SYNTHESIS OF 1,7-DIOXASPIRO[5.5]UNDECANES[1]

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Abstract - Method for preparing 1,7-dioxaspiro[5.5]undecanes are reviewed and are classified according to synthetic strategy. A major strategic category covered by this review includes methods that rely on the acid-catalyzed ketalization of a 1,9-dihydroxynonan-5-one or some functionally equivalent unit containing the ketone group in a masked form such as an enol ether, a thioenol ether, a dithioketal, or a hydrazone. Other strategies detailed in this review include Michael-type cyclization, intramolecular directed aldol reaction of a trimethylsilyl enol ether with a dioxocarbocation, spirocycization of hypoiodities, hetero Diels-Alder cycloadditions, and ring expansion. These various strategies are also discussed in terms of their control of stereochemistry.

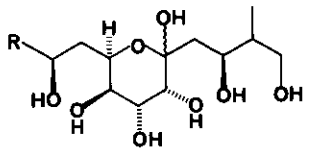
INTRODUCTION

The 1,7-dioxaspiro[5.5]undecane structural unit is widely represented in natural products. It is found in the pheromones of the olive fly Dacus oleae[2,3] and the bee Andrena wilkella,[4] in anti-parasitic agents such as the avermectins[5] and the milbemycins,[6] in polyether antibiotics such as A-23187,[7] salinomycin,[8] narasin,[9] noboritomycin A and B,[10] okadaic acid,[11] acanthifolicin,[12] aplysiatoxin,[13] oligomycin B,[14] and botrycidin,[15] and in the fungal-derived toxins in talaromycin A and B.[16] Syntheses of several of these natural products and of related model systems have appeared in recent years. This review is meant to serve as a catalog of these synthetic efforts and the focus of the coverage is on the strategies used to construct the 1,7-dioxaspiro[5.5]undecane system. The control of stereochemistry is also discussed. The text is organized in the following way:

1. Construction of formal 1,9-dihydroxynonan-5-one units
   a. degradation of natural products
   b. additions to δ-valerolactones
   c. enol ether syntheses
   d. dithioketal alkylation
   e. alkylation of active methylene compounds
   f. nitrile oxide cycloaddition
   g. acetylenes and olefins as latent ketone groups
   h. formate carbonyl as a latent ketone group
2. Hetero Diels-Alder cycloaddition
3. Intramolecular Michael-type addition reactions
4. Organoselenium mediated cyclization
5. Intramolecular directed aldol reaction
6. Spiroketalization through hypoiodite intermediates
7. Ring expansion

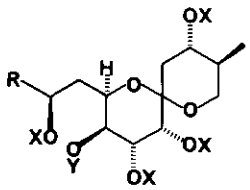
1. Construction of Formal 1,9-Dihydroxynonan-5-one Units

1,7-dioxaspiro[5.5]undecanes have arisen in several cases from the degradation of complex natural products in which the skeletal arrangement of functionality contained a 1,9-dihydroxynonan-5-one grouping. Two examples of this type of transformation were seen in the degradation of palytoxin and zearalenone. Ozonolysis of N-(p-bromobenzoyl)palytoxin followed by reduction with $NaBH_4$ gave a mixture of polyols (1), which when treated with acetic acid gave a mixture of spiroketals (2).[17] Kishi et al. used chiral intermediates to demonstrate the absolute stereochemistry in (2) through the transformation of (3) to (4) using acetic acid.[18]



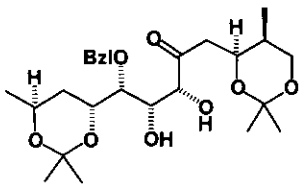
1

HOAc →



2 X = Y = H

R = C-24 to C-40 of palytoxin



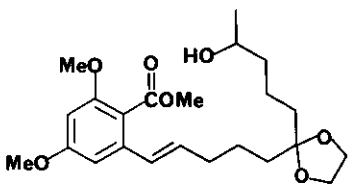
3

HOAc →

4 X = Ac , Y = Bzl

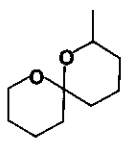
R = $CH_2CH_2CH_2OBzl$

The methyl ester ethylene ketal (5) derived from zearalenone gave the spiroketal (6) following the sequence of ozonolysis, $NaBH_4$ reduction, and treatment with acid.[19] In a related observation, Merck researchers showed that the diol (7) derived from dibenzylzearalenone rearranged readily to spiroketal (8).[20]



5

1) O_3 →
2) $NaBH_4$
3) $H^{\oplus}$



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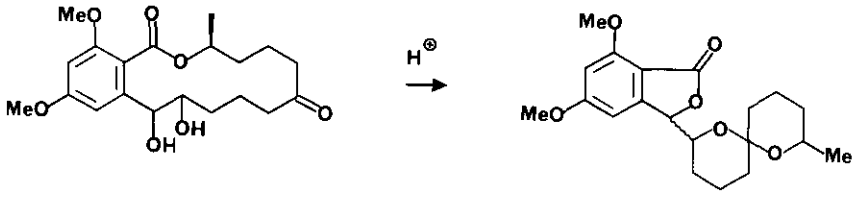
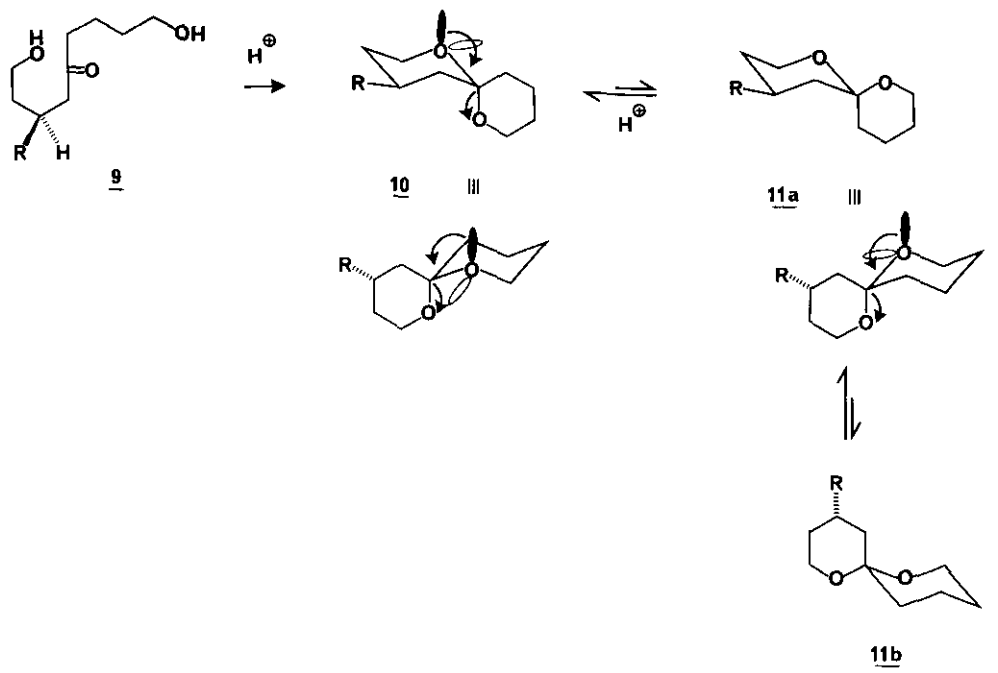


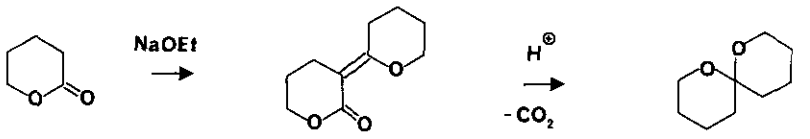
7 8

Before discussing the synthesis of 1,7-dioxaspiro[5.5]undecanes it is useful to mention an important facet of stereochemical control that pertains to many of the strategies described in this review. Syntheses of 1,7-dioxaspiro[5.5]undecanes that use standard disconnections that give a 1,9-dihydroxynonan-5-one, or some formal equivalent thereof, are subject to anomeric control.[21,22] Thus, for example, when a dihydroxyketone such as (9) undergoes acid-catalyzed spiroketalization, the two anomeric ketals (10) and (11a) each bearing an equatorial R substituent, are possible products. Both of these ketals are interconvertable by acid catalysis, and, as is shown by the equilibrium arrows, the predominant anomer is the one in which both ether oxygens are axial substituents at C-2 of a tetrahydropyran ring. This stereochemistry permits two favorable stereoelectronic arrangements of the non-bonded electron pair on each ether oxygen with a corresponding α-anomeric oxygen. Anomer (11a) can only achieve one such favorable interaction, and its conformer (11b) has no favorable stereoelectronic effects. Diastereoselection, where it is applicable in the following syntheses, is governed by anomeric control.



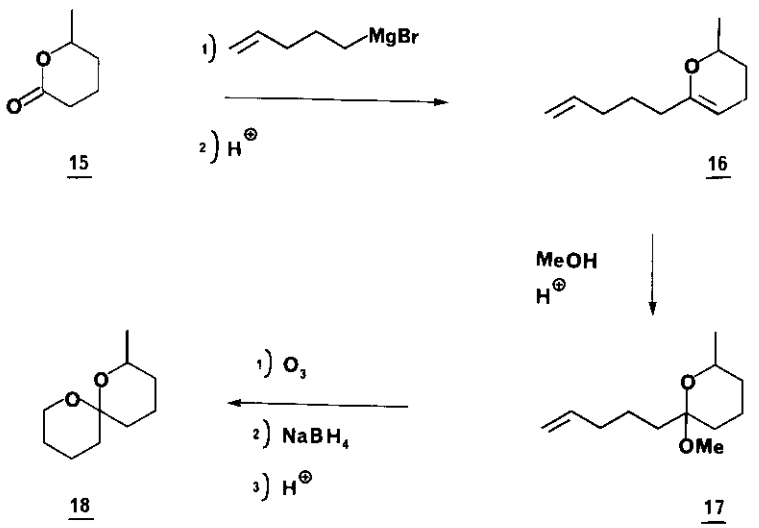
9 10 11a 11b

Carbanion addition to δ-valerolactones has been the basis of many syntheses of 1,7-*dioxaspiro*[5.5]*undecanes*. A very simple and procedurally straightforward example of the construction of such a system was the Claisen condensation of δ-valerolactone (12) with itself. This went initially to intermediate (13), which then gave the spiroketal (14) in 62% overall yield through a series of ring opening, decarboxylation, and spiroketalization steps.[2]



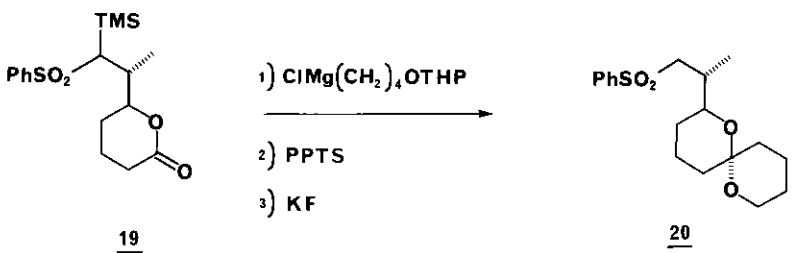
12 13 14

The following four examples show the synthesis of 1,7-dioxaspiro[5.5]undecanes initiated by the addition of an appropriately functionalized Grignard reagent to a δ-valerolactone. Addition of 4-pentenylmagnesium bromide to lactone (15) produced initially a 1,2-adduct, which was transformed to dihydropyran (16) in 50% yield upon distillation. The eventual transformation of (16) into the spiroketal (18) entailed conversion first to methyl ketal (17) followed by ozonolysis, $NaBH_4$ reduction and acid-catalyzed spiroketalization.[19]



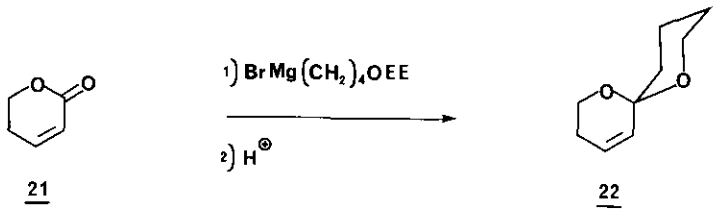
15 16 17 18

Isobe et al. made the spiroketal intermediate (20) in 53% overall yield through the three-step sequence of Grignard addition to lactone (19) followed by acid-catalyzed spiroketalization and desilylation.[23]

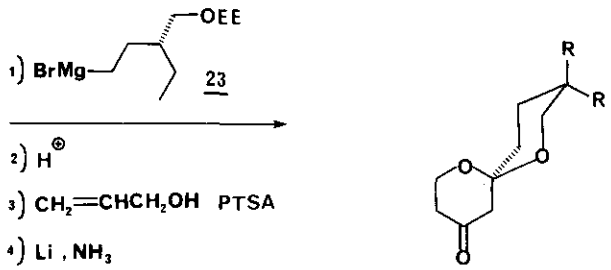


19 20

In a model study related to the syntheses of talaromycin A and B Smith showed that lactone (21) reacted with the Grignard reagent derived from the ethoxyethyl ether of 4-bromo-1-butanol to give a ca. 35% yield of spiroketal (22) after acidic workup. In like manner the diastereomeric spiroketals (24) and (25) were produced as an 8.5:1 mixture starting with the addition of the chiral Grignard reagent (23) to lactone (21).[24]



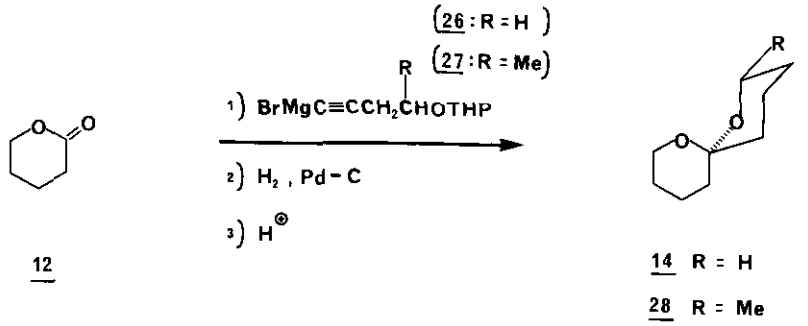
21 22



24 : R = Et , R = H

25 : R = H , R = Et

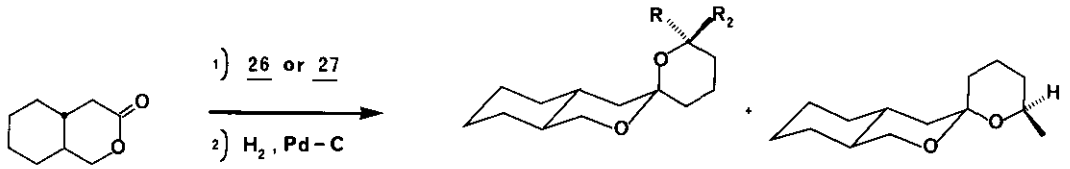
Several groups have used the addition of acetylenic Grignard and lithium reagents to δ-lactones to establish the carbon framework for a 1,9-dihydroxynonan-5-one system. In a classic study of stereoelectronic effects and conformational analysis of spiroketals Deslongchamps et al. prepared the spiroketals (14), (28), (30), (31), (32), and (33) through addition of an acetylenic Grignard to a lactone followed in sequence by catalytic hydrogenation, protective group hydrolysis, and acid-catalyzed spiroketalization.[25]



12

14 R = H

28 R = Me



29

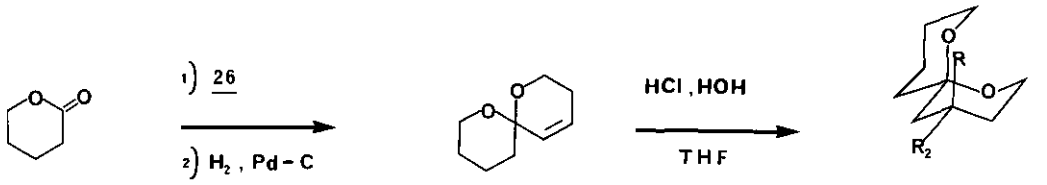
30 : R = R2 = H

31 : R = Me , R2 = H

32 : R = H , R2 = Me

33

Baker et al. prepared one of the minor constituents of olive fly pheromone (35) starting with the reaction of acetylenic Grignard reagent (26) with δ-valerolactone (12). The initial 1,2-addition product was reduced with Lindlar catalyst and spiroketalized with acid to give the olefinic spiroketal (34). Acid-catalyzed hydration of (34), in all likelihood occurring via the intermediacy of the ring-opened α,β-unsaturated ketone, afforded (35) and (36) in a ratio of 20:1 and in 60% overall yield from (12).[3]



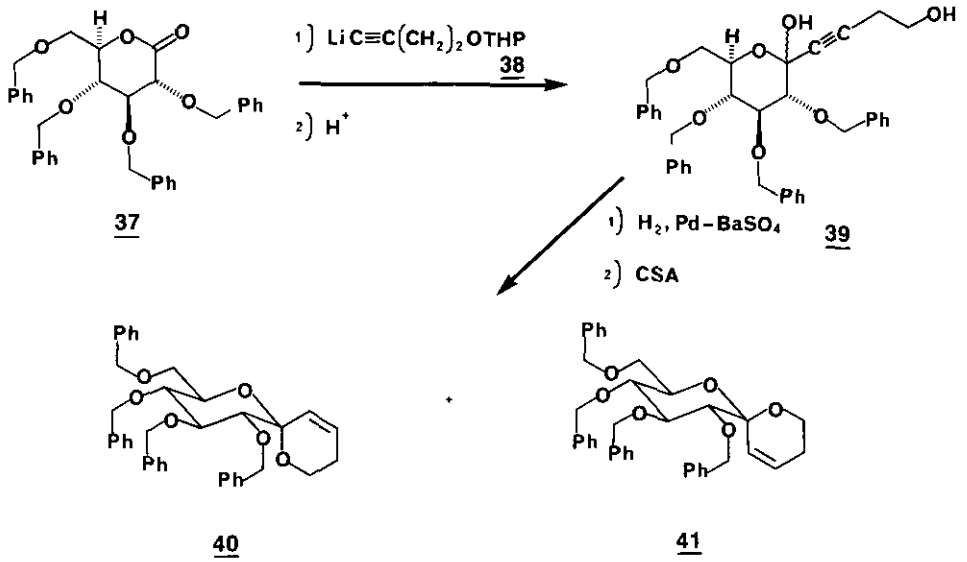
12

34

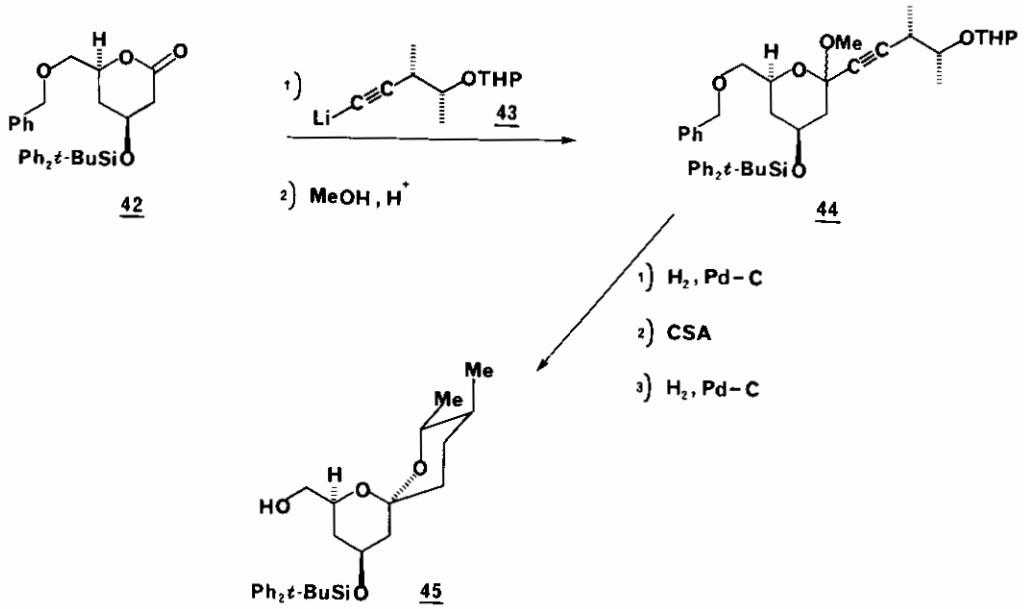
35 : R = H , R2 = OH

36 : R = OH , R2 = H

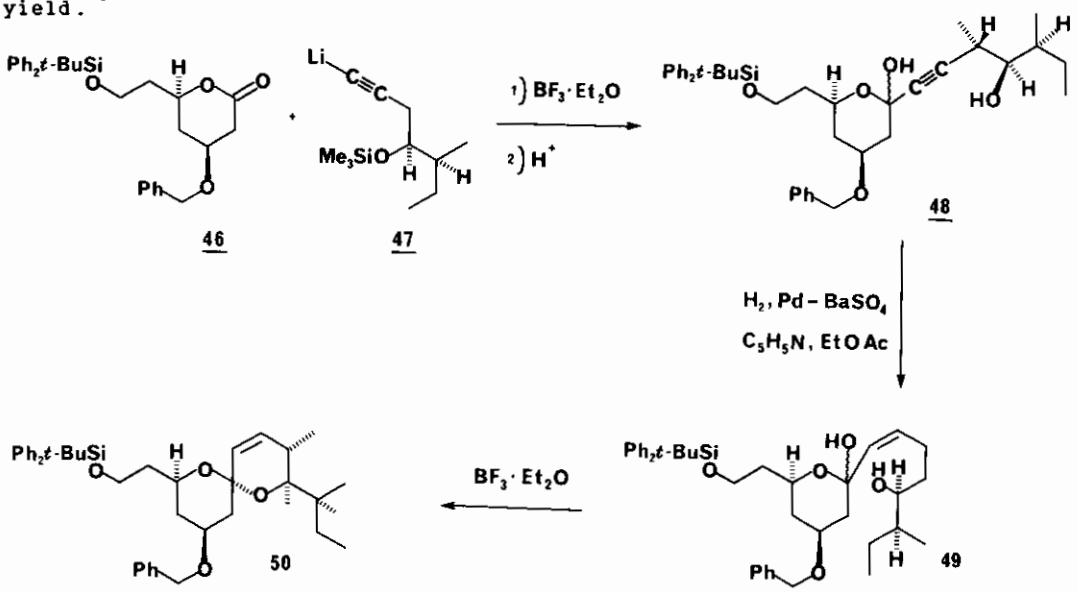
In a model study the condensation of 2,3,4,5-tetrabenzyl-D-glucono-1,5-lactone (37) with lithium acetylide (38) gave a 92% yield of lactol (39). Lindlar reduction of (39) followed by acid-catalyzed spiroketalization gave a mixture of (40) and (41) in 97% yield. Prolonged treatment of this mixture with camphorsulfonic acid (CSA) gave the more stable isomer (40) in 87% yield.[26]



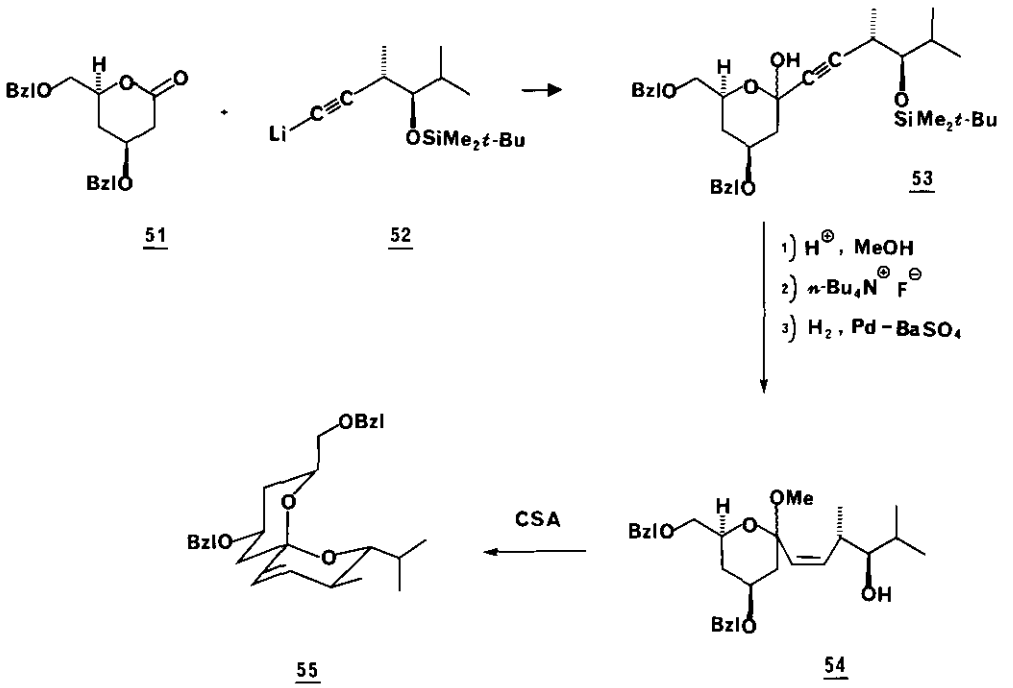
In their synthesis of the spiroketal fragment of milbemycin β_1 and β_3 Baker et al. showed that the chiral lactone (42) derived from glucose was converted to ketal (44) in two steps and in essentially qualitative yield. Catalytic reduction of the triple bond and spiroketalization afforded (45) in 30% overall yield from (43).[27] This synthesis illustrated an interesting facet of anomeric control. The lithium acetylide (43) was only partially resolved and thus one might have expected to get diastereomeric spiroketals from this sequence. However, the diastereomeric material derived from the enantiomer of (43) could not form a spiroketal, since such a spiroketal would have had two axial methyl groups. Thus this sequence provided an example of diastereostereoselection in which the preference of the spiroketal to exist in the α-anomeric form allowed one or more stereocenters in one ring to control a stereocenter in another ring.



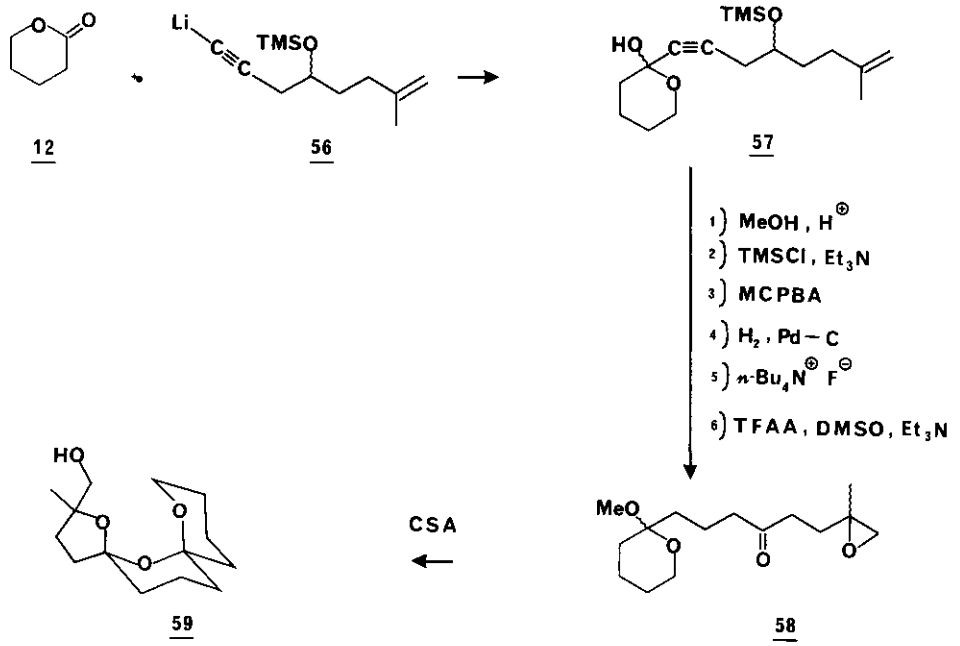
Hanessian et al. prepared the enantiomerically pure form of avermectin B_{1a} spiroketal (50) by condensation of lactone (46) with lithium acetylide (47) in the presence of 1.9 equivalents of $BF_3 \cdot Et_2O$. The yield of lactol (48) was only 38%. Moreover, condensation of (46) with (47) in the absence of $BF_3 \cdot Et_2O$ gave significant amounts of elimination products. This result was in striking contrast to the uneventful analogous condensation of (42) with (43). Reduction of (48) and spiroketalization of the product (49) gave (50) in 80% yield.[28]



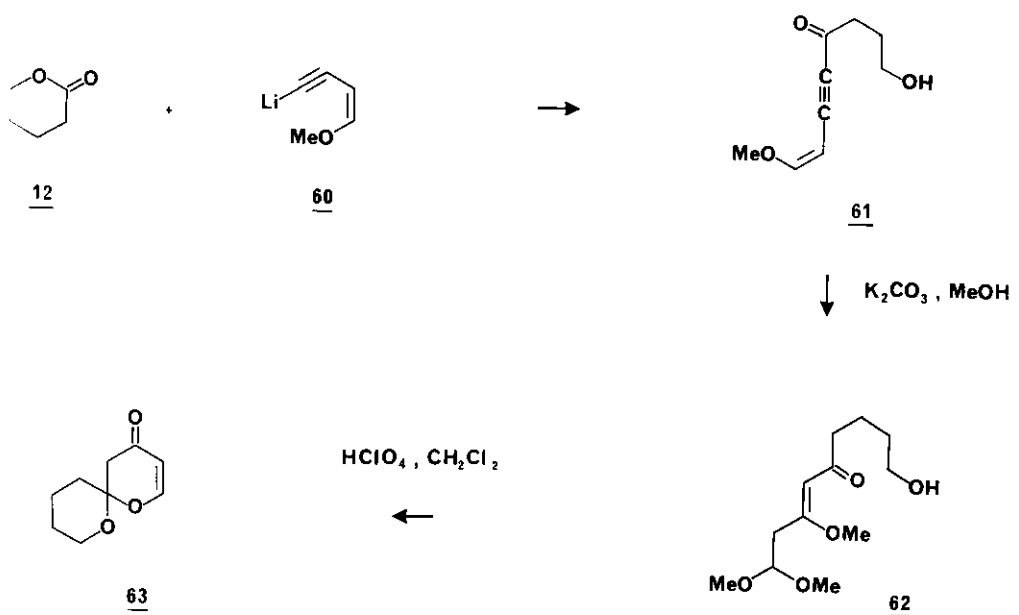
Baker et al. also used the condensation of an acetylide with a δ-valerolactone to prepare the spiroketal units of avermectins β_{1b} and β_{2b}. Condensation of the chiral lactone (51) with lithioacetylide (52) gave lactol (53) in 53% yield. Subsequent steps provided spiroketal (55) in 83% yield.[29]



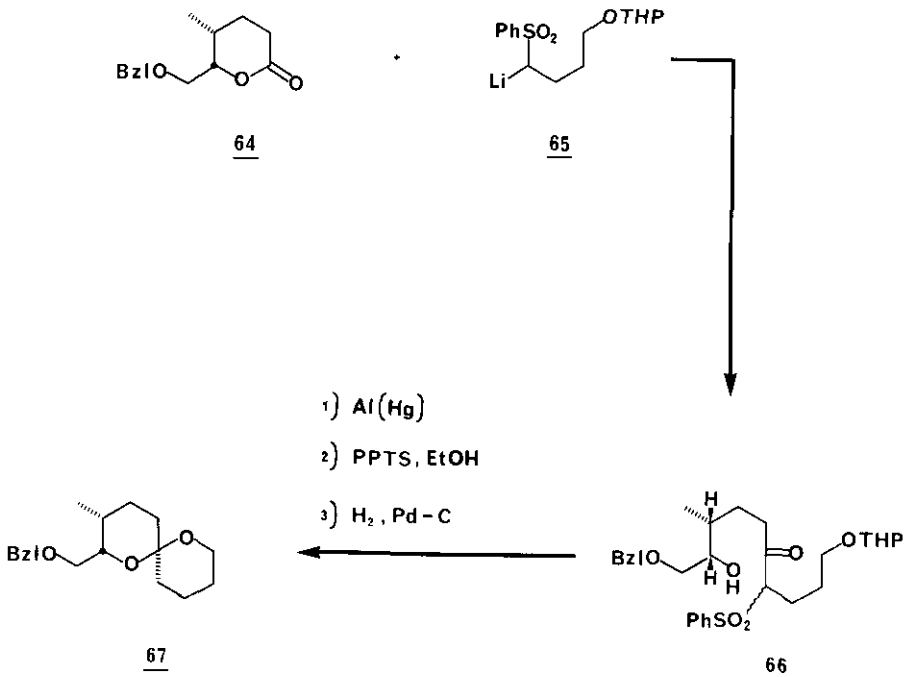
The addition of acetylide (56) to lactone (12) initiated the synthesis of models containing the 1,6,8-trioxaspiro[4.1.5.3]pentadecane system of salinomycin and narasin. The 1,2-adduct (57) was transformed into epoxy ketone (58), which upon treatment with CSA gave the single spiroketal (59). The stereochemistry of the carbon bearing the hydroxymethyl group was not determined.[30]



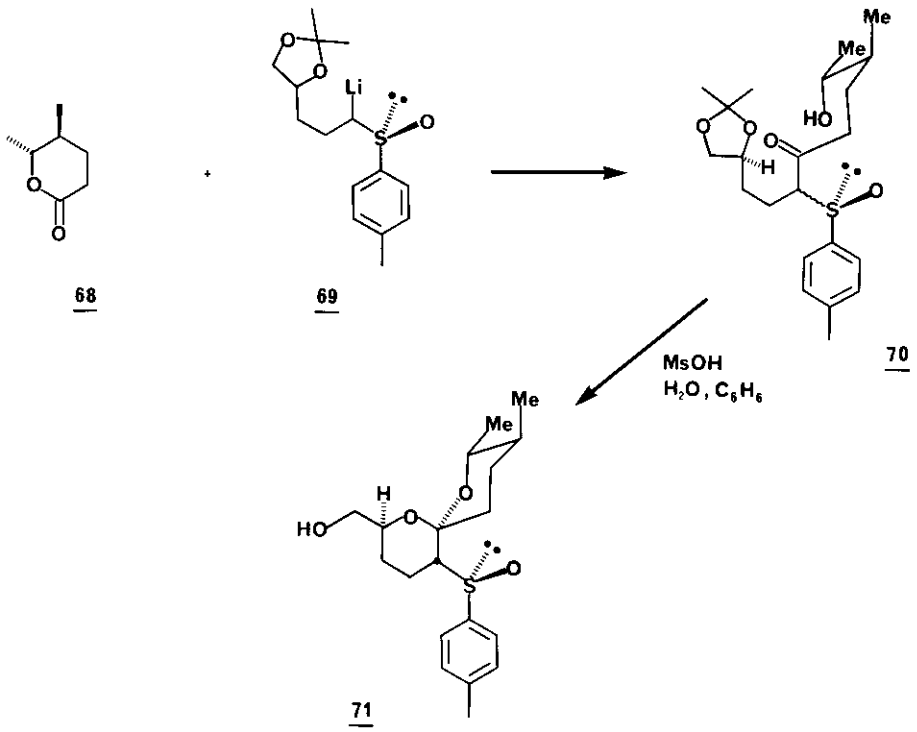
Crimmins et al. prepared the simple 1,7-dioxaspiro[5.5]undec-2-en-4-one (63) through the three step sequence starting with the addition of acetylide (60) to δ-valerolactone (12).[31]



Two groups have employed the condensation of a δ-valerolactone with an α-sulfonyl or an α-sulfinyl stabilized carbanion to establish the carbon framework of a 1,9-dihydroxynonan-5-one unit. Condensation of the lactone (64) with three equivalents of the lithio phenylsulfonyl species (65) gave an 86% yield of the β-ketosulfone (66), which upon desulfurization with aluminum amalgam, acid-catalyzed spiroketalization, and debenzylation afforded (67) in 79% yield.[23] In their total synthesis of milbemycin β_3 Williams et al.[32] condensed the chiral lactone (68) with the (R)-α-lithiosulfinyl carbanion (69) to obtain a mixture of the two diastereoisomeric β-ketosulfoxides (70). Acid catalyzed spiroketalization afforded a single diastereoisomer (71), which represents a noteworthy example of asymmetric induction. The epimerization of the sulfoxide moiety was directed by the combination of the other chiral centers in the molecule such that all of the substituents in the spiroketal achieved equatorial positions.

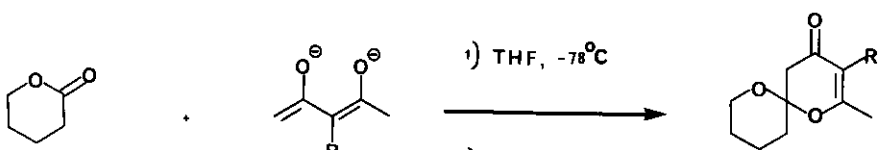


64 65 66 67



68 69 70 71

A final example of the use of a δ-valerolactone in the construction of 1,7-dioxaspiro[5.5]undecanes comes from the addition of pentane-2,4-dione dianions to δ-valerolactone (12) to give ultimately the spiroketals (72) and (73).[33]

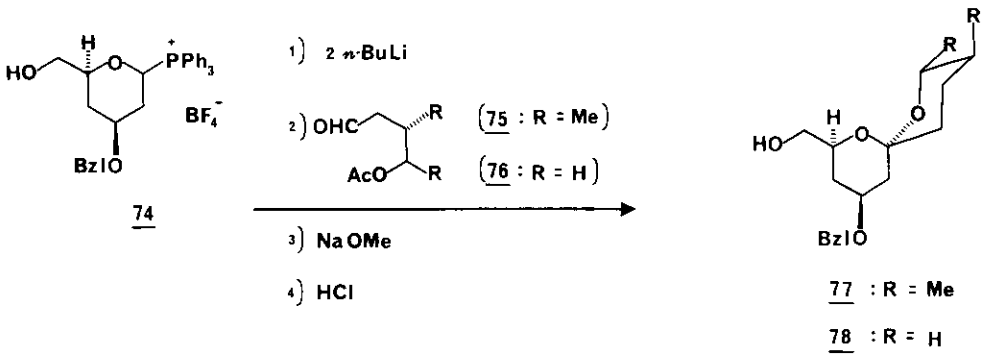


12

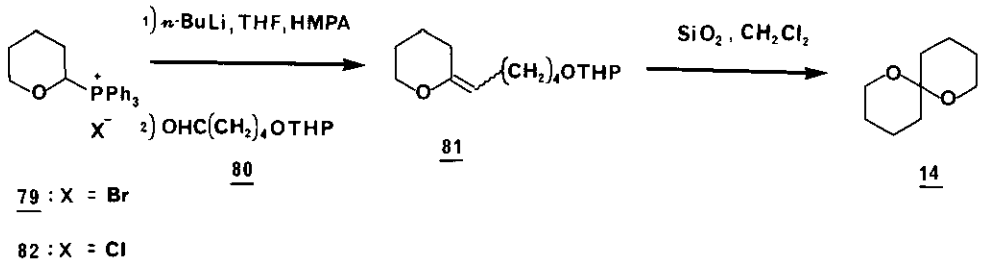
72 : R = H

73 : R = Me

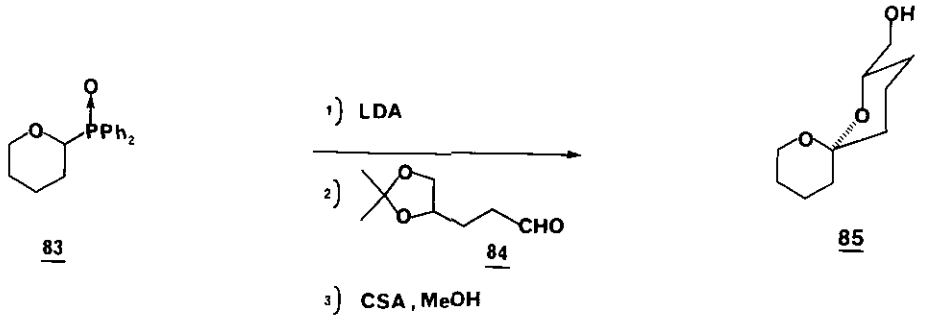
A very frequently used strategy for synthesizing 1,9-dihydroxynonan-5-ones has been to mask the ketone functionality in the form of an enol ether. Several groups have used Wittig reagents in this regard. Condensation of the ylide from (74) with aldehydes (75) and (76) followed by deprotection and acid-catalyzed spiroketalization gave (77) and (78) in 36 and 40% yield respectively.[34]



Similarly, it was reported that the ylide from phosphonium salt (79) could be condensed with aldehyde (80) and the resulting enol ether (81) could then be transformed into olive fly pheromone (14) in 62% overall yield.[35]

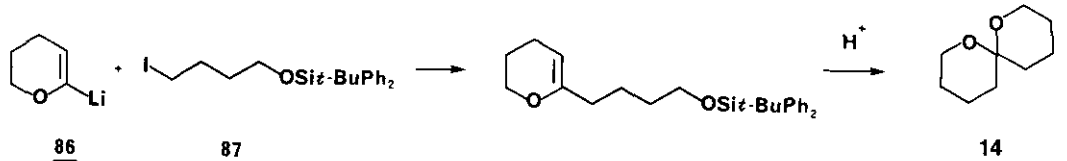


The diphenylphosphine oxide (83) was prepared by heating phosphonium salt (82) with NaOH. This phosphine oxide was a versatile reagent for the synthesis of enol ethers and, for example, condensation of the lithiated (83) with aldehyde (84) followed by spiroketalization gave (85) in 40% overall yield.[36]



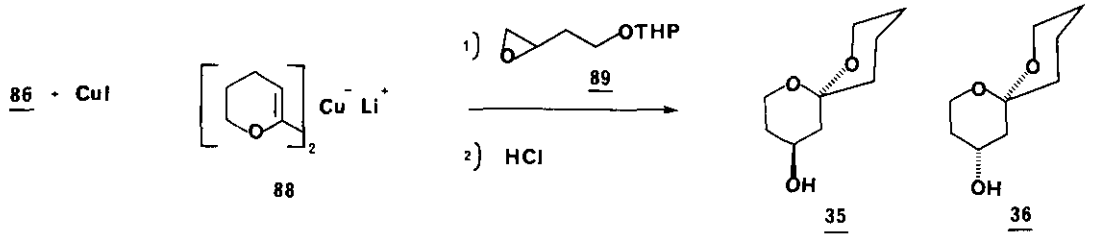
83 84 85

Alkylation of a 2-dihydropyranyl anion has been used to prepare 2-substituted dihydropyrans that were transformed into 1,7-dioxaspiro[5.5]undecanes by acid catalysis. 2-Lithiodihydropyran (86) was alkylated with (87) and the resulting adduct was then converted into (14) in 67% overall yield.[37]



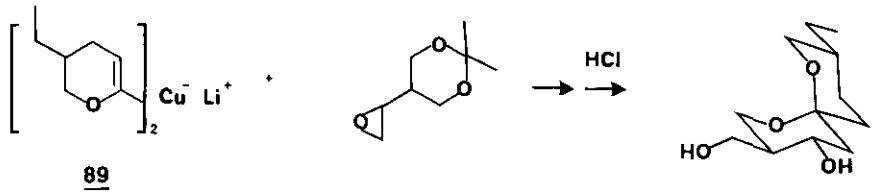
86 87 14

Condensation of the unsubstituted dihydropyranyl cuprate (88) with an epoxide led in two steps to a 95:5 mixture of diastereoisomers (35) and (36).[38]

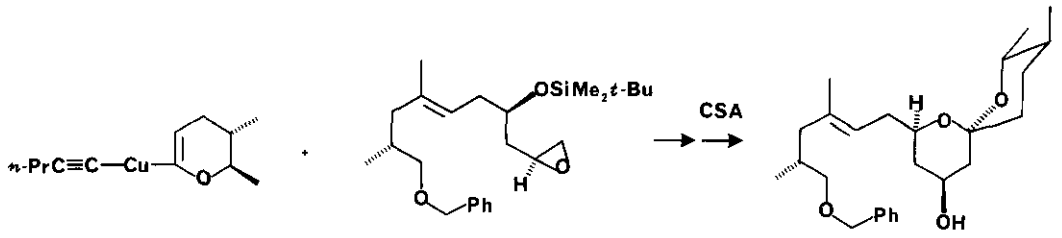


88 35 36

Two other examples of the use of dihydropyranyl cuprates were in the conversion of (89) to talaromycin B (90)[39] and the use of mixed cuprate (91) to prepare the spiroketal (92).[40]

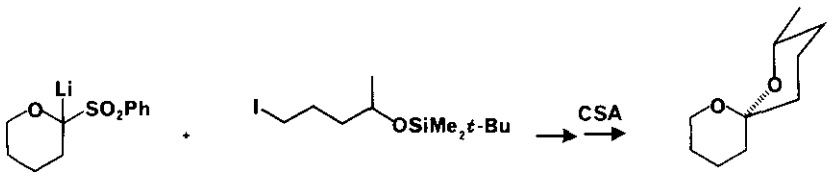


89 90



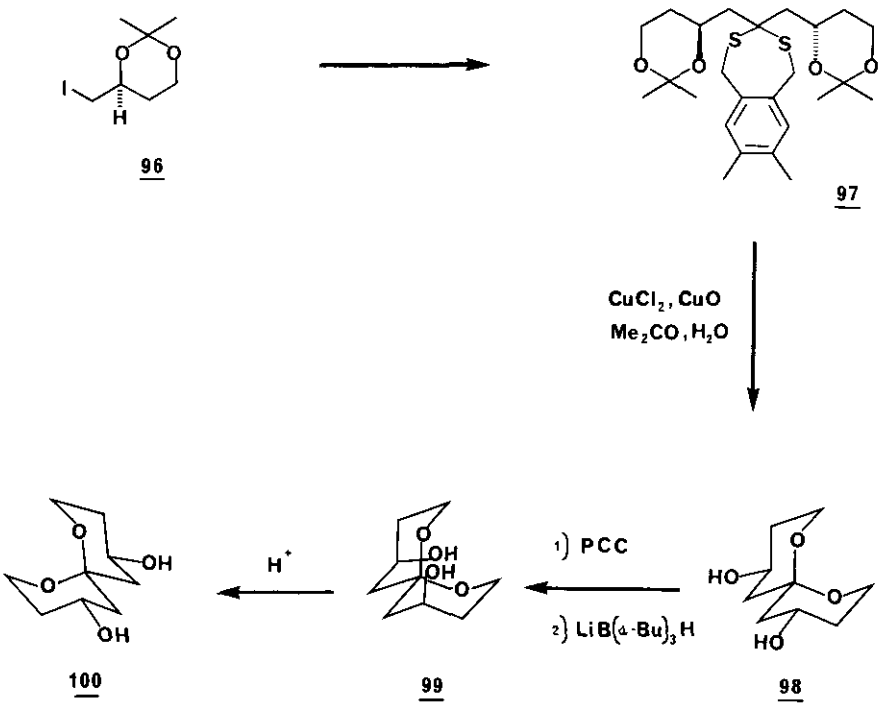
91 92

Alkylation of sulfone anion (93) followed by elimination of the elements of benzene sulfinic acid served as an equivalent strategy for the alkylation with a dihydropyran anion. Thus, condensation of (93) with iodide (94) and treatment of the adduct with acid gave the spiroketal (95) in 47% overall yield.[41]

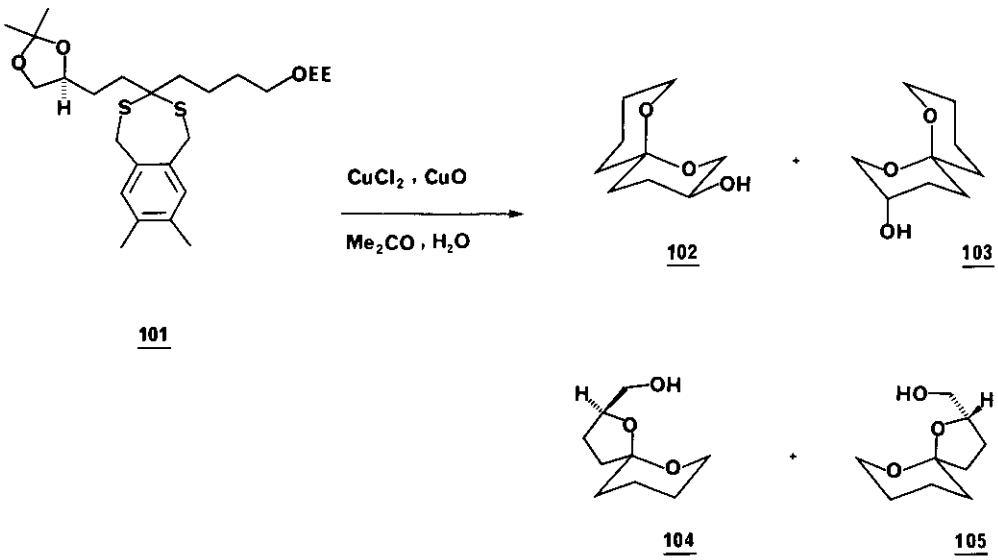


93 94 95

The strategy of carbonyl umpolung has been used frequently for the construction of 1,9-dihydroxynonan-5-one units; however, to date the reported examples have used exclusively dithioketals, and no use has been made of alternatives such as aliplatic nitro compounds or α-aminonitriles to achieve carbonyl umpolung. In a synthesis of the two enantiomers of olive fly pheromone (14) Mori et al. made clever use of combination of the anomeric control in spiroketals and the preference for equatorial substituents to control the absolute stereochemistry at the spiroketal carbon. The dithiepin (97) was prepared by bisalkylation with iodide (96). Hydrolysis of the dithioketal led in 87% yield to the (4S,6S,10S) spiroketal (98) as a single product. Oxidation of (98) with PCC followed by reduction with $LiB(sec\text{-}Bu)_3H$ gave the diaxial diol (4R,6S,10R)-(99). Treatment of (99) with acid led to hydroysis and reketalization to give the diequatorial diol (4R,6R,10R)-(100).[42]

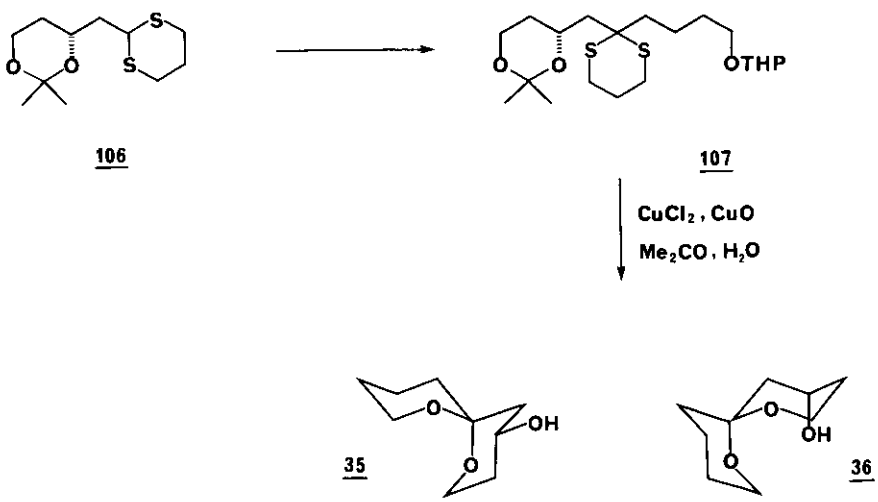


In a related study it was shown that the dithiepin (101) gave a complex mixture of spiroketals (102)-(105) upon dithioketal hydrolysis.[43]



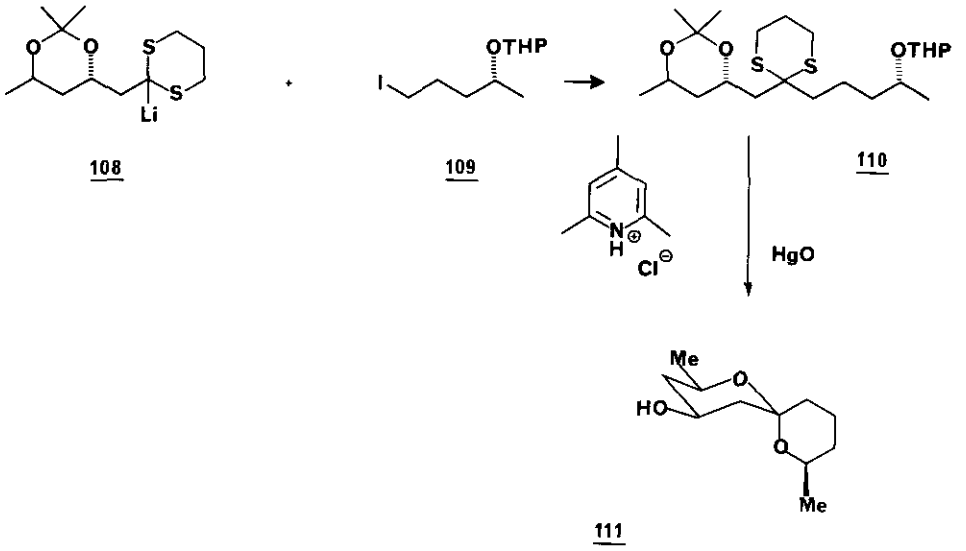
101 102 103 104 105

The dithiane (106) obtained from D-glucose was alkylated with the THP ether from 4-chloro-1-butanol to give the masked 1,9-dihydroxynonan-5-one (107) in 75% yield. Removal of the protective groups and spiroketalization gave a 1.86:1 mixture of the chiral forms of (35) and (36).[44]



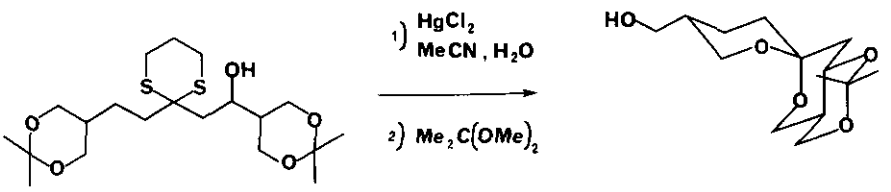
106 107 35 36

In a synthesis of the pheromones of the bee Andrena wilkella the lithiated D-threo dithiane (108) was alkylated with (R)-(109) to give (110). Removal of the protective groups from (110) gave spiroketal (111).[45]

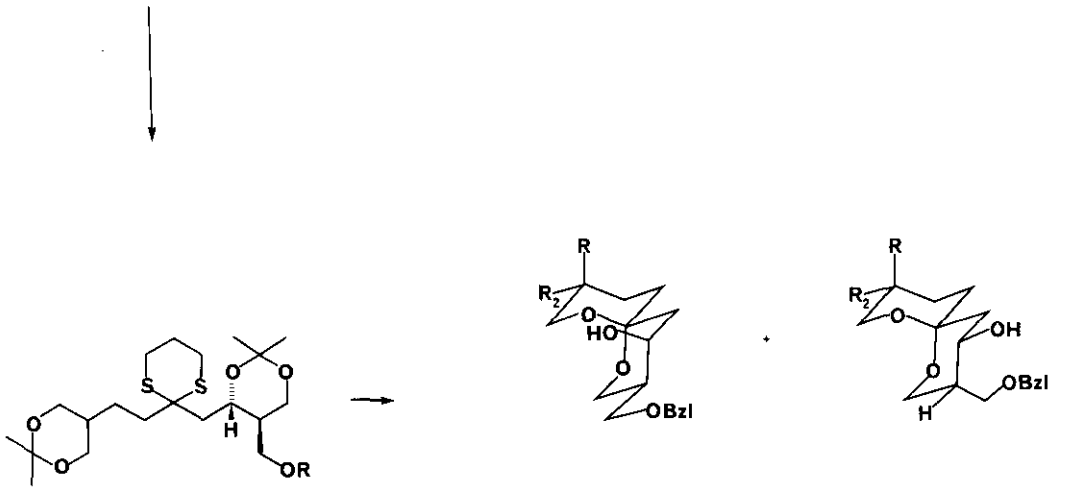


108 109 110 111

The versatility of the dithiane alkylation strategy was demonstrated nicely by Schreiber in syntheses of talaromycins A and B. The dithiane (112) was hydrolyzed with $HgCl_2$ in aqueous acetonitrile and the resulting material was treated with dimethoxypropane and acid to give spiroketal acetonide (113) in 65% yield.[46] Compound (112) was rearranged to (114) upon treatment with CSA in acetone, and the benzyl ether (115) was then converted into a mixture of spiroketals (116)-(119). A series of conditions was explored to determine ways of controlling the equilibration of this mixture. The axial hydroxyl substituted isomers (116) and (117) predominated with CSA in dichloromethane, whereas the diequatorial substituted hydroxyl isomers predominated when the equilibration was carried out with acid in a polar solvent such as aqueous THF, methanol, or dimethyl sulfoxide. These results were interpreted in terms of there being a stabilization of an intramolecular hydrogen bond between the C-4 hydroxyl and the neighboring ketal oxygen in the cases of (116) and (117), and a stabilization by hydrogen bonding to solvent in the cases where (118) and (119) were the predominant isomers.[47]



112 113



114 : R = H

115 : R = CH_2Ph

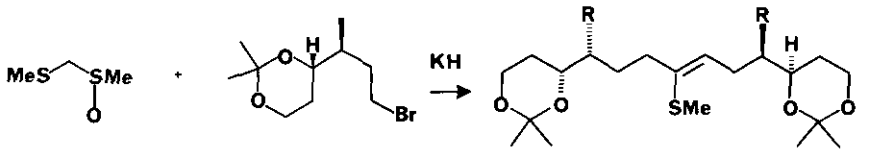
116 : R = H, R_2 = CH_2OH

117 : R = CH_2OH, R = H

118 : R = H, R_2 = CH_2OH

119 : R = CH_2OH, R_2 = H

In model studies related to the synthesis of the ionophore A-23187 Evans et al. condensed methyl methylthiomethylsulfoxide (120) with bromides (121) and (122) to give the diastereomeric pairs (123) + (125) and (124) + (126). Treatment of the 1:1 mixture of vinyl sulfides (123) + (125) with $HgCl_2$ in aqueous acetonitrile followed by azeotropic removal of water gave the crystalline spiroketal (127) in 89% yield based on (123), and an oil (128) + (129) in 40% yield based on (125). Similar hydrolysis of the 1:1 mixture of vinyl sulfides (124) + (126) led only to the isolation of spiroketal (130) in 40% yield based on (124).[48]



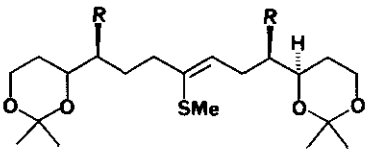
120

121 : R = H

122 : R = Me

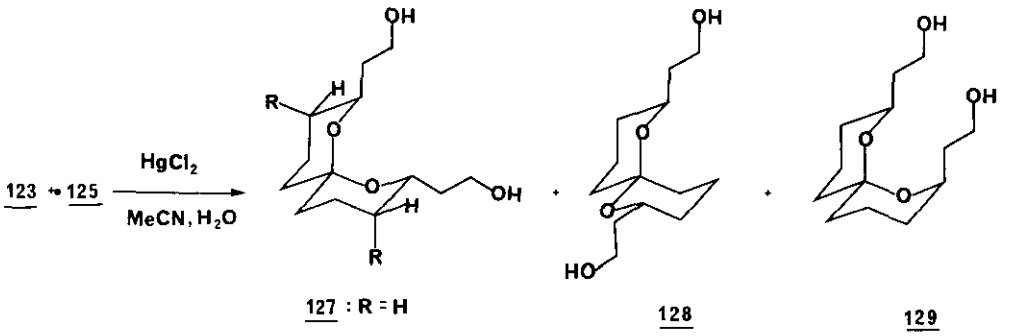
123 : R = H

124 : R = Me



125 : R = H

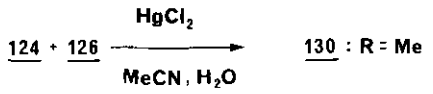
126 : R = Me



127 : R = H

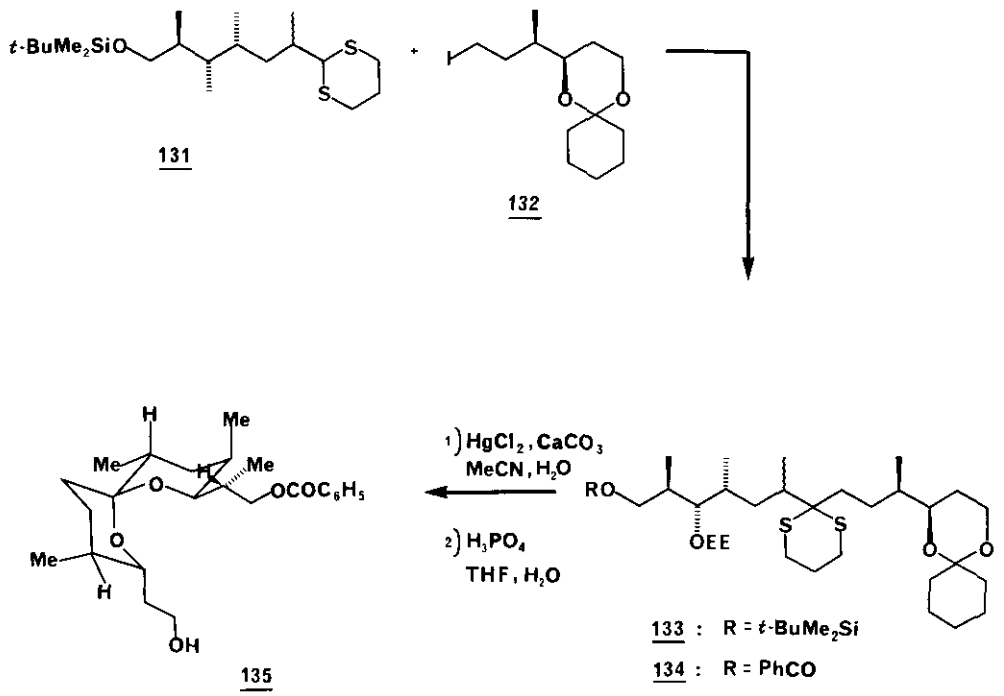
128

129

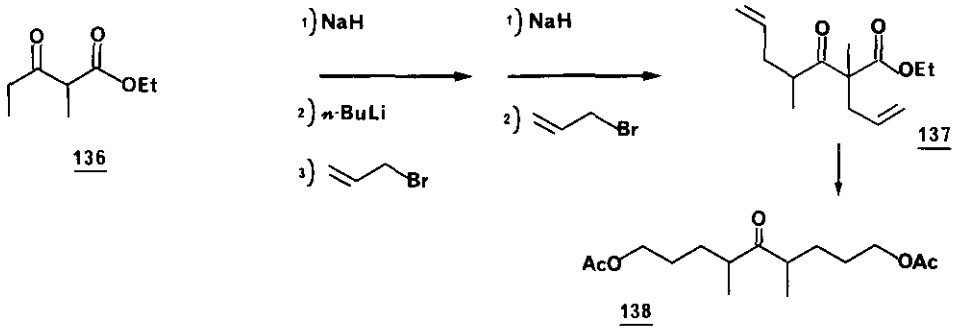


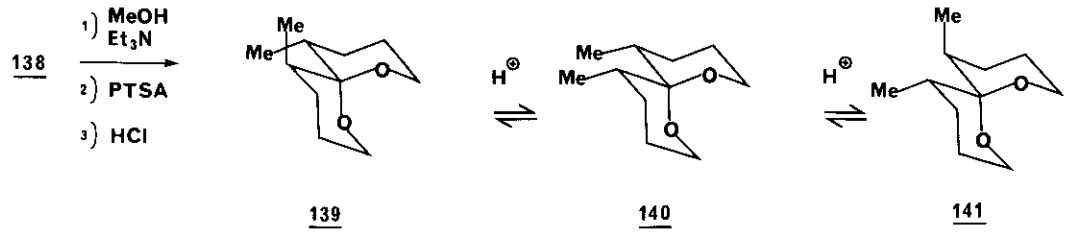
130 : R = Me

In the synthesis of the ionophore A-23187, Nakahara et al. prepared the dithiane (131) from D-glucose. Deprotonation of (131) with t-BuLi followed by condensation with (132) gave the key intermediate (133). This material was converted into the benzoate (134), which was then deprotected and spiroketalized to give (135) in 66% yield.[49] This synthesis illustrates a diastereoselection for the epimerizable C-5 methyl through 1,4- and 1,6-asymmetric induction exerted by the C-2 and C-8 substituents.



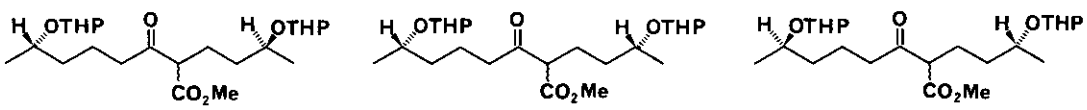
Several examples exist wherein a 1,9-dihydroxynonan-5-one unit was constructed through bisalkylation of an equivalent of a 1,3-dianion of acetone. Bisalkylation of ß-ketoester (136) gave (137), which was converted into diacetate (138) in several steps. Hydrolysis of (138) and acid-catalyzed spiroketalization resulted in epimerization of the methyl groups and produced an equilibrium mixture of the three spiroketals (139)-(141). The diequatorial substituted (139) constituted 96.8% of this mixture.[25]



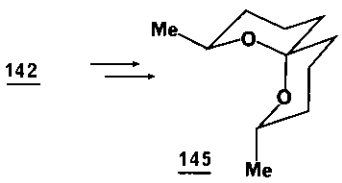


139 140 141

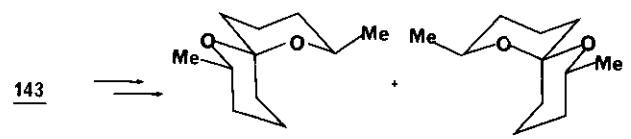
Synthesis of the three stereoisomers of 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane was initiated by sequential alkylation of methyl acetoacetate with the chiral forms of 3-tetrahydropyranyloxy-1-iodobutane to give diastereoisomers (142) - (144). The sequence of hydrolysis, decarboxylation, deprotection, and acid-catalyzed spiroketalization applied to each of these isomers gave the individual isomers (145) - (148). In each case the absolute stereochemistry of the ketal carbon was directed by having the two methyl substituents occupy equatorial positions.[50]



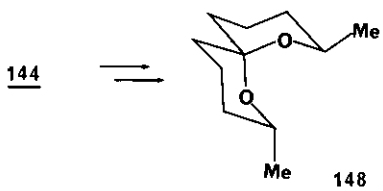
142 143 144



145

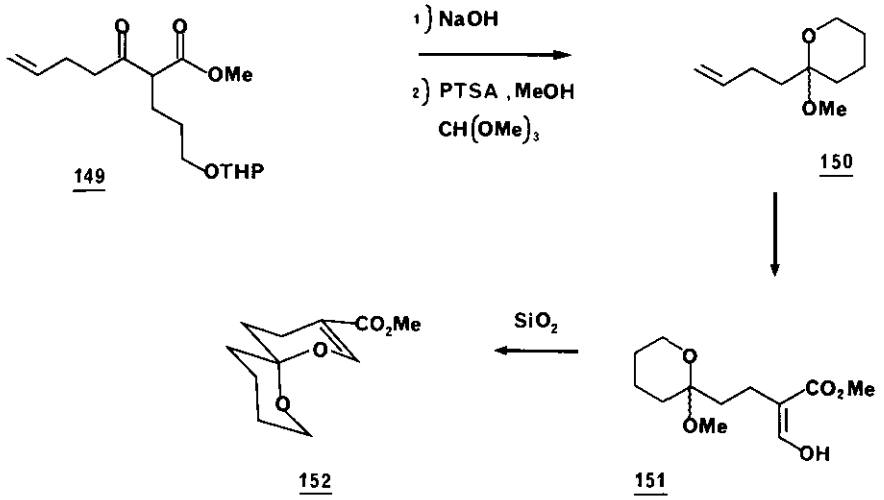


146 147



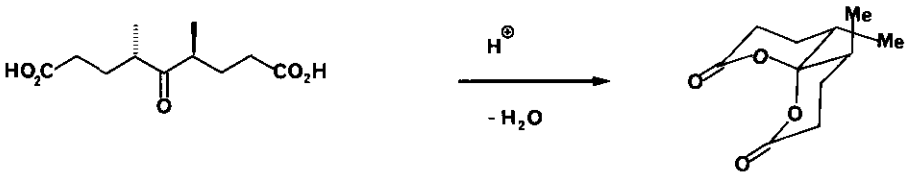
148

In a stereocontrolled synthesis of the C-1 to C-7 fragment of erythronolide A Deslongchamps et al. produced spiroketal (152) from methyl acetoacetate. Dialkylation of methyl acetoacetate gave (149), which was converted into tetrahydropyran (150) by hydrolysis, decarboxylation and ketalization. (150) was converted into hydroxymethylene ester (151) in several steps, and this material was rearranged into the 1,7-dioxaspiro[5.5]undecane (152) by treatment with SiO_2.[51]



149 150 151 152

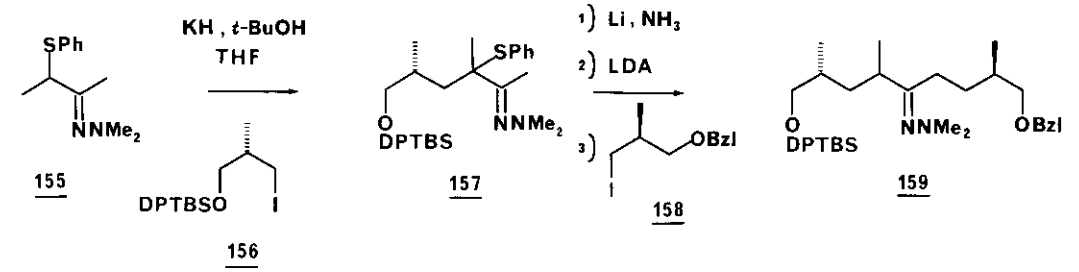
The dimethyl keto diacids (153) were synthesized as a 1:1 mixture of meso and *dl* isomers by twofold Michael reaction of the pyrrolidine enamine of 3-pentanone with methyl acrylate. Acid-catalyzed azeotropic removal of water from (153) gave a single dilactone (154) in ca. 50% yield.[52]

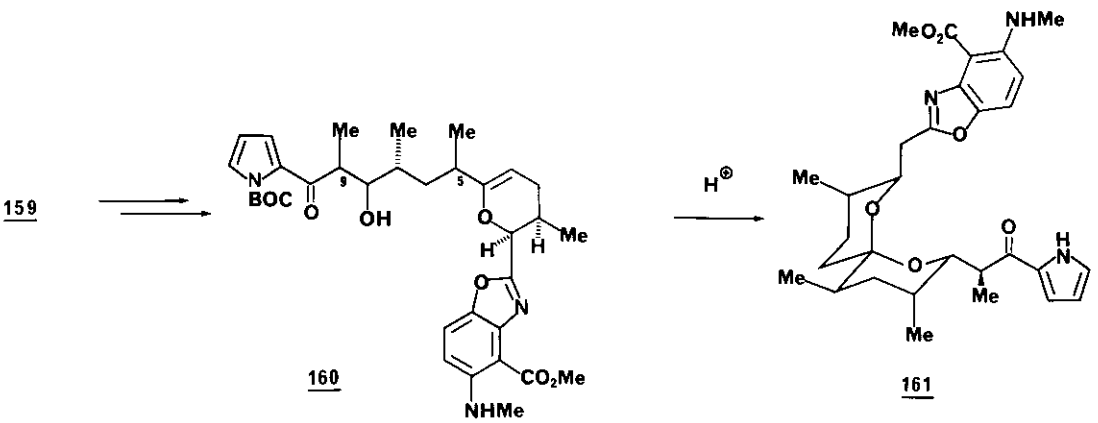


153 154

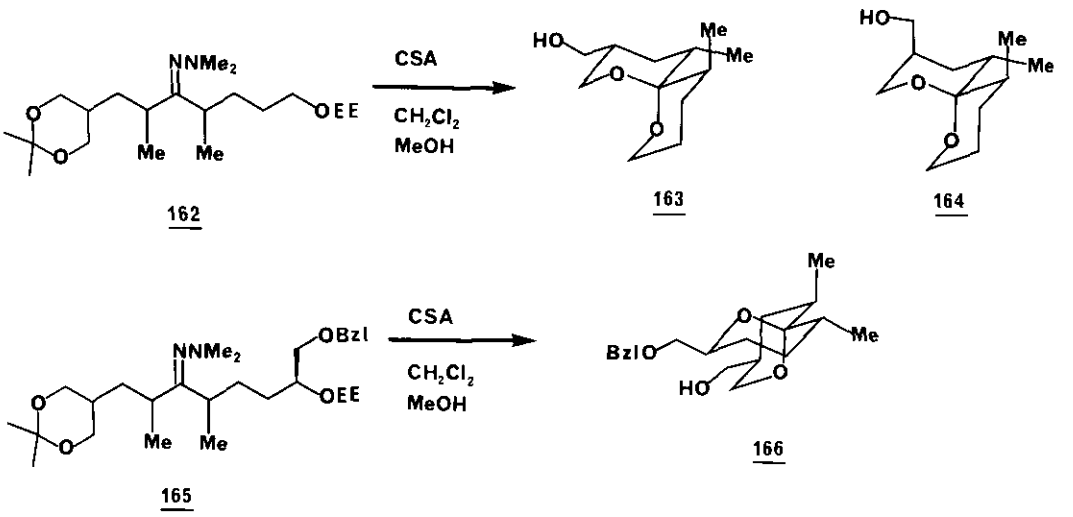
Evans et al. employed two consecutive alkylations of a dimethylhydrazone to construct the formal 1,9-dihydroxynonan-5-one system used in the synthesis of A-23187. Regiospecific alkylation of (155) with iodide (156) gave (157).

Reductive removal of the phenylthio moiety followed by regioselective alkylation with iodide (158) gave the protected 1,9-dihydroxynonan-5-one (159), which was transformed in several steps to dihydropyran (160). Treatment of (160) with acidic ion exchange resin in toluene at 100°C produced the loss of the pyrrole protective group, the epimerization of the methyls at C-15 and C-19, and spiroketalization to give A-23187 (161).[53]



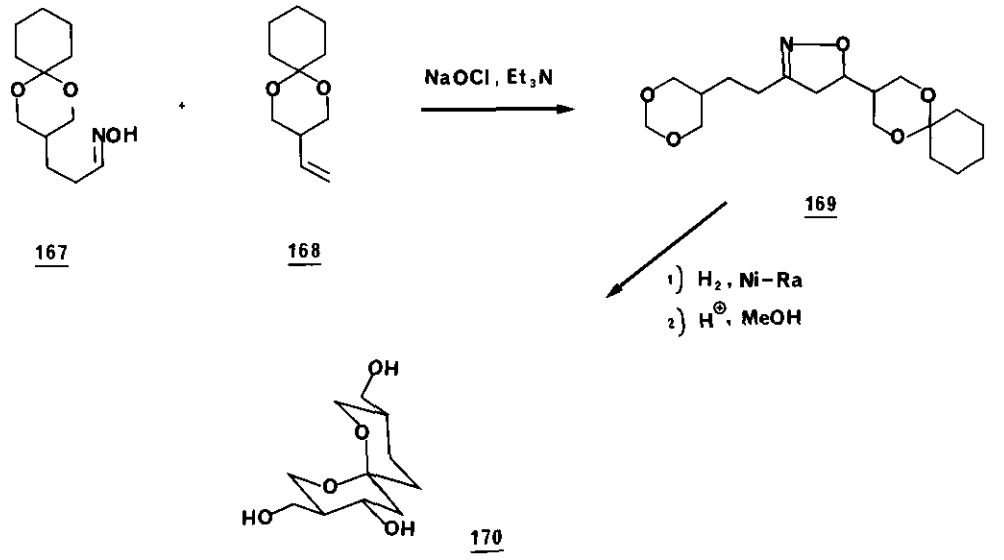


Schreiber has also employed the strategy of consecutive alkylations of a dimethylhydrazone to assemble the skeleton for a 1,7-dioxaspiro[5.5]undecane. Compound (162) was prepared by alkylation of the dimethylhydrazone from 3-pentanone. Reaction of (162) with CSA gave a 6:1 equilibrium mixture of spiroketals (163) and (164). The dimethylhydrazone (165) upon treatment with CSA gave spiroketal (166) with remarkable diastereoselectivity. The C-2 benzyloxymethyl substituent controlled the stereochemistry at the prochiral carbones C-5, C-6, C-9, and C-11. The equilibration of the C-5 and C-11 methyl groups represented a 1,4- and 1,6-asymmetric induction and the 1,8-asymmetric induction at C-9 was obtained through an 8:1 diastereotopic selectivity in the ketalization.[54]



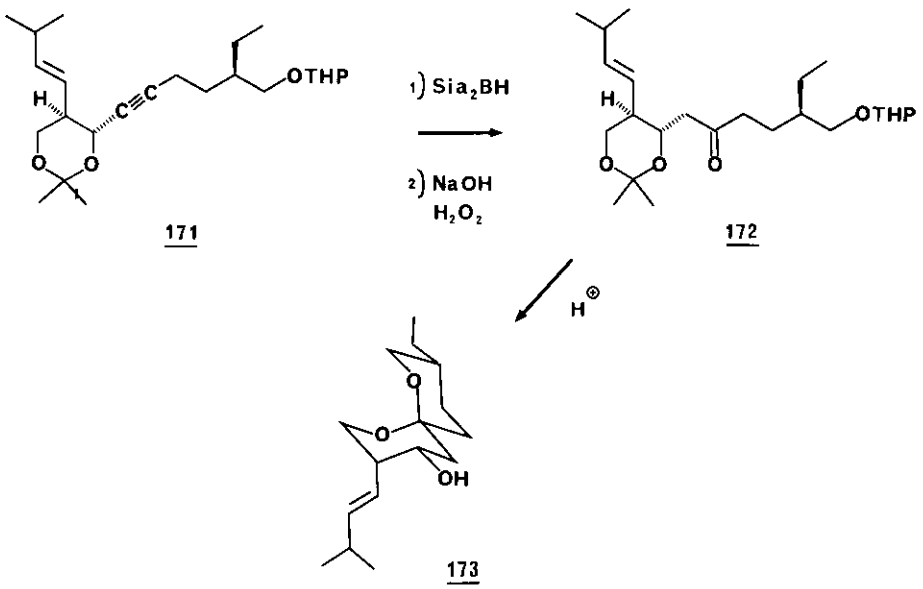
162 163 164 165 166

Nitrile oxide cycloaddition to an olefin was used for the construction of the 1,9-dihydroxynonan-5-one unit of talaromycin B. Reaction of a mixture of oxime (167) and olefin (168) with sodium hypochlorite and triethylamine gave the 1,3-dipolar cycloadduct (169) in 67% yield. Hydrogenolysis and spiroketalization afforded (170) in 67% yield.[55]



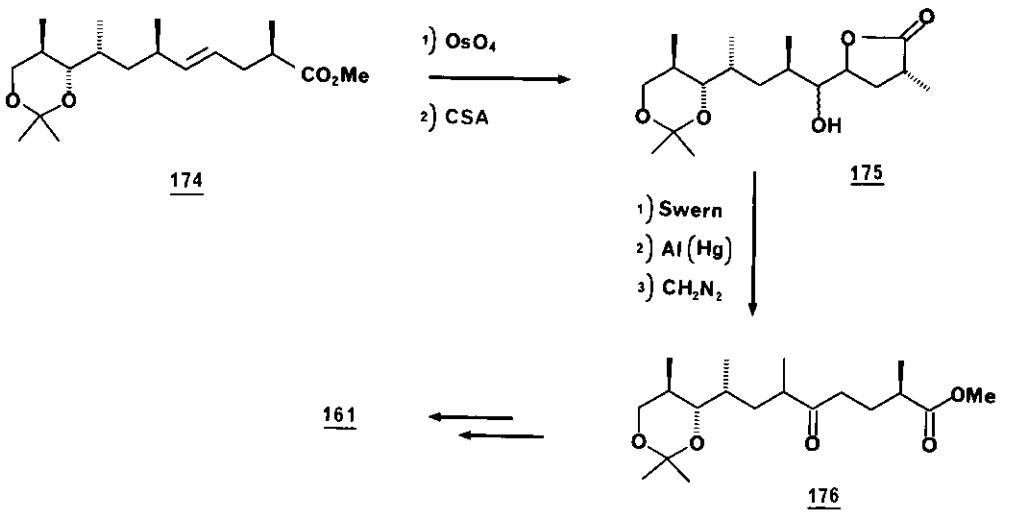
167 168 169 170

Acetylenes and olefins have been used as latent carbonyl groups in the construction of a 1,9-dihydroxynonan-5-one system. Midland converted acetylene (171) to ketone (172) in 40% yield by hydroboration. The other possible regioisomeric ketone was also produced in equal yield. Acidic hydrolysis and spiroketalization gave (173) in 94% yield, and this material was subsequently converted into (-)-talaromycin A.[56]



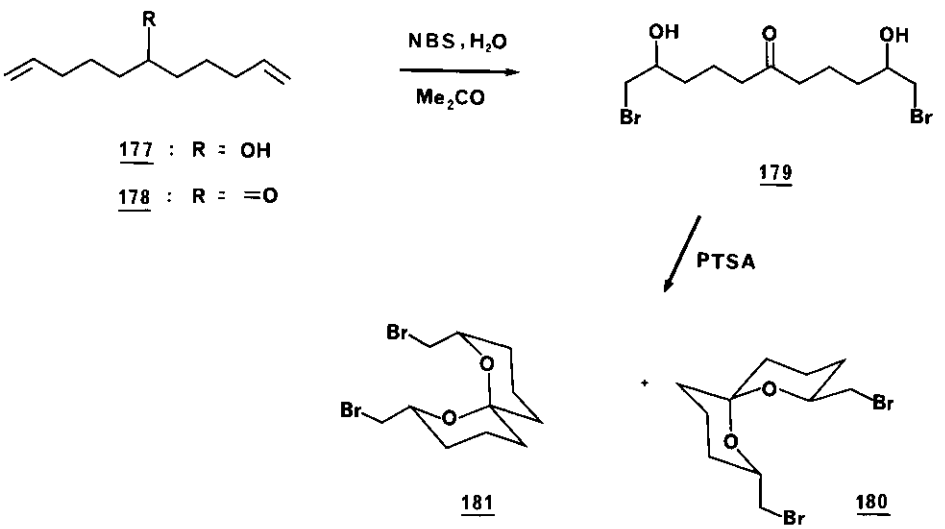
171 172 173

A key sequence in the synthesis of A-23187 by Grieco et al. consisted of transforming the olefin in (174) into a ketone. First (174) was converted into a glycol. The hydroxyls were differentiated through the formation of a δ-lactone with the neighboring ester function. Oxidation of the alcohol in (175) gave a ketone which was then reacted with aluminum amalgam followed by esterification to give (176). The ketone function in (176) was slated to become the spiroketal carbon in A-23187 (161).[57]



174 175 176 161

Cresp and Sondheimer used the formate carbonyl as a lynchpin for assembling a 1,9-dihydroxynonan-5-one system. Addition of 5-pentenyl Grignard reagent to methyl formate gave carbinol (177), which was then oxidized to (178). Addition of HOBr across the two double bonds of (178) gave a mixture of dl and meso bromohydrins (179). Spiroketalization of this mixture gave a 1:1 mixture of (180) and (181) in 70% yield.[58]

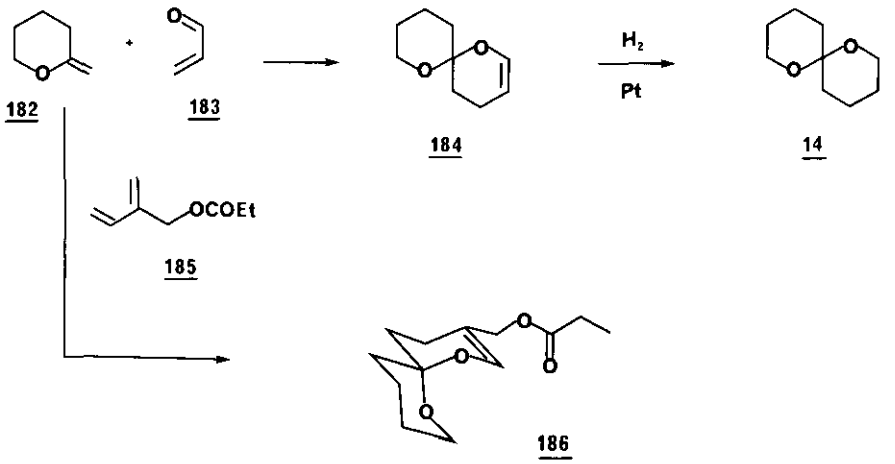


177 : R = OH
178 : R = =O

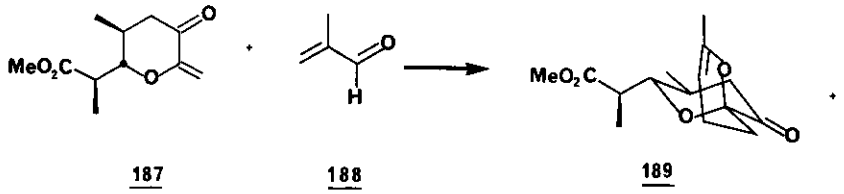
179 181 180

2. Hetero Diels-Alder Strategy

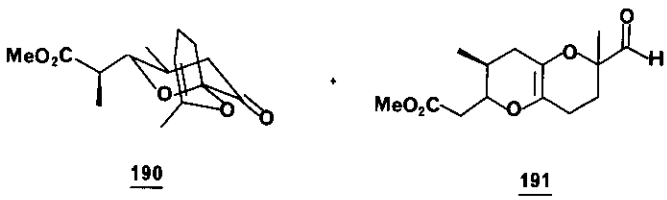
The 4 + 2 cycloaddition of an α,β-unsaturated aldehyde to a pyranoid vinyl ether has been developed into a versatile strategy for the construction of 1,7-dioxaspiro[5.5]undecanes. It is in principle more convergent than methods that rely on building up 1,9-dihydroxynonan-5-one units. Condensation of (182) with acrolein (183) gave cycloadduct (184) in 72% yield.[59] Catalytic reduction of (184) gave olive fly pheromone (14) in 93% yield.[60] Several substituted systems were also constructed by this technique. The allylic ester (186), an intermediate in the synthesis of an erythronolide A fragment, was made in 85% yield by condensation of (182) with (185).[51]



Ireland and coworkers utilized the hetero Diels-Alder reaction in their synthesis of macrolides.[61,62] Condensation of (187) with (188) gave a 72% yield of a 4.8:1 mixture of the two diastereoisomeric 1,7-dioxaspiro[5.5]undecanes (189) and (190) along with 5% yield of the alternate 4 + 2 cycloadduct (191).



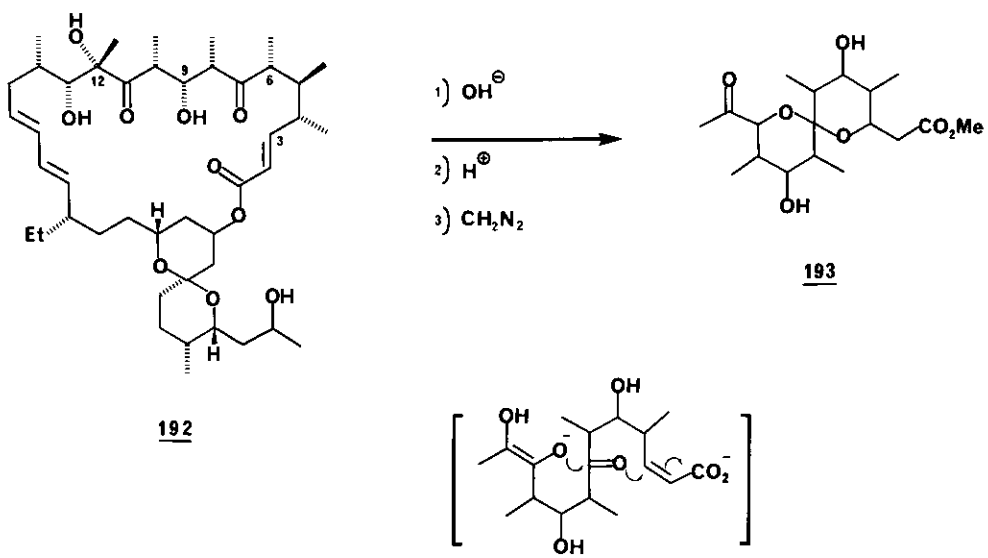
187 188 189



190 191

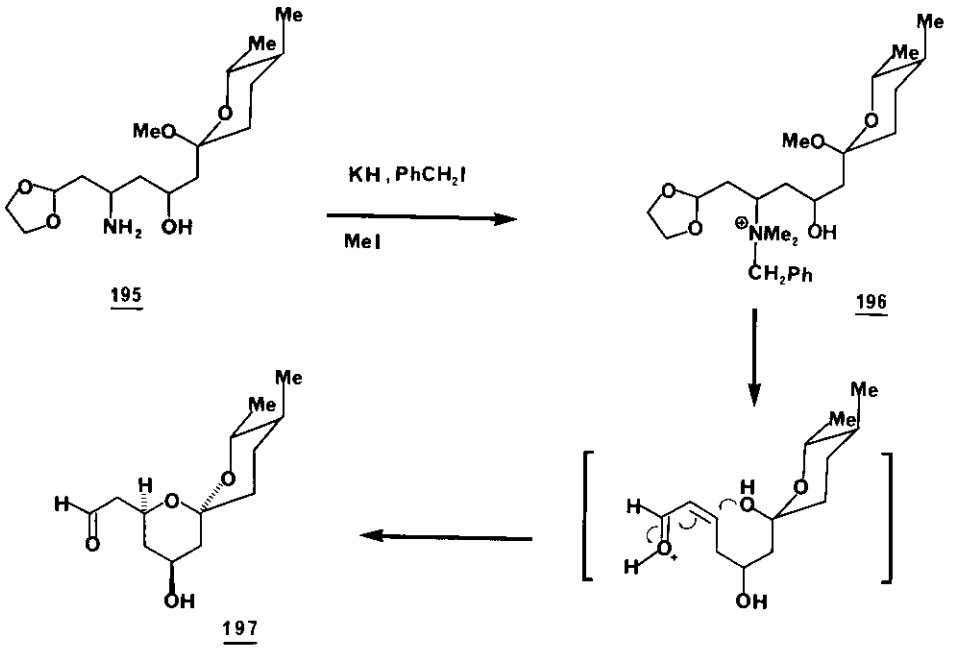
3. Intramolecular Michael-Type Reactions

An interesting example of an internal Michael-type spiroketalization was noted in the structure determination of rutamycin B. Base-catalyzed degradation of rutamycin B (192) followed by acidification and esterification with diazomethane resulted in the isolation of spiroketal (193). This result was explained by an internal Michael-type addition in intermediate (194), which comprises the C-1 to C-12 fragment of (192).[15]



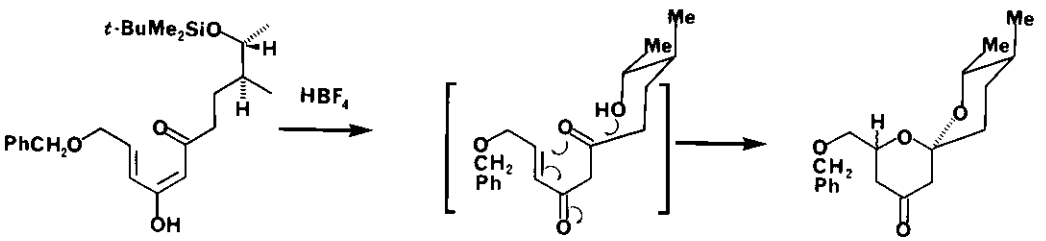
192 193 194

Smith employed a similar strategy in his synthesis of milbemycin β_3. Conversion of aminoalcohol (195) into quaternary (196) followed by hydrolysis and ß-elimination provided spiroketal (197) in 20 to 25% yield.[63]



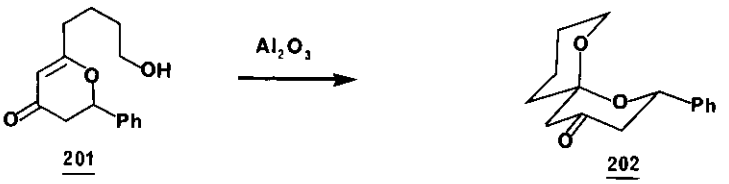
195 196 197

In a synthesis of a fragment of milbemycin β_3 it was shown that (198) formed spiroketal (199) in 40% yield by treatment with HBF_4 in diethyl ether.[64]



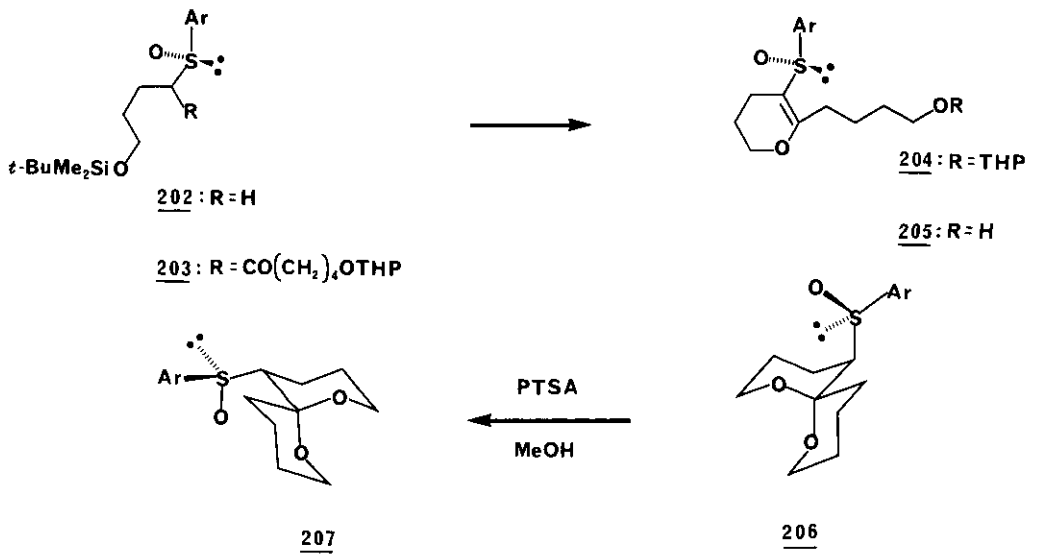
198 199

Danishevsky demonstrated that dihydro-δ-pyrones such as (200) underwent Michael-type spirocyclization on alumina to give (201).[65]



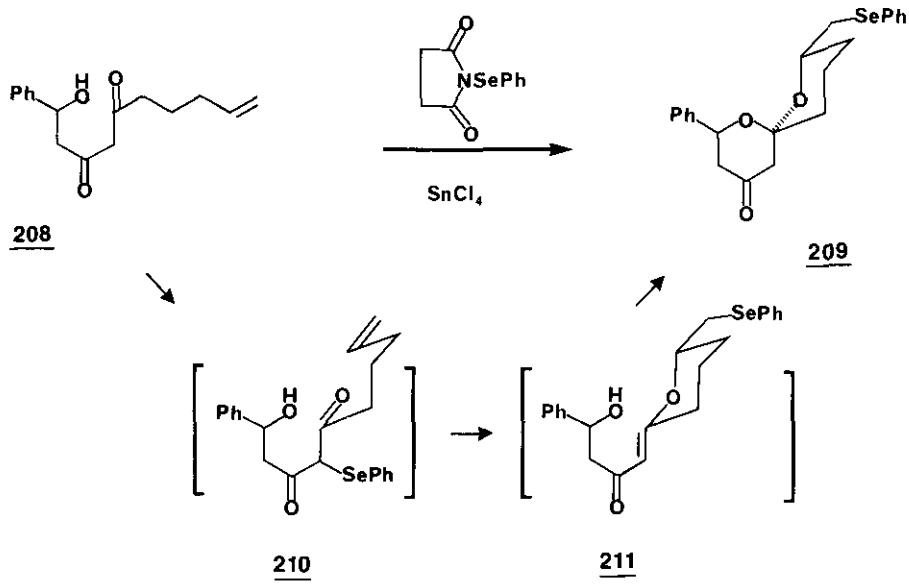
201 202

In an application of an internal Michael-type addition to a vinyl sulfoxide Iwata et al. were able to use a chiral sulfoxide moiety to control the absolute stereochemistry of the spiroketal carbon in an enantioselective synthesis of the enantiomers of the olive fly pheromone (14). The ß-ketosulfoxide (203), which was prepared by condensation of lithiated sulfoxide (202) with methyl 5-(tetrahydro-2H-pyran-2-yl)oxyvalerate, gave (204) upon deprotection and treatment with PTSA and $MgSO_4$. Deprotection of (204) gave the hydroxy vinylsulfoxide (205). Cyclization of (205) was accomplished by treatment with NaH to give the kinetically controlled product (206) containing the axial substituted sulfoxide. Treatment of (206) with PTSA in methanol gave the thermodynamically controlled product (207). Desulfurization of (206) and (207) gave (R)-(14) and (S)-(14) respectively.[66]



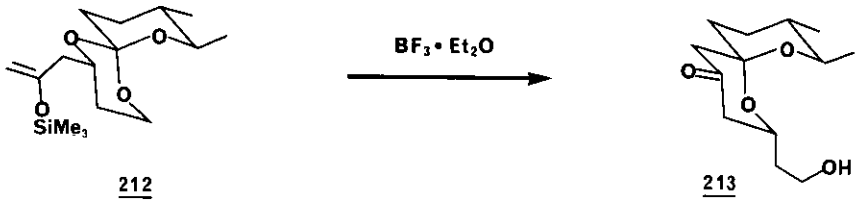
4. Organoselenenium-Mediated Cyclization

Ley et al. described the preparation of spiroketal (209) in 50% yield through the reaction of open-chain diketo olefin (208) with N-phenylselenophthalimide and tin(IV) chloride.[67] The authors proposed that (208) first underwent selenation of the central carbon of the ß-dicarbonyl system to give (210). This intermediate then went through a Lewis acid-catalyzed rearrangement with migration of the phenylseleno group to form intermediate (211), which then proceeded to spiroketal (209) with anomeric control.

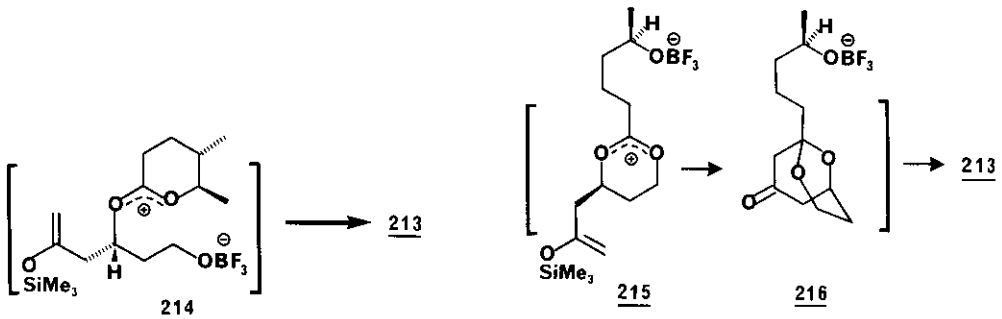


5. Intramolecular Directed Aldol Reaction

Kocienski et al. produced an application of an intramolecular directed aldol reaction in a synthesis of the 1,7-dioxaspiro[5.5]undecane system of milbemycin $ß_3$. Reaction of orthoester (212) with one equivalent of $BF_3 \cdot Et_2O$ gave sprioketal (213) in 35% yield.[68] The instability of the products under the reaction conditions was noted as a potential drawback to this method. Both dioxonium ions (214) and (215) were possible intermediates. Intermediate (214) could go directly to (213), whereas (215) would have to proceed first to (216) and then undergo acetal exchange to give (213).

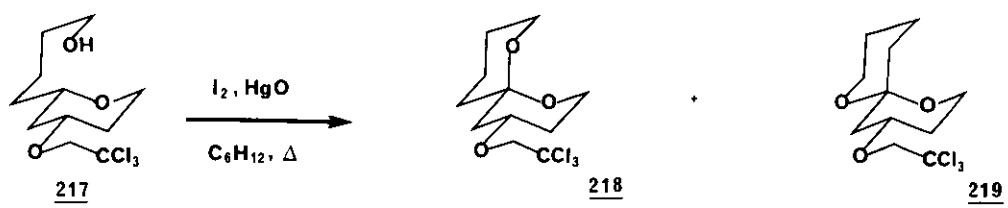


212 213

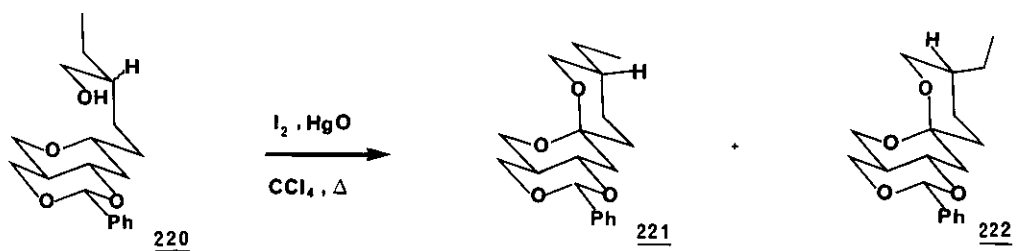


6. Formation of Spiroketals Through Hypoidite Intermediates

Two reports have described the formation of a 1,7-dioxaspiro[5.5]undecane system via hypoidite intermediates. Treatment of alcohol (217) with I_2-HgO in cyclohexane at reflux gave the spiroketals (218) and (219). Treatment of this mixture with TFA gave (218), the product of anomeric control.[69] A similar strategy was used in the synthesis of (±)-talaromycin B. Heating a mixture of diastereomeric alcohols (220) with I_2-HgO in CCl_4 at reflux gave a 3:1 mixture of diastereoisomers (221) and (222) in 55% yield.[70]

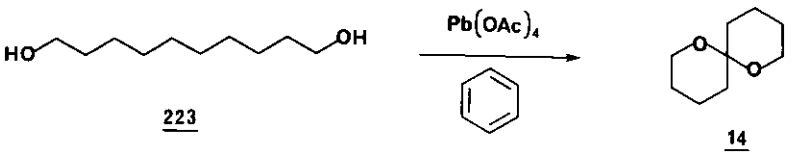


217 218 219



220 221 222

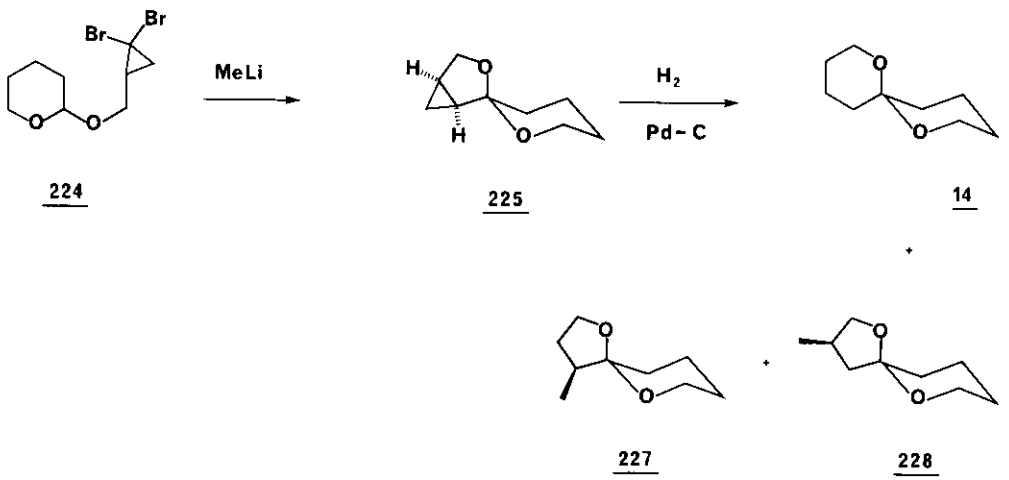
In a somewhat related case it was shown that treatment of 1,10-decanediol (223) with lead tetraacetate in refluxing benzene gave (14) in 3.3% yield.[71]



223 14

7. Ring Expansion Strategy

Reaction of dibromocyclopropane (224) with methyllithium produced a 20% yield of the spiroketal (225), in which the cyclopropane CH_2 and the 6-membered ring ether oxygen were syn. Hydrogenolysis of (226) in the presence of Pd-C gave the 1,7-dioxaspiro[5.5]undecane (14) and the two other possible hydrogenolysis products (227) and (228).[72] The low yield of the carbenoid insertion reaction and the lack of chemoselectivity in the hydrogenolysis are clear obstacles to the wide application of this synthetic strategy.



224 225 14

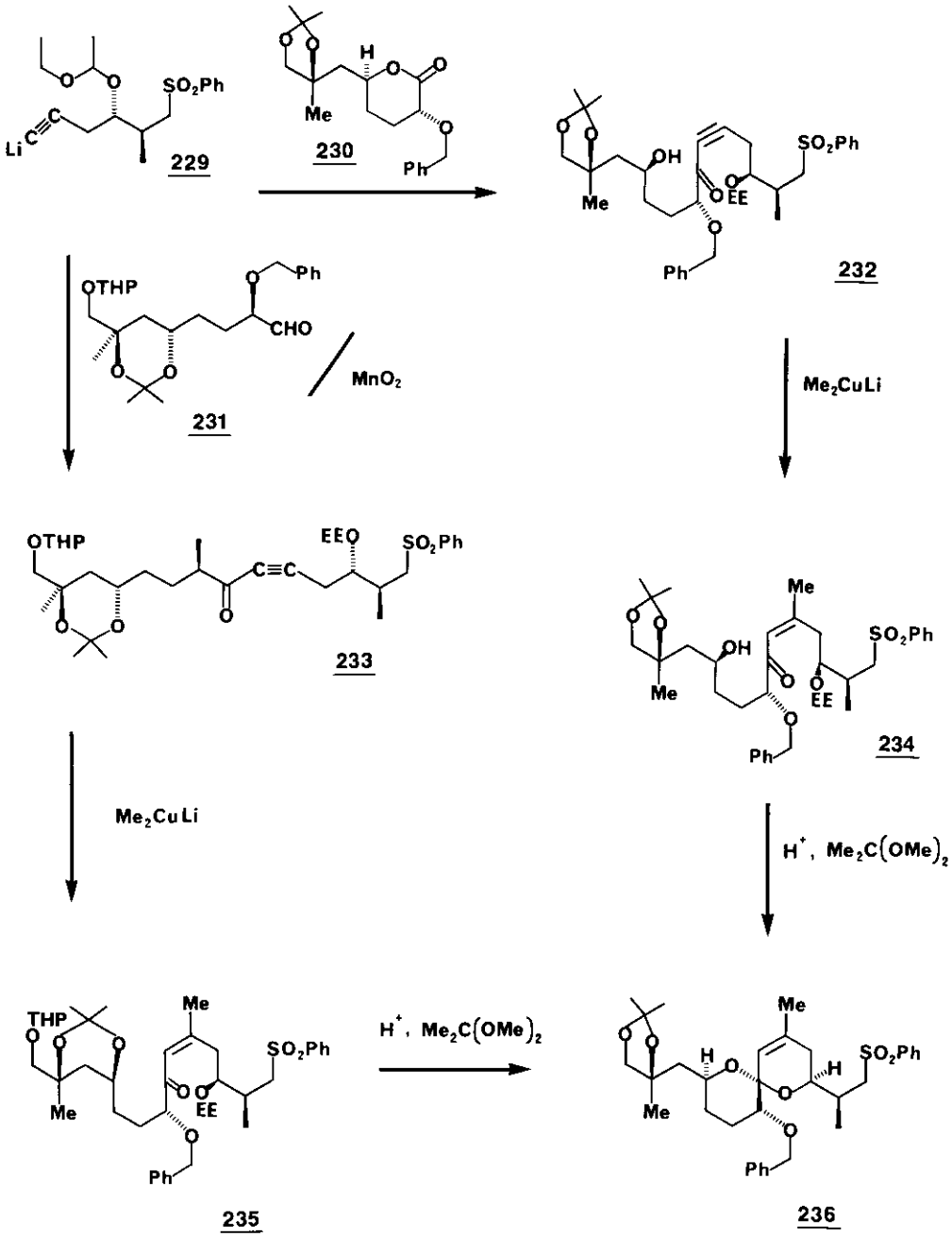
227 228

The foregoing description of the syntheses of 1,7-dioxaspiro[5.5]undecanes has displayed various threads of intense synthetic activity, the majority of which have been reported within the last five years. Much of this work has been

directed at finding efficient solutions to stereochemical and logistical problems associated with assembling complex natural products. Among these efforts the syntheses of milbemycin β_3,[32,62] A-23187,[53,57] and talaromycin A and B[46,47,54,55,70] are noteworthy examples of the present state of the art of total synthesis. No less engaging are the syntheses of the chiral insect pheromones, especially the work of Mori[42] and Iwata[66] in which the stereochemistry at a chiral ketal carbon was skillfully manipulated by the application of the principle of anomeric control. Other lessons that have emerged from this body of work on spiroketals have come from the demonstrations of strategies for using 1,7-dioxaspiro[5.5]undecane system to control diasteroselection in a complex synthesis. In this regard the work of Deslongchamps,[51] Schreiber,[54] and Ireland[62] have been especially heuristic. Finally, while it is clear that the majority of the syntheses of 1,7-dioxaspiro[5.5]undecanes fall into the category of assembly of formal 1,9-dihydroxynonan-5-one units destined for acid-catalyzed spiroketalization, it is also true that the literature is liberally sprinkled with fascinating and less obvious alternative strategies for the construction of the spiroketal unit, and thus the work viewed from this perspective shows the rich variety of approaches that are available to the modern synthetic chemist.

ADDENDUM

Following the completion of this manuscript Isobe et al. published additional results from their studies on okadaic acid. Condensation of lithioacetylide (229) with lactone (230) and aldehyde (231) gave propargylic ketones (232) and (233) respectively. Treatment of each ketone with lithium dimethylcuprate gave enones (234) and (235). These were converted into spiroketal (236) by acid catalysis.[73]


Li
SO2Ph
229
H
Me
230
Ph
OH
OEE
SO2Ph
Me
Ph
232
OTHP
Ph
CHO
231
MnO2
Me2CuLi
OTHP
EEO
SO2Ph
233
Me2CuLi
Me
OH
SO2Ph
Me
OEE
Ph
234
H+, Me2C(OMe)2
THP
Me
SO2Ph
Me
OEE
Ph
235
H+, Me2C(OMe)2
Me
H
H
SO2Ph
Me
Ph
236

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