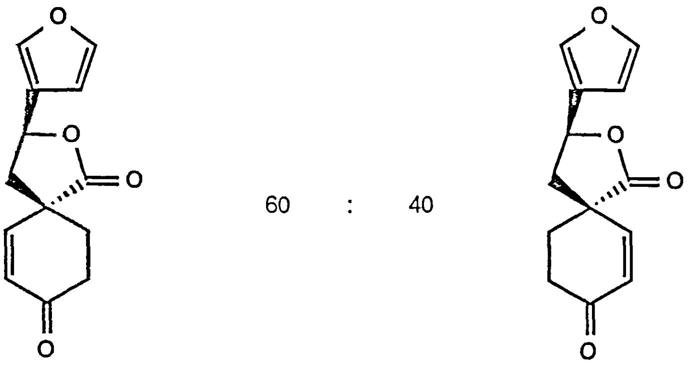
It was decided to use the method developed by Whittle[35] in our laboratories, during the synthesis of ajugarin 1 (44). The diene (41) and lactone (62), along with a few crystals of hydroquinone to suppress any radical polymerisation, were sealed in a pressure vessel previously washed with base and treated with hexamethyldisilazane, and degassed. The evacuated vessel was then heated to 130°C for 14 hours, yielding a dark brown tar. On subsequent hydrolysis with dilute aqueous hydrochloric acid in THF, this yielded a mixture of products. It was found that by sequential columning, first with dichloromethane, then with a diethyl ether/petroleum spirit mixture, produced a mixture of two main products, with only very minor amounts of other materials. The two component mixture was subjected to high pressure liquid chromatography, to give firstly the enone adduct (73) in 20% yield, followed by the uneliminated methoxy derivative (74) in 8% yield (scheme 31).



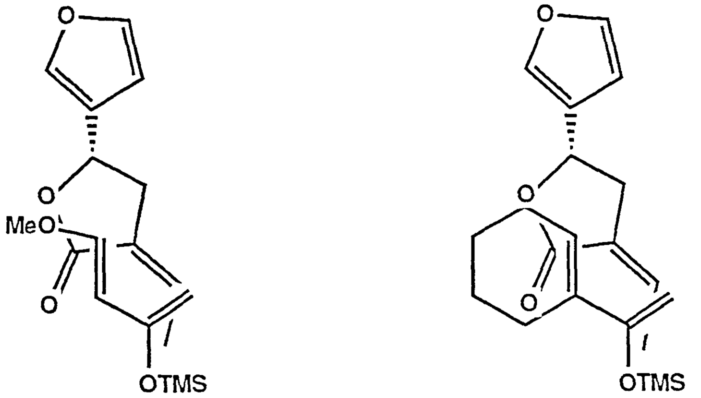
41 62 73 74

Scheme 31.

^{13}C nmr of the enone (73) showed twinned peaks, as did the proton spectrum, in a ratio of 60 : 40. This mixture of diastereoisomers proved inseparable by chromatographic means, but crystals suitable for X-ray analysis were obtainable. These crystals also proved to be a diastereomeric mixture, with the two diastereoisomers packing closely in the same crystal. The x-ray, however, confirmed the structure of the enone as that expected, in a diastereomeric ratio of 60 : 40.



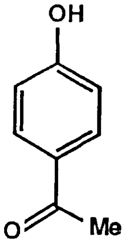
Although the major isomer was the expected product, the sterically demanding furan ring did not appear to interact significantly with the Danishefsky diene. However, it was felt that the steric requirements of the real system would confer a greater selectivity on the reaction (scheme 32).



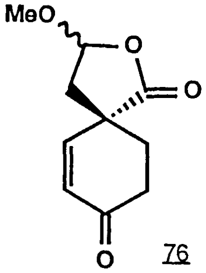
Scheme 32.

Pleasingly, in view of the possible antifeedant nature of the target clerodane natural products, both enone mixture (73) and the methoxy compound (74) showed signs of biological activity in our preliminary screening tests, though in both cases only at a relatively high concentration.

It was hoped that the yield of the cycloaddition reaction might be improved by using even more forcing conditions. Exposure of the reaction mixture, prepared as before, to a temperature of 160°C for fourteen hours, led to a single product, isolated in 40% yield (based on the desired product (73)). This product was not a previously isolated material, and proton nmr confirmed the lack of a furan moiety, although the presence of an enone system, and a methoxy group was indicated. The possibility that this might be a product of self condensation of the diene (75), as Whittle had previously shown occurring,[35] was dispelled due to the lack of aromatic charecter. The product was tentatively assigned as a decomposed form of the required product, (76), based on an apparent molecular weight of 196 mass units (FAB mass spectrometry).



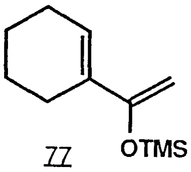
75



76

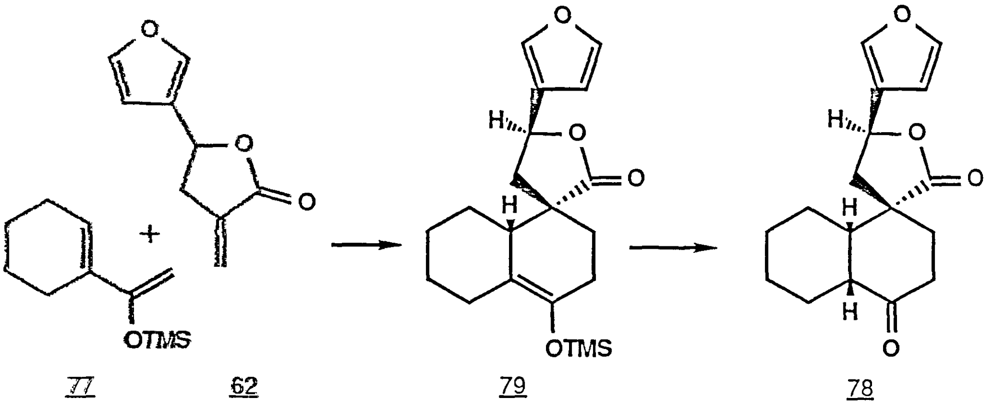
In another attempt to force the cycloaddition reaction, the substrates were subjected to high pressure (12Kbar) at 50°C, but this only led to polymerisation of the starting materials.

Our attention next turned to a diene capable of yielding the required decalin unit. Having had some success with the Danishefsky diene, it was felt that a corresponding trimethylsilyloxy diene (77) would react with the lactone dienophile.



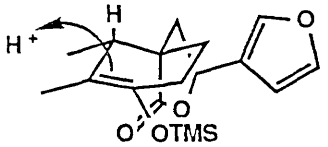
77

Diene (77) was prepared from 1-acetylcyclohexene using the same modified procedure as for the Danishefsky diene, yielding the required (77) 98% pure after distillation, in 70% yield. Again, attempts to catalyse the cycloaddition with Lewis acids only led to decomposition of the diene, or of both reactants, and high pressure (12Kbar) conditions gave no reaction. Treatment at 130°C for fourteen hours in an analogous system to that used previously, followed by protic hydrolysis (dilute hydrochloric acid in THF), induced a cycloaddition reaction leading to a mixture of decalin products, containing two major diastereoisomers. High pressure liquid chromatography, followed by recrystallisation gave the adduct (78) in 28% yield. The crystals proved suitable for X-ray analysis, showing a single diastereoisomer (figure 3).[36] Surprisingly, it was found that although this isomer was the expected product in relation to the stereochemistry about C_9, C_{10}, and C_{12}, the hydrolysis of the intermediate silyl enol ether (79) had led to the formation of the cis decalin (scheme 33).



Scheme 33.

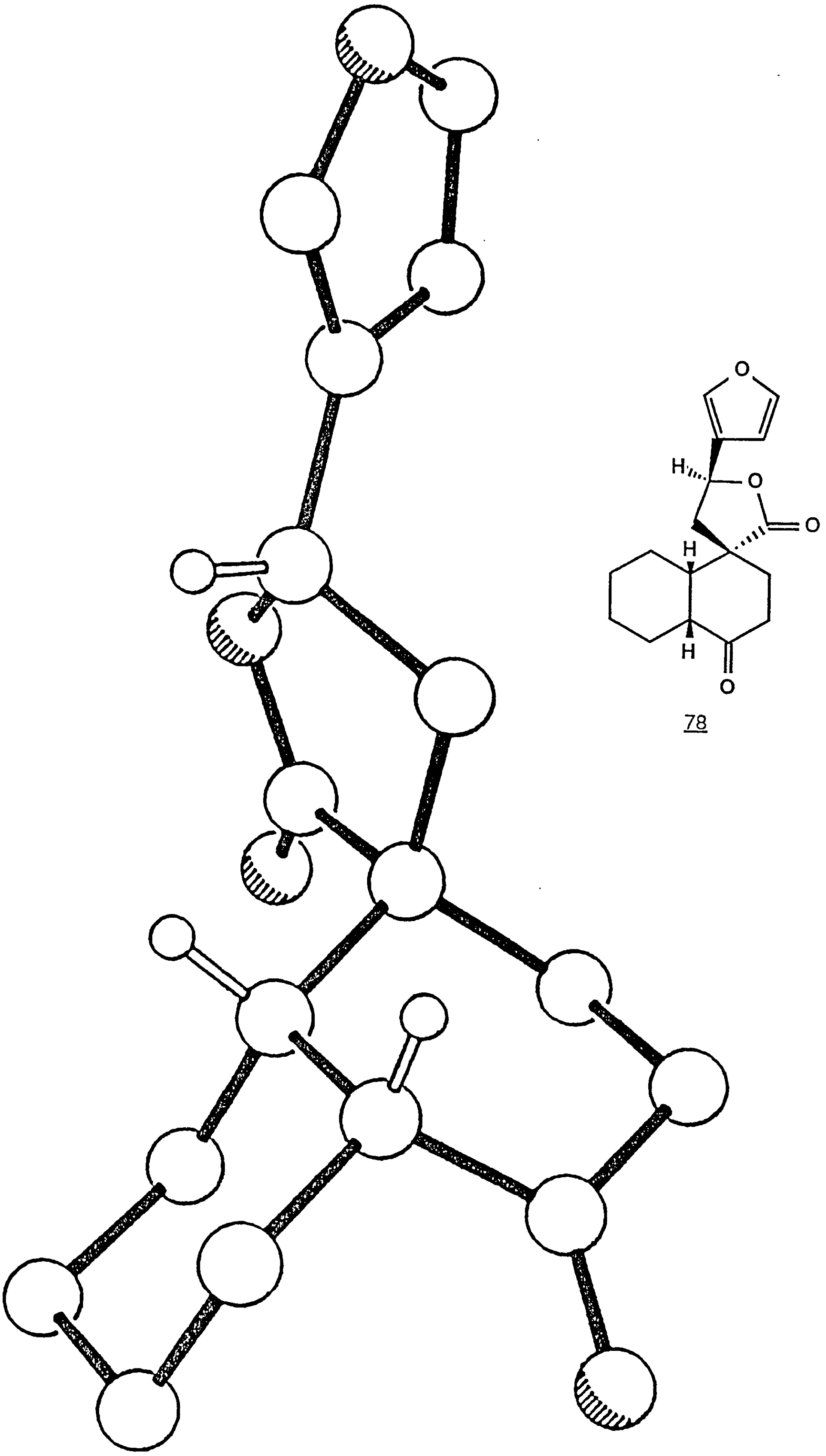
Consideration of a model of enol ether (79) showed that steric hindrance caused by the lactone carbonyl group presented the β-face of the system as a much less hindered approach for the protonation (scheme 34).



Scheme 34.

However, as the resultant product from this reaction was not that required in the correct system, where the enol ether would be taken through to an enone, investigation of the isomerisation of (78) to the trans decalin was not considered further.

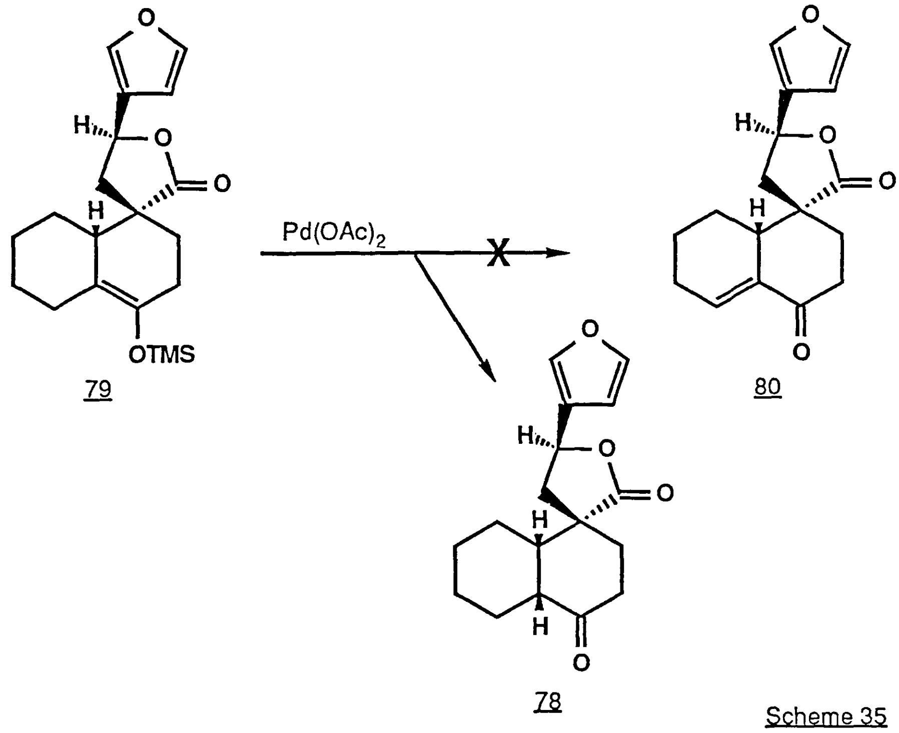
Repeated attempts to convert the silyl enol ether (79) to the enone (80) directly were carried out, using the system of Saegusa.[37] Thus enol ether (79) was treated with 1.5 equivalents of palladium acetate and benzoquinone in acetonitrile. Although apparent reduction of the palladium acetate occurred, with a deposition of a platinum 'mirror',



78

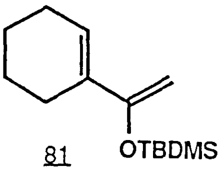
Figure 3.

on work up only the product of protonation of the enol ether was obtained, again with the cis ring geometry, to give (78) (scheme 35).



Scheme 35

Although the transformation of the enol ether to an enone was an important part of the proposed synthesis, it was felt that an improvement in the yields of the initial cycloaddition reaction was rather more important. By monitoring the Diels-Alder reaction by thin layer chromatography, it appeared that decomposition of the starting diene to its acetyl precursor occurred rapidly, preventing any further reaction, even though an excess of the diene was used. Therefore, a more stable diene for this cycloaddition reaction seemed logical, and the t-butyldimethylsilyl diene (81) was an obvious choice.

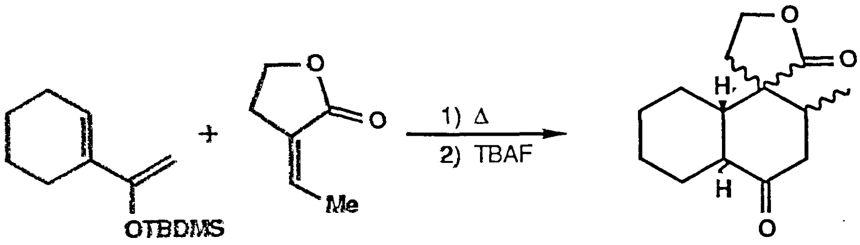


81

Attempts to prepare (81) by treatment of acetylcyclohexene with t-butyldimethylsilyl chloride in the presence of potassium hydride[38] were unsuccessful. Treatment of acetylcyclohexene with LDA, followed by quenching with the silyl chloride[39] gave the required (81) in high purity (95%) in 89% yield after distillation.

With a ready supply of this new diene to hand, a repeated set of Diels-Alder reactions using Lewis acid catalysis were attempted, again with disappointing results. However, the stability of the initial diene was noticeably improved compared to the corresponding trimethylsilyl derivative.

Cycloaddition reactions between Danishefsky's diene (41) and the other model dienophile (63) were also attempted. In these cases, no reaction occurred either under catalysed or forcing temperature and/or pressure conditions. The reaction of the trimethylsilyldiene (77) and lactone (63) under the same conditions used previously for the furyl lactone (62), led to only decomposition of the diene at 130°C over twenty-four hours. However, the reaction between diene (81) and the lactone (63) could be carried out at 160°C, with no significant decomposition of the diene. Work up of the reaction mixture yielded a complex mixture of products, which were treated without further purification with tetrabutylammonium fluoride, to give a mixture of diastereoisomers (82) in 30% overall yield (scheme 36).

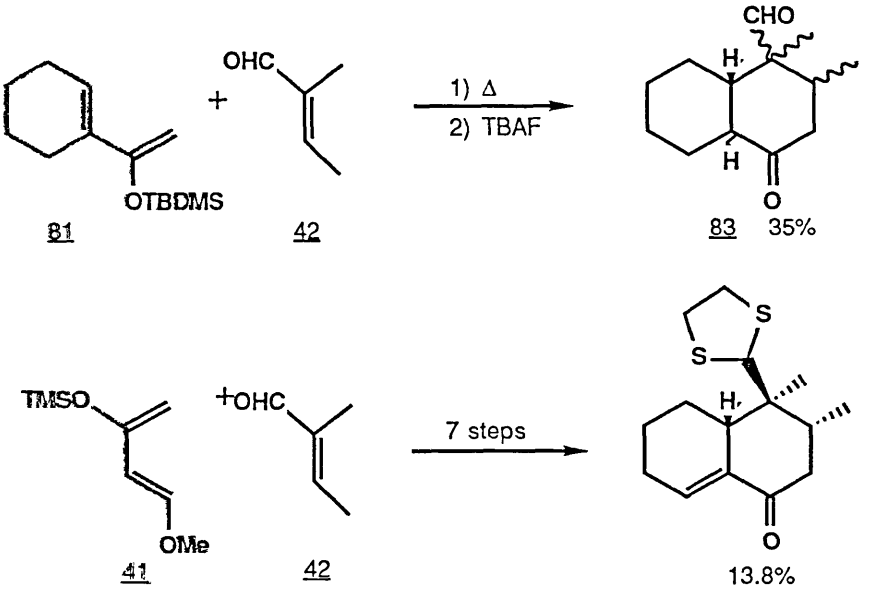


81 63 82

Scheme 36.

The high field nmr of (82) showed three sets of methyl doublets overlaying one another, indicating at least three diastereoisomers, and gas chromatographical examination confirmed the presence of at least three isomers. Attempts to separate the diastereomeric mixture by high pressure liquid chromatography were unsuccessful, both with normal and reverse phase conditions.

In a separate approach towards clerodin and ajugarin classes of clerodanes, the use of the stable diene (81) with tiglic aldehyde (42) as the dienophile ought to allow a much shorter approach to a decalin system (83), containing an aldehydic function at the C_{10} position, than that used previously by Ley.[9] Hence diene (81) and tiglic aldehyde (42) were heated at 160°C for seventeen hours under the normal conditions, to yield a diastereomeric mixture of the desired adduct, but in only 33% yield (scheme 37).



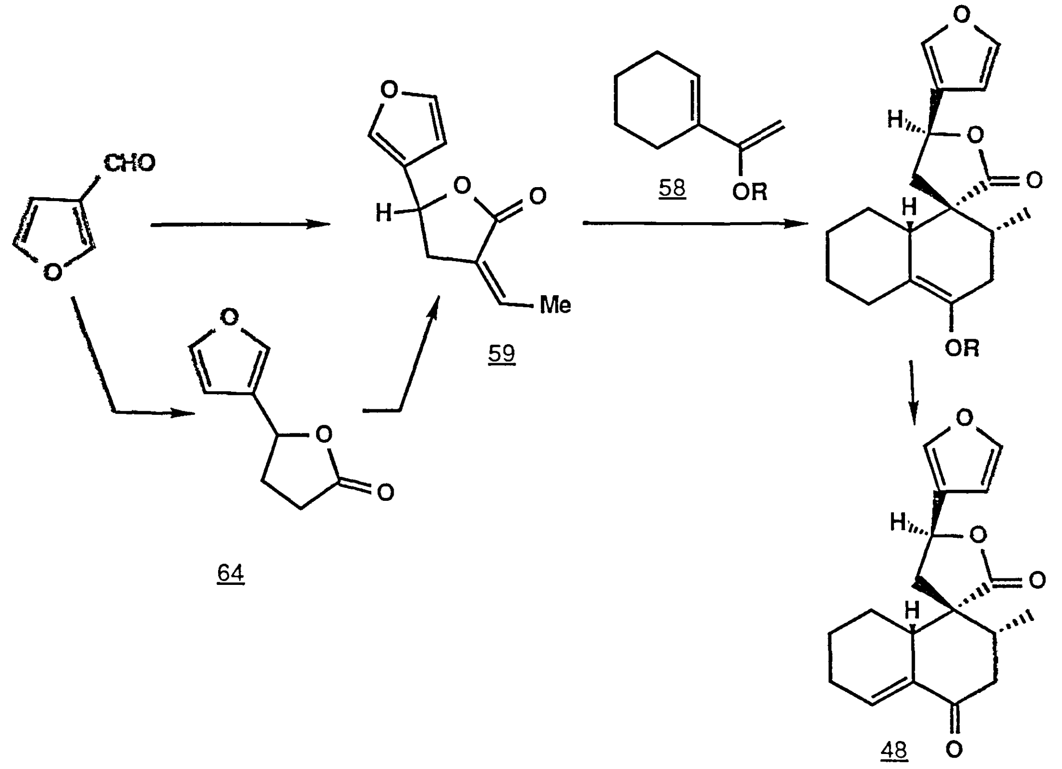
Scheme 37.

Unfortunately, the mixture contained four separate aldehydic components, and although the major isomer proved separable by high pressure liquid chromatography, it constituted only 40% of the product mixture, an overall yield of only 13.2%, comparably lower than that from the previous route.

3. Synthesis of Key Intermediate (48).

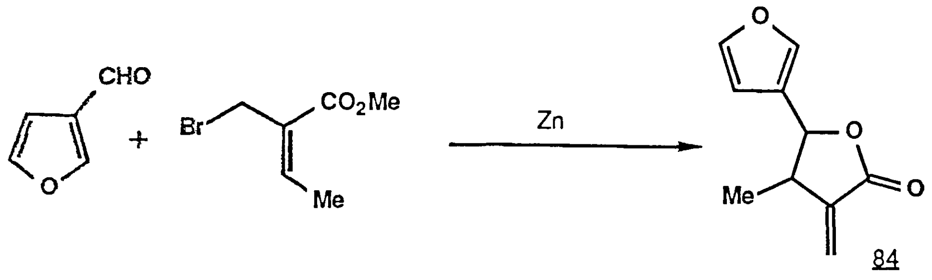
3.1. Achiral Approaches to 5-(3'-Furyl)butyrolactone.

The proposed synthetic route through to the pivotal enone (48) was discussed in section 2.2, and is summarised in scheme 38.


CHO
O
H
O
O
Me
59
O
O
O
64
58
OR
O
H
O
O
H
OR
O
H
O
O
H
48
O

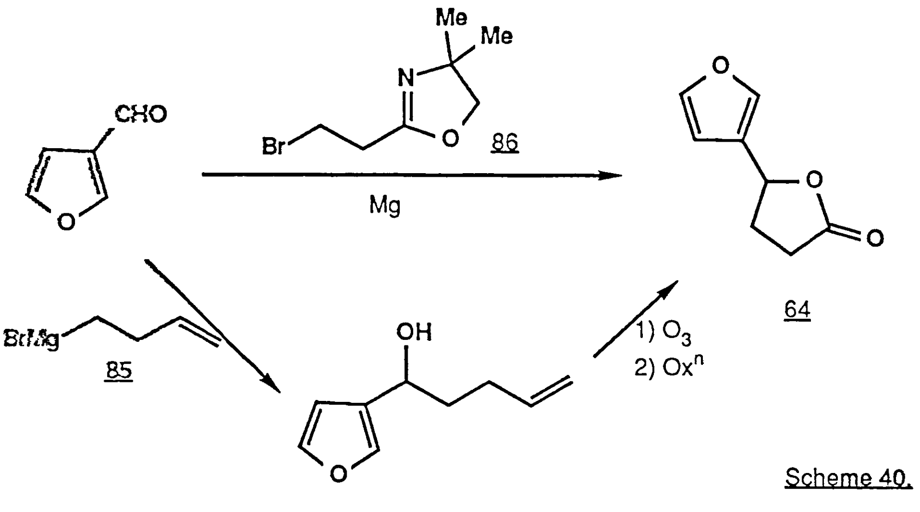
Scheme 38.

Originally, it was hoped to prepare the dienophile (59) by a direct reaction analogous to the formation of the methylene lactone (62). However, brief investigation of this process confirmed the results already reported by Loffler et al.,[40] that this reaction leads to the corresponding α-methylene-β-methyl lactone (84) as the only product (scheme 39).


CHO
O
+
Br
CO2Me
Me
Zn
O
O
O
Me
84

Scheme 39.

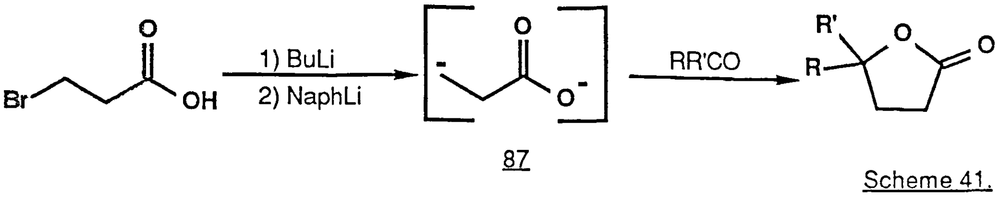
It was therefore necessary to devise a route to 5-(3'-furyl)-γ-butyrolactone (64), and to use the methods of introduction of the ethylidene unit already discussed. An attempt to carry out a Reformatsky style reaction using 3-bromopropionic acid esters unfortunately gave no reaction, even under ultrasonic conditions. The Grignard reaction of an aldehyde with the organometallic species (85) derived from 4-bromobutene, followed by ozonolytic cleavage of the olefin unit was considered as a convenient method of preparing γ-lactones. The furan ring, however, we knew would be unstable to these conditions. Use of a masked ester, such as the oxazoline (86) described by Meyers,[41] to form a Grignard reagent, was considered a possibility (scheme 40).



Scheme 40.

However, all attempts to form the oxazoline (86) from the corresponding bromo-acid and 2-amino-2-methylpropan-1-ol were unsuccessful. A similar attempt to use a Grignard reagent derived from tetrahydropyranyl protected 3-bromopropan-1-ol also met with no success.

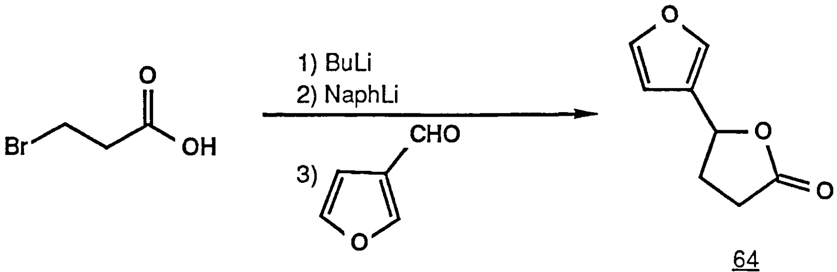
The formation of an equivalent to the 3-deprotonated propionic acid group has been reported.[42] Treatment of 3-bromo-propionic acid sequentially with butyl lithium and lithium naphthalenide reportedly forms the dianionic species (87), which undergoes reaction with aldehydes and ketones to yield γ-lactones (scheme 41).



87

Scheme 41.

Lithium naphthalenide was prepared by stirring a solution of naphthalene in THF over lithium for several hours. We later found that the use of freshly recrystallised naphthalene, finely cut lithium (rather than dispersion) and ultrasound conditions led to the formation of a dark green solution of the naphthalenide in minutes, and complete conversion in one to two hours (exposure to ultrasound conditions for more than three hours led to decomposition of the naphthalenide). Treatment of the lithium salt of the bromo-acid with this solution, followed by addition of furan-3-carboxaldehyde gave a crude product, which on purification via medium pressure liquid chromatography gave the desired lactone (64) in 41% yield (scheme 42).



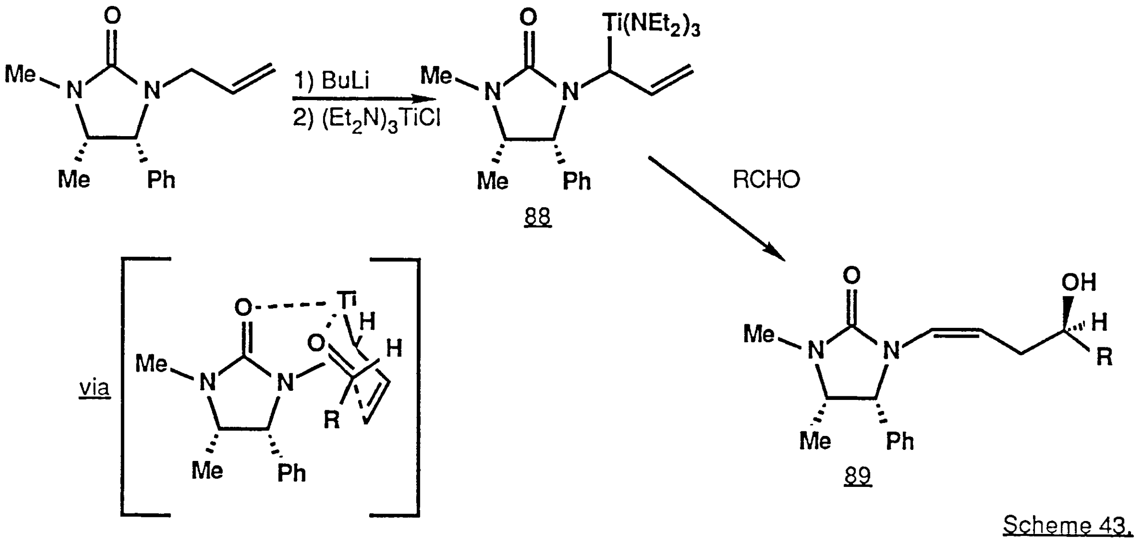
64

Scheme 42.

Although only a moderate yield, this reaction could be readily scaled up to multigram quantities without lowering of product yield.

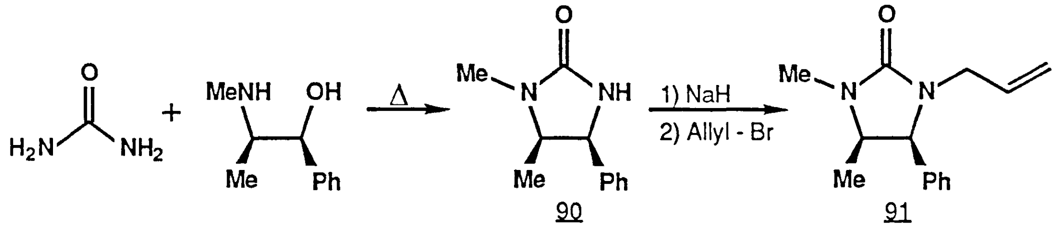
3.2. Approaches to Chiral 5-(3'-Furyl)butyrolactone.

As indicated in section 2.2, it was hoped that an enantiospecific synthesis could be based on a route starting from the optically pure S enantiomer of lactone (64). Initially, our approach was devised using an asymmetric attack of an organometallic species on furan-3-carboxaldehyde, using the method of Helmchen and co-workers.[43] In this paper, a homo aldol attack of an organotitanium species incorporating an ephedrine derived chiral auxiliary (88) was described, with a chair like transition state assumed to control the high diastereoselectivity of the reaction, and hence the enantiomeric excess of the resultant lactone after cleavage of the auxiliary unit (scheme 43).



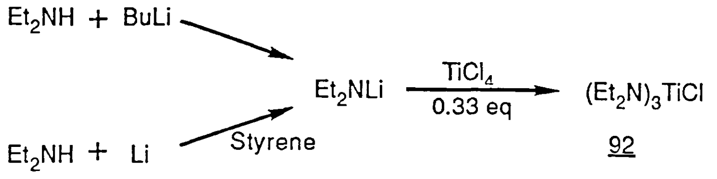
Scheme 43.

The resultant stereochemistry of product (89) is R at the reaction centre (when R=furan), thus we needed to generate the enantiomeric metallospecies. (+)-Ephedrine hydrochloride and urea were fused together, to yield a crystalline adduct (90) in 70% yield after recrystallisation. Attempts to introduce the required allyl substituent were initially unsuccessful, with problems of solubility of (90) in THF. The sodium salt of (90) was found to present even greater problems of solubility. It was found that by use of a large amount of solvent, the adduct (90) could be dissolved completely, but treatment with sodium hydride immediately gave a crystalline precipitate. However, stirring of the precipitate in the presence of allyl bromide over twenty hours led to the formation of a colloidal precipitate of sodium bromide, and loss of the crystalline species, leading to an essentially quantitative yield of the crude adduct, recrystallisation giving 80-85% of the required allyl species (91) (scheme 44).



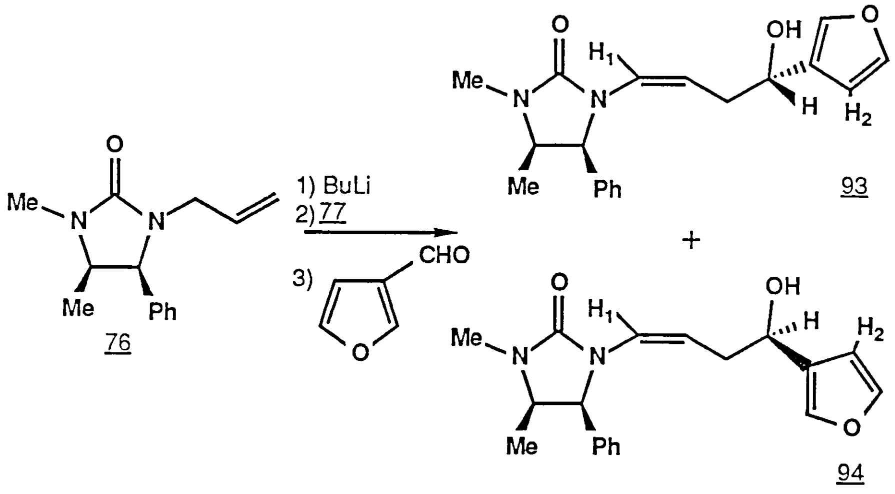
Scheme 44.

The reaction requires the use of an organotitanium species generated from tris-(diethylamino)titanium chloride (92). The literature method[44] for the preparation of this species involved the formation of lithium diethylamide from diethylamine and lithium metal in the presence of styrene, followed by the addition of titanium tetrachloride, but this route was originally found to be unreliable, and an alternative approach using diethylamine and butyl lithium to generate the lithio species was adopted. However, preparation of (92) on a large scale was successfully carried out by the previous method via ultrasonic activation of the lithium metal (scheme 45).



Scheme 45.

The titanium species could be readily distilled to yield a dark red-brown liquid, but this was found to be unstable on storage. The reaction requires the use of a THF solution of (92), hence the freshly distilled titanium species was immediately dissolved in THF to give a solution of known molarity, which proved stable for storage at -10°C over several weeks. Treatment of the allyl substrate (91) with butyl lithium, followed by transmetallation with (92), gave the required organometallic species, which was quenched with furan-3-carboxaldehyde to yield the adduct (93), though in only 27.5% yield. High field nmr showed this product to contain 90% of one diastereoisomer, with 10% of a minor product assigned as the unwanted diastereoisomer (94) on the basis of the similarity of the high field spectrum to (93) (scheme 46). In the original publication, it was found that diastereomeric excesses of up to 200 : 1 could be achieved only after recrystallisation, but in the case of adducts (93) and (94) the product was a viscous oil, even after repeated columning, and a crystalline solid could not be obtained.



nmr data (δ)

93: N-Me 2.81, s, H-1 6.10, d, H-2 6.31, s

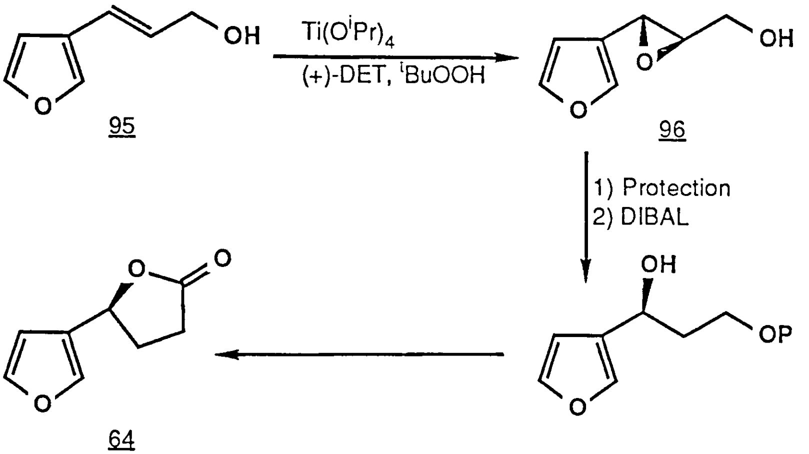
94: N-Me 2.83, s, H-1 5.98, d, H-2 6.35, s

90 : 10 93 : 94

Scheme 46

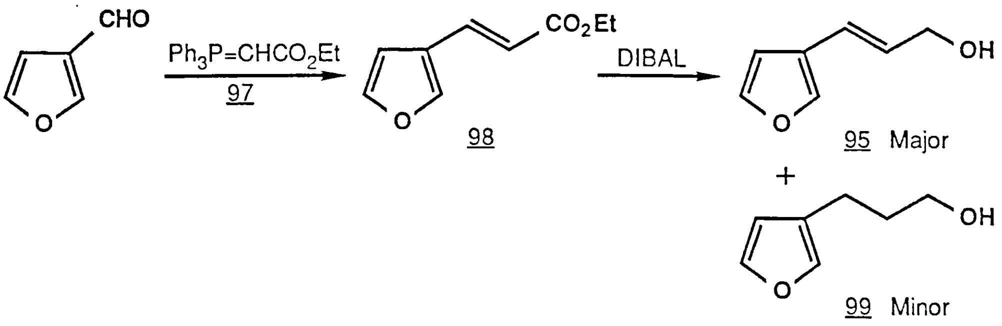
Treatment of the mixture of (93) and (94) with methanolic sulphuric acid, the reported method of cleavage of the enamine linkage,[45] led to total decomposition of the material, presumably due to the mineral acid conditions attacking the furan ring. Attempts to effect the cleavage with other acidic conditions, including HCl/THF, Methanol/ Amberlyst 15, and Lewis acids all led to either no reaction or loss of material. Extended treatment with either Amberlyst 15 or a trace of sulphuric acid in anhydrous methanol gave a small amount of a product, but this appeared to be the result of addition of methanol to the olefinic bond.

This route was therefore abandoned in favour of a route using an asymmetric epoxidation to introduce the correct chirality. It was envisaged that Sharpless epoxidation[46] of the allylic alcohol (95) would lead to a substrate (96) suitable for transformation into the desired lactone (64) (scheme 47).


OH
Ti(O^{i}Pr)$_4$
(+)-DET, ^{t}BuOOH
95
O
OH
96
1) Protection
2) DIBAL
OH
OP
64

Scheme 47

Thus, treatment of furan-3-carboxaldehyde with the stabilised Wittig reagent (97)[47] gave the desired trans olefin (98) as the only product. Reduction with di-isobutylaluminium hydride (DIBAL) gave the allylic alcohol (95), with only minor amounts of the saturated (99) (scheme 48).


CHO
Ph$_3$P=CHCO$_2$Et
97
CO$_2$Et
98
DIBAL
OH
95 Major
+
OH
99 Minor

Scheme 48.

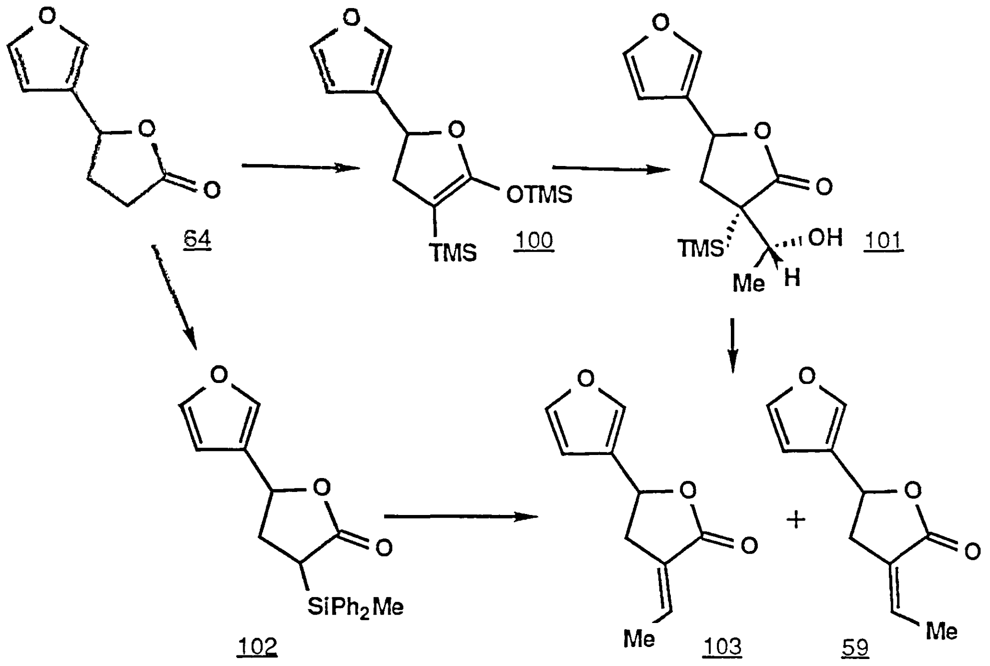
The allylic alcohol was treated under Sharpless conditions using (+)-diethyl tartrate. However, after purification of the resultant epoxide (96), a yield of only 15% was obtained, with no optical activity evident by polarimetric measurement. Although disappointing, the low yield was not totally unexpected, as we had already considered that the double bonds of the furan ring may be susceptable to attack by epoxidising reagents, especially when utilising directional reagents with a directing hydroxyl group present close to the ring (section 2.3). Also, the lack of stereoselectivity was not wholly unexpected, as the epoxide was being formed in essentially a benzylic position, and was thus suceptible to ring opening.

Although further approaches to the chiral system were considered, for instance the use of microbial reduction, the asymmetric approach to the clerodanes was abandoned in favour of the achiral synthesis, with relative stereochemical control, owing to the time available for these studies.

3.3. Stereospecific Introduction of the Ethylidene Unit.

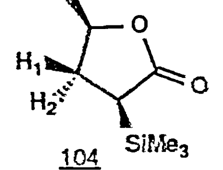
Two routes from a butyrolactone to an α-ethylidene lactone had been investigated (section 2.3), and although the route using a diphenylmethylsilyl group had only given the unwanted E geometry, it was decided to investigate both routes, in order to discover any possible effect of the γ-furyl substituent in lactone (64) (scheme 49).

Treatment of the lactone (64) with two equivalents of trimethylsilyl triflate in the presence of triethylamine cleanly gave the the required α-silyl silyl enol ether (100), which was utilised directly (as for (69), section 2.3). Hoever, in order to characterise the enol ether (100), some of the material was hydrolysed using dilute hydrochloric acid in THF, to yield the α-trimethylsilyl lactone, as a mixture of cis and trans diastereoisomers (104) and (105), separable by column chromatography, in a 1 : 1 ratio.

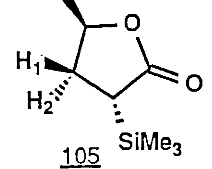

OTMS
TMS
TMS
OH
Me
H
SiPh$_2$Me
Me
Me
64
100
101
102
103
59

Scheme 49.

The assignment of cis and trans was based on the β-hydrogen signals in the high field nmr. In the cis isomer (104) both H_a and H_b occur as triplets due to the similar angles of the α and γ protons to both protons, with H_a experiencing the effect of two trans protons and H_b two cis. Conversely, in the trans isomer (105) the β protons both experience one trans and one cis coupling, shown by their occurrence as double doublets in the spectra.



104

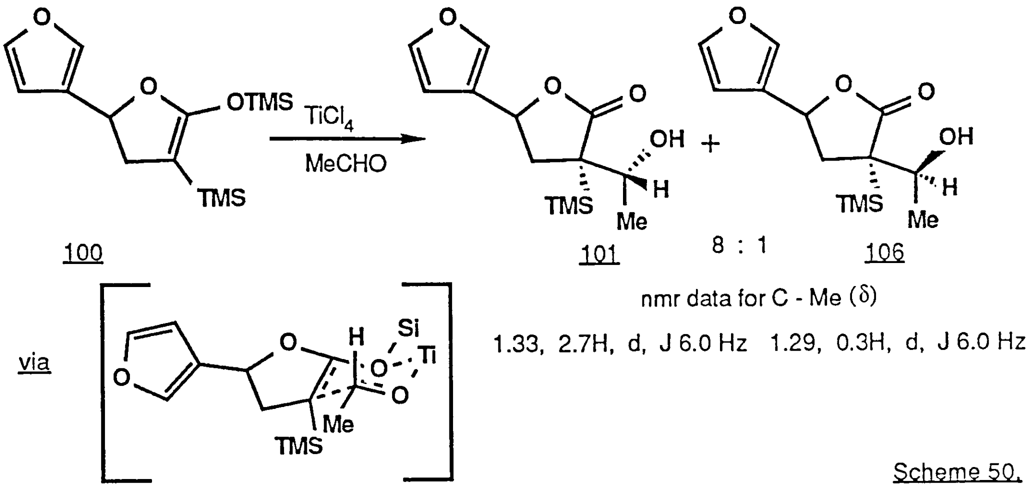


105

nmr data for H_1 and H_2 (δ)

2.45, t, J 6.5 Hz	2.02, ddd, J 12.5 10.3 9.0 Hz
2.49, t, J 6.8 Hz	2.63, ddd, J 12.5 10.0 6.8 Hz

Treatment of the silyl enol ether (100) with acetaldehyde in the presence of titanium tetrachloride gave a crystalline product, with high field nmr indicating a mixture of diastereoisomers (101) : (106) with an 8 : 1 ratio based on methyl doublet signals (scheme 50).



100

101

106

nmr data for C - Me (δ)

1.33, 2.7H, d, J 6.0 Hz 1.29, 0.3H, d, J 6.0 Hz

Scheme 50.

The aldol adducts (101) and (106) proved inseparable, and were treated with boron trifluoride etherate to give an anti elimination to the ethylidene lactone in an essentially quantitative yield. Capillary gas chromatography indicated the presence of two isomers in the reaction, with a ratio of 92 : 8. High pressure liquid chromatography separation of the two isomers proved viable, and pleasingly high field nmr indicated the major isomer to be the desired product (59). Nuclear Overhauser investigation of the two compounds confirmed this, as shown in figures 4 and 5. In the case of the minor E isomer (103) (figure 4), irradiation of the methyl signal produced positive nOe responses at the vinyl position, and also at the β-hydrogens. For the major Z isomer (59) (figure 5), irradiation of the more informative vinyl signal was considered unsuitable (unlike in the simple butyrolactone case, section 2.3) due to the proximity of the furan C_4-H signal, which would lead to complex and possibly misleading results. Hence, irradiation was carried out on the methyl signal, giving a strong positive result at the vinylic position, with only minor enhancement

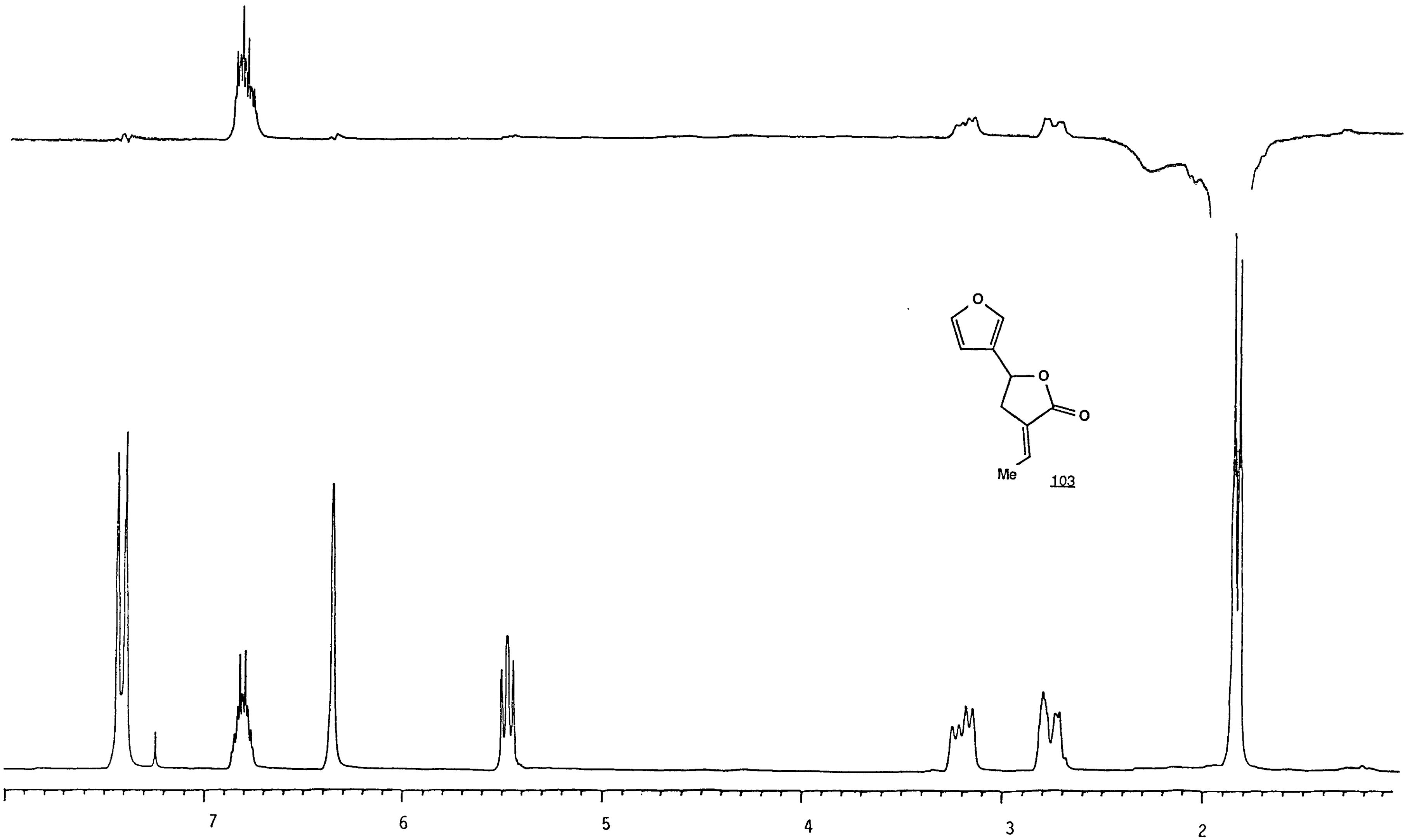


Figure 4.

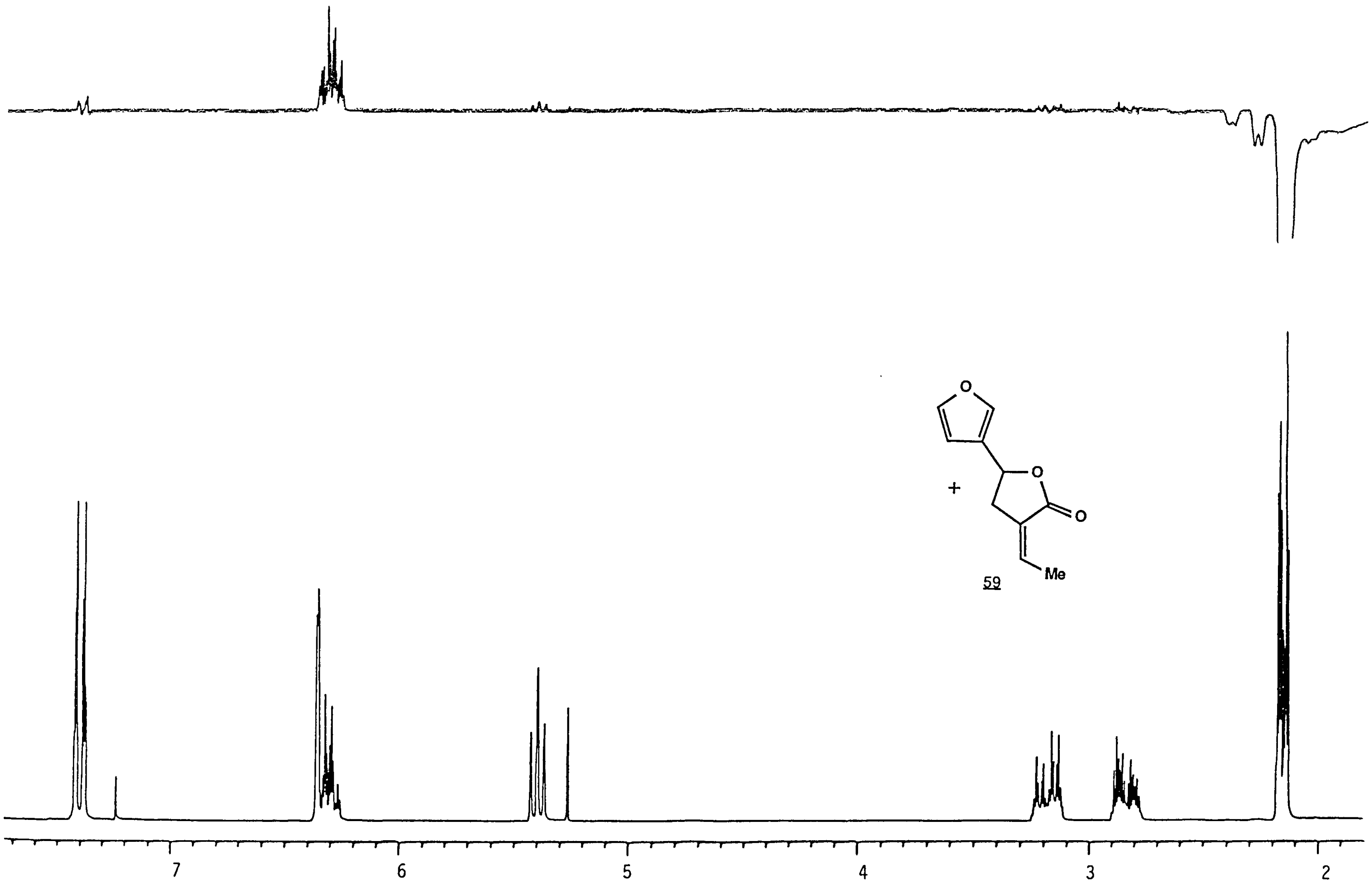
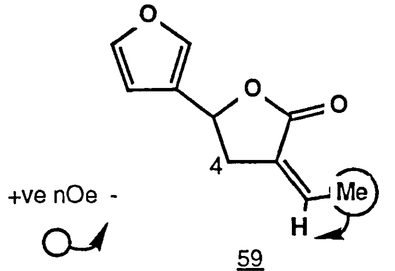


Figure 5.

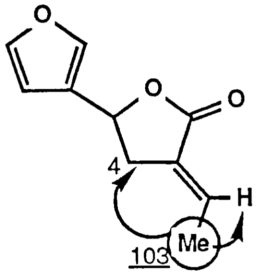
of the β-hydrogen signal, attributed to long range homo-allylic coupling, and not, when in comparison to figure 4, a positive nOe result.



59

nmr data (δ)

Me	2.17, dt,	J 7.3 2.3 Hz
C4-H2.83,	ddquint,	J 15.5 6.5 2.3 Hz
C4-H3.18,	ddquint,	J 15.5 7.5 2.3 Hz
C=CH 6.31,	qt,	J 7.3 2.3 Hz



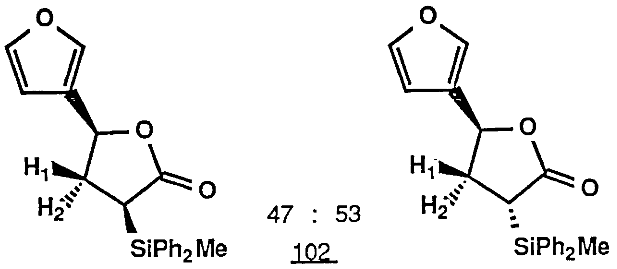
103

nmr data (δ)

Me	1.84, dt,	J 6.8 2.0 Hz
C4-H2.85,	ddd,	J 16.0 5.5 3.2 2.0 Hz
C4-H3.20,	dddq,	J 16.0 8.3 3.2 2.0 Hz
C=CH 6.81,	qt,	J 6.8 3.2 Hz

Unfortunately, it was found that upon increasing the scale of the elimination reaction, the Z : E ratio fell to only around 75 : 25, and could not be improved upon by alteration of the reaction conditions. However, the two isomers were readily separable by preparative high pressure liquid chromatography, leading to the synthetically necessary geometrically pure olefins in reasonable quantities.

Having achieved a high sterioselectivity with this route, we next investigated the possibility of stereocontrolled preparation of the ethylidene lactone (59) using the diphenylmethylsilyl route,[33] as this had the advantage of needing only two reaction steps, and did not involve the formation of relatively unstable intermediates such as the silyl enol ether (100). Treatment of the lactone (64) with lithium di-isopropylamide (LDA) followed by diphenylmethylsilyl chloride gave a diastereomeric mixture of the required adduct (102) in 67% yield. As for the butyrolactone system (section 2.3), no products from silylation on the carbonyl oxygen could be detected. The two diastereoisomers proved separable by column chromatography to give a 57 : 43 ratio of trans to cis isomers, with assignments again based on the splitting patterns of the β-hydrogens, in comparison with the analogous trimethyl silyl diastereoisomers (104) and (105).



47 : 53

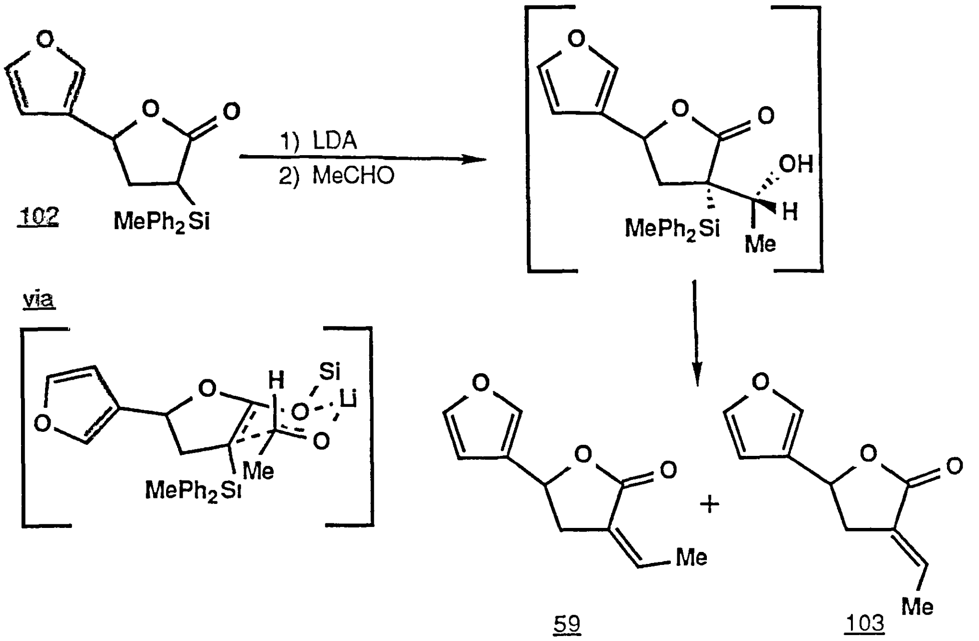
102

nmr data for H_1 and H_2 (δ)

2.42 - 2.51, m

2.09, ddd, J 13.0 11.3 9.3 Hz
2.62, ddd, J 13.0 9.7 7.0 Hz

Deprotonation of the silyl compound (102) with LDA, followed by treatment with acetaldehyde and heating to reflux gave the required elimination products in 55% yield, but with a Z : E ratio of 2 : 7 determined by capillary gas chromatography. Although a higher overall yield of the ethylidene compounds from the starting lactone (64) was obtained by this sequence as opposed to the trimethylsilyl route (34% compared to 23%), the geometrical ratio was unsatisfactory, giving a lower overall yield of the required Z isomer (59) (7.6% compared to 17.3%). It was felt that the lithium enolate aldol reaction may have been occurring with a similar transition state to that for the titanium mediated trimethylsilyl route, and thus some diastereoselectivity might have occurred, as shown in scheme 51. Therefore, elimination of the unisolated aldol product from the reaction between the lithium enolate of (102) and acetaldehyde was effected using boron trifluoride. This led to a change in the geometrical ratio of (59) : (103) to 45 : 55 in a 75% yield, thus indicating that, assuming an anti elimination of the silyl alcohol, no diastereoselection in the aldol process had occurred.



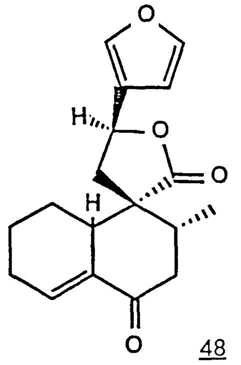
Elimination	ratio (59 : 103)
Thermal	22 : 77
$BF_3.OEt_2$	45 : 55

Scheme 51.

The possibility of achieving some selectivity by transmetallation of the lithium enolate of (102) with titanium was considered, but the stereoselectivity of the trimethylsilyl route, plus the ability to preparatively separate the two isomers, led us to choose the first method as the means of preparation of the required dienophile (59).

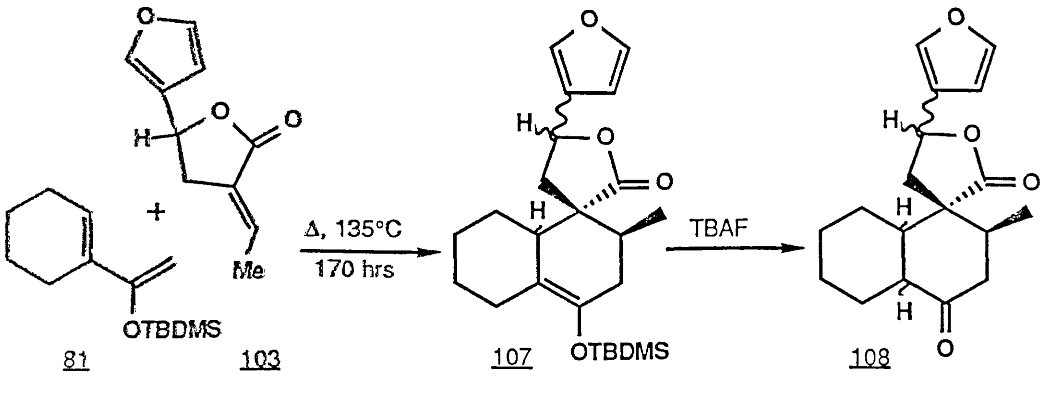
3.4. Preparation of Enone Intermediate (48).

With the required dienophile in hand, albeit in racemic form, we turned our attention to the preparation of the key intermediate (48).



48

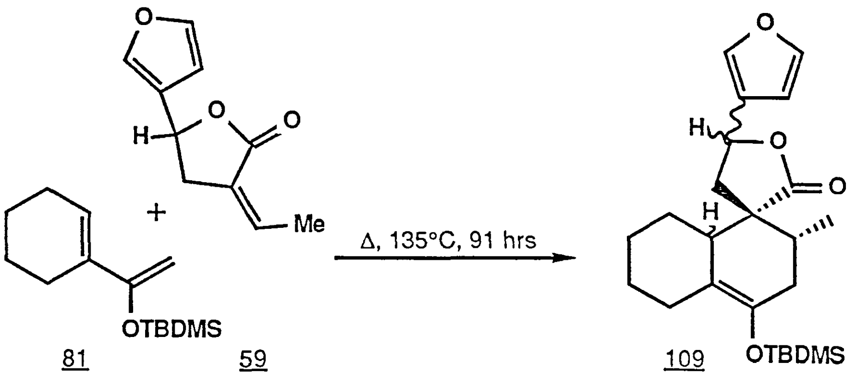
During the preparation of the dienophile (59), a usable amount of the E isomer (103) had also been prepared in a geometrically pure form, and it was considered that this dienophile would provide an excellent model for the crucial cycloaddition reaction. The E-ethylidene lactone (103) was mixed with an excess of the t-butyldimethylsilyl diene (81), together with a trace of hydroquinone to suppress polymerisation, in a presilylated pressure vessel, and evacuated. Monitoring of the reaction by thin layer chromatography indicated a steady reaction at 135-140°C, with complete consumption of the dienophile after 170 hours, and with evidence of only minor decomposition of the diene under the reaction conditions. Work up of the reaction without hydrolysis of the resultant enol ether gave the Diels-Alder product (107) as a mixture of diastereoisomers. The product was contaminated with 1-acetylcyclohexene from the decomposition of the diene, which was inseparable by chromatographic means. The furan proton signals in the high field nmr indicated the presence of at least two isomers, but a greater number was indicated by the complexity of the C_8-methyl signal, though this was partially obscured by the t-butyl signal. A portion of the mixture was therefore treated with tetrabutylammonium fluoride to hydrolyse the silyl enol ether, and thus to facilitate the removal of the 1-acetylcyclohexene contaminant and clarify the proton nmr (scheme 52).



Scheme 52.

Ketone (108) was obtained as a mixture of apparently three major diasteroisomers, in the ratio of 5 : 3 : 2 as indicated by gas chromatography and high field nmr. Unfortunately, these proved inseparable by either conventional column or high pressure liquid chromatographical techniques, and the complexity of the high field proton nmr precluded any further elaboration of the component structures.

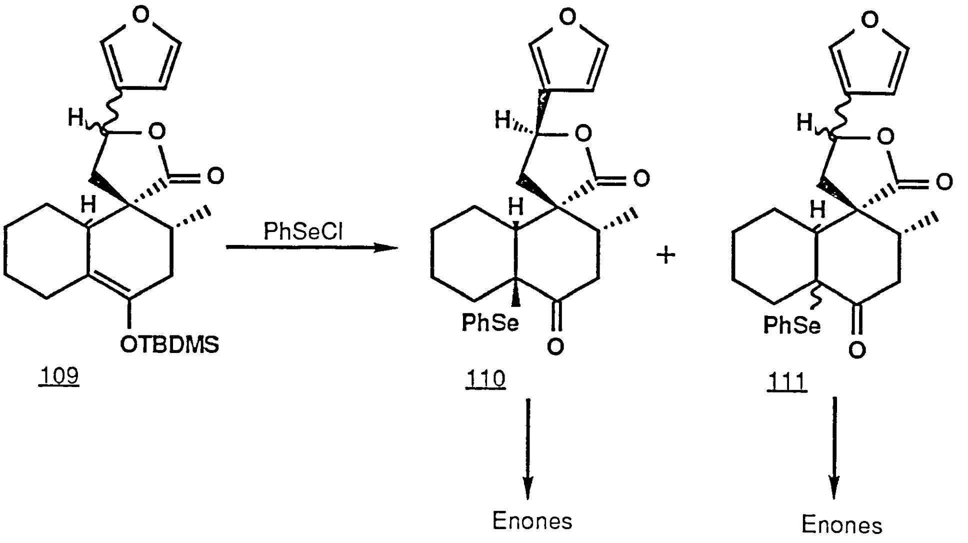
The cycloaddition reaction of the Z dienophile (59) with diene (81) proved more facile, with complete reaction occurring after only 91 hours under the same conditions. The isolated products were again contaminated with 1-acetylcyclohexene, but this proved separable by high pressure liquid chromatography, to give a mixture of diastereoisomers of adduct (109), with apparently three components in the ratio of 6 : 3 : 1 by gas chromatographic analysis (scheme 53).



Scheme 53.

It was considered that these diastereoisomers would prove to be separable as the corresponding enones, and this transformation was considered next. Attempts to form the enone from (109) directly by treatment with palladium acetate and benzoquinone[37] proved unsuccessful, as did the use of the palladium/triphenylphosphine system devised by Tsuji.[48] The use of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) has been documented as effecting the transformation of a silyl enol ether to an enone,[49] but extended heating with a large excess of freshly sublimed DDQ led to only quantitative recovery of the enol ether (109). Although we had hoped to perform the transformation in a single step, this did not prove viable, and the use of a selenated intermediate was therefore considered. Treatment of the diastereomeric mixture from the cycloaddition with phenylselenyl chloride gave two selenation products. The major of these was apparently a single diastereoisomer (110) as indicated by high field nmr, obtained in a 44% yield, whilst the minor product (111), obtained in a 26% yield, was a mixture of at least two diastereoisomers.

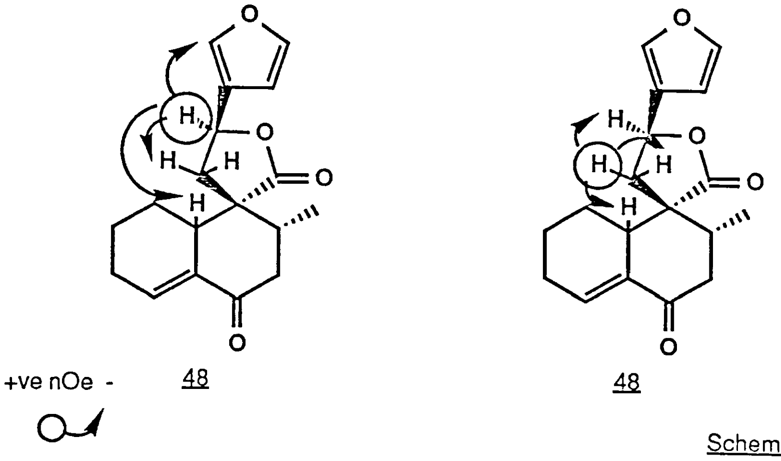
Although it was hoped that the major product was the desired diastereoisomer, it was considered that the enone system would prove more readily usable for extensive charecterisation studies, and therefore the two selenation products (110) and (111) were treated with meta-chloroperbenzoic acid to effect syn elimination of the selenoxides (scheme 54).



Scheme 54.

The major selenide (110), after oxidation and elimination, consistently gave two products in a 3 : 1 ratio. These products proved separable by high pressure liquid chromatography, and both contained an enone system, as indicated by infra-red spectroscopy.

High resolution nmr appeared to show both compounds as single diastereoisomers, but only the minor product exhibited the expected enone signal at δ7.03. ^{13}C nmr of the minor product showed no appreciable twinning of signals. Nuclear Overhauser investigation was used to determine the relative stereochemical relationship of the C_9, C_{10}, and C_{12} positions (figure 6). Irradiation at the C_{12} proton led to a positive nOe response at the signal at δ2.76, assigned as the C_{11} proton cis to the C_{12} proton, whilst a coupled response at δ2.12 indicated the trans C_{11} proton. Other positive responses were noted at the furan signals, and the signal at δ1.43. Irradiation at the δ2.76 C_{11} proton gave positve nOe responses at the other C_{11}position, the C_{12} proton signal (δ5.40), and also at δ1.43. This signal consisted of a quartet, not apparently coupled to the methyl doublet, and was consequentially assigned as the C_{10} proton of the desired enone (48) (scheme 55).



Scheme 55

For the major elimination product, the high field nmr showed a lack of both an enone proton around δ7 and a signal around δ1.4, assigned as the C_{10} proton in the minor isomer. Consideration of these lacking signals led us to conclude that the major product was the 5-10 enone (112). Selenation of the enol ether (109) could be expected to have occurred from the β-face, by analogy to the hydrolysis product of the

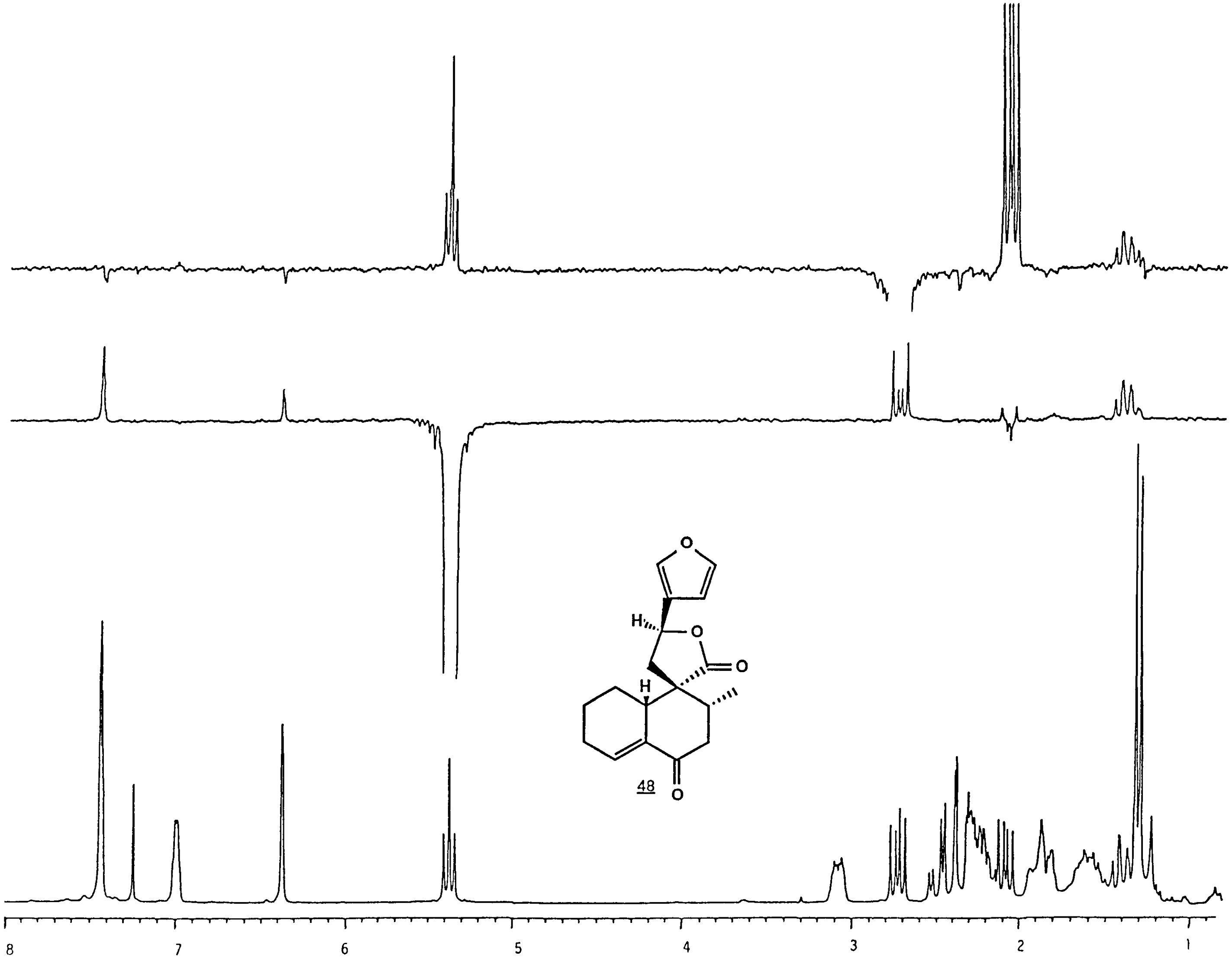
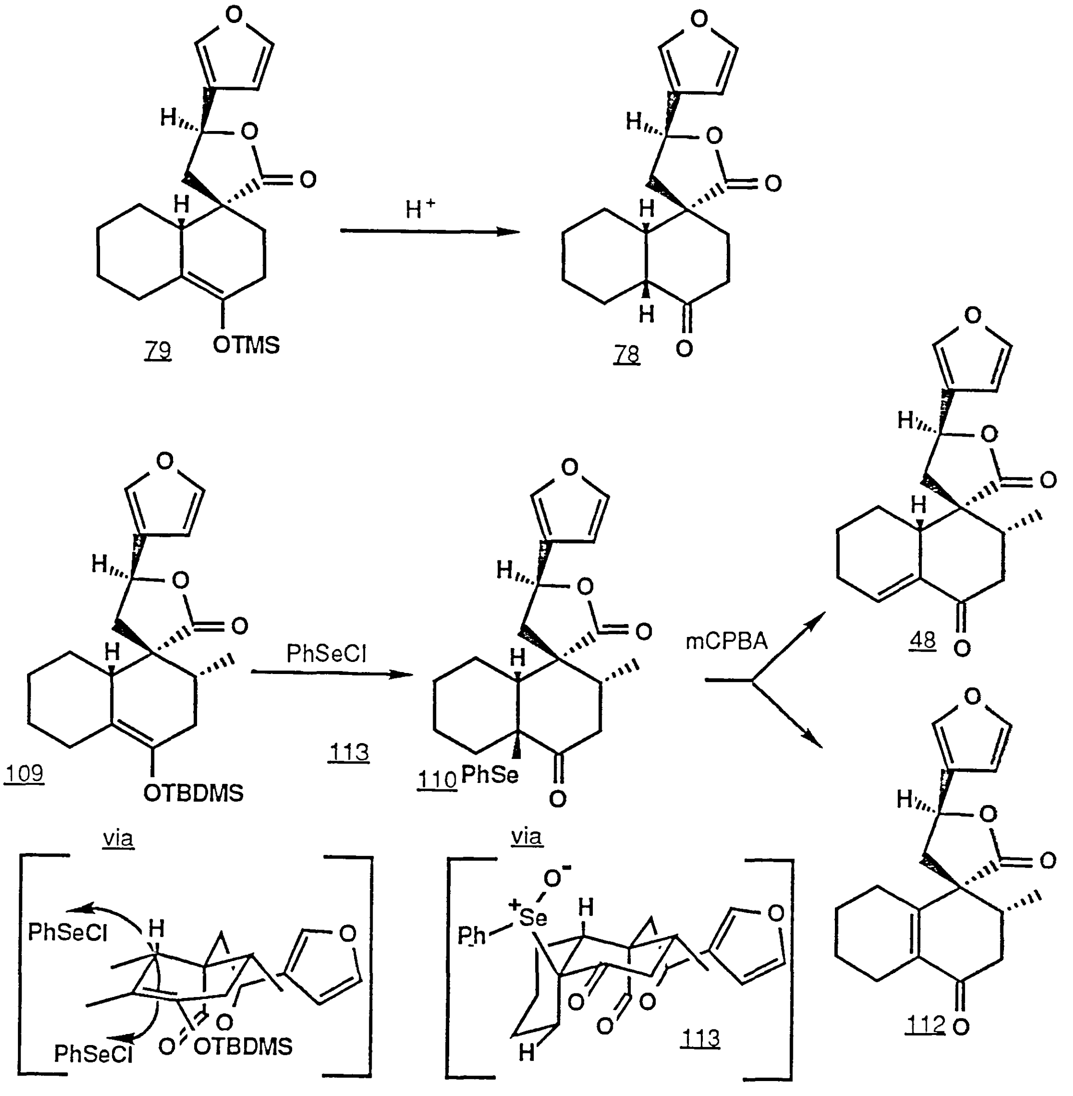


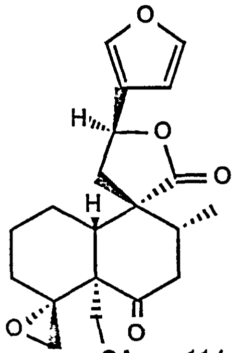
Figure 6.

model system (78), due to the steric hindrance of the α-face caused by the lactone carbonyl. Models of the cis decalin selenide (110) and the corresponding selenoxide (113) show an elimination across the ring junction favoured, with the C_{10} proton held in a syn orientation. Elimination to give the 4-5 enone (48), where the C_4 proton is in a gauche position relative to the selenoxide, appears to be disfavoured by possible steric interaction between the phenyl ring and decalin protons (scheme 56).


79
OTMS
H⁺
78
109
OTBDMS
PhSeCl
113
110
PhSe
mCPBA
48
112
via
PhSeCl
PhSeCl
OTBDMS
via
Ph
Se
O⁻
113

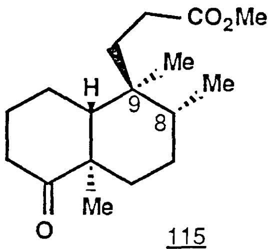
Scheme 56.

Comparison of the minor product (48) with teucrin H_3 (19-acetyl-gnaphalin) (114)^{50} ,a natural compound containing a similar 6-oxo functionality, showed two major discrepancies (figure 7). The methyl doublet signal in the synthetic compound occurred at δ1.35, whilst that of the natural product was at δ1.07. Also, the signal for the C_7-α proton in the natural compound occurred as a triplet (δ3.53) whereas in the synthetic compound, the corresponding signal (δ3.12) appeared as a multiplet.



114

It was thought that conformational differences for the two systems might account for the apparent discrepancies. The change in the methyl chemical shift was significant, as a study[51] carried out on the methyl signals of various simple natural clerodanes such as (115) has shown that the nmr signals for methyls at the C_8 and C_9 positions differ by around 0.2 ppm depending on the orientation of the methyl groups, with an axial methyl consistantly occurring at a higher δ value.



115

Calculations carried out using a computer molecular modelling system[52] also indicated that the methyl group in the natural compound (114) adopts an equatorial position, whilst in the synthetic enone (48) the minimum energy conformation has the methyl in an axial

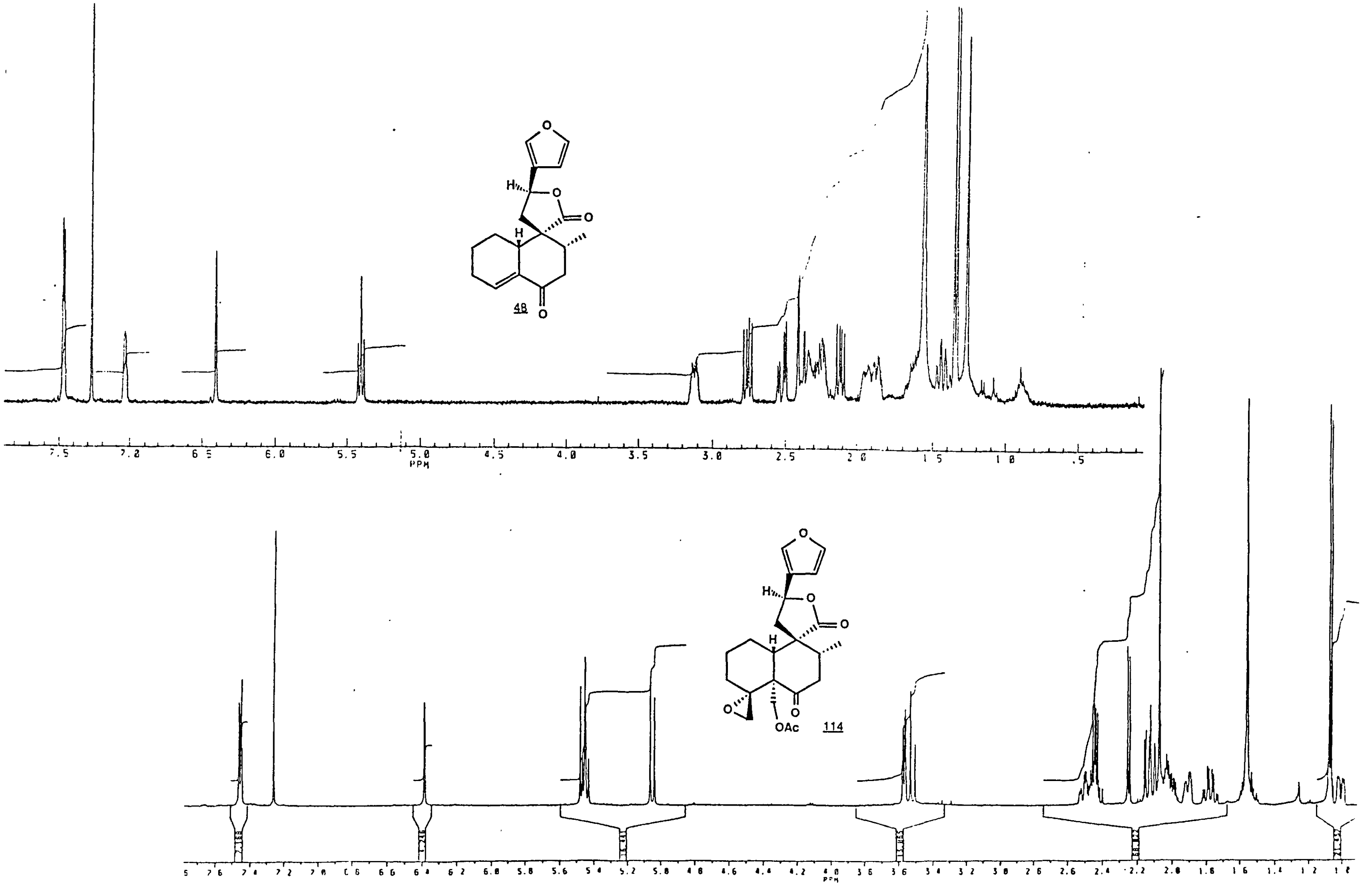
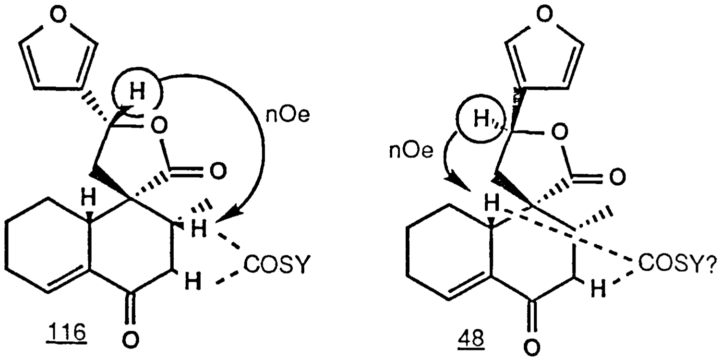


Figure 7.

orientation (figure 8).

This conformation would explain the apparent difference in the C_7-αH signal, since for teucrin H_3 (114) this proton is coupled to its geminal proton, and to a trans-diaxial C_8 proton, giving the triplet signal. In the synthetic (48) one would expect a geminal coupling, but only a gauche coupling to the C_8 proton. However, this still did not explain the complexity of the signal, nor could the assignment of the δ3.12 signal as the C_7 proton be justified. In the natural product (114) the C_7-α proton is influenced both by the adjacent carbonyl, and by a through space effect from the lactone carbonyl, thus deshielding this proton. In the enone (48), however, if the axial methyl structure was correct, the lactone carbonyl is held away from this position. A 2 dimensional COSY spectrum was obtained for the δ1.0-δ3.5 region in order to clarify the couplings within the system (figure 9). The assignment of the C_{11} protons from the earlier nOe studies was confirmed, with the signals at δ2.12 and δ2.76 showing a strong coupling. However, the signal at δ3.12, thought initially to be a C_7 proton, showed a coupling to the signal at δ1.43, assigned by the earlier nOe studies as the C_{10} proton. This led us to doubt our original assignment and nOe interpretations, since a coupling between these two signals would be expected if the δ1.43 proton was the C_8-H signal. Consideration of this fact along with the previous nOe results would imply the structure was the C_{12} epimer of (48), compound (116) (scheme 57).

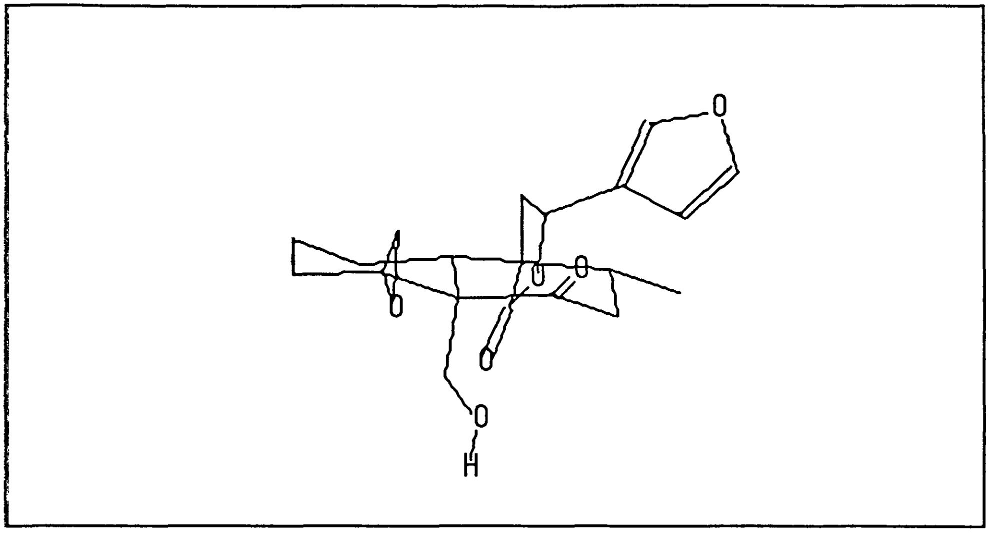


116

48

Scheme 57.

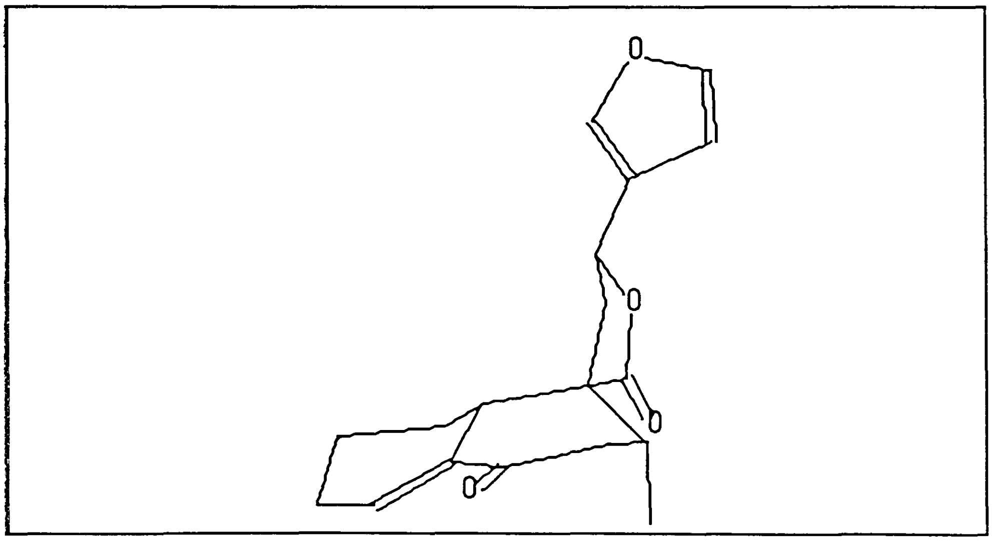
MODEL Version KSIC 1.3 MINIMIZATION MODE
Structure Name: Teucrin H-3 (114)



```
MM2 STRAIN ENERGY =     79.6254 (     79.6254) KCAL/MOLE

ESTR =      7.2823     EBND =     36.0901
ES-B =      0.5707     ETOR =     26.1474
EVDW =      9.1822     EDIP =      0.3527
```

MODEL Version KSIC 1.3 MINIMIZATION MODE
Structure Name: Synthetic enone (48).



```
MM2 STRAIN ENERGY =     32.8115 (     32.8115) KCAL/MOLE

ESTR =      2.0224     EBND =     17.1381
ES-B =      0.4092     ETOR =      5.2128
EVDW =      8.2198     EDIP =     -0.1907
```

Figure 8.

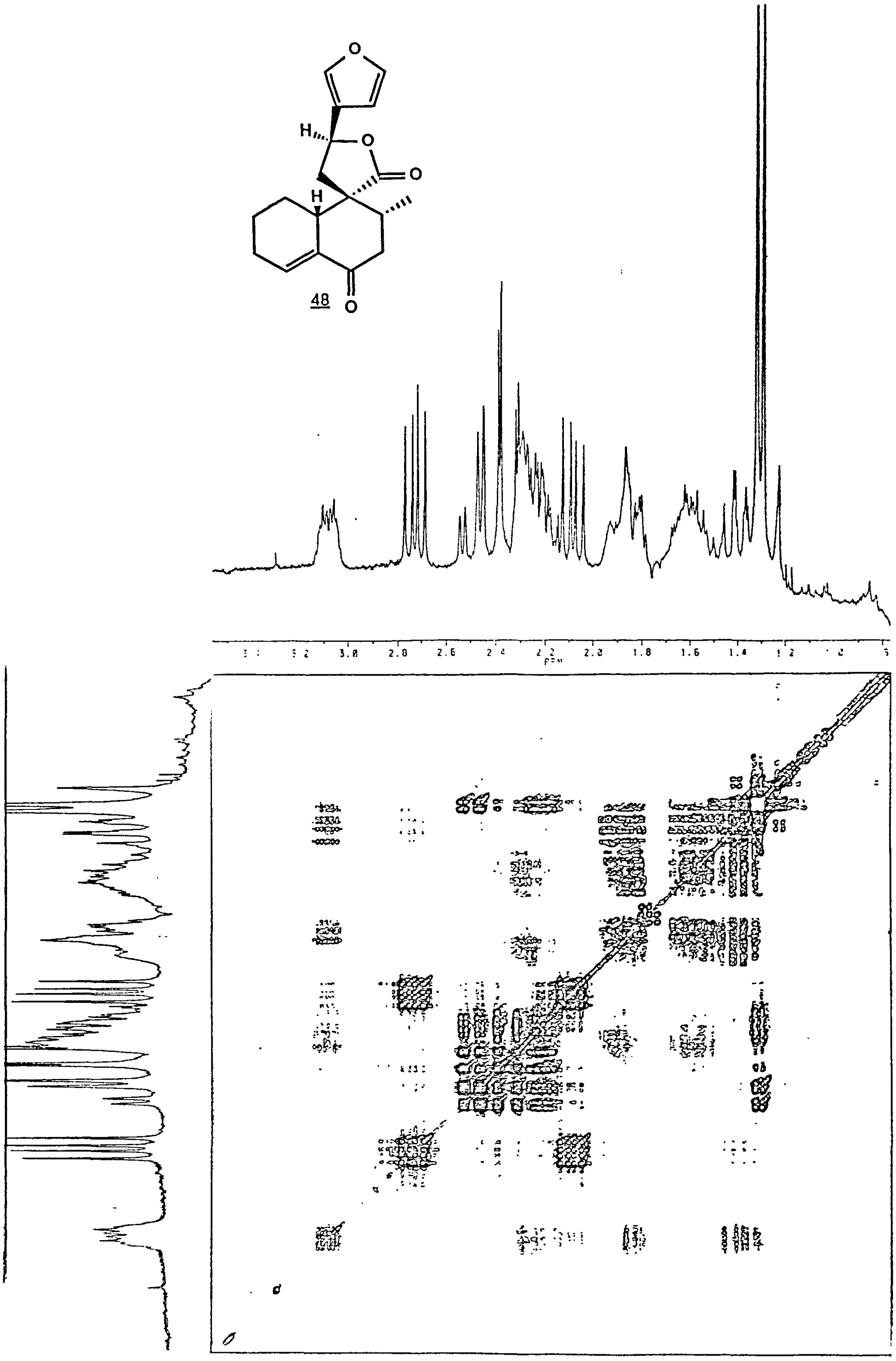


Figure 9.

However, the 2 dimensional spectrum also showed that the methyl signal was coupled to two protons at δ2.25 and δ2.52, and only possibly coupled to the δ1.43 signal. As one would expect this last coupling to be the major signal for methyl coupling in (116), it was considered that the possible coupling was merely an artifact of the strength of the methyl signal, giving a symmetrical pattern on the 2D spectrum both above and below the methyl signal. The discrepancy of the coupling constants for the methyl doublet (J=7Hz) and the δ1.43 quartet (J=11Hz) gave another reason for disregarding (116) as the possible structure. The signals at δ2.52 and δ2.39 both showed a geminal coupling of 17.5Hz, with coupling between the two signals indicated by the 2D spectrum, along with a coupling of the δ2.52 signal to the methyl doublet. A calculation of the splitting pattern of the C_8 proton signal based on the δ2.52 and δ2.39 signals being the C_7 protons showed a strong resemblance to the signal at δ2.25, already shown coupled to the methyl doublet by the 2D spectrum, and thus this signal was assigned as the C_8 proton (figure 10).

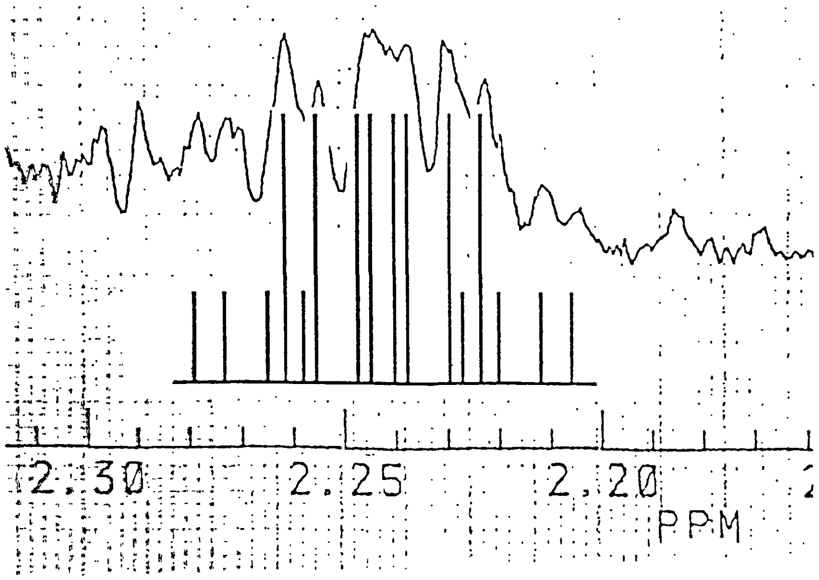
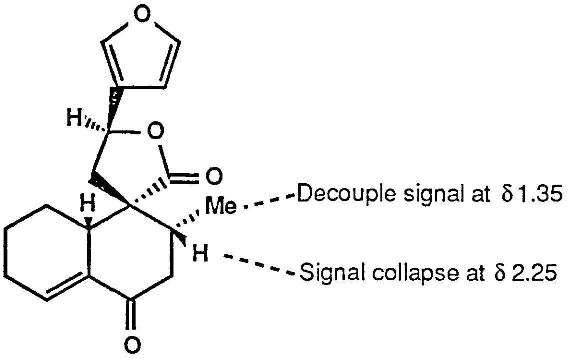


Figure 10.

However, this still left the signal at δ3.12 as unassigned. Consideration of the proposed conformer of (48) (scheme 52) showed a possible through space deshielding of the C_1-α proton by the lactone carbonyl and, in conjunction with the COSY demonstrated coupling of this signal to the C_{10} proton, thus led us to assign the δ3.12 signal as the C_1-α proton.

Final confirmatiom of the proposed structure was achieved by a decoupling experiment (figure 11). Decoupling of the C_8-Me signal (δ1.35) gave no change to the signal at δ1.43, but gave a collapse of the multiplet at δ2.25. This was consistent with the structural assignements for enone (48), with the δ2.25 signal assigned as the C_8 proton, rather than for enone (116), where the C_8 proton was assigned as the δ1.43 signal (scheme 58).



48 Scheme 58.

Having exhaustively examined the product from the major selenation product (110), we turned our attention to the minor product (111). Syn elimination of the corresponding selenoxide led to a mixture of products (117), with at least three components in a 2 : 2 : 1 ratio indicated by capillary gas chromatography. These proved inseparable by high pressure liquid chromatography, though infra-red and mass spectra indicated that the products were enones of the correct molecular weight. High field nmr showed a complexity of signals, though interestingly the two major components gave methyl doublet signals widely separated, at δ0.87 and δ1.21. Consideration of these signals, in comparison to the results reported by Gayen[51] (vide

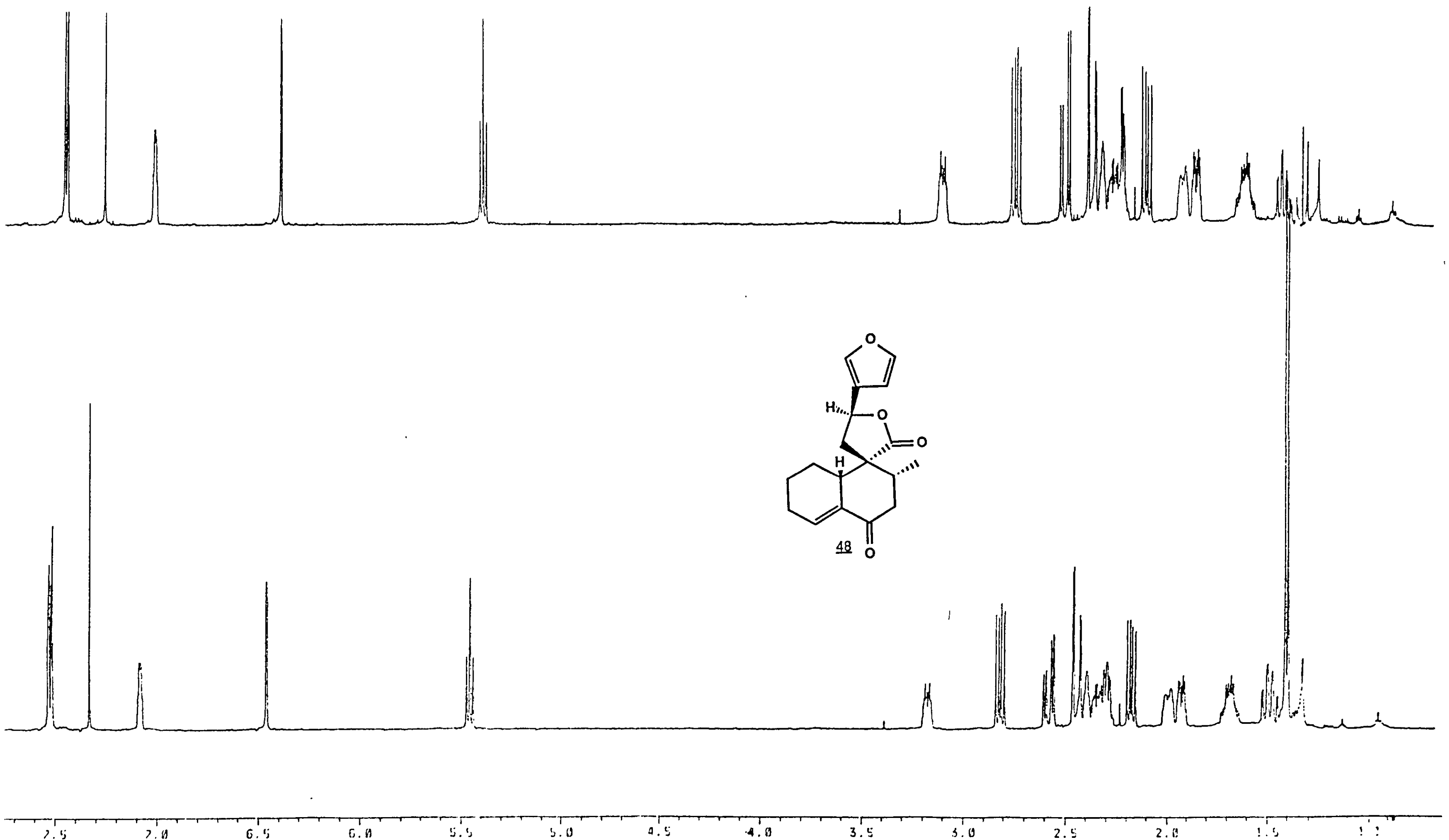
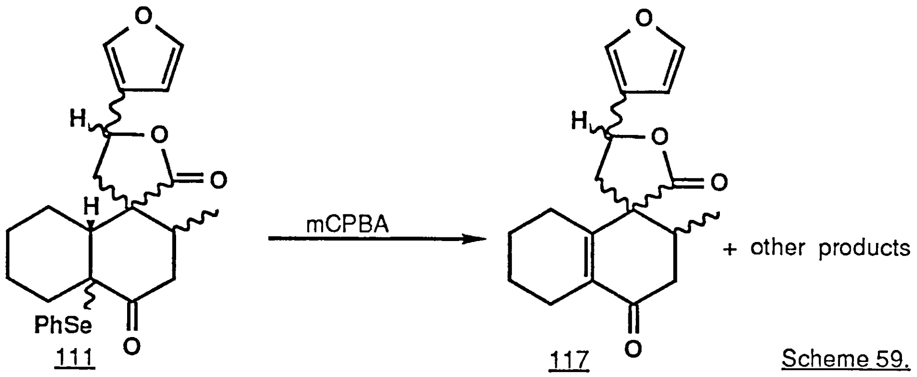


Figure 11.

supra), implied that the two major components differ in their orientation of the methyl substituent, with axial and equatorial methyls respectively. More disappointing, however, was the complete lack of an enone signal in the $\delta 6.5$-$\delta 7.5$ region, with not even an apparent minor signal. Extrapolation of our conclusions from the major selenide elimination (110 to 48/112) led us to conclude that the selenation of the enol ether (109) to give the minor component (111) had also occurred to yield the cis decalin selenide, and that elimination had occurred across the 5-10 ring junction to yield the enones (117) (scheme 59).



Scheme 59.

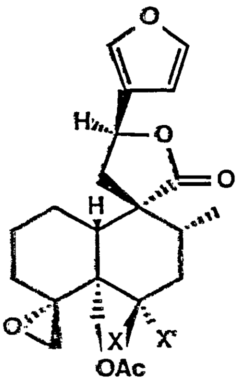
Moreover, the presence of at least three components in the mixture implied that the minor selenation products were those resulting from an alternative cycloaddition adduct, either via a non cis-endo reaction, or possibly the alternative regioisomeric outcome. However, the inability to separate the components precluded any further charecterisation of these products.

Having obtained the key intermediate for the synthetic strategy, enone (48), albeit as a minor isomer, we next turned our attention to synthetic approaches to the C_4-C_6 substitution patterns of various natural clerodanes.

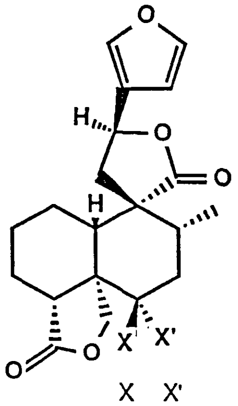
4. Model Systems for C_4-C_6 Substitution.

4.1. Introduction.

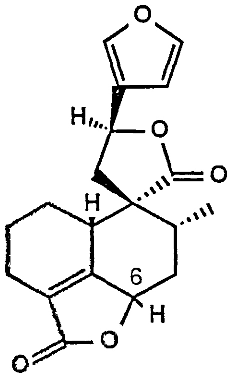
Four systems of C_4-C_6 substitution were chosen for investigation, incorporating three different approaches from the same enone intermediate (48). Three of these are typical systems found in clerodanes from the teucrium genus (Labiatae):[14] the 4,18-epoxy-19-acetoxy system typified by teucjaponins A (49) and B (50), and gnaphalin (51); a C_4-C_5 fused γ-lactone as in teuchamaedryn B (52), teucrin E (53) and 6-keto-teuscordin (54); and a C_4-C_6 fused unsaturated γ-lactone such as in teucvin (56) and teuflin (57). The fourth system chosen is found in compounds generated by the baccharis genus (Compositae): a C_4-C_6 γ-lactone with an C_5 hydroxymethyl substituent, such as in bacchotricuneatin B (118).[53] A synthetic approach to (118) and derivatives of this structure would require modifications to the dienophile of the previous strategy, in order to allow for the introduction of a C_8 methylene substituent rather than the methyl group.



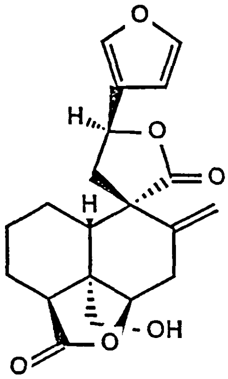
	R	X	X'
49	Ac	OH	H
50	Ac	H	OH
51	H	=O	



	X	X'
52	OH	H
53	H	OH
54	=O	



	C_6-H
56	β
57	α

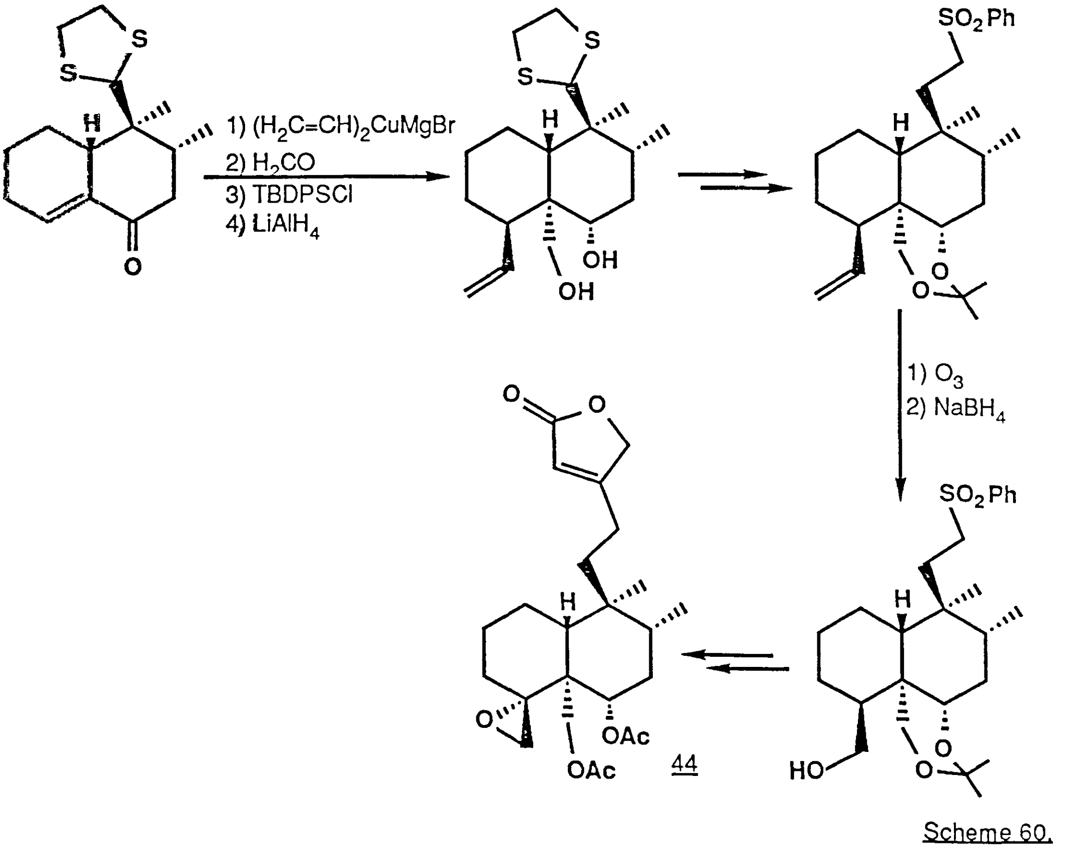


118

Of these natural products, all but those first detailed (49 to 51) possess a γ-lactone substituent with the carbonyl adjacent to C_4, and a common approach to these substitution patterns from the enone (48) was considered feasable. Furthermore, the arrangement of the substituents in the (52)-(54) and (118) compounds differ only in the hydroxyl unit used to form the γ-lactone, and thus a common approach to these systems, with careful use of protection, was envisaged.

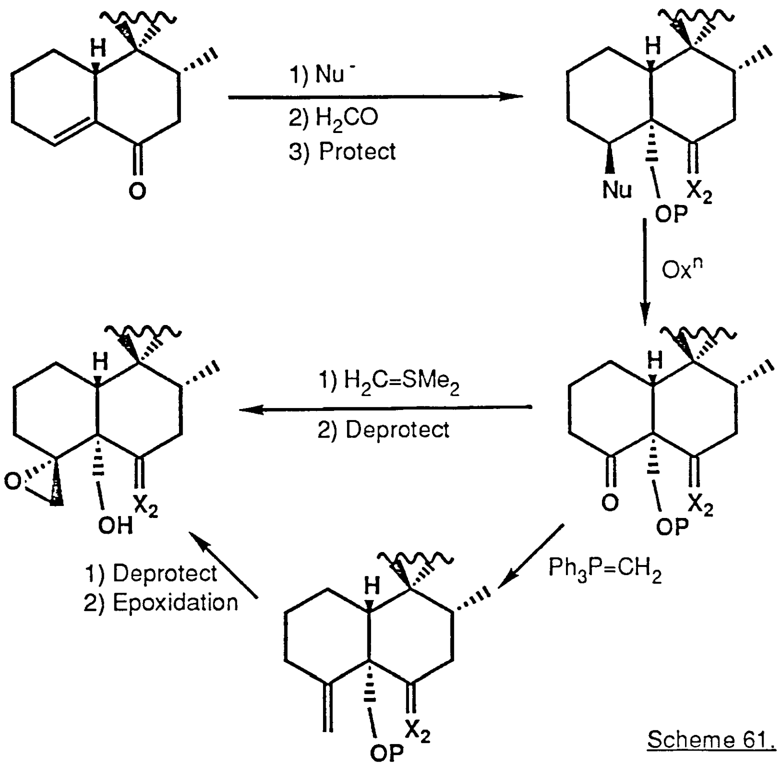
4.2. Approaches to the Epoxide Acetate System.

The substitution pattern in (49) to (51) is essentially that found in ajugarin 1 (44), differing in only the oxidation state at C_6. However, an approach similar to the ajugarin synthesis of Ley[9] (scheme 60) was not possible, due to the expected instability of the furan group to the ozonolytic conditions used to cleave the vinyl adduct to a hydroxymethyl substituent, and to cis hydroxylating agents (section 2.3) which could provide an alternative means of effecting the transformation.



Scheme 60.

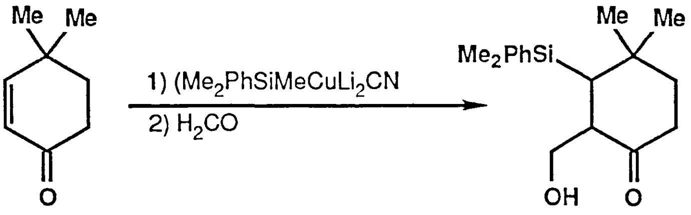
However, the introduction of the C_5 substituent by use of monomeric formaldehyde quenching of an enolate resulting from conjugate addition was considered the best method of introduction of the C_{19} carbon. An approach was considered using a heteroatomic nucleophile as the conjugate attacking species, with the resultng C_4 substituent acting as a masked carbonyl moiety, thus allowing for the introduction of the epoxide unit either by initial conversion of the ketone to the methylene compound, then hydroxyl directed epoxidation, or by direct treatment with a sulphur ylid[54] (scheme 61).



Scheme 61.

Initially, tin was chosen as the heteroatom, based on the work of Still.[55] However, attempts to obtain conjugate addition of the lithium salt of tri-n-butyl tin hydride to enones were unsuccessful. We next considered the use of silicon as a masked hydroxyl group, as reported by Fleming.[56] Cuprate reagents derived from dimethylphenylsilyl chloride were reported to add conjugately to enone systems. A solution of dimethylphenylsilyl lithium was therefore prepared by treatment of the respective chloride with lithium metal, preactivated by ultrasound, to give a dark red solution of the lithio species. The molarity of this solution was measureable by titration, and was found to remain constant over several weeks when stored at -30°C.

The initial choice of enone was the commercially available 4,4-dimethylcyclohex-2-enone (119). Preparation of a mixed cuprate species was effected by treatment of copper (I) cyanide with one equivalent of the silyl lithium solution, followed by one equivalent of methyl lithium, and this species was subsequently treated with enone (119). After apparent consumption of the starting enone (thin layer chromatography), the resultant enolate was quenched with a THF solution of monomeric formaldehyde, prepared by the method of Simpkins,[4] to yield the desired adduct (120) in 51% yield (71% based on recovered starting enone (119)) (scheme 62).

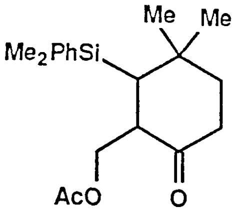


119

120

Scheme 62.

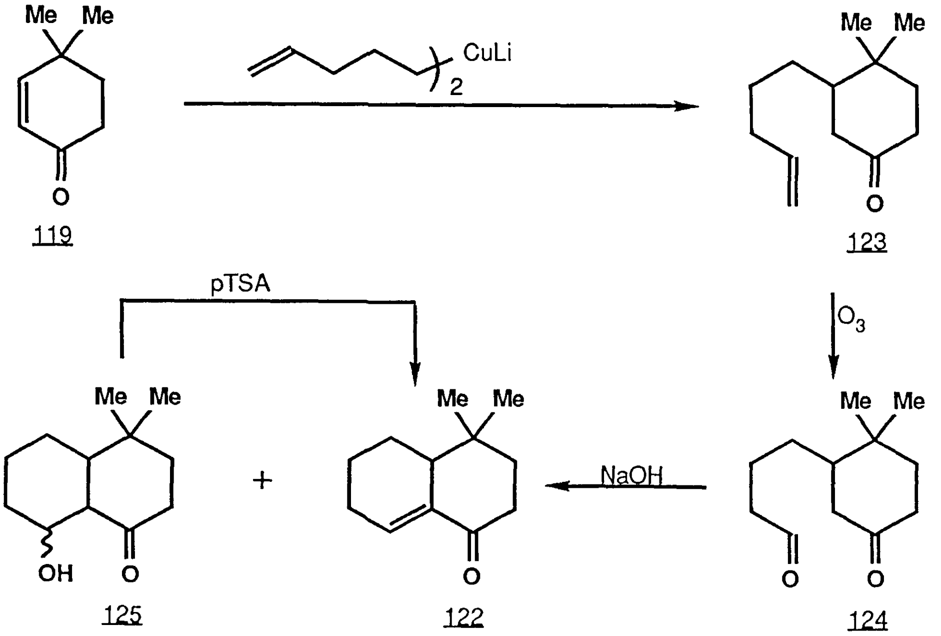
We had previously found that compounds with the α-hydroxymethyl ketone structure were susceptible to retro-aldol reaction, and so the adduct (120) was treated with acetic anhydride , pyridine, and 4-(dimethylamino)pyridine (DMAP) to yield the acetylated compound (121).



121

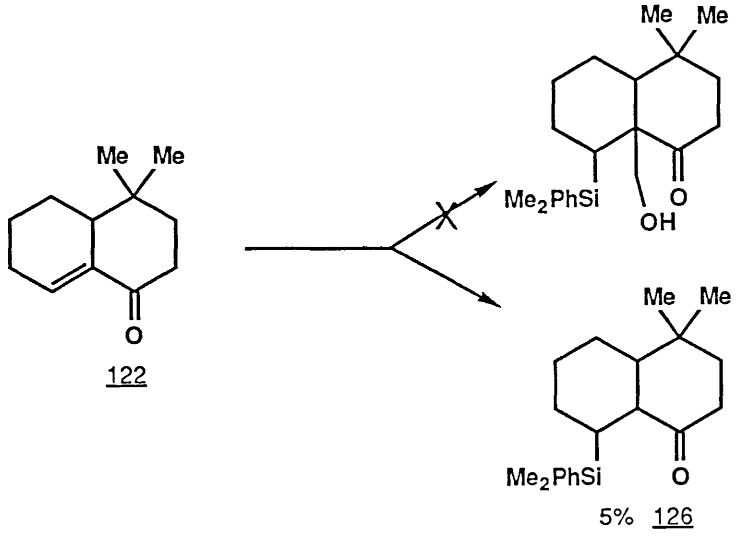
Transformation of the silyl group into a hydroxyl moiety had been reported as a two stage process, with initial exchange of the phenyl group for a fluorine atom, followed by oxidative cleavage of the silyl group.[57] Unfortunately, treatment of the acetylated compound (121) with tetrafluoroboric acid, followed by meta-chloroperbenzoic acid led to only deacetylation of (121), although the acetyl group had been reported stable to the reaction conditions.[57]

A more representative model enone (122) was also used, with enone (122) having already been used as a model in the approaches to ajugarin 1 (44).[4] Treatment of 4,4-dimethylcyclohex-2-enone (119) with the cuprate reagent derived from 5-bromopentene gave the product (123) in 89% yield. Ozonolysis of (123) led to the aldehyde (124) in essentially quantitative yield, and aldol condensation with sodium hydroxide gave the enone (122) in 35% yield, and the hydroxy compound (125) (43% yield), readily converted to the desired enone with para-toluene sulphonic acid (scheme 63).



Scheme 63.

However, all attempts to obtain conjugate addition of the silyl cuprate reagent, followed by formaldehyde quench of the resultant enolate, met with no success, though a small amount (5%) of conjugate addition product (126) was obtained (scheme 64).



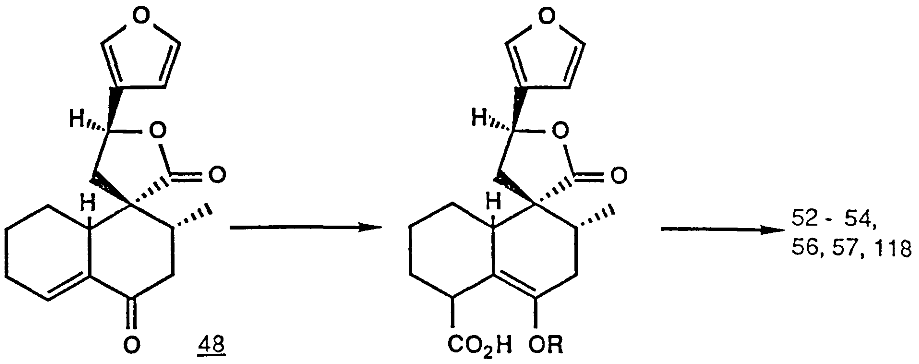
122

5% 126

Scheme 64.

4.3. Approaches to γ-Lactone C_{19} Compounds.

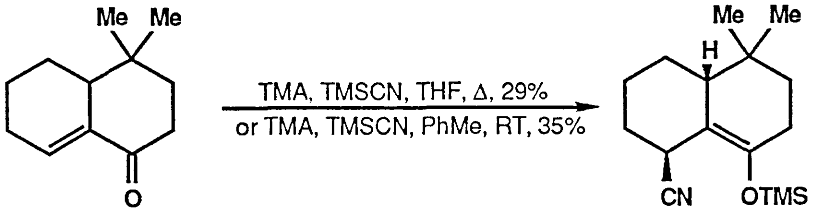
In order to prepare the lactone system of (52)-(54), and bacchotricuneatin B (118), the introduction of an acid group, in a conjugate manner, to enone (48) was envisaged. The product resulting should also be suitable for transformation to the des-C_{19} compounds (56) and (57) (scheme 65).



48

Scheme 65.

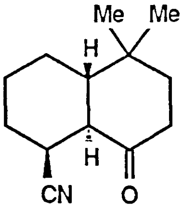
The use of a cyano group as a masked acid functionality was chosen, as hydrocyanation of enones in a conjugate manner has been documented in the literature.[58] Treatment of the model enone (122) with trimethylsilyl cyanide in the presence of trimethylaluminium gave the conjugate addition product, silyl enol ether (127), either in THF at reflux (29% yield), or in toluene at room temperature (35% yield), though all attempts to increase these moderate yields were unsuccessful (scheme 66).



122 127

Scheme 66.

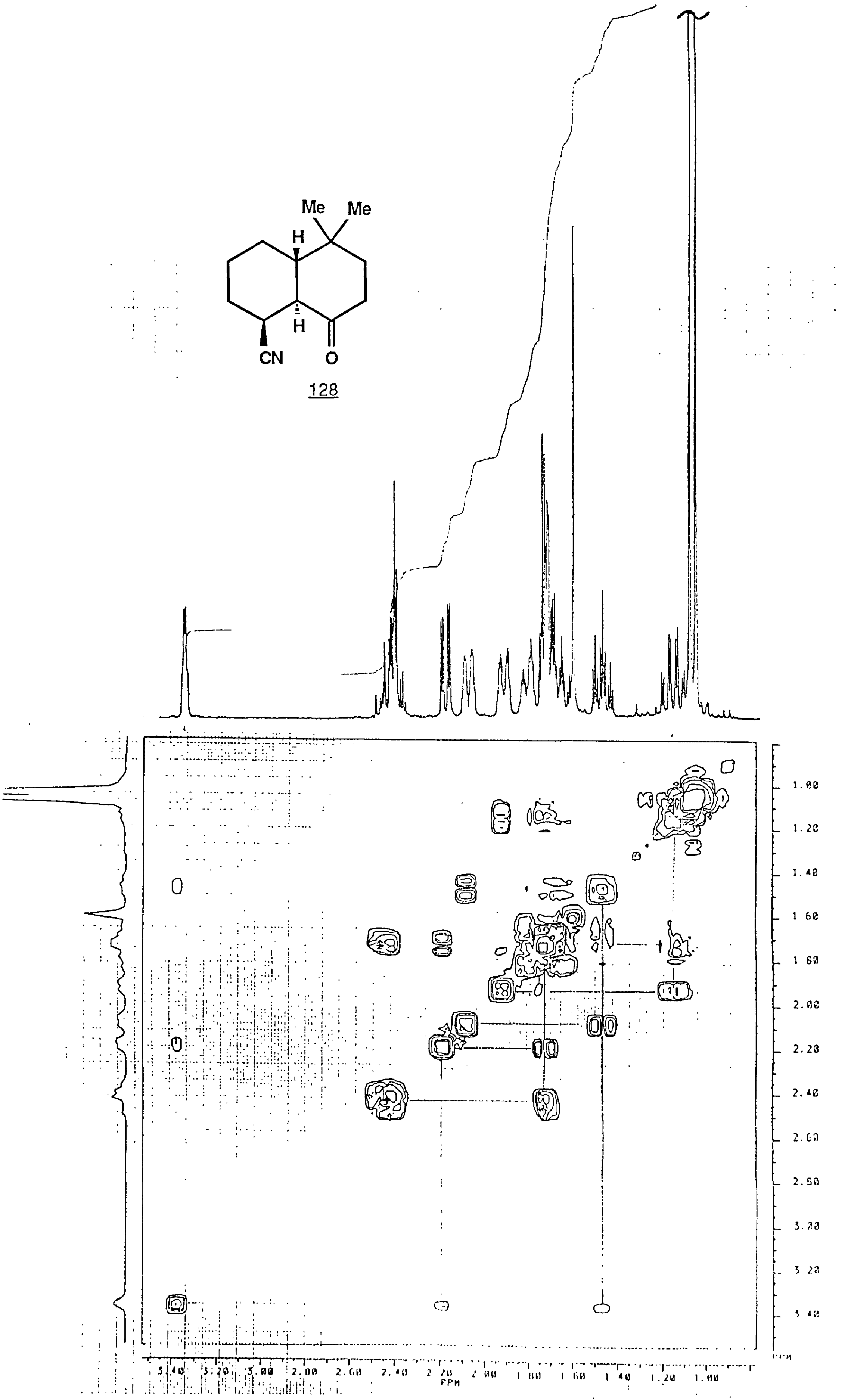
In an attempt to prove the expected stereochemistry of the adduct as the axial cyano product, and as an aid for interpretation of the spectra resulting from the more complex real system, a portion of this material was hydrolysed with dilute hydrochloric acid in THF to yield the ketone (128).



128

High field nmr of this compound showed the signal for the proton at the C_4 position as a complex doublet at $\delta 3.37$. The major coupling component of this signal was 3.8Hz, indicating an axial-equatorial or equatorial-equatorial coupling. No larger axial-axial coupling was present, as would be expected if the C_4 proton was in an axial orientation, thus confirming the cyano group as in the axial position (assuming a trans decalin product). To facilitate the assignment of the remaining signals, a 2 dimensional COSY spectrum was also obtained (figure 12). The C_4 proton showed coupling to a double doublet signal at δ2.19, and a triple triplet system at δ1.46. The coupling pattern of the δ2.19 signal indicated this proton was coupled to only one other proton, in the δ1.70-δ1.76 region, and thus this signal was assigned as the C_5 proton. The magnitude of its coupling to the C_{10} proton (J=12.5Hz) confirmed a trans decalin arrangement. The signal at δ1.46 was thus assigned as the C_3 axial proton, since the equatorial signal would not be expected to show two large couplings (geminal and axial-axial), but only a large geminal doublet together with splittings smaller in size. The 2D spectrum also identified the C_3 equatorial proton as the δ2.08 signal. The two proton signal at δ2.41 was assigned as the two C_7 protons, and thus the C_8 protons were indicated to be in the δ1.70-δ1.76 multiplet. The signal at δ1.14 showed three large couplings and one small, as would be expected from the C_1 axial position (geminal, two axial-axial, and axial-equatorial) and this was shown from the 2D spectrum to be coupled to the signal previously assigned as the C_{10} proton, and the signal at δ1.92, thus assigned as the C_1 equatorial proton. Finally, assignment of the C_2 axial and equatorial protons as the δ1.67 and δ1.81 signals was made, with both exhibiting the expected splitting patterns.

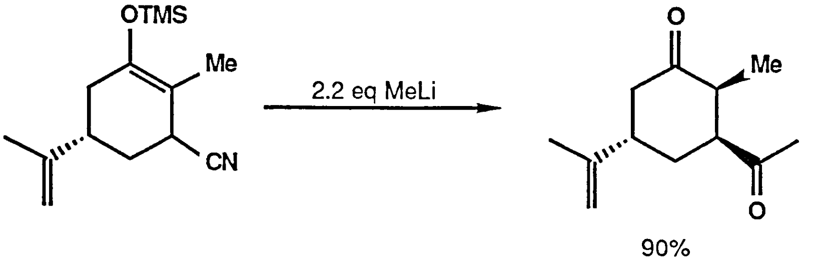
The next stage of the synthesis required the introduction of a C_{19} carbon, and use of the monomeric formaldehyde methodology with the silyl enol ether (127) was proposed. The possibility of protonation at the C_5 position occurring in competition with the desired monomeric formaldehyde quench meant the preclusion of fluoride desilylating agents (due to their standard water content), and the use of mineral acids to effect the desilylation. The generation of lithium enolates from silyl enol ethers with methyl lithium is well documented.[59] However, treatment of the silyl enol ether (127) with one equivalent of methyl lithium, followed by addition of the monomeric formaldehyde



128

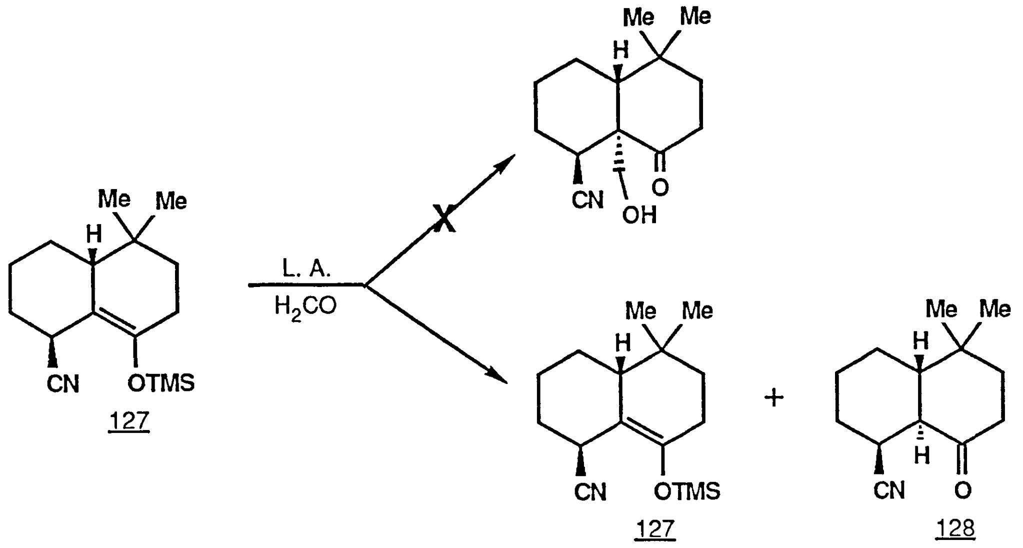
Figure 12.

solution led to a complex mixture of products, apparently due to attack of the methyl lithium on the nitrile group in addition to the silyl group, giving rise to ketone products. In retrospect, this result was not surprising, as the use of excess methyl lithium on cyano silyl enol ethers derived by the same route has been reported by Samson and Vandewalle[60] (scheme 67).



Scheme 67.

We next considered the use of Lewis acids to remove the silyl group,[61] thus allowing the required aldol condensation. The silyl enol ether had been prepared using trimethylaluminium, and it was therefore thought that milder Lewis acids might not effect the transformation, as was indeed found to be the case for zinc chloride, diethylaluminium chloride and boron trifluoride etherate. Tin tetrachloride gave no reaction at temperatures below -30°C, and at higher temperatures yielded only the ketone (128), even in the presence of a large excess of the monomeric formaldehyde solution. However, it had been shown in the studies towards ajugarin 1 (44)[4] that the monomeric formaldehyde rapidly polymerised at temperatures above -45°C, and it was therefore hoped that titanium tetrachloride might allow a lower reaction temperature. However, treatment of the enol ether (127) with titanium tetrachloride at -78°C gave no reaction, with cleavage of the silyl group only occurring on warming to -40°C, and the sole product was again the ketone (128), even in the presence of a large excess of freshly generated monomeric formaldehyde (scheme 68).



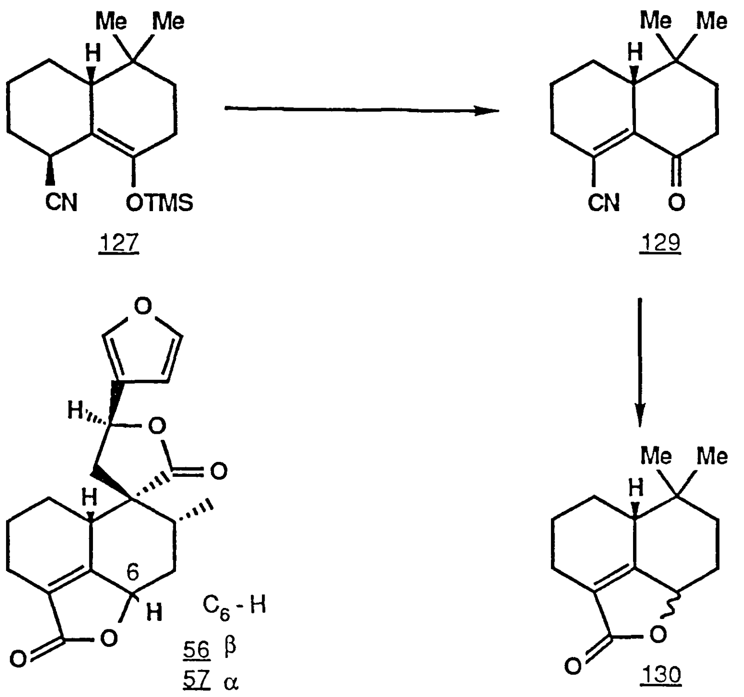
Lewis acid, conditions		% products	
$BF_3.OEt_2$	RT	95	0
$ZnCl_2$	RT	95	0
Et_2AlCl	RT	95	0
$SnCl_4$	-30°C	10	80
$TiCl_4$	-78°C	95	0
$TiCl_4$	-40°C	0	85

Scheme 68.

Without the ability to transform the silyl enol ether (127) into an enolate capable of an aldol attack on formaldehyde, we could not incorporate the C_{19} hydroxymethyl unit into our synthetic products, and thus we were constrained to approach the des-C_{19} compounds typified by (56) and (57).

4.4. Approaches to the γ-Lactone des-C_{19} System.

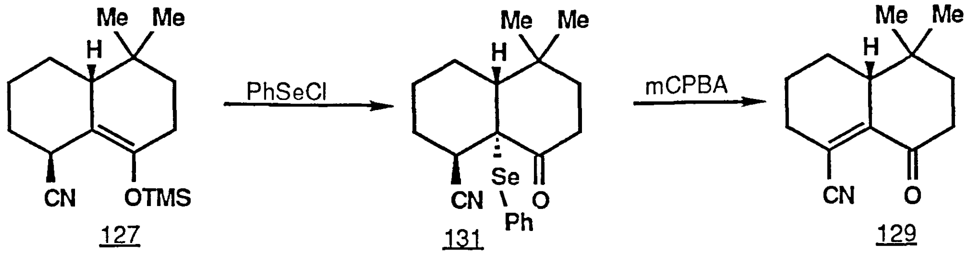
Having prepared the silyl enol ether (127), the transformation to a conjugated enone system (129) was next considered. Reduction of the ketone, and hydrolysis of the nitrile group should lead to the desired unsaturated lactone (130) (scheme 69).



Scheme 69.

The stability of the silyl enol ether (127) to Lewis acids had been surprising, but it was hoped that a direct transformation of (127) to enone (129) would be favoured, leading as it does to an extended conjugated system. However, treatment of the enol ether (127) with either of the palladium based reagents[37,48] used in section 3.4 to effect the desired reaction gave no success. Similarly, treatment of (127) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[49] gave no reaction, even with a large excess of freshly sublimed DDQ added portionwise over two days, in benzene at reflux.

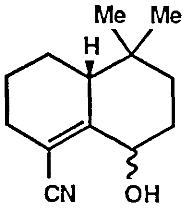
It was therefore decided to use a two step selenation and elimination route to the desired (129). However, unlike the problems observed during the preparation of the enone (48) (section 3.4), the selenation was expected to precede with formation of the trans decalin selenide (131), as in the case of hydrolysis to the ketone (128), due to the steric effect of the axial cyano group. This would then lead exclusively to the desired enone (129), favoured by conjugation, rather than across the ring junction, as this would require an anti elimination of the intermediate selenoxide (scheme 70).



Scheme 70.

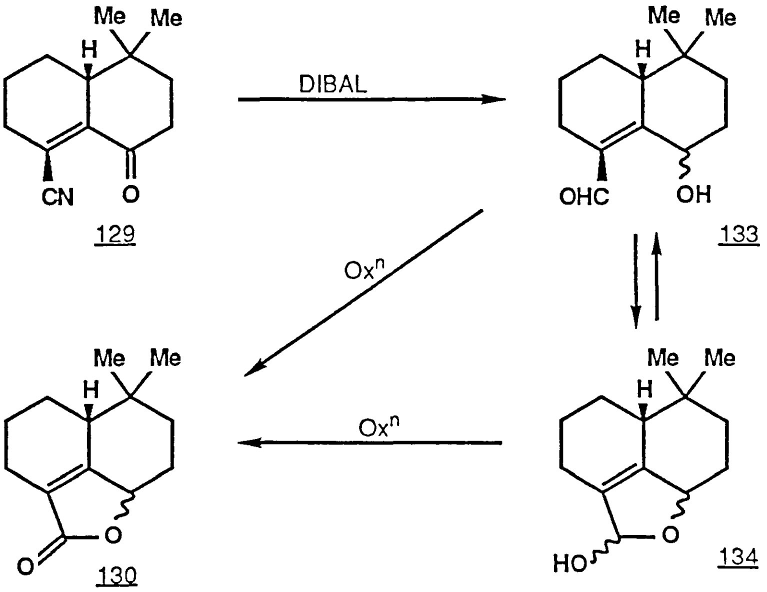
Treatment of (127) with phenylselenyl chloride smoothly led to the crystalline selenide (131) in 65% yield. Oxidation with meta-chloroperbenzoic acid at 0°C gave only a very slow reaction, and it was found necessary to allow the elimination to occur at room temperature, although the reaction did not procede to completion, to yield 59% of the required enone (129) (75% based on recovered (131)).

With the required enone (129) in hand, the transformation of this enone to the final lactone (130) was studied. The cyclisation of 3-cyano alcohols to γ-lactones has been reported,[62] and thus it was necessary to reduce the ketone functionality in the presence of the α,β-unsaturated nitrile. Sodium cyanoborohydride was chosen to accomplish this reaction, due to its recorded ability to reduce enone systems to the corresponding allylic alcohols, and its unreactivity towards the nitrile group.[63] Cyanoborohydride was added to the enone (129), and the pH of the reaction held at 4-5 by the addition of ethanolic hydrochloric acid, monitored by the use of congo red indicator. However, although the indicator gave evidence of a reaction taking place, only a small amount of an apparently reduced material was evident, with over 70% recovery of the starting enone (129). The minor product was not the required alcohol (132), but an unidentifiable product, lacking nitrile functionality, as indicated by the infra-red spectrum.



132

Di-isobutylaluminium hydride (DIBAL) was next chosen as the reducing agent for the system. It was considered that the ability of DIBAL to reduce enones to allylic alcohols, and nitriles to the corresponding aldehydes[64] should lead to either the hydroxy aldehyde (133), or lactol (134), which could be readily oxidised to the required lactone (130) (scheme 71).

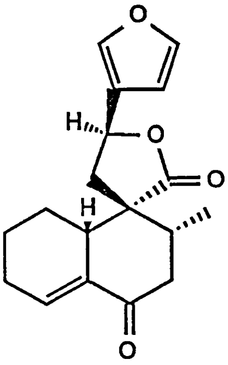


Scheme 71.

However, treatment of the enone (129) with DIBAL at room temperature or below, for extended periods of time, gave no reaction. The use of DIBAL in THF at reflux gave loss of the enone (129), but no aldehyde (133) or lactol (134) were available from the complex mixture of products obtained.

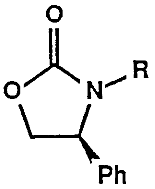
5. Future Considerations.

The preparation of the enone (48) marks the first synthetic approach towards natural clerodanes containing the furyl spirolactone arrangement.



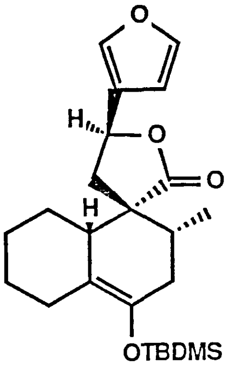
48

A chiral approach to (48) is still a desirable target, with the route from the ephedrine auxiliary the most promising of those tried, though an alternative approach using the methodology developed by Evans[65] would perhaps yield better results, based on a chiral auxiliary such as (135).



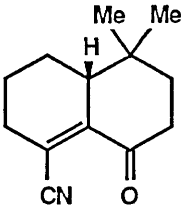
135

The Diels-Alder reactions were achieved in fairly good yields, though further improvement would appear unlikely unless an effective catalytic system can be devised. The greatest problem with the approach to (48) appears to be the incorporation of the desired 4-5 enone, though a direct transformation of the silyl enol ether (109) to the enone (48) by transition metal mediated reaction may be possible, although our investigation of the palladium based routes gave no positive results.



109

Finally, the incorporation of the C_4-C_6 substituents into the synthetic material appears to be more problematic than was originally thought, although the preparation of the model C_4-C_6 unsaturated lactone system requires only the perfection of a suitable reducing system for enone (129).



129

However, applicaton of this approach to the total synthesis, requiring as it does a selenation at the C_5 position, may present difficulties, as might any other approach to the alternative targets containing an α-substituent at the C_5 position, due to the steric inhibition of this centre by the lactone carbonyl, thus favouring the β-face for attack of the incoming species.

EXPERIMENTAL

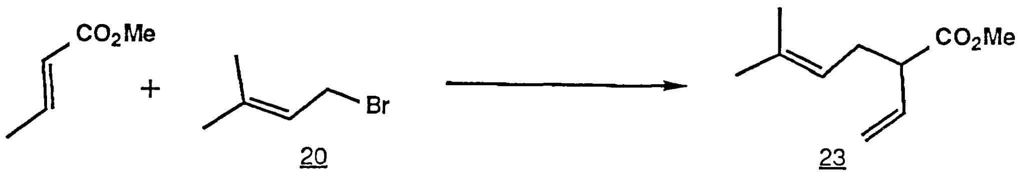
Experimental.

Melting points for solid products were determined using a Kofler hot stage apparatus and are uncorrected; products without melting points were colourless oils unless otherwise stated. Infra-red spectra were recorded on a Perkin-Elmer 983G grating infra-red spectrophotometer using thin film, solution in $CHCl_3$, or as pressed KBr discs. ^1H nmr spectra were obtained for solutions in $CDCl_3$ with Me_4Si as internal standard, and were recorded on a Varian EM-360A (60 MHz), Bruker WM-250 (250 MHz), Varian XL-300 (300 MHz), Bruker WM-400 (400 MHz), or Bruker AM-500 (500 MHz) machines. Mass spectra were determined with a VG micromass 7070B instrument. Elemental microanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory. Optical rotations were recorded on an Optical Activity AA-1000 polarimeter.

Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel F_{254} plates, and preperative chromatography was carried out on columns of Merck Kieselgel 60 (230-400 mesh) under low pressure; silica gel refers to the above grade of silica. Medium pressure liquid chromatography was carried out on silica gel using a Gilson 303 pump on a glass column (6.5 cm internal diameter, 94 cm length). Analytical and preperative high pressure liquid chromatography was performed using a Gilson 303 pump and a Gilson Holochrome ultra-violet detector, with Dynamax 250mm x 41.4mm (internal diameter) or 250mm x 21mm (internal diameter) Si (ordinary) or C-18 (reverse phase) Macro-HPLC columns. Analytical gas chromatography was performed on a Perkin-Elmer Sigma 3 gas chromatograph using a 30m x 0.25mm bonded FSOT Superox column. Ultrasonication was carried out in a Semat ultrasound cleaning bath (80W, 55kHz).

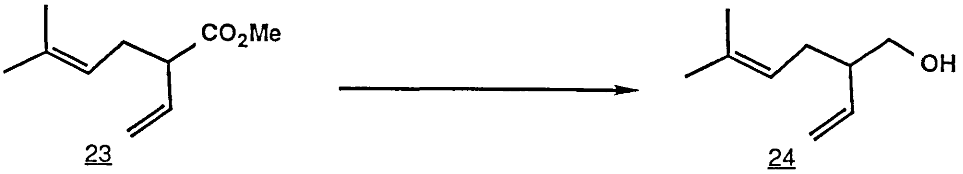
Petrol refers to light petroleum ether with boiling range 40-60°C unless otherwise stated, and was redistilled before use. Ether refers to diethyl ether, and was distilled from sodium-benzophenone ketyl under argon before use, as was tetrahydrofuran (THF). Anhydrous dimethylformamide (DMF) and high pressure liquid chromatography grade 2-propanol (isopropanol) were purchased from Aldrich chemical Co. Ltd., glass distilled hexane was purchased from BDH Ltd., and were all used without further purification. Toluene and benzene were dried over sodium wire under argon, and toluene was distilled from sodium under argon before use. Dichloromethane (DCM) was distilled from phosphorus pentoxide under argon before use, and acetonitrile was distilled from calcium hydride under argon. All other solvents and reagents were purified by standard techniques. Saturated refers to aqueous solutions, and brine is saturated NaCl. Solutions were dried over anhydrous magnesium or sodium sulphate, and evaporated with a rotary evaporator, followed by static evaporation with an oil pump.

Preparation of Methyl 5-methyl-2-vinylhex-4-enoate (23).



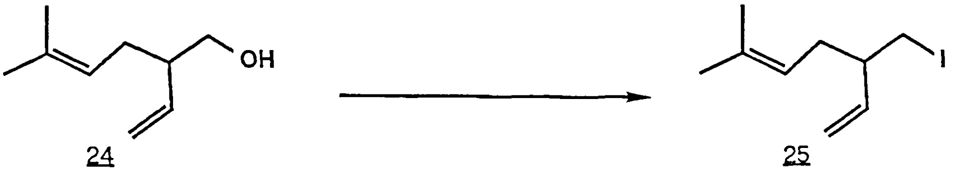
To a stirred solution of di-isopropylamine (1.52ml, 10.9mmol) in THF (8ml) at 0°C under argon was added n-butyl lithium (6.80ml of a 1.60M solution in hexanes, 10.9mmol). After 10 minutes the solution was cooled to -78°C, and HMPA (2.73ml) added, giving a yellow solution. Methyl crotonate (1.07g, 10.7mmol) in THF (4ml) was added dropwise, giving a dark yellow solution, and the reaction mixture was stirred for 15 minutes. Dimethylallyl bromide (20) (1.80g, 12.1mmol) was added dropwise, giving a red colouration, the reaction was stirred for a further 15 minutes, poured into water (30ml), and extracted with ether (3 x 10ml). The ethereal solution was washed with water (3 x 15ml), saturated NH_4Cl (30ml), brine (30ml), and dried. Solvent removal at reduced pressure and column chromatography (10% ether - petrol) gave methyl 5-methyl-2-vinylhex-4-enoate (23) (1.24g, 69%), δ(250 MHz): 1.61 (3H, d, J 3.0 Hz, C-Me), 1.69 (3H, d, J 2.0 Hz, C-Me), 2.15 - 2.49 (2H, m, $Me_2C{=}CHCH_2$), 3.05 (1H, dt, J 9.0 7.5 Hz, MeO_2CCH), 3.68 (3H, s, OMe), 4.97 - 5.18 (3H, m, $C{=}CH_2$ and $CH{=}CMe_2$), and 5.84 (1H, ddd, J 17.5 10.0 9.0 Hz, $CH{=}CH_2$); ν_{max} (film) 1736 and 1639 cm^{-1}; m/z 168(M^+), 153 (M^+ - Me), and 69; (Found: C, 71.17; H, 9.73. $C_{10}H_{16}O_2$ requires: C, 71.39; H, 9.59%).

Preparation of 3-Hydroxymethyl-6-methylhepta-1,5-diene (24).



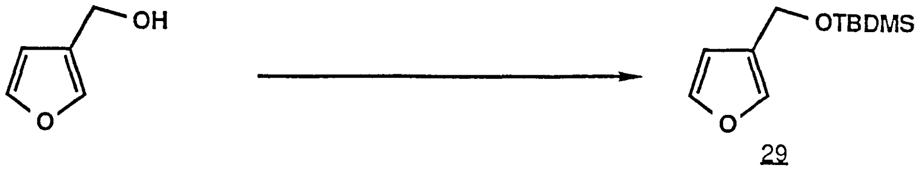
To a stirred suspension of lithium aluminium hydride (122mg, 3.24mmol) in ether (10ml) at 0°C under argon was added ester (23) (0.45g, 2.70mmol) in ether (5ml), and the reaction was warmed to RT and stirred for two hours. The reaction was cooled to 0°C, and water (10ml) was added dropwise, the mixture was poured into 1N H_2SO_4 (15ml), and extracted with ether (2 x 15ml). The combined ethereal extracts were washed with water (20ml) and brine (20ml), dried, and concentrated under reduced pressure. Column chromatography (10 to 30% ether - petrol) gave 3-hydroxymethyl-6-methylhepta-1,5-diene (24) (265mg, 70%), δ(250 MHz): 1.62 (3H, s, C-Me), 1.71 (3H, d, J 2.0 Hz, C-$\underline{Me}$), 1.76 (1H, br s, O$\underline{H}$), 2.08 (2H, m, $Me_2C=CHC\underline{H}_2$), 2.27 (1H, m, $HOCH_2C\underline{H}$), 3.40 - 3.60 (2H, m, $C\underline{H}_2OH$), 5.08 - 5.17 (3H, m, $CH=C\underline{H}_2$ and $\underline{H}C=CMe_2$), and 5.66 (1H, ddd, J 17.5 12.5 8.0 Hz, $C\underline{H}=CH_2$); ν_{max} (film) 3362, 1639, and 1450 cm^{-1}; $\underline{m}/\underline{z}$ 122($\underline{M}^+$ - H_2O); (Found: C, 76.88; H, 11.79. $C_9H_{16}O$ requires: C, 77.09; H, 11.50%).

Preparation of 3-Iodomethyl-6-methylhepta-1,5-diene (25).



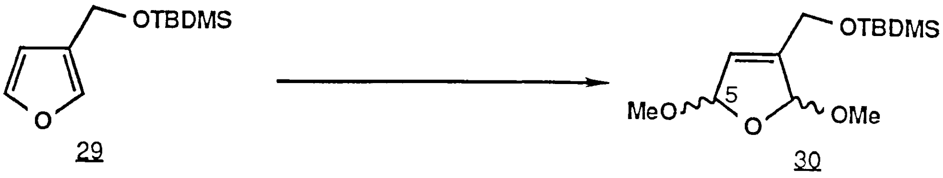
To a stirred solution of triphenylphosphine (1.97g, 7.5mmol) in ether (10ml) and acetonitrile (4ml) at RT was added imidazole (0.51g, 7.5mmol) and di-isopropylamine (1.05ml, 7.5mmol). Alcohol (24) (0.70g, 5.0mmol) was added in ether (2ml), followed by iodine (1.91g, 7.5mmol), giving an exothermic reaction. After 15 minutes, the solution was diluted with ether (20ml), the resultant white precipitate was filtered off, and the filtrate was concentrated at reduced pressure. The resulting material was suspended in ether (1ml) and extracted with petrol (2 x 20ml). The combined petrol extracts were concentrated at reduced pressure, and the material columned (0 to 10% ether - petrol) to give 3-iodomethyl-6-methylhepta-1,5-diene (25) (0.80g, 64%), δ(250 MHz): 1.64 (3H, s, C-$\underline{Me}$), 1.70 (3H, s, C-$\underline{Me}$), 1.95 - 2.27 (3H, m, $Me_2C=CHC\underline{H}_2C\underline{H}$), 3.18 (2H, dd, J 10.8 6.2 Hz, $C\underline{H}HI$), 3.21 (2H, dd, J 10.8 6.2 Hz, $CH\underline{H}I$), 5.02 - 5.17 (3H, m, $CH=C\underline{H}_2$ and $C\underline{H}=CMe_2$), and 5.65 (1H, ddd, J 17.5 10.8 7.5 Hz, $C\underline{H}=CH_2$); ν_{max} (film) 1639 and 1448 cm^{-1}; $\underline{m}/\underline{z}$ 249($\underline{M}^+$ - H) and 123($\underline{M}^+$ - I).

Preparation of 3-(t-Butyldimethylsilyloxymethyl)furan (29).



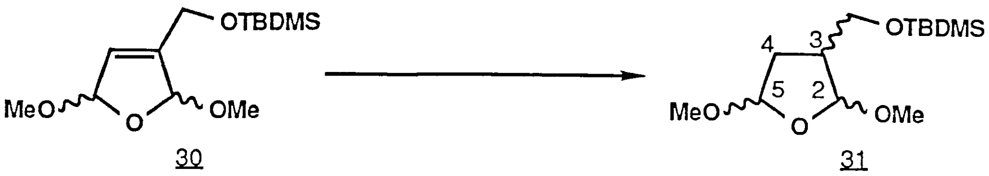
To a stirred solution of imidazole (17.02g, 0.25mol) in DMF (10ml) under argon at RT was added 3-furanmethanol (28) (9.81g, 0.10mol) in DMF (5ml), followed by t-butyldimethylsilyl chloride (18.09g, 0.12mol) in DMF (5ml), and the reaction was stirred for 14 hours. The reaction mixture was poured into water (60ml), extracted with ether (3 x 50ml), the ethereal extracts were combined and washed with water (23 x 50ml) and brine (50ml). The ethereal solution was dried, concentrated at reduced pressure, and subjected to column chromatography (15% ether - petrol) to yield 3-(t-butyldimethylsilyloxymethyl)furan (29) (23.3g, 95%), δ(60 MHz): 0.08 (6H, s, Si$\underline{Me}_2$), 0.91 (9H, s, Si$^t\underline{Bu}$), 4.51 (2H, s, C$\underline{H}_2$OSi), 6.25 (1H, m, furan C_4-$\underline{H}$), and 7.28 (2H, m, furan C_2-$\underline{H}$, furan C_5-$\underline{H}$); ν_{max} (film) 1469, 1094, and 839 cm^{-1}; $\underline{m}/\underline{z}$ 212($\underline{M}^+$), 197($\underline{M}^+$ - Me), and 155($\underline{M}^+$ - ^{t}Bu).

Preparation of 3-(t-Butyldimethylsilyloxymethyl)-2,5-dimethoxydihydro-2,5H-furan (30).



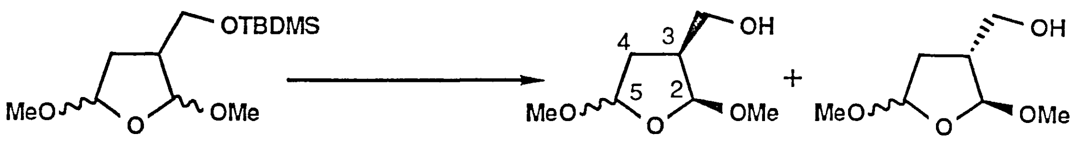
To a stirred suspesion of sodium carbonate (4.42g, 41.7mmol) in methanol (40ml) at -5°C was added the protected alcohol (29) (2.12g, 10.0mmol) in methanol (5ml). Bromine (0.53ml, 10.3mmol) was added dropwise in methanol (10ml) over 10 minutes, and the resultant red-brown solution was stirred for 30 minutes at 0°C. The reaction mixture was poured into brine (60ml) and extracted with benzene (3 x 20ml). The combined organic extracts were dried, concentrated at reduced pressure, and subjected to column chromatography (10 to 20% ether - petrol) to give firstly recovered protected alcohol (29) (0.30g, 14%), followed by *3-(t-butyldimethylsilyloxymethyl)-2,5-dimethoxydihydro-2,5H-furan* (30) (2.13g, 78%, 90% based on recovered (29)) as a mixture of *cis* and *trans* isomers, δ(250 MHz): 0.08 (6H, s, Si$\underline{\text{Me}}_2$), 0.91 (9H, s, Si$^t\underline{\text{Bu}}$), 3.37 (1.5H, s, O$\underline{\text{Me}}$), 3.39 (1.5H, s, O$\underline{\text{Me}}$), 3.41 (1.5H, s, O$\underline{\text{Me}}$), 3.42 (1.5H, s, O$\underline{\text{Me}}$), 4.29 (2H, br s, C$\underline{\text{H}}_2$OSi), 5.49 (0.5H, br s, MeOC$\underline{\text{H}}$), 5.59 (0.5H, br s, MeOC$\underline{\text{H}}$), 5.76 (0.5H, d, J 2.0 Hz, MeOC$_5\underline{\text{H}}$), 5.86 (0.5H, br s, MeOC$\underline{\text{H}}$), and 5.93 (1H, br s, C=C$\underline{\text{H}}$C); ν_{max} (film) 1680, 1091, and 838 cm^{-1}; *m/z* 274(M^+), 243(M^+ - MeO) and 217(M^+ - Bu); (Found: C, 56.90; H, 9.28. $C_{13}H_{26}O_4Si$ requires: C, 56.90; H, 9.55%).

Preparation of 3-(t-Butyldimethylsilyloxymethyl)-2,5-dimethoxytetrahydrofuran (31).



To a vigorously stirred suspension of 5% palladium on carbon (50mg) in methanol (40ml) under argon at RT was added the dihydrofuran (30) (0.5g, 1.82mmol) in methanol (10ml). The flask was purged with hydrogen, and kept under a slight positive pressure of hydrogen for two hours. The flask was then purged with argon, the solution was filtered, and concentrated at reduced pressure, followed by column chromatography (10% ether - petrol) to give 3-(t-butyldimethylsilyloxymethyl)-2,5-dimethoxytetrahydrofuran (31) (0.37g, 74%) as a mixture of diastereoisomers, δ(250 MHz): 0.09 (3H, s, SiMe), 0.12 (3H, s, SiMe), 0.86 (9H, s, Si^{t}Bu), 1.50 - 1.70 (1H, m, C_3-H), 2.26 (2H, m, C_4-H$_2$), 3.36 (3H, s, OMe), 3.39 (3H, s, OMe), 3.50 - 3.70 (2H, m, CH$_2$OH), 4.89 (0.5H, d, J 4.0 Hz, C_2-H), 4.95 (0.5H, d, J 2.0 Hz, C_2-H), and 5.08 (1H, m, C_5-H); ν_{max} (film) 2930, 1467, and 1090 cm^{-1}; m/z 275(M$^+$ - H), 245(M$^+$ - MeO), and 219(M$^+$ - ^{t}Bu); (Found: (M$^+$ - MeO), 245.1567. $C_{12}H_{25}O_3Si$ requires: (M$^+$ - MeO), 245.1573).

Preparation of 2,5-Dimethoxy-3-hydroxymethyltetrahydrofuran (32).



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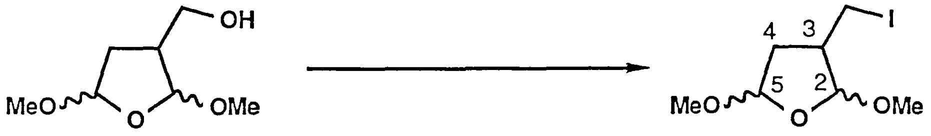
To a stirred solution of protected tetrahydrofuran (31) (1.30g, 4.7mmol) in THF (15ml) at RT under argon was added dropwise tetrabutylammonium fluoride (12ml of a 1M solution in THF, 12mmol), and the solution was stirred for 3 hours. The reaction mixture was poured into water (50ml), and extracted with ether (3 x 30ml). The combined ethereal extracts were washed with water (3 x 30ml), brine (30ml), dried, and concentrated under reduced pressure. Column chromatography (40 to 60% ether - petrol) gave a diastereomeric mixture of 2,5-dimethoxy-3-hydroxymethyltetrahydrofuran (32) (0.60g, 79%). Further chromatography (30 to 60% ether - petrol) gave firstly 2,3-cis-2,5-dimethoxy-3-hydroxymethyltetrahydrofuran (32) (0.32g, 42%), δ(250 MHz): 1.98 (1H, ddd, J 13.0 10.0 4.0 Hz, C_4-H), 2.23 (1H, ddd, J 13.0 10.0 5.0 Hz, C_4-H), 2.35 - 2.50 (2H, m, C_3-H and CH_2OH), 3.44 (3H, s, OMe), 3.47 (3H, s, OMe), 3.69 - 3.85 (2H, m, CH_2OH), 5.02 (1H, d, J 5.0 Hz, C_2-H), and 5.15 (1H, dd, J 5.0 4.0 Hz, C_5-H); ν_{max} (film) 3431, 2933, and 1102 cm^{-1}; *m/z* 161(M^+ - H), 143(M^+ - H - H_2O), and 131(M^+ - MeO); (Found: (M^+ - MeO), 131.0702. $C_6H_{11}O_3$ requires: (M^+ - MeO), 131.0708); followed by 2,3-*trans*-2,5-dimethoxy-3-hydroxymethyltetrahydrofuran (32) (0.25g, 33%), δ(250 MHz): 2.25 - 2.45 (3H, m, C_3-H and C_4-H_2), 2.59 (1H, br s, CH_2OH), 3.40 (3H, s, OMe), 3.42 (3H, s, OMe), 3.69 - 3.74 (2H, br s, CH_2OH), 5.05 (1H, d, J 2.0 Hz, C_2-H), and 5.13 (1H, dd, J 5.0 2.0 Hz, C_5-H); ν_{max} (film) 3433, 2835, and 1105 cm^{-1}; *m/z* 161(M^+ - H) and 131(M^+ - MeO); (Found: (M^+ - MeO), 131.0702. $C_6H_{11}O_3$ requires: (M^+ - MeO), 131.0708).

Preparation of 2,5-Dimethoxy-3-iodomethyltetrahydrofuran (27).



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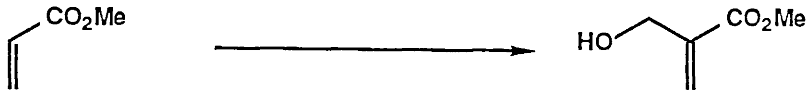
To a stirred solution of triphenylphosphine (1.21g, 4.63mmol) in ether (7ml) and acetonitrile (3ml) at RT was added imidazole (0.32g, 4.63mmol) and di-isopropylamine (0.65ml, 4.63mmol). A diastereomeric mixture of tetrahydrofuran (32) (0.50g, 3.10mmol) was added in ether (2ml), followed by iodine (1.17g, 4.63mmol), giving an exothermic reaction. After 15 minutes, the solution was diluted with ether (15ml), the resultant white precipitate was filtered off, and the filtrate was concentrated at reduced pressure. The resulting material was suspended in ether (1ml) and extracted with petrol (2 x 20ml).

The combined petrol extracts were concentrated at reduced pressure, and the residue subjected to column chromatography (10 to 30% ether - petrol) to give a diastereomeric mixture of 2,5-dimethoxy-3-iodomethyltetrahydrofuran (27) (0.56g, 60%), δ(250 MHz): 1.72 (1H, br d, J 12.0 Hz, C_3-H), 2.35 (1H, ddd, J 17.0 8.0 4.0 Hz, C_4-H), 2.41 - 2.63 (1H, m, C_4-H), 3.10 - 3.40 (2H, m, CH_2I), 3.36 (3H, s, OMe), 3.39 (3H, s, OMe), 4.86 (0.5H, d, J 4.0 Hz, C_2-H), 4.93 (0.5H, d, J 2.0 Hz, C_2-H), and 5.52 (1H, dd, J 5.0 2.0 Hz, C_5-H); ν_{max} (film) 2833 and 1100 cm^{-1}; m/z 272(M^+), 271(M^+ - H), 241(M^+ - H_2CO), and 143(M^+ - I); (Found: (M^+ - H), 270.9834. $C_7H_{12}O_3I$ requires: (M^+ - H), 270.9831).

Preparation of Methyl 2-hydroxymethylprop-2-enoate (66).



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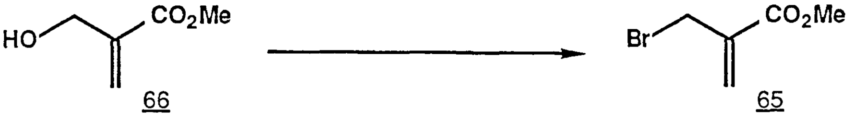
To a stirred solution of 1,4-diazabicyclo[2,2,2]octane (7.30g, 0.065mol) in methyl acrylate (117ml, 1.30mol) at RT was added paraformaldehyde (61g), and the resultant slurry was stirred for 7 days. The mixture was filtered, and the solid residue was washed with ether (5 x 100ml). The ethereal washings and the filtrate were combined, and the solution washed rapidly with 3N HCl (100ml) and saturated Na_2CO_3 (2 x 100ml). The aqueous washings were re-extracted with ether (3 x 50ml) and the combined organic solutions were washed with brine (100ml) and dried. Concentration at reduced pressure followed by removal of excess methyl acrylate on a static oil pump gave methyl 2-hydroxymethylprop-2-enoate (66) (87g, 58%) used without further purification, δ(250 MHz): 3.76 (3H, s, OMe), 4.27 (2H, s, C$\underline{H}_2$OH), 4.80 (1H, br s, CH$_2$O$\underline{H}$), 5.82 (1H, s, C=C$\underline{H}$ trans to ester), and 6.27 (1H, s, C=C$\underline{H}$ cis to ester); ν_{max} (film) 3526, 1718, and 1637 cm^{-1}; spectrally identical to reported material.[26]

Preparation of Methyl 2-bromomethylprop-2-enoate (65).



a) With Hydrobromic Acid.

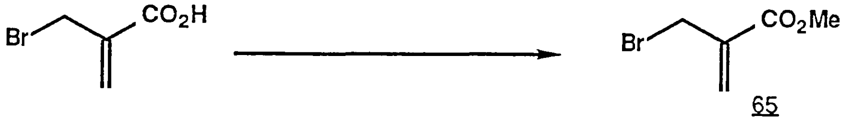
Methyl 2-hydroxymethylprop-2-enoate (66) (2.90g, 24.9mmol) was dissolved in hydrobromic acid (9.66g of a 48% aqueous solution) at RT, and concentrated sulphuric acid (0.61g) was added dropwise with stirring. The reaction was stirred for 2 days, then ether (10ml) was added, the reaction mixture was seperated, and the organic layer was washed with saturated Na_2CO_3 (3 x 20ml), water (20ml) and dried. Solvent remoival at reduced pressure and column chromatography (20% ether - petrol) gave methyl 2-bromomethylprop-2-enoate (65) (1.12g, 26%), δ(250 MHz): 3.75 (3H, s, O$\underline{Me}$), 4.11 (2H, br s, C$\underline{H}_2$Br), 5.90 (1H, br s, C=C$\underline{H}$ trans to ester), and 6.28 (1H, br s, C=C$\underline{H}$ cis to ester); ν_{max} (film) 2952, 1723, and 1627 cm^{-1}; spectrally identical to the reported material.[26]

b) With N-Bromosuccinamide (NBS).

To a stirred solution of NBS (2.32g, 12.9mmol) in DCM (25ml) under argon at 0°C was added dimethylsulphide (1.14ml, 15.5mmol), giving a yellow precipitate. The reaction mixture was cooled to -20°C, and methyl 2-hydroxymethylprop-2-enoate (66) (1.00g, 8.6mmol) was added in

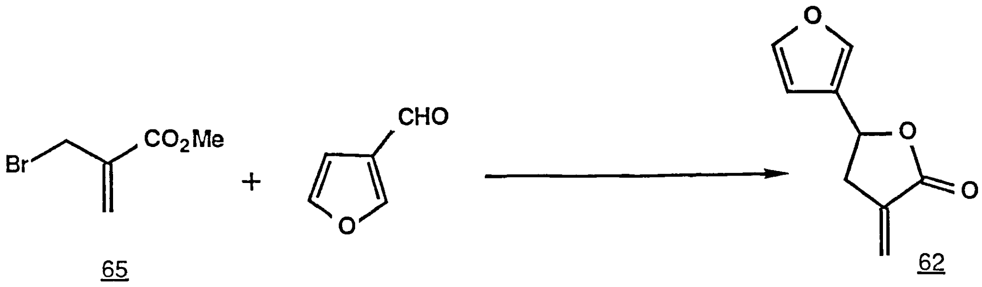
DCM (5ml) over 5 minutes. The reaction was warmed to 0°C and stirred for 24 hours. The reaction mixture was then diluted with petrol (60ml) and poured into water (60ml) precooled to 0°C. The organic phase was separated, washed with brine (20ml), filtered through a pad of silica gel, and concentrated under reduced pressure. Column chromatography (20% ether - petrol) gave methyl 2-bromomethylprop-2-enoate (65) (0.37g, 24%), identical in all respects to the previously prepared material.

Preparation of Methyl 2-bromomethylprop-2-enoate (65).



To a stirred solution of 2-bromomethylprop-2-enoic acid (0.165g, 1.0mmol) in methanol (15ml) at 0°C was added concentrated sulphuric acid (0.1ml) and the reaction was heated at reflux for 16 hours. The solution was poured into water (25ml), extracted with ether (3 x 20ml), and the combined ethereal extracts were washed with saturated $NaHCO_3$ (2 x 20ml), water (20ml), brine (20ml), and dried. Concentration under reduced pressure and column chromatography (20% ether - petrol) gave methyl 2-bromomethylprop-2-enoate (65) (0.14g, 81%), identical in all respects to the previously prepared material.

Preparation of 5-(3'-Furyl)-3-methylidenetetrahydrofuran-2-one (62).



a) Under Thermal Conditions.

To a stirred suspension of zinc metal powder (70mg, 1.07mmol), freshly activated by sequential treatment with dilute hydrochloric acid, water, acetone, and drying at 50°C, in THF (1ml) under argon at RT was added furan-3-carboxaldehyde (90mg, 0.94mmol) in THF (1ml) and bromomethyl acrylate (65) (180mg, 1.00mmol) in THF (1ml). The reaction mixture was heated at reflux for 2 hours, then poured into 3N HCl (10ml) containing crushed ice (10g). The mixture was extracted with ether (3 x 15ml), and the combined ethereal extracts were washed with saturated $NaHCO_3$ (10ml), water (10ml), and dried. Concentration at reduced pressure and column chromatography (30 to 50% ether - petrol) gave 5-(3'-furyl)-3-methylidenetetrahydrofuran-2-one (62) (81.2mg, 55%), m.p. 27°C; δ(250 MHz): 2.93 (1H, ddt, J 17.0 6.5 3.0 Hz, H_2C=CC$\underline{H}$HC), 3.32 (1H, ddt, J 17.0 8.0 3.0 Hz, H_2C=CCH$\underline{H}$C), 5.51 (1H, dd, J 8.0 6.5 Hz, OC$\underline{H}$-(furan)), 5.70 (1H, t, J 3.0 Hz, C=C$\underline{H}$ trans to C=O), 6.29 (1H, t, J 3.0 Hz, C=C$\underline{H}$ cis to C=O), 6.39 (1H, dd, J 2.0 1.5 Hz, furan C_4-$\underline{H}$), 7.44 (1H, m, furan C_5-$\underline{H}$), and 7.48 (1H, m, furan C_2-$\underline{H}$); ν_{max} ($CHCl_3$) 2925, 1763, and 1665 cm^{-1}; m/z 164(M^+) and 95(FuranCO^+); (Found: C, 65.77; H, 5.00. $C_9H_8O_3$ requires: C, 65.85; H, 4.91%).

b) Under Ultrasonic Conditions.

To a suspension of zinc metal powder (0.82g, 11.8mmol), activated as previously detailed, in THF (5ml) under argon at RT was added furan-3-carboxaldehyde (1.05g, 10.5mmol) in THF (5ml) and bromomethyl acrylate (65) (2.10g, 11.7mmol) in THF (5ml), and the reaction mixture was subjected to sonication for 2 minutes. The reaction mixture was poured into 3N HCl (30ml) containing crushed ice (30g) and extracted with ether (3 x 50ml). The combined ethereal extracts were washed with saturated $NaHCO_3$ (30ml), water (30ml), brine (20ml) and dried. Concentration at reduced pressure and column chromatography (30 to 50% ether - petrol) gave 5-(3'-furyl)-3-methylidenetetrahydrofuran-2-one (62) (1.55g, 90%), identical in all respects to that prepared previously.

Standard Procedure for Stability Assessment of 5-(3'-Furyl)-3-methylidenetetrahydrofuran-2-one (62) to Lewis Acids.

To a stirred solution of lactone (62) (50mg, 0.3mmol) in DCM (3ml) under argon at -78°C was added the required Lewis acid (0.06mmol, 0.2eq). For each acid (see table 1, section 2.3) the reaction was carried out three times, alternatively stirred at -78°C for 14 hours; warmed to -10°C and stirred for 14 hours; and warmed to RT and stirred for 14 hours. The reaction mixture was then poured into water (10ml) at 0°C, and extracted with DCM (3 x 8ml). The combined organic extracts were washed with saturated NH_4Cl (10ml), saturated $NaHCO_3$ (10ml), and water (10ml), dried, and concentrated under reduced pressure. Resultant yields were based on the weight of recovered material, with purity monitored by ^1H nmr (see table 1, section 2.3).

Standard Procedures for Stability Assessment of 5-(3'-Furyl)-3-methylidenetetrahydrofuran-2-one (62) to Epoxidation Conditions.

a) With meta-Chloroperbenzoic Acid (mCPBA).

To a stirred solution of lactone (62) (50mg, 0.3mmol), both with and without exo-methylenecyclohexane (67) (29mg, 0.3mmol), containing solid Na_2HPO_4 (200mgs) in DCM (2ml) under argon at 0°C was added mCPBA (97mg of an 80% mixture, 0.45mmol) in DCM (2ml) and the reactions stirred at 0°C for the chosen length of time (3 or 14 hours). In all cases the solution was filtered, washed with saturated Na_2SO_3 (2ml), saturated $NaHCO_3$ (2ml), dried, and concentrated at reduced pressure. Column chromatography (30 to 50% ether - petrol) gave recovered methylidene lactone (62), as shown in table 2, section 2.3.

b) With Vanadyl Acetoacetonate.

To a stirred solution of lactone (62) (50mg, 0.3mmol), both with and without exo-methylenecyclohexane (67) (29mg, 0.3mmol), in benzene (2ml) under argon at 0°C was added vanadyl acetoacetonate (20mgs) in benzene (2ml), followed by t-butylhydroperoxide (0.33ml of a 1M solution in toluene, 1.0mmol). The reactions were warmed to RT and stirred for the required length of time (either 3 or 14 hours). In all cases saturated Na_2SO_3 (3ml) was added, and the resultant solution extracted with DCM (3 x 10ml). The combined extracts were washed with saturated $NaHCO_3$ (10ml), dried, concentrated at reduced pressure, and subjected to column chromatography (30 to 50% ether - petrol) to give recovered methylidene lactone (62), as shown in table 2, section 2.3.

Standard Procedures for Stability Assessment of 5-(3'-Furyl)-3-methylidenetetrahydrofuran-2-one (62) to cis-Hydroxylation and Cleavage Conditions.

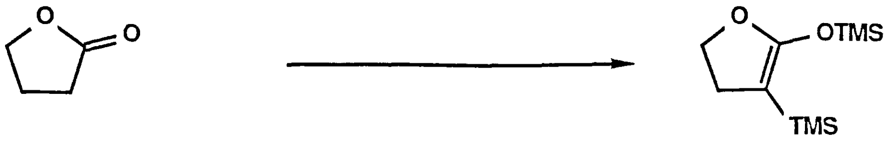
a) With Osmium Tetroxide.

To a stirred solution of lactone (62) (50mg, 0.3mmol), both with and without vinylcyclohexane (68) (33mg, 0.3mmol) containing osmium tetroxide (5mg) in ether (1ml) and acetone (4ml) under argon at 0°C was added hydrogen peroxide (0.04ml of a 30% aqueous solution, 0.3mmol), and the reactions stirred for 3 hours at 0°C. For both cases saturated Na_2SO_3 (5ml) was added, and the reaction mixture was extracted with DCM (3 x 10ml). The combined extracts were washed with saturated NH_4Cl (10ml), saturated $NaHCO_3$ (10ml), water (10ml), and dried. The solvent was removed at reduced pressure, and in both reactions the residue showed no recoverable lactone (62) present (see table 2, section 2.3).

b) With Sodium Periodate.

Sodium periodate (71mg, 0.33mmol) was dissolved in water (3ml) with stirring at 0°C, and a solution of lactone (62) (50mg, 0.3mmol), both with and without vinylcyclohexane (68) (33mg, 0.3mmol) in ethanol (2ml) was added, and the reactions were stirred for 14 hours at 0°C. In both cases the reaction mixtures were filtered, and the filtrate extracted with DCM (2 x 10ml). The combined organic extracts were treated with activated charcoal and dried, concentrated at reduced pressure, and the residues subjected to column chromatography (30 to 50% ether - petrol) to give recovered methylidene lactone (62), as shown in table 2, section 2.3).

Preparation of 3-Trimethylsilyl-2-trimethylsilyloxydihydro-4,5H-furan (69).



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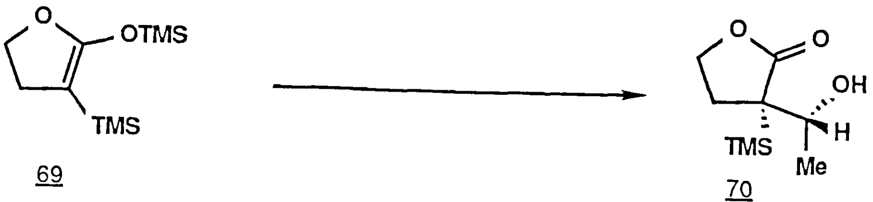
To a stirred solution of triethylamine (2.24g, 22mmol) in ether (17ml) under argon at RT was added dropwise trimethylsilyltrifluoromethanesulphonate (4.92g, 22mmol), and the reaction mixture cooled to 0°C. γ-Butyrolactone (0.86g, 10mmol) was added dropwise in ether (3ml), the reaction was allowed to warm to RT, and stirring was continued for 30 minutes. The ethereal phase was separated, the non-ethereal phase was washed with ether (2 x 10ml), and the combined ethereal solutions were concentrated at reduced pressure. Bulb to bulb distillation gave 3-trimethylsilyl-2-trimethylsilyloxy-dihydro-4,5H-furan (69) (2.00g, 87%) as a pale yellow oil, b.p. 110°C at 4 mm Hg (Lit.,[66] 35°C at 0.008 mm Hg); δ(60 MHz): 0.08 (9H, s, $Si\underline{Me}_3$), 0.23 (9H, s, $Si\underline{Me}_3$), 2.57 (2H, t, J 9.0 Hz, $OCH_2C\underline{H}_2C$), and 4.45 (2H, t, J 9.0 Hz, $OC\underline{H}_2CH_2C$); ν_{max} (film) 2957, 1646, 1076, and 756 cm^{-1}; spectrally identical to reported material.[66]

Preparation of (3S*,1'R*)-3-(1'-Hydroxyethyl)-3-trimethylsilyltetrahydrofuran-2-one (70).



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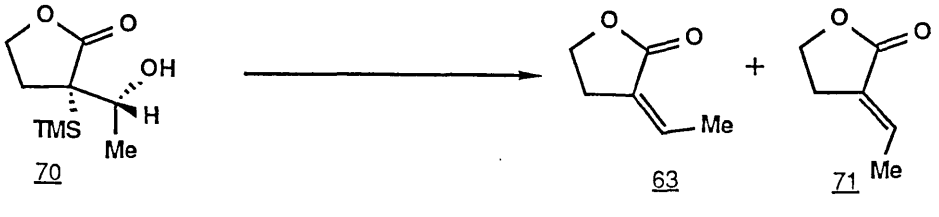
To a stirred solution of redistilled acetaldehyde (4.21ml, 75.3mmol) in DCM (20ml) under argon at -78°C was added titanium tetrachloride (4.14ml, 37.7mmol) dropwise over 10 minutes, giving a yellow precipitate. Freshly prepared silyl enol ether (69) (8.69g, 37.7mmol) was added dropwise in DCM (30ml) over 30 minutes, and the resultant mixture was stirred for a further 90 minutes at -78°C, giving a yellow solution. Methanol (40ml) was added at -78°C, the reaction mixture was poured into water (100ml), and the solution was extracted with ether (3 x 150ml). The combined ethereal extracts were washed with water (50ml) and brine (50ml), dried, and concentrated at reduced pressure. Column chromatography (30 to 50% ether - petrol) gave ($3S^*,1'R^*$)-3-(1'-hydroxyethyl)-3-trimethylsilyltetrahydrofuran-2-one (70) (4.10g, 68%) m.p. 48-50°C; δ(250 MHz): 0.21 (9H, s, Si$\underline{Me}_3$), 1.26 (3H, d, J 7.0 Hz, CH$\underline{Me}$), 2.25 (1H, ddd, J 13.5 8.0 4.0 Hz, $OCH_2C\underline{H}HC$), 2.41 (1H, ddd, J 13.5 9.5 8.5 Hz, $OCH_2CH\underline{H}C$), 2.83 (1H, br s, O$\underline{H}$), 4.17 (1H, ddd, J 9.0 8.5 8.0 Hz, $OC\underline{H}HCH_2C$), 4.32 (1H, ddd, J 9.5 9.0 4.0 Hz, $OCH\underline{H}H_2C$), and 4.37 (1H, q, J 7.2 Hz, C$\underline{H}$Me); ν_{max} ($CHCl_3$) 3496, 2929, 1717, and 1186 cm^{-1}; $\underline{m}/\underline{z}$ 201($\underline{M}^+$ - H), 187($\underline{M}^+$ - Me), and 143($\underline{M}^+$ - Me - CO_2); spectrally identical to reported material.[31]

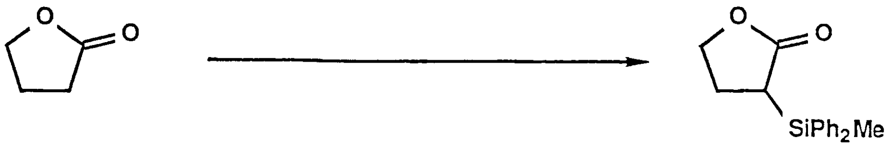
Preparation of Z and E 3-Ethylidenetetrahydrofuran-2-one (63) and (71) from (70).



To a stirred solution of lactone (70) (0.90g, 4.5mmol) in DCM

(50ml) under argon at -30°C was added boron trifluoride diethyl etherate (5.61ml, 45mmol) dropwise over 5 minutes, and the reaction mixture was stirred for 16 hours at -30°C. The reaction mixture was poured into saturated NH_4Cl (50ml), and extracted with DCM (3 x 50ml). The combined organic extracts were washed with water (50ml), dried, and concentrated at reduced pressure. Column chromatography (15 to 30% ether - petrol) gave firstly Z 3-ethylidenetetrahydrofuran-2-one (63) (0.28g, 55%), δ(250 MHz): 2.15 (3H, dt, J 7.0 2.5 Hz, C=CHMe), 2.88 (2H, tquint, J 7.3 2.5 Hz, OCH_2CH_2C), 4.29 (2H, t, J 7.3 Hz, OCH_2CH_2C), and 6.30 (1H, qt, J 7.0 2.5 Hz, C=CHMe); ν_{max} (film) 2859, 1748, and 1672 cm^{-1}; m/z 122(M^+); spectrally identical to reported material;[31] followed by E 3-ethylidenetetrahydrofuran-2-one (71) (0.20g, 40%), δ(250 MHz): 1.83 (3H, dt, J 7.0 2.0 Hz, C=CHMe), 2.84 (2H, tdq, J 7.3 3.0 2.0 Hz, OCH_2CH_2C), 4.34 (2H, t, J 7.3 Hz, OCH_2CH_2C), and 6.77 (1H, qt, J 7.0 3.0 Hz, C=CHMe); ν_{max} (film) 2916, 1746, and 1669 cm^{-1}; m/z 122(M^+); spectrally identical to reported material.[31]

Preparation of 3-Diphenylmethylsilyltetrahydrofuran-2-one (72).

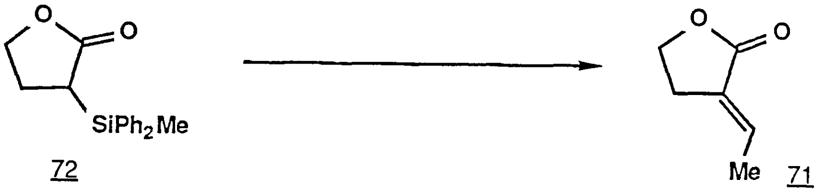


72

To a stirred solution of di-isopropylamine (0.80ml, 6.0mmol) in THF (5ml) under argon at -78°C was added n-butyl lithium (4.0ml of a 1.5M solution in hexanes, 6.0mmol). The reaction mixture was warmed to 0° C, stirred for 15 minutes, and cooled to -78°C. γ-Butyrolactone (0.43g, 5.0mmol) in THF (5ml) was added, and the reaction stirred for

30 minutes, then diphenylmethylsilyl chloride (1.15g, 5.0mmol) in THF (5ml) was added dropwise. The reaction mixture was stirred at -78°C for 90 minutes, then warmed to RT and stirred for another 60 minutes. The reaction mixture was poured into petrol (40ml) and washed with water (2 x 30ml), brine (30ml) and dried. Concentration at reduced pressure, and column chromatography (10 to 30% ether - petrol) gave 3-diphenylmethylsilyltetrahydrofuran-2-one (72) (1.07g, 76%), δ(250 MHz): 0.73 (3H, s, SiMe), 2.17 (1H, ddt, J 12.8 7.8 5.0 Hz, OCH$_2$CHHC), 2.49 (1H, dddd, J 12.8 10.0 8.8 7.8 Hz, OCH$_2$CHHC), 2.69 (1H dd, J 10.0 5.0 Hz, SiCHC), 3.69 (1H, dt, J 8.8 7.8 Hz, OCHHCH$_2$), 4.14 (1H, td, J 8.8 5.0 OCHHCH$_2$), and 7.34 - 7.65 (10H, m, SiPh$_2$); ν_{max} (film) 3067, 2978, 1748, 1129, and 792 cm^{-1}; m/z 282(M$^+$), 254(M$^+$ - CO), and 197(SiPh$_2$Me$^+$); spectrally identical to reported material.[67]

Preparation of E 3-Ethylidenetetrahydrofuran-2-one (71) from (72).



To a stirred solution of di-isopropylamine (0.52ml, 3.96mmol) in THF (5ml) under argon at -78°C was added n-butyl lithium (2.64ml of a 1.5M solution in hexanes, 3.96mmol). The reaction mixture was warmed to 0°C, stirred for 15 minutes, and cooled to -78°C. Silyl lactone (72) (0.97g, 3.44mmol) in THF (5ml) was added dropwise, and the reaction stirred for 30 minutes, then redistilled acetaldehyde (0.19ml, 3.44mmol) was added. The reaction mixture was warmed to RT over 30 minutes, then heated at reflux for 15 minutes. Trimethylsilyl chloride (5ml) was added and the reaction mixture was poured into petrol (30ml), washed with water (2 x 10ml), and 10% NH_4Cl (10ml), and dried. Solvent removal at reduced pressure and column chromatography (10 to 50% ether - petrol) gave firstly γ-butyrolactone (0.21g, 70%) followed by E 3-ethylidenetetrahydrofuran-2-one (71) (34mg, 10%), identical in all respects to that prepared previously.

Standard Procedure for Cycloaddition Reactions in the Presence of Lewis Acids.

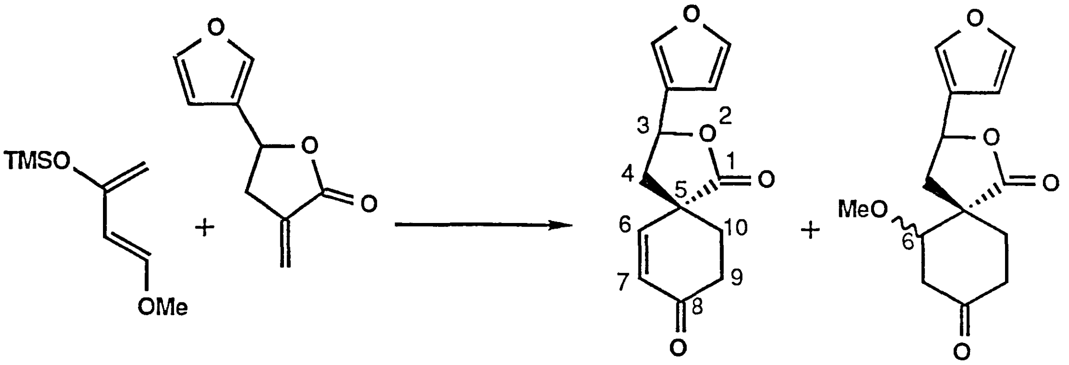
a) With Zinc Dichloride.

To a stirred suspension of anhydrous zinc dichloride (68.1mg, 0.5mmol) in THF (3ml) under argon at RT was added a mixture of diene (0.5mmol) and dienophile (0.5mmol) in THF (2ml). The reaction was heated at reflux and monitored by TLC (20% ether - petrol), indicating no reaction in all cases after 7 days.

b) With Other Lewis Acids.

To a stirred mixture of diene (0.5mmol) and dienophile (0.5mmol) in DCM (3ml) under argon at -78°C was added the required Lewis acid (0.1mmol, 0.2eq), and the mixture stirred at -78°C with monitoring by TLC (20% ether - petrol). If no loss of material was evident after 2 hours, the reaction was allowed to warm to RT over 3 hours, again monitored by TLC. If still no reaction was evident, the mixture was stirred for up to 7 days at RT. Once loss of one or both of the starting materials was complete, the reaction mixture was poured into water (10ml) and extracted with ether (3 x 10ml). The combined ethereal extracts were washed with water (2 x 10ml) and brine (10ml), dried, concentrated at reduced pressure, and subjected to column chromatography (10 to 70% ether - petrol) to isolate any unreacted material, decomposed material, and possible cycloaddition products (see section 2.4).

Preparation of 1,8-Dioxo-3-(3'-furyl)-2-oxaspiro[4,5]dec-6-ene (73) and 1,8-Dioxo-3-(3'-furyl)-6-methoxy-2-oxaspiro[4,5]decane (74).

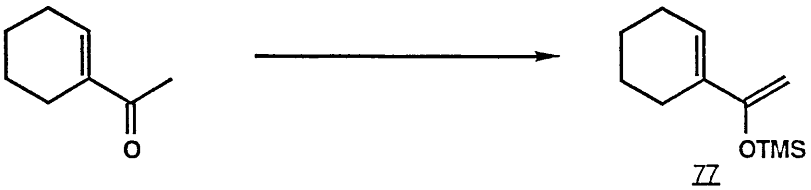


41 62 73 74

Danishefksy diene (41) (0.89g, 5.2mmol) and methylidene lactone (62) (0.66g, 4.0mmol) were placed in a base washed, presilylated 3oz pressure vessel and hydroquinone (2mg) added. The reaction mixture was degassed by evacuation and flushing with argon 3 times, then sealed under vacuum, and heated at 130°C for 14 hours. The resultant tar was dissolved in THF (10ml) and a solution of 3N HCl (0.2ml) in THF (10ml) was added. The reaction was stirred for 3 hours, then poured into saturated $NaHCO_3$ (10ml). The solution was extracted with ether (4 x 20ml), and the combined ethereal extracts were washed with saturated $NaHCO_3$ (2 x 10ml), saturated NH_4Cl (10ml), water (2 x 10ml), and brine (10ml). The ethereal solution was dried, concentrated at reduced pressure, and subjected to column chromatography (DCM) to give firstly unreacted methylidene lactone (62) (58mg, 8.8%) followed by a mixture of cycloaddition products (0.3g). Further column chromatography (10 to 50% ether - petrol) gave firstly 1,8-dioxo-3-(3'-furyl)-6-methoxy-2-oxaspiro[4,5]decane (74) (84mg, 8%), m.p.

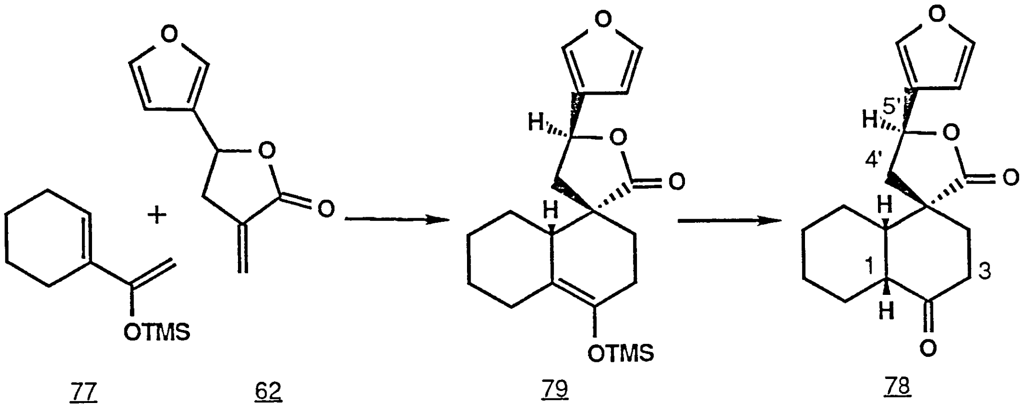
95-96°C; δ(250 MHz): 1.92 (1H, ddd, J 13.0 5.8 4.0 Hz, C_{10}-H), 2.05 (1H, m, C_{10}-H), 2.11 (1H, dd, J 12.8 7.3 Hz, C_4-H), 2.24 (1H, ddd, J 14.3 5.8 0.8 Hz, C_9-H), 2.42 (1H, ddd, J 14.3 10.5 0.8 Hz, C_7-H), 2.53 (1H, dtd, J 14.5 4.0 1.5 Hz, C_9-H), 2.97 (1H, ddd, J 14.3 4.8 1.5 Hz, C_7-H), 3.01 (1H, dd, J 12.8 7.3 Hz, C_4-H), 3.38 (3H, s, OMe), 3.79 (1H, dd, J 10.5 4.8 Hz, C_6-H), 5.58 (1H, t, J 7.5 Hz, C_3-H), 6.42 (1H, m, furan C'_4-H), 7.46 (1H, t, J 1.5 Hz, furan C'_5-H), and 7.49 (1H, m, furan C'_2-H); v_{max} (KBr) 1749, 1708, and 1098 cm^{-1}, m/z 264(M^+), 232(M^+ - MeOH), 204(M^+ - MeOH - CO) and 95(FuranCO$^+$); (Found: C, 63.76; H, 6.19. $C_{14}H_{16}O_5$ requires: C, 63.63; H, 6.10%); followed by 1,8-Dioxo-3-(3'-furyl)-2-oxaspiro[4,5]dec-6-ene (73) (185mg, 20%) as a mixture of diastereoisomers, m.p. 113-114°C; δ(400 MHz): 2.10 - 2.63 (3H, m, C_{10}-H_2 and C_4-H), 2.69 (0.8H, t, J 12.5 Hz, C_9-H_2 minor), 2.73 (1.2H, t, J 13.3 Hz, C_9-H_2 major), 3.01 (0.6H, dd, J 16.0 4.2 Hz, C_4-H major), 3.05 (0.4H, dd, J 18.0 8.0 Hz, C_4-H minor), 5.56 (0.4H, dd, J 10.0 4.2 Hz, C_3-H minor), 5.64 (0.6H, dd, J 8.2 7.2 Hz, C_3-H major), 6.15 (0.6H, d, J 10.2 Hz, C_7-H major), 6.17 (0.4H, d, J 10.2 Hz, C_7-H minor), 6.44 (0.6H, m, furan C'_4-H major), 6.46 (0.4H, m, furan C'_4-H minor), 6.64 (0.4H, d, J 10.2 Hz, C_6-H minor), 6.79 (0.6H, d, J 10.2 Hz, C_6-H major), 7.48 (1H, m, furan C'_5-H), 7.51 (0.4H, m, furan C'_2-H minor), and 7.53 (0.6H, m, furan C'_2-H major); v_{max} (KBr) 1765, 1673, and 1021 cm^{-1}; m/z 232(M^+), 204(M^+ - CO), 188(M^+ - CO_2), and 95(FuranCO$^+$); (Found: M^+, 232.0735. $C_{13}H_{12}O_4$ requires: M^+, 232.0736).

Preparation of 1-(1'-Trimethylsilyloxyvinyl)cyclohex-1-ene (77).



Anhydrous zinc dichloride (32mg, 0.23mmol) was suspended in triethylamine (1.85g, 18.3mmol) under argon at RT, and stirred for 60 minutes, giving a white dispersion. The reaction mixture was cooled to 0°C, and 1-acetylcyclohexene (1.00g, 8.1mmol) was added in benzene (3ml) followed rapidly by trimethylsilyl chloride (1.69g, 16.5mmol) in one portion. The reaction mixture was stirred for 30 minutes at RT, giving a purple colouration, then for 14 hours at 40°C. The mixture was poured into ether (20ml), filtered through a short column of celite, and eluted with ether (60ml). The eluant was concentrated to 5ml under reduced pressure, then diluted with ether (10ml). The filtration sequence was repeated 3 times, the final eluant was concentrated at reduced pressure, and distilled under reduced pressure through a 12cm Vigreux column to give 1-(1'-Trimethylsilyloxyvinyl)-cyclohex-1-ene (77) (1.11g, 70%), b.p. 85°C at 0.01 mm Hg (Lit.,[68] 111-115°C at 18 mm Hg); δ(250 MHz): 0.21 (9H, s, Si$\underline{Me}_3$), 1.50 - 1.75 (4H, br m, cyclohexyl-$\underline{H}$), 1.95 - 2.30 (4H, br m, cyclohexyl-$\underline{H}$), 4.18 (1H, s, CH=C$\underline{H}$H), 4.30 (1H, s, CH=CH$\underline{H}$), and 6.15 (1H, br m, C$\underline{H}$=CH$_2$); ν_{max} (film) 2935, 1648, 1590, and 1084 cm^{-1}; $\underline{m}/\underline{z}$ 196($\underline{M}^+$), 181($\underline{M}^+$ - Me), and 123($\underline{M}^+$ - SiMe$_3$).

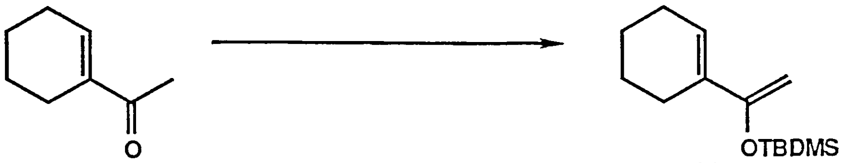
Preparation of Spiro[6β-bicyclo[4.4.0]decan-2-one-5,3'-5'-(3''-furyl)-tetrahydrofuran-2'-one] (78).



Cyclohexyl diene (77) (1.70g, 9.4mmol) and methylidene lactone (62) (1.18g, 7.2mmol) were placed in a base washed, presilylated 3oz pressure vessel and hydroquinone (2mg) added. The reaction mixture was degassed by evacuation and flushing with argon 3 times, then sealed under vacuum, and heated at 130°C for 15 hours. The resultant material was dissolved in THF (10ml) and a solution of 3N HCl (0.2ml) in THF (10ml) was added. The reaction was stirred for 3 hours, then poured into saturated NaHCO$_3$ (10ml). The solution was extracted with ether (4 x 20ml), and the combined ethereal extracts were washed with saturated NaHCO$_3$ (2 x 10ml), saturated NH$_4$Cl (10ml), water (2 x 10ml), and brine (10ml). The ethereal solution was dried, concentrated at reduced pressure, and subjected to column chromatography (20 to 60% ether - petrol) to give firstly 1-acetylcyclohexene (0.5g), followed by starting methylidene lactone (62) (0.12g, 10%) and finally a mixture of apparent cycloaddition products (0.70g). High pressure liquid chromatography (21mm Si column, 5% isopropyl alcohol - hexane, uv detection 235nm) gave a diastereomeric mixture of spiro[6β-bicyclo-[4.4.0]decan-2-one-5,3'-5'-(3''-furyl)tetrahydrofuran-2'-one] (78) (0.58g, 28%, 31% based on recovered (62)), m.p. 152-153°C; δ(250 MHz): 1.10 - 1.40 (4H, m, decalin-H), 1.42 - 1.55 (1H, m, decalin-H), 1.71 -

1.87 (3H, m, decalin-H), 1.89 - 2.01 (1H, m, decalin-H), 2.04 - 2.15 (1H, m, decalin-H), 2.15 - 2.62 (5H, m, decalin-H including C_1-H, C_3-H and C'_4-H_2), 2.98 (1H, m, C_3-H), 5.48 (0.5H, t, J 7.0 Hz, C'_5-H), 5.57 (0.5H, dd, J 10.8 5.5 Hz, C'_5-H), 6.41 (0.5H, br s, furan C''_4-H), 6.46 (0.5H, br s, furan C''_4-H), 7.47 (1H, br s, furan C''_5-H), 7.49 (0.5H, br s, furan C''_2-H), and 7.54 (0.5H, br s, furan C''_2-H); ν_{max} (KBr) 2940, 1758, 1714, and 1160 cm^{-1}; m/z 288(M^+), 260(M^+ - CO), 194(M^+ - furanCO), and 95(furanCO^+); (Found: C, 71.04; H, 7.12. $C_{17}H_{20}O_4$ requires: C, 70.81; H, 6.99%).

Preparation of 1-(1'-t-Butyldimethylsilyloxyvinyl)cyclohex-1-ene (81).

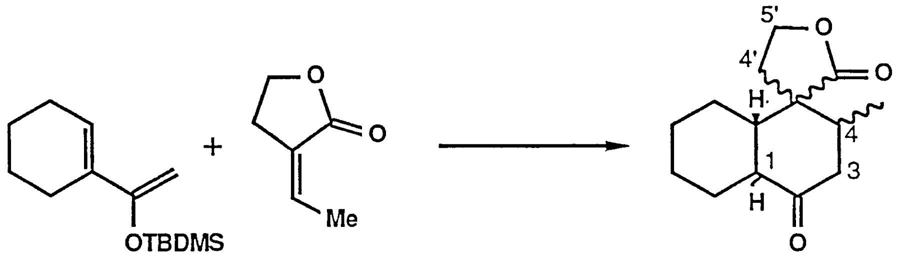


81

To a stirred solution of di-isopropylamine (6.96ml, 48.5mmol) in THF (80ml) under argon at -10°C was added n-butyl lithium (27.15ml of a 1.51M solution in hexanes, 40.7mmol), and the reaction was stirred for 10 minutes, then cooled down to -78°C. 1-Acetylcyclohexene (4.22g, 33.8mmol) in THF (35ml) was added dropwise and stirring continued for 15 minutes. A solution of t-butyldimethylsilyl chloride (6.44g, 42.7mmol) in HMPA (28ml) was added dropwise over 10 minutes, and the reaction mixture warmed to RT over 60 minutes. Petrol (70ml) was added, and the reaction mixture was washed with water (5 x 100ml) and brine (2 x 100ml), dried, and concentrated at reduced pressure. Distillation under reduced pressure through a 12cm Vigreux column gave 1-(1'-t-butyldimethylsilyloxyvinyl)cyclohex-1-ene (81) (7.19g, 89%), b.p. 140°C at 0.05 mm Hg (Lit.,[39] 120-140°C at 0.05 mm Hg); δ(250

MHz): 0.19 (6H, s, SiMe$_2$), 0.98 (9H, s, SiBu), 1.50 - 1.72 (4H, br m, cyclohexyl-H), 2.10 - 2.20 (4H, br m, cyclohexyl-H), 4.18 (1H, s, CH=CHH), 4.35 (1H, s, CH=CHH), and 6.27 (1H, br m, CH=CH$_2$); ν_{max} (film) 2930, 1645, 1593, and 1087 cm^{-1}; m/z 238(M^+), 223(M^+ - Me), and 182(M^+ - Bu).

Preparation of Spiro[bicyclo[4,4,0]decan-2-one-5,3'-tetrahydrofuran-2'-one] (82).

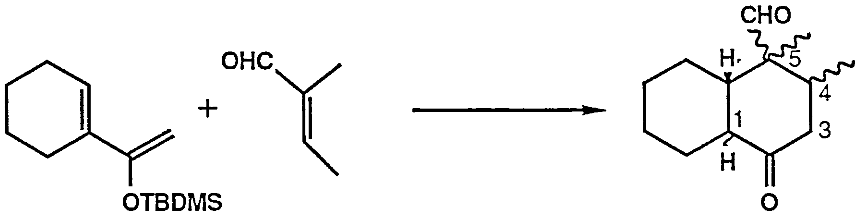


81 63 82

Cyclohexyl diene (81) (1.07g, 4.5mmol) and ethylidene lactone (63) (0.16g, 1.5mmol) were placed in a base washed, presilylated 3oz pressure vessel and hydroquinone (2mg) added. The reaction mixture was degassed by evacuation and flushing with argon 3 times, then sealed under vacuum, and heated at 160°C for 16 hours. The resultant mixture was dissolved in THF (15ml) and tetrabutylammonium fluoride (5ml of a 1M solution in THF, 5mmol) was added with stirring. After 2 hours, the reaction mixture was poured into 1N HCl (10ml) and extracted with ether (3 x 20ml). The combined ethereal extracts were washed with saturated NaHCO$_3$ (2 x 15ml), water (15ml), and brine (20ml), and the solution was dried and concentrated at reduced pressure. Column chromatography (10 to 70% ether - petrol) gave firstly 1-acetylcyclohexene (93mg) followed by a diastereomeric mixture of spiro[bicyclo[4,4,0]decan-2-one-5,3'-tetrahydrofuran-2'-one] (82) (105mg, 30%), δ(250 MHz): 0.90 (3H, m, C$_4$-Me), 1.05 - 1.27

(4H, m, decalin-H), 1.65 - 1.85 (4H, m, decalin-H), 1.90 - 2.08 (2H, m, decalin-H), 2.15 - 2.38 (3H, m, C_1-H and C'_4-H_2), 2.40 - 2.70 (1H, m, C_3-H), 3.34 - 3.60 (1H, m, C_3-H), and 4.15 - 4.38 (2H, m, C'_5-H); ν_{max} 2934, 1754, 1709, and 1189 cm^{-1}; m/z 236(M^+), 221(M^+ - Me), 208(M^+ - CO), and 194(M^+ - CO_2); (Found: M^+, 236.1417. $C_{14}H_{20}O_3$ requires: M^+, 236.1412).

Preparation of 4,5-Dimethyl-5-formylbicyclo[4,4,0]decan-2-one (83).



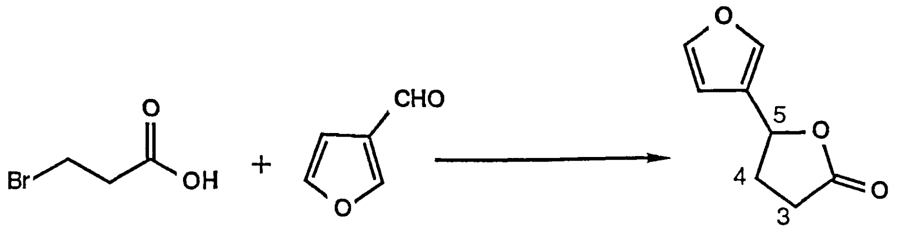
81 42 83

Cyclohexyl diene (81) (6.20g, 26mmol) and tiglic aldehyde (42) (1.24g, 15mmol) were placed in a base washed, presilylated 3oz pressure vessel and hydroquinone (2mg) added. The reaction mixture was degassed by evacuation and flushing with argon 3 times, then sealed under vacuum, and heated to 150°C for 3 days. The resultant mixture was dissolved in THF (25ml) and tetrabutylammonium fluoride (30ml of a 1M solution in THF, 30mmol) was added with stirring. After 4 hours, the reaction mixture was poured into 1N HCl (25ml) and extracted with ether (3 x 50ml). The combined ethereal extracts were washed with saturated $NaHCO_3$ (2 x 30ml), water (30ml), and brine (30ml), and the solution was dried and concentrated at reduced pressure. Column chromatography (20 to 40% ether - petrol) gave 4,5-dimethyl-5-formylbicyclo[4,4,0]-decan-2-one (83) (0.96g, 33%) as a diastereomeric mixture, ν_{max} (film) 2930, 1730, and 1712 cm^{-1}; m/z 208(M^+), 180(M^+ - CO), and 165(M^+ - CO - Me). High pressure liquid chromatography (21mm Si column, 5% isopropyl alcohol - hexane, uv detection 240nm) of a portion of the material gave firstly 40% of a single diastereoisomer, δ(400 MHz): 0.93 (3H, d, J 7.0 Hz, C_4-Me), 1.12 (3H, s, C_5-Me), 1.13 - 1.25 (4H, m, decalin-H), 1.54 - 1.62 (2H, m, decalin-H), 1.70 - 1.83 (3H, br m, decalin-H), 1.95 - 2.05 (1H, br m, decalin-H), 2.17 (1H, dd, J 14.0 3.0 Hz, C_3-H), 2.35 - 2.45 (1H, br m, C_1-H), 2.64 (1H, dd, J 14.0 6.0 Hz, C_3-H), and 9.79 (1H, s, CHO); followed by 60% of a mixture of 3 other diastereoisomers, δ(400 MHz): 0.81 (0.6H, d, J 7.0 Hz, C_4-Me), 0.88 (1.5H, d, J 6.5 Hz, C_4-Me), 0.96 (0.9H, d, J 7.0 Hz, C_4-Me), 1.08 - 1.20 (5.5H, m, decalin-H, including 1.10, s, C_5-Me and 1.19, s, C_5-Me), 1.28 (1.5H, s, C_5-Me), 1.31 - 1.45 (2H, m, decalin-H), 1.65 - 1.80 (2H, m, decalin-H), 1.98 - 2.17 (2H, m, decalin-H), 2.19 - 2.37 (2H, m, C_1-H and C_3-H), 2.59 - 2.73 (1H, m, C_3-H), 9.39 (0.3H, s, CHO), 9.54 (0.5H, s, CHO), and 9.98 (0.2H, s, CHO).

Preparation of Lithium naphthalenide using ultrasound.

Lithium metal (0.21g, 30mmol) was freshly cut from stick lithium into pioeces of 2-3mm dimensions, and subjected to ultrasound in ether (10ml) under argon for 5 minutes. The lithium was then dried under a stream of dry argon, and added to a solution of naphthalene (3.84g, 30mmol, freshly recrystallised from acetone) in THF (125ml) under argon at RT. The reaction was subjected to ultrasound for 2 hours, yielding a 0.22M solution of lithium naphthalenide as a dark green solution which was utilised immediately.

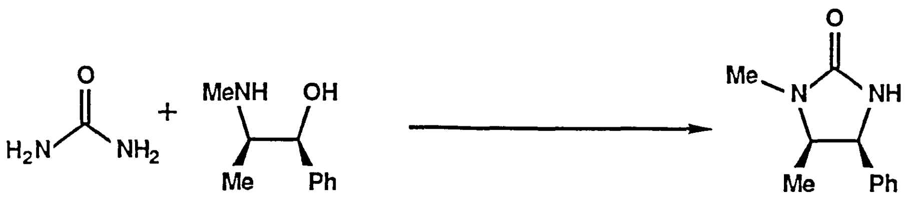
Preparation of 5-(3'-Furyl)tetrahydrofuran-2-one (64).



64

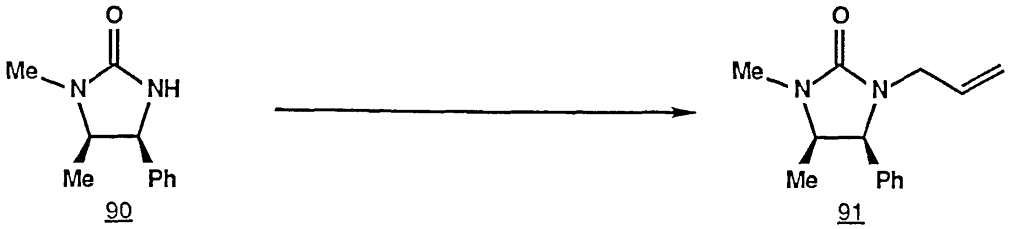
To a stirred solution of 3-bromopropionic acid (0.92g, 6.0mmol) in THF (25ml) under argon at -78°C was added n-butyl lithium (4ml of a 1.5M solution in hexanes, 6.0mmol) dropwise over 30 minutes. The resultant white dispersion was added dropwise to a stirred solution of lithium naphthalenide (46ml of a 0.22M solution in THF, 10.0mmol) under argon at -78°C, giving a brown solution. Furan-3-carboxaldehyde (0.32g, 3.3mmol) was added in THF (5ml) and the reaction mixture was stirred for 60 minutes, giving a cloudy yellow solution. The reaction was then warmed to 0°C over 3 hours, giving a clear yellow solution, and poured into cold 5% NaOH (40ml). The aqueous phase was separated, washed with ether (2 x 20ml), and acidified with 1N HCl (80ml), then extracted with ether (3 x 100ml). The combined ethereal solutions were washed with saturated $NaHCO_3$ (2 x 50ml), water (2 x 50ml), and brine (50ml), and dried. Solvent removal at reduced pressure, and column chromatography (50% ether - petrol) gave 5-(3'-furyl)-tetrahydrofuran-2-one (64) (0.62g, 41%), δ(250 MHz): 2.23 (1H, m, C_4-$\underline{H}$), 2.50 - 2.67 (3H, m, C_4-$\underline{H}$ and C_3-$\underline{H}_2$), 5.48 (1H, br dd, J 8.0 5.0 Hz, C_5-$\underline{H}$), 6.41 (1H, dd, J 1.5 1.0 Hz, furan C'_4-$\underline{H}$), 7.43 (1H, t, J 1.5 Hz, furan C'_5-$\underline{H}$), and 7.48 (1H, m, furan C'_2-$\underline{H}$); ν_{max} (film) 1771, 1598, and 1160 cm^{-1}; $\underline{m}/\underline{z}$ 152($\underline{M}^+$), 124($\underline{M}^+$ - CO), 108($\underline{M}^+$ - CO_2), and 95(furanCO^+); (Found: C, 63.42; H, 5.54. $C_8H_8O_3$ requires: C, 63.17; H, 5.31%). For larger scale preparations (0.25 molar) separation of the product was effected by medium pressure liquid chromatography.

Preparation of 3-Methyl-4(R)-methyl-5(S)-phenyl-1,3-diazolidin-2-one (90).


90

(+)-Ephedrine hydrochloride (25g, 124mmol) and urea (22.5g, 375mmol) were heated together at 175°C for 30 minutes, followed by 60 minutes at 210°C, giving a clear melt. After cooling, the mixture was broken up in water (200ml), filtered, washed with 3N HCl (2 x 50ml) and water (3 x 50ml), and dried under reduced pressure. Recrystallisation from ethanol gave 3-methyl-4(R)-methyl-5(S)-phenyl-1,3-diazolidin-2-one (90) (16.67g, 71%), m.p. 172-174°C (Lit.,[43] 177-179°C for enantiomer); $[\alpha]_D^{25}$ +43.9° (c 1.1, MeOH) (Lit.,[43] $[\alpha]_D^{25}$ -44.5° (c 3, MeOH) for enantiomer); δ(250 MHz): 0.78 (3H, d, J 6.5 Hz, CHMe), 2.80 (3H, s, NMe), 3.85 (1H, dq, J 9.0 6.5 Hz, CHMe), 4.72 (1H, d, J 9.0 Hz, PhCH), 5.05 (1H, br s, NH), and 7.37 (5H, s, CHPh); ν_{max} ($CHCl_3$) 3278, 2974, 1700, and 765 cm^{-1}; m/z 190(M^+), 175(M^+ - Me), and 132(M^+ - PhH).

Preparation of 1-Allyl-3-methyl-4(R)-methyl-5(S)-phenyl-1,3-diazolidin-2-one (91).


90 91

Sodium hydride (0.23g of a 57% dispersion in mineral oil, 5.5mmol) was washed with 30-40° petrol under argon, dried, and suspended in THF (10ml) under argon at RT. A solution of the ephedrine adduct (90) (0.95g, 5.0mmol) in THF (90ml) was added dropwise over 30 minutes, giving a pale yellow crystalline precipitate, which was stirred at RT for 60 minutes. Allyl bromide (1.20g, 10mmol) was added, and the reaction mixture was stirred for 20 hours, giving loss of the crystalline precipitate and producing a white colloidal precipitate. The reaction mixture was poured into 1N HCl (50ml), and extracted with DCM (3 x 80ml). The combined organic extracts were washed with saturated $NaHCO_3$ (2 x 50ml), water (50ml), and dried. Concentration at reduced pressure gave a solid which was recrystallized from petrol - ethyl acetate to give 1-allyl-3-methyl-4(R)-methyl-5(S)-phenyl-1,3-diazolidin-2-one (91) (0.98g, 85%) as pale orange crystals, m.p. 65-67°C (Lit.,[43] 68-69.5°C for enantiomer); $[\alpha]_D^{25}$ -18.5° (*c* 2.2, MeOH) (Lit.,[43] $[\alpha]_D^{22}$ +22.7° for enantiomer); δ(250 MHz), 0.75 (3H, d, J 6.5 Hz, CH$\underline{\text{Me}}$), 2.87 (3H, s, N$\underline{\text{Me}}$), 3.08 (1H, br dd, J 15.0 7.8 Hz, $H_2C=CHC\underline{H}H$), 3.73 (1H, dq, J 8.8 6.5 Hz, C$\underline{\text{H}}$Me), 4.32 (1H, ddt, J 15.0 4.3 1.5 Hz, $H_2C=CHCH\underline{H}$), 4.67 (1H, d, J 8.8 Hz, PhC$\underline{\text{H}}$), 4.95 (1H, dq, J 17.0 1.5 Hz, CCH=C$\underline{\text{H}}$H), 5.07 (1H, dq, J 10.0 1.5 Hz, CCH=CH$\underline{\text{H}}$), 5.70 (1H, dddd, J 17.0 10.0 7.5 4.3 Hz, $C\underline{H}=CH_2$), and 7.10 - 7.37 (5H, m, CH$\underline{\text{Ph}}$); ν_{max} ($CHCl_3$) 2974, 1699, 1603, and 762 cm^{-1}; *m/z* 230(*M*$^+$), 215(*M*$^+$ - Me), and 189(*M*$^+$ - allyl).

Preparation of Tris-(diethylamino)titanium (IV) Chloride (92).

a) Using n-Butyl Lithium.

$$Et_2NH \quad + \quad {}^{n}BuLi \longrightarrow Et_2NLi \xrightarrow{TiCl_4} Ti(NEt_2)_3Cl$$

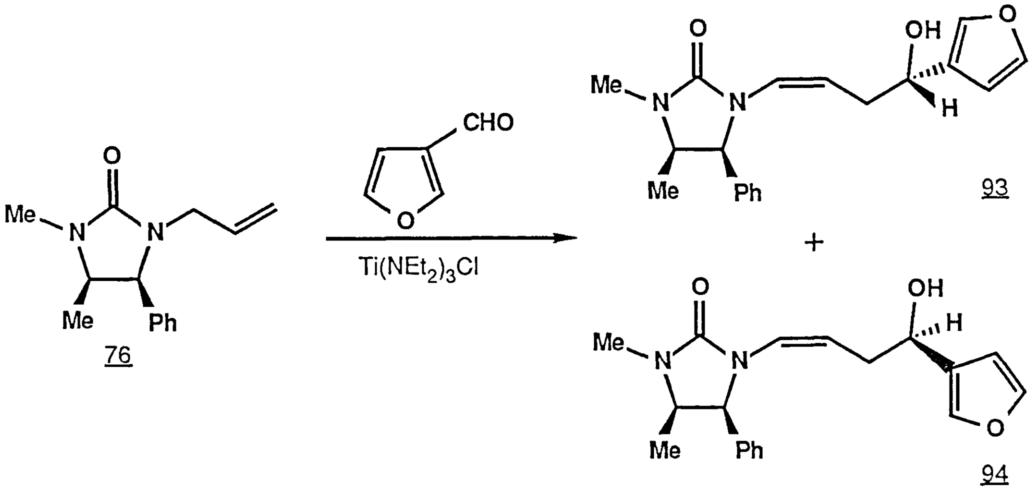
To a solution of diethylamine (7.31g, 100mmol) in ether (50ml) under argon at 0°C was added n-butyl lithium (69ml of a 1.45M solution in hexanes, 100mmol) dropwise over 20 minutes. The reaction was stirred for 30 minutes, then titanium tetrachloride (6.33g, 33mmol) in toluene (15ml) was added over 10 minutes, and the reaction heated at reflux for 60 minutes. Solvent removal at reduced pressure followed by bulb to bulb distillation at reduced pressure gave tris-(diethylamino)titanium (IV) chloride (92) (6.12g, 61%), b.p. 125°C at 0.4 mm Hg (Lit.,[44] 94-96°C at 0.02 mm Hg); δ(60 MHz): 1.23 (3H, t, J 13.0 Hz, $CH_2C\underline{H}_3$), 3.95 (2H, q, J 13.0 Hz, $C\underline{H}_2CH_3$).

b) Using Lithium Metal.

$$Et_2NH + Li + \text{Styrene} \longrightarrow Et_2NLi \xrightarrow{TiCl_4} Ti(NEt_2)_3Cl$$

To freshly cut lithium (7.7g, 1.1mol), preactivated with ultrasound (see preparation of lithium naphthalenide) in ether (400ml) under argon at RT was added diethylamine (73.1g, 1.0mol) and the reaction mixture was heated at reflux. Styrene (52.1g, 0.5mol) in ether (150ml) was added dropwise over 60 minutes, and the reaction was kept at reflux for a further 14 hours. The mixture was cooled to 0°C, and a solution of titanium tetrachloride (63.3g, 0.33mol) in toluene (150ml) was added. The reaction was then heated at reflux for 2 hours, and the solvent removed by distillation at atmospheric pressure. Distillation at reduced pressure gave tris-(diethylamino)-titanium (IV) chloride (92) (60.6g, 61%), b.p. 96°C at 0.05 mm Hg (Lit.,[44] 94-96°C at 0.02 mm Hg); identical in all respects to the previously prepared material.

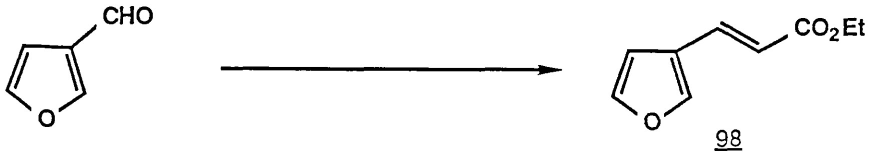
Preparation of 4'(S)-1-(4'-(3''-Furyl)-4'-hydroxybut-1'(Z)-enyl)-3-methyl-4(R)-methyl-5(S)-phenyl-1,3-diazolidin-2-one (93) and 4'(R)-1-(4'-(3''-Furyl)-4'-hydroxybut-1'(Z)-enyl)-3-methyl-4(R)-methyl-5(S)-phenyl-1,3-diazolidin-2-one (94).



To a stirred solution of n-butyl lithium (4.3ml of a 1.35M solution in hexanes, 5.82mmol) in THF (5ml) under argon at -78°C was added allyl compound (91) (1.20g, 5.20mmol) in THF (4ml). The reaction mixture was stirred for 30 minutes, then tris-(diethylamino)titanium (IV) chloride (92) (3.0ml of a 1.9M solution in THF, 5.82ml) was added over 5 minutes. The reaction was warmed to -30°C over 60 minutes, and stirred for 45 minutes at -30°C. Furan-3-carboxaldehyde (0.49g, 5.20mmol) in THF (2ml) was added, and stirring continued for 3 hours at -30°C. Water (10ml) was added, the mixture was extracted with ether (3 x 15ml), and the combined ethereal extracts were washed with 10% $NaHSO_3$ (20ml) and dried. Concentration at reduced pressure and column chromatography (60 to 100% ether - petrol) gave a mixture of 4'(S)-1-(4'-(3''-furyl)-4'-hydroxybut-1'(Z)-enyl)-3-methyl-4(R)-methyl-5(S)-phenyl-1,3-diazolidin-2-one (93) and 4'(R)-1-(4'-(3''-furyl)-4'-hydroxybut-1'(Z)-enyl)-3-methyl-4(R)-methyl-5(S)-phenyl-1,3-diazolidin-2-one (94) (0.47g, 28%) as a 9 : 1 mixture, $[\alpha]_D^{25}$ +46.0° (c 1.54, MeOH); δ(250 MHz): 0.78 (3H, d, J 6.5 Hz, CHMe), 2.40 - 2.60

(2H, m, C=CHC$\underline{H}_2$), 2.81 (2.7H, s, N$\underline{Me}$ major), 2.83 (0.3H, s, N$\underline{Me}$ minor), 3.60 (1H, br s, O$\underline{H}$), 3.86 (1H, dq, J 8.0 6.5 Hz, C$\underline{H}$Me), 4.63 (1H, br dd, J 7.5 5.0 Hz, C$\underline{H}$OH), 4.83 (1H, dt, J 8.5 7.5 Hz, NCH=C$\underline{H}$), 4.96 (1H, d, J 8.0 Hz, C$\underline{H}$Ph), 5.98 (0.1H, br d, J 8.0 Hz, NC$\underline{H}$=CH minor), 6.10 (0.9H, dt, J 8.5 1.5 Hz, NC$\underline{H}$=CH major), 6.31 (0.9H, m, furan C''$_4$-$\underline{H}$ major), 6.35 (0.1H, m, furan C''$_4$-$\underline{H}$ minor), 7.13 (2H, m, furan C''$_2$-$\underline{H}$ and C''$_5$-$\underline{H}$), and 7.33 (5H, m, CH$\underline{Ph}$); ν_{max} (film) 3394, 2926, 1702, and 1604 cm^{-1}; $\underline{m/z}$ 326($\underline{M}^+$), and 230($\underline{M}^+$ - furanCO); (Found: $\underline{M}^+$, 326.1628. $C_{19}H_{22}N_2O_3$ requires: $\underline{M}^+$, 326.1630).

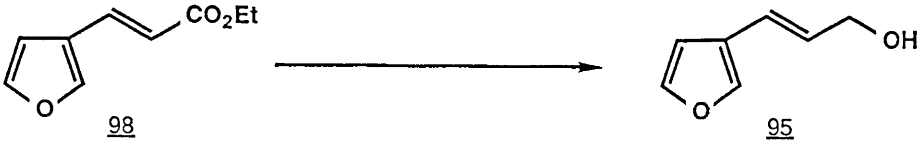
Preparation of Ethyl 3-(3'-furyl)-2(E)-propenoate (98).



98

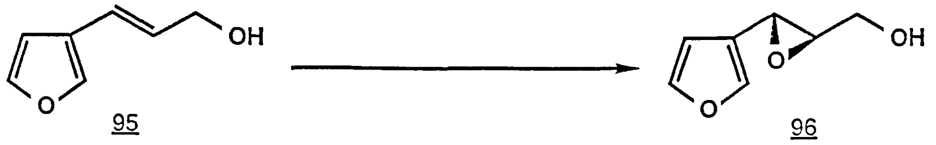
To a stirred solution of stabilised Wittig reagent (97) (2.82g, 8.1mmol) in DCM (15ml) under argon at RT was added furan-3-carboxaldehyde (0.78g, 8.1mmol) in DCM (10ml). The reaction mixture was stirred for 60 minutes, then the solvent was removed at reduced pressure. The residue was taken up in DCM (1ml), ether (10ml) was added, and the resultant precipitate was filtered off. Concentration of the filtrate at reduced pressure, followed by column chromatography (20% ether - petrol), gave ethyl 3-(3'-furyl)-2($\underline{E}$)-propenoate (98) (0.83g, 62%), m.p. 38.5°C; δ(250 MHz): 1.32 (3H, t, J 6.5 Hz, $CO_2CH_2C\underline{H}_3$), 4.25 (2H, q, J 6.5 Hz, $CO_2C\underline{H}_2CH_3$), 6.15 (1H, d, J 15.0 Hz, $EtO_2CC\underline{H}$=CH), 6.59 (1H, br d, J 2.0 Hz, furan C'$_4$-$\underline{H}$), 7.42 (1H, br s, furan C'$_5$-$\underline{H}$), 7.58 (1H, d, J 15.0 Hz, EtO_2CCH=C$\underline{H}$), and 7.65 (1H, s, furan C'$_2$-$\underline{H}$); ν_{max} ($CHCl_3$) 1697, 1638, and 1153 cm^{-1}; $\underline{m/z}$ 166($\underline{M}^+$), 138($\underline{M}$+ - $H_2C=CH_2$), and 121($\underline{M}$+ - CH_2CH_2OH); (Found: $\underline{M}$+, 166.0623. $C_9H_{10}O_3$ requires: $\underline{M}^+$, 166.0630).

Preparation of 3-(3'-Furyl)-2(E)-propen-1-ol (95).



To a stirred solution of ester (98) (0.34g, 2.05mmol) in THF (20ml) under argon at -78°C was added di-isobutylaluminium hydride (4.1ml of a 1M solution in THF, 4.10mmol), the reaction was warmed to RT, and stirred for 14 hours. Water (4ml) was added, and the reaction mixture was poured into ethyl acetate (40ml) over solid Na_2SO_4 (2g) with rapid stirring. After thirty minutes the granular precipitate was filtered, and the filtrate was washed with water (20ml), brine (20ml), and dried. Concentration at reduced pressure and column chromatography (50% ether - petrol) gave 3-(3'-furyl)-2($\underline{E}$)-propen-1-ol (95) (0.18g, 69%), δ(250 MHz): 1.62 (1H, br s, O$\underline{H}$), 4.33 (2H, dd, J 6.0 1.5 Hz, $C\underline{H}_2OH$), 6.07 (1H, dt, J 15.8 6.0 Hz, $HOCH_2C\underline{H}=CH$), 6.46 (1H, dt, J 6.0 1.5 Hz, $HOCH_2CH=C\underline{H}$), 6.52 (1H, d, J 2.0 Hz, furan C'_4-$\underline{H}$), 7.35 (1H, t, J 2.0 Hz, furan C'_5-$\underline{H}$), and 7.40 (1H, m, furan C'_2-$\underline{H}$); ν_{max} (film) 3339, 2924, and 1665 cm^{-1}; $\underline{m/z}$ 124($\underline{M}^+$), 107($\underline{M}^+$ - OH), and 95($\underline{M}^+$ - HCO); (Found: $\underline{M}^+$, 124.0521. $C_7H_8O_2$ requires: $\underline{M}^+$, 124.0524).

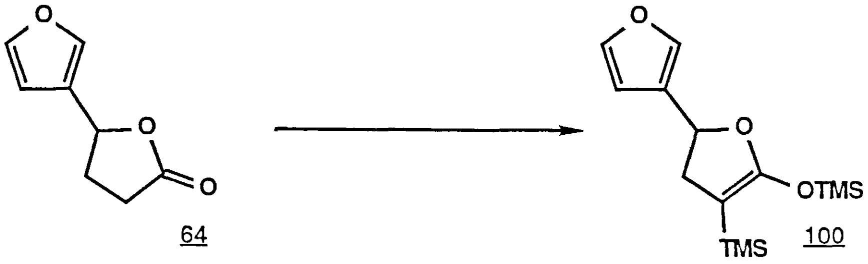
Attempted preparation of 3-(3'-Furyl)-2-propen-1-ol-2(R),3(S)-oxiran (96).



To a stirred solution of titanium (IV) isopropoxide (0.12g, 1.0mmol) in DCM (5ml) under argon at -78°C was added (+)-diethyl tartrate (0.20g, 1.2mmol). Allylic alcohol (95) (0.12g, 1.0mmol) was added dropwise in DCM (1ml), followed by t-butylhydroperoxide (2ml of a 1M solution in toluene, 2.0mmol) precooled to -30°C. The reaction mixture was allowed to warm to -25°C, and retained at -25°C for 3 hours. Ether (5ml) and saturated Na_2SO_4 (2ml) were added, and the reaction mixture was warmed to RT and stirred for 2 hours. The solution was filtered through a pad of celite, and washed through with ether (10ml). The filtered precipitate was extracted with boiling ethyl acetate (50ml), filtered through a pad of celite, and washed through with boiling ethyl acetate (50ml). The ethyl acetate and ethereal solutions were combined, a mixture of saturated sodium fluoride (5ml) and acetonitrile (5ml) was added, and the reaction mixture was stirred for a further 60 minutes. The resultant mixture was filtered, the organic phase was separated, and the aqueous phase was extracted with ethyl acetate (2 x 20ml). The combined organic solutions were dried, concentrated at reduced pressure, and subjected to column chromatography (10 to 35% ether - petrol) to give 3-(3'-furyl)-2-propen-1-ol-2,3-oxiran (96) (20mg, 15%), $[\alpha]_D^{25}$ 0.0° ($\underline{c}$ 0.48, MeOH); δ(250 MHz): 2.10 (1H, br s, O$\underline{H}$), 3.11 (1H, m, $HOCH_2\overset{O}{C\underline{H}\text{-}CH}$), 3.82 (1H, d, J 4.0 Hz, $HOCH_2\overset{O}{CH\text{-}C\underline{H}}$), 3.92 - 4.00 (2H, br m, $C\underline{H}_2OH$), 6.29 (1H, dd, J 2.5 1.5 Hz, furan $C'_4\text{-}\underline{H}$), 7.38 (1H, t, J 1.5 Hz, furan

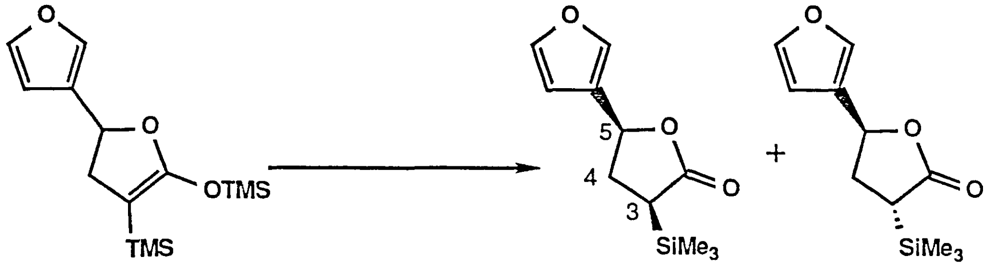
C'$_5$-H), and 7.40 (1H, br s, furan C'$_2$-H); ν_{max} (film) 3430, 1605, and 1503 cm^{-1}; m/z 140(M$^+$), 124(M$^+$ - O), and 123(M$^+$ - OH).

Preparation of 5-(3'-Furyl)-3-trimethylsilyl-2-trimethylsilyloxydihydro-4,5H-furan (100).



To a stirred solution of triethylamine (2.23g, 22mmol) in ether (20ml) under argon at RT was added dropwise trimethylsilyltrifluoromethanesulphonate (4.93g, 22mmol), and the reaction mixture cooled to 0°C. Furyl lactone (64) (1.52g, 10mmol) was added dropwise in ether (5ml), the reaction was allowed to warm to RT, and stirring was continued for 30 minutes. The ethereal phase was separated, the non-ethereal phase was washed with ether (2 x 10ml), and the combined ethereal solutions were concentrated at reduced pressure to give 5-(3'-furyl)-3-trimethylsilyl-2-trimethylsilyloxydihydro-4,5H-furan (69) (2.80g, 95%) as a pale orange oil, utilised without any further purification, δ(60 MHz): 0.08 (9H, s, SiMe_3), 0.25 (9H, s, SiMe_3), 2.83 (2H, br d, J 8.0 Hz, C=C(SiMe$_3$)CH_2CH), 5.38 (1H, br t, J 8.0 Hz, C=C(SiMe$_3$)CH$_2$CH), 6.43 (1H, m, furan C'$_4$-H), and 7.44 (2H, m, furan C$_2$-H and C$_5$-H); ν_{max} (film) 2952, 1643, 1595, and 845 cm^{-1}.

Preparation of *cis* and *trans* 5-(3'-Furyl)-3-trimethylsilyl-tetrahydrofuran-2-one (104) and (105).



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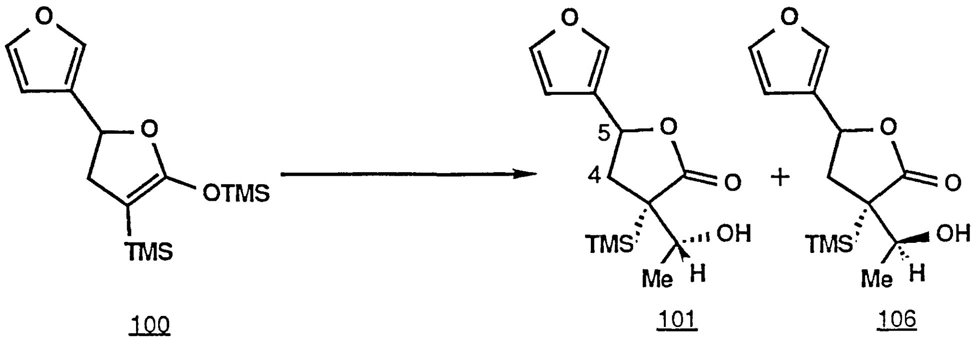
To a stirred solution of silyl enol ether (100) (0.15g, 0.5mmol) in THF (10ml) at RT was added a solution of 3N HCl (0.5ml) in THF (5ml), and the reaction stirred for 30 minutes. The reaction mixture was poured into saturated $NaHCO_3$ (10ml) and extracted with ether (3 x 20ml). The combined ethereal extracts were washed with water (2 x 10ml) and brine (20ml), dried, and concentrated at reduced pressure. Column chromatography (50% ether - petrol) gave a mixture of *cis* and *trans* *5-(3'-Furyl)-3-trimethylsilyltetrahydrofuran-2-one* (104) and (105) (0.10g, 90%), ν_{max} (film) 2954, 1750, 1597, and 842 cm^{-1}; *m/z* 224(M^+), and 209(M^+ - Me); (Found: C, 58.83; H, 7.26. $C_{11}H_{16}O_3Si$ requires: C, 58.89; H, 7.19%). Further column chromatography (30 to 50% ether - petrol) of a portion of the product gave firstly *trans silyl lactone* (105), δ(250 MHz): 0.15 (9H, s, Si*Me*$_3$), 2.02 (1H, ddd, J 12.5 10.3 9.0 Hz, C_4-*H*), 2.25 (1H, dd, J 10.3 10.0 Hz, C_3-*H*), 2.63 (1H, ddd, J 12.5 10.0 6.8 Hz, C_4-*H*), 5.39 (1H, dd, J 9.0 6.8 Hz, C_5-*H*), 6.39 (1H, br d, J 2.0 Hz, furan C'_4-*H*), 7.42 (1H, br t, J 2.0 Hz, furan C'_5-*H*), and 7.44 (1H, m, furan C'_2-*H*); followed by *cis silyl lactone* (104), δ(250 MHz): 0.22 (9H, s, Si*Me*$_3$), 2.29 (1H, dd, J 6.8 6.3 Hz, C_3-*H*), 2.45 (1H, t, J 6.5 Hz, C_4-*H*), 2.49 (1H, t, J 6.8 Hz, C_4-*H*), 5.34 (1H, t, J 6.5 Hz, C_5-*H*), 6.40 (1H, m, furan C'_4-*H*), 7.42 (1H, br t, J 2.0 Hz, furan C'_5-*H*), and 7.45 (1H, m, furan C'_2-*H*).

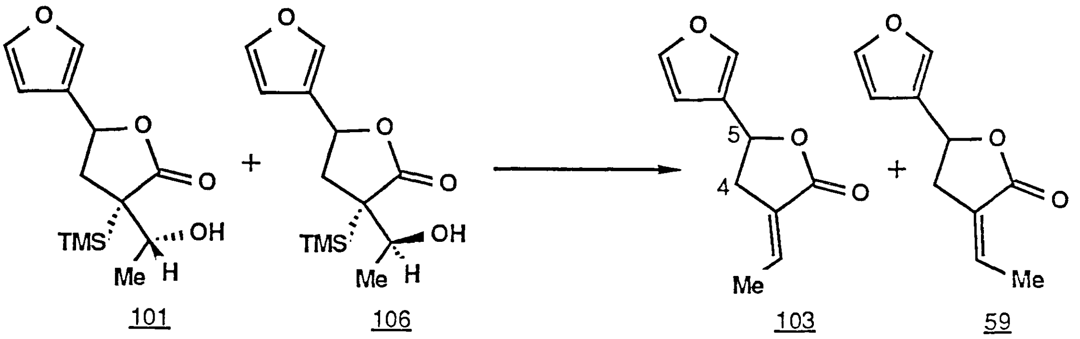
Preparation of (3S*,1'R*)-5-(3''-Furyl)-3-(1'-hydroxyethyl)-3-trimethylsilyltetrahydrofuran-2-one (101) and (3S*,1'S*)-5-(3''-Furyl)-3-(1'-hydroxyethyl)-3-trimethylsilyltetrahydrofuran-2-one (106).



To a stirred solution of redistilled acetaldehyde (3.69ml, 66.0mmol) in DCM (70ml) under argon at -78°C was added titanium tetrachloride (3.62ml, 33.0mmol) dropwise over 10 minutes, giving a yellow precipitate. Freshly prepared silyl enol ether (100) (9.78g, 33.0mmol) was added dropwise in DCM (30ml) over 30 minutes, and the resultant mixture was stirred for a further 90 minutes at -78°C, giving a yellow solution. Methanol (40ml) was added at -78°C, the reaction mixture was poured into water (100ml), and the solution was extracted with ether (3 x 150ml). The combined ethereal extracts were washed with water (50ml) and brine (50ml), dried, and concentrated at reduced pressure. Column chromatography (40 to 70% ether - petrol) gave firstly a mixture of cis and trans 5-(3'-Furyl)-3-trimethylsilyltetrahydrofuran-2-one (104) and (105) (0.95g, 13%) identical to the previously prepared samples, followed by a diastereomeric mixture of (3S*,1'R*)-5-(3''-furyl)-3-(1'-hydroxyethyl)-3-trimethylsilyltetrahydrofuran-2-one (101) and (3S*,1'S*)-5-(3''-furyl)-3-(1'-hydroxyethyl)-3-trimethylsilyltetrahydrofuran-2-one (106) (4.60g, 52%) m.p. 89-90°C; δ(250 MHz): 0.15 (9H, s, SiMe$_3$), 1.29 (0.3H, d, J 6.0 Hz, CHMe), 1.33 (2.7H, d, J 6.0 Hz, CHMe), 2.15 (1H, dd, J 14.0 8.7

Hz, C_4-H), 2.23 (1H, br s, OH), 2.72 (1H, dd, J 14.0 8.3 Hz, C_4-H), 4.35 (1H, br q, J 6.0 Hz, CHMe), 5.41 (1H, br t, J 8.5 Hz, C_5-H), 6.40 (1H, br s, furan C''_4-H), and 7.44 (2H, m, furan C''_2-H and C''_5-H); ν_{max} ($CHCl_3$) 3480, 2927, 1747, 1597, and 1185 cm^{-1}; m/z 268(M^+), 253(M^+ - Me), and 250(M^+ - H_2O); (Found: C, 58.32; H, 7.46. $C_{13}H_{20}O_4Si$ requires: C, 58.17; H, 7.51%).

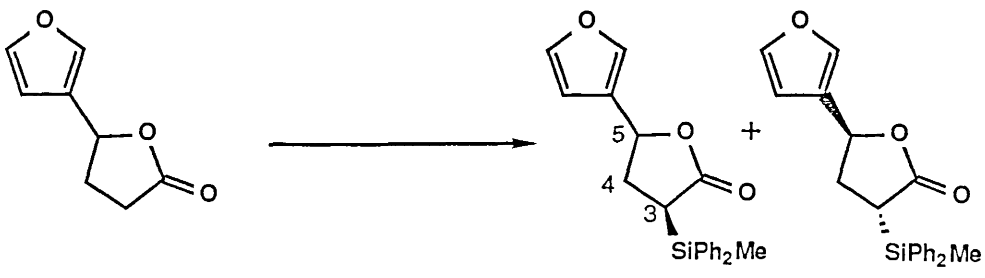
Preparation of Z and E 3-Ethylidene-5-(3'-furyl)tetrahydrofuran-2-one (59) and (103) from (101) and (106).



To a stirred solution of aldol product (101) and (106) (138mg, 0.51mmol) in DCM (10ml) under argon at -30°C was added boron trifluoride diethyl etherate (0.64ml, 5.1mmol), and the reaction mixture was stirred for 16 hours. The mixture was poured into saturated NH_4Cl (10ml) and extracted with DCM (3 x 15ml). The combined organic extracts were washed with water (2 x 15ml), dried, and concentrated at reduced pressure. Column chromatography (20 - 50% ether - petrol) gave a mixture of Z and E 3-ethylidene-5-(3'-furyl)-tetrahydrofuran-2-one (59) and (103) (90.3mg, 99%) in a 92 : 8 ratio (GC analysis). High pressure liquid chromatography (21mm Si column, 10% isopropyl alcohol - hexane, uv detection 254nm) gave firstly Z-3-ethylidene-5-(3'-furyl)tetrahydrofuran-2-one (59) (78.3mg, 86%), δ(250 MHz): 2.17 (3H, dt, J 7.3 2.3 Hz, C=CHMe), 2.83 (1H, ddquint, J 15.5

6.5 2.3 Hz, C_4-*H*), 3.18 (1H, ddquint, J 15.5 7.5 2.3 Hz, C_4-*H*), 5.39 (1H, dd, J 7.5 6.5 Hz, C_5-*H*), 6.31 (1H, qt, J 7.3 2.3 Hz, C=C*H*Me), 6.36 (1H, dd, J 2.0 1.0 Hz, furan C'_4-*H*), 7.38 (1H, t, J 2.0 Hz, furan C'_5-*H*), and 7.42 (1H, dt, J 2.0 1.0 Hz, furan C'_2-*H*); ν_{max} (film) 2920, 1755, 1670, and 1020 cm^{-1}; *m*/*z* 178(*M*$^+$), 163(*M*$^+$ - Me), and 135(*M*$^+$ - Me - CO); (Found: C, 67.20; H, 5.89. $C_{10}H_{10}O_3$ requires: C, 67.40; H, 5.66%); followed by *E*-3-ethylidene-5-(3'-furyl)tetrahydrofuran-2-one (103) (8.0mg, 8%), δ(250 MHz): 1.84 (3H, dt, J 6.8 2.0 Hz, C=CH*Me*), 2.85 (1H, dddq, J 16.0 5.5 3.2 2.0 Hz, C_4-*H*), 3.20 (1H, dddq, J 16.0 8.3 3.2 2.0 Hz, C_4-*H*), 5.47 (1H, dd, J 8.3 5.5 Hz, C_5-*H*), 6.35 (1H, dd, J 2.0 1.0 Hz, furan C'_4-*H*), 6.81 (1H, qt, J 6.8 3.2 Hz, C=C*H*Me), 7.40 (1H, t, J 2.0 Hz, furan C'_5-*H*), and 7.43 (1H, dt, J 2.0 1.0 Hz, furan C'_2-*H*); ν_{max} (film) 2920, 1757, 1668, and 1023 cm^{-1}; *m*/*z* 178(*M*$^+$), 163(*M*$^+$ - Me), and 135(*M*$^+$ - Me - CO); (Found: *M*$^+$, 178.0636. $C_{10}H_{10}O_3$ requires: *M*$^+$, 178.0629).

Preparation of 3-Diphenylmethylsilyl-5-(3'-furyl)tetrahydrofuran-2-one (102).

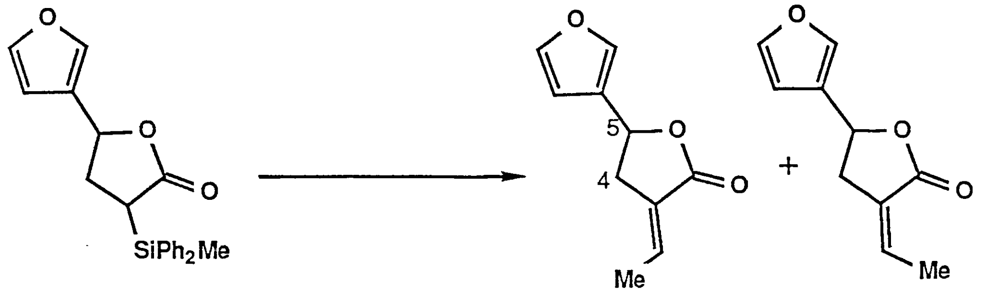


64 102

To a stirred solution of di-isopropylamine (0.80ml, 6.0mmol) in THF (5ml) under argon at -78°C was added n-butyl lithium (4.0ml of a 1.5M solution in hexanes, 6.0mmol). The reaction mixture was warmed to 0° C, stirred for 15 minutes, and cooled to -78°C. Furyl lactone (64) (0.76g, 5.0mmol) in THF (5ml) was added, and the reaction stirred for

30 minutes, then diphenylmethylsilyl chloride (1.15g, 5.0mmol) in THF (5ml) was added dropwise. The reaction mixture was stirred at -78°C for 90 minutes, then warmed to RT and stirred for another 60 minutes. The reaction mixture was poured into petrol (40ml) and washed with water (2 x 30ml), brine (30ml) and dried. Concentration at reduced pressure, and column chromatography (10 to 50% ether - petrol) gave firstly trans 3-diphenylmethylsilyl-5-(3'-furyl)tetrahydrofuran-2-one (trans-102) (0.67g, 38%), δ(250 MHz): 0.74 (3H, s, SiMe), 2.09 (1H, ddd, J 13.0 11.0 9.3 Hz, C_4-H), 2.62 (1H, ddd, J 13.0 9.7 7.0 Hz, C_4-H), 2.84 (1H, dd, J 11.0 9.7 Hz, C_3-H), 5.35 (1H, dd, J 9.3 7.0 Hz, C_5-H), 5.95 (1H, dd, J 2.0 1.5 Hz, furan C'_4-H), and 7.25 - 7.74 (12H, m, $SiPh_2$ and furan C'_2-H and C'_5-H); ν_{max} (film) 3067, 2984, 1736, 1588, and 790 cm^{-1}; m/z 348(M^+), 333(M^+ - Me), 320(M^+ - CO), and 197($SiPh_2Me^+$); (Found: C, 72.36; H, 5.88. $C_{21}H_{20}O_3Si$ requires: C, 72.40; H, 5.80%); followed by cis 3-diphenylmethylsilyl-5-(3'-furyl)-tetrahydrofuran-2-one (cis-102) (0.50g, 29%), δ(250 MHz): 0.78 (3H, s, SiMe), 2.42 - 2.51 (2H, m, C_4-H_2), 2.87 (1H, dd, J 9.3 5.5 Hz, C_3-H), 4.78 (1H, t, J 7.8 Hz, C_5-H), 6.29 (1H, dd, J 2.0 1.5 Hz, furan C'_4-H), and 7.30 - 7.72 (12H, m, $SiPh_2$ and furan C'_2-H and C'_5-H); ν_{max} (film) 3065, 2984, 1738, 1584, and 791 cm^{-1}; m/z 348(M^+), 333(M^+ -Me), 320(M^+ - CO), 271(M^+ - Ph), and 197($SiPh_2Me^+$); (Found: M^+, 348.1177. $C_{21}H_{20}O_3Si$ requires: M^+, 348.1181).

Preparation of Z and E 3-Ethylidene-5-(3'-furyl)tetrahydrofuran-2-one (59) and (103) from (102).



102 103 59

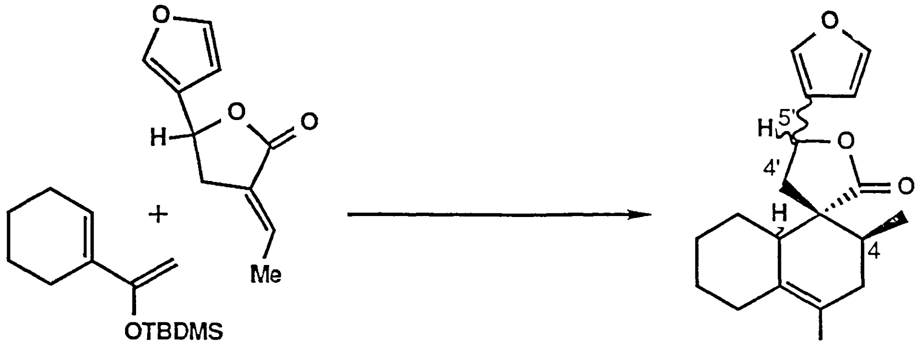
a) With Thermal Elimination.

To a stirred solution of di-isopropylamine (0.45ml, 3.44mmol) in THF (5ml) under argon at -78°C was added n-butyl lithium (2.29ml of a 1.5M solution in hexanes, 3.44mmol). The reaction mixture was warmed to 0°C, stirred for 15 minutes, and cooled to -78°C. Silyl lactone (102) (1.04g, 2.99mmol) in THF (5ml) was added dropwise, and the reaction stirred for 30 minutes, then redistilled acetaldehyde (0.17ml, 2.99mmol) was added. The reaction mixture was warmed to RT over 30 minutes, then heated at reflux for 15 minutes. Trimethylsilyl chloride (5ml) was added and the reaction mixture was poured into petrol (30ml), washed with water (2 x 10ml), and 10% NH_4Cl (10ml), and dried. Solvent removal at reduced pressure and column chromatography (30 to 50% ether - petrol) gave a mixture of *Z* and *E* 3-ethylidene-5-(3'-furyl)tetrahydrofuran-2-one (59) and (103) (291mg, 55%). High pressure liquid chromatography (21mm Si column, 10% isopropylalcohol - hexane, uv detection 254nm) gave firstly *Z*-3-ethylidene-5-(3'-furyl)-tetrahydrofuran-2-one (59) (60mg, 12%), identical in all respects to the previously prepared sample, followed by *E*-3-ethylidene-5-(3'-furyl)tetrahydrofuran-2-one (103) (210 mg, 39%), identical in all respects to the previously prepared material.

b) With Boron Trifluoride Mediated Elimination.

To a stirred solution of di-isopropylamine (0.35ml, 2.65mmol) in THF (5ml) under argon at -78°C was added n-butyl lithium (1.76ml of a 1.5M solution in hexanes, 2.65mmol). The reaction mixture was warmed to 0°C, stirred for 15 minutes, and cooled to -78°C. Silyl lactone (102) (0.80g, 2.30mmol) in THF (5ml) was added dropwise, and the reaction stirred for 30 minutes, then redistilled acetaldehyde (0.13ml, 2.30mmol) was added. The reaction mixture was warmed to 0°C over 60 minutes, then cooled to -30°C and boron trifluoride diethyl etherate (2.87ml, 23.0mmol) was added dropwise over 5 minutes. The reaction mixture was stirred for 14 hours at -30°C, then poured into saturated NH_4Cl (20ml), and extracted with DCM (3 x 20ml). The combined organic extracts were washed with water (2 x 20ml), and dried. Solvent removal at reduced pressure and column chromatography (30 to 50% ether - petrol) gave a mixture of Z and E 3-ethylidene-5-(3'-furyl)tetrahydrofuran-2-one (59) and (103) (310mg, 75%). High pressure liquid chromatography (21mm Si column, 10% isopropylalcohol - hexane, uv detection 254nm) gave firstly Z-3-ethylidene-5-(3'-furyl)-tetrahydrofuran-2-one (59) (130mg, 31%), identical in all respects to the previously prepared sample, followed by E-3-ethylidene-5-(3'-furyl)tetrahydro-furan-2-one (103) (160 mg, 39%), identical in all respects to the previously prepared material.

Preparation of Spiro[2-t-butyldimethylsilyloxy-4β-methyl[4,4,0]dec-1,2-ene-5,3'-5'-(3''-furyl)tetrahydrofuran-2'-one] (107).

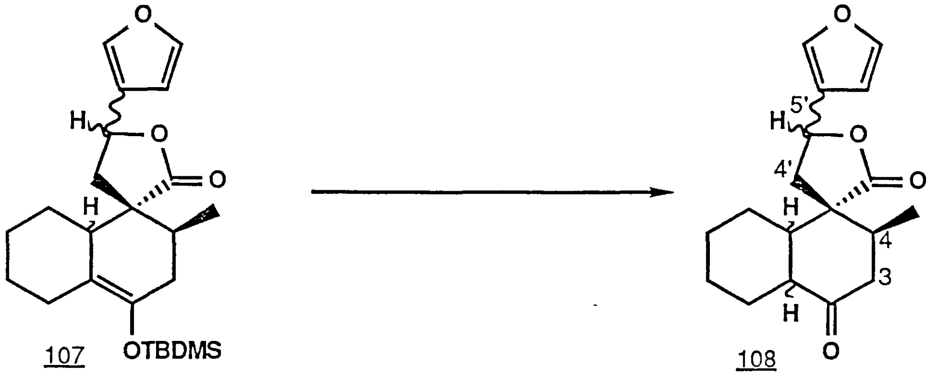


81 103 107

E-Ethylidene lactone (103) (0.89g, 5.0mmol) and cyclohexyl diene (81) (3.58g, 15mmol) were placed in a base washed, pre-silylated 3oz pressure vessel, and hydroquinone (2mg) addded. The reaction mixture was degassed by evacuation and flushing with argon 3 times, then sealed under vacuum and heated to 135°C. The reaction was monitored by TLC (50% ether - petrol), indicating loss of the dienophile after 170 hours. The reaction mixture was dissolved in DCM (40ml), and adsorbed onto silica gel (9g). Solvent removal at reduced pressure gave an adsorbed sample which was subjected to column chromatography (0 to 15% ether - petrol) to give a diastereomeric mixture of spiro[2-t-butyldimethylsilyloxy-4β-methyl[4,4,0]dec-1,2-ene-5,3'-5'-(3''-furyl)tetrahydrofuran-2'-one] (107) (1.16g, 51%), contaminated with 1-acetyl-cyclohexene (0.6g), δ(250 MHz): 0.09 (6H, s, Si$\underline{Me}_2$), 0.87 (1.5H, dt, J 11.8 1.3 Hz, C_4-$\underline{Me}$), 0.89 - 0.94 (10.5H, m, Si$\underline{Bu}$ and C_4-$\underline{Me}$), 1.10 - 1.52 (4H, m, decalin-$\underline{H}$), 1.60 - 1.85 (4H, m, decalin-$\underline{H}$), 1.90 - 2.04 (1H, m, decalin-$\underline{H}$), 2.09 - 2.24 (3H, m, decalin-$\underline{H}$), 2.34 (0.5H, dd, J 13.0 7.8 Hz, $C_{4'}$-$\underline{H}$), 2.57 (0.5H, br dd, J 13.0 8.8 Hz, $C_{4'}$-$\underline{H}$), 2.89 (1H, br m, $C_{4'}$-$\underline{H}$), 5.30 (0.5H, br m, C'_5-$\underline{H}$), 5.47 (0.5H, br dd, J 8.8 7.5 Hz, C'_5-$\underline{H}$), 6.33 (0.2H, br s, furan C''_4-$\underline{H}$), 6.39 (0.8H, br s, furan C''_4-$\underline{H}$), 7.38 (0.2H, br s, furan C''_5-$\underline{H}$), 7.42 (0.8H, br s, furan C''_5-$\underline{H}$), and 7.47 (1H, m, furan

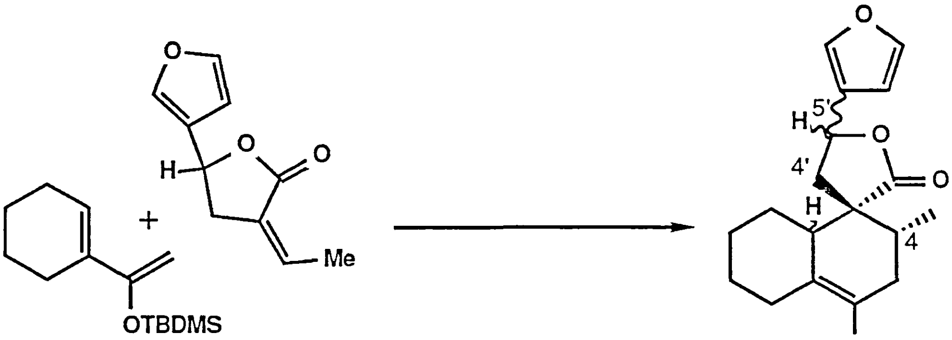
C''$_2$-H); ν_{max} (film) 2930, 1763, 1665, and 1179 cm-1; m/z 416(M+), 401(M$^+$ - Me), 359(M$^+$ - Bu), and 322(M$^+$ - furanCO); (Found: M$^+$, 416.2376. $C_{24}H_{36}O_4Si$ requires: M$^+$, 416.2382).

Preparation of Spiro[4β-methyl[4.4.0]decan-2-one-5,3'-5'-(3''-furyl)-tetrahydrofuran-2'-one] (108).



To a stirred solution of cycloaddition adduct (107), (1.26g of a 66% mixture with 1-acetyl-cyclohexene, 2mmol) in THF (10ml) under argon at 0°C was added tetrabutylammonium fluoride (4ml of a 1M solution in THF, 4mmol) and the reaction was warmed to RT and stirred for 30 minutes. The mixture was poured into 1N HCl (10ml), and the solution was extracted with ether (4 x 20ml). The combined ethereal extracts were washed with saturated $NaHCO_3$ (2 x 15ml), water (15ml), brine (15ml) and dried. Concentration at reduced pressure and column chromatography (20 to 50% ether - petrol) gave firstly 1-acetylcyclohexene (0.40g), followed by a diastereomeric mixture of spiro[4β-methyl[4.4.0]decan-2-one-5,3'-5'-(3''-furyl)tetrahydrofuran-2'-one] (108) (0.42g, 70%) in a 5 : 3 : 2 ratio (GC analysis), δ(400 MHz): 0.96 (3H, m, C$_4$-Me), 1.10 - 1.50 (4H, m, decalin-H), 1.72 - 1.88 (3H, m, decalin-H), 1.90 - 2.10 (2H, m, decalin-H), 2.18 - 2.45 (3H, m, decalin-H and C'$_4$-H), 2.47 - 2.76 (2H, m, decalin-H and C'$_4$-H), 2.92 (0.2H, dd, J 13.0 8.0 Hz, C$_3$-H), 3.10 (0.3H, m, C$_3$-H), 3.70 (0.5H, dd, J 12.0 6.0 Hz, C_3-*H*), 5.43 (0.7H, m, C'_5-*H*), 5.54 (0.3H, dd, J 9.0 6.0 Hz, C'_5-*H*), 6.40 (1H, m, furan C''_4-*H*), and 7.49 (2H, m, furan C''_2-*H* and C''_5-*H*); ν_{max} (film) 2933, 1750, 1709, 1599, and 1183 cm^{-1}; *m/z* 302(M^+), 257(M^+ - CO_2H), and 208(M^+ - furanCO); (Found: C, 71.38; H, 7.32. $C_{18}H_{22}O_4$ requires: C, 71.50; H, 7.33%).

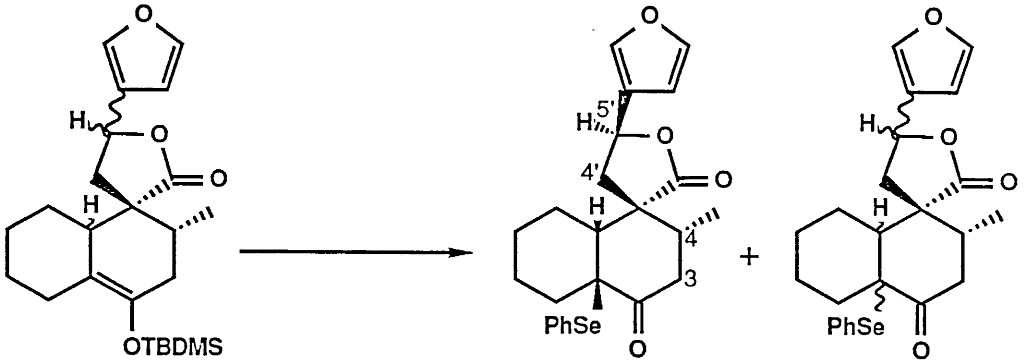
Preparation of Spiro[2-t-butyldimethylsilyloxy-4α-methyl[4,4,0]dec-1,2-ene-5,3'-5'-(3''-furyl)tetrahydrofuran-2'-one] (109).



81 59 109

Z-Ethylidene lactone (59) (0.89g, 5.0mmol) and cyclohexyl diene (81) (3.58g, 15mmol) were placed in a base washed, pre-silylated 3oz pressure vessel, and hydroquinone (2mg) addded. The reaction mixture was degassed by evacuation and flushing with argon 3 times, then sealed under vacuum and heated to 135°C. The reaction was monitored by TLC (50% ether - petrol), indicating loss of the dienophile after 91 hours. The reaction mixture was dissolved in DCM (40ml), and pre-adsorbed onto silica gel (9g), as for the preparation of (107). The adsorbed sample was subjected to column chromatography (0 to 15% ether - petrol) to give a mixture of cycloaddition products and 1-acetyl-cyclohexene. High pressure liquid chromatography (42mm Si column, 1% isopropyl alcohol - hexane, uv detection 240nm) gave a diastereomeric mixture of spiro[2-t-butyldimethylsilyloxy-4α-methyl[4,4,0]dec-1,2-ene-5,3'-5'-(3''-furyl)tetrahydrofuran-2'-one] (109) (0.96g, 46%), in a 6 : 3 : 1 ratio (GC analysis), δ(250 MHz): 0.12 (6H, s, Si$\underline{Me}_2$), 0.85 - 0.97 (9H, m, Si$\underline{Bu}$), 1.03 (0.9H, d, J 7.0 Hz, C_4-$\underline{Me}$), 1.12 (1.8H, d, J 7.0 Hz, C_4-$\underline{Me}$), 1.21 (0.3H, d, J 7.0 Hz, C_4-$\underline{Me}$), 1.23 - 2.55 (12H, m, decalin-$\underline{H}$), 2.67 - 3.04 (2H, m, C'_4-$\underline{H}_2$), 5.28 - 5.45 (1H, br m, C'_5-$\underline{H}$), 6.40 (1H, m, furan C''_4-$\underline{H}$), and 7.42 (2H, br m, furan C''_2-$\underline{H}$ and C''_5-$\underline{H}$); ν_{max} (film) 2930, 1763, 1655, and 1181 cm^{-1}; $\underline{m/z}$ 416($\underline{M}^+$), 401($\underline{M}^+$ - Me), and 322($\underline{M}^+$ - furanCO); (Found: $\underline{M}^+$, 416.2376. $C_{24}H_{36}O_4Si$ requires: $\underline{M}^+$, 416.2382).

Preparation of Spiro[4α-methyl-1β-phenylselenyl-6β-[4.4.0]decan-2-one-5,3'-5'-(3''-furyl)tetrahydrofuran-2'-one] (110) and other diastereoisomers (111).

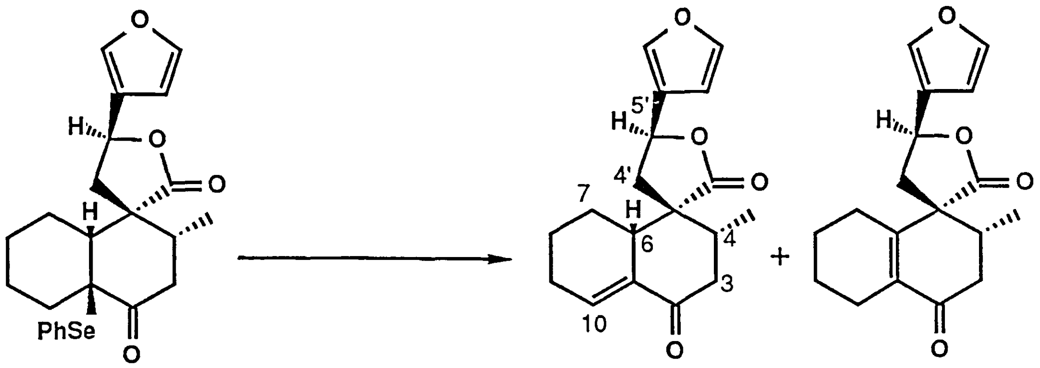


109 110 111

To a stirred solution of cycloaddition products (109) (0.208g, 0.5mmol) in DCM (9ml) under argon at -78°C was added phenylselenyl chloride (95.7mg, 0.5mmol) dropwise in DCM (1ml). The reaction was stirred for 5 minutes, then saturated $NaHCO_3$ (5ml) was added at -78°C with vigorous stirring. The reaction mixture was poured into saturated $NaHCO_3$ (10ml), and extracted with DCM (3 x 15ml). The combined organic extracts were washed with water (2 x 15ml), dried, concentrated at reduced pressure and subjected to column chromatography (10 to 60% ether - petrol) to yield firstly spiro[4α-

methyl-1β-phenylselenyl-6β-[4,4,0]decan-2-one-5,3'-5'-(3''-furyl) tetrahydrofuran-2'-one] (110) (102mg, 44%), m.p. 178°C; δ(250 MHz): 1.04 (1H, m, decalin-H), 1.17 (3H, d, J 6.8 Hz, C_4-Me), 1.30 (1H, m, decalin-H), 1.49 (3H, m, decalin-H), 1.78 (2H, br m, decalin-H), 2.11 (1H, m, decalin-H), 2.41 (1H, dd, J 13.5 10.0 Hz, C'_4-H), 2.50 (1H, m, decalin-H), 2.64 (2H, m, decalin-H including C_3-H), 2.79 (1H, dd, J 13.5 5.5 Hz, C'_4-H), 3.22 (1H, m, C_3-H), 5.49 (1H, dd, J 10.0 5.5 Hz, C'_5-H), 6.46 (1H, dd, J 1.5 1.0 Hz, furan C''_4-H), 7.36 (2H, m, SePh), 7.44 (4H, m, SePh and furan C''_5-H), and 7.55 (1H, t, J 1.5 Hz, furan C''_2-H); ν_{max} ($CHCl_3$) 2934, 1762, 1690, and 796 cm^{-1}; m/z 458(M^+), 301(M^+ - SePh), and 273(M^+ - SePh - CO); (Found: C, 63.10; H, 5.72. $C_{24}H_{26}O_4Se$ requires: C, 63.02; H, 5.73%); followed by a diastereomeric mixture of spiro[4α-methyl-1-phenylselenyl[4,4,0]decan-2-one-5,3'-5'-(3''-furyl)tetrahydrofuran-2'-one] (111) (61mg, 26%), m.p. 187°C; δ(250 MHz): 0.95 (1H, m, decalin-H), 1.12 (1H, dd, J 7.0 1.5 Hz, C_4-Me), 1.19 (2H, d, J 7.0 Hz, C_4-H), 1.20 - 1.51 (3H, m, decalin-H), 1.55 - 1.99 (3H, m, decalin-H), 2.15 - 2.38 (2H, m, decalin-H), 2.40 - 2.57 (2H, m, decalin-H and C'_4-H), 2.65 - 2.95 (2H, m, decalin-H and C'_4-H), 3.08 (1H, m, C_3-H), 5.48 (1H, m, C'_5-H), 6.41 (1H, m, furan C''_4-H), and 7.28 - 7.40 (7H, m, SePh and furan C''_2-H, C''_5-H); ν_{max} ($CHCl_3$) 2934, 1757, 1708, 1689, and 797 cm^{-1}; m/z 458(M^+), and 301(M^+ - SePh); (Found: (M^+ - PhSeH), 300.137. $C_{24}H_{26}O_4Se$ requires: (M^+ - PhSeH), 300.136).

Preparation of Spiro[4α-methyl-6β-[4,4,0]-1,10-decen-2-one-5,3'-5'-(3''-furyl)tetrahydrofuran-2'-one] (48) and Spiro[4α-methyl[4,4,0]-1,6-decen-2-one-5,3'-5'-(3''-furyl)tetrahydrofuran-2'-one] (112).

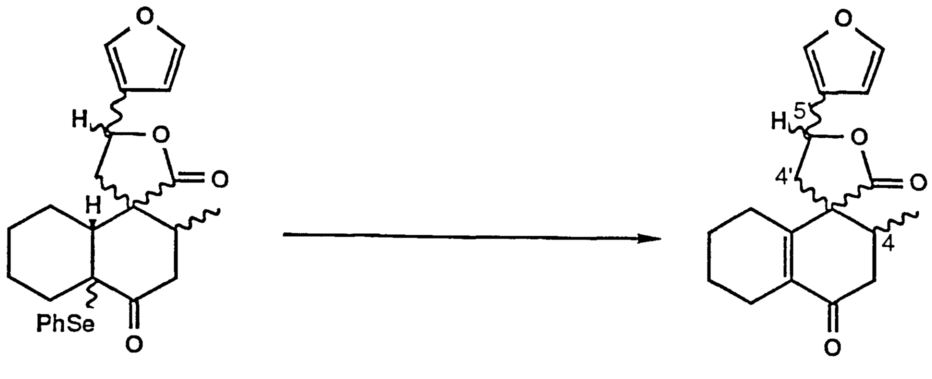


110 48 112

To a stirred solution of selenide (110) (220mg, 0.48mmol) in DCM (6ml) under argon at 0°C was added dropwise meta-chloroperbenzoic acid (68.5mg of an 80% mixture, 0.49mmol) in DCM (4ml). The reaction was stirred for 10 minutes at 0°C, then saturated Na_2SO_3 (5ml) was added, and the reaction mixture was poured into saturated $NaHCO_3$ (15ml). The solution was extracted with DCM (3 x 20ml), the combined organic extracts were washed with water (2 x 15ml), dried, concentrated under reduced pressure, and subjected to column chromatography (50 to 70% ether - petrol) to yield a mixture of enones (48) and (112) (90mg, 62%) in a 1 : 3 ratio (GC analysis). High pressure liquid chromatography (42mm C18 column, 40% water - methanol, uv detection 254nm) gave firstly spiro[4α-methyl[4,4,0]-1,6-decen-2-one-5,3'-5'-(3''-furyl)tetrahydro-furan-2'-one] (112) (58mg, 40%), m.p. 145°C; δ(300 MHz): 1.14 (3H, d, J 6.3 Hz, C_4-Me), 1.50 - 1.68 (2H, m, decalin-H), 1.78 (1H, m, C_4-H), 2.16 - 2.29 (3H, m, decalin-H), 2.34 - 2.48 (2H, m, allylic decalin-H), 2.37 (1H, dd, J 16.3 4.3 Hz, C_3-H), 2.41 (1H, dd, J 14.1 8.4 Hz, C'_4-H), 2.61 (1H, dd, J 13.8 8.4 Hz, C'_4-H), 2.70 (1H, dd, J 16.3 11.2 Hz, C_3-H), 3.84 (1H, tt, J 11.0 6.2 Hz, C_7-H ax), 5.55 (1H, t, J 8.4 Hz, C'_5-H), 6.43 (1H, dd, J 2.0 1.0

Hz, furan C''_4-H), 7.47 (1H, br t, J 1.0 Hz, furan C''_5-H), and 7.54 (1H, m, furan C''_2-H); ν_{max} ($CHCl_3$) 2935, 1747, 1664, and 1163 cm^{-1}; m/z 300(M^+), 272(M^+ - CO), and 256(M^+ - CO_2); (Found: M^+, 300.137. $C_{18}H_{20}O_4$ requires: M^+, 300.136); followed by spiro[4α-methyl-6β-[4,4,0]-1,10-decen-2-one-5,3'-5'-(3''-furyl)tetrahydrofuran-2'-one] (48) (19mg, 13%), m.p. 132°C; δ(400 MHz): 1.35 (3H, d, J 7.0 Hz, C_4-Me), 1.43 (1H, br q, J 11.0 Hz, C_6-H), 1.57 - 1.69 (2H, m, decalin-H), 1.84 - 1.97 (2H, m, decalin-H), 2.12 (1H, dd, J 13.5 8.0 Hz, C'_4-H *cis* to furan), 2.25 (1H, m, C_4-H), 2.28 - 2.36 (1H, m, decalin-H), 2.39 (1H, dd, J 17.5 2.5 Hz, C_3-H), 2.52 (1H, dd, J 17.5 5.8 Hz, C_3-H), 2.76 (1H, dd, J 13.5 8.0 Hz, C'_4-H *trans* to furan), 3.12 (1H, m, C_7α-H), 5.40 (1H, t, J 8.0 Hz, C'_5-H), 6.40 (1H, m, furan C''_4-H), 7.03 (1H, m, enone C_{10}-H), 7.46 (1H, t, J 1.5 Hz, furan C''_5-H), and 7.48 (1H, m, furan C''_2-H); ν_{max} ($CHCl_3$) 2936, 1760, 1685, 1610, and 1183 cm^{-1}; m/z 300(M^+), 272(M^+ - CO), and 255(M^+ - CO_2H); (Found: M^+, 300.137. $C_{18}H_{20}O_4$ requires: M^+, 300.136).

Preparation of a Diastereomeric Mixture of Spiro[4-methyl[4,4,0]-1,6-decen-2-one-5,3'-5'-(3''-furyl)tetrahydro-furan-2'-one] (117) from (111).



111

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To a stirred solution of selenides (111) (35.4mg, 0.077mmol) in DCM

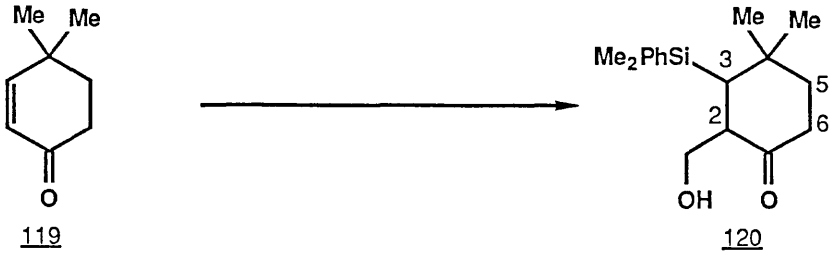
(2ml) under argon at 0°C was added dropwise meta-chloroperbenzoic acid (11.2mg of an 80% mixture, 0.080mmol) in DCM (1ml). The reaction was stirred for 10 minutes at 0°C, then saturated Na_2SO_3 (1ml) was added, and the reaction mixture was poured into saturated $NaHCO_3$ (5ml). The solution was extracted with DCM (3 x 5ml), the combined organic extracts were washed with water (2 x 5ml), dried, concentrated under reduced pressure, and subjected to column chromatography (50 to 90% ether - petrol) to yield a diastereomeric mixture of spiro[4-methyl-[4,4,0]-1,6-decen-2-one-5,3'-5'-(3''-furyl)tetrahydro-furan-2'-one] (117) (15mg, 65%), δ(250 MHz): 0.87 (2H, m, including d, J 7.0 Hz, C_4-Me), 1.19 - 1.32 (5H, m, decalin-H, including d, J 7.0 Hz, C_4-Me), 1.57 - 1.80 (4H, m, decalin-H), 2.20 - 2.82 (5H, m, decalin-H and C'_4-H_2), 5.51 (1H, br dd, J 9.0 7.0 Hz, C'_5-H), 6.52 (1H, br s, furan C''_4-H), and 7.49 (2H, m, furan C''_2-H and C''_5-H); ν_{max} ($CHCl_3$), 2934 1763, 1663, and 1160 cm^{-1}; m/z 300(M^+), 272(M^+ - CO), 255(M^+ - CO_2H) and 95(furanCO$^+$); (Found: M^+, 300.137. $C_{18}H_{20}O_4$ requires: M^+, 300.136).

Preparation of Dimethylphenylsilyl Lithium.

$$PhMe_2SiCl \quad + \quad Li \longrightarrow PhMe_2SiLi$$

To a stirred dispersion of freshly cut, ultrasound activated lithium (2.10g, 0.3mol, see preparation of Lithium naphthalenide for activation procedure) in THF (200ml) under argon at -8°C was added dimethylphenylsilyl chloride (17g, 0.1mol) in THF (50ml). The reaction was stirred at -8°C for 48 hours, giving a deep red solution of dimethylphenylsilyl lithium, which was stored at -15°C.[56] Titration of the solution was carried out by adding the dimethylphenylsilyl lithium solution (1ml) to water (5ml) at 0°C, followed by titration of the resultant base with 1N HCl solution,[69] showing a molarity of 0.37M, unchanged over several weeks.

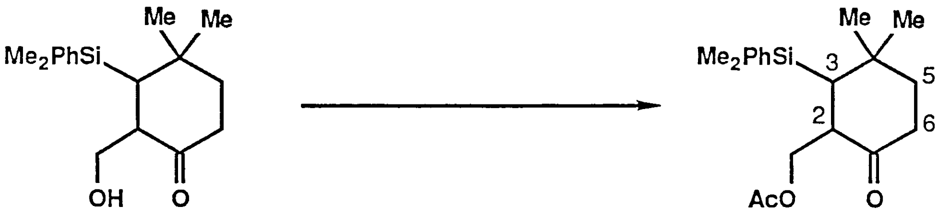
Preparation of 4,4-Dimethyl-3-dimethylphenylsilyl-2-hydroxymethyl-cyclohexan-1-one (120).



Anhydrous copper(I)cyanide (268mg, 3.0mmol) in a flame dried three necked flask was purged 5 times with dry argon by evacuation and flushing with argon. Dimethylphenylsilyl lithium solution (8.18ml of a 0.37M solution in THF, 3.0mmol) was added under argon at -5°C with stirring, and the reaction was stirred for a further 15 minutes. Methyl lithium (2.14ml of a 1.4M solution in hexanes, 3.0mmol) was added dropwise, the mixture was stirred for a further 15 minutes, and then cooled to -50°C. Enone (119) (372.5mg, 2.5mmol) was added dropwise in THF (5ml), and the reaction was stirred for 3 hours. Excess monomeric formaldehyde solution (20ml of a solution in THF) was added, the reaction was stirred for 60 minutes at -50°C, then warmed to 0°C over 45 minutes. The reaction mixture was poured into saturated NH_4Cl (30ml) containing aqueous ammonia (0.5ml of sp.gr. 0.880 ammonia solution), and the solution was extracted with ethyl acetate (3 x 25ml). The combined organic extracts were washed with water (3 x 20ml), brine (20ml), dried, and concentrated at reduced pressure. Column chromatography (20 to 70% ether - petrol) gave

firstly unreacted 4,4-dimethylcyclohex-2-enone (119) (105.8mg, 28%) followed by 4,4-dimethyl-3-dimethylphenylsilyl-2-hydroxymethylcyclohexan-1-one (120) (370.3mg, 51%, 71% based on recovered (119)), m.p. 80-82°C; δ(250 MHz): 0.42 (3H, s, SiMe), 0.44 (3H, s, SiMe), 0.99 (3H, s, C_4-Me), 1.17 (3H, s, C_4-Me), 1.27 (1H, d, J 9.0 Hz, C_3-H), 1.73 (2H, m, C_5-$\underline{H}_2$), 2.25 - 2.58 (4H, m, C_1-H, C_6-$\underline{H}_2$ and OH), 3.41 (2H, br m, $C\underline{H}_2OH$), 7.32 (3H, m, SiPh), and 7.50 (2H, m, SiPh); ν_{max} ($CHCl_3$) 3570, 2937, 1687, and 1144 cm^{-1}; m/z 260($\underline{M}^+$ - H_2CO), 245($\underline{M}^+$ - H_2CO - Me), and 204($\underline{M}^+$ - H_2CO - Ph); (Found: ($\underline{M}^+$ - H_2CO), 260.1601. $C_{16}H_{24}O_2Si$ requires: ($\underline{M}^+$ - H_2CO), 260.1596).

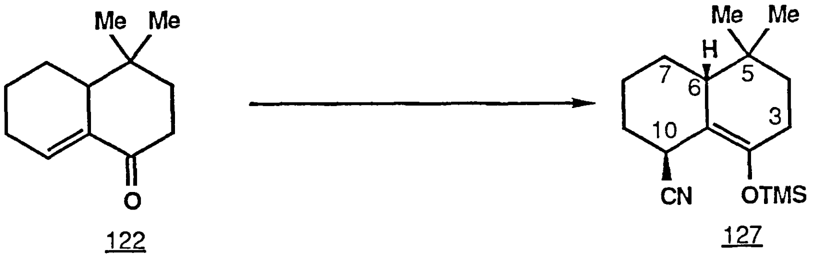
Preparation of 2-Acetoxymethyl-4,4-dimethyl-3-dimethylphenylsilyl-cyclohexan-1-one (121).



120 121

To a stirred solution of silyl alcohol (120) (0.29g, 1.0mmol) in pyridine (2ml) at 0°C was added dimethylaminopyridine (DMAP) (5mg), followed by acetic anhydride (0.16g, 1.5mmol), the reaction mixture was allowed to warm to RT and stirred for 2 hours. The mixture was poured into cold 1n HCl (5ml), and extracted with ether (3 x 10ml). The combined ethereal extracts were washed with cold 1N HCl (2 x 5ml), saturated $NaHCO_3$ (2 x 10ml), water (2 x 10ml), brine (10ml) and dried. Solvent removal under reduced pressure and column chromatography (30 to 50% ether - petrol) gave 2-acetoxymethyl-4,4-dimethyl-3-dimethylphenylsilylcyclohexan-1-one (121) (0.28g, 85%), δ(250 MHz): 0.41 (3H, s, Si$\underline{Me}$), 0.45 (3H, s, Si$\underline{Me}$), 1.03 (3H, s, C_4-$\underline{Me}$), 1.09 (3H, s, C_4-$\underline{Me}$), 1.32 (1H, d, J 7.0 Hz, C_3-$\underline{H}$), 1.66 (2H, m, C_5-$\underline{H}_2$), 1.90 (3H, s, O$\underline{Ac}$), 2.41 (2H, m, C_6-$\underline{H}_2$), 2.63 (1H, td, J 7.0 4.5 Hz, C_2-$\underline{H}$), 3.86 (1H, dd, J 11.5 4.5 Hz, C$\underline{H}$HOAc), 4.02 (1H, dd, J 11.5 7.0 Hz, CH$\underline{H}$OAc), 7.34 (3H, m, Si$\underline{Ph}$), and 7.53 (2H, m, Si$\underline{Ph}$); ν_{max} (film) 2956, 1741, 1709, and 817 cm^{-1}; $\underline{m/z}$ 332($\underline{M}^+$), 317($\underline{M}^+$ - Me), 272($\underline{M}^+$ - AcOH), and 257($\underline{M}^+$ - Me - AcOH); (Found: C, 68.80; H 8.63. $C_{19}H_{28}O_3Si$ requires: C, 68.63; H 8.49%).

Preparation of 10β-cyano-5,5-dimethyl-2-trimethylsilyloxy-6β-bicyclo-[4,4,0]dec-1,2-ene (127).



a) With THF as Solvent.

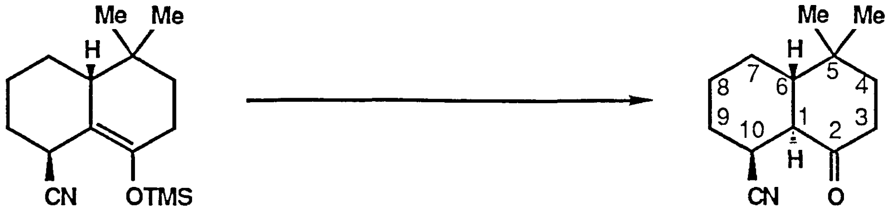
To a stirred solution of trimethylsilyl cyanide (0.11g, 1.1mmol) in THF (2ml) under argon at RT was added trimethylaluminium (0.5ml of a 2M solution in hexane, 1.0mmol) dropwise, and the mixture was stirred for 30 minutes, then cooled to 0°C. Enone (122) (89mg, 0.5mmol) was added dropwise in THF (1ml), and the reaction heated at reflux for 14 hours. The reaction was cooled to 0°C, and saturated NH_4Cl (3ml) was added dropwise over 10 minutes, the reaction mixture was extracted with ether (2 x 25ml), and the ethereal layers were washed with saturated NH_4Cl (15ml), saturated $NaHCO_3$ (15ml), water (15ml), and brine (15ml). The solution was dried, concentrated at reduced pressure, and subjected to column chromatography (0 to 10% ether - petrol) to give 10β-cyano-5,5-dimethyl-2-trimethylsilyloxy-6β-bicyclo-

[4.4.0]dec-1,2-ene (127) (40.1mg, 29%), δ(250 MHz): 0.19 (9H, s, SiMe_3), 0.81 (3H, s, C_5-Me), 0.93 (3H, s, C_5-Me), 1.28 - 1.49 (4H, m, decalin-H), 1.64 - 1.88 (3H, m, decalin-H), 1.93 (1H, br s, C_6-H), 2.02 (3H, m, C_3-H_2 and C_7-H), and 4.12 (1H, br d, J 4.5 Hz, C_{10}-H); ν_{max} (film) 2942, 2232, 1676, and 1253 cm^{-1}; m/z 277(M^+), 262(M^+ - Me), 251(M^+ - CN), and 221(M^+ - $Me_2C=CH_2$); (Found: C, 69.29; H, 9.95; N, 5.19. $C_{16}H_{27}NOSi$ requires: C, 69.25; H, 9.81; N, 5.05%).

b) With Toluene as Solvent.

To a stirred solution of trimethylsilyl cyanide (0.11g, 1.1mmol) in toluene (2ml) under argon at RT was added trimethylaluminium (0.5ml of a 2M solution in hexane, 1.0mmol) dropwise, and the mixture was stirred for 30 minutes, then cooled to 0°C. Enone (122) (89mg, 0.5mmol) was added dropwise in toluene (1ml), and the reaction was warmed to RT and stirred for 16 hours. The reaction was cooled to 0°C, and saturated NH_4Cl (5ml) was added dropwise over 10 minutes, the reaction mixture was extracted with ether (3 x 25ml), and the ethereal layers were washed with saturated NH_4Cl (15ml), saturated $NaHCO_3$ (15ml), water (15ml), and brine (15ml). The solution was dried, concentrated at reduced pressure, and subjected to column chromatography (0 to 10% ether - petrol) to give 10β-cyano-5,5-dimethyl-2-trimethylsilyloxy-6β-bicyclo[4.4.0]dec-1,2-ene (127) (48.0mg, 35%), identical in all respects to the previously prepared material.

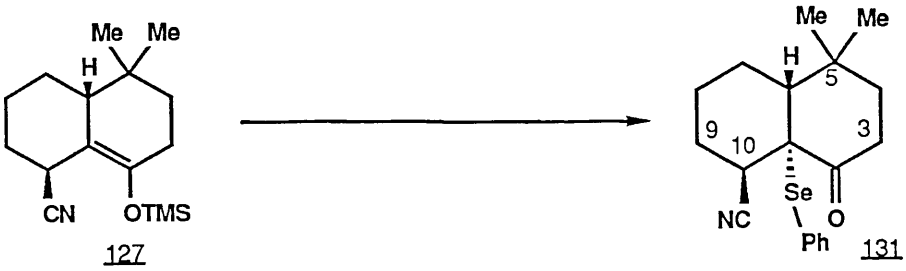
Preparation of 10β-cyano-5,5-dimethyl-1α,6β-bicyclo[4,4,0]decan-2-one (128).



127 → 128

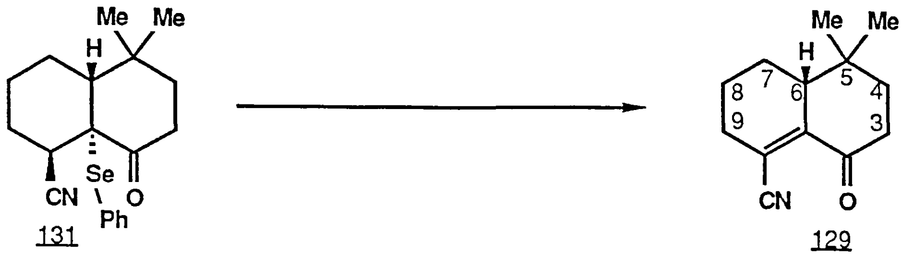
To a stirred solution of silyl enol ether (127) (20mg, 0.07mmol) in THF (2ml) at RT was added 1N HCl (0.2ml) in THF (2ml), and the reaction mixture was stirred for 60 minutes. The mixture was neutralised with saturated $NaHCO_3$ (2ml), and the solution was extracted with ether (3 x 5ml). The combined ethereal extracts were washed with water (2 x 5ml), brine (5ml), dried and concentrated at reduced pressure. Column chromatography (20 to 40% ether - petrol) gave 10β-cyano-5,5-dimethyl-1α,6β-bicyclo[4,4,0]decan-2-one (128) (13.8mg, 96%), m.p. 116°C; δ(400 MHz): 1.04 (3H, s, C_5-$\underline{Me}$), 1.07 (3H, s, C_5-$\underline{Me}$), 1.14 (1H, qd, J 12.8 3.8 Hz, C_7-$\underline{H}$ ax), 1.46 (1H, tt, J 13.5 4.0 Hz, C_9-$\underline{H}$ ax), 1.67 (1H, qt, J 13.2 3.5 Hz, C_8-$\underline{H}$ ax), 1.70 - 1.76 (3H, m, C_4-$\underline{H}_2$ and C_6-$\underline{H}$), 1.81 (1H, dm, J 13.5 Hz, C_8-$\underline{H}$ equat), 1.92 (1H, dm, J 13.0 Hz, C_7-$\underline{H}$ equat), 2.08 (1H, dm, J 13.5 Hz, C_9-$\underline{H}$ equat), 2.19 (1H, dd, J 12.5 3.8 Hz, C_1-$\underline{H}$), 2.41 (2H, m, C_3-$\underline{H}_2$), and 3.37 (1H, dm, J 3.8 Hz, C_{10}-$\underline{H}$); ν_{max} ($CHCl_3$) 2945, 2242, and 1708; $\underline{m/z}$ 205($\underline{M}^+$), 190($\underline{M}^+$ - Me), 178($\underline{M}^+$ - CN), and 172($\underline{M}^+$ - CO); (Found: $\underline{M}^+$, 205.1471. $C_{13}H_{19}NO$ requires: $\underline{M}^+$, 205.1466).

Preparation of 10β-cyano-5,5-dimethyl-1α-phenylselenyl-6β-bicyclo-[4,4,0]decan-2-one (131).



To a stirred solution of silyl enol ether (127) (83mg, 0.3mmol) in DCM (6ml) under argon at -78°C was added phenylselenyl chloride (59mg, 0.3mmol) dropwise in DCM (1ml). The reaction was stirred for 30 minutes, then saturated $NaHCO_3$ (7ml) was added at -78°C with vigorous stirring. The reaction mixture was poured into saturated $NaHCO_3$ (10ml), and extracted with DCM (3 x 15ml). The combined organic extracts were washed with water (2 x 15ml), dried, concentrated at reduced pressure and subjected to column chromatography (5 to 20% ether - petrol) to give 10β-cyano-5,5-dimethyl-1α-phenylselenyl-6β-bicyclo[4,4,0]decan-2-one (131) (70mg, 65%), m.p. 171°C; δ(250 MHz): 1.02 (3H, s, C_5-Me), 1.20 (3H, s, C_5-Me), 1.65 - 1.98 (7H, m, decalin-H), 2.05 (1H, m, C_9-H equat), 2.35 (1H, dt, J 15.2 4.2 Hz, C_3-H equat), 2.42 (1H, tt, J 13.0 4.5 Hz, C_9-H ax), 2.70 (1H, br m, C_{10}-H), 3.48 (1H, ddd, J 15.2 13.0 5.5 Hz, C_3-H ax), and 7.32 (5H, m, SePh); ν_{max} (KBr) 3075, 2933, 2236, 1690, and 742 cm^{-1}; m/z 361(M^+), 204(M^+ - SePh), and 177(M^+ - SePh - HCN); (Found: M^+, 631.0955. $C_{19}H_{23}NOSe$ requires: M^+, 631.0945).

Preparation of 10-cyano-5,5-dimethyl-6β-bicyclo[4,4,0]dec-1,10-en-2-one (129).



131 129

To a stirred solution of selenide (131) (60mg, 0.17mmol) in DCM (7ml) under argon at 0°C was added dropwise *meta*-chloroperbenzoic acid (43mg of an 80% mixture, 0.20mmol) in DCM (3ml). The reaction was warmed to RT and stirred for 30 minutes. Saturated Na_2SO_3 (2ml) was added, the reaction mixture was poured into saturated $NaHCO_3$ (5ml), and the solution was extracted with DCM (3 x 10ml). The combined organic extracts were washed with saturated $NaHCO_3$ (2 x 10ml), water (10ml), dried, and concentrated under reduced pressure. Column chromatography (30 to 70% ether - petrol) gave firstly unreacted selenide (131) (13mg, 22%), followed by 10-cyano-5,5-dimethyl-6β-bicyclo[4,4,0]dec-1,10-en-2-one (129) (20mg, 59%, 75% based on recovered (131)), δ(250 MHz): 0.92 (3H, s, C_5-Me), 1.05 (3H, s, C_5-Me), 1.20 - 1.40 (2H, m, C_7-H's or C_8-H's), 1.72 (2H, dd, J 8.0 6.0 Hz, C_4-H_2), 1.91 (2H, m, C_7-H's or C_8-H's), 2.31 (2H, m, C_9-H_2), 2.38 (1H, m, C_6-H), and 2.55 (2H, m, C_3-H_2); ν_{max} (film) 2953, 2215, 1690, 1599, and 1153 cm^{-1}; *m/z* 203(M^+), 188(M^+ - Me), 175(M^+ - CO), and 160(M^+ -Me - CO); (Found: M^+, 203.1308. $C_{13}H_{17}NO$ requires: M^+, 203.1310).

Appendix 1.

Crystal Data for (78).[36]

$C_{17}H_{20}O_4$, $\underline{M}$ = 288.3, triclinic, $\underline{a}$ = 6.246(2), $\underline{b}$ = 10.219(3), $\underline{c}$ = 12.572(5)Å, α = 110.08(3), β = 93.86(3), γ = 95.48(3)°, $\underline{U}$ = 746Å^3, space group $\underline{P\bar{1}}$, $\underline{Z}$ = 2, D_c = 1.28gcm^{-3}, μ(Cu-$\underline{K}_\alpha$) = 7cm^{-1}, $\underline{F}$(000) = 308. 1540 independent reflections (θ < 50°) were measured on a Nicolet R3m diffractometer with Cu-$\underline{K}_\alpha$ radiation (graphite monochromator) using ω-scans. Of these 1160 had $|\underline{F}_0| > 3\sigma(|\underline{F}_0|)$ and were considered to be observed. The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically. The positions of the hydrogen atoms were idealised, C-H = 0.96Å, assigned isotropic thermal parameters, $\underline{U}$(H) = 1.2$\underline{U}_{eq}$(C), and allowed to ride on their parent carbon atoms. Refinement converged to give $\underline{R}$ = 0.057, $\underline{R}_w$ = 0.059 [$w^{-1} = \sigma^2(\underline{F}) + 0.00151F^2$]. The maximum residual electron density in the final Δ$\underline{F}$ map was 0.19eÅ^{-3} and mean and maximum shift/error in final refinement were 0.001 and 0.002 respectively.

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