Chemistry of Spiroketals

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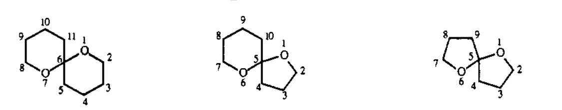
Contents

I. Introduction

Spiroketals[1] enjoy widespread occurrence as substructures of naturally occurring substances from many sources, including insects, microbes, plants, fungi, and marine organisms. The increasing pharmacological importance of compounds containing spiroketal assemblies has triggered intense interest in both their synthesis and chemical reactivity. The purpose of this review is not only to compile and categorize the chemistry of spiroketals but also to provide analysis that may suggest further directions of research in this area. We have taken a phenomenological approach to presenting most of the information as opposed to one based on target molecule structure or reaction type as in previous reviews.[2] The literature since about 1970 is more voluminous and has been stressed at the expense of the older literature, although key contributions occurred before 1970 as well.

The first part of the article will review spiroketal-containing natural products with brief mention of their pharmacology and/or ecology. This section will be organized both chronologically and by metabolite source. Following this will be a discussion of the conformational preferences of spiroketals based on observations from a number of laboratories. The main part of the review will cover spiroketal synthesis, organized by type-of-bond formation. The article concludes with various transformations involving intact spiroketals, a relatively neglected area of study.

The vast majority of chemistry in this area is focused on the spiroketal general ring systems A, B, and C, presumably because most natural products fall into one of these structural categories.



1,7-Dioxaspiro[5.5]undecane A | 1,6-Dioxaspiro[4.5]decane B | 1,6-Dioxaspiro[4.4]nonane C

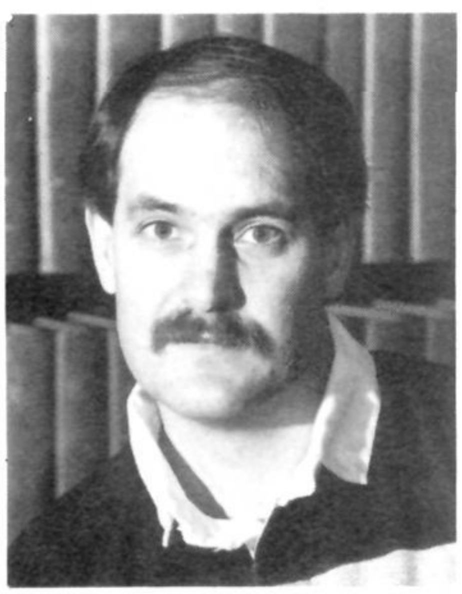
II. Survey of Naturally Occurring Spiroketals

A. Pre-1970 Metabolites

1. Steroidal Saponins and Sapogenins

The earliest examples of spiroketal structure in nature are the steroidal saponins and sapogenins (Scheme 1). Originally isolated from plants found in the southwestern United States and Mexico during the 1930s and 1940s, the compounds in this class are glycosides (saponins) in which the aglycone (sapogenin) consists of a steroidal nucleus containing a spiroketal assembly fused to the D-ring. Glycosylation is usually found on the A-ring. At that time, the steroid nucleus

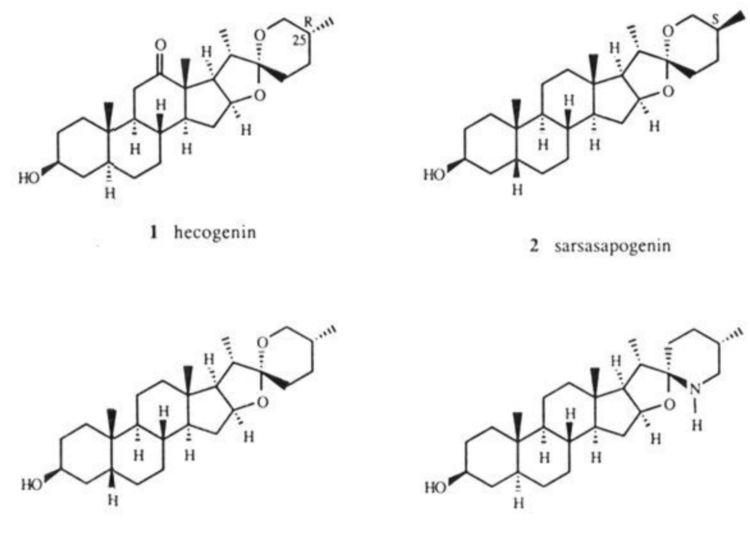
Françoise Perron is native of France, where in 1980 she received her Baccalaureat in Sciences. She became strongly interested in chemistry while studying at Chateaubriand, Ecole de Mathematiques Superieures, in Rennes. In 1986 she obtained her Diploma of Engineer in Chemistry from E.S.C.I.L. (Ecole Superieure de Chimie Industrielle de Lyon). She then decided to conduct research in organic chemistry in the United States as an exceptional learning experience. She is currently completing her Ph.D. research at Wayne State University with Professor Kim Albizati. Her research interests reside in the development of new synthetic methods oriented toward the construction of structurally complex oxygenated heterocycles as key targets of biologically active natural products. Besides chemistry, she is fond of classical dance, piano, and SCUBA.



Kim F. Albizati was born in Burbank, CA, in 1954 as the last of four children. He attended Bellarmine–Jefferson High School where he first encountered chemistry but was too involved in sports to understand or appreciate it. He moved to the University of California at Irvine in 1972, where organic chemistry finally supplanted basketball as his life's major interest. Under the guidance of Prof. Hal Moore, he saw the beauty of science in general and organic chemistry in particular and received a B.A. degree in chemistry in 1976. He earned the Ph.D. degree at UCLA in 1983 in the laboratories of the late Prof. Robert V. Stevens, the consummate teacher and scientist. He moved next to the Scripps Institution of Oceanography in La Jolla and spent 2 years in the laboratories of Prof. John Faulkner, broadening his already long-term interest in the chemistry of marine natural products and learning how to run a research group. He joined the chemistry faculty at Wayne State University in 1985, where his research interests involve the development of new chemical processes and their application to marine natural products synthesis. When not engaged in chemistry and raising graduate students, his activities include snow and water skiing, SCUBA, and, of course, basketball.

was of more interest to synthetic chemists, and spiroketal chemistry was relatively neglected (vide infra). Several reviews of basic steroidal saponins and sapogenins are available.[3,4] Over 200 saponins have been isolated, which precludes a full listing here. Most

SCHEME 1. Steroidal Sapogenins



1 hecogenin 2 sarsasapogenin 3 smilagenin 4 tomatidine

structural variations tend to occur in the steroid nucleus or sugar components. Variation in the spiroketal subunit is relatively rare, with only a handful of variants known. The two most common spiroketal substructures are illustrated in **1** and **2**, which differ only in the configuration at C25. For the most part, the spiroketals lack further functionality. An interesting structural variation is exhibited by tomatidine[5] (**4**) and related spirosolanes,[6] containing an aza analogue of a spiroketal. Largely due to the work of Marker,[7,8] the structures of the majority of the saponin aglycones were described in the 1940s, with chemical interconversions being the major criterion of structure in this prespectroscopic period. The metabolites originally were named after their natural sources, resulting in designations such as smilagenin, hecogenin, and yuccagenin. These colorful names have only been partially supplanted by more efficient nomenclature. Recent isolations have utilized the spirostan naming system[9] but common names are, nevertheless, appended to the metabolites as well. Studies of the biological activities of steroidal saponins and sapogenins are extensive and the reader is directed to reviews in this area.[3–5]

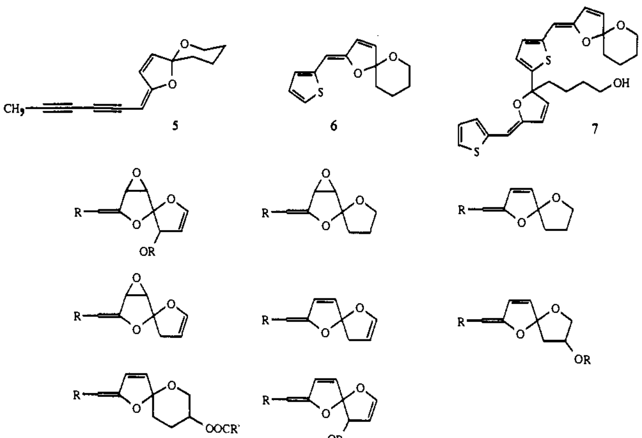
2. Spiroketal Enol Ethers of the Anthemidae and Related Substances

Primarily through the efforts of Bohlmann and coworkers, a large number of spiroketal enol ethers of the [4.5] and [5.5] type were found in the plant family Asteraceae. The compounds characteristically contain one or more acetylene units in the side chain and are found as either isomer of the enol ether olefin. Functionality is often found in one or both rings. Some of the diversity of the spiroketal patterns in this series is listed in Scheme 2. The most common "side chain" is of the enediyne type shown in **5**, although there are also several examples of thioether- and thiophene-containing groups (**6** and **7**[10]) as well. A full compilation of structures and references up to 1973 may be found in ref 11. Since the early 1970s work in this area has been sparse.[12]

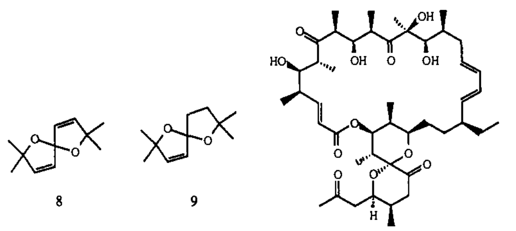
3. Spiroketals from Miscellaneous Sources

A few substances isolated before 1970 do not fall into one of these two major classes. The relatively simple "oxetone" **8** and its derivative **9** were isolated from Japanese hop oil[13] and are the oldest "simple" spiroketals. In 1958, Lardy and co-workers demonstrated

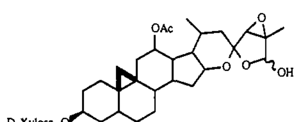
SCHEME 2. Spiroketal Enol Ethers from the Family Asteraceae



that the antibiotic oligomycin acts as a potent inhibitor of oxidative phosphorylation.[14] Oligomycin was subsequently found to be made up of three compounds, one of which, oligomycin B (**10**), was characterized by X-ray crystallography.[15] Similar in structure to a steroidal sapogenin is actein (**11**), a metabolite of *Actea racemosa*.[16] The molecule is a rare example of a naturally occurring "hemispiroketal" possessing a hydroxyl group at the 2-position, thus endowing **11** with hemiacetal-like properties.



8 9 10 oligomycin B



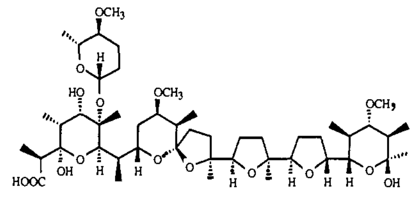
11 actein

B. Post-1970 Metabolites

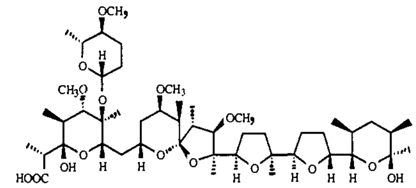
1. *Polyether Ionophores from the Order Actinomycetales*

A third large class of naturally occurring spiroketals are polyketide-derived polyether antibiotics produced by filamentous branching bacteria. Reviews of pharmacological,[17a] structural,[17b,c] spectroscopic,[17b] and synthetic[17b,18] aspects of these metabolites have recently appeared. More highly functionalized than previous examples, the spiroketal subunit is actually a very small part of these rather elaborate molecules. The description of the structure of monensin in 1967[19] coupled with the discovery of its ionophoric properties initiated the extensive and wide-ranging interest in polyethers that continues to this day. There are upward of 80 polyethers that contain at least one spiroketal substructure. Space limitations prevent an exhaustive structural description. Instead, examples of some structurally distinctive spiroketal ring systems are shown in Scheme 3 to illustrate the functional and stereochemical diversity of this class. 1,6-Dioxaspiro[4.5]decanes predominate in this series, with the main structural variations being due to the presence or absence of methyl, hydroxy, and alkoxy groups. Narasin (**17**),[20] salinomycin (**18**),[21] and their analogues[22,23] (Scheme 4) are rare, if not unique, examples of trioxadispiroketal-containing compounds in nature. There are also examples in this category of compounds containing two spiroketal substructures, as exemplified by lenoremycin (**23**)[24] and dianemycin (**22**).[25] Understandably, X-ray crystallography has played a major role in structure elucidation of these antibiotics.[17b]

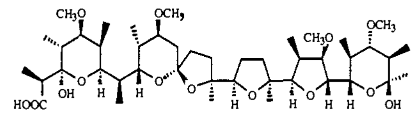
SCHEME 3. Naturally Occurring Polyether Ionophores



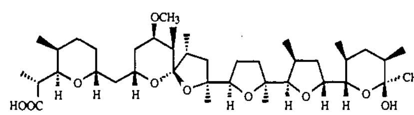
12 etheromycin



13 sepiamycin (carriomycin, A204A, K41A,K41B)

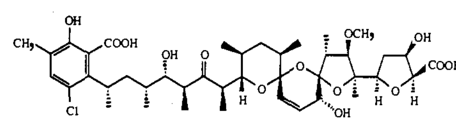


14 lonomycin A (lonomycin B and C, mutalomycin, laidlomycin, monensin A, B and C)

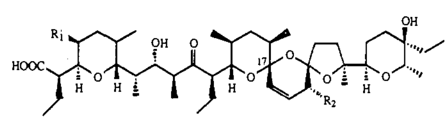


15 nigericin (grisorixin, A6016)

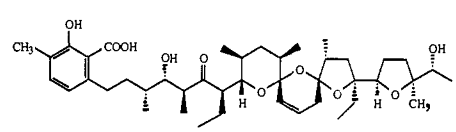
SCHEME 4. Naturally Occurring Trioxadispiroketals



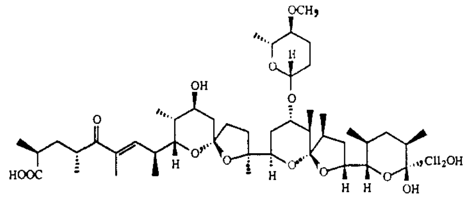
16 norboriiomycin A (norboriiomycin B)



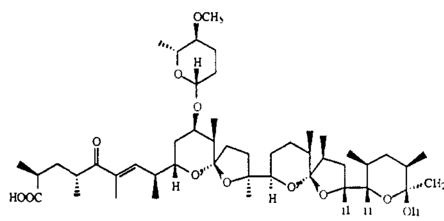
		R_1	R_2	
17	narasin	CH_3	OH	
18	salinomycin	H	OH	
19	deoxy (O-8)-epi-17-salinomycin	H	H	(epi C-17)
20	deoxy (O-8) salinomycin	H	H	



21 CP 44,661



22 dianemycin



23 lenoremycin

2. C25 Bitter Principles from the Genus Cneorum

A number of related compounds containing spiro[4.4] and spiro[4.5] ring systems were isolated from western Mediterranean coastal trees in the genus *Cneorum* by Mondon in the 1970s.[26,27] These densely functionalized C25 metabolites are summarized in Schemes 5 and 6. The structures were assigned principally by spectroscopic methods and chemical interconversions. Most unusual in this series are cneorines Q (**30**) and NP_{29} (**34**), the only examples of naturally occurring spiroketals containing hydroperoxide units. It is tempting to speculate that compounds **30** and **34** are on the biogenetic pathway by which the cneorines are assembled. No significant biological activity has been reported pertaining to this series of metabolites.

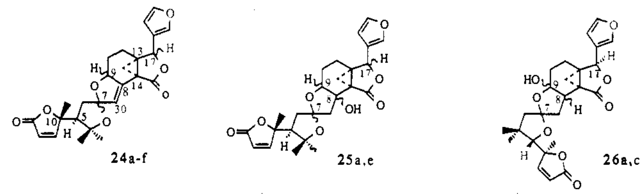
3. Insect Pheromones

Many species of flying insects have been found to elaborate simple spiroketals that exhibit pheromonal activity.[28-31] Thus far, the compounds isolated contain unbranched carbon skeleta and are further functionalized in only a few cases. Frequently, several stereoisomers and structural isomers of one formula are found in the same organism, perhaps suggesting that some of the metabolites may be artifacts of isolation. However, in many cases identification has been made on the basis of gas chromatographic and/or mass spectral identity[29a] with known compounds or mixtures, in which case no manipulation is involved that may lead to isomerization. The metabolites are organized in Schemes 7–10 according to ring system with the source organisms listed underneath. These compounds played an important role in the early synthesis work, providing simple target molecules on which to test synthetic methodology.

4. Milbemycin–Avermectins

The description of the milbemycin and closely related avermectin antibiotics has generated the most activity in spiroketal synthesis. Structural summaries of these and related 16-membered macrolides are shown in Scheme 11. As a class, they exhibit medicinally significant insecticidal and acaricidal activity. Coupled with low mammalian toxicity, these compounds hold enormous potential for the treatment of parasitic infections. In particular, ivermectin or 22,23-dihydroavermectin B_1, derived from avermectin B_1 by selective hydrogenation using Wilkinson's homogeneous catalyst (Scheme 11), has been shown to be effective in containing the transmission of *Onchocerca volvulus* microfilariae by the black fly *Simulium yahense*.[32] Females of this species are responsible for the spread of onchocerciasis, a parasitic disease sometimes resulting in permanent blindness, which affects 20–40 million people worldwide. The isolation, structure determination, biosynthesis, and some of the early chemistry in this area have been reviewed.[33] Relatively rigid molecules, the absolute configurations of avermectins B_{1a} and B_{2a} have been determined by X-ray crystallography combined with chemical degradation.[34] Most of the synthetic work on spiroketals to date has been concerned with this series of compounds.

SCHEME 5. *Cneorum* Bitter Principles



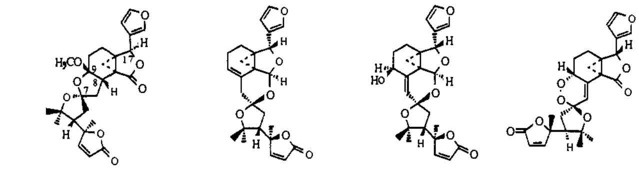
24a-f 25a,e 26a,c

tricoccine		C_7	C_9	C_{17}
C	24a	R	S	S
C_1	24b	S	S	S
B	24c	R	S	R
B_1	24d	S	S	R
R_2	24e (R)	R	S	
R_5	24f (S)	R	R	

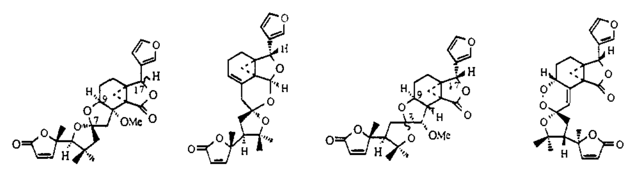
cneorine-tricoccine		C_7	C_8	C_9	C_{17}
D	25a	S	S	S	S
H	25b	R	S	S	S
N	25c	S	S	S	R
O	25d	R	S	S	R
R_6	25e	S	R	S	R

cneorine-tricoccine		C_7	C_8	C_9
S_2	26a	R	S	R
S_1	26b	S	S	R
S_5	26c	S	S	S

SCHEME 6



27 tricoccine S_{10} 28 S_{42} 29 S_{33} 30 cneorine Q



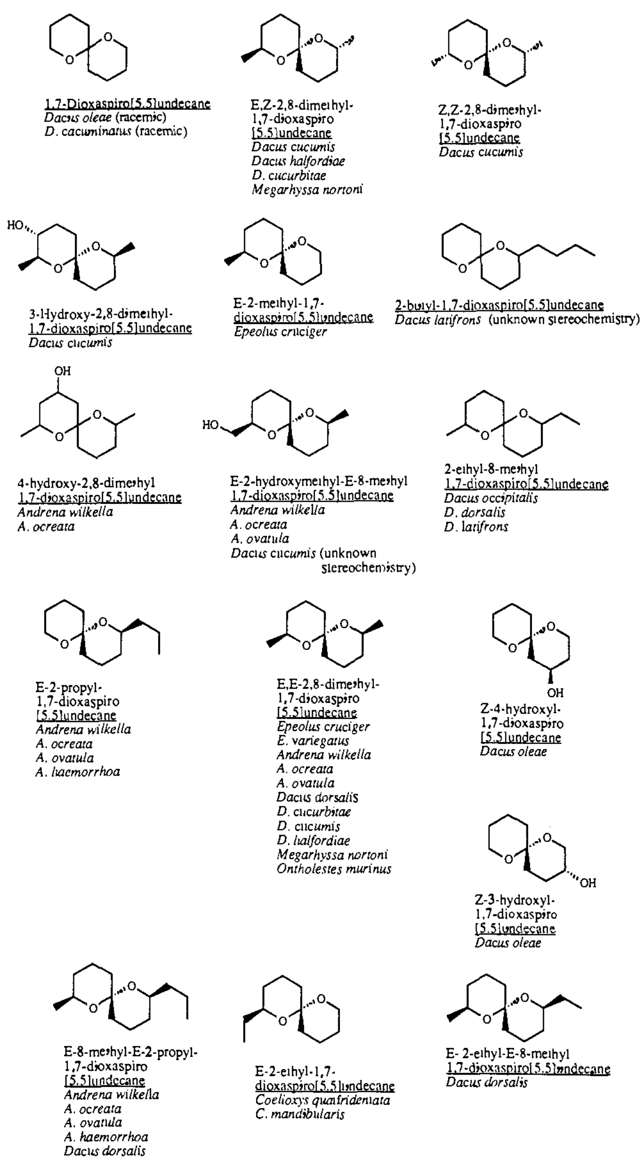
31 cneorine A 32 S_4 33 tricoccine R_3 34 cneorine NP_{29}

5. Spiroketals of Marine Origin

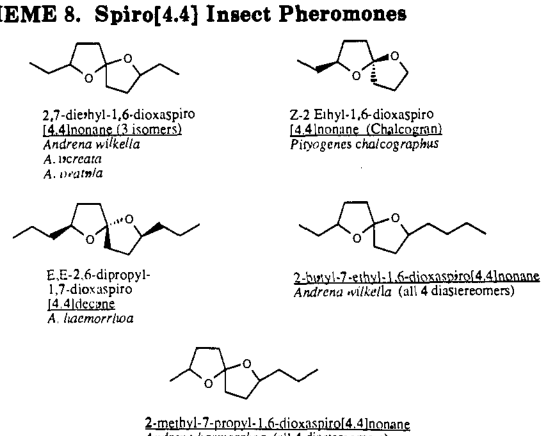
The identification of spiroketals from the marine environment is a relatively recent phenomenon. At this time there does not appear to be any biogenetic pattern to the metabolites or their sources. Most exhibit toxicity in some form.

Acanthafolicin[35] (**40**) and okadaic acid[36] (**41**) were the first polyether carboxylic acids described from marine sources (Scheme 12). Although initially isolated from sponges, the compounds are believed to be produced by symbiotic microorganisms and are the causative agents of "diarrhetic shellfish poisoning", a widespread, nonfatal toxic event. Dinophysistoxins-1 (**42**) and -3

SCHEME 7. Spiro[5.5] Insect Pheromones

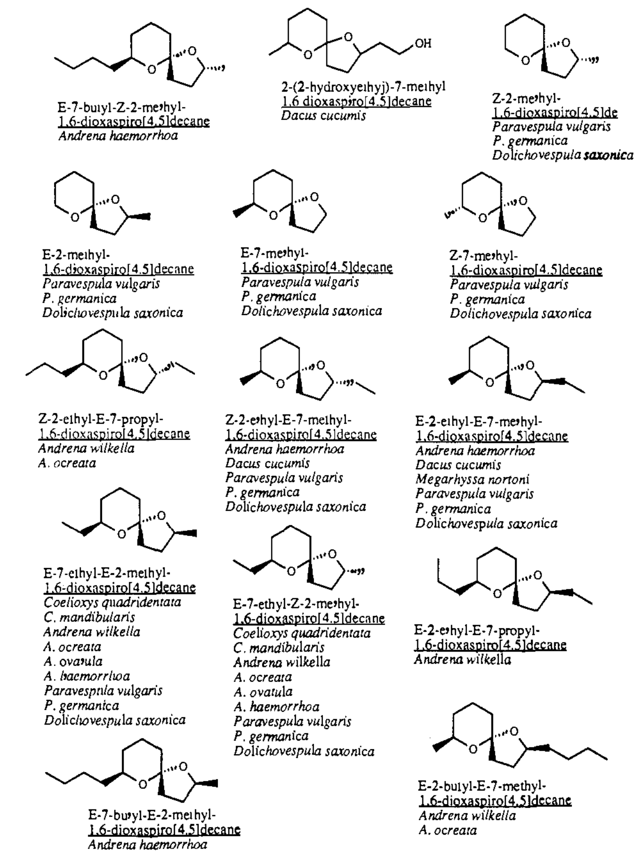


SCHEME 8. Spiro[4.4] Insect Pheromones

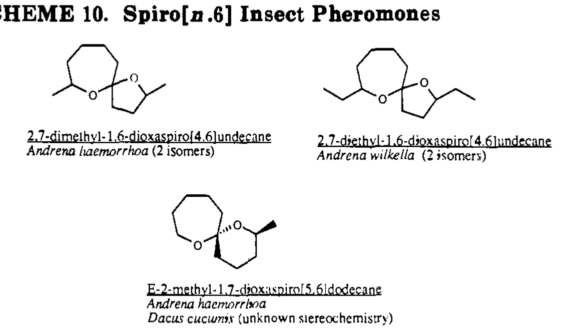


(43) and pectenotoxins-1, -2, and -3 (44–46) were later isolated from toxic scallops and mussels.[37] Most noteworthy among these structures is the rare episulfide ring fused to the 1,7-dioxaspiro[5.5]undecane of 40. Halichondrins (47, 48a,b)[38] may also be classified as polyethers and are presumably of polyketide origin.

SCHEME 9. Spiro[4.5] Insect Pheromones



SCHEME 10. Spiro[n.6] Insect Pheromones

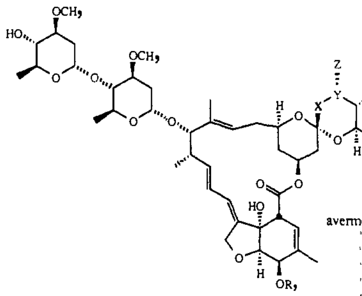


The marine coelenterate *Echinopora lamellosa* elaborates a number of secondary metabolites common to terrestrial plants.[39] Included among them is smilagenin (3), a common steroidal sapogenin.

A number of toxic metabolites (Scheme 13) from blue-green algae[40] have been described that contain unique spiroketal substructures. Several compounds in this series show cancer activity, including tumor-promoting properties. Curiously, other members have been shown to be responsible for a contact dermatitis (colloquially known as "swimmer's itch") that afflicts certain Pacific islands in the summer months.[41]

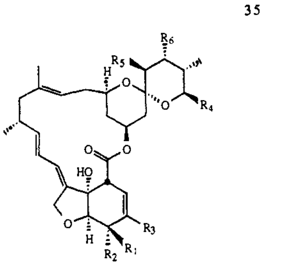
The gorgonian *Isis hippuris* produces a series of steroidal compounds containing a 1,6-dioxaspiro[4.4]-nonane system fused to the D-ring (Scheme 14), similar to the steroidal sapogenins.[42] The spiro center (22*R*) was found to irreversibly isomerize to 22*S* under acidic conditions. This might be the source of a misassignment of the structure of hippurin-1 (64). The configuration of the spiro carbon of hippurin-1 was corrected by Higa[43] on the basis of spectroscopic measurements.

SCHEME 11. Milbemycin-Avermectin Metabolites



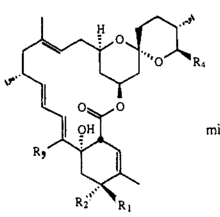
35

	R_1	R_2	X—Y	Z
avermectin A_{1a}	CH_3	CH_3	CH=C	H
" A_{1b}	CH_3	H	CH=C	H
" A_{2a}	CH_3	CH_3	CH_2—CH	OH
" A_{1b}	CH_3	H	CH_2—CH	OH
" B_{1a}	H	CH_3	CH=C	H
" B_{1b}	H	H	CH=C	H
" B_{2a}	H	CH_3	CH_2—CH	OH
" B_{2b}	H	H	CH_2—CH	OH
ivermectin from B_{1a}	H	CH_3	CH_2—CH_2	H
from B_{1b}	H	H	CH_2—CH_2	H



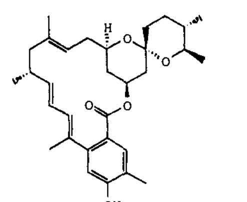
36

	R_1	R_2	R_3	R_4	R_5	R_6
milbemycin α_1	OH	H	CH_3	CH_3	H	H
α_2	OCH_3	H	CH_3	CH_3	H	H
α_3	OH	H	CH_3	CH_2CH_3	H	H
α_4	OCH_3	H	CH_3	CH_2CH_3	H	H
α_5	OH	H	CH_3	CH_3	OH	$OCOCH(CH_3)$n-Bu
α_6	OCH_3	H	CH_3	CH_3	OH	$OCOCH(CH_3)$n-Bu
α_7	OH	H	CH_3	CH_2CH_3	OH	$OCOCH(CH_3)$n-Bu
α_8	OCH_3	H	CH_3	CH_2CH_3	OH	$OCOCH(CH_3)$n-Buh
α_9	OH	H	CH_2O_2C—2-pyrrole	CH_3	H	H
α_{10}	OH	H	CH_2O_2C—2-pyrrole	CH_2CH_3	H	H
D	OH	H	CH_3	$CH(CH_3)_2$	H	H
F	OH	H	CH_2O_2C—2-pyrrole	$CH(CH_3)_2$	H	H
G	OH	H	CH_3	$CH(CH_3)_2$	H	H
J	O		CH_3	CH_3	H	H
K	O		CH_3	CH_2CH_3	H	H

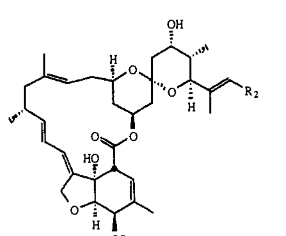


37

	R_1	R_2	R_3	R_4
milbemycin β_1	H	OCH_3	CH_2OH	CH_3
β_2	H	OCH_3	CH_2OH	CH_2CH_3
E	H	OCH_3	CH_2OH	$CH(CH_3)_2$
H	O		CH_3	$CH(CH_3)_2$



38 milbemycin β_3



39

	R_1	R_2
LL-F28249 α	H	$CH(CH_3)_2$
LL-F28249 β	CH_3	$CH(CH_3)_2$
LL-F28249 γ	H	CH_3
LL-F28249 λ	CH_3	CH_3

The remaining examples represent a sporadic potpourri of structures and organisms. Obtusin (**71**)[44] is a member of an interesting class of straight-chain C15 halo ethers[45] isolated primarily from red algae. Partial spiroepimerization occurs on treatment of **71** with anhydrous CF_3COOD at −5 °C to give a 7:3 mixture of obtusin and its C9 epimer isoobtusin.

Like the anhydrotoxins of the Oscillatoriaceae (Scheme 13), the brown algal metabolite cystoketal **72** contains a 2,3-unsaturated pyran ring.[46] Siphonarins A (**73**) and B (**74**) and their dihydro analogues also contain mobile hemispiroketals and are produced by two species of air-breathing molluscs in the genus *Siphonaria*.[47] Also found in a *Siphonaria* species and termed a "spiroketal", the related metabolite muamvatin (**83**)[48] is more of a "bridged ketal" (Scheme 15). Calyculins A–C (**77–80**)[49] from *Discodermia calyx* possess a *gem*-dimethyl group at the 4-position of the tetrahydrofuran of a 1,6-dioxaspiro[4.5]decane ring. In this and a few other cases the placement of a *gem*-dialkyl group at this position is at least partially responsible for the resulting spiroketal conformation.

Although originally misassigned,[50] the structures of psammaplysins A and B have been shown to be **81** and **82** by X-ray analysis.[51] These sponge metabolites contain (arguably) the most unusual spiroketal ring system found in nature so far. The gross structure of the antifungal polyether macrolide goniodomin A[52] (**85**) has been described on the basis of spectral data. Asperketal B (**86**) and its analogues originate from the Caribbean sea whip *Eunicea asperula* and were assigned diterpenoid structures on the basis of spectroscopic and chemical studies.[53]

Coralloidolide B (**84**) is the first cembranoid found in a Mediterranean alcyonacean.[54] Cephalostatins 1–4 (**90–93**) from the marine worm *Cephalodiscus gilchristi* are described as powerful cell growth inhibitors[55] (Scheme 16).

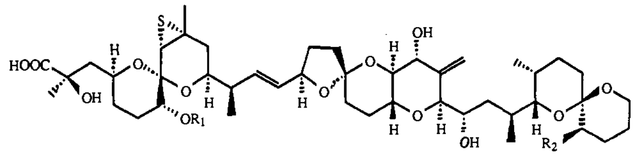
6. Spiroketals from Miscellaneous Sources

The divalent cation ionophore A23187 (calcimycin (**94**), Scheme 17) was the first of a small group of antibiotics isolated from streptomycetes containing a nitrogen heterocycle as well as spiroketal subassemblies.[56] These compounds possess the relatively rare ability to transport alkaline earth metal cations across membranous barriers. Talaromycins A (**99**) and B (**100**) were isolated from the toxicogenic fungus *Talaromyces stipitatus* by Lynn[57] (Scheme 17). Because of their relatively simple and pseudosymmetrical structure, these metabolites played similar roles as stimuli in the development of spiroketal synthesis. Recently, three new isomers of **99** have been described.[58] Likewise, phyllanthocin (**103**)[59] and the related breynolide (**107**)[60] and breynogenin (**108**)[61] were among the first 1,6-dioxaspiro[4.5]decanes of intermediate complexity to attract attention from synthetic organic chemists. Metabolites **94–103** have been synthesized several times (vide infra).

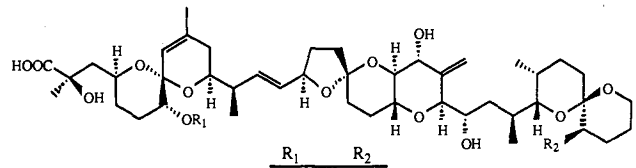
A chemical study of tobacco flavor (*Nicotina tabacum*) uncovered spiroxabovolide (**104**)[62] as a minor constituent, the gross structure of which has been confirmed by synthesis. Two metabolites possessing spiroketals have been isolated from plants in the genus *Grindelia*. Grindelistrictic acid (**105**)[63] (chrysothame[64]) and strictanonic acid (**106**)[63] appear to be of terpene origin, the former being a rare example of a spiroketal lactone.

The macrolide cytovaricin[65] was isolated from a streptomycete and shown to possess structure **109** by X-ray crystallography (Scheme 18). Saponaceolide A

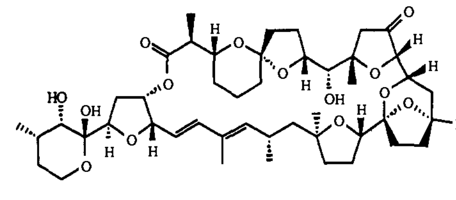
SCHEME 12



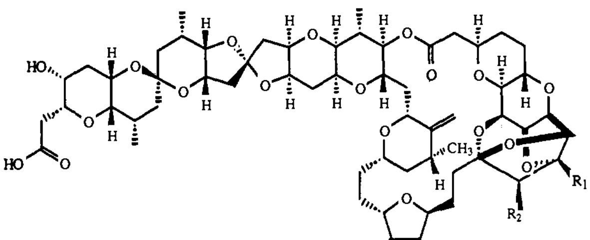
40 acanthafolicin



	R_1	R_2
41 okadaic acid	H	H
42 dinophysistoxin-1	H	CH_3
43 dinophysistoxin-3	acyl	CH_3

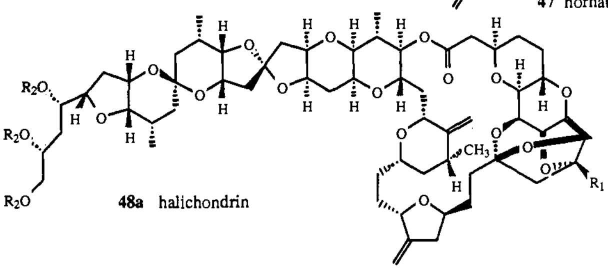


44 pectenotoxin-1 (R = CH_2OH)
45 pectenotoxin-2 (R = CH_3)
46 pectenotoxin-3 (R = CHO)



47 norhalichondrin

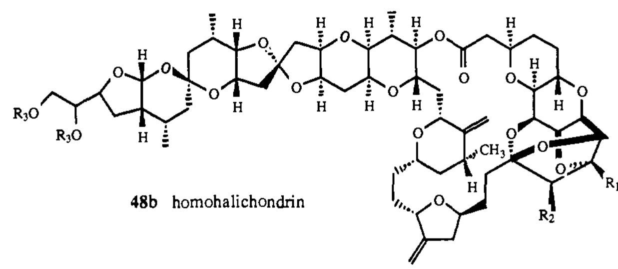
	R_1	R_2
norhalichondrin A	OH	OH
norhalichondrin B	H	H
norhalichondrin C	OH	H



48a halichondrin

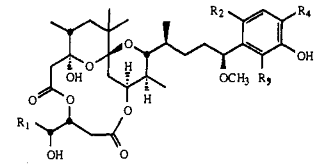
	R_1	R_2
halichondrin B	H	H
halichondrin C	OH	H

	R_1	R_2	R_3
homohalichondrin A	OH	OH	H
homohalichondrin B	H	H	H
homohalichondrin C	H	OH	H

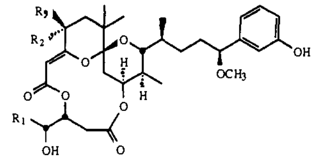


48b homohalichondrin

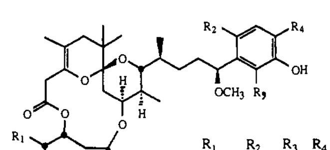
SCHEME 13. Marine Blue-Green Algae Metabolites



	R_1	R_2	R_3	R_4
49 aplysiatoxin	CH_3	Br	H	H
50 debromoaplysiatoxin	CH_3	H	H	H
51 oscillatoxin A	CH_3	Br	Br	Br
52 19,21-dibromoaplysiatoxin	H	H	Br	Br
53	H	Br	H	H
54	H	Br	H	Br
55	CH_3	Br	H	Br

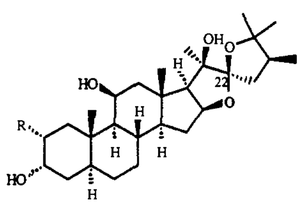


	R_1	R_2	R_3
56 oscillatoxin B1	CH_3	OH	CH_3
57 oscillatoxin B2	CH_3	CH_3	OH
58 31-noroscillatoxin B	H	(CH_3, OH)	

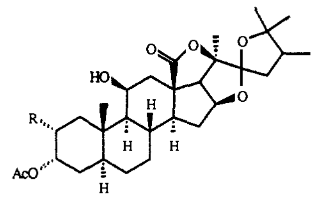


	R_1	R_2	R_3	R_4
59	CH_3	Br	H	H
60	CH_3	I	H	H
61	CH_3	Br	Br	Br
62	H	H	H	H
63	CH_3	Br	H	Br

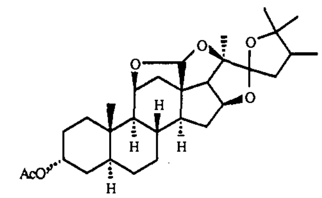
SCHEME 14



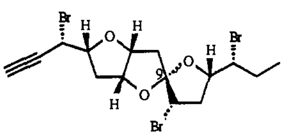
64 hippurin-1 (R = OAc)
65 22-epi-hippurin-1 (R = OAc, epi-C-22)
66 hippuristanol (R = H)
67 22-epi-hippuristanol (R = H, epi-C-22)
68 2α-hydroxyhippuristanol (R = OH)



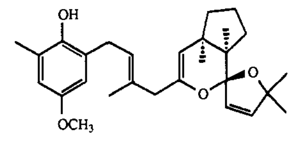
69



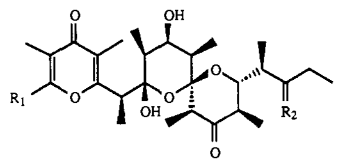
70



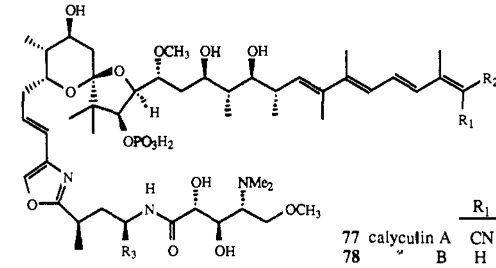
71 obtusin



72 cystoketal

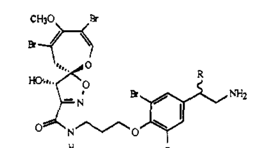


		R_1	R_2
73	siphonarin-A	CH_3	O
74	siphonarin-B	CH_2CH_3	O
75	dihydrosiphonarin-A	CH_3	
76	dihydrosiphonarin-B	CH_2CH_3	

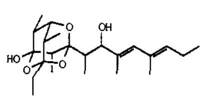


			R_1	R_2	R_3
77	calyculin	A	CN	H	H
78	"	B	H	CN	H
79	"	C	CN	H	CH_3
80	"	D	H	CN	CH_3

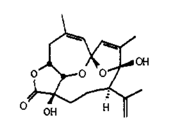
SCHEME 15



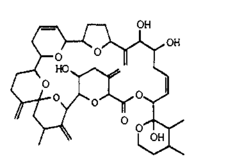
81 psammaplysin-A (R = H)
82 psammaplysin-B (R = OH)



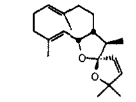
83 muamvatin



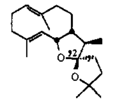
84 coralloidolide B



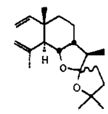
85 goniodomin A



86 asperketal B

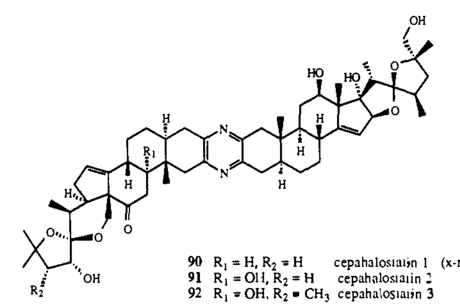


87 asperketal D
88 asperketal E (C-12 epimer)

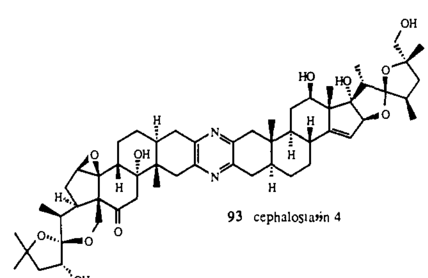


89 asperketal F

SCHEME 16



90 R_1 = H, R_2 = H cephalostatin 1 (x-ray)
91 R_1 = OH, R_2 = H cephalostatin 2
92 R_1 = OH, R_2 = CH_3 cephalostatin 3



93 cephalostatin 4

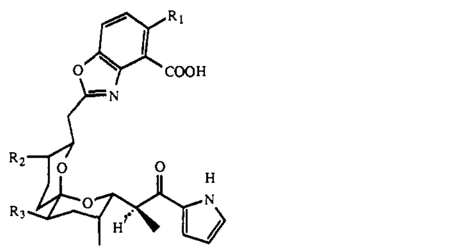
(110) was recently isolated from *Tricholoma saponaceum* and possesses a C2-hydroxylated spiroketal that is more extensively bridged.[66] The orthosomycin antibiotics are microbial metabolites built from one or more orthoester-linked carbohydrate residues. Wright has reviewed this area,[67] emphasizing both structure and biological activity. Like the prototypical flambamycin (111), the molecules possess saccharide-like structures incorporating the only examples of naturally occurring spirocyclic ortholactones.

III. Conformational Aspects

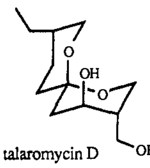
A. General Comments

1,7-Dioxaspiro[5.5]undecanes have been studied intently and are the most easily analyzed for preferred conformations. Three factors have been observed to influence conformational preferences in this system: (1) steric influences, (2) anomeric and related effects,[68] and (3) intramolecular hydrogen bonding and other chela-

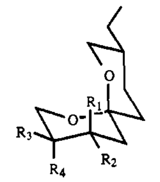
SCHEME 17



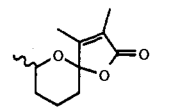
94 R_1 = $NHCH_3$; R_2, R_3 = CH_3 A-23187 (calcimycin)
95 R_1 = H; R_2, R_3 = CH_3 cezomycin
96 R_1 = OH; R_2, R_3 = H CP 61405
97 R_1 = OH; R_2 = CH_3, R_3 = H X-14885A
98 R_1 = OH; R_2, R_3 = CH_3 AC 7320



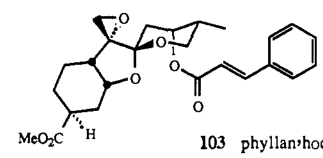
talaromycin D



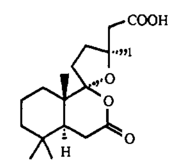
talaromycin		R_1	R_2	R_3	R_4
99	A	H	OH	H	CH_2OH
100	B	H	OH	CH_2OH	H
101	C	OH	H	H	CH_2OH
102	E	OH	H	CH_2OH	H



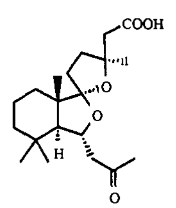
104 spiroxabovolide



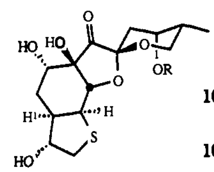
103 phyllanthocin



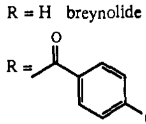
105 grindelistrictic acid (chrysothame)



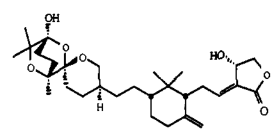
106 stricTanonic acid



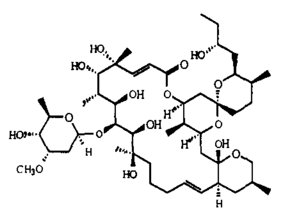
107 R = H breynolide

108 R =  breynogenin

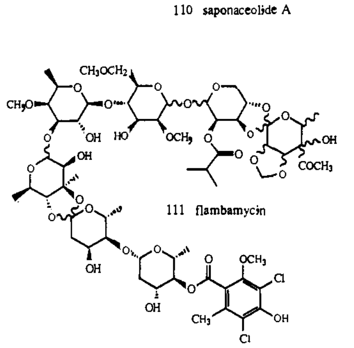
SCHEME 18



110 saponaceolide A

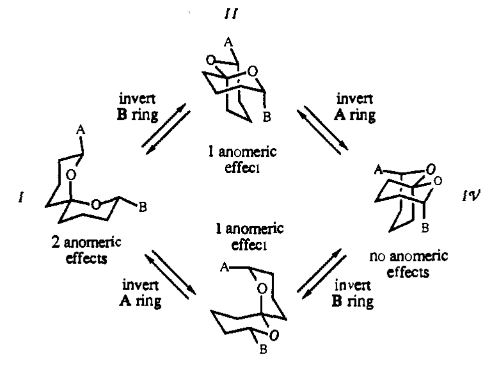


109 cytovaricin



111 flambamycin

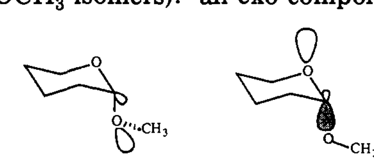
SCHEME 19. All-Chair Conformations of 1,7-Dioxaspiro[5.5]undecanes



tion effects. Discussion of the latter factor is put off until section III.C.

As expected, the typical preference for substituents to reside in equatorial positions is important and in carbocyclic systems is normally an overriding factor. However, as will become evident, this must be balanced against the stabilizing consequences of the anomeric and related effects in tetrahydropyrans. There are cases in which the anomeric effect outweighs the equatorial preference of alkyl substituents. However, when the two factors are reinforcing, that is, when anomeric effects are maximized and 1,3-diaxial interactions are minimized, one can make a confident prediction of molecular conformation. Predictions are more tenuous when one of the preferences must be compromised.

In cases of unsymmetrical substitution, there are four possible all-chair conformers corresponding to independent inversion of each ring. This is illustrated in Scheme 19. In the completely unsubstituted ring system, it has been shown,[69] and is generally accepted, that I is the most stable conformer of this ring system. This has been ascribed to maximization of a thermodynamic anomeric effect. There are many postulated origins of the anomeric effect, including syn-axial 1,3-repulsions of lone-pair orbitals (rabbit ear effects),[70] electrostatic repulsions,[71] dipolar interactions,[72] and n–σ^* stabilizations.[68,73] The last hypothesis, originally put forth by Altona,[74] has received significant attention recently[75] and advocates a stabilizing overlap of a ring oxygen lone-pair orbital with an exocyclic C–O bond. Further, stabilization is maximized when the two reside in an antiperiplanar arrangement. The phenomenon may be characterized as two components (shown only for axial OCH_3 isomers): an exo component (113) in

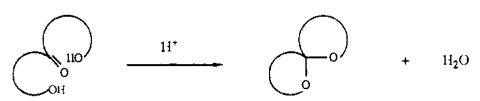


113 *exo* anomeric effect 112 *endo* anomeric effect

which there is overlap between a nonbonding oxygen orbital (the "donor") and the σ* orbital of the ring C–O bond (the "acceptor"), and an endo component (112) in which there is overlap between the ring oxygen nonbonding orbital (donor) and the σ* orbital of the nonring oxygen (acceptor). These effects have been suggested to be reinforcing[69] or opposing.[76] Whatever is the origin and interaction of these effects, it is clear that there is a heavy preference for a carbon–oxygen bond at the 2-position of a tetrahydropyran ring to reside in an axial orientation, and this has a profound influence on the conformation of spiroketals. This is evident in the conformations of naturally occurring spiroketals and in the thermodynamic acid-catalyzed spirocyclizations of dihydroxy ketones or an equivalent thereof (section III.C).

B. Conformations of Naturally Occurring Spiroketals

Early work on the synthesis of complex spiroketals proceeded on the assumption that the configuration of the spiro carbon of the natural metabolites corresponded to the thermodynamically most stable form. Therefore, acid-promoted spirocyclization (114 → 115)



114 115

of a dihydroxy ketone precursor would proceed to give the correct configuration at the spiro center, given that the substitution pattern (and other perhaps unknown factors) closely mimicked that of the natural product. This was generally found to be a valid assumption. Early work in many systems then focused on the assembly of fully functionalized precursors that were then cyclized in a thermodynamic acid-catalyzed process completing the ring system. Examination of the solid-state structures of naturally occurring spiroketals reveals that the majority appear to reside in predictable conformations in which steric effects are minimized and "anomeric effects" are maximized. Several natural product spiroketal conformations have been redrawn in an approximate fashion from computer-generated crystal structures and are shown in Scheme 20. Several of these structures deserve comment.

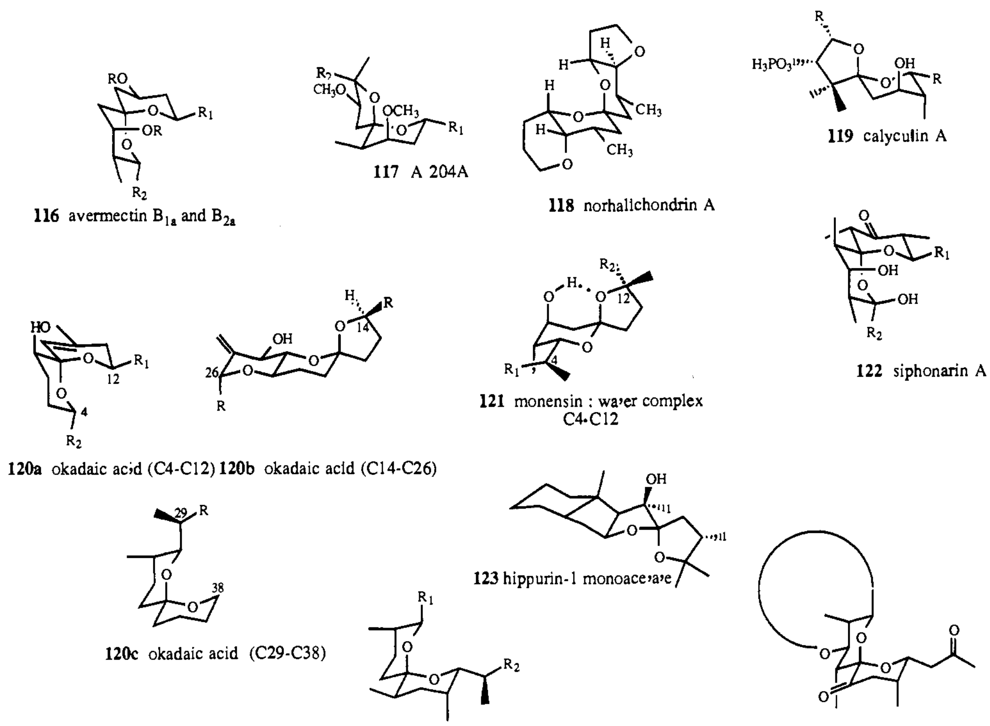
In the cases of spiro[5.5] systems the bisaxial arrangement of spiro C–O bonds is commonly observed in both saturated and unsaturated ring systems. This trend is supported by many examples of synthetic compounds containing this ring system that have been spectroscopically or crystallographically characterized (vide infra). The X-ray crystal structures of avermectin B_{1a} and B_{2a} aglycones indicate that the spiroketals reside in the anomerically favored conformation 116.[34b] Their solution conformations appear to mirror their conformations in the solid state as judged spectroscopically. It does not appear that the macrolide bridge is a factor in determining the most favorable spiroketal conformation since both tetrahydropyran rings contain the largest substituents in equatorial positions. Perhaps the most thoroughly studied spiro[4.5] examples are those present in polyether antibiotics. The X-ray crystallography of several members of this family, mostly as heavy metal atom salts, has been reviewed by Paul.[17b] In cases studied in which there are no significant differences between the conformations of the free acids and the metal salts, the C–O bond in the five-membered ring is axial to the six-membered ring with the other C–O bond in a roughly axial orientation with respect to the five-membered ring. This is exemplified in the spiroketal conformation of A 204A shown in 117. Interestingly, in the monensin–water complex (121), as well as in various salts of monensin, both the C5 methyl and the C6 hydroxyl are axially disposed. This conformation may be stabilized by an O4-H- - -O6 intramolecular hydrogen bond.[17b] Whether or not this conformational preference applies in simpler compounds will require further examples before the generalization can be made. Fewer data are available for spiro[4.4] ring systems; however, hippurin-1 monoacetate (123) shows a similar arrangement.

Two naturally occurring compounds that do not reside in a bis-diaxial C–O conformation are shown in Scheme 21. The aplysiatoxin–oscillatoxin spiroketal, presumably a readily equilibratible hemiacetal-like system, exhibits the rough conformation shown in 126 in which one spiro C–O bond is oriented equatorially. Inversion of the hemiacetal ring to a bis-diaxial C–O conformation, perhaps accompanied by epimerization at the hemiacetal carbon, would result in a 1,3-diaxial dimethyl interaction of the indicated (asterisks) methyl groups. This apparently is sufficient to discourage the anomerically favored conformation. However, it is difficult to ignore the conformational influence of the macrocyclic tether connecting the two rings of the spiroketal, as this may have an appreciable effect in determining preferred conformations in large, structurally complex molecules. This might also be the case with pectenotoxin-1 (127) in which there does not appear to be anomeric stabilization of the spiroketal, at least not in the solid state.

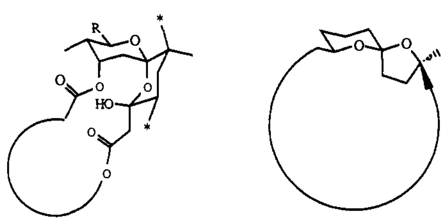
C. Conformational Effects on Spiroketal Reactivity: Acid-Catalyzed Spirocyclization and Spiroisomerization

Nowhere is the preference for axial spiro C–O bonds in these ring systems more apparent than in the acid-catalyzed spirocyclizations of dihydroxy ketones or an equivalent. Numerous synthetic strategies have taken advantage of an inherent thermodynamic bias in the formation of 1,7-dioxaspiro[5.5]undecane ring systems. Deslongchamps has studied this phenomenon intently and has made important contributions to understanding the origin of the anomeric effect and its role in determining the conformations of simple and complex spiroketals. The initial study[69] relied on evaluations of steric and anomeric effects present in the various spiroketal conformers. This analysis led to predictions of conformational preference of several simple spiroketals, including the parent unsubstituted system 129. This compound was synthesized by treating the blocked dihydroxy ketone 128 with acid under equilibrating conditions to effect deprotection and cyclization to 129. The spiroketal was shown by ^{13}C NMR to exist predominantly, if not exclusively, in the bis-diaxial C–O

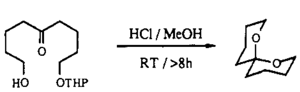
SCHEME 20. Conformations of Spiroketal Substructures of Various Natural Products


116 avermectin B_{1a} and B_{2a}; 117 A 204A; 118 norhalichondrin A; 119 calyculin A; 120a okadaic acid (C4-C12) 120b okadaic acid (C14-C26); 121 monensin : water complex C4-C12; 122 siphonarin A; 120c okadaic acid (C29-C38); 123 hippurin-1 monoacetate; 124 calcimycin; 125 oligomycin B

SCHEME 21


126 aplysiatoxin-oscillatoxin spiroketal conformation; 127 pectenotoxin-1 spiroketal

arrangement shown. The same conformation was found for a number of substituted 1,7-dioxaspiro[5.5]unde-

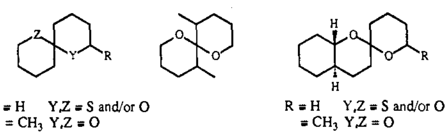


128 129

canes as well as for some monothia and dithia analogues (Scheme 22).[77] It was suggested that the accepted value (1.4–1.5 kcal/mol, at the time) for "an anomeric effect" be considered a minimum. This paper[69] has become the most frequently cited work by the synthetic community concerned with spiroketal synthesis and structure, with some workers using a similar analysis of more complex ring systems.[78]

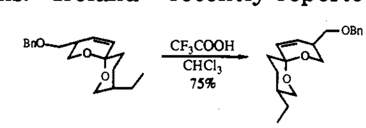
There are numerous examples of spiroisomerization in which steric and anomeric factors serve to favor one isomer. A typical example was reported by Iwata[79] in which a spiroketal (**133**) containing an axial ethyl group underwent isomerization at the spiro carbon to give a diastereomer (**134**) that can adopt a configuration in which steric effects are minimized and anomeric effects are maximized. Many cases are straightforward and amenable to simple conformational analysis. The generality and predictability of the spiroketal conformations will become more apparent in the section on synthesis. The stabilizing influence of the anomeric

SCHEME 22



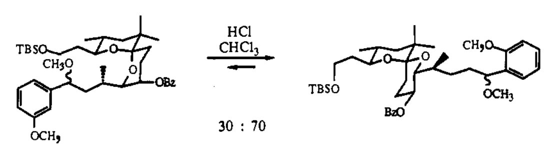
130 131 132

effect can, however, be overpowered by severe steric interactions. Ireland[78] recently reported the equili-



133 134

bration of spiroketals **135** and **136**. In this case, the bis-diaxial C–O arrangement in **135** was isomerized to

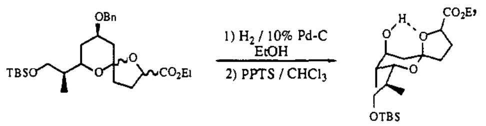


135 136

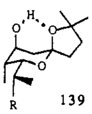
the less anomerically favorable isomer **136**. This may be due to the presence of two axial substituents in **135**, including an interaction between spiroketal C–O and a secondary alkyl group. In this case, the relief in steric crowding in **135** caused by two axial groups outweighed the ground-state stabilization of an anomeric effect.

There has been less information and less consistency and predictability in the formation of spiro[4.5] and spiro[4.4] ring systems (cf. chalcogran syntheses). This will also become apparent in the section on spiroketal synthesis. However, several spiroisomerizations of highly substituted [4.4] systems were utilized in the structure elucidation of the *Cneorum* metabolites[26,27] described in section II.B.2. It is clear from data in [5.5] systems that the influence of the anomeric effect is regular and predictable and that confident synthesis planning may be based on an anomerically driven ring closure under thermodynamic conditions.

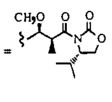
Intramolecular hydrogen bonding and related chelation phenomena have been shown to be an important influence on the thermodynamic stabilities and therefore on product ratios in these ring systems. Hydrogen bonding is especially prevalent between axial hydroxyl groups and a 1,3-diaxial C–O spiro bond. Several examples of this phenomenon have been characterized. Ireland[80] found that each of the four isomers of spiroketal **137** isomerized to one of two compounds (**138**),



137 138



139

R = 

both of which possessed the same configuration at the spiro center and were epimeric only at the carboethoxy-bearing carbon. The presence of an intramolecular hydrogen bond in this system from the hydroxyl to the diaxial spiro oxygen was inferred from a sharp IR absorption at 3560 cm^{-1}. Walba came to the same conclusion with a similar molecule using X-ray crystallography.[81] These results are not surprising, given the similarity of these systems to monensin, which also exhibits an intramolecular hydrogen bond as the free acid (**121**).

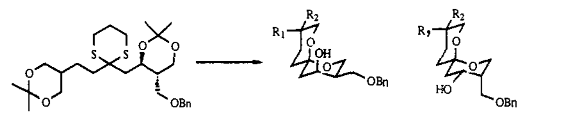
In a spiro[5.5] system, Ley[82] characterized the hydrogen-bonded conformation of **140** by X-ray crystallography. Other scattered examples have been reported.[83]

140 by x-ray

As expected, the effect can be attenuated by use of hydrogen-bonding solvents such as water, alcohols, and DMSO. This has been demonstrated in a study of the deprotection/spirocyclization of **141** under various conditions (Scheme 23).[84] In hydrogen-bonding solvents, isomers **142Y** and **142Z** were favored at equilibrium. However, in a poorly-hydrogen-bonding solvent such as CH_2Cl_2 (entries 2 and 6), isomers **142W** and **142X** were favored. This as hypothesized to be due to the presence of an intramolecular hydrogen bond from the axial hydroxyl to the diaxial spiro oxygen, which should stabilize **142W** and **142X** relative to **142Y** and **142Z** in relatively nonpolar aprotic solvents. Note that in the example of Ireland cited earlier in this section (**137** → **138**) the equilibration solvent was $CHCl_3$.

The converse of this situation has been observed many times in the literature. When the racemic alcohol **143**[85] was treated with acid under protic solvent conditions, the *Dacus oleae* pheromones **144** and **145** were

SCHEME 23



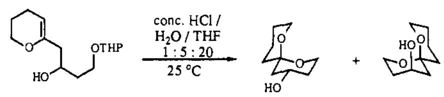
141

142W R_1 = H; R_2 = CH_2OH
X R_1 = CH_2OH; R_2 = H

142Y R_1 = H; R_2 = CH_2OH
Z R_1 = CH_2OH; R_2 = H

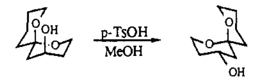
entry	conditions	spiroketal ratios W	X	Y	Z
1	a. Amberlyst-15 / MeOH b. $Hg(OAc)_2$ aq. CH_3CN c. 10% aq. HOAc/Et_2O	1.1	1.0	2.4	1.8
2	CSA / CH_2Cl_2	17.4	4.0	2.8	1.0
3	CSA / DMSO	4.6	1.0	17.2	3.4
4	CSA / MeOH	4.7	1.0	6.6	1.6
5	2N HCl / aq. THF (1:5)	4.6	1.0	5.5	1.2
6	$ZnCl_2$ / CH_2Cl_2	66.0	29.0	4.0	1.0

formed in a 20:1 ratio, respectively, in which the (presumably) hydrogen-bonded conformer was not favored



143 144 145

at equilibrium under these conditions. This agrees with the results of Mori,[86] who found that axial alcohol **146** isomerizes to an 88:7 mixture of **147** and **146** when treated with *p*-TsOH in MeOH. A more dramatic example is the isomerization of the bis-diaxial alcohol **148** to the all-equatorial isomer **149** on treatment with dilute aqueous acid.[83]



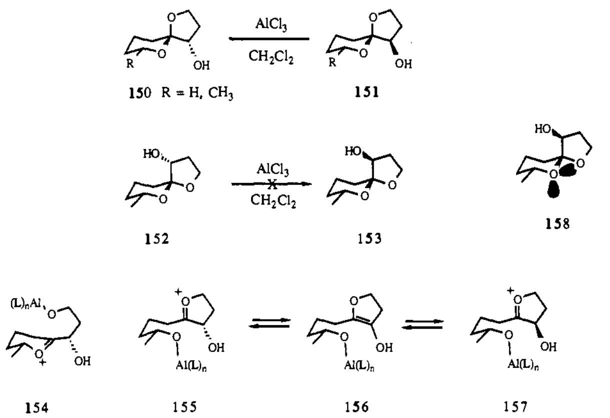
146 147

148
(structure by x-ray)
149

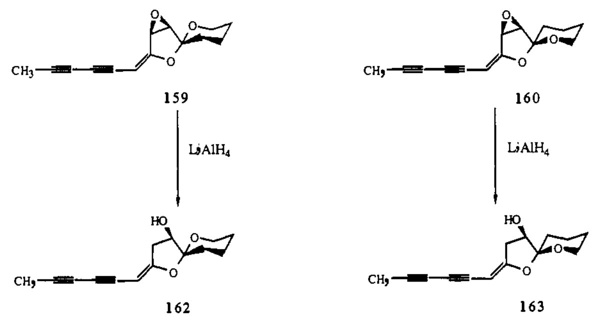
One must conclude from the above data that the preference for substituents to be equatorial is dominant. However, the cases cited also point to the importance of intramolecular hydrogen bonding in stabilizing spiroketal conformations and thus in affecting product ratios in thermodynamically controlled spirocyclization and isomerization reactions.

Related to the intramolecular hydrogen-bonding phenomenon in these systems is a metal chelation phenomenon reported by various workers. Descotes[87] described the $AlCl_3$-catalyzed spiroisomerizations shown in Scheme 24. In the axial C–O cases **150** (R = H or CH_3), the favored isomer at equilibrium is the one in which the hydroxyl and the spiro oxygen are oriented cis on the tetrahydrofuran ring (**151**). This was ascribed to bidentate chelation of the Lewis acid by these two groups, thus favoring **151** at equilibrium. When R = H, simple isomerization by Lewis acid assisted opening of one ring to an oxonium ion and reclosure on the opposite face can account for the isomerization. However, in the case where an additional sterogenic center is present (R = CH_3), a different course of events must be occurring. Under nonaqueous Lewis acid conditions it is reasonable to assume that one or both of the oxonium ions **154** and **155** are in equilibrium with **150** (R = CH_3). Epimerization at the carbons α to the spiro center is a common occurrence (see next section), oc-

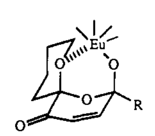
SCHEME 24



SCHEME 25



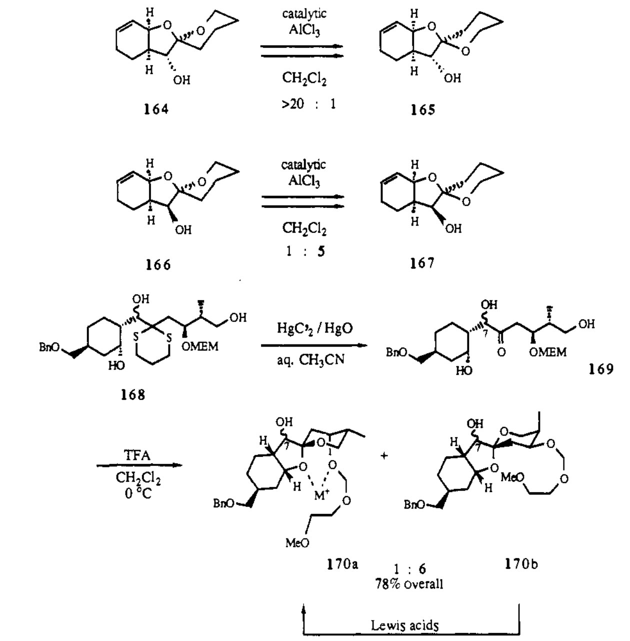
curring in this case perhaps via an enediol-like intermediate **156** which can be reprotonated from the opposite face, eventually producing the favored isomer **151**. The spiro isomer **152**, however, did not undergo equilibration to **153** under these conditions. Molecular models indicate that bidentate chelation of **153** by Lewis acids is stereoelectronically unfavorable (see **158**) relative to **152**. Along this line, the ^{1}H NMR lanthanide shift data,[12,88] reflecting the coordinating ability of isomers **162** and **163** with Eu(fod)$_3$, played a major role in the elucidation of the relative stereochemistries of epoxy spiroketal enol ethers **159–160** (Scheme 25) and hemispiroketals **161**. Kurth[89] described an isomeriza-



161 R = H, CH$_3$

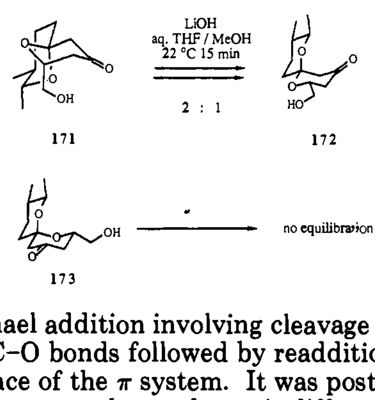
tion in a tricyclic system using the conditions of Descotes (Scheme 26). In this case **166** was isomerized to a mixture in which **167** predominated and **165** isomerized almost exclusively to **164**. In both cases, the isomer in which the hydroxyl is cis to the spiro C–O bond was favored, suggesting a stabilizing chelation of the metal between these two oxygen atoms. Williams[90] described a phenomenon in a similar, but more highly functionalized ring system. Compound **168** was treated with HgCl$_2$/HgO in aqueous CH$_3$CN to remove the dithiane protecting group. Further treatment of **169** with protic acids resulted in a 6:1 mixture of **170b** and **170a**, respectively. It was found that resubmission of **170a** to the cyclization conditions did not result in equilibration to **170b**. This suggests that under these conditions **170a** and **170b** are formed in a kinetically controlled cyclization. During attempted optimization of the formation of the desired isomer **170a**, compound **170b** was found

SCHEME 26



to isomerize to the desired **170a** when treated with a variety of Lewis acids (ZnBr$_2$, TiCl$_4$, and SnCl$_4$). This phenomenon was independent of the configuration at C7 (phyllanthocin numbering), suggesting that the hydroxyl group on this carbon is not involved in the isomerization. This differs from the results of Kurth and may be due to chelation of the Lewis acid metal atoms as shown in **170a**, which would no doubt be assisted by the presence of a MEM group.[91] Most interesting, however, is the production of a stable magnesium chelation complex of **170a** when **170b** was treated with Mg(TFA)$_2$. The complex could be isolated by chromatography on silica and was found to be spectrally similar to free **170a** except for broadening of the ^{1}H NMR signals. The complex was freed of magnesium by addition of buffered EDTA.

A base-induced isomerization of spiroketals was reported by Williams.[92] When compound **172** was treated with LiOH in THF/MeOH, partial isomerization of the spiro center occurred to give a 2:1 mixture of **171** and **172**, respectively. This appears to be proceeding by

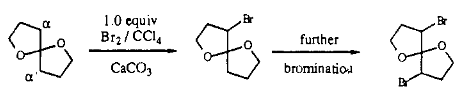


retro-Michael addition involving cleavage of either of the spiro C–O bonds followed by readdition from the opposite face of the π system. It was postulated that there is not a great thermodynamic difference between **171** and **172** since alleviation of the steric compression of the axial hydroxymethyl group in **171** comes at the expense of one "anomeric effect" in proceeding from **171** to **172**. When the isomer **173** is treated with the same conditions, no equilibration takes place. This is reasonable, because only this configuration and conformation maximize anomeric stabilization and minimize 1,3-diaxial interactions.

To summarize, in addition to the obvious steric factors, the anomeric effect and, to a lesser extent, internal hydrogen bonding can influence the thermodynamic stabilities and therefore the relative conformational populations of spiroketals.

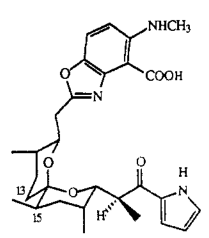
D. Conformational Effects on Spiroketal Reactivity: Cα Epimerization

A confluence of the above factors can limit the conformational freedom of a spiroketal to the point that it exhibits characteristics of a relatively inflexible ring system, with particular reference to chemical reactivity. There are many examples of stereospecificity in the reactions of heavily substituted spiroketals which will be detailed in section V. One conformationally related phenomenon of interest that has proven to be of benefit in synthesis planning is the equilibration of substituents present at the α and α' carbons. That this might be possible was foreshadowed by Dedek[93a] and Ponomarev[93b] in extensive studies of the parent spiroketal 174.



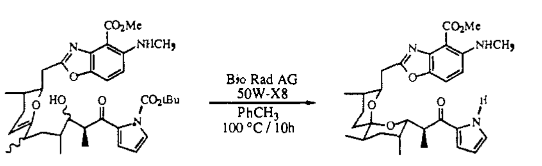
174 175 176

Treatment of 174 with bromine led to the monobromo derivative 175, which could be further brominated to 176, presumably via enolic intermediates. The α and α' positions of spiro[5.5] derivatives were shown to be enolizable and equilibratible by Evans[94] in a synthesis of calcimycin. Model studies confirmed that deuterium exchange selectively occurred at C13 and C15 when 177



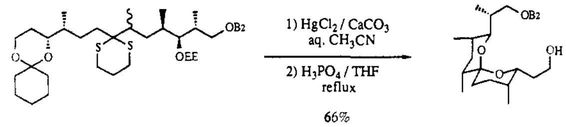
177

was treated with DCl/dioxane with heating for 18 h. This led to the synthetic simplification that the methyl group at C15 need not be introduced stereospecifically since it appeared to occupy the most stable equatorial position in the natural product. This was indeed the case as the precursor 178 (as a 30:70 erythro:threo



178 177

mixture of diastereomers at the carbinol center) equilibrates to a single equatorial methyl isomer 177 at C15 of the closed system. This pioneering simplification was used by Nakahara[95] some years later in a dithiane-based approach to calcimycin in which the two diastereomers represented by 179 cyclized to a single C15 isomer 180 in 66% yield.

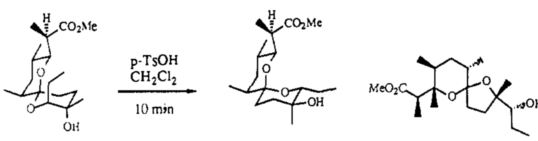


179 180

A similar tactic was used by Hoye[96] in a diastereoselective synthesis of invictolide in 1981 (Scheme 27). The ca. 1:1 diastereomeric mixture of 181 was spirocyclized with equilibration to the all-equatorial isomer 182. This was bismethylated predominantly axially to provide 183 as the major product and then opened to the diacid 185, which was eventually converted to invictolide (186). A similar approach was described by Schreiber[97] in which the dimethylhydrazone isomers 187 cyclized/equilibrated to the spiroketal mixture in which the all-equatorially-substituted isomer 188b predominated. This compound was eventually converted to invictolide.

Related cases investigated by Ireland[98] are not so one-sided. The equilibration of a small series of structurally related spiroketals is shown in Scheme 28. As can be seen, there are no structurally dominating thermodynamic factors in these isomer pairs.

Equilibrations of this nature are sensitive to the strength of the acid employed. For example, Deslongchamps[99] found that dihydroxy ketone 192 closed very readily to spiroketal 193 on treatment with $HOAc/CH_2Cl_2$ without epimerization of the indicated (asterisk) axial methyl group (Scheme 29). However, the structurally related 194 easily underwent epimerization at this center to 195 on treatment with p-TsOH/acetone. Curiously, Cα isomerization did not occur in a case studied by Ireland.[98a] Spiroketal 196



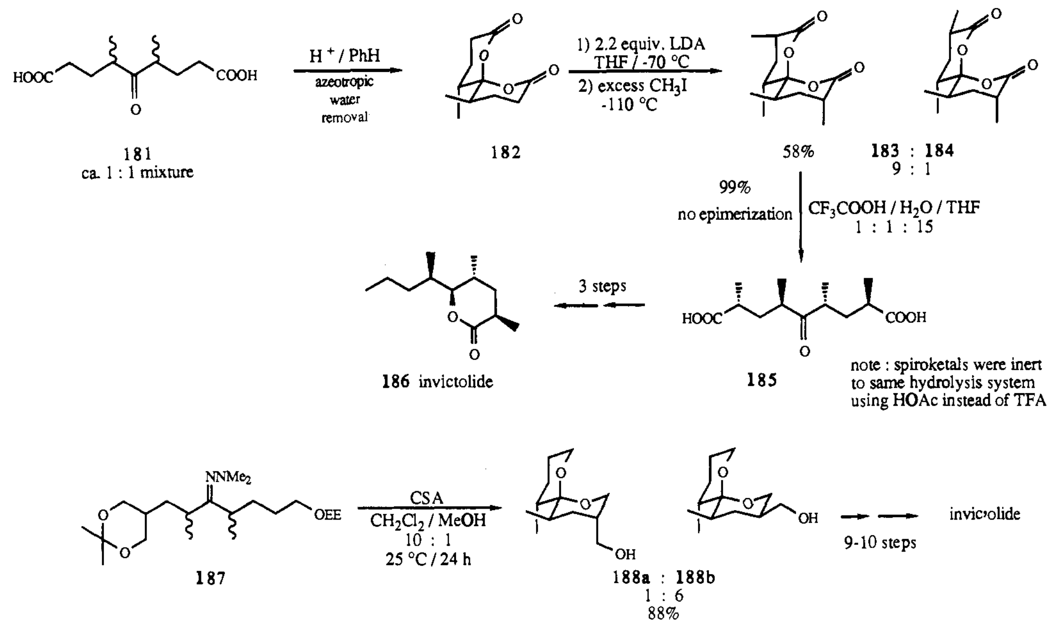
196 197 53% 198 47%

spiroepimerized to the anomerically favored 197 under the influence of p-TsOH.[98a] In this transformation, isomerization of 196 to 197 was favored not only by the maximization of anomeric effects but also by the trade-off in energy in exchanging a 1,3-diaxial ethyl $\leftrightarrow$ C–O interaction and an axial OH group in 196 for an axial methyl group in 197. The system is more complicated than this simple analysis, however, since a large amount of the spiro[4.5] isomers 198 (epimeric at the spiro carbon) was formed as well.

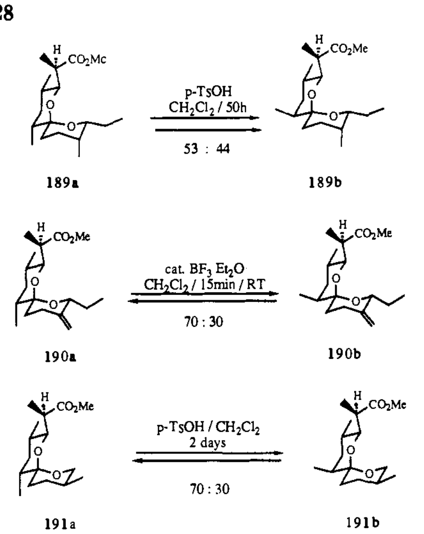
E. Conformations of Trioxadispiroketals

These tricyclic systems are much more complex than spiroketals. Much of the study so far has been concerned with heavily substituted compounds, such that general principles applicable to spiroketals must be applied carefully. A few interesting facets have been uncovered.

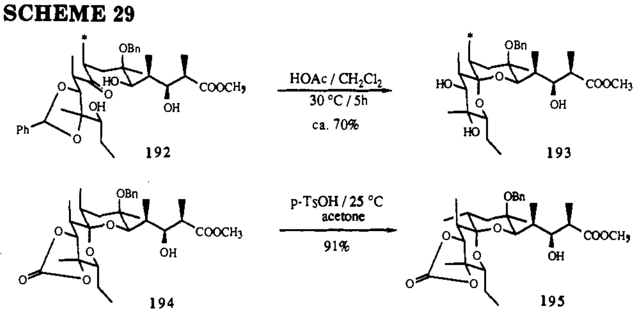
SCHEME 27



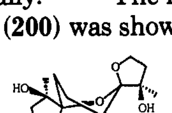
SCHEME 28



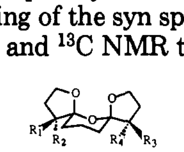
SCHEME 29



Descotes studied 1,6,8-trioxadispiro[4.1.4.3]tetradecanes (199–201) both spectroscopically and crystallographically.[83,100] The middle ring of the syn spiro C–O isomers (200) was shown by ^1H and ^{13}C NMR to adopt a chair conformation. The anti spiro C–O isomers (199) were shown to prefer a twist-boat form by X-ray crystallography. This was rationalized as a way of maximizing anomeric stabilization. However, one might argue that the twist-boat conformation avoids serious 1,3-diaxial interactions (see 201) peculiar to the substitution pattern of these compounds.

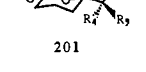


199 *anti* spiro C-O



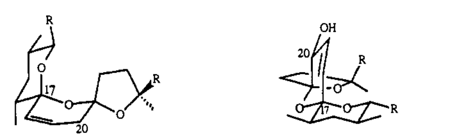
200 *syn* spiro C-O

R_1	R_2	R_3	R_4
CH_3	OH	OH	CH_3
CH_3	OH	CH_3	OH
OH	CH_3	OH	CH_3



201

Unfortunately, the only trioxadispiroketal ring system of practical interest (see Scheme 4) has been studied primarily as heavily functionalized derivatives. Approximate drawings of the two naturally occurring trioxadispiroketal subunits found in the narasin–salinomycin series and in the C17 epi series of these metabolites are shown in 202 and 203, respectively. In

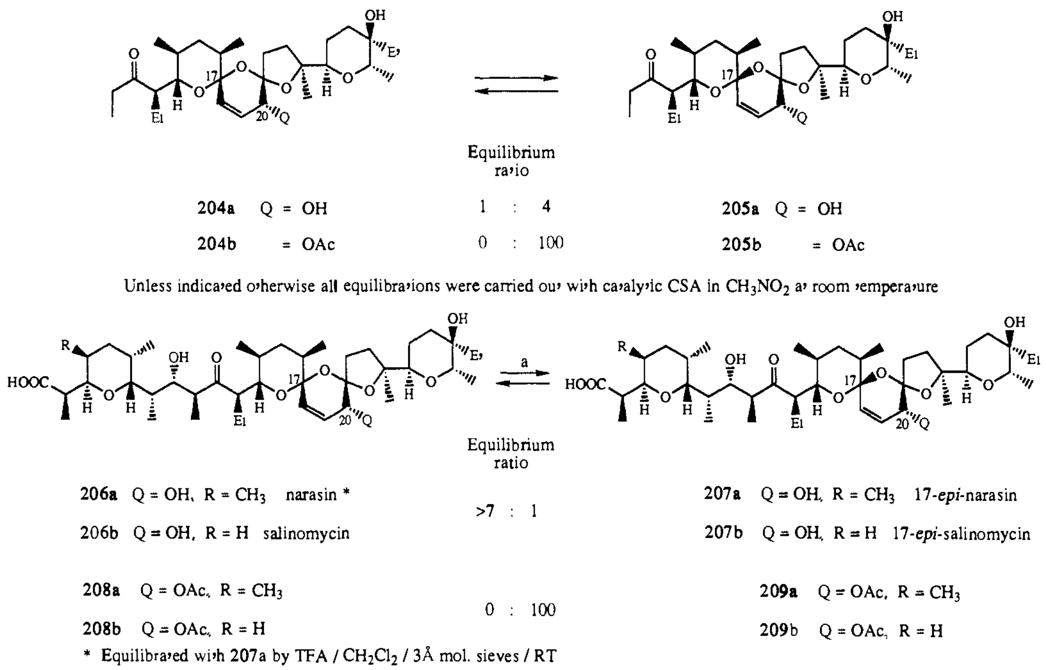


202 20-deoxy-C17-*epi* series 203 narasin - salinomycin series

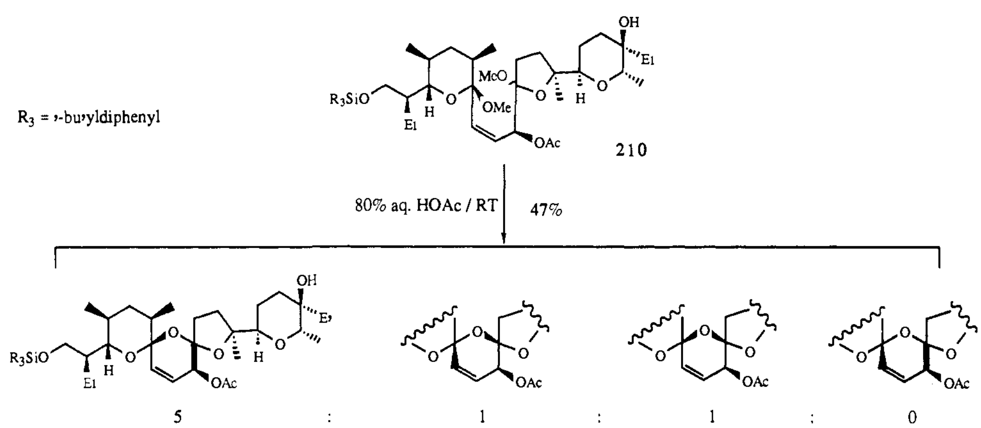
neither case are anomeric effects maximized. In fact, the molecules exhibit vastly different shapes, with the epi series adopting an extended three-dimensional shape while salinomycin (as the *p*-iodophenacyl ester) prefers a much more compact shape.[17b,22b,101] These complexities make analysis somewhat difficult, but there has been an attempt at understanding the conformational quirks of the narasin–salinomycin polyethers.

In explorations into the synthesis of narasin and salinomycin, Kishi made a key fundamental observation of these systems, which is diagrammed in Scheme 30. That is, in synthetic intermediates such as **204a** and **204b**, protic acid catalyzed equilibration of the trioxadispiroketal ring system reveals that the C17 epi isomers **205** are favored, regardless of the nature of the group Q. This holds true with the natural product C20 acetates **208** and with a synthetic C20 epimer acetate (Scheme 31). However, when the natural products themselves (**206**) are equilibrated, the natural configuration and not the C17 epi configuration is favored in both narasin and salinomycin. This indicates that the C20 hydroxyl group is somehow involved in determining

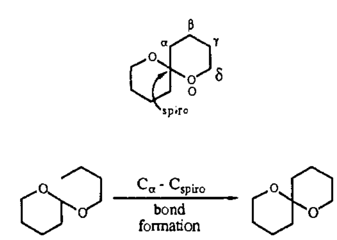
SCHEME 30. Spiroepimerizations of Trioxadispiroketals



SCHEME 31



SCHEME 32



the thermodynamically preferred configuration and conformation of the trioxadispiroketal ring system in these molecules. However, from the tertiary structure and the extensive hydrogen bonding as revealed by X-ray crystallographic analysis, it is clear that these exceedingly complex molecules are not good models of fundamental conformational preferences in trioxadispiroketals, and general conclusions should not be made.

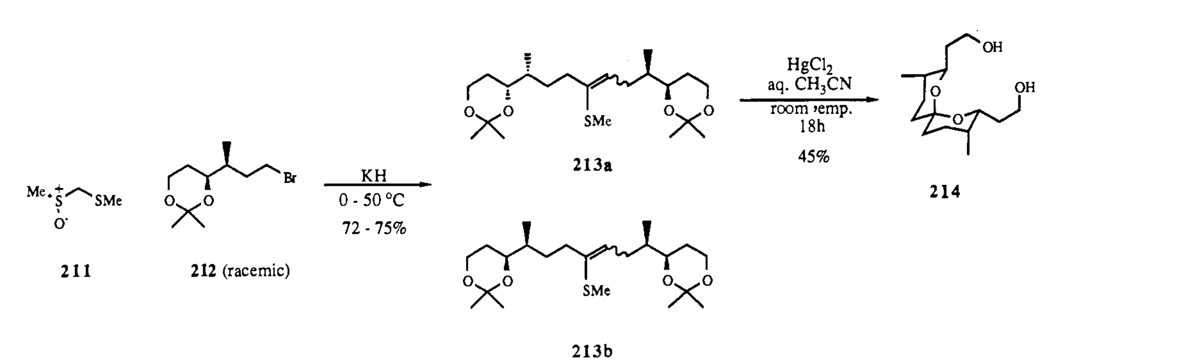
IV. Spiroketal Synthesis

Although several strategies have evolved for spiroketal synthesis, the acid-catalyzed cyclization of dihydroxy ketones, or an equivalent thereof, is the predominant ring-forming process. Most of the early approaches took this course. Later work concentrated on devising new and more efficient methods for assembling the dihydroxy ketone precursors. There are a few alternative strategies not involving C–O bond formation to close the second ring. The discussion will be divided into two major sections. The first will contain acid-catalyzed spiroketalizations and the methods for preparing the precursors. The second section will outline approaches not utilizing this method.

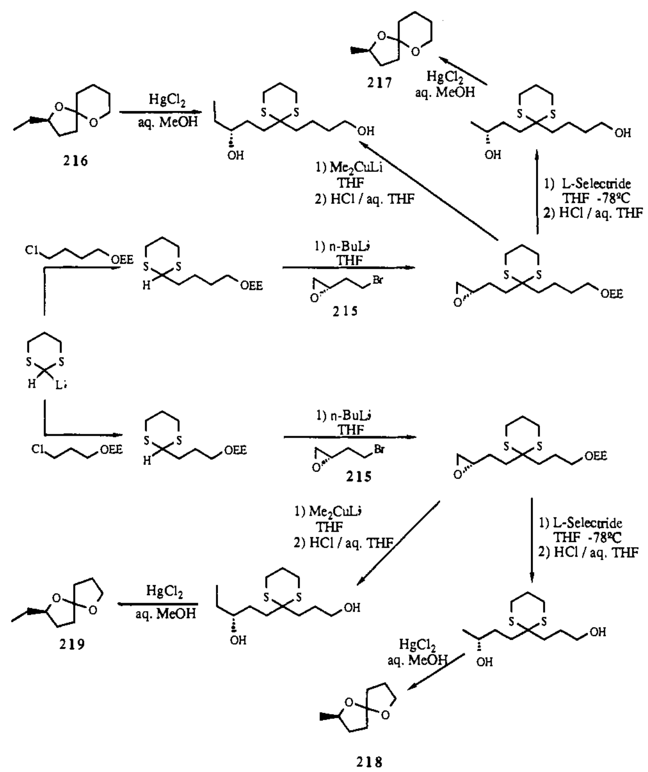
A. Acid-Catalyzed Spiroketalizations

Intramolecular acid-catalyzed ketalization of dihydroxy ketones or some equivalent thereof is an extremely facile process. When a ketal is formed intermolecularly from a ketone and an alcohol or diol, water is normally removed from the reaction physically by a Dean–Stark trap, by absorption by molecular sieves, or by chemical means. In spiroketalizations, removal of water in this manner is not a requirement in many cases. This suggests that there is a large thermodynamic difference between dihydroxy ketones and spiroketals, much larger than in the intermolecular counterpart. In many cases, it is even difficult to prevent the spiroketal from forming.

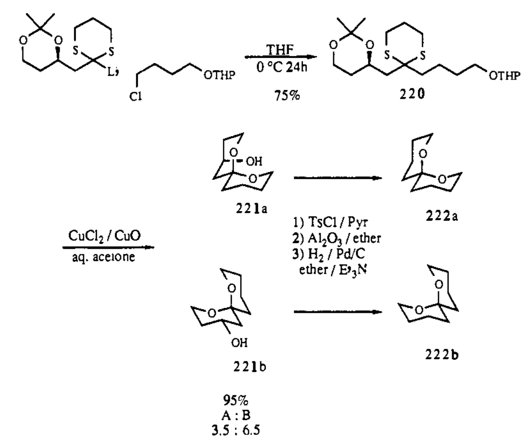
SCHEME 33



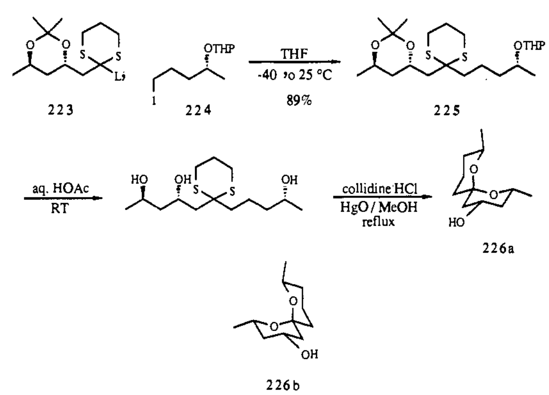
SCHEME 34



SCHEME 35



SCHEME 36



This section is organized according to the key bond or bonds formed in assembling the precursors. Bond-forming nomenclature will follow the labeling scheme shown in Scheme 32, where the atoms are assigned as α, β, ..., etc. with respect to the spiro carbon and not the heteroatoms.

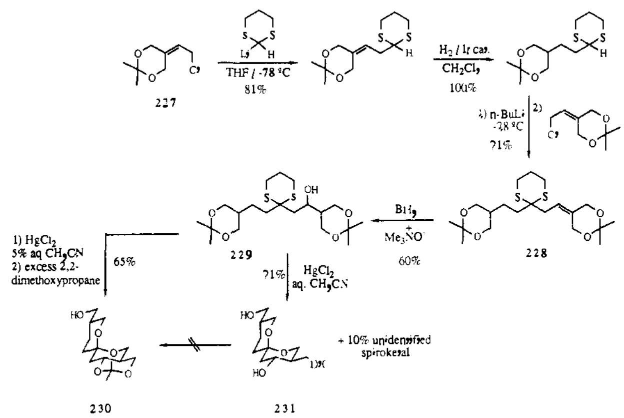
The synthetic methods in this area can be phenomenologically subdivided into classes based on which bond is formed to produce the precursors to cyclizations. By far the most frequently employed strategy is to use the carbonyl group (the incipient spiro carbon) as a point of attachment. This is classified here as a C_α–C_{spiro} strategy. C_α–C_β strategies are also common, but other modes of connection are rare.

1. C_α–C_{spiro} Bond-Forming Strategies

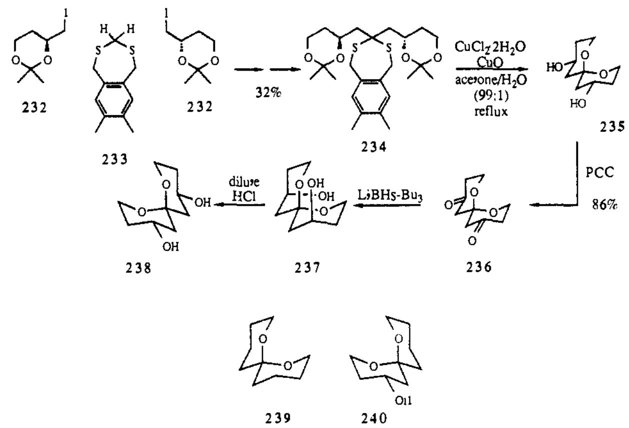
(*a*) *1,3-Dithiane Riveting Approach.* Acyl anion equivalents such as 1,3-dithiane and similar substances are ideal reagents for connecting two hydroxyalkyl fragments to a *pro*-carbonyl group that will eventually become the spiro carbon. One of the first examples of this strategy was put forth by Evans[94] in model studies directed toward the synthesis of calcimycin. The riveting agent **211** was alkylated with the racemic bromide **212** to give the expected mixture of isomers **213** after sulfoxide elimination (Scheme 33). Separation of **213a** and hydrolysis mediated by Hg(II) led to the major spiroketal **214**, shown to possess the desired relative stereochemistry for eventual calcimycin synthesis, although lacking a methyl group α to the spiro carbon. This C_α–C_{spiro} technology was not used by Evans in a later successful approach to calcimycin (**94**). However, this strategy has been employed by many groups in the synthesis of a large number of enantiomerically pure simple spiroketals. Seebach[102] used the optically pure bromo epoxide **215** (Scheme 34) available from (*S*)-(–)-malic acid in a unified approach to the four spiroketal pheromones **216–219**, all of which were obtained as 3:2 mixtures of diastereomers at the spiro carbons.

Francke[103a] and Redlich[103b] used essentially identical approaches to prepare optically pure insect pheromones. The parent spiroketals **222a,b** were synthesized from a single precursor (**220**), which, after cyclization, gave the hydroxylated spiroketals **221a** and **221b** of opposite configuration at the spiro center, depicted in Scheme 35. Deoxygenation of the separated isomers gave the enantiomerically pure unsubstituted 1,7-dioxaspiro-

SCHEME 37

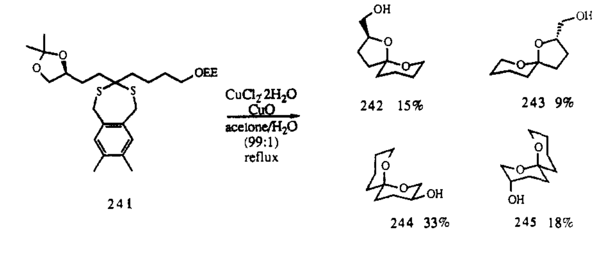


SCHEME 38



[5.5]undecanes **222a** and **222b**. The unsymmetrical spiroketal **226a** (Scheme 36) was synthesized by alkylating the optically pure lithium reagent **223** with the optically pure iodide **224** to give **225**. Hydrolysis and Hg(II)-mediated spirocyclization led to enantiomerically pure **226a**. The enantiomer **226b** was synthesized by an enantiomeric sequence of reactions. Schreiber[104] sequentially alkylated 1,3-dithiane with **227** to obtain the bisacetonide **228** (Scheme 37). Hydroboration–oxidation gave **229**, which was deprotected and cyclized to form **231** in 71% yield along with 10% of an unidentified spiroketal. Triol **231** could not be manipulated to produce **230** but hydrolysis of **229** followed by in situ protection was successful in producing the talaromycin B precursor **230**.

The analogous reagent **233** was utilized by Mori[86,105] to synthesize pheromones of both the spiro[5.5] and spiro[4.5] type. Sequential alkylation[86] of **233** with the iodide **232** gave **234**, which led to the symmetrical spiroketal **235**, the conformation of which was established by X-ray crystallography (Scheme 38). Oxidation with PCC and reduction with LiBH(sec-Bu)$_3$ gave the bisaxial diol **237**, which rearranges to the equatorial isomer **238**, possessing the opposite spiro configuration. This general sequence[105a] was used to prepare both



optically pure enantiomers of **239** and the monohydroxylated pheromone **240**. However, the hydrolysis of a similarly prepared precursor **241** led to a mixture of the four spiroketals **242–245**.

Thomas[106] used an alkylation–epoxide opening sequence to synthesize optically active dithianes **246–249**. Hydrolytic unmasking and spirocyclization of these substances produced spiroketal subassemblies **250–252** related to the milbemycin–avermectins (Scheme 39). The marine tumor promoter debromoaplysiatoxin (Scheme 13) was synthesized for the first time by Kishi[107] using a dithiane anion–epoxide coupling reaction (Scheme 40). The two optically active partners **253** and **254** were synthesized and joined to give **255**. After several steps, the hydroxy diketone precursor **256** was produced and found to exist in the open-chain form. No closure to a C2-hydroxylated "hemispiroketal" such as that present in **257** and the natural products themselves occurred. However, under conditions for macrolide formation, the observed product in 61% yield was the protected debromoaplysiatoxin derivative **257**. From these results it appears that a preassociation process, such as macrocyclization, may be required in order to form the spiroketal assembly of the aplysiatoxin–oscillatoxin metabolites.

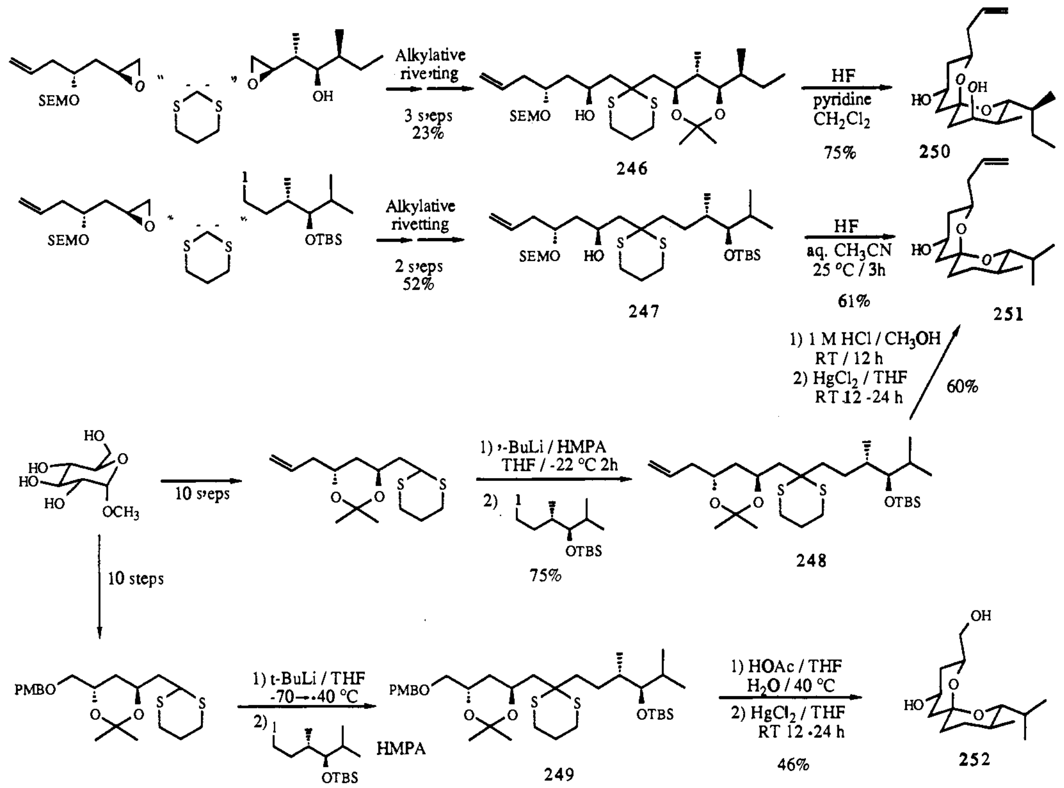
Nakahara,[95] using essentially the same approach as Evans, alkylated the dithiane **259** (available from D-glucose) with the optically active iodide **258** to obtain the calcimycin precursor **260** as a mixture of isomers at the indicated center (Scheme 41). Cyclization not only led to the correct configuration at the spiro carbon (**261**) but also resulted in the correct equatorial configuration of the methyl group α to the spiro carbon, presumably by equilibration.

Williams[90] utilized the addition of the dithiane **263** (Scheme 42) to the aldehyde **262** to give a mixture of diastereomeric triols **264** after desilylation. In contrast to other cases, dethioketalization could be performed without successive spiroketalization in this case to give **265**. Cyclization of either isomer with protic acids then gave an apparently kinetic mixture of spiroketal isomers **266** and **267**. Fortunately, treatment of the mixture with Lewis acids results in isomerization of the undesired **266** to the desired isomer **267**.

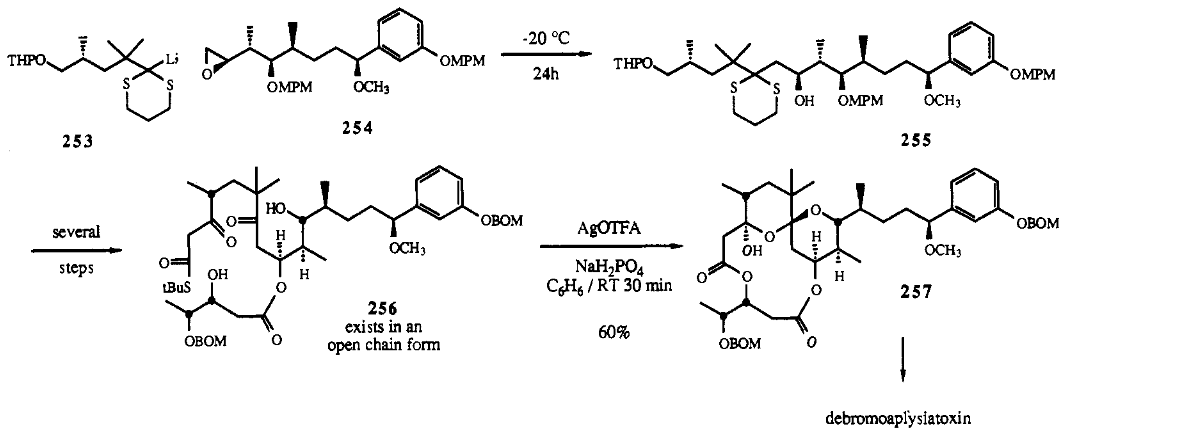
(*b*) *Simple Addition to Lactones.* A variety of nucleophiles have been added to lactone carbonyls to produce the ketone eventually destined to be the spiro carbon. This is an attractive approach because a five- or six-membered lactone is a useful template on which relative and absolute stereochemistry may be established. The addition of an optically pure nucleophilic species to an optically pure lactone allows combination of two stereogenically pure fragments and constitutes a convenient and convergent approach to spiroketal synthesis.

(*i*) *Addition of Acetylide Anions.*[108] Some of the earliest work utilizing this approach was performed by Smith[109] and Silverstein,[110] who synthesized a large number of simple spiroketals. A general sequence is exemplified in a synthesis of chalcogran (**271**) isomers (Scheme 43) involving addition of an acetylide anion **268** to the optically pure lactone **269**, hydrogenation of the resulting alkyne **270**, and acid-promoted spiroketalization. In this case **271** was produced as a 2:1 mixture of E/Z isomers optically pure at C2. The reactions were normally carried out without purification

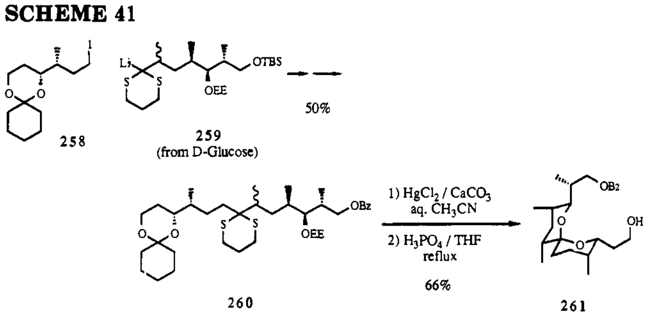
SCHEME 39



SCHEME 40



SCHEME 41

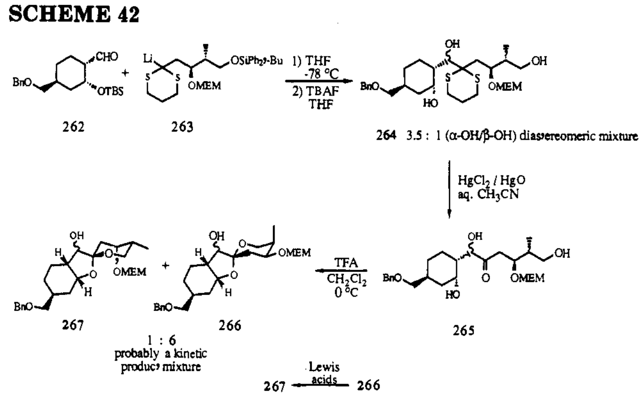


of intermediates and resulted in mixtures of spiroketals in almost all cases.

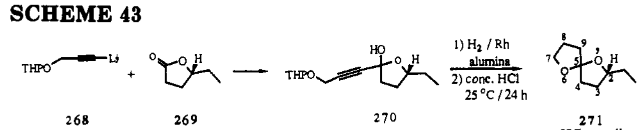
In studies of the anomeric effect, Deslongchamps[69] used this method to synthesize the spiroketals shown in Scheme 22, a typical sequence being shown in Scheme 44 for the synthesis of the conformationally locked spiroketal **272**.

Baker[111] utilized this strategy in a unified approach to the spiroketal substructures of the milbemycin–avermectin antibiotics described in Scheme 45. Addition

SCHEME 42

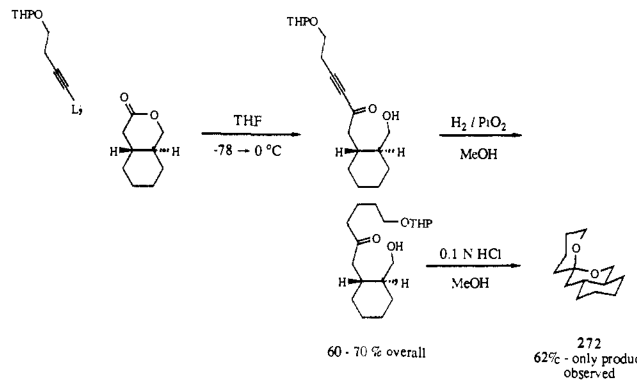


SCHEME 43

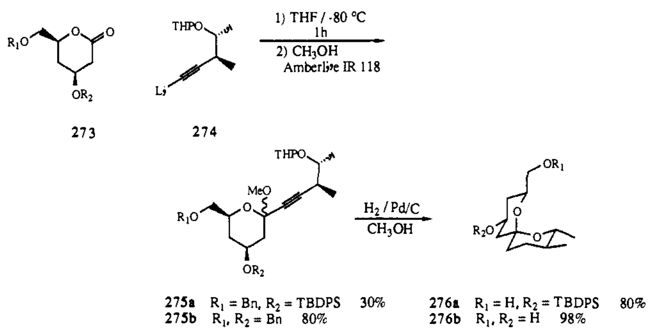


of the optically active acetylide **274** to the optically active lactone **273** and subsequent glycosidation re-

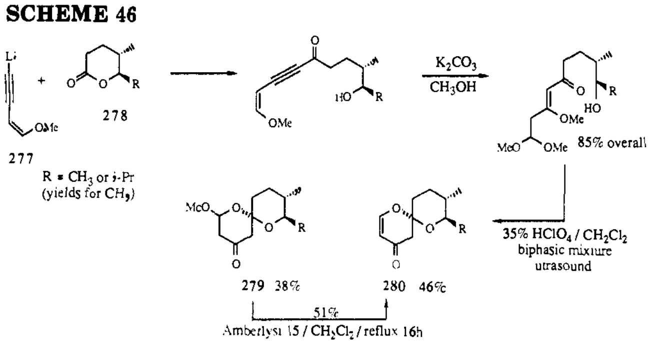
SCHEME 44



SCHEME 45



SCHEME 46

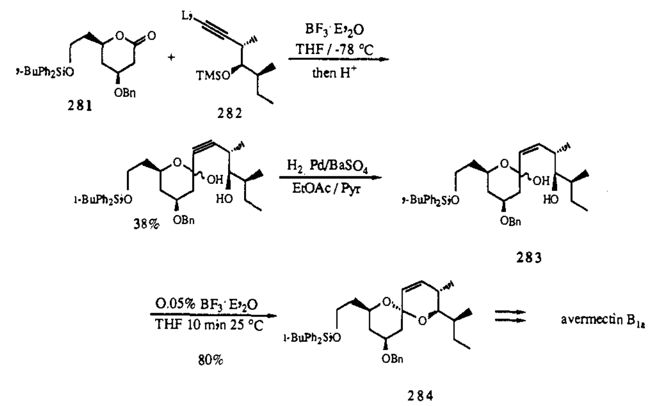


sulted in 275. Hydrogenation of the alkyne and concomitant cleavage of the benzyl groups were effected with a Pd/C catalyst. This procedure resulted in in situ ring closure to the spiroketals 276 eventually used in a synthesis of (+)-milbemycin β_3. Langlois[112] described a nearly identical sequence. Searching for a formyl dianion equivalent, Crimmins[113] developed the use of the lithium reagent 277 (Scheme 46) for milbemycin–avermectin synthesis. In this approach, the lactone fragment 278 comprises the opposite ring.

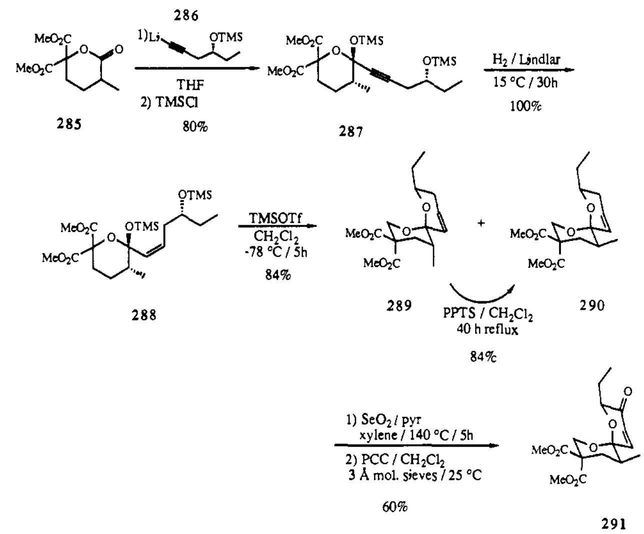
The lactone addition strategy is perfectly suited to the production of spiroketal subunits that contain C22–C23 unsaturation such as those present in many avermectins. Both Hanessian and Baker used semihydrogenation of an alkyne in lactone–acetylide adducts to prepare the spiroketal unit of the avermectin B_{1a} aglycone (Scheme 47, Hanessian approach[114]). The Baker approach[115] is essentially identical. Final spiroketalization to 284 did not occur under the hydrogenation conditions but had to be induced by acid. In these structurally complex cases only a single configuration at the spiro carbon corresponding to the configuration of the natural products was generally produced, presumably because the systems possess significant bias due the heavy substitution patterns involved.

In a synthesis of erythromycin A (Scheme 48), Deslongchamps[116] added the optically active acetylide 286

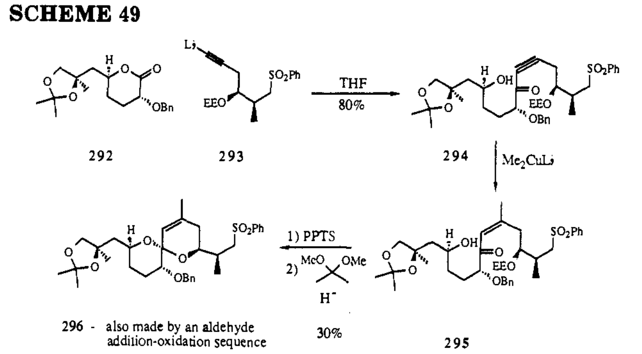
SCHEME 47



SCHEME 48



SCHEME 49

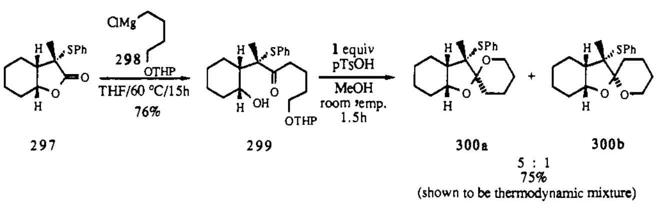


to the racemic lactone 285 to give 287. Semihydrogenation led to the olefin 288. Spirocyclization mediated by TMSOTf at low temperature led to a mixture of spiroketals 289 and 290 epimeric at the position α to the spiro carbon as expected. This center was equilibrated to the desired isomer 290 with mild acid as in other cases.

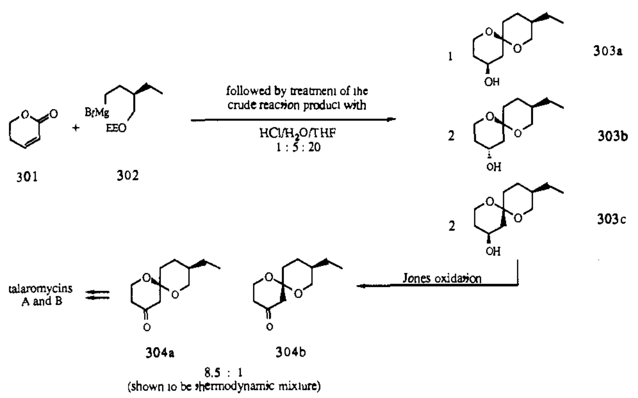
In one of many approaches to spiroketals using lactones, Isobe[117] connected the two optically active fragments 292 and 293 (Scheme 49) to give the α,β-alkynyl ketone 294. Treatment of 294 with methyl cuprate resulted in 295, which was spirocyclized to 296, one of three spiroketal subunits present in okadaic acid (41).

(*ii*) *Addition of Other Nonstabilized Organometallics*. Lactones also accept sp^3-hybridized organometallic reagents readily. Iwata[118] treated the bicyclic lactone 297 with the THP-protected Grignard reagent 298 to give the γ-hydroxy ketone 299, which, upon cyclization, gave the thermodynamic mixture of

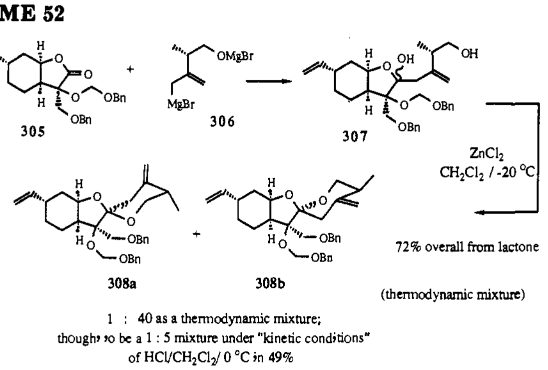
SCHEME 50



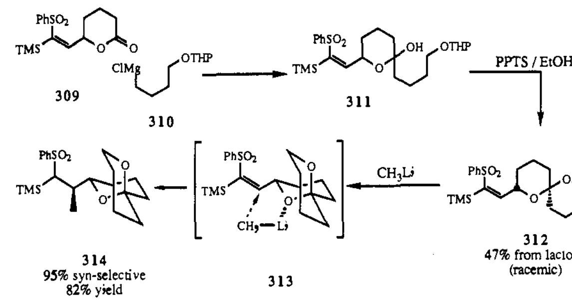
SCHEME 51



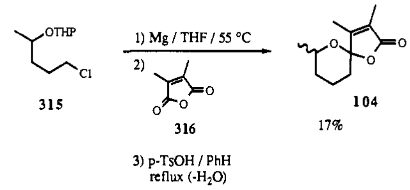
SCHEME 52



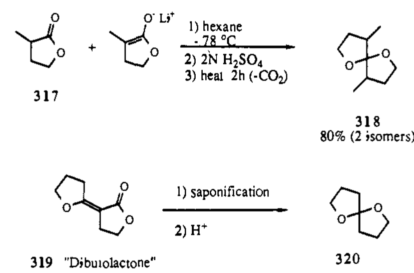
SCHEME 53



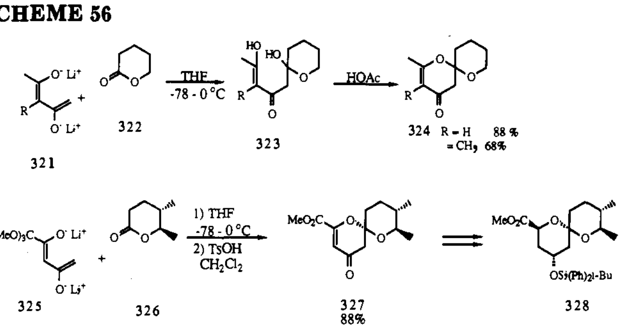
SCHEME 54



SCHEME 55



SCHEME 56



isomeric spiroketals **300a** and **300b** (Scheme 50). In a synthesis of (−)-talaromycins A and B, Smith[119] added the Grignard reagent **302** to the unsaturated lactone **301** (Scheme 51). No description of the resulting intermediate was given. However, after hydrolysis a mixture of three spiroketals (**303a–c**) was obtained. Jones oxidation reduced this to a mixture of two spiroketals (**304**), one of which was eventually converted to (−)-talaromycins A and B. Collum[120] added the allylic Grignard reagent **306** to the γ-lactone **305** (Scheme 52) to give an addition product **307**, which was cyclized to give the thermodynamically favored spiro[4.5] product **308b**. Under "kinetic" conditions (HCl/CH_2Cl_2/0 °C) **308b** was favored over **308a** by only a 5:1 ratio.

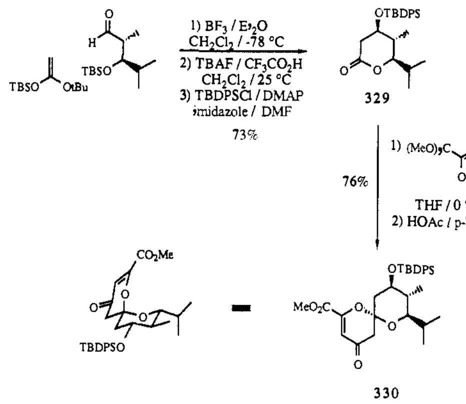
Isobe[121] combined lactone **309** with the THP-protected Grignard reagent **310** and obtained a single spiroketal **312** after hydrolysis with PPTS/EtOH (Scheme 53). The bisaxial arrangement of the C–O bonds of **312** allowed the chelation-controlled addition of methyllithium to the α,β-unsaturated sulfone (see **313**) to give **314** with high stereoselectivity.

To confirm the structure of spiroxabovolide (**104**), a flavor component of *Burley* tobacco, Demole[62] described a synthesis shown in Scheme 54. Dimethylmaleic anhydride (**316**) was combined with the THP-protected Grignard reagent **315**, and the crude intermediate was refluxed in benzene in the presence of catalytic *p*-toluenesulfonic acid to yield spiroxabovolide (**104**) in 17% yield.

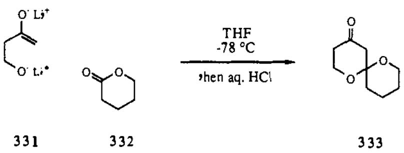
(*iii*) *Addition of Stabilized Carbanions.* Stabilized carbanions such as enolates and related substances have been used much less frequently than the more reactive organometallics. Knorr[122] self-condensed α-methyl-γ-butyrolactone (**317**) and obtained the spiroketal **318** after hydrolysis and decarboxylation (Scheme 55). Due to the conditions employed it is reasonable to assume that this is the thermodynamic product mixture. This process is essentially the same as the oldest known method of spiroketal synthesis. In the late 1880s, Fittig and Strom[123a] described the structure of **320**, a saponification product of butyrolactone dimer **319**. This is classified as an "acyl lactone rearrangement", which has been briefly reviewed.[123b]

Enolate anions are convenient annelation reagents that have seen considerable success in spiroketal synthesis. Barrett developed β-diketone dianions as general reagents for the synthesis of milbemycin–avermectin spiroketals.[124] In model studies, the reaction of **321** (Scheme 56) with lactones leads to addition products

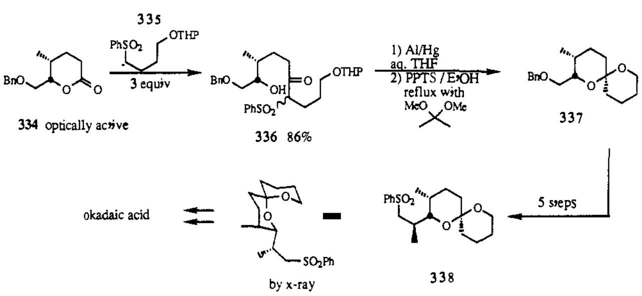
SCHEME 57



SCHEME 58

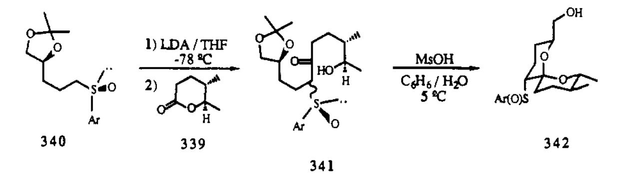


SCHEME 59



that can be cyclized with acid to the C2–C3 unsaturated spiroketals **324** in high yield. This approach was exploited in a synthesis of milbemycin β_3 by use of the carboxyl-protected reagent **325** and the popular optically pure lactone **326**, providing the spiroketal **327**, which was eventually converted to **328** and thence to the natural product. Addition of the same reagent (Scheme 57) to the more highly oxygenated lactone **329** results in the spiroketal **330**, a potential intermediate for avermectin synthesis.[125] Martin[126] utilized a β-hydroxy ketone dianion (**331**) in a reaction with δ-valerolactone (**332**) to produce the spiroketal **333** in moderate yield (Scheme 58).

Both α-sulfonyl and -sulfinyl carbanions have been used in lactone additions. Isobe[121] combined sulfone **335** with the substituted lactone **334** to produce **336** (Scheme 59). Reductive desulfurization and acid-catalyzed closure proceeded to a single isomer **337** eventually useful in their synthesis of okadaic acid. Brimble[127] essentially described the same approach in simpler systems. In a synthesis of milbemycin β_3, Williams[128] opened the lactone **339** with the optically active sulfoxide **340** to give a mixture of β-keto sulfoxides **341**. Treatment of this mixture with catalytic MsOH in wet benzene gave rise to spiroketal **342** (75% for the two steps), which probably possesses the indicated conformation due to maximization of anomeric effects and equilibration of the sulfoxide to an equatorial position. The corresponding axial sulfoxide was obtained in about 10% yield, but this also could be utilized in the synthetic scheme.



(*c*) *Vinyl Ether Alkylations*. Many strategies in this category start with one intact ring and then add the components of the second ring followed by acid-catalyzed spirocyclization. A near-antithetic version of the simple addition of nucleophiles to lactones is alkylation of α-lithiated vinyl ethers. This is exemplified by the work of Amouroux[129] in which dihydropyran was deprotonated by n-BuLi to **343** and then alkylated with alcohol-protected iodides to **344** (Scheme 60). Deprotection of the alcohol led to ring closure to form either the spiro[4.5] or spiro[5.5] systems (**345**).

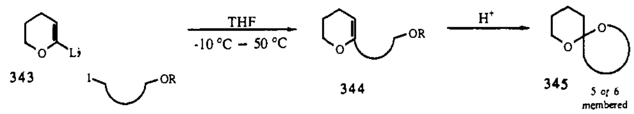
Boeckman[130] originally described this approach with a single example in 1978. This was later used in a synthesis of calcimycin[131] as shown in Scheme 61. The two optically active fragments (**346** and **347**) were coupled via the carbanion of **346** generated by tin–lithium exchange. The adduct **348** could be cyclized directly to **350a**. In a clever ring closure, the vinyl ether **348** was treated with the Simmons–Smith reagent to give diastereomeric cyclopropanes **349**. When this mixture was treated with 2 equiv of p-TsOH/benzene, the cyclopropane presumably opens to an oxonium ion, allowing spirocyclization to occur to **350b**. As seen in other calcimycin work, this methyl group equilibrates to the thermodynamically favored equatorial position.

Kocienski[132] utilized the cuprate of α-lithiodihydropyran derivatives in epoxide-opening reactions to synthesize hydroxylated spiroketals (Scheme 62). This strategy was used in the synthesis of talaromycin B in which the two racemic pieces **351** and **352** were connected to give **353** as a 1:1 mixture of diastereomers which was not purified but was cyclized directly to give racemic **100** in 24% overall yield for the two steps. 4-Epitalaromycin B (**102**) was obtained in 14% yield. The process was further exploited in a synthesis of two milbemycin β_3 spiroketal intermediates **357** by coupling optically active precursors **354** and **355** (Scheme 63). Cyclization again proceeded to give the predictable product **357** in which steric effects are minimized in a bisaxial arrangement of the spiro C–O bonds. The strategy has also been used in the synthesis of *Dacus oleae* pheromones.[85] Kurth[89] combined α-lithiodihydropyran with the Diels–Alder adduct **358** and treated the resulting mixture with aqueous HF to give a mixture of four spiroketals (**359a–d**) in a model study directed toward phyllanthoside and breynolide synthesis, depicted in Scheme 64.

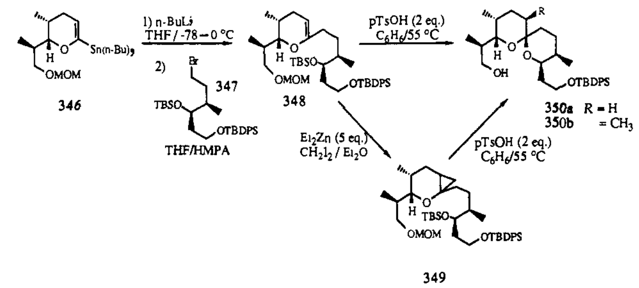
Chavdarian[133] recently reported that 5-oxo-1,7-dioxaspiro[5.5]undecanes **362** can be prepared via condensation of 2-lithiodihydropyran with γ-butyrolactones in a two-step process. The acid-catalyzed cyclization proceeded somewhat slowly, although with excellent yields. In substituted cases (R_1, $R_2 \neq$ H), a major isomer was commonly produced, possessing the predictable conformation **363** (Scheme 65).

(*d*) *Olefination Processes*. A related approach involves the implementation of Wittig, Horner–Wittig, or other olefination processes using intact tetrahydropyran- or tetrahydrofuran-containing ylide or carban-

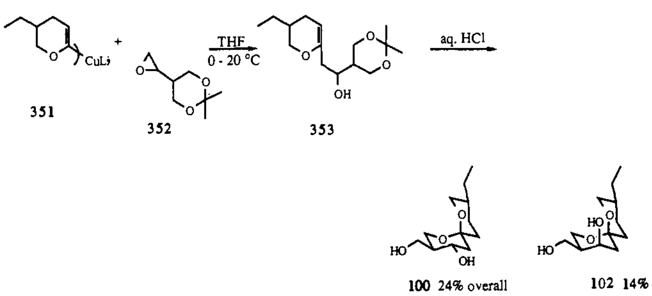
SCHEME 60



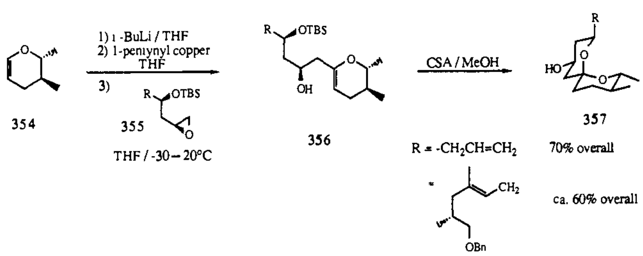
SCHEME 61



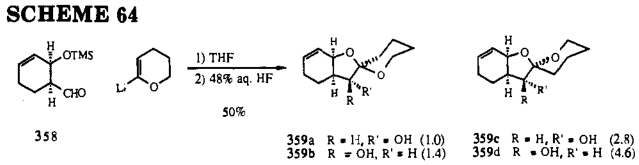
SCHEME 62



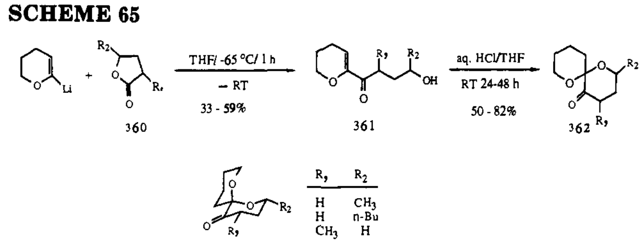
SCHEME 63



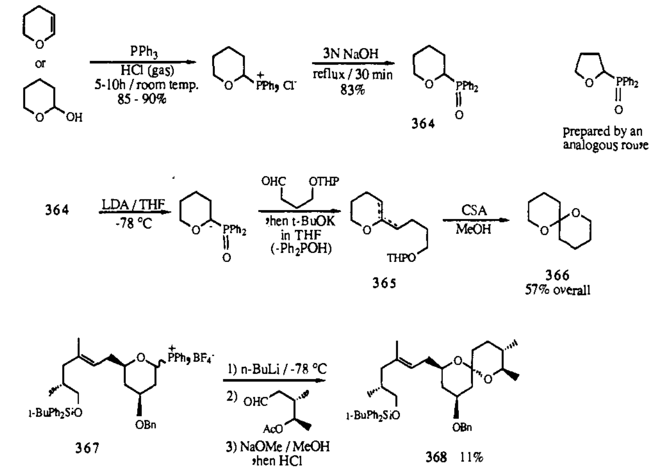
SCHEME 64



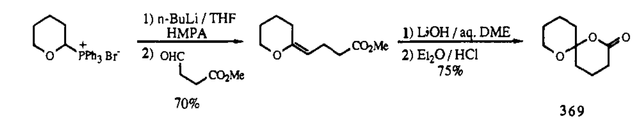
SCHEME 65



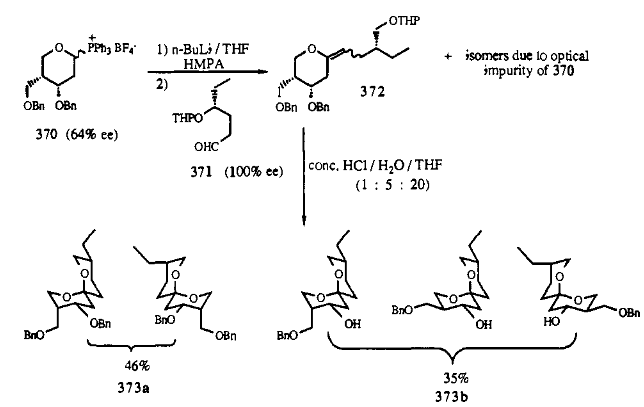
SCHEME 66



SCHEME 67



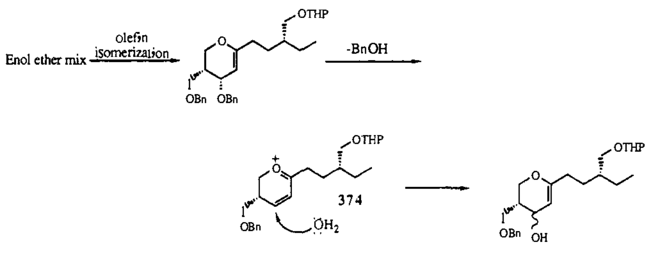
SCHEME 68



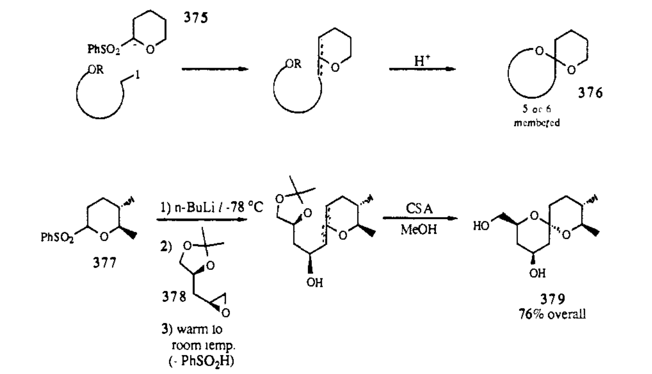
ionic reagents. Ley[134] pioneered the use of several reagents in this category, including phosphine oxides of general structure **364**, made by the process shown in Scheme 66. Deprotonation with LDA at low temperature followed by treatment with γ-hydroxy-protected aldehydes provides a mixture of vinyl ethers **365** after elimination of diphenylphosphine oxide. Alcohol deprotection and spirocyclization provided the parent spiroketal **366** in good overall yield. The same group also carried out Wittig-type olefinations utilizing phosphoranes generated from tetrahydropyranyl phosphonium salts. The olefination cyclization sequence starting from the phosphonium salt **367** provided the milbemycin spiroketal subunit **368** in 11% yield.[135] Yields have ranged up to 40% with this two-step protocol in similar substrates. Falck[136] described the same process to prepare **366** in addition to the spirolactone **369** using ylide chemistry (Scheme 67). (−)-Talaromycins A and B were synthesized by Mori[137] using the optically impure (64% ee) phosphonium salt **370** and the optically pure aldehyde **371** (Scheme 68). The resulting olefinic product **372** was obtained as a mixture of several enol ether isomers, as expected. Cyclization of the mixture resulted in five spiroketals in which apparent isomerization of the carbinol carbon had occurred. This was rationalized by formation of a vinylic oxenium ion **374** which was nonselectively trapped by water (Scheme 69). This phenomenon was earlier observed by the same workers in a simpler system.[138]

The corresponding sulfonyl-stabilized carbanions have also been used in the olefin-forming step. Several simple spiroketals were prepared by a general method

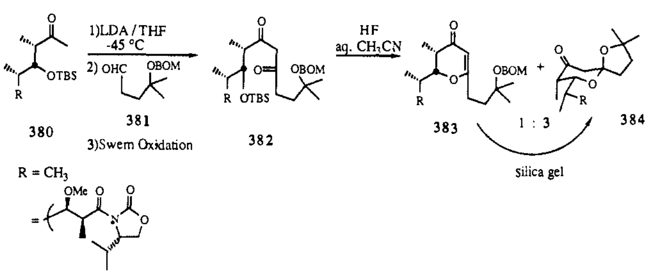
SCHEME 69



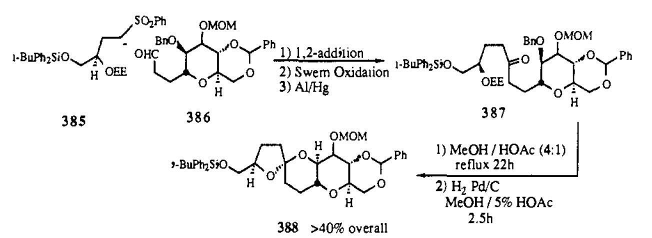
SCHEME 70



SCHEME 71



SCHEME 72

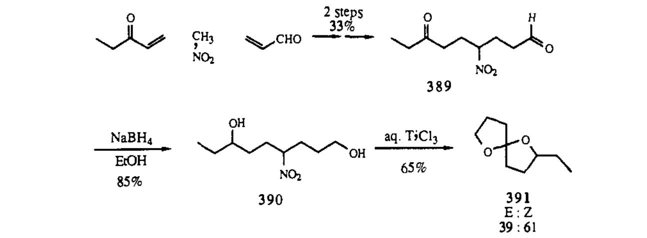


described by Ley[139] and shown in Scheme 70 (375–376). In addition, the optically active sulfone 377 (as its anion) was used to open the epoxide 378, resulting in a mixture of olefins after elimination of $PhSO_2H$. Anomerically determined spirocyclization of this substance provided the spiroketal 379 in good yield.[140]

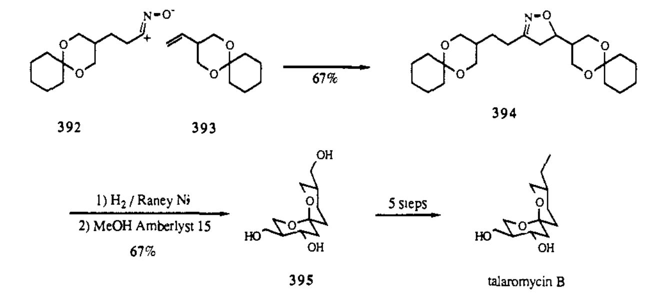
(*e*) *Miscellaneous C_{spiro}–C_α Strategies.* Walba[81] added the enolate of ketone 380 to the aldehyde 381 followed by oxidation to give the β-diketone 382. Ring closure of this substance produced the monensin spiroketal model 384 along with the dihydro-4-pyrone 383, which further closed to 384 upon treatment with silica gel (Scheme 71). In this case, reaction of the enolate of 380 with lactones and equivalents was not successful.

The α-sulfonyl carbanion 385 was combined with the aldehyde 386 to give an intermediate alcohol which was oxidized and desulfurized to give ketone 387 (Scheme 72). Cleavage of the protecting groups and cyclization led to the spiroketal 388 as part of Isobe's synthesis of okadaic acid.[141]

SCHEME 73



SCHEME 74

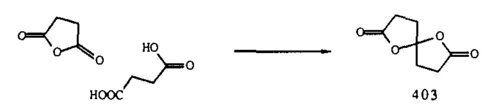


Rosini[142] utilized nitromethane as a multiple coupling reagent in a synthesis of (*E*)- and (*Z*)-chalcogran. Sequential conjugate additions of nitromethane to ethyl vinyl ketone and then to acrolein provided the dicarbonyl compound 389 (Scheme 73). Reduction to the diol 390 was effected with $NaBH_4$. Treatment with $TiCl_3/H_2O$ in a modern version of the Nef reaction provided racemic chalcogran (391) as a 39:61 *E*/*Z* mixture.

Kozikowski[143] utilized 1,3-dipolar cycloaddition of nitrile oxides to olefins as a method of establishing key C–O and C–C bonds of talaromycin B (Scheme 74). Cycloaddition of the nitrile oxide 392 (generated via the sodium hypochlorite oxidation of an oxime) to the olefin 393 gave the adduct 394 in 67% yield. Reductive cleavage of the N–O bond and hydrolysis produced a β-hydroxy ketone which could be spirocyclized to the racemic talaromycin B precursor 395.

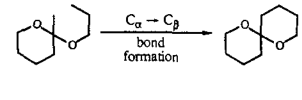
An early synthesis of 1,6-dioxaspiro[4.4]nonanes was described by Burgstahler[144] (Scheme 75) in 1973, which involved the addition of the dianion of 2-methyl-3-butyn-2-ol 396 to ethyl formate generating the triol 397. This served as the branch point intermediate in the synthesis of 400–402. Note that the oxidation of 399 or 398 resulted in in situ closure of the rings to 400 and 402, respectively.

In a pre-1900 paper, Volhard described the preparation of the spirobislactone 403 from succinic anhydride and succinic acid.[145]

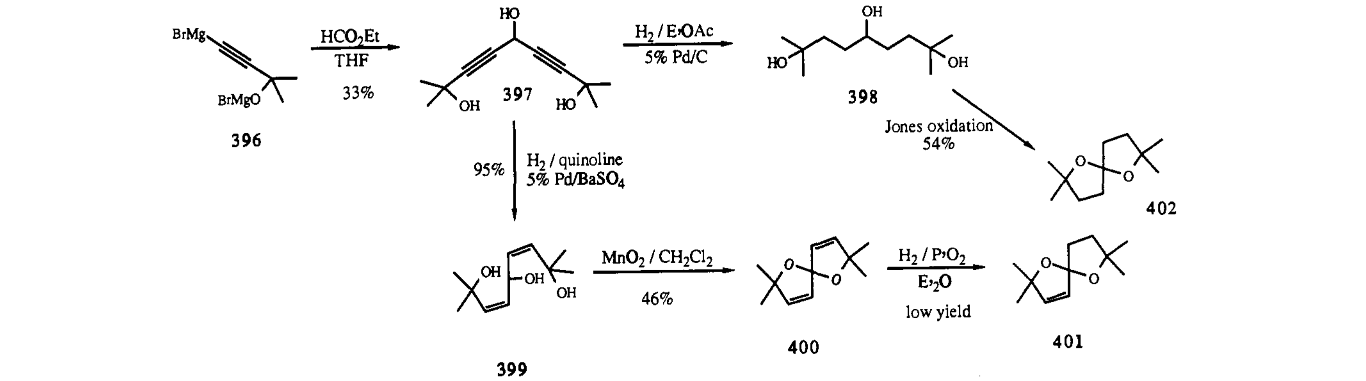


2. C_α–C_β Bond-Forming Strategies

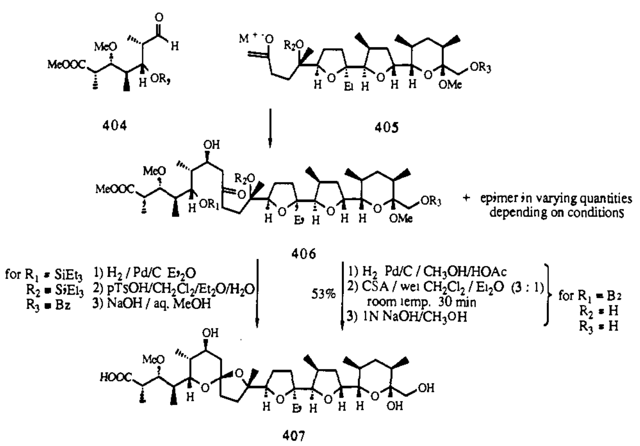
Most of the strategies in this category involve the use of enolate anions or an equivalent where the carbonyl group is the *pro*-spiro carbon atom.



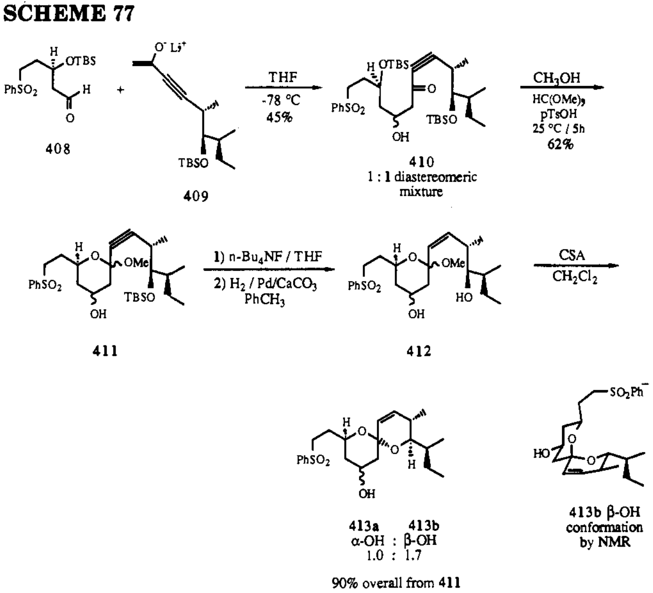
SCHEME 75



SCHEME 76



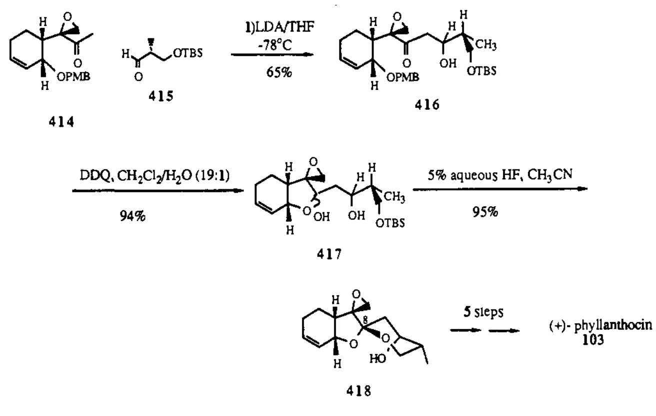
SCHEME 77



(a) *Enolate-Carbonyl* (*Aldol*) *Condensation.* Taking advantage of the developing improvements in directed aldol condensation at the time, Still[146a] and Kishi[146b] connected two large fragments (**404** and **405**, Scheme 76) late in their respective monensin syntheses to produce **406**. The dihydroxy ketones generated from **406** were cyclized to form the 1,6-dioxaspiro[4.5]decane ring system of the natural product (**407**), with the only structural differences being the identities of protecting groups. Both groups obtained a single spiroketal isomer upon ring closure corresponding to that in monensin.

Hirama[147] treated the aldehyde **408** (Scheme 77) with the ketone enolate **409** and obtained a 1:1 diastereomeric mixture of aldol adducts **410** which was hydrogenated to the seco compound **412**, still as a mixture of carbinol diastereomers. Closure of the second ring to **413** occurred with good induction at the spiro carbon, but still gave a 1.7:1 β-OH:α-OH ratio of carbinol isomers. The ratio could be improved to 4.1:1 by Collins oxidation of the mixture followed by $LiAlH_4$ reduction. The structure and conformation of the major product (**413**, β-OH) were determined by ^{1}H NMR.

SCHEME 78

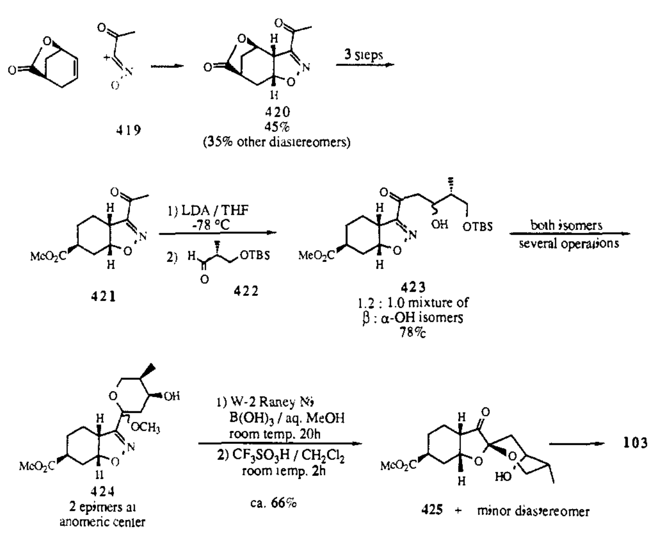


Burke[148] proposed a convergent enantioselective synthesis of (+)-phyllanthocin, relying upon a "Cram-cyclic" stereocontrolled aldol condensation of the enolate derived from optically active epoxy ketone **414** and optically active aldehyde **415** (Scheme 78). The silyl cleavage of hemiacetal **417** occurred with concomitant ring closure with complete stereoselectivity at C8. Finally Rh(I)-catalyzed hydroformylation followed by a few routine transformations yielded the desired target **103**.

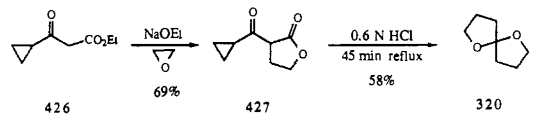
In another approach to phyllanthocin, Martin[149] added the enolate of ketone **421** (Scheme 79) to the aldehyde **422**, resulting in a 1.2:1.0 mixture of diastereomers **423**, both of which could be used to eventually produce the glycoside **424**. The isoxazoline ring of **424** was reductively cleaved and hydrolyzed to the corresponding β-hydroxy ketone, which was directly spirocyclized to **425** possessing the correct configuration of stereogenic centers for conversion to phyllanthocin **103**. The cyclization was stated to be a kinetic process, although no evidence for this belief was given.

(b) *Enolate Alkylations.* β-Keto ester alkylations have been used by a number of groups to establish one of the C_α–C_β bonds. This is exemplified by a method dating back to 1956 by Hart[150] in which the β-keto ester **426** was alkylated with ethylene oxide, resulting in the

SCHEME 79

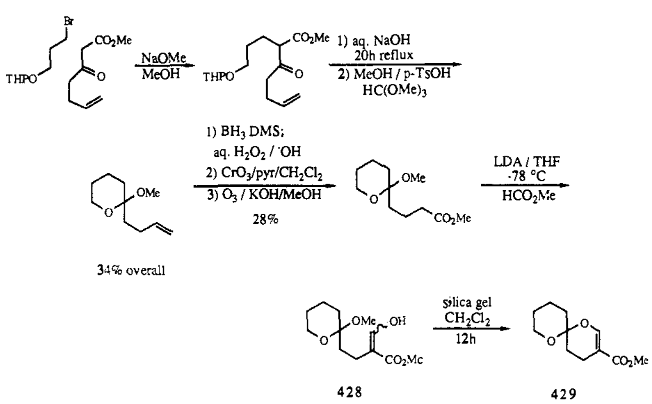


lactone 427. Treatment with aqueous HCl provides the parent spiroketal 320 in 58% yield. In this and many of the following approaches the ester or lactone carbonyl is eventually extruded, and the ketone carbonyl is the *pro*-spiro carbon.

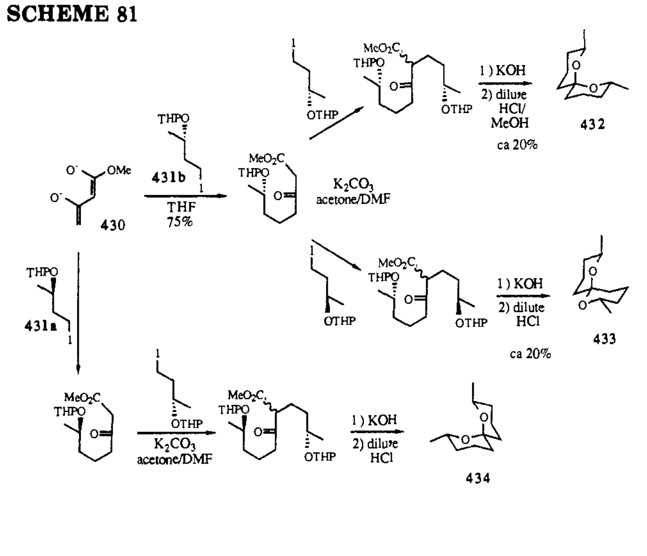


Deslongchamps[151] described the synthesis of unsaturated spiroketal 429 by a classical acetoacetic ester approach (Scheme 80). Note the closure of the malonic

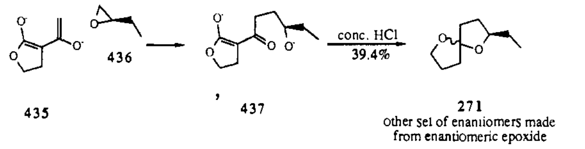
SCHEME 80



SCHEME 81



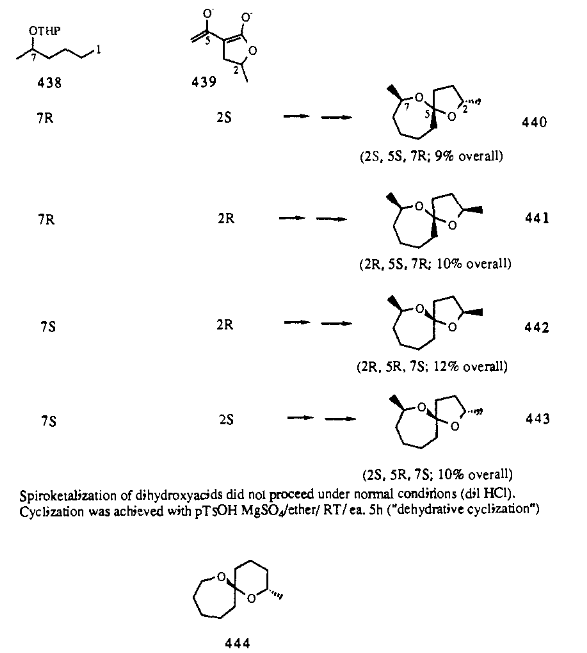
semialdehyde 428 to form the final ring. Mori[152] effectively utilized (Scheme 81) the dianion of ethyl acetoacetate 430 to construct optically pure insect pheromone spiroketals 432–434 by sequential alkylation with optically pure alkyl halides 431a and 431b containing stereogenically pure *pro*-carbinol centers. The approach is not limited to β-keto esters. By combining the α-acyl lactone dianion 435 and the optically active



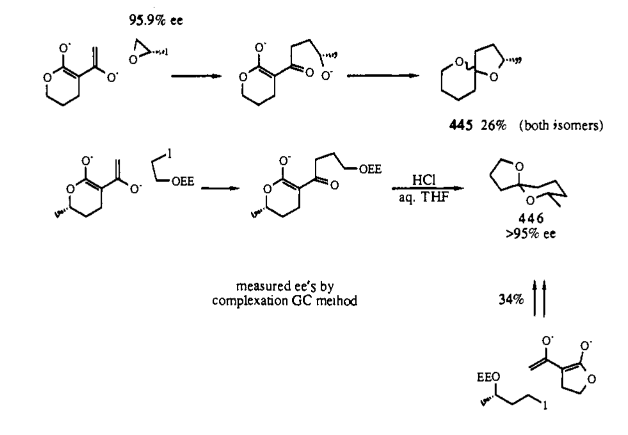
epoxide 436, the addition product 437 was formed. Treatment of this anionic intermediate with concentrated HCl effected lactone opening, decarboxylation, and spirocyclization (not necessarily in that order) to give a mixture of two epimeric spiroketals 271 optically homogeneous at the carbon bearing the ethyl group.[153] The opposite sets of enantiomers were also made from the enantiomeric epoxide. In a related approach (Scheme 82), four of the eight possible isomers of 2,7-dimethyl-1,6-dioxaspiro[4.6]undecane (440–443) have been synthesized by starting with optically active alkyl halides 438 and lactones 439.[154] The related metabolite 444 was synthesized by using similar technology.[155] Schurig[156] described essentially the same chemistry (Scheme 83) in the δ-valerolactone series to synthesize the spiro[4.5] systems in 445 and 446. The enantiomeric excess of the products was determined by a complexation GC method developed by these workers.

Julia[157] took advantage of the double deprotonation of 2,5-pentanedione (447) to construct the milbemycin–avermectin intermediate 450 (Scheme 84). The cyclic β-diketone dimedone (451) was used by Pettit[158] to construct the model compound 455 (Scheme 85) to investigate the reductive ring opening of spiroketals related to steroidal sapogenins. After alkylation to 452, vigorous hydrolysis and esterification led to 453, which was converted to 455 by a standard sequence. An

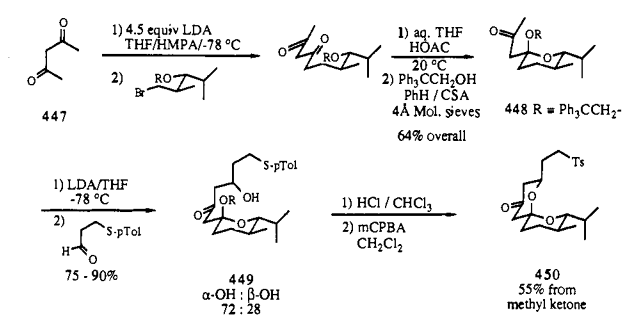
SCHEME 82



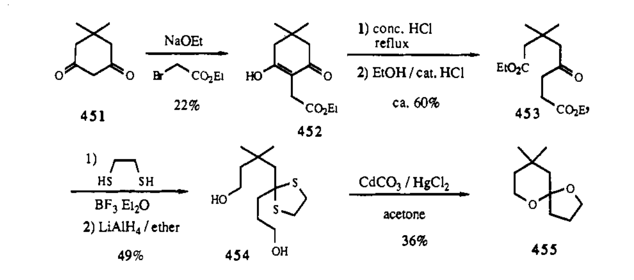
SCHEME 83



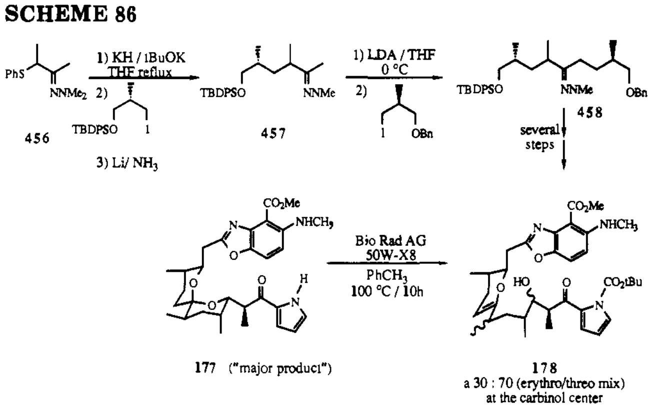
SCHEME 84



SCHEME 85



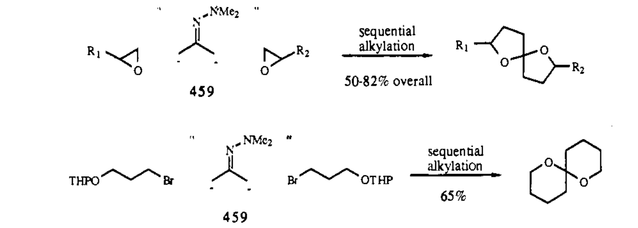
SCHEME 86



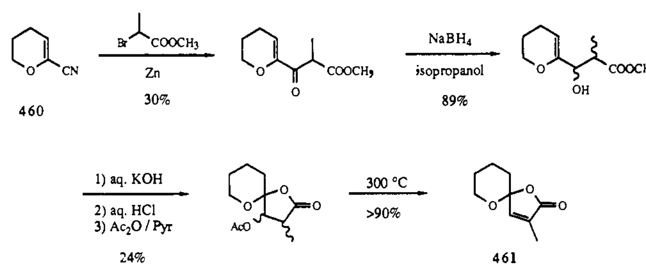
earlier version of this approach was described by Stetter and Rahout.[159]

(c) *N,N-Dimethylhydrazone Alkylations.* Evans[160] used sequential dimethylhydrazone alkylation to produce the acyclic precursor to the calcimycin spiroketal as shown in Scheme 86. This differs somewhat from an earlier study from this laboratory in which a model spiroketal precursor was synthesized by a C_{spiro}–C_α strategy using a sulfur-stabilized carbanion to connect two large structural fragments (211 → 214). Note again the equilibration of the C_α-methyl group to the equatorial position during the spirocyclization step (178 → 177). In later work, both Enders[161] and Mitra[162] described the sequential alkylation of acetone dimethylhydrazone (**459**) with epoxides and alkyl halides respectively in the synthesis of simple spiroketals (Scheme 87).

SCHEME 87



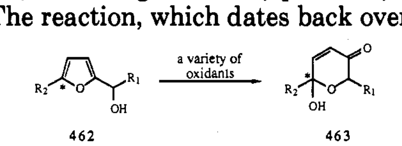
SCHEME 88



(d) *Miscellaneous Processes.* In an early report, Piancatelli[163] used the Reformatsky reaction of methyl α-bromopropionate/Zn with the nitrile **460** as the key bond-forming step in the synthesis of the unsaturated spirolactone **461**, as described in Scheme 88.

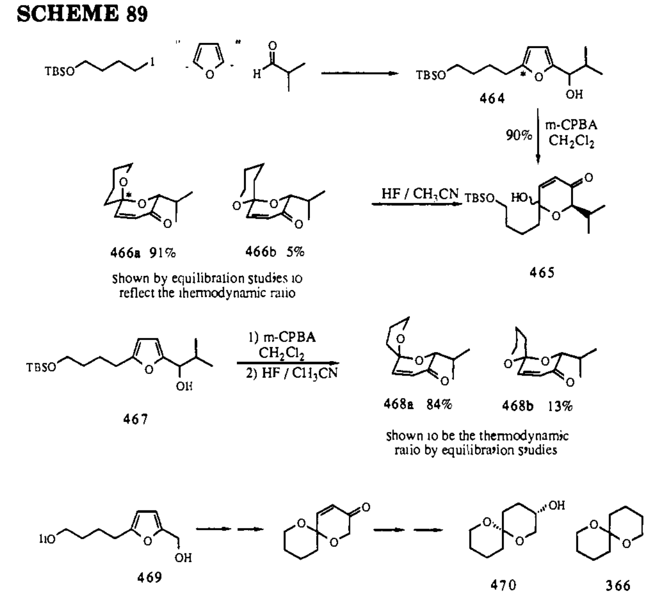
3. Oxidation–Reduction of Furan Derivatives

The oxidation–rearrangement of 2-furyl carbinols **462** to dihydropyranones **463** can be effected by a number of reagents, including bromine, peracids, PCC, and others. The reaction, which dates back over 80 years,

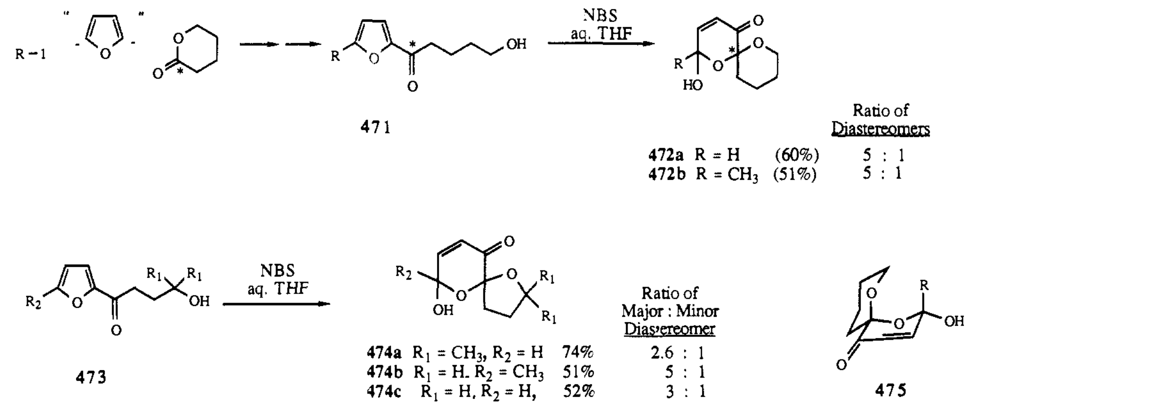


is occasionally "rediscovered" and a new chapter is added to the chemistry of furan. DeShong[164] effectively utilized this oxidation in spiroketal synthesis (Scheme 89). Using the facile α-metalation and alkylation of

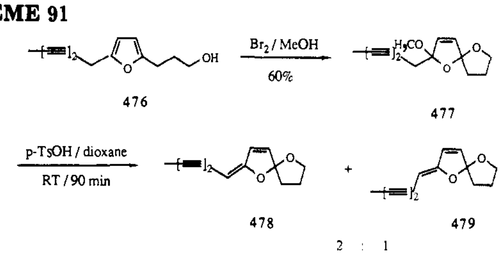
SCHEME 89



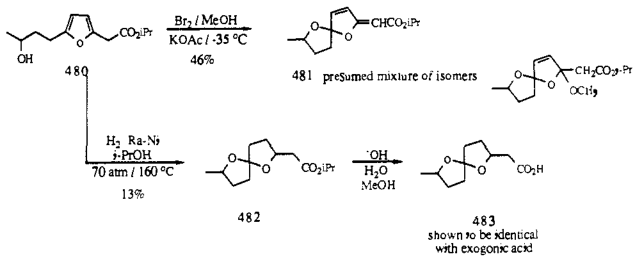
SCHEME 90



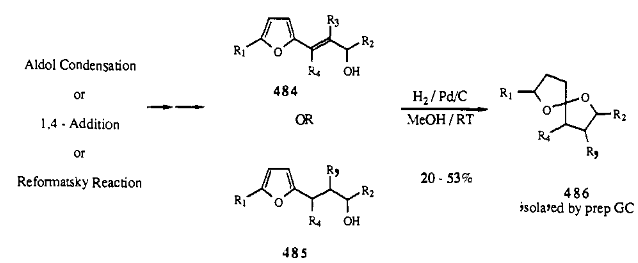
SCHEME 91



SCHEME 92



SCHEME 93



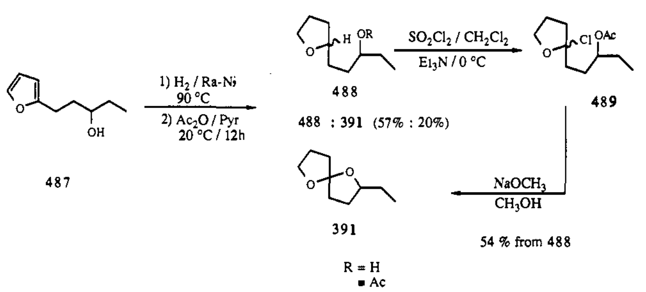
furan, one can readily assemble appropriately functionalized 2-furyl carbinol precursors. Oxidation–rearrangement of **464** with *m*-CPBA gave the hemiacetal **465**. Desilylation and spirocyclization were accomplished with HF in acetonitrile to provide the thermodynamic mixture of spiroketals **466a,b**. The analogous precursor **467** gave rise to the spiro[4.5] derivatives **468a,b**, also a thermodynamic mixture favoring the predictable isomer **468a**. The insect pheromones **470** and **366** were synthesized in racemic form with this technology.

To synthesize the more highly oxygenated spiroketals of the aplysiatoxin–oscillatoxin class, Perron[165] has described the oxidation–rearrangement of 2-furyl ketones of general structure **471** (Scheme 90). These substrates are also easy to assemble by sequentially alkylating furan first with an alkyl halide and then with a lactone providing **471**. These were found to exist solely in the open-chain form in dilute solutions of typical NMR solvents. Treatment of **471** with 2 equiv of *N*-bromosuccinimide in aqueous THF provided a mobile mixture of two "hemispiroketals" **472a,b**. The major isomer was found to possess conformation **475** by ^{1}H NMR NOE and lanthanide induced shift ^{1}H NMR spectroscopy, while the minor isomer was found to possess an axially disposed hydroxyl group. The corresponding spiro[4.5] systems **474** could be constructed with γ-butyrolactones. This strategy was subsequently used in the production of trioxadispiroketals (vide infra).

Bohlmann[166a] developed a method for the synthesis of spiroketal enol ethers of the type described in section II.A.2 based on classical furan oxidation. The furan derivative **476** was constructed by sequential metalation and alkylation of furan (Scheme 91). Treatment of **476** with bromine in methanol induces a twofold ring closure, presumably via keto alcohol intermediates leading to the formation of the desired acetylenic spiro[4.4] ring systems **477**. After elimination of methanol, both *Z* and *E* isomers **478** and **479** obtained are identical with the nature spiroketal enol ethers. A related entry into spiroketal enol ethers was described by Dedek.[166b] Treatment of the furan alcohol **480** with bromine in methanol produces a poorly characterized intermediate which, on distillation, loses methanol to produce the vinyl ether **481** in moderate yield as a mixture of diastereomers (Scheme 92).

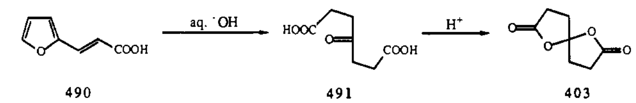
These same workers also reported the reductive cyclization of the furan derivative **480** yielding the saturated spiroketal **482** in low yield. This substance was saponified to **483** and shown to be identical with exogonic acid, a degradation product obtained by the alkaline hydrolysis of the resin of *Ipomea operculata* (Brazilian jalap).[167] This reductive cyclization was first reported in 1934 by Burdick and Adkins as a general method for the synthesis of 1,6-dioxaspiro[4.4]nonanes via hydrogenation of acrolein furan adducts in the presence of Raney nickel.[168a,b] Subsequently, Alexander[168c] and Ponomarev[168d] synthesized a variety of spiroketals via the hydrogenation of γ-furylalkanols over a nickel catalyst at 120–150 °C. In order to study the mass spectral fragmentation of 1,6-dioxaspiro[4.4]nonanes related to chalcogran, Francke[169] used a similar partial reduction of 3-(2-furyl)propanols leading to several spiro[4.4]ketals in 20–53% yield (Scheme 93). Catalytic hydrogenation of **484** or **485** (prepared in a

SCHEME 94



number of ways) with Pd/C in methanol led to the spiroketals **486** in a nonstereoselective fashion and were isolated by preparative gas chromatography. A furan reduction was also utilized by Torgov[170] in a synthesis of chalcogran, described in Scheme 94. Hydrogenation–cyclization resulted in **391** as well as the product of complete furan ring saturation, **488**. However, **488** could be converted to **391** via **489** in a process involving regiospecific α-chlorination and subsequent solvolytic ring closure.

In 1890 Volhard reported a fairly simple synthesis of the spirobislactone **403** via alkaline hydrolysis of 2-furylacrylic acid (**490**), producing the keto diacid **491**, which was cyclized with acid to **403**.[171]



4. Miscellaneous Processes

The methods in this category are not easily placed in any of the preceding categories in a phenomenological sense. While it is easy to imagine the generality of most of the following protocols, this has not been demonstrated in most cases.

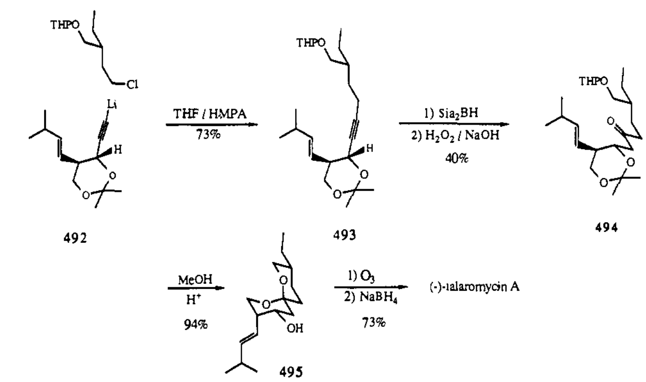
Midland[172] used the regiospecific hydroboration of alkyne **493** to produce the spirocyclization substrate **494**, which eventually culminated in a stereospecific synthesis of (−)-talaromycin A (Scheme 95). In this clever approach, a terminal alkyne served as a latent synthon for an acyl anion.

Grieco[173] synthesized calcimycin according to the design shown in Scheme 96. Final closure was acid catalyzed and did not take advantage of the easy equilibration of the indicated α-methyl group as dis previous workers. In a synthesis of the monensin spiroketal, Ireland[80] converted the bicyclic ketal **496** to the spiroketal **497** using a standard series of manipulations (Scheme 97). Before successfully realizing the synthesis of milbemycin β_3, Smith[174] discarded the approach shown in Scheme 98 due to lack of stereoselectivity in the reduction of the ketone **500**.

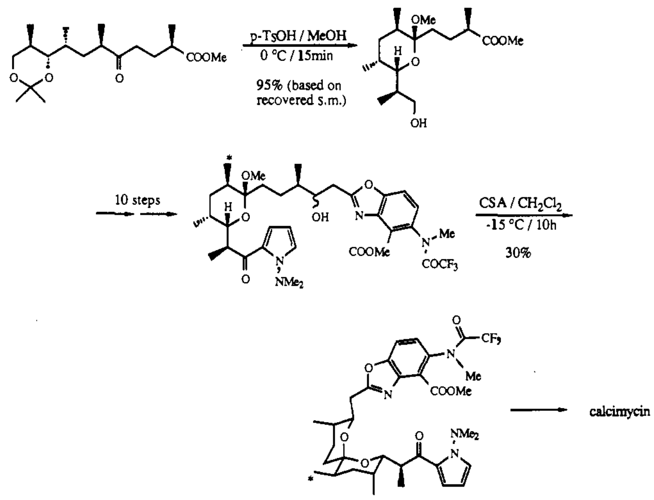
Kocienski[175] has shown that allenic ethers **502** and **504** (Scheme 99) produced by base-induced alkyne isomerizations or other processes are regiospecifically protonated and undergo cyclization to the unsaturated spiroketal **503**. This method allows entry into unsaturated spiroketals of general structure **507** without production of furans **508** observed with other methods.

Gonzalez-Sierra[176] described the partial synthesis (Scheme 100) of metabolites from plants of the genus *Grindelia*. (+)-Methyl strictanonate (**512**) was produced from epoxide **509**, readily available from grindelic acid (**513**), the most abundant diterpene acid from

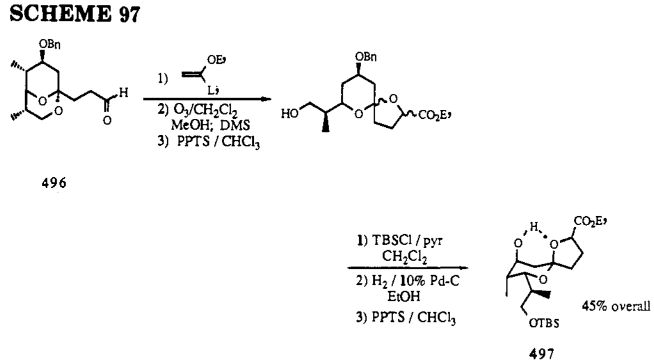
SCHEME 95



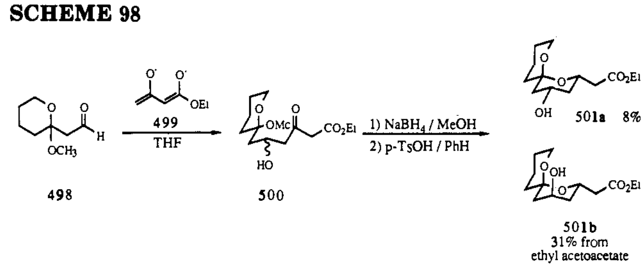
SCHEME 96



SCHEME 97

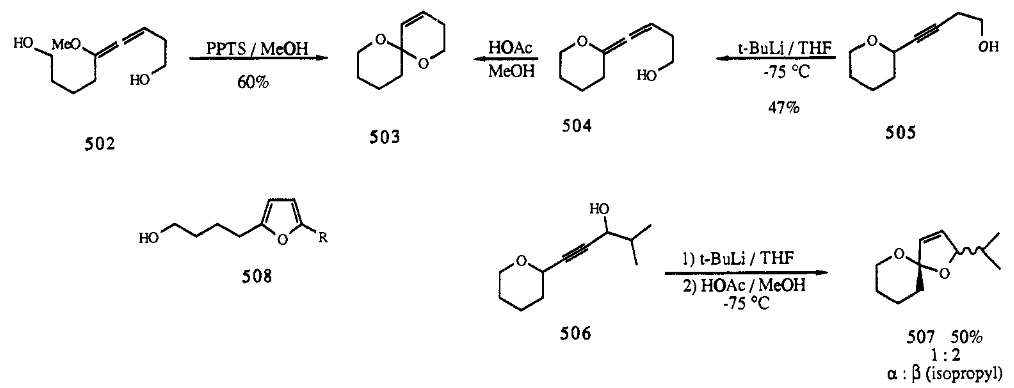


SCHEME 98

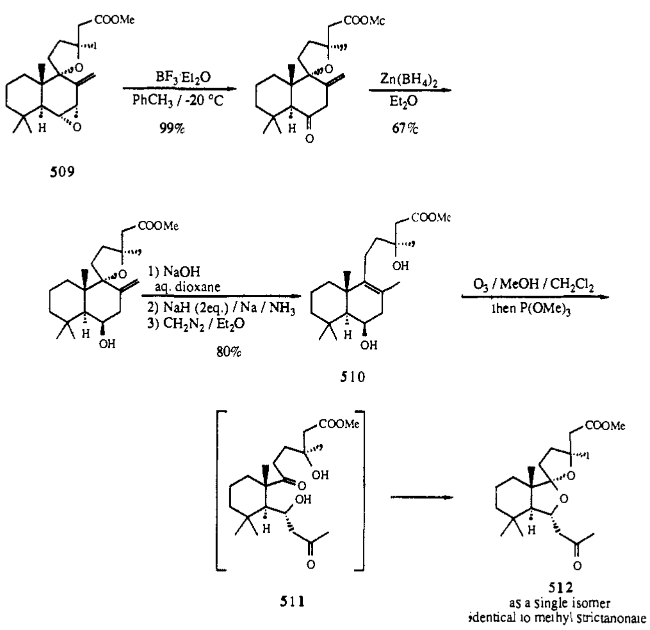


several *Grindelia* species.[177] The route involves the cleavage by ozonolysis of the olefin **510** to the dihydroxy ketone **511**, which closes to methyl strictanonate (**512**) as the only spiroketal isomer observed. In a second partial synthesis,[177a] grindelic acid (**513**) was converted to the spiroketal **516** using a similar strategy (Scheme 101). Oxidative cleavage of olefin **514** led to hemiacetal

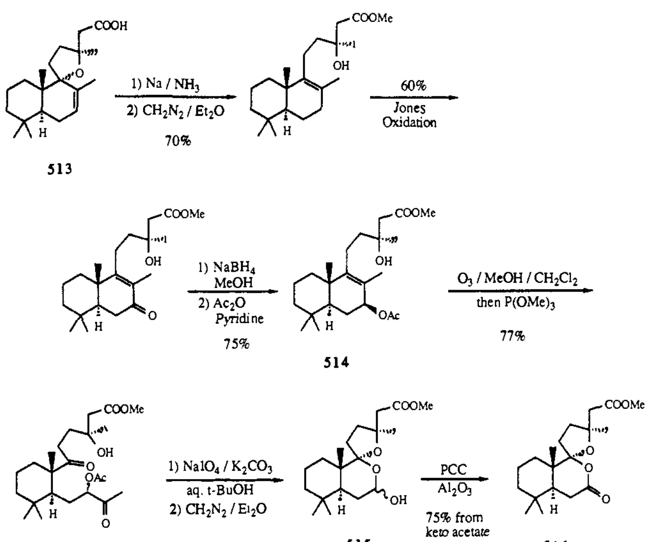
SCHEME 99



SCHEME 100



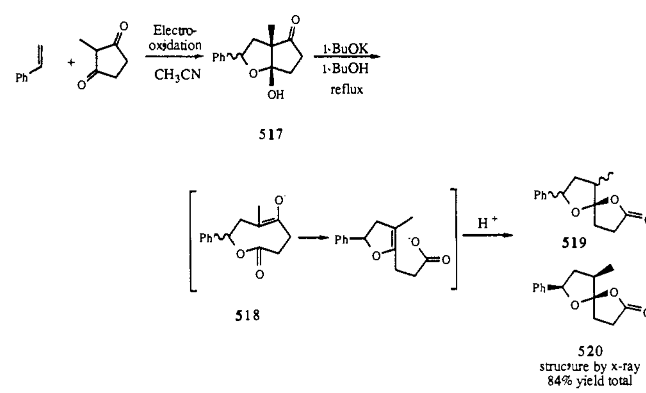
SCHEME 101



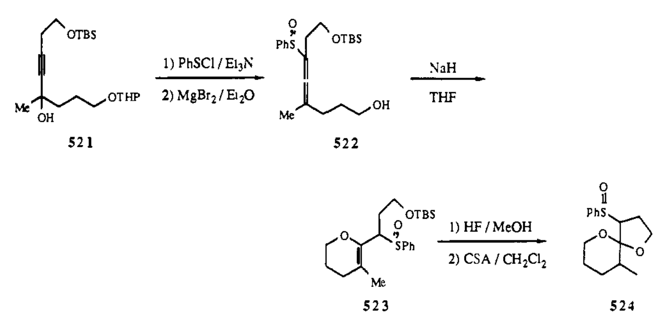
515, which was oxidized with PCC to the spirolactone 516, shown to be identical with the methyl ester of grindelistrictic acid.

Isoe[178] generated the spiro[4.4] ring system using an electrooxidation method. It was found that a general [3 + 2] cycloaddition takes place between olefins and

SCHEME 102



SCHEME 103

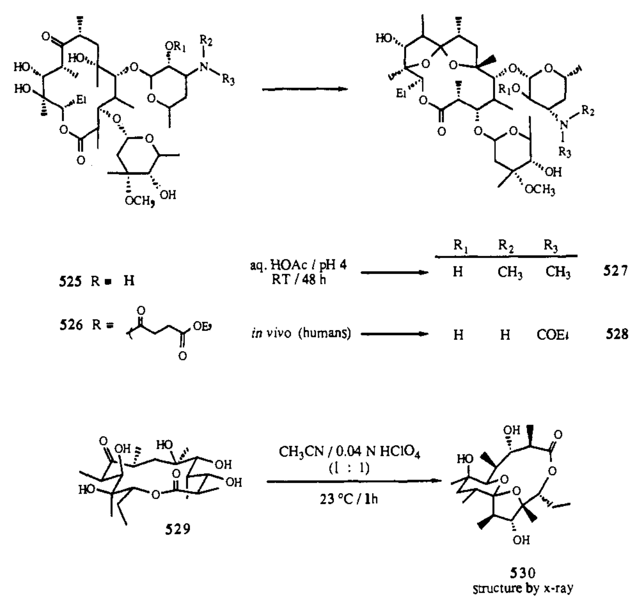


1,3-diketones when the diketone is electrochemically oxidized, resulting in bicyclic adducts such as 517 (Scheme 102). When 517 is treated with *t*-BuOK/*t*-BuOH followed by an acidic workup, spirolactones 519 and 520 are formed, the latter confirmed by X-ray crystallography. A mechanism involving the eight-membered lactone 518 has been postulated for this transformation.

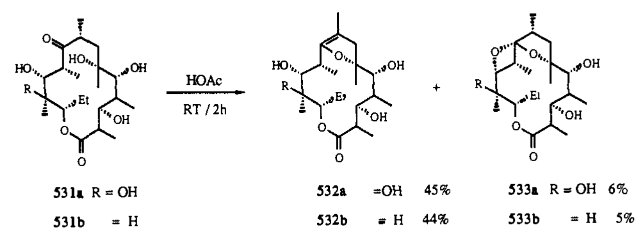
The key step in Parsons' strategy[179] involves intramolecular conjugate addition of alkoxides to allene sulfoxides, described in Scheme 103. When alcohol 522 was treated with 1 equiv of NaH in ether, cyclization to the dihydropyran derivative 523 occurred. Removal of the silyl protecting group and acidic cyclization yielded spiroketal 524.

Certain macrolide antibiotics undergo transannular ring closure to spiroketals. This has been studied most intently in the erythromycins, although other macrolides undergo the ring closure as well.[180a] Erythromycin A and its aglycone (Scheme 104) undergo closure to spiroketals of both the spiro[4.4] (527)[180b] and spiro[4.5] type (530).[181] The transformation 526 → 528 occurs when erythromycin A ethyl succinate is metabolized in

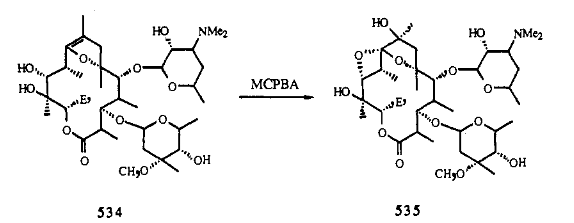
SCHEME 104



SCHEME 105



SCHEME 106



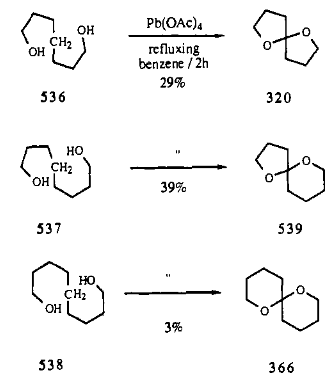
humans.[182] There are reports that erythronolides A and B (**531a,b**, the aglycones of erythromycins (Scheme 105)) undergo closure to rare examples of 1,5-dioxaspiro[3.4]octane derivatives **533a,b** under very mild conditions in low yield.[183] A similar, but oxidative, spirocyclization (**534** → **535**) was reported by Zamojski[184] to take place when **534** was treated with *m*-CPBA (Scheme 106).

B. Processes Not Involving Internal Ketalization

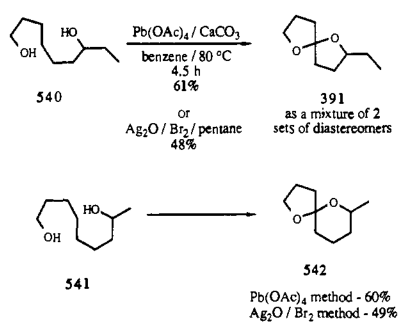
1. C_{spiro}–O Bond Formation

(*a*) *Oxidation via Alkoxy Radical Processes.* (*i*) *Hypohalite Method.* Oxidation of methylenes and especially of activated methines can be carried out with a number of oxidizing agents and involves the facile transfer of hydrogen atoms to alkoxy radicals five or six atoms away. The reaction was recently reviewed[185] and is relatively well characterized for a number of reagents.[186] In 1969, Micovic[187] described the oxidation of unbranched α,ω-diols to, among many other compounds, the parent [4.4], [4.5], and [5.5] spiroketal ring systems (Scheme 107). The yields were generally low

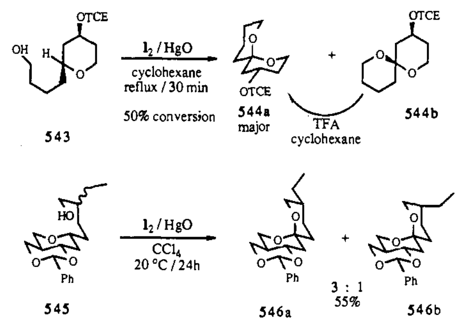
SCHEME 107



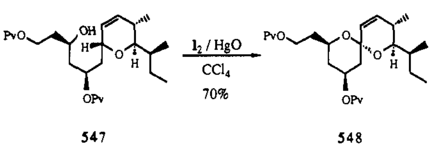
SCHEME 108



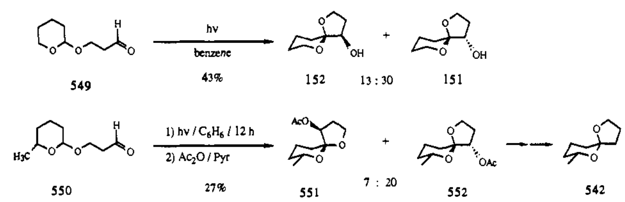
SCHEME 109



SCHEME 110

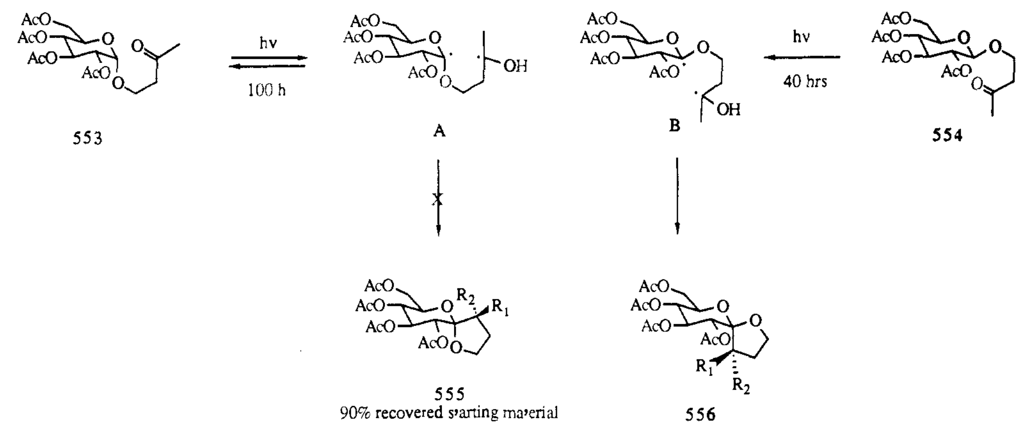


SCHEME 111



and other reaction products included various aldehydes, acetate esters, and nonspirocyclic ethers. Diols larger than nine carbons did not provide spirocyclic products. The method was applied to the synthesis of chalcogran by Cekovic.[188] 1,7-Nonanediol (**540**) was converted to **391** as a mixture of diastereomers by either $Pb(OAc)_4$ or the related Ag_2O/Br_2 (hypobromite) method (Scheme 108). The pheromone **542** was similarly produced from 1,8-nonanediol (**541**) and points to the

SCHEME 112

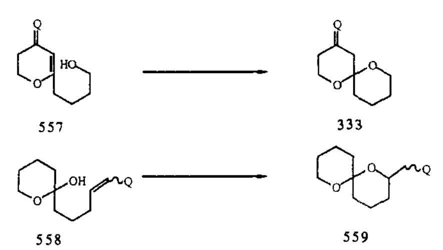


R_1	R_2	
OH	CH_3	33%
CH_3	OH	11%

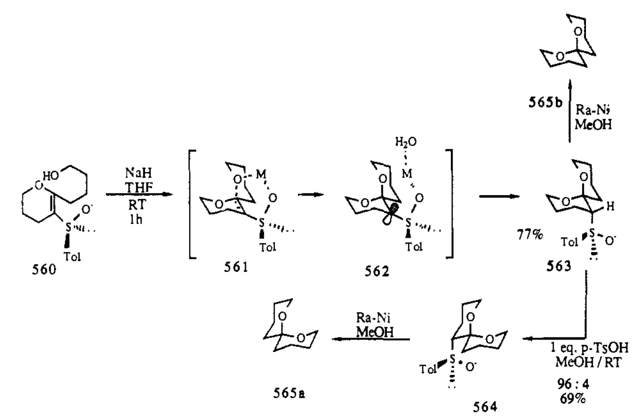
selectivity of the method. Kay[189] used the more highly functionalized substrates **543** and **545** to produce functionalized spiroketals **544** and **546a,b**, presumably via alkyl hypoiodite intermediates (Scheme 109). Compound **546a** eventually led to talaromycin B. Taking this lead, Danishefsky[190] used an analogous closure (**547** → **548**) to complete the spiroketal subunit of avermectin A_{1a} (Scheme 110). This latter case attests to the chemo- and regioselectivity of the hypoiodite and related methods for the formation of oxygen heterocycles.

(*ii*) *Norrish Type II Photoreaction.* An elegant approach to spirocyclic systems via photochemical cyclization was described by Descotes.[87] Irradiation of aldehydes such as **549** and **550** (Scheme 111) in which there are no hydrogens on the atom γ to the carbonyl and in which an acetal hydrogen is situated δ to the carbonyl results in hydrogen atom abstraction and cyclization of the resulting biradicals to mixtures of spiroketals in moderate yield. Such a Norrish type II photochemical process represents a general route to 1,6-dioxaspiro[4.5]decanes which has been applied to the synthesis of the *Paravespula vulgaris* pheromone **542**. Photocyclization of related sugar derivatives is highly dependent on the configuration of the anomeric center (Scheme 112) and on the nature of the substituents at C_2.[191] Indeed, the photolysis of β-glycosides,[192] β-mannosides,[193] and α-arabinopyranosides[192a] occurs rapidly with retention of configuration (**544**–**556**), while that of the α analogues (**553**) proceeds somewhat slowly, if at all.

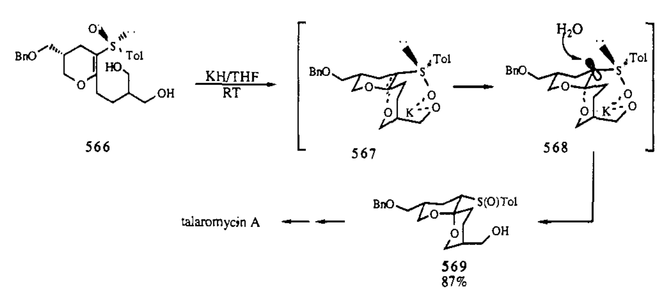
(*b*) *Ring Closures Involving "Conjugate Addition".* Several methods involve the use of apparent 1,4-addition of a hydroxyl group to an α,β-unsaturated ketone or other functional group in which either an anomeric (**558** → **559**) or a nonanomeric hydroxyl group (**557** → **333**) undergoes exocyclic closure to form the second ring. These kinds of reactions have frequently been



SCHEME 113



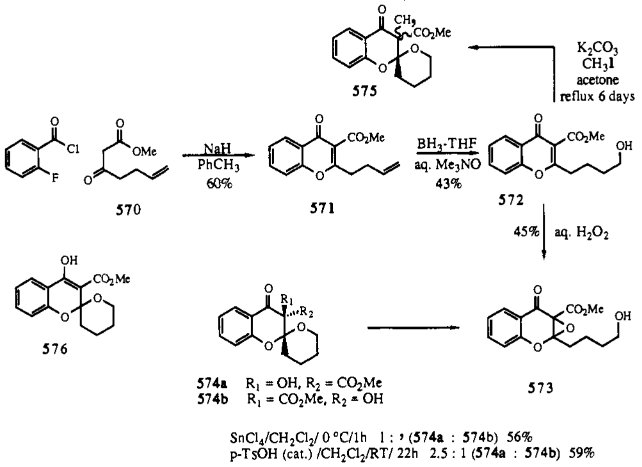
SCHEME 114



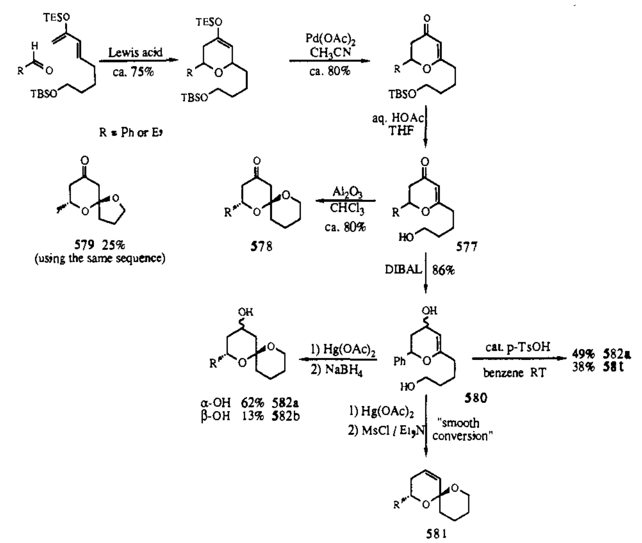
promoted by acid, which blurs the boundary between classical Michael addition and alternative ionic processes. These kinds of reactions are referred to as conjugate additions only in the formal sense.

Iwata[194] developed the use of chiral unsaturated sulfoxides in spiroketal synthesis (Scheme 113). Treatment of hydroxy sulfoxide **560** with NaH presumably generates alkoxide **561**, which undergoes stereospecific 1,4-addition and quenching to give the axial sulfoxide isomer **563**. The results have been rationalized by invoking chelated transition structures for both ring closure (**561**) and subsequent protonation (**562**). This appears to be a kinetic process since **563** is easily isomerized to the more thermodynamically stable **564** with TsOH/MeOH. Raney nickel desulfurization of **563** or **564** led to the enantiomerically pure **565b** and **565a**, respectively. This was extended to the substrate **566**[79] (Scheme 114), which was postulated to close via the tridentate transition structure **567**. In this case,

SCHEME 115



SCHEME 116



however, protonation (**567** → **568**) was rationalized differently than in the **561** → **562** conversion. The resulting product **569** was converted to talaromycin A.

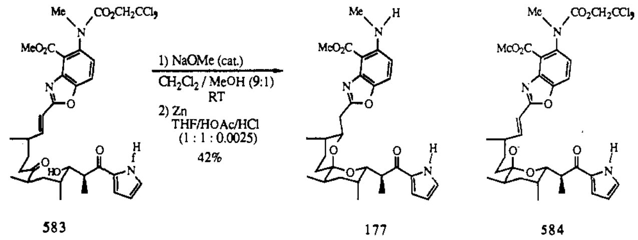
Wallace[195] used two methods for producing spiroketals from the 4-pyrone derivative **572** (Scheme 115). Treatment of **572** with K_2CO_3/CH_3I/acetone induced a slow ring closure to **575** postulated to be driven to completion by alkylation of the intermediate addition product **576** resulting from conjugate addition. Alternatively, closure was carried out by initial epoxidation of the olefin **572**. Acid-assisted opening of the epoxide by the alcohol proceeded to give a mixture of the two spiroketals **574a** and **574b**. Danishefsky[196] carried out a related spiroketalization of the pyrone **577** (Scheme 116) promoted by neutral alumina, reported to give solely the isomer **578** in 80% yield. The spiro[4.5] system **579** was produced via an analogous sequence of transformations. 4-Pyrone **577** was reduced with Dibal to the allylic alcohol **580**, which could be closed to spiroketals by (1) Ferrier rearrangement to a **581**/**582a** mixture, (2) oxymercuration–demercuration to **582a**,**b**, or (3) an oxymercuration–deoxymercuration sequence to give the unsaturated spiroketal **581**. This latter transformation had been previously reported by Descotes.[192b]

In the previously cited cases the ring closures have involved (at least in the formal sense) a nonanomeric hydroxyl group adding to a conjugated system. A number of examples exist that can be rationalized by the conjugate addition of an anomeric hydroxyl to a conjugated system. Kishi[197] treated to keto alcohol **583** with catalytic NaOMe in CH_2Cl_2/MeOH and obtained, after amine deprotection, the spiroketal **177**, depicted in Scheme 117. The reaction was postulated to occur via conjugate addition of the anomeric alkoxide **584**, although arguments can be made for **177** being either a kinetic or a thermodynamic product. Also, it is not clear that equilibration did not occur during the Zn/H^+ deprotection step.

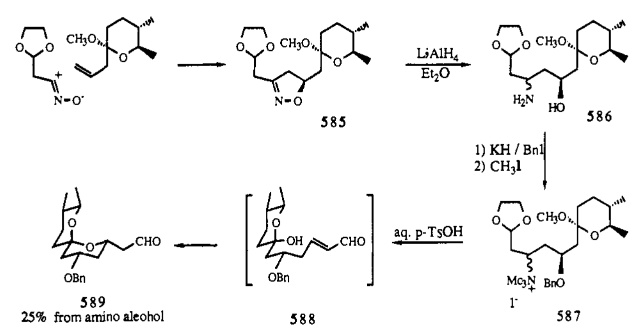
A similar closure was thought to occur during a step in a milbemycin β_3 synthesis reported by Smith[174] (Scheme 118). The enal precursor **588** was constructed by using 1,3-dipolar cycloaddition of a nitrile oxide to an olefin to give isoxazole **585**. Successive reduction, benzylation, and amine quaternization led to **587**. Treatment of this substance with aqueous *p*-TsOH provided the spiroketal **589**, thought to arise by an acid-catalyzed 1,4-addition to the conjugated enal **588**. Again, an argument can be made for either a kinetic or a thermodynamic process operating in this case.

Williams[92] carried out the spirocyclization shown in Scheme 119 to give a pair of diastereomeric spiroketals **592**. This is thought to occur via the endocyclic conjugate addition of the hemiacetal hydroxyl **591** to the enone. Partial cyclization to **591** occurs when the silyl ether **590** is treated with acidic ion-exchange resin in toluene at 100 °C, which loosely suggests that the cyclization proceeds via endocyclic closure of this intermediate.

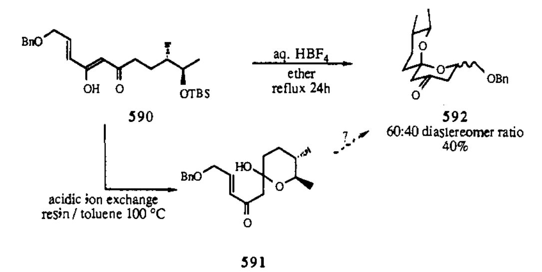
SCHEME 117



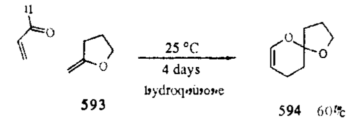
SCHEME 118



SCHEME 119

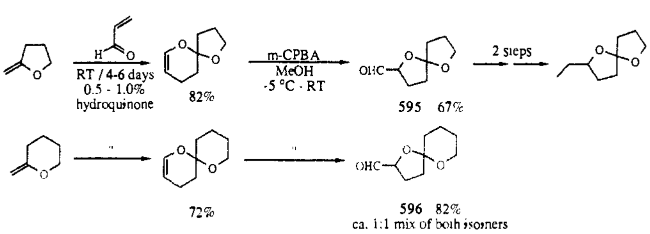


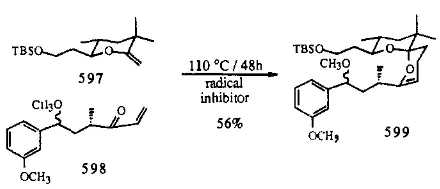
(*c*) *Hetero Diels–Alder Cycloaddition.* The cycloaddition between vinyl ethers and α,β-unsaturated carbonyl compounds has been known for some time. Paul and Tchelitcheff[198] originally described the reaction between α-methylenetetrahydrofuran (**593**) and acrolein resulting in a spirocyclic [4 + 2] adduct **594** in 60% yield. This cycloaddition was essentially repeated



by Ireland,[199] who obtained **594** in 82% yield. The resulting 2,3-unsaturated spiroketals could be oxidatively rearranged to the ring-contracted spiroketals **595** and **596** with *m*-CPBA in methanol (Scheme 120). A recently described approach[78] to the aplysiatoxin–oscillatoxin metabolites utilizes this cycloaddition variant. The enone **598** and vinyl ether **597** were combined to

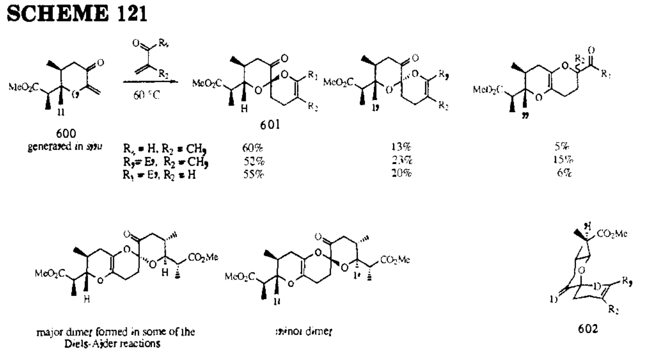
SCHEME 120



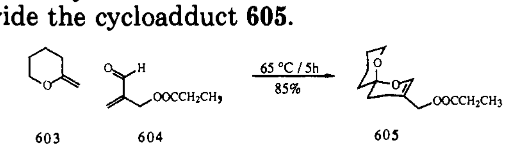


form the adduct **599** in 56% yield along with substantial quantities of starting vinyl ether and oligomerized enone. The additive (4-hydroxy-2,2,6,6-tetramethylpiperidinyl)oxy radical minimized the amounts of enone-derived side products in this reaction.

SCHEME 121



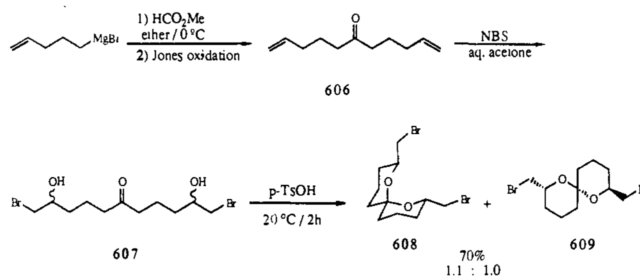
The related and well-known dimerization of acrolein and its derivatives has proven particularly fruitful for Ireland and Deslongchamps in complex spiroketal synthesis. When the labile α,β-unsaturated ketone **600** (Scheme 121) is generated in situ in the presence of acceptors, a variety of cycloadducts are formed.[98a] The conformation of the major cycloadducts **601** was indicated to be as shown in **602** by NMR consistent with the conventional wisdom already presented. In related work geared to the synthesis of erythronolide A, Deslongchamps[151] carried out the cycloaddition between the parent vinyl ether **603** and acrolein derivative **604** to provide the cycloadduct **605**.



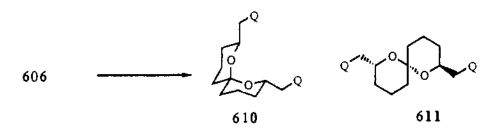
(*d*) *Cation-Initiated Olefin Cyclization.* Several examples in this category involve the formation of more than two bonds in a single process. In all cases except one, C–O bond formation is involved, to either the spiro carbon, the γ or δ carbon of the five- or six-membered ring, or both.

Although not strictly falling into this category, an early cyclization carried out by Sondheimer[200a] constitutes a fundamental contribution to modern spiroketal synthesis (also see ref 94) and is related to the cycli-

SCHEME 122

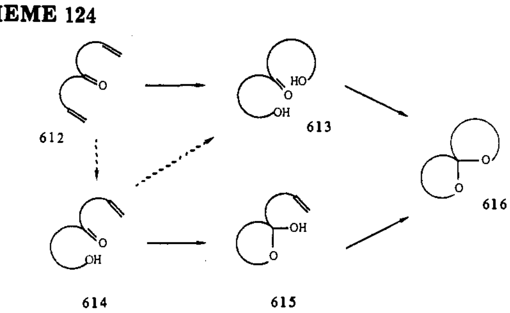


SCHEME 123

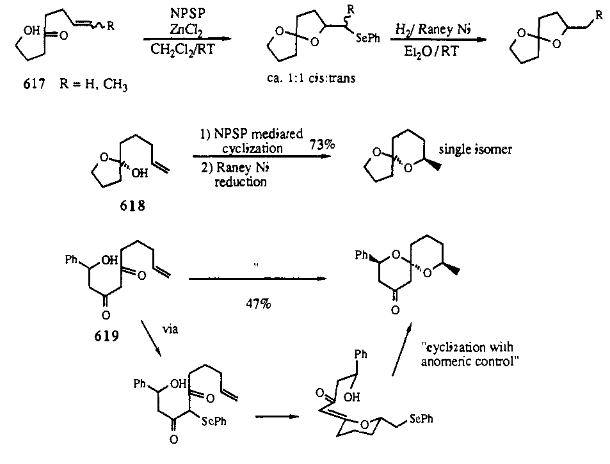


	Reagent	610/611 Product ratio (% yield)	Q
Mehta	PhSeCl / aq. CH_3CN	7 : 3 (75)	-SePh
Kitching	1) $Hg(OAc)_2$ / aq. THF; 2) aq. NaCl	major : minor (>90)	-HgCl

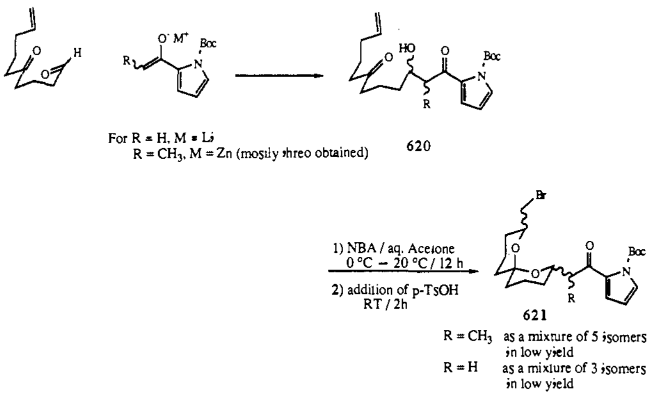
SCHEME 124



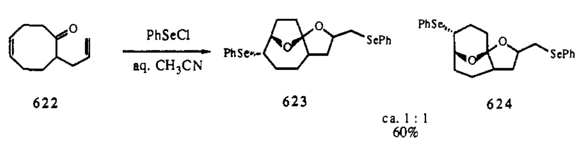
SCHEME 125



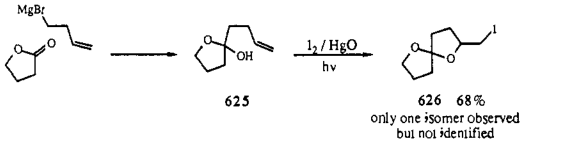
SCHEME 126



zations to be described. The dienone **606** (Scheme 122) was subjected to bromohydrin formation and the product **607** was directly cyclized with *p*-TsOH to a nearly equal mixture of diastereomers **608** and **609**, the former isomer's structure confirmed by X-ray crystallographic analysis.[200b] It was reasonably assumed that the addition of "HOBr" across the olefins was nonstereoselective, resulting in both sets of diastereomeric bromohydrins, each of which cyclized to only one spiroketal isomer. This is quite similar to later approaches in which the olefin addition products were not isolated. Mehta[201] and Kitching[202] reported similar processes (Scheme 123) with the same substrate utilizing aqueous reagent systems (**606** → **610** and **611**). Products configurationally identical with Sondheimer's were observed in these cases. While the intervention of discrete double-addition products (**613** (Scheme 124)) followed by acid-catalyzed spirocyclization (to **616**) is reasonable, an alternative is the cyclization of intermediate hemiacetals directly to spiroketals (**615** → **616**). This latter pathway was observed by Ley[82,203] in the nonaqueous cyclizations of olefinic hemiacetals (**618**) and the corresponding hydroxy ketones (**617** and **619**) mediated by *N*-phenylselenophthalimide (NPSP)/$ZnCl_2$ (Scheme 125). Sharpless[204] observed a similar phenomenon in monocyclization initiated by *p*-ClPhSeBr. As expected, enhanced stereoselectivity is observed under anhydrous conditions and where cyclic hemiacetal intermediates are involved. Kitching[202] reported a spirocyclization analogous to the NPSP cases, but initiated by Hg(II). A cyclization similar to the Sondheimer case and using the same reagents was recently reported by Jeminet[205] in which the hydroxy ketone **620** (as a mixture of diastereomers) was converted to spiroketals **621** (Scheme 126). Worthy of note in this area is a case reported by Mehta[201] involving a transannular spirocyclization (**622** → **623** and **624**). Compounds **623** and **624** are rare examples of spiroketals in which the two rings are bridged by a small carbon chain.

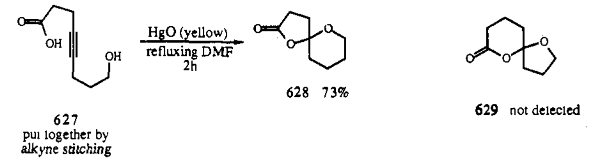


Kraus[206] reported a transformation related to the above processes. Treatment of the olefinic hemiketal **625** with mercuric oxide/iodine under photochemical irradiation results in the production of **626** as a single unassigned



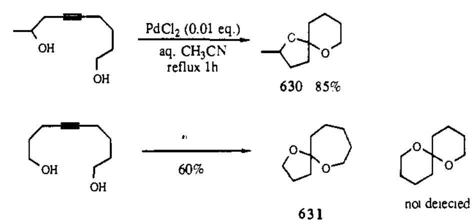
diastereomer. The reaction was claimed to be a radical cyclization although simple cationic iodoetherification is also plausible. Evidence for an alkoxy radical mechanism for this transformation was presented by using an unrelated substrate, although no control studies with **625** were reported.

Two examples of spirocyclizations involving alkynes have been described. Yamamoto[207] reported the conversion of the acetylenic hydroxy acid **627** to the spirolactone **628** with HgO in refluxing DMF. Only this



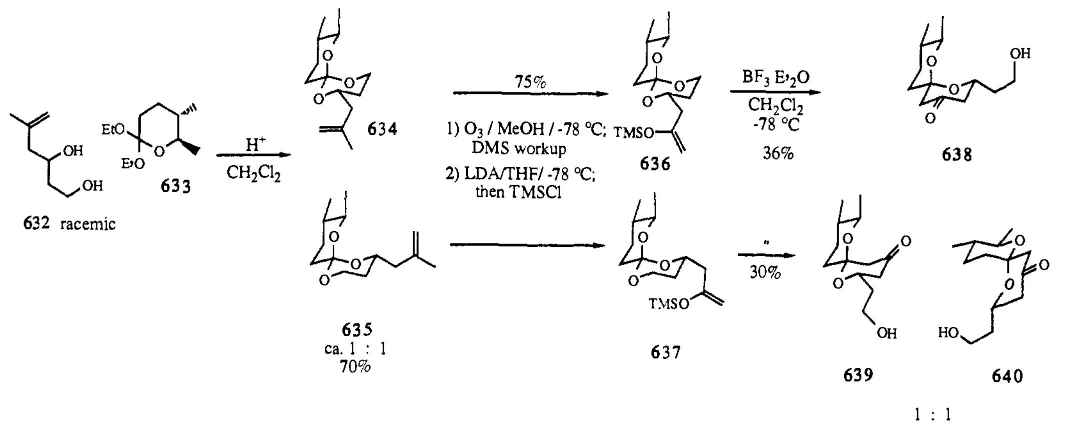
single example was disclosed. It is interesting to note that the isomeric compound **629** was not observed in the product mixture. Utimoto[208] cyclized a series of alkynediols to spiroketals using $PdCl_2$ (Scheme 127). The pheromone-like spiro systems **630** and **631** were produced as diastereomeric mixtures, however. One of the few examples of the 1,6-dioxaspiro[4.6]undecane ring systems (**631**) was attained with this method. The isomeric spiro[5.5] system was not detected in this cyclization.

SCHEME 127

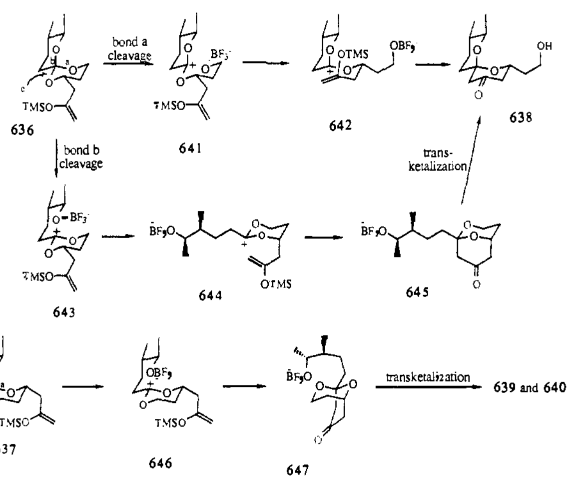


Kocienski[209] reported one of the very few examples of closure of a spiroketal ring by carbon–carbon bond formation. This creative approach involves the cyclization of a dioxenium cation onto an electron-rich olefin producing a spiro[5.5] intermediate for milbemycin β_3 synthesis (Scheme 128). The racemic diol **632** was transorthoesterified onto the optically active lactone **633** to provide a 1:1 mixture of diastereomeric ortholactones **634** and **635**. These were separated and independently converted to silyl ethers **636** and **637**, respectively. Treatment of **636** with boron trifluoride etherate at low temperature leads to spiroketal **638**. Identical treatment of **637** led to a 1:1 mixture of spiroketals **639** and **640**. These transformations were rationalized as shown in Scheme 129. Cleavage of either bond a or b in **636** is anomerically favored over bond c and leads to dioxenium cations **641** and **643**, respectively. Cation **641** can directly cyclize to give **638** via a transition structure in which anomeric effects are maximized and steric effects are minimized. Carbocyclization of cation **643** can only occur in one fashion and leads to bicyclic ketal **645**, which can rearrange by transketalization to the more thermodynamically stable **638** under the conditions of the reaction. Similar reasoning can rationalize the cyclization of **646**. Products **639** and **640** can be

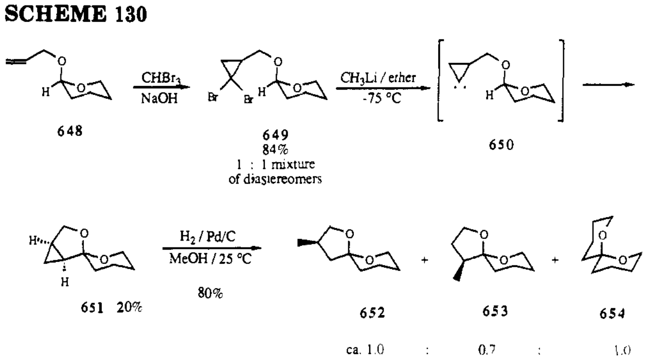
SCHEME 128



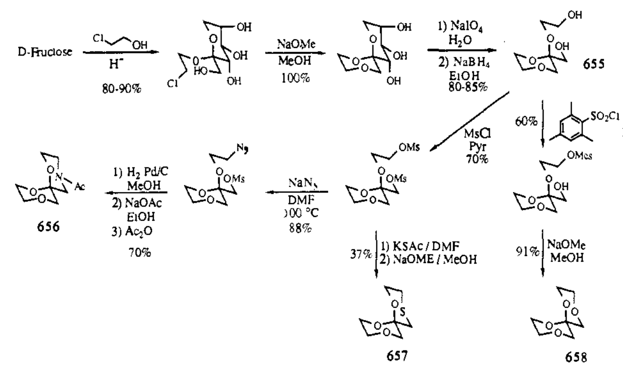
SCHEME 129



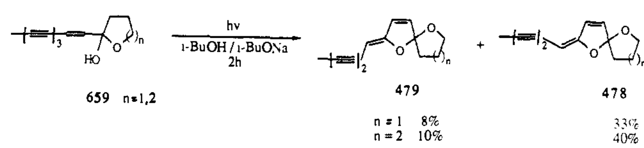
SCHEME 130



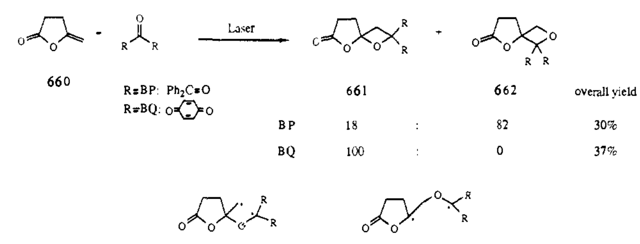
SCHEME 131



SCHEME 132



SCHEME 133



seen to arise via (anomerically favored) bond b cleavage to dioxenium cation **646**. This can cyclize to bicyclic ketal **647**, which can undergo transketalization to give rise to the observed products. This clearly is a more complex process mechanistically than the above rationalizations imply, especially in light of the observed yields and potential for side reactions under strongly Lewis acidic conditions. In any case, use of optically pure *S*-diol **632** in this process leads to a single ortholactone **634**, which, in turn, leads to spiroketal **638**, a useful intermediate in a milbemycin β_3 synthesis.

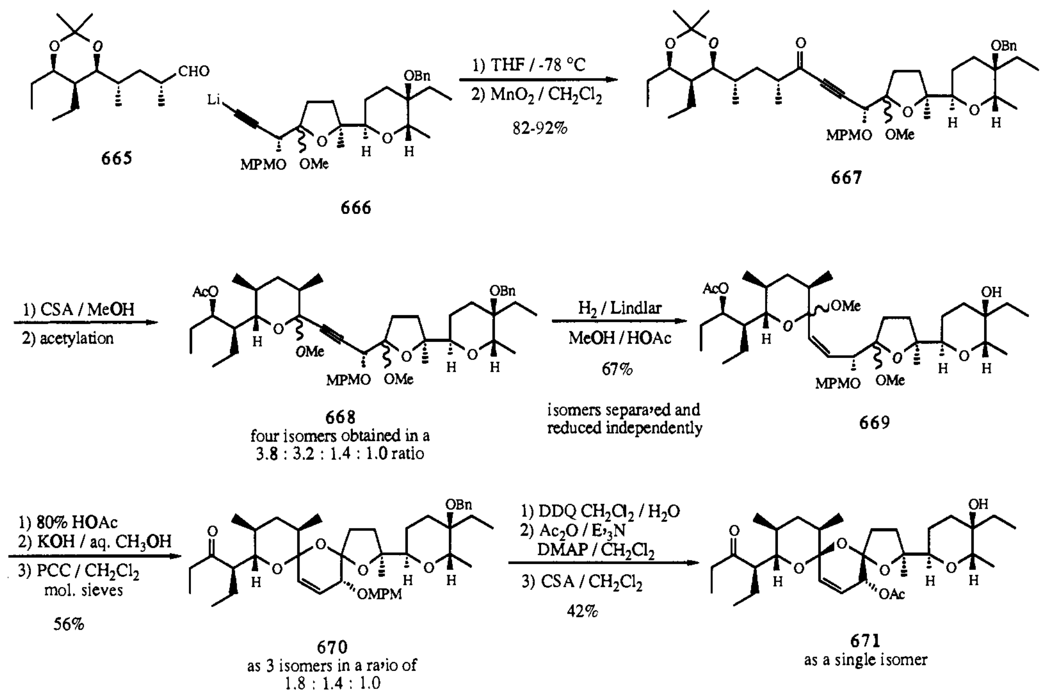
2. Miscellaneous Processes

Brinker[210] described the only synthesis of spiroketals based on carbenes. The dibromocyclopropane **649** was treated with methyllithium, presumably generating the carbene **650**, which underwent intramolecular C–H insertion to produce spiroketal **651** in modest yield, as illustrated in Scheme 130. Hydrogenation of this substance gave rise to three spiroketals **652–654**, each of which arises by cleavage of a different bond of the cyclopropane ring.

In a carbohydrate-based approach (Scheme 131), Richardson first converted D-fructose to the optically pure diol **655**.[211] This intermediate was converted into spiroketals **656–658** using intramolecular displacement reactions.

Bohlmann[212] reported the photochemical approach to spiroketal enol ethers shown in Scheme 132. The cyclic hemiacetals **659** were assembled by a carbonyl addition–oxidation sequence. When **659** was irradiated in the presence of *t*-BuONa, olefin isomerization and cyclization resulted in the production of both (*Z*)- and (*E*)-olefin isomers **479** and **478** in moderate yield. This approach is complementary to a furan oxidation approach to the same compounds (section IV.A.3).

SCHEME 134



Several unusual spiroketals were reported by Adam[213] in using laser photochemistry. For example, the UV–vis laser irradiation of 4-penten-4-olide (**660**) with benzophenone (BP) or with *p*-benzoquinone (BQ) under an argon atmosphere afforded the acetal-type oxetanes **661** and **662** (Scheme 133). With BQ the oxetane regioisomer **661** was obtained with no trace of the regioisomeric **662**. The regioselectivity of the benzophenone cycloaddition was rationalized in terms of radical stabilization energies, which predict that the lactone **664**-BP is by ca. 2 kcal/mol of lower energy than the methylene radical site in **663**-BP.

C. Trioxadispiroketal Synthesis

While there are a large number and variety of methods that have been used to synthesize spiroketals, very few methods have been applied to the synthesis of trioxadispiroketals. The only examples of this ring system in nature appear to be polyethers of the narasin–salinomycin class. The remarkable syntheses of compounds in this series by Yonemitsu and by Kishi highlight this area.

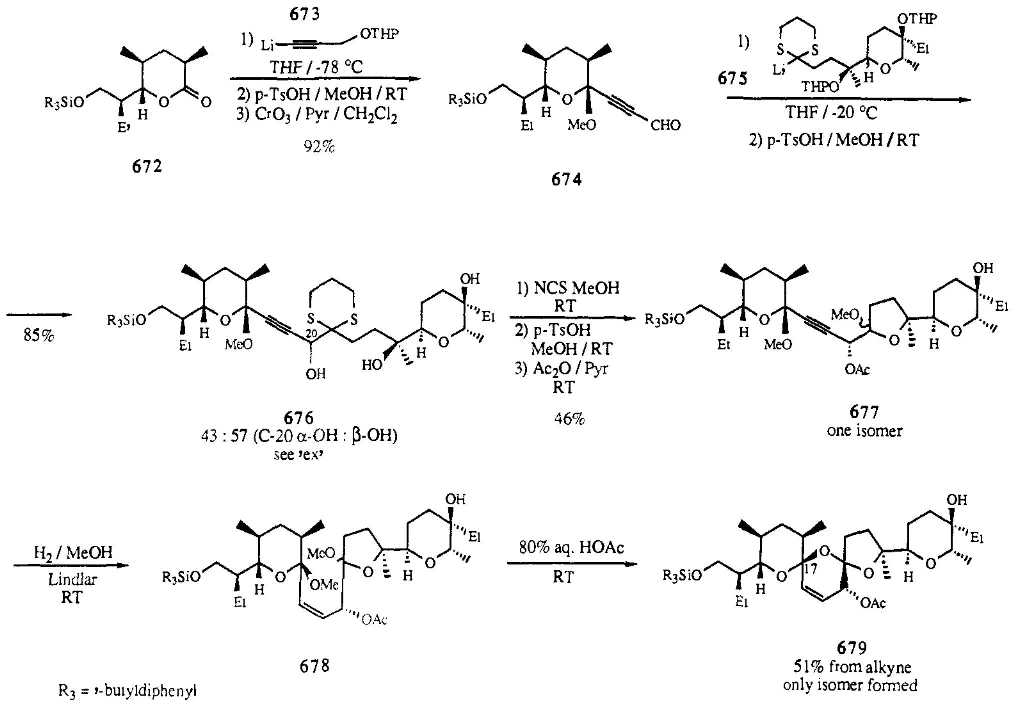
Yonemitsu[214a] used a C_{spiro}–C_α strategy (Scheme 134) to link two large fragments (**665** and **666** → **667**) via the addition of an acetylide anion to an aldehyde followed by oxidation to the conjugated ynone **667**. After several routine manipulations arriving at a mixture of bisacetals **669**, the system is closed by forming the middle ring in an acid-promoted process giving three isomers of the trioxadispiroketal **670**. This mixture was then treated with DDQ to remove the MPM group and in the process, the tertiary alcohol was debenzylated to a mixture of diols. Acetylation of the secondary alcohol on the middle ring of the trioxadispiroketal gave a mixture of acetates. Acid-catalyzed isomerization with CSA/CH_2Cl_2 provided compound **671** as the sole product in 42% yield overall for the three steps. An alternative yet similar approach was also described from the same laboratory.[214b]

The Kishi approach (Scheme 135) to the same metabolites uses a combination of dithiane riveting and acetylide addition to a lactone to construct the trioxadispiroketal carbon skeleton.[215] The lactone **672** was alkylated with acetylide **673** to produce the addition product **674** after aldehyde unmasking. After standard manipulations, the dithiane **675** was added to aldehyde **674** followed by glycosidation to produce a mixture of C20 carbinols **676**. The isomers were separated at this point and the unwanted β-OH epimer could be recycled by an oxidation–reduction sequence. The correct α-carbinol was carried through to the olefin **678** and final closure was effected with aqueous acetic acid to produce a single trioxadispiroketal isomer **679** that is epimeric at C17 with respect to narasin and salinomycin. As was seen earlier in section III.E, molecules in the 17-epi series could be completely isomerized to the desired configuration at a later stage in the synthesis.

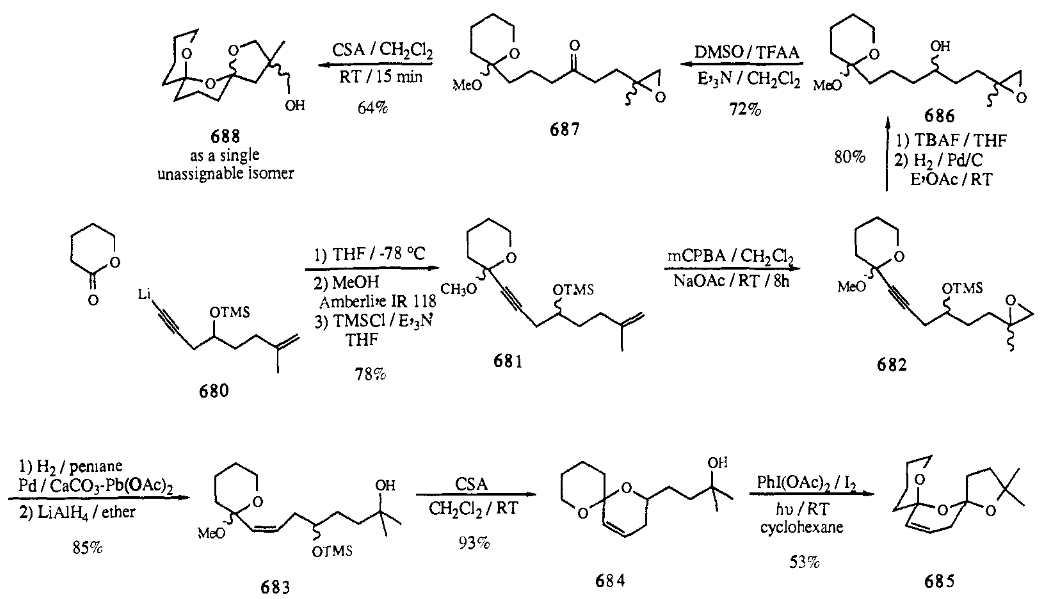
Two model studies in the same series were described. Baker[216] combined a lactone addition reaction with a photochemical free radical process to produce the tricyclic model compound **685** in eight steps (Scheme 136). The racemic lithium reagent **680** was added to the δ-valerolactone followed by glycosidation and resilylation to give **681**. Epoxidation of the olefin to **682** was nonspecific as expected. Semihydrogenation of the alkyne and epoxide cleavage with $LiAlH_4$ led to **683**. The first two rings were closed in an acid-catalyzed process to **684**. Oxidative cyclization using the hypoiodite method provided a single trioxadispiroketal **685** in 53% yield, the structure of which was assigned by spectroscopic methods. The intermediate epoxide **682** could also be transformed to the saturated compound **687** by the series of steps shown. The final cyclization is a variant of the known cyclization of epoxy ketones that has been useful in the production of bridged internal ketals[217] and, in this case, gives spiroketal **688** as a single unassignable isomer.

2-Furyl ketone oxidation and rearrangement (section IV.A.3) is neatly suited for preparing ring systems of this type. Perron[165] successively metalated and alkyl-

SCHEME 135



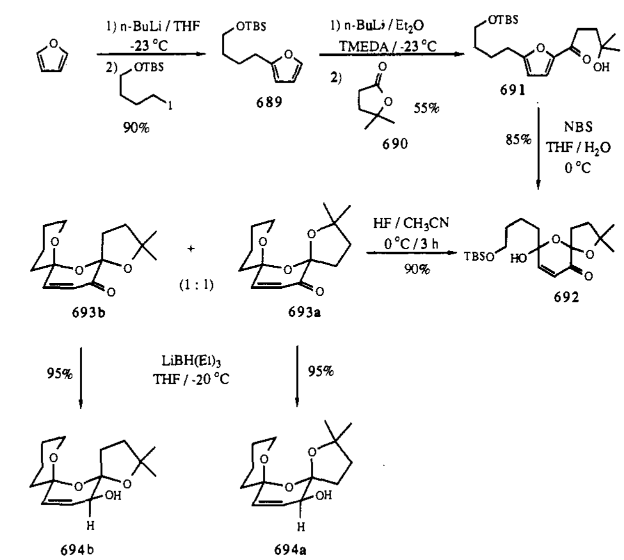
SCHEME 136



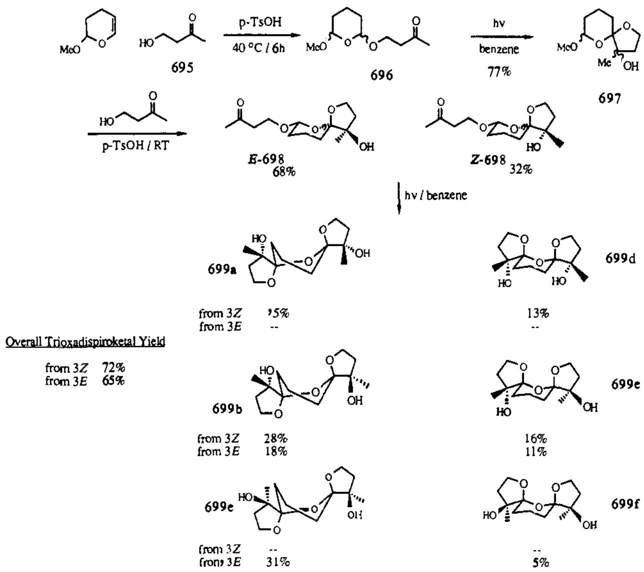
ated furan to produce the 2-furyl ketone substrate **691**. NBS oxidation and hemiacetal formation provide **692** as a mixture of isomers which was directly desilylated and cyclized to a 1:1 mixture of functionalized trioxadispiroketals **693a** and **693b**. The structure and conformations of both isomers were determined by extensive one- and two-dimensional ^{1}H and ^{13}C NMR experiments. Reduction of each isomer with $LiBHEt_3$ gave rise to a single allylic alcohol isomer in each case. The compound **694a** possesses the configuration of the natural polyethers narasin and salinomycin and their analogues (Scheme 137).

Descotes described an entirely different approach[83,218,219] using the Norrish type II cleavage described earlier in section IV.B.1.a. Tetrahydropyranylation of the keto alcohol **695** led to a mixture of isomers **696**. Irradiation of a benzene solution of **696** led to a mixture of four spiroketals of gross structure **697** in 77% yield. This represents a much better conversion than similar examples cited in section IV.B.1.a. Transacetalization of this mixture led to a 2:1 mixture of spiroketals (*E*)-**698** and (*Z*)-**698**, as shown in Scheme 138. Nonstereoselective photocyclization of the mixture led to all six possible diastereomeric trioxadispiroketals **699a–f** in the indicated ratios. That no spiroepimerization took place during the cyclization was shown by irradiating the individual isomers (*E*)-**698** and (*Z*)-**698**, which led to only the four expected isomers in each case. The characterization and conformations of **699a–f** were discussed in section III.E.

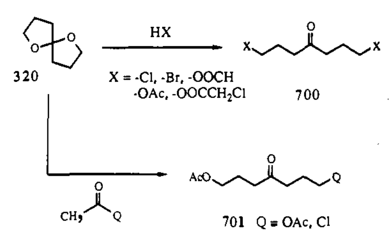
SCHEME 137



SCHEME 138



SCHEME 139

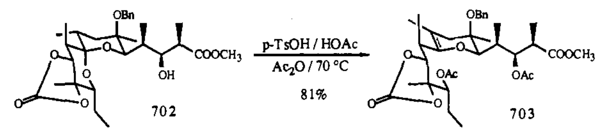


V. Reactions of Spiroketals

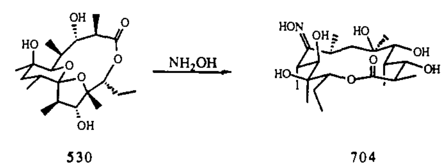
A. Conversion to Open-Chain Derivatives

The reversal of the spirocyclization reaction has been accomplished on both simple and complex derivatives. Because of the large thermodynamic difference between dihydroxy ketones and spiroketals, with the latter being favored, one must effectively trap the open-chain form as a derivative of either the carbonyl group or the alcohols.

Fittig[123b,c] originally described the opening of spiroketals to ketones by treatment with mineral acids. This was later extended by Dedek[93a] and others[150,220] and is shown in Scheme 139. These conditions are not compatible with highly functionalized substrates. Deslongchamps[221] partially opened spiroketal **702** by treatment with *p*-TsOH in the presence of acetic anhydride to trap any intermediate alcohols. The result was the half-open dihydropyran derivative **703**.



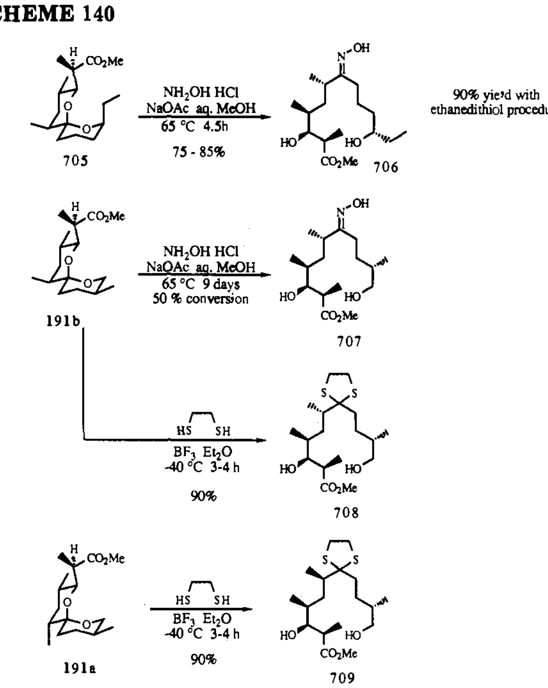
Both Ireland and Deslongchamps strategically used spiroketals as templates to establish relative stereochemistry in the synthesis of complex medium size ring containing compounds. A method for opening the template to free the acyclic derivative was therefore needed. Corey[181] followed the lead of Graf and Dahlke[167a] and Dedek[93a] and found that the erythronolide A spiroketal **530** could be opened to the oxime **704** by treatment with hydroxylamine. Ireland[98a] found



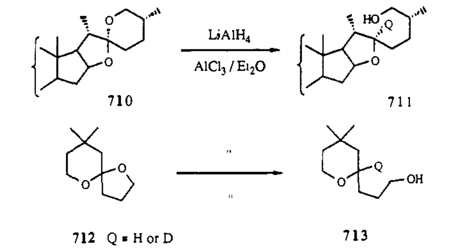
that this approach (Scheme 140) was not entirely successful in less substituted cases such as **705** and **191b**. However, conversion of spiroketals to open-chain dithiolane derivatives could be accomplished in high yield at −40 °C with ethanedithiol and boron trifluoride etherate. Under these conditions no epimerization of the Cα methyl group occurred as seen in earlier cases (section III.D).

Reductive ring opening of spiroketals to monocyclic compounds can be accomplished with $LiAlH_4/AlCl_3$ in ether. This was found first in the steroidal sapogenin series and was found to give products in which only the tetrahydropyran ring had been cleaved (**710** → **711** (Scheme 141)).[222] Subsequent studies by Pettit[158] es-

SCHEME 140

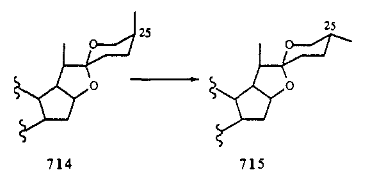


SCHEME 141

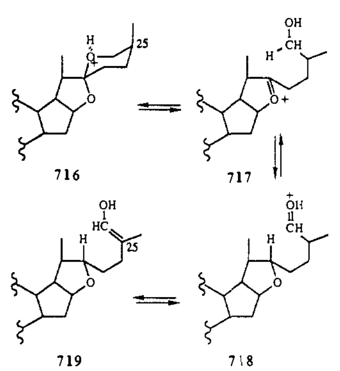


tablished that hydride transfer occurred directly from the reducing agent to the spiro carbon. However, in a simpler model system (712 → 713), only the tetrahydrofuran ring was opened.

Along this line, extensive investigations in the steroidal sapogenin series have established that upon treatment with acid, isomerization[223] occurs at C25 solely, leaving the spiro center intact (714 → 715).

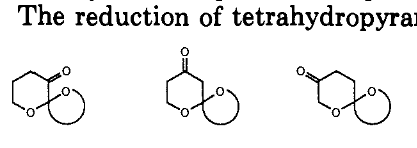


Woodward[223e] proposed that the epimerization involves acid-catalyzed cleavage of the tetrahydropyran ring, followed by reversible intramolecular hydride transfer to the oxonium ion intermediate 717, yielding species 718. The readily established equilibrium between 718 and its enol form 719 accounts for the isomerization at C25.



B. Carbonyl Reduction

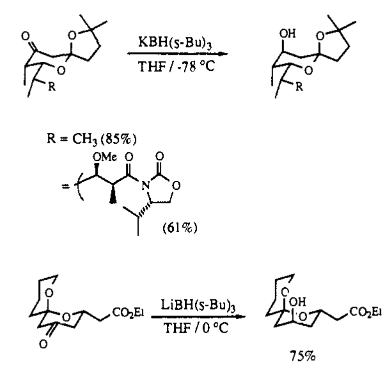
Most reductions in this category involve cyclohexanone derivatives. There are three possible locations of a ketone carbonyl with respect to the spiro carbon (720–722). The reduction of tetrahydropyran-4-one



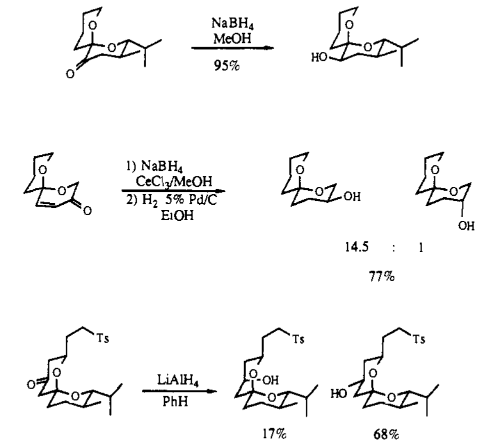
derivatives 721 has been studied most intently since many naturally occurring spiroketals possess hydroxyl groups at this position.

The presence of the spiro center appears to impart a negligible effect on the stereoselectivity of ketone reductions. For example, bulky reducing agents known to give axial alcohols with simple cyclohexanone derivatives also give predominantly axial alcohols in these systems as well. Two examples[81,174] are shown in

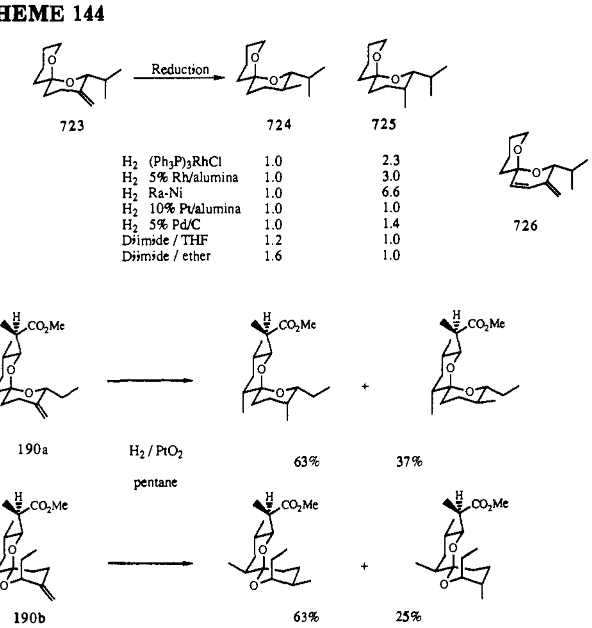
SCHEME 142



SCHEME 143



SCHEME 144

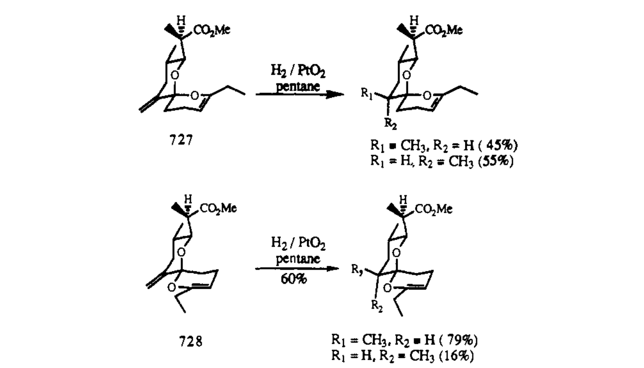


Scheme 142 although there are many cases of this phenomenon.[78,86,164] In contrast, $NaBH_4$ and $LiAlH_4$ give predominantly equatorial alcohols (Scheme 143;[157,164] for other examples, see ref 105, 113, 119 and 128).

C. Reduction of C=C

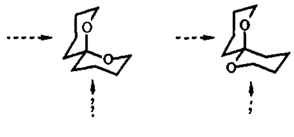
Reductions of C=C in spiroketal systems which establish relative stereochemistry have only been studied systematically in a few cases and do not proceed with a high degree of stereoselectivity.

SCHEME 145



In a study of exocyclic olefin reduction of the substrate **723** (Scheme 144) DeShong[164] found that metal-catalyzed hydrogenation gave the axial methyl isomer as the major product, whereas reduction with diimide gave a slight predominance of the equatorial methyl isomer. Reductions of the related substrate **726** led to mixtures of both **724** and **725** in addition to nonolefinic products. In a related substrate (**190a**), Ireland observed roughly the same degree of selectivity for the axial methyl isomer. However, when the spiro center of **190a** is inverted such that the ethyl group on the adjacent carbon is axial (**190b**), reduction proceeds from the opposite face of the olefin to give the equatorial methyl isomer as the major product. This is most easily explained as a response to greater steric hindrance to equatorial reduction in **190b** vs **190a**. Ireland[98b] examined other cases of exocyclic olefin reduction in an attempt to control the stereochemistry of secondary methyl groups. In the spiro series denoted by structure **727** stereoselectivity is poor. However, the epimeric series **728** shows reasonable selectivity for the axial methyl isomer (Scheme 145).

Endocyclic olefin reduction has been studied in only a few cases. Reduction of the anomerically maximized spiroketals[98,125,164] **729–731** (Scheme 146) all proceed primarily, if not exclusively, from equivalent and least hindered faces of the olefins to provide the saturated spiroketals **732–734**. These results and those to follow in the next section show that addition to endocyclic olefins in the spiro[5.5] ring system can be highly stereoselective and tends to occur from the side of the molecule away from the axial bond at the spiro carbon. This is most easily explained as a hindrance phenomenon.



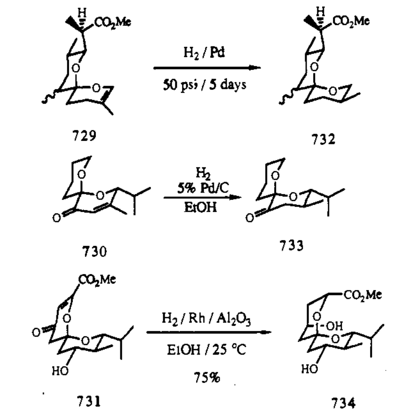
I II

D. Electrophilic and Related Addition Reactions

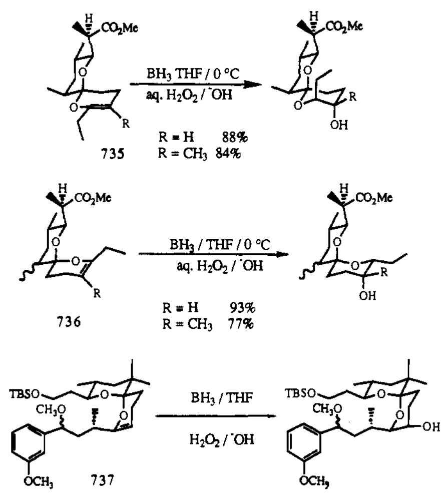
1. Hydroboration–Oxidation

Hydroboration of endocyclic olefins tends to occur from the side of the ring away from the axial bond at the spiro carbon. Ireland repeatedly observed this phenomenon and typical cases are shown in Scheme 147.[78,98] Even with the least sterically demanding hydroboration reagent, addition was regio- and stereospecific and did not depend on the configuration at the spiro carbon.

SCHEME 146



SCHEME 147



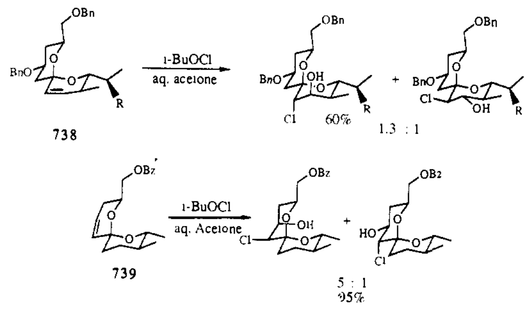
2. Electrophilic Additions

Addition of electrophiles to olefins in the α,β position proceeds with decreased stereoselectivity but with high regiospecificity in the few reported examples. Electrophilic chlorohydroxylation (Scheme 148) of spiroketals **738**[224] and **739**[128] proceeds with variable stereoselectivity, but in each case only the isomers with the chlorine closest to the spiro center are observed. This may be attributed to the inductive electron-withdrawing effect of two oxygen atoms attached to the spiro carbon. One might expect decreased positive charge character at the α carbon and therefore reaction of onium ion intermediates with nucleophiles at the β carbon. Qualitatively similar results were obtained by DeShong[164] and Iwata[79] in the oxymercuration–demercuration of **740** and **743**, respectively (Scheme 149). Note, however, the difference in the results with $Hg(OAc)_2$ with these two substrates.

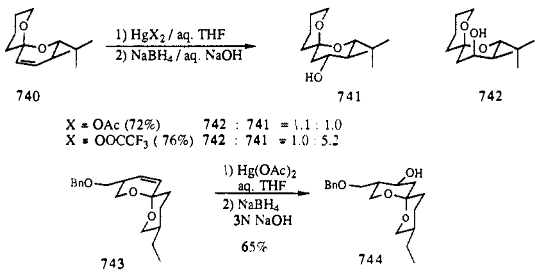
E. Miscellaneous Reactions

Many other kinds of reactions using intact spiroketals have been examined. Most of those not cited are single examples in a class of reactions or were not felt to be of sufficient generality or interest to warrant individual examination. Some of these include enolate alkylation,[78,116,119,125] conjugate additions,[113,116] addition of organometallic reagents to carbonyls,[116,164] [3.3] sigmatropic rearrangement,[116,151] epoxidation,[163,164,224] epoxide opening,[164,224] iodolactonization,[116,151] displacements,[105a] and oxidations.[78]

SCHEME 148



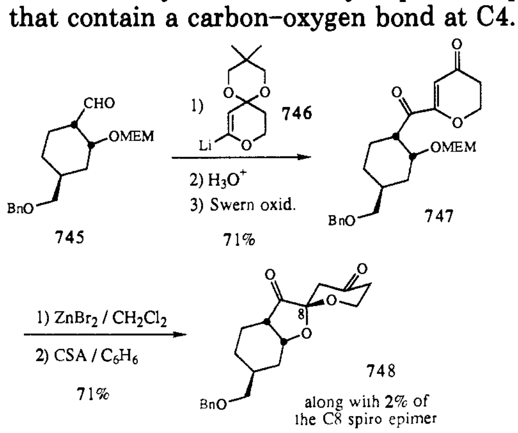
SCHEME 149



VI. Conclusion

Although both natural and synthetic spiroketals have been studied for some time, intense interest in these ring systems has only arisen in the past 10 years. This was primarily due to the increasing number of medicinally and ecologically important compounds containing spiroketal substructures. Synthetic methodological research was stimulated by the description of many naturally occurring compounds of low to intermediate structural complexity to which new methodology could be easily applied. Research in this area is still on the upswing, as judged by the number of papers appearing on a yearly basis. This is appropriate since many problems in this area have yet to be adequately addressed.

Note Added in Proof. We regret the inadvertent omission from the main text of work by Smith.[225] In a synthesis of phyllanthocin, the aldehyde **745** was combined with the vinyl ether **746** to give an adduct that was hydrolyzed and oxidized to the diketone **747**. On removal of the MEM group and cyclization with CSA in dry benzene, the spiroketal **748** was produced, apparently as a kinetic product. The lithium reagent **746** was produced by deprotonation of the corresponding hydrocarbon by *t*-BuLi/THF and represents a C4-oxidized dihydropyran unit. This is of significance because of the many biomedicinally important spiroketals that contain a carbon–oxygen bond at C4.



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(1) After much consideration, we have decided to use the more popular term "spiroketal" and not "spiroacetal" although the latter is more correct by IUPAC standards.
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