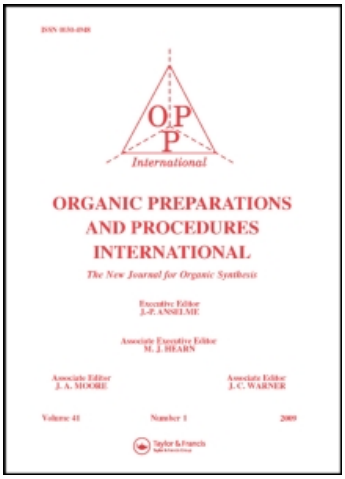

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SYNTHESES OF AVENACIOLIDE AND RELATED *bis*LACTONES. A REVIEW

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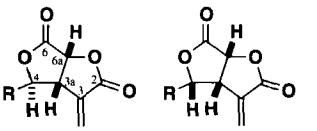
INTRODUCTION

Avenaciolide (**1**) is a naturally occurring antifungal compound that was first isolated by Brookes, Tidd, and Turner[1] from *Aspergillus avenaceus* H. Smith. It was also subsequently obtained from cultures of *Aspergillus fischeri* var. glaber.[2] The peculiar bislactonic structure of **1**, assigned to avenaciolide,[3] was later confirmed by a more detailed NMR study,[4] by total synthesis,[5,6] and by crystallographic data.[7] The tentative absolute configuration assigned to avenaciolide was corrected by its synthesis using carbohydrates as starting materials.[8,9] ^{13}C-NMR spectra of ^{13}C-labelled avenaciolides show a biosynthetic origin from 3-oxododecanoic acid and succinic acid.[10] Isoavenaciolide (**3**) has been isolated in a small amount from large-scale growing of *Aspergillus avenaceus* H. Smith.[11] 4-epi-Ethisolide[11] (**2**) and ethisolide[12] (**4**) are related compounds, isolated from unidentified species of *Penicillium,* having different alkyl chains. Of these, avenaciolide exhibits the most diverse and potent biological activity, including inhibition of fungal spore germination,[1] antibacterial action,[1] and inhibition of glutamate transport in rat liver mitochondria.[13]



1 R = C_8H_{17}-*n* **3** R = C_8H_{17}-*n*
2 R = C_2H_5 **4** R = C_2H_5

Although these compounds are relatively small in size, the combination of biological activity and unique structures has attracted much synthetic attention. The present paper will describe the different approaches oriented to the synthesis of these metabolites. A table of Abbreviations is given on p. 320.

I. GENERAL STRATEGIES

The fundamental part of the synthesis of the avenaciolides is the construction of the bislactone fragment. Many strategies have been considered based on carbon-carbon or carbon-oxygen bond formation or a combination of both. In order to systematize the present review we will organize the sections taking into consideration the bond formation used to build up the fused ring fragment and/or to achieve the final stereochemistry (Scheme 1). Of course, a scheme of this kind should be taken as a

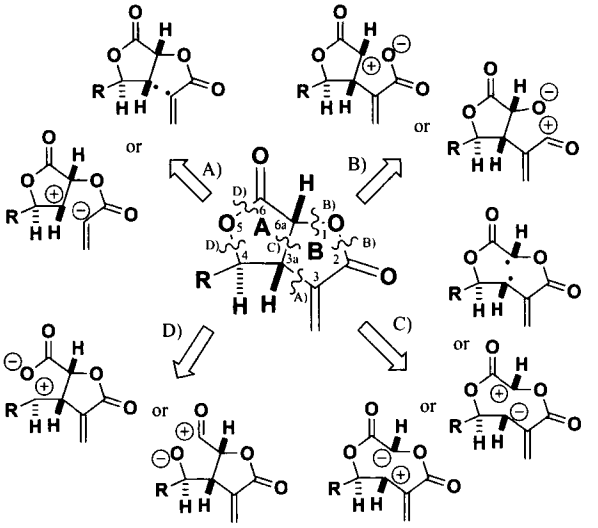
simple indication since in some cases the described syntheses may use more than one guideline. Thus, two major criteria of organization will be followed: in one case considering the order of the ring synthesized first (**A** or **B**), the second organizing the syntheses in accordance with the bond formation critical in the synthesis:

Approach A): Synthesis of the lactone **B** by the C_3-C_{3a} bond formation.

Approach B): Synthesis of the lactone **B** by the O_1-C_{6a} or O_1-C_2 bond formation.

Approach C): Usually *via* the synthesis of lactone **A** by the C_{3a}- C_{6a} bond formation.

Approach D): Synthesis of lactone **A** by the O_5-C_6 or C_4-O_5 bond formation.



Scheme 1. Summary of Approaches in the Synthesis of Avenaciolide

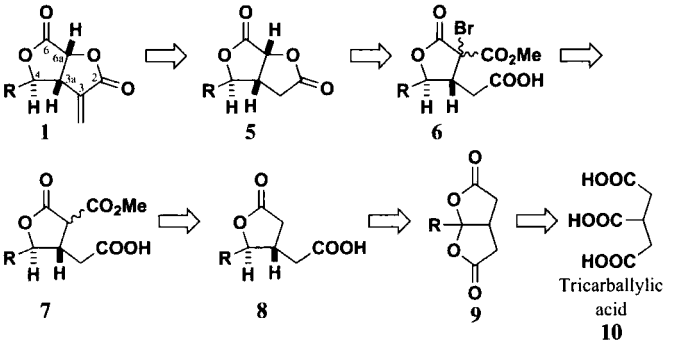
II. SYNTHESES USING FORMATION OF RING-A FIRST

This section will deal with those syntheses using a product in which lactone **A** is already present or latent. Usually, the formation of lactone **B** is the most demanding process in terms of achieving the final stereochemistry.

1. The Parker and Johnson Synthesis of Avenaciolide.

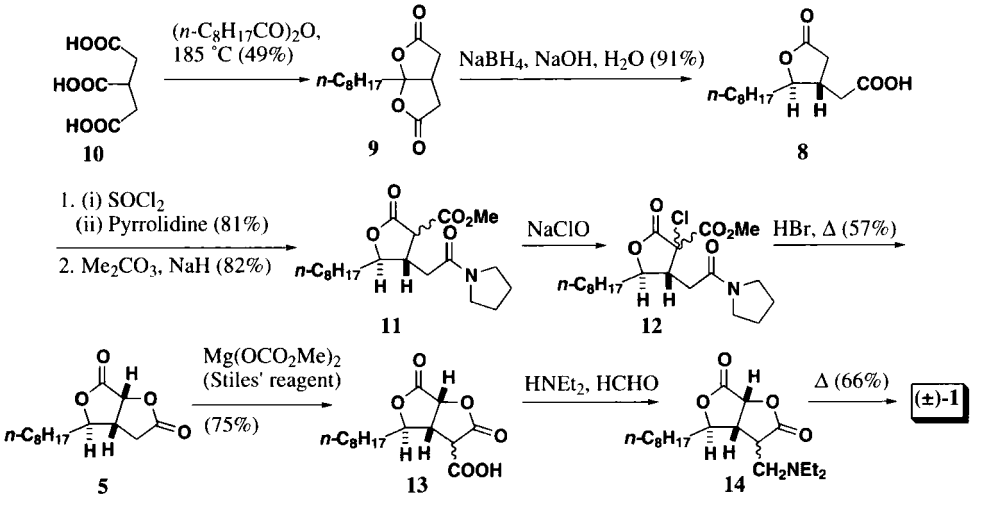
We will consider the first total synthesis of the racemic form of **1**, performed by Parker and Johnson.[5] This synthesis could be included under the approach B) and it is based on the retrosynthetic analysis outlined in Scheme 2. This approach is especially important for two major reasons: 1) it was the synthesis used to corroborate the proposed structure of avenaciolide,[1] and 2) it contains important points for the subsequent synthetic work. The synthesis takes advantage of the possibility of the introduction of methylene groups adjacent to a butyrolactone carbonyl group. After the pioneering work of Parker and Johnson[5] this step has been considered to be a standard to perform such a transformation. Thus, most of the syntheses of avenaciolide and its family have been focused on the intermediate **5** performing the methylenation as the final step. With such methodology previously available[14] the synthesis of the bislactone **5** was considered by an intramolecular substitution of a carboxylic group

over a bromide located in the α-position relative to the carbonyl group located in the γ-lactone **A**. The activated compound **6** could be obtained from the less functionalized *trans*-substituted butyrolactone **8** by selective carbomethoxylation. The synthesis of the necessary γ-lactone **8** could be contemplated by the reduction of the bislactone **9** available from tricarballylic acid through a Fittig condensation.[15]



Scheme 2

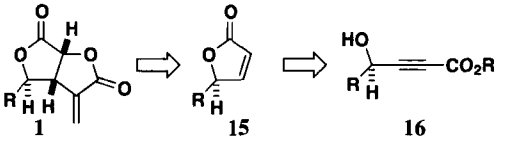
The synthesis of avenaciolide begins with the acylative decarboxylation of tricarballylic acid by *n*-nonanoic anhydride. Reduction of the bislactone **9** with sodium borohydride led to the *trans*-disubstituted γ-lactone **8** in high yield. In order to prevent the functionalization of the acidic residue, **8** was converted to the amide *via* the acid chloride. The carbomethoxylation of the α-position relative to the carbonyl-γ-lactone was then cleanly performed to give the ester **11**. This β-dicarbonyl compound reacted rapidly with sodium hypochlorite or bromine or iodine in the presence of a weak base such as sodium acetate. Interestingly, when the haloamidoester **12** was submitted to acidic reflux followed by azeotropic removal of water the concomitant cyclization, ester hydrolysis and decarboxylation led to the desired bislactone **5**. The use of Stiles' reagent[16] afforded the acid **13** that was submitted to decarboxylative methylenation to lead cleanly to avenaciolide (**1**).



Scheme 3. The Parker and Johnson Synthesis of Avenaciolide

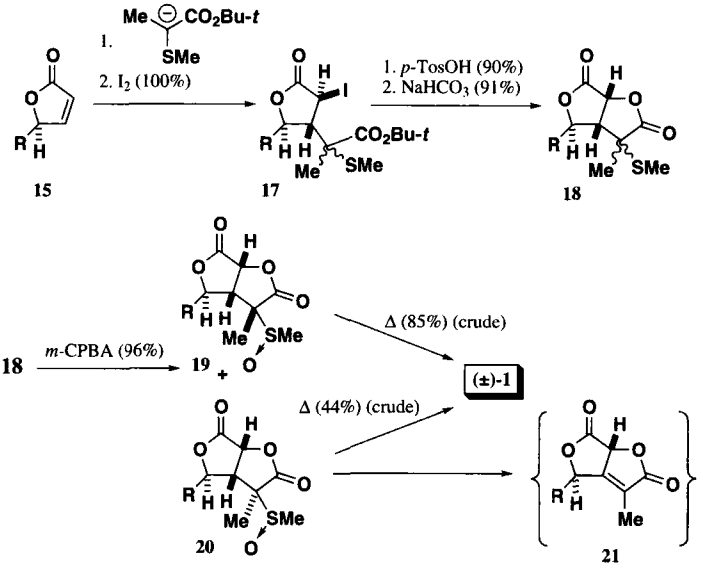
2. Ionic Approaches

The synthesis of the avenaciolide family through the C_3-C_{3a} bond formation of lactone **B** (Approach A) in Scheme 1 has been extensively used. Essentially, the methods could be classified as radical or ionic considering the type of reaction used to form such a bond. The necessary precursors are usually available from the suitable butenolides **15** that are synthesized from the propargylic esters **16** (Scheme 4).[17]



Scheme 4

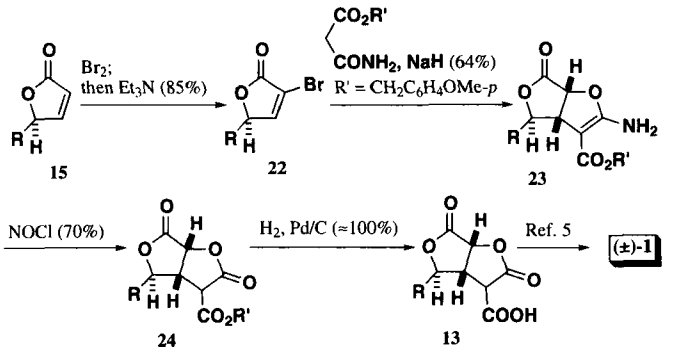
Within the ionic methodologies, the Michael addition of stabilized carbanions to the α,β-unsaturated-γ-lactone has been successfully applied. Using this approach Schlessinger *et al.*[18] introduced the desired *trans*-substitution necessary to gain access to avenaciolide using the lithium salt of *t*-butyl 2-thiomethylpropionate followed by quenching with iodine (Scheme 5). The acidic removal of the *t*-butyl ester and subsequent treatment with sodium bicarbonate led to the bis lactone **18**. Interestingly, the use of the thiomethyl group geminal to the α-methyl substituent in C_3 permits the generation of the α-methylene group of lactone **B**. Thus, when the mixture of sulfides **18** was oxidized and submitted to pyrolytic elimination in acetic anhydride a 60% crude yield of avenaciolide was obtained. It should be indicated that while the β-methyl sulfoxide **19** yielded satisfactorily the desired avenaciolide, the α-isomer **20** gave poor yields of **1**. A plausible explanation of this fact could be the



Scheme 5. Schlessinger *et al.* Synthesis of Avenaciolide

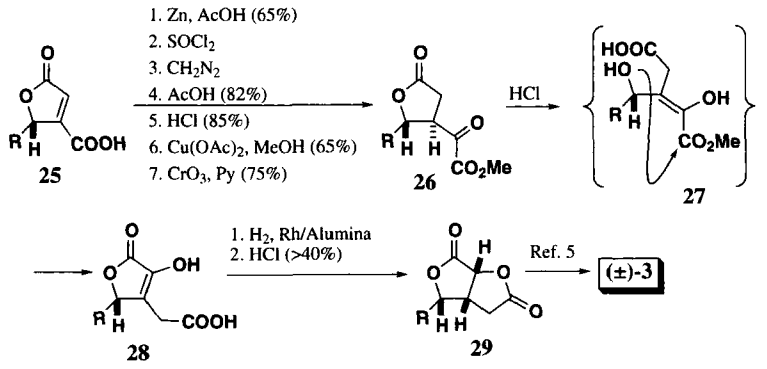
elimination leading to the unstable compound **21**. Alternatively, the pyrolysis in succinic anhydride yielded **1** with improved yield.

The addition of bromine to butenolides, followed by elimination, provides a doubly activated system **22** that permits, by the use of a suitable nucleophile, consecutive addition and further cyclization. The set of reactions used by Takei *et al.*[19] provided the correct stereochemistry in the ring junction, indicating that the addition reaction of the sodium salt of methyl malonamate to the butenolide proceeded stereoselectively and that the stereochemical relationship between the alkyl substituent and the lactone ring was *trans*. Mild hydrolysis of the enamine **23** provided the bis lactone ester **24** which by hydrogenolysis gave the known intermediate **13**, converted to avenaciolide (**1**) by the procedure reported by Parker and Johnson.[5]



Scheme 6. Takei *et al.* Synthesis of Avenaciolide

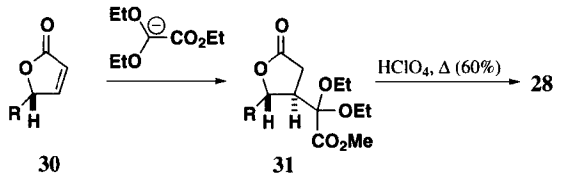
The substituted aconic acid **25**, available from 2-nonylidenesuccinic acid by concomitant electrophilic iodocyclization and iodine elimination, was used by Yamada *et al.*[20] to prepare the α-carbonyl **26** which when submitted to acidic transesterification, *via* the enol ester **27**, afforded the α-hydroxy-α,β-unsaturated-γ-lactone **28**. Catalytic hydrogenation and acidic treatment produced the bislactone **29** which was transformed into isoavenaciolide (**3**) using the above described methodology.[5]



Scheme 7. Yamada *et al.* Synthesis of Isoavenaciolide

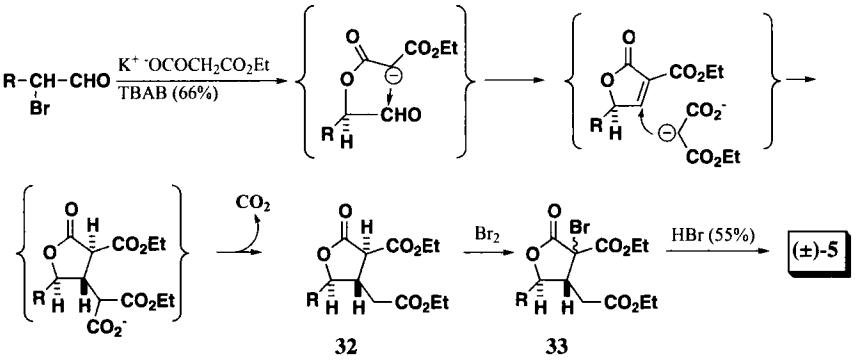
A more efficient preparation of **28** was achieved through the synthetic equivalent **31** of the

α-keto ester **26** by Schlessinger *et al.*[18b] The key step was the conjugate addition of the latent carbonyl anion to the butenolide **30**. Concomitant cleavage of the acetonide and rearrangement under acidic conditions yielded the α-hydroxy butenolide **28,** converted to isoavenaciolide (**3**).



Scheme 8. Schlessinger *et al.* Alternative Synthesis of Intermediate 28 in the Synthesis of Isoavenaciolide

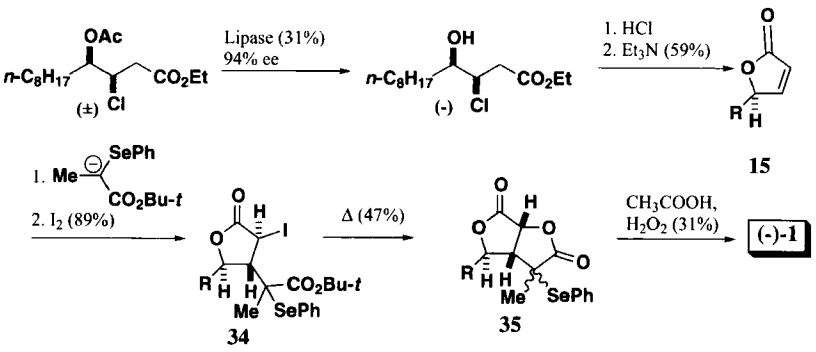
The treatment of an α-haloaldehyde with the potassium salt of ethyl malonate (Scheme 9) under phase-transfer catalysis conditions was used by Takeda *et al.* to obtain the all-*trans* substituted γ-lactone **32** in one step.[21] The treatment with an equivalent amount of Br_2 gave the bromo derivative **33** which after heating, under acidic conditions, provided the intermediate **5,** described above.



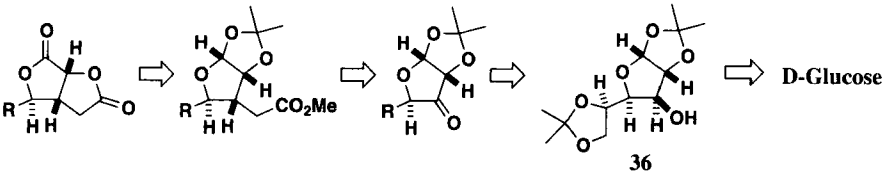
Scheme 9. Takeda *et al.* Approach to the Synthesis of Avenaciolide

The use of optically active butenolides provides the final compounds in enantiomeric forms. Thus, Tsuboi *et al.*[22] prepared the butenolide **15** in 94% ee making use of the kinetic resolution of ethyl 4-acetoxy-3-chlorododecanoate by lipase-catalyzed hydrolysis. The Michael addition of *t*-butyl 2-selenophenylpropionate and the subsequent iodination afforded the *trans*-addition product **34**. Thermal treatment gave the selenophenyl bislactone **35** for which oxidation was simultaneous with the elimination of the phenylselenoxide group, affording (-)-avenaciolide (**1**) in 31% yield.

The use of the C_3-C_{3a} bond formation through sugar derivatives has been used for the synthesis of the members of the avenaciolide family. Making use of this strategy, Fraser-Reid *et al.*[8] and, almost simultaneously, Ohrui *et al.*[9] published the first synthesis of avenaciolide with the correct stereochemistry of the natural product.[8] The approach is based on the introduction, through a glucose derivative, of the alkyl functionality in C_{3a} *via* a Wittig-type reaction and further stereoselective hydrogenation controlled by neighboring groups.

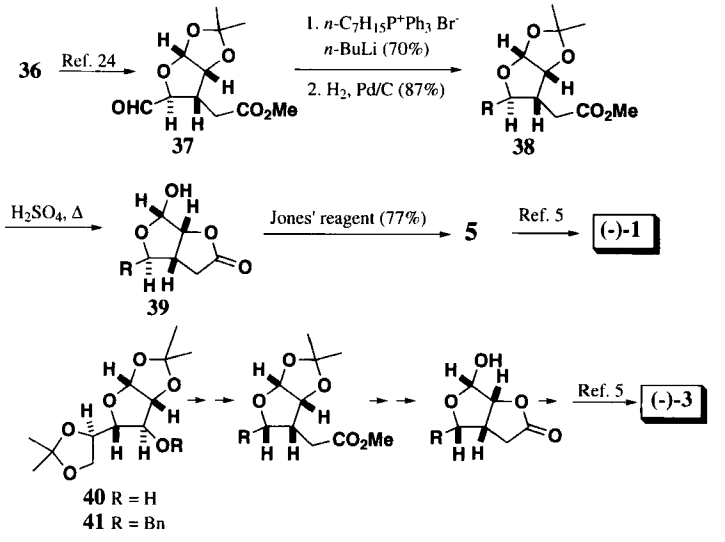


Scheme 10. Tsuboi *et al.* Synthesis of (-)-Avenaciolide



Scheme 11

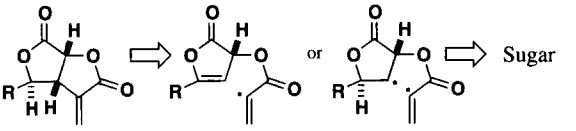
The aldehyde **37** was prepared from diacetone glucose **36** by a previously reported procedure.[23] Wittig reaction and hydrogenation provided the correct alkyl chain at C_4 without any epimerization at the carbon vicinal to the aldehyde. Treatment of **38** with acid produced simultaneous removal of the acetonide and γ-lactonization to the hemiacetal **39** that was oxidized to the known intermediate **5**. The methylenation procedure described by Parker and Johnson[5] led to (-)-**1** showing that the configuration of natural avenaciolide is 3_aR, 4*R* and 6_aR. Alternatively, diacetone galactose[24] **40** was benzylated to **41** and submitted to a similar sequence of reactions to obtain (-)-isoavenaciolide (**3**).[25]



Scheme 12. Fraser-Reid *et al.* Syntheses of (-)-Avenaciolide and (-)-Isoavenaciolide

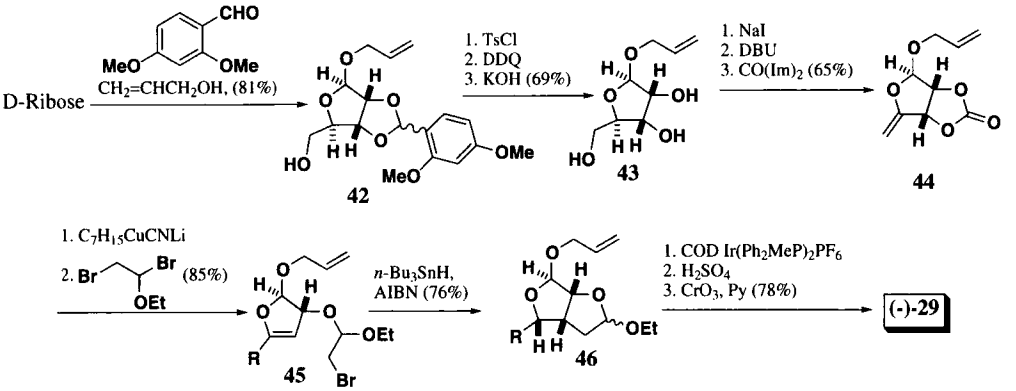
3. Radical Approaches

The formation of lactone **B** by an intramolecular radical addition through sugar derivatives has been used to obtain enantiomerically pure substances. To control the stereochemistry in the newly-created stereocenter, usually the radical used to initiate the cyclization is located in a chain linked to vicinal oxygen. The acceptor position is either a double bond or another radical.



Scheme 13

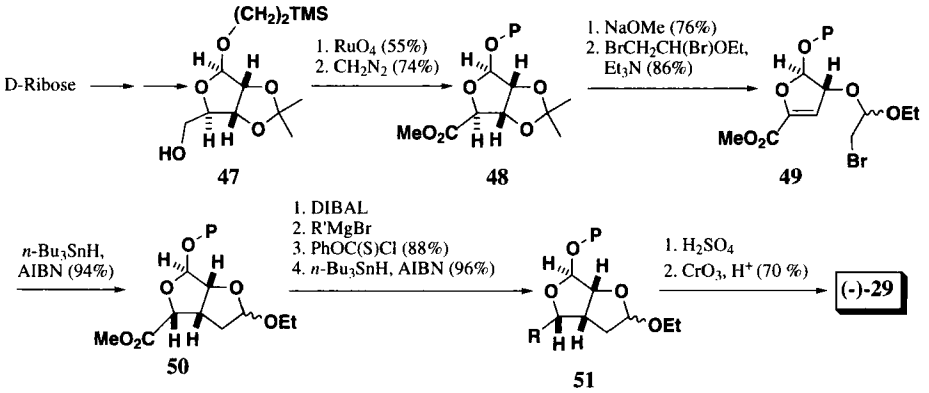
Starting from D-ribose Dugger *et al.*[26] performed the total synthesis of **29**. The treatment of D-ribose with allyl alcohol and 2,4-dimethoxybenzaldehyde afforded the furanoside **42** as a mixture of diastereoisomers. Tosylation of the primary alcohol followed by oxidation of the dimethoxybenzylidene acetal and hydrolysis produced diol **43**. Sequential treatment with iodide and elimination produced the vinyl carbonate **44**. S_N2' substitution using the suitable alkyl cyanocuprate and further bromoacetalation produced the desired intermediate **45**. Free radical cyclization gave the bisacetal **46** as a mixture at the new acetal center but with complete control of the stereochemistry of the centers in the ring. Isomerization of the double bond of the allylic unit, complete acidic cleavage of the acetals and further oxidation produced the known bislactone **29**.



Scheme 14. Dugger *et al.* Approach to the Synthesis of (-)-Isoavenaciolide

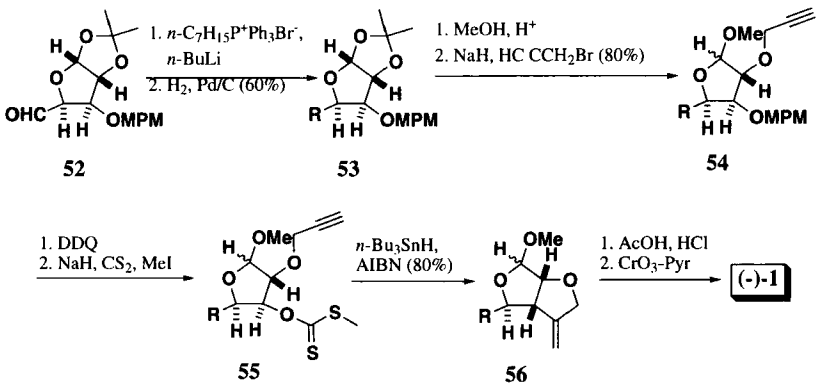
Using also D-ribose as starting material Wee[27] described an alternative synthesis of (-)-isoavenaciolide (**3**) and (-)-ethisolide (**4**). The unprotected primary alcohol **47** was cleanly oxidized to the acid with ruthenium tetroxide[28] and subsequently transformed into the corresponding methyl ester **48**. Basic elimination and subsequent alkylation of the free alcohol provided the bromo ketal **49**, necessary for the free radical ring formation. Tri-*n*-butyltin hydride-mediated cyclization proceeded efficiently to the bicyclic ester **50**. Selective reduction of the ester group provided an aldehyde unit

suitable for the introduction of the chain *via* addition of a Grignard reagent. Free radical reduction of the secondary alcohol provided the bis-ketal **51** which after acidic treatment and oxidation gave the known bislactone (-)-**29**. α-Methylenation using the procedure of Parker and Johnson[5] provided (-)-isoavenaciolide (**3**) or (-)-ethisolide (**4**).



Scheme 15. Wee's Approach to the Synthesis of (-)-Isoavenaciolide

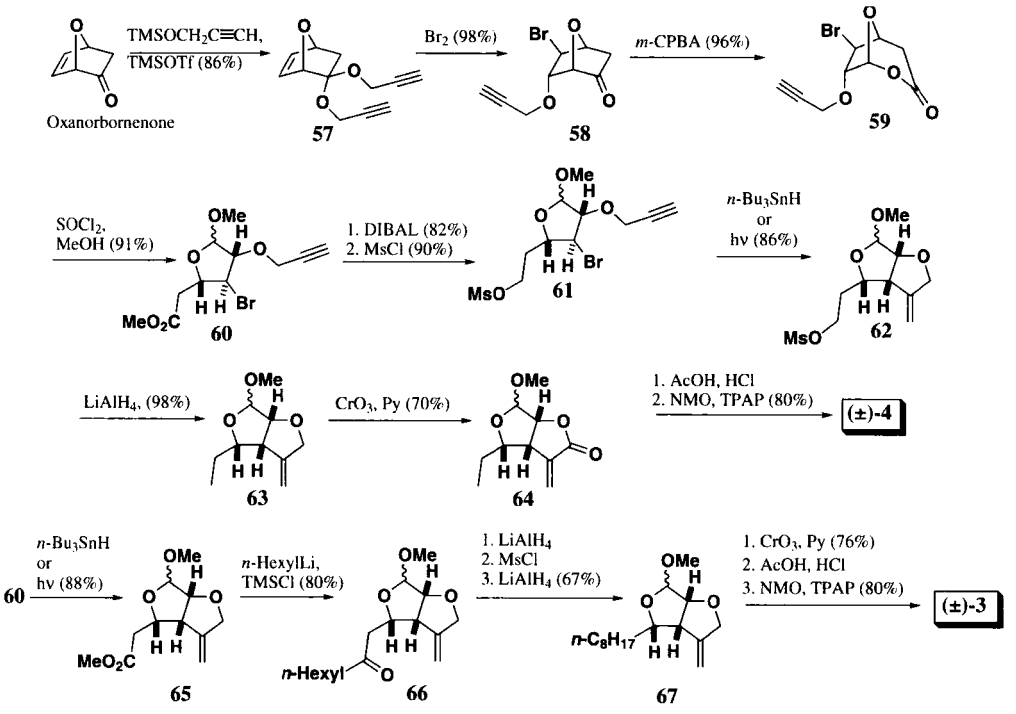
In a similar manner Sharma *et al.*[29] using the aldehyde **52** available from D-glucose[30] performed the stereoselective C_3-C_{3a} bond formation incorporating simultaneously the exo-methylene group at C_2. In this case the free radical is generated at the ring and the acceptor is an acetylene group. Thus, the side chain extension was achieved by Wittig reaction of **52** followed by catalytic hydrogenation of the resultant olefin to obtain **53**. Methanolysis and subsequent reaction with propargyl bromide afforded **54**. The propargylic ether takes advantage of two different functions: a protecting group during the transformation at C-3 OH of the sugar derivative and the required carbon framework through intramolecular radical cyclization. After cleavage of the methoxyphenylmethyl group the produced alcohol was converted to the xanthate ester **55** which underwent the desired cyclization to afford the single isomer **56**. With all the stereocenters in place, the two remaining transformations were carried out in stepwise manner. Thus, hydrolysis of **56** followed by simultaneous oxidation of



Scheme 16. Sharma *et al.* Synthesis of (-)-Avenaciolide

the allylic methylene and hemiacetal functionalities gave avenaciolide (**1**). The same methodology was used to synthesize 4-epi-ethisolide (**4**) using the suitable alkyl radical at the Wittig step.[31]

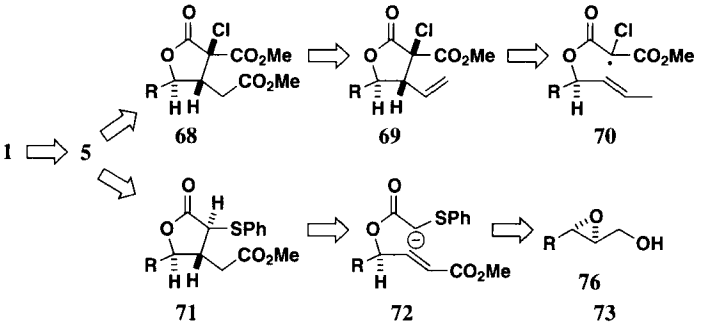
A free radical cyclization is also the key step in a synthesis of ethisolide (**4**) and isoavenaciolide (**3**) reported by Cossy *et al.*[32] The oxanorbornenone[33] was transformed into ketal **57** by acidic treatment with propargylic silyl ether. The treatment of **57** with bromine produced regioselective and stereoselective migration of one propargylic group yielding **58**. Baeyer-Villiger oxidation of ketone **58** furnished lactone **59**. Treatment of **59** with methanolic thionyl chloride gave a mixture of two anomeric furanosides **60** (8:1). Reduction of **60** to the corresponding alcohol and mesylation produced **61**. The bicyclic structure of ethisolide was built up *via* free radical generation with *n*-Bu_3SnH-AIBN or irradiating at 254 nm. The 5-*exo*-dig radical cyclization took place, giving **62** as the only detected diastereoisomer. Reduction of the mesylate to **63** and oxidation provided the α-methylene lactone **64** that after acidic hydrolysis and oxidation yielded ethisolide. In a divergent manner, the ester **60** was submitted to free radical cyclization to **65**. Addition of hexyllithium in the presence of trimethylchlorosilane produced the corresponding ketone **66** that was reduced to **67**. The application to **67** of the series of reactions described above afforded isoavenaciolide.



Scheme 17. Cossy *et al.* Syntheses of Ethisolide and Isoavenaciolide

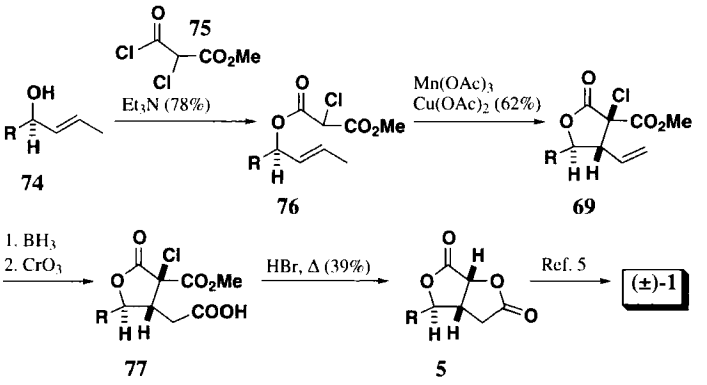
The C-C cyclization of an unsaturated linear secondary ester with a defined stereochemistry could be the base of the γ-lactone **A**. Obviously, for this type of methodology a suitable activation of the α-position of the carbonyl group should first be generated in order to react with the unsaturated

position at the *exo*-tet position. Two major approaches have been considered with this basic strategy depending on the kind of reaction used at the cyclization step. In one case an α-carbonyl radical was intramolecularly trapped with the suitable double bond,[34] while in the other the intramolecular Michael addition of an γ-acyloxy unsaturated ester was used to perform the cyclization.[35]



Scheme 18

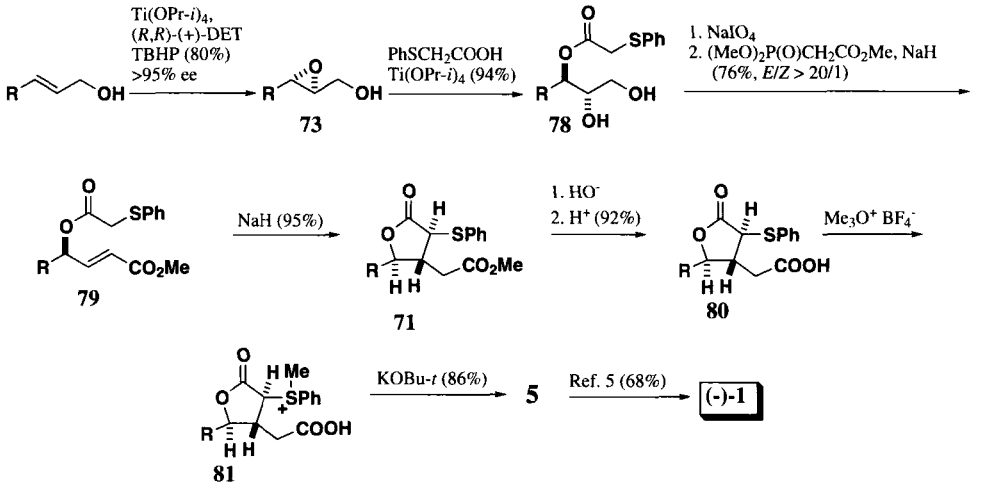
The intramolecular free radical cyclization of allylic α-chloromalonates has been described by Snider and McCarthy.[34] Esterification of 4*E*-dodecen-2-ol **74** with monomethyl α-chloromalonate chloride (**75**) yielded the chloromalonate ester **76.**[36] Oxidative free-radical cyclization of **76** provided **69** as the major stereoisomer. Hydroboration of **69** followed by oxidation gave crude **77** that was cyclized under acidic conditions to **5**.[21] Methylenation in the usual manner[5] afforded avenaciolide.



Scheme 19. Snider and McCarthy Synthesis of Avenaciolide

Our approach to the synthesis of avenaciolide[35] was based on the base-induced cyclization of enantiomerically enriched γ-[(phenylthio)acyl]α,β-unsaturated esters **72.** Katsuki-Sharpless asymmetric epoxidation[37] of undec-2-en-1-ol gave the epoxy alcohol **73** that was regioselectively opened with phenylthioacetic acid to the diol **78.**[38] The diol ester **78** was submitted to degradative oxidation, and the resulting aldehyde homologated *via* a Horner-Wadsworth-Emmons reaction to the α,β-unsatured ester **79**. Basic treatment of **79** provided **71** as the only isolated stereoisomer.[39] The bislactone skeleton was synthesized taking advantage of the presence of a sulfide group as a potential leaving group.[40] Thus, hydrolysis of the ester **71** provided the carboxylic acid **80** that was alkylated to the sulfonium salt **81.**

The basic treatment of **81** produced an intramolecular substitution affording the bislactone **5** as the only stereoisomer. Methylenation by the Parker and Johnson[5] method yielded avenaciolide.



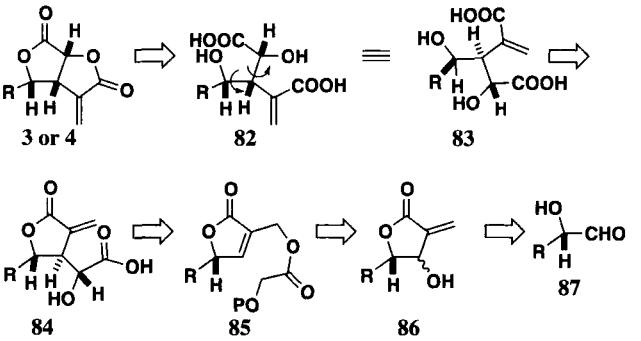
Scheme 20. Martín *et al.* Synthesis of (-)-Avenaciolide

III. SYNTHESES USING SIMULTANEOUS CONSTRUCTION OF BOTH RINGS

Some syntheses of avenaciolide are performed taking advantage of the great thermodynamic stability of the γ-lactol or γ-lactone units for the construction of both cycles in the same step.

1. Double Lactonization.

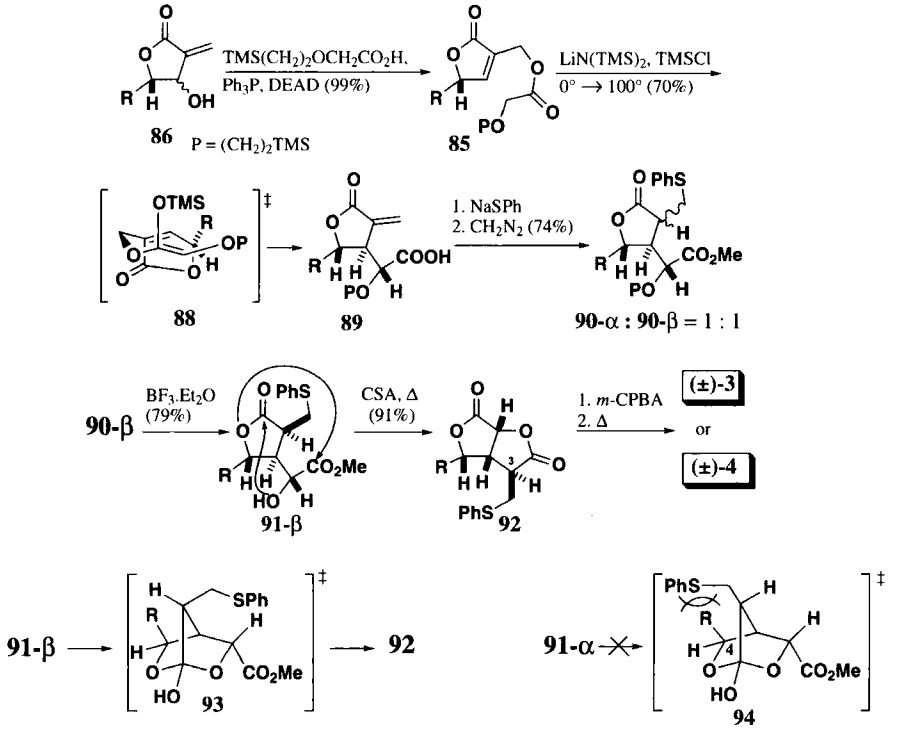
The synthesis of α-alkoxy-β-alkyl-γ,δ-unsaturated esters by an ester enolate Claisen[41] rearrangement of glycolate esters of α-hydroxymethyl butenolides and an acid-induced intramolecular transesterification, are the key steps of the syntheses of the whole avenaciolide family reported by Burke *et al.*[42] Retrosynthetic analysis of both lactones for isoavenaciolide (**3**) and ethisolide (**4**) leads to the corresponding *bis* (hydroxy acids) **82**. Rotation of 180° about the three indicated σ-bonds leads to an equivalent structure **83** more obviously related to the product. Finally,



Scheme 21

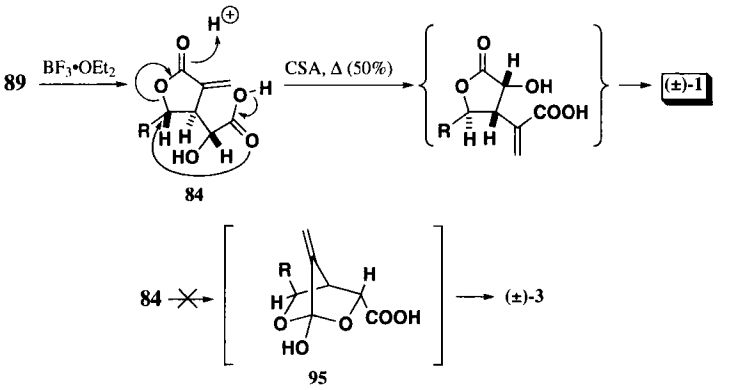
lactonization of the indicated residues and application of a retrograde Claisen rearrangement affords the butenolide glycolate ester **85**.

The β-hydroxy-α-methylene lactone **86**, available from the aldehyde **87** by previously reported methodology,[43] was submitted to Mitsunobu-type[44] coupling with O-protected glycolic acid yielding by an S_N2' substitution the enolate Claisen substrate **85**. When **85** was submitted to basic treatment at low temperature (-100°) and the resulting silyl ketene was allowed to reach room temperature, the rearranged carboxylic acid **89** was obtained with great diastereoisomeric excess (>20:1) and with the correct stereochemistry at the C_{3a}, C_4 and C_{6a} sites. The C_4 substituent serves as a diastereocontrol element favoring the [3,3]-sigmatropic rearrangement to occur involving the less encumbered β-face of the butenolide olefin, as portrayed in **88**. The α-methylene lactone was temporarily protected as the thiophenol adduct, leading after esterification to the separable epimeric esters **90-α** and **90-β** (1:1), which were individually treated with BF_3-OEt_2 to cleave the β-(trimethylsilyl)ethyl ether. Only stereoisomer **91-β** underwent bis(transesterification) leading to the bislactonic sulfide **92**, while the alcohol **91-α** was unreactive under these conditions. Oxidation of **92** and thermolysis of the crude sulfoxide gave isoavenaciolide (**3**) or ethisolide (**4**) depending on the length of the alkyl chain of the precursor **86**. The reactivity difference between **91-α** and **91-β** was accounted evaluating the transient structures **93** and **94**. Unreactive **91-α** would achieve the dioxabicyclo[2.2.1]heptane structure **94**. However, a serious steric conflict between the C-4 substituent and the phenylsulfide group would results.



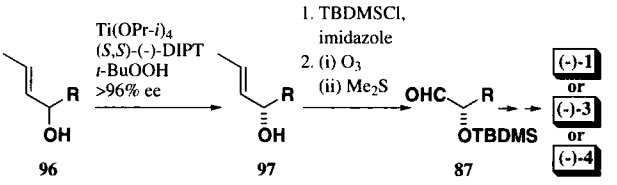
Scheme 22. Burke *et al.* Syntheses of Isoavenaciolide and Ethisolide

Interestingly, when the free hydroxy acid **84** was submitted to the acidic transesterification conditions the product of the reaction directly gave avenaciolide (**1**), formed *via* the nucleophile/electrophile pairing indicated. The curious involvement of the α-methylene unit in **84** against the intramolecular attack leading to **95** was explained by the added strain resulting from the presence of a trigonal- instead of a tetrahedral-carbon in the analogous bridged bicyclic structure.



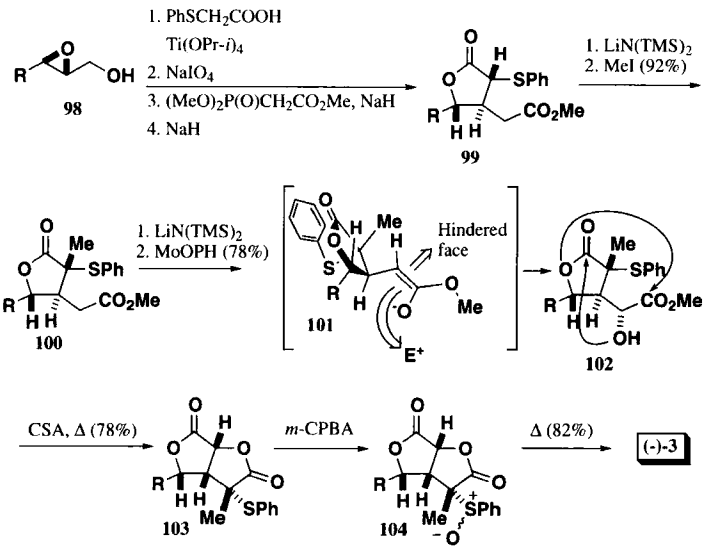
Scheme 23. Burke *et al.* Synthesis of Avenaciolide

Production of ethisolide, isoavenaciolide, and avenaciolide in their natural, levorotatory forms was accomplished by synthetic sequences analogous to those employed in the racemates. The C_4 stereocenter was set by employing enantiomerically (>96% ee) enriched α-siloxy aldehydes **87** as the electrophile partner in the synthesis of the enantiomers of **86**.[43] Kinetic resolution of the racemic allylic alcohols **96**[45] by Katsuki-Sharpless asymmetric epoxidation with (-)-diisopropyl tartrate afforded the (*S*)-allylic alcohols **97**.[46] Alcohol protection as the *tert*-butyldimethylsilyl ethers and ozonolysis gave the (*S*)-aldehydes **87**.



Scheme 24. Burke *et al.* Enantiomeric Approach to the Syntheses of Avenaciolides

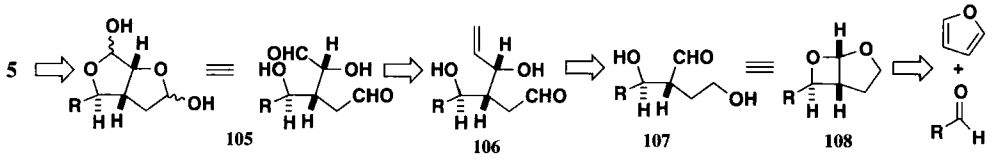
The above mentioned double transesterification is also the base of the synthesis of isoavenaciolide (**3**) reported by our group.[35] The application of the methodology described in Scheme 20 using the enantiomeric epoxy alcohol **98** provided **99**.[39] Interestingly, the alkylation of the γ-lactone enolate yielded the contrasteric product **100**.[47] The necessary α-hydroxy ester was obtained *via* the enolate **101** with high stereoselection, providing **102** as the only isolated isomer. The heating of **102** with a catalytic amount of acid yielded the bislactone **103** *via* the double transesterification procedure outlined above.[42] The oxidation of **103** provided the sulfoxides **104**, that when heated afforded isoavenaciolide.



Scheme 25. Martín *et al.* Synthesis of (-)-Isoavenaciolide

2. Double Lactol Formation.

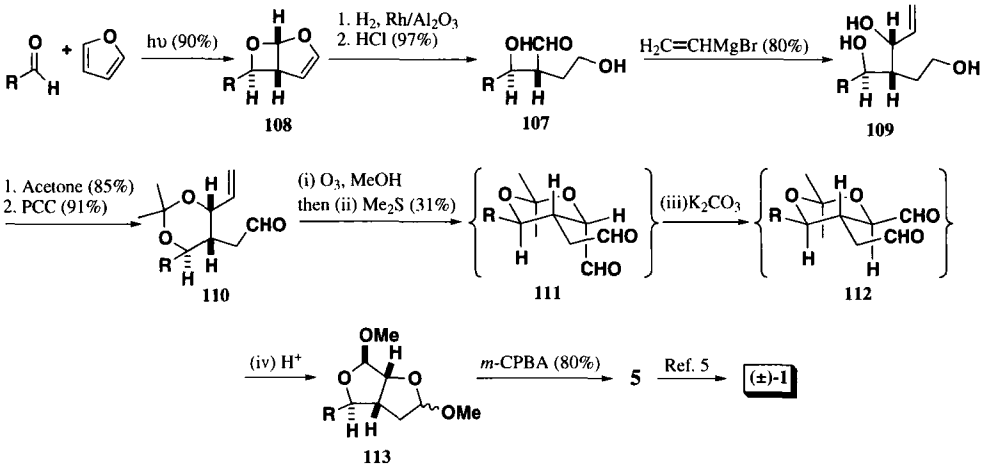
The possibility, used above, of the double cyclization to obtain the necessary bislactone has been extended to the equivalent bislactol. Thus, Schreiber and Hoveyda[48] reported a synthesis of racemic avenaciolide (**1**) *via* the intermediate **5** obtained by the oxidation of the bislactol **105**. The synthesis of such an α-hydroxy aldehyde could be visualized from the allylic alcohol **106** that tentatively could be available from the aldehyde **107**. Such an aldehyde is synthetically equivalent to the acetal **108** that is readily available by a Paternö-Büchi photocycloaddition of furan and nonanal.



Scheme 26

Photocycloaddition of nonanal in furan provided the single exo-substituted oxetane **108**. Hydrogenation of **108** and hydrolysis provided the lactol **107** without complication arising from epimerization. Treatment of the lactol with vinyl magnesium bromide yielded the expected triol **109** as a 5:1 mixture, although with the wrong stereochemistry at the created carbinol center. Triol differentiation was effectively achieved *via* the formation of the corresponding acetonide, which oxidation of the remaining primary alcohol gave **110.** The final skeleton construction and correction of the wrong stereocenter was achieved in an one-pot operation consisting of ozonolysis, reduction, base-catalyzed epimerization of intermediate **111** to **112**, and acidification, leading to the *bis*(methoxy lactols) **113** as a 2:1 mixture of methoxy anomers. Grieco oxidation[49] provided **5** that was converted

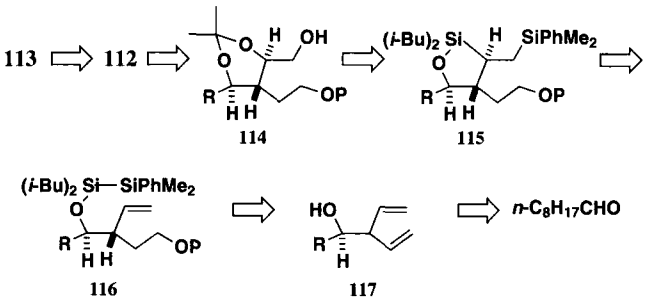
to avenaciolide (**1**) by the Parker and Johnson method.[5]



108 **107** **109** **110** **111** **112** **113**

Scheme 27. Schreiber-Hoveyda Synthesis of Avenaciolide

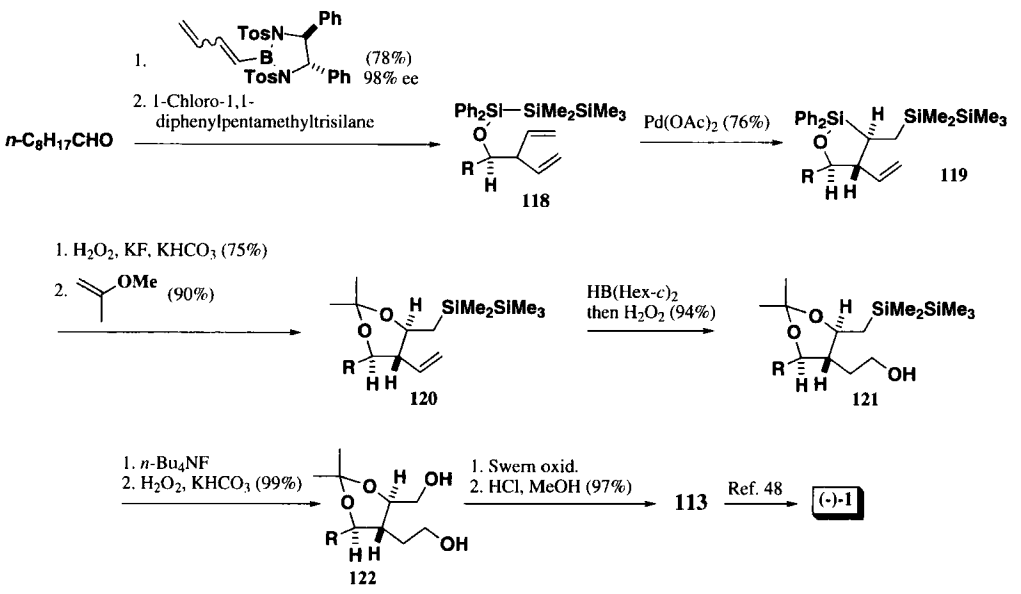
Ito *et al.* have described the synthesis of enantiomerically enriched **113**[50] by the use of precursor **112**, available from **114** *via* oxidation of the primary alcohol. The 1,2-diol system could be obtained from the corresponding Si-C bond by oxidation of **115**. The necessary bis-silylation could be achieved by an intramolecular addition of the Si-Si bond of the suitable disilanyl homoallylic alcohol **116**, by a procedure previously reported by the authors.[51] The necessary bis-homoallylic alcohol **117** could be obtained from nonanal *via* enantioselective allylation.[52]



114 **115** **116** **117**

Scheme 28

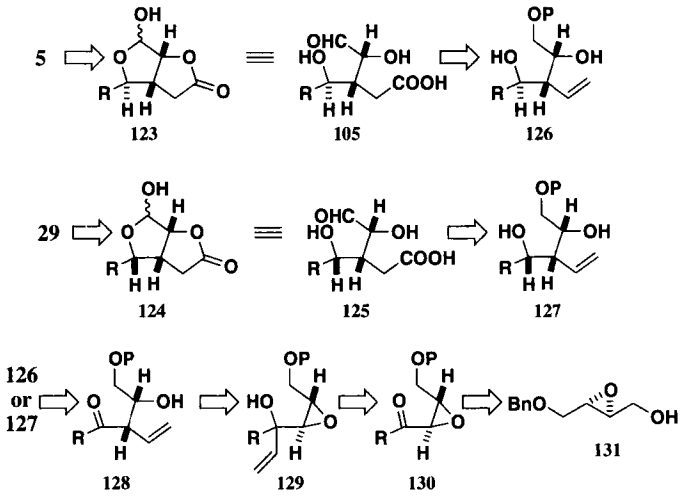
The optically active (>98% ee) (*R*)-3-vinyl-1-undecen-4-ol **117** was prepared by γ-pentadienylation of nonanal, using a pentadienylborane reagent with Corey's chiral auxiliary.[52] Intramolecular disilanyl silylation assisted by palladium gave diastereoselectively (4:1) the silatetrahydrofuran **119**. Selective oxidation of the Si-C bond gave a diol, whose hydroxyl groups were protected as the acetonide **120**. Hydroboration and basic peroxide oxidation led to the primary alcohol **121** that was converted to the diol **122** by oxidative cleavage of the Si-C bond. The *bis*-lactol **113** was prepared in high yield by Swern oxidation of the two primary alcohols and subsequent acidic deprotection of the acetonide in methanol. The application of the methodology described above[48] led to avenaciolide.



Scheme 29. Ito *et al.* Synthesis of (-)-Avenaciolide

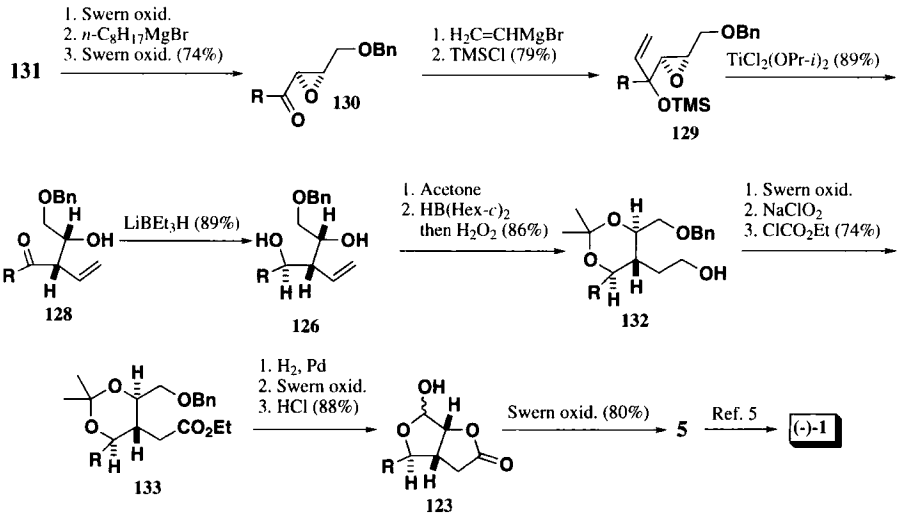
3. Double Cyclization to Mixed Lactol-Lactone.

The double cyclization leading to mixed lactol and lactone has also been used. Suzuki and Tsuchihashi *et al.*[53] reported a stereo-divergent asymmetric synthesis of avenaciolide (**1**) and isoavenaciolide (**3**) *via* a 1,2-rearrangement of enantiomerically enriched epoxy alcohol derivatives. The attention was focused again on intermediates **5** and **29** as direct precursors of the natural products. In both cases the synthesis of the final bislactone is considered by the oxidation of the corresponding mono-lactols **123** and **124**. The synthetically equivalent diol **105** and **125** could be contemplated to arise from the vinyl derivatives **126** and **127**. With control of the stereochemistry of the reduction, the ketone **128** could be a common intermediate for both avenaciolide and isoavenaciolide. The authors found that such 2-vinyl aldols can be nicely obtained by Lewis acid-catalyzed rearrangement of the vinyl carbinols **129**, the synthesis of which is easily performed from epoxy ketone **130** available from the known epoxy alcohol **131**.



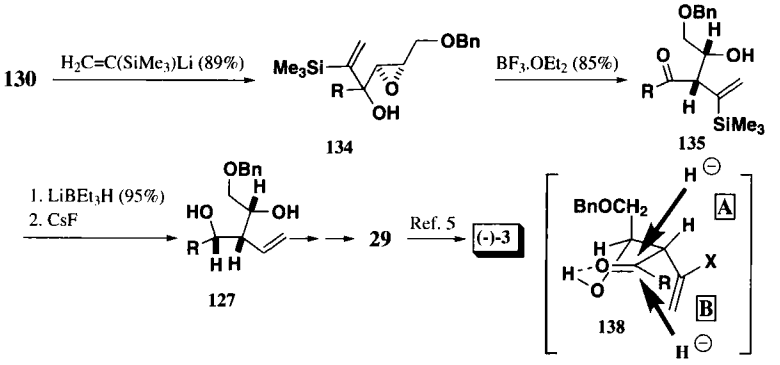
Scheme 30

The epoxy alcohol **131** was prepared by the Katsuki-Sharpless asymmetric epoxidation[37] or from tartaric acid,[54] which in turn was converted to the ketone **130** and the epoxy silyl ether **129**. Subsequent 1,2- rearrangement was cleanly effected by Lewis acid to the *threo* 2-vinyl aldol **128** as the single isomer. Reduction of the ketone **128** provided the 1,2-syn isomer **126**. Diol protection as acetonide and oxidative hydroboration yielded **132**. Oxidation of the primary alcohol in two steps gave the corresponding carboxylic acid, which was directly esterified to afford **133**. After removal of the benzyl group and Swern oxidation,[55] the resulting aldehyde was submitted to acidic hydrolysis to give the lactol **123**. Finally, oxidation of **123** to bislactone **5** and methylenation by the Parker-Johnson procedure[5] gave avenaciolide.



Scheme 31. Suzuki and Tsuchihashi *et al.* Synthesis of (-)-Avenaciolide

In order to control the stereoselectivity in the reduction of the ketone **135** to obtain **127**, it was necessary to introduce an additional trimethylsilyl group in the vinyl group. Thus, the treatment of ketone **130** with 1-trimethylsilyl-vinyl lithium followed by quenching with trimethylsilyl chloride provided **134**, that when submitted to acidic rearrangement led to the aldol **135** as the sole stereoisomer. Interestingly, the reduction of the ketone **135** and further desilylation afforded the epimeric diol **127**. A similar sequence of reactions to those described previously led to isoavenaciolide. A hydrogen-bonded model **136** accounts for the outcome of the reductions with and without the $SiMe_3$ group, when the balance of the 1,2-effect [by $H_2C{=}C(X)$-] and the 1,3-effect (by $BnOCH_2$-) are considered. Thus, depending on the importance of these effects, the favored trajectory of the hydride attack becomes **A** for **128** (X = $SiMe_3$) or **B** for **135** (X = H).



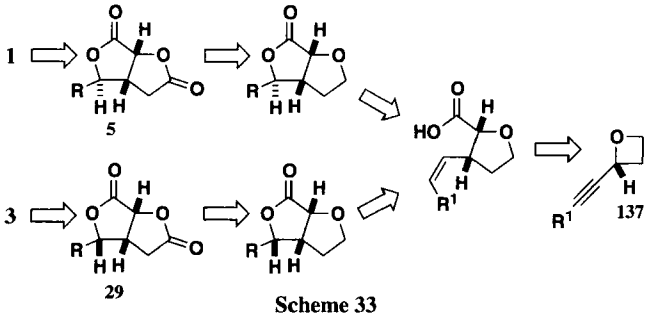
Scheme 32. Suzuki and Tsuchihashi *et al.* Synthesis of (-)-Isoavenaciolide

IV. SYNTHESES USING FORMATION OF RING-B FIRST

In this section we will consider those syntheses in which the lactone **B** is formed first.

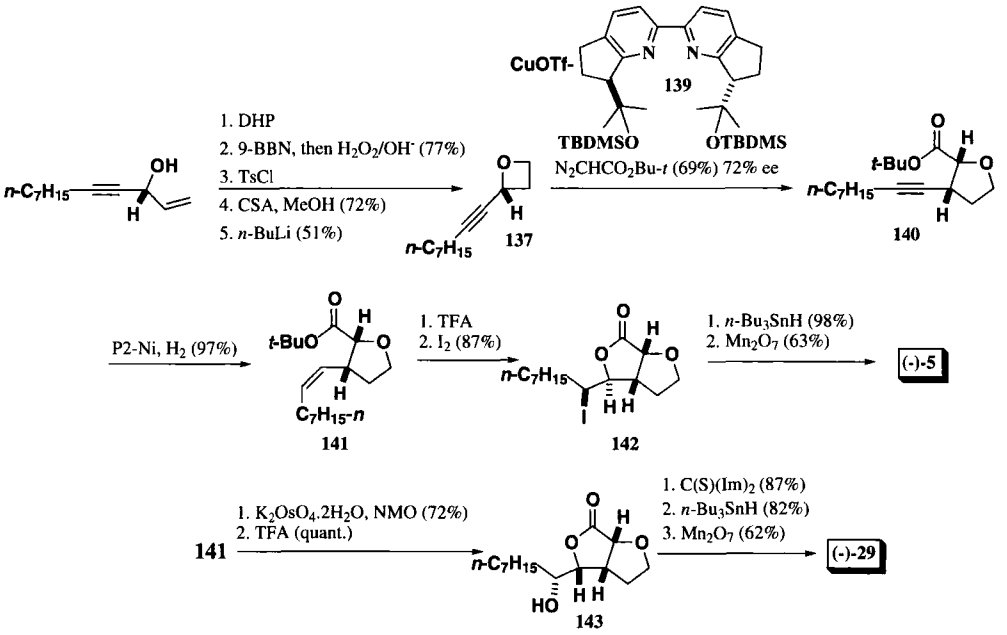
1. Tetrahydrofurans as Precursors.

Very recently, Katsuki *et al.*[56] have reported the formal synthesis of (-)-**1** and (-)-**3** taking advantage of a ring expansion of optically active α-alkynyl oxetanes. Considering the possible oxidation of tetrahydrofurans to γ-lactones,[57] this methodology would permit the synthesis of ring **B** with the correct stereochemistry at carbons C_{3a} and C_{6a} (Scheme 33). The formation of the lactone **A** could be considered by electrophilic cyclization using the oxygen O_5 of the latent carboxylic group over the suitable double bond available from the alkynyl group.



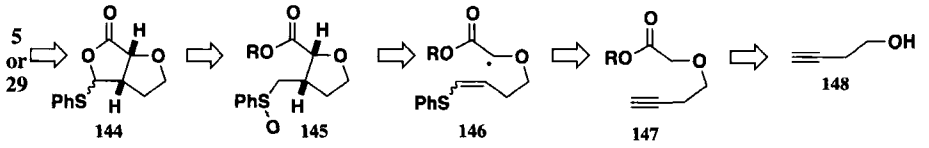
Scheme 33

The required oxetane **137** was prepared from (R)-nonyl vinyl carbinol, available from the racemic form through kinetic resolution.[46] The ring expansion with the Cu(I)OTf-chiral bipyridine (**139**) complex afforded the desired *cis*-tetrahydrofuran **140**, which was reduced to the *Z*-olefin **141,** used, after crystallization, to obtain the lactone **A** *via*-electrophilic cyclization using iodine. Reductive dehalogenation and oxidation of the obtained tetrahydrofuran provided in optically active form the known precursor of avenaciolide **5**. In divergent mode, the common intermediate **141** was selectively dihydroxylated and transesterified to the lactone **143**.The secondary hydroxylic group was removed by the Barton reaction[58] and the resulting tetrahydrofuran was oxidized to the lactone **B**, the precursor of isoavenaciolide **29**.



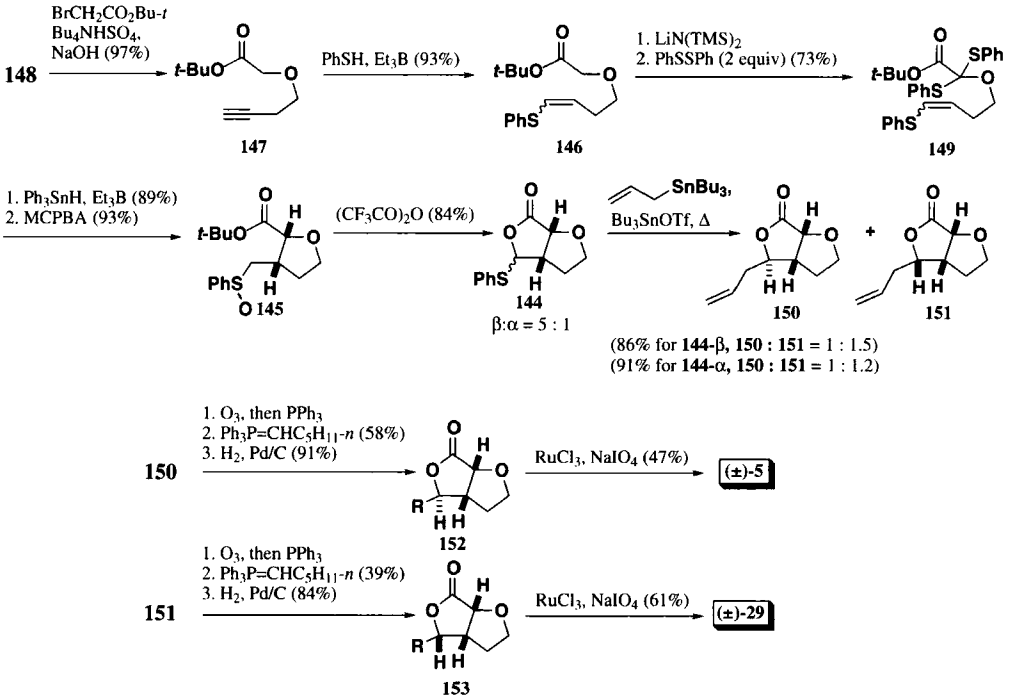
Scheme 34. Katsuki *et al.* Approaches to the Syntheses of (-)-Avenaciolide and (-)-Isoavenaciolide

The construction of a tetrahydrofuran ring has also been used as the central point in an additional synthesis of avenaciolide and isoavenaciolide reported by Burke *et al.*[59] The normethylene analogs **5** and **29** have been repeatedly used as intermediates in the total synthesis of avenaciolides. The introduction of the n-octyl side chain at the C_4 center and oxidation of the C_2 methylene could form the bislactones **5** and **29** divergently from the bicyclic intermediate **144**. The bicyclo[3.3.0]etherlactone **144** could be obtained from the *syn* 2,3-disubstituted tetrahydrofuran **145** using a Pummerer rearrangement-intramolecular trapping.[60] The radical cyclization of a vinyl sulfide such as **146**,



available *via* the acetylene **147**, from the commercially available homopropargylic alcohol **148**, should provide **145**.[61]

The phase transfer *O*-alkylation of 3-butyn-1-ol (**148**) produced the alkyne **147**, which was subsequently converted to the vinyl sulfide **146** under mild radical conditions. After bis(phenylsulfenylation), the radical cyclization of **149** provided the desired *syn* diastereoisomer as the slightly favored product. Interestingly, the minor *anti* isomer could be recycled to the desired *syn* isomer by the kinetic protonation of the derived ester enolate. Oxidation to the corresponding sulfoxide **145** and Pummerer rearrangement, produced after intramolecular trapping[60] the bicyclic adduct **144** as a 5:1 mixture of diastereoisomers. These products were converted to the olefins **150** and **151** under Keck's *C*-glycosylation conditions.[62] Utilizing an ozonolysis-Wittig homologation sequence, chain elongation was accomplished on **150** and **151** to furnish *Z*-olefins that were hydrogenated to **152** and **153**. The ruthenium tetroxide oxidation of the C_2 methylenes provided 3-normethyleneavenaciolide (**5**) and normethyleneisoavenaciolide (**29**), respectively.

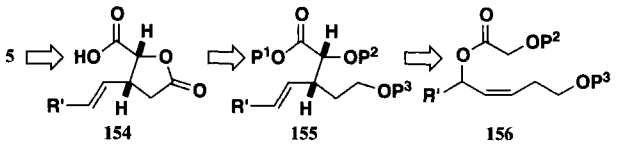


Scheme 35. Burke *et al.* Radical Approach to the Syntheses of Avenaciolide and Isoavenaciolide

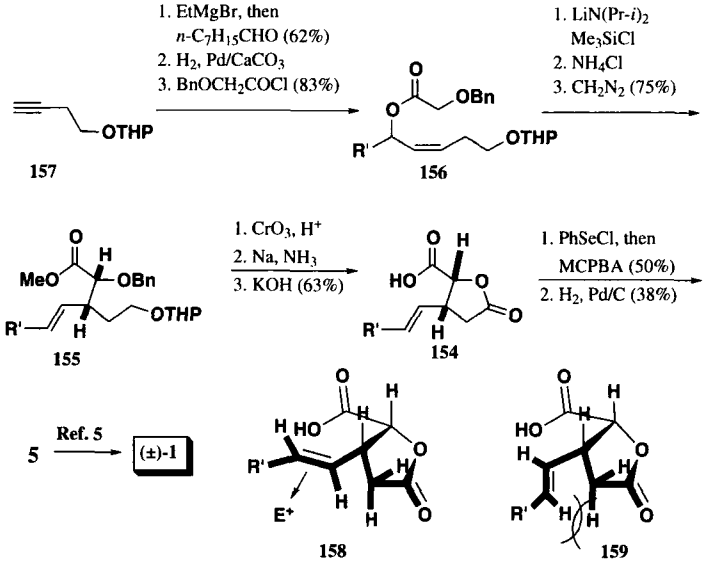
2. Stepwise Cyclization of Linear Precursors.

An alternative retrosynthetic consideration of avenaciolide suggests that the γ-lactone **A** could be formed by electrophilic cyclization of the carboxylic acid in **154**. In this approach, reported by Kallmerten and Gould,[63] the lactone **B** in such a structure could arise from the protected diol **155**. The analysis of **155** suggests that the structural and stereochemical elements would be rapidly derived

from the Claisen rearrangement of a suitably functionalized allylic glycolate **156**.

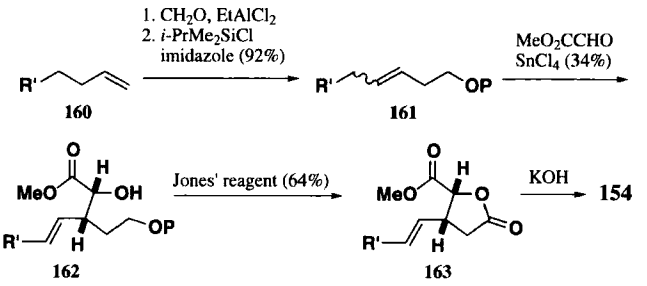


The required (*Z*)-glycolate **156** was prepared in three steps from the protected butynol **157** by Grignard formation and treatment with octyl aldehyde, followed by Lindlar hydrogenation and acylation. Enolate Claisen rearrangement[41] of **156** using the authors' modification[64] gave the anti ester **155**. Treatment of **155** with Jones reagent afforded a carboxylic acid that upon debenzylation and ester hydrolysis yielded the lactone **154**. Electrophilic cyclization using phenyl selenyl chloride, *via* the preferred conformer **158**, subsequent oxidative elimination and catalytic hydrogenation gave **5** that was converted to avenaciolide by the Parker and Johnson method.[5]



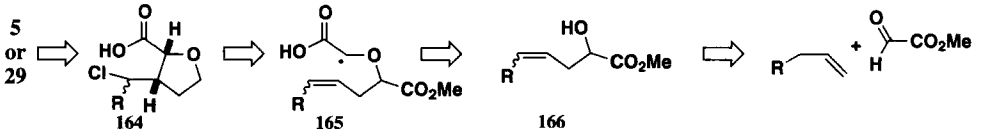
Scheme 36. Kallmerten and Gould Synthesis of Avenaciolide

The intermolecular glyoxylate-ene reaction with homoallylic ethers provided the intermediate **162** with high stereocontrol. This methodology, described by Mikami, Shimizu and Nakai,[65] started from 1-decene **160** with an allylic addition to formaldehyde[66] yielding **161**. The reaction of **161** with methyl glyoxylate gave the *E*-ester **162**, irrespective of the ene geometry, that submitted to chemoselective oxidation furnished the lactone **163**. Basic hydrolysis of **163** led to the intermediate **154** used above[63] for the synthesis of avenaciolide.

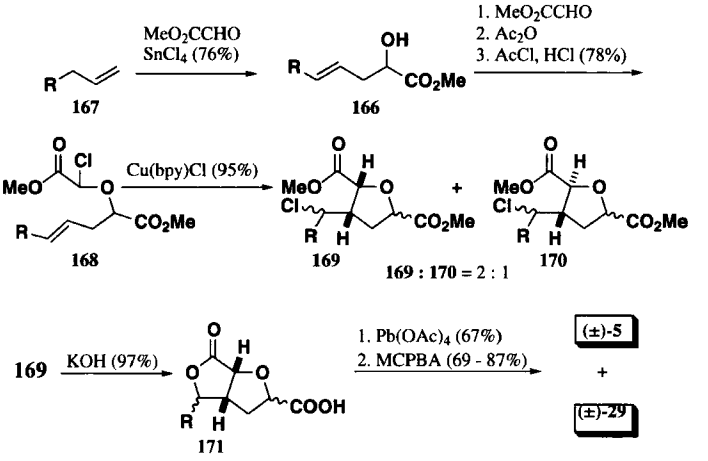


Scheme 37. Mikami, Shimizu and Nakai Approach to the Synthesis of Avenaciolide

The synthesis of both avenaciolide and isoavenaciolide could be envisioned by the cyclization of a functionalized tetrahydrofuran **164** available by a radical-annelation *via* **165**. The necessary precursor could be made available from a homoallylic alcohol **166**, that as above could be obtained by an ene reaction with a glyoxalate having a terminal alkene.[65]



The above-mentioned radical cyclization is the basis of the syntheses reported by Hiemstra, Speckamp *et al.*[67] in which the ring formation involves the treatment of 2(3-alken-1-oxy)-2-chloroacetates with a catalytic amount of Cu(bpy)Cl.[68] α-Hydroxy ester **166** was prepared in one step from 1-undecene **167** and methyl glyoxylate giving preferentially the *E*-isomer. Treatment with methyl glyoxylate, further acetylation and conversion to the chloride **168** were accomplished giving a

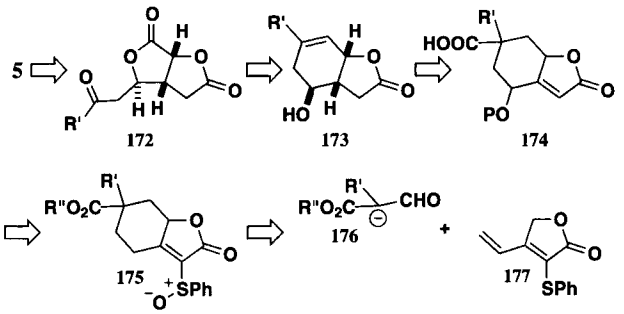


Scheme 38. Hiemstra and Speckamp *et al.* Approach to the Syntheses of Avenaciolide and Isoavenaciolide

diastereoisomeric mixture. Chlorine-transfer radical cyclization in the presence of the copper catalyst afforded a mixture of tetrahydrofurans **169** and **170**. The basic cyclization of **169** produced the diastereoisomeric mixture **171** that was oxidatively decarboxylated[69] to the precursor **5** of avenaciolide and **29** of isoavenaciolide.

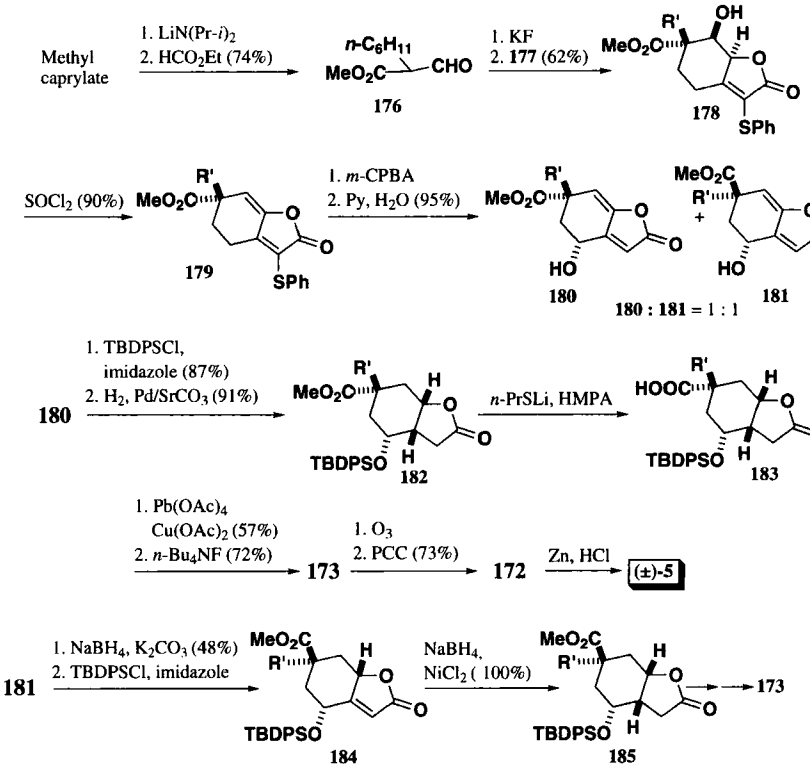
3. C-C Fragmentation.

The access to 4-oxygenated perhydrobenzofuran-2-ones[70] is the basis of the reported synthesis of avenaciolide by Yoshikoshi *et al.*[71] The intermediate **5** could be obtained by reduction of the ketone **172** accessible from oxidative cleavage of the cyclohexene in **173**, obtainable *via* the oxidative decarboxylation of a carboxylic acid such as **174**. A critical step in the synthesis would be the rearrangement of a sulfoxide like **175** to generate the desired oxidation at C_4. Finally, the synthesis of the necessary perhydro-3-phenylbenzofuran-2-one would be accessible by annelation by the use of the anion generated from an α-formyl ester **176** with 2,5-dihydro-3-phenylthio-4-vicinylfuran-2-one **177**.



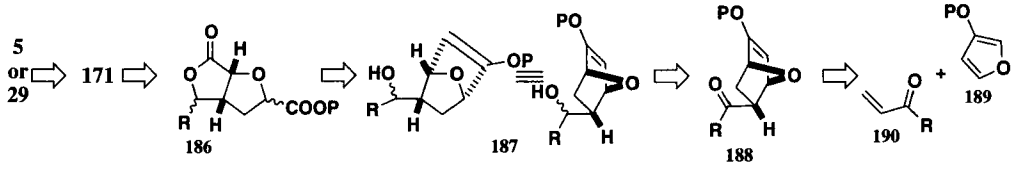
Methyl α-formylcaprylate (**176**), obtained from methyl caprylate, reacted with **177** to give a diastereoisomeric mixture (2.5:1), in which **178** was the major isomer. The dehydration of **178** provided cleanly the unsaturated sulfide **179** that was oxidized to yield the rearranged mixture **180** and **181** (1:1). Both compounds were successfully used for the synthesis of avenaciolide by different pathways. In one case, **180** was protected and stereoselectively hydrogenated to the γ-lactone **182**, whose ester was selectively hydrolyzed. Carboxylic acid **183** was oxidatively decarboxylated giving a mixture of olefins, which were separated after desilylation to give **173**. The oxidative ozonolysis of **173** provided the ketone **172** that was reduced *via* a modified Clemmensen reaction, yielding the precursor of avenaciolide **5**. On the other hand, the isomer **181** afforded the butenolide **184** by reduction under alkaline conditions and protection of the hydroxyl group as *t*-butyldimethylsilyl ether. The olefinic double bond of the butenolide ring **184** was reduced to the saturated γ-lactone **185** that was converted to **173** by the same sequence of reactions described above.

The synthesis of both **5** and **29** by the oxidative decarboxylation of **171** was originally described by Masamune *et al.*[69] The two carboxylic groups could be obtained by the oxidative cleavage of the double bond in the vinyl ether **187** in which the different substitution provides the necessary chemical differentiation to perform the lactone **A** formation. The *endo*-adduct **188** could be obtained by a cycloaddition reaction of a 3-substituted furan **189** and the suitable unsaturated ketone **190** as the dienophile.

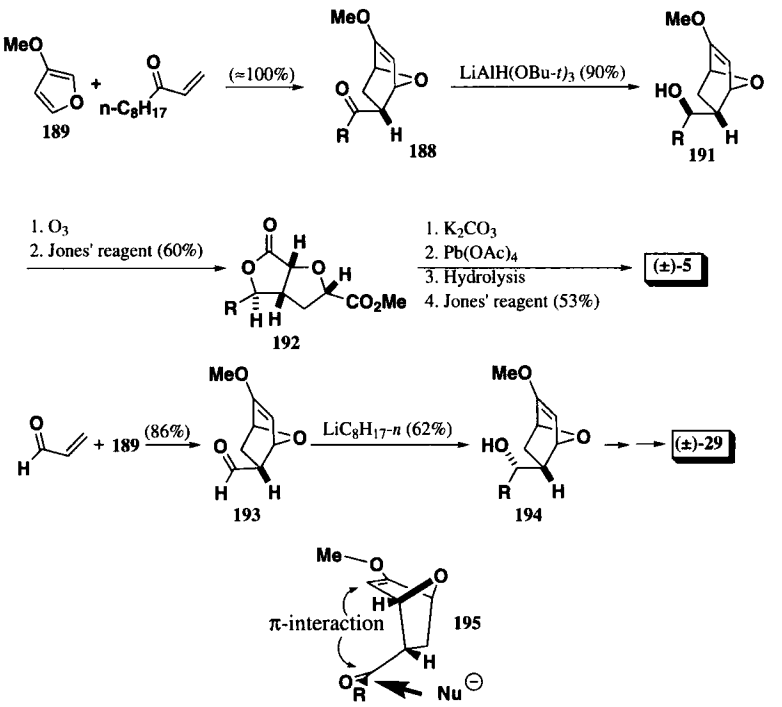


Scheme 39. Yoshikoshi *et al.* Approach to the Synthesis of Avenaciolide

Reduction of **188**, prepared from 3-methoxyfuran **189** and octyl vinyl ketone, produced only the diastereoisomeric alcohol **191**. Ozonolysis of **191** followed by Jones oxidation effected formation of the lactone-ester **192**. This ester, when hydrolyzed and then oxidized, was converted into lactone

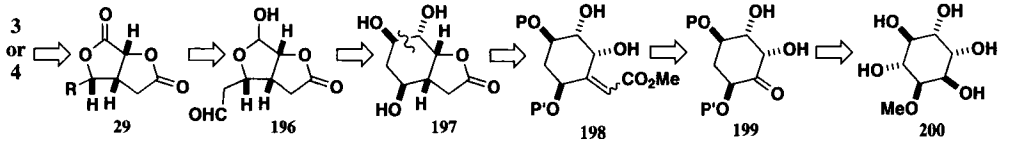


acetates, which without further purification and on hydrolysis and subsequent Jones oxidation, gave the precursor **5** of avenaciolide. Alternatively, the addition of *n*-octyl lithium to the adduct **193**, prepared from acroleine and **189**, afforded the epimeric alcohol **194**, that when submitted to a similar sequence of steps afforded the precursor **29** of isoavenaciolide. The high stereoselectivity in the addition reactions in both **188** and **193** is accounted for by the attack of the nucleophiles from the less hindered side of the carbonyl compounds assuming conformations **195** with maximum overlap of the π-orbitals at electron-rich and electron-deficient double bonds.



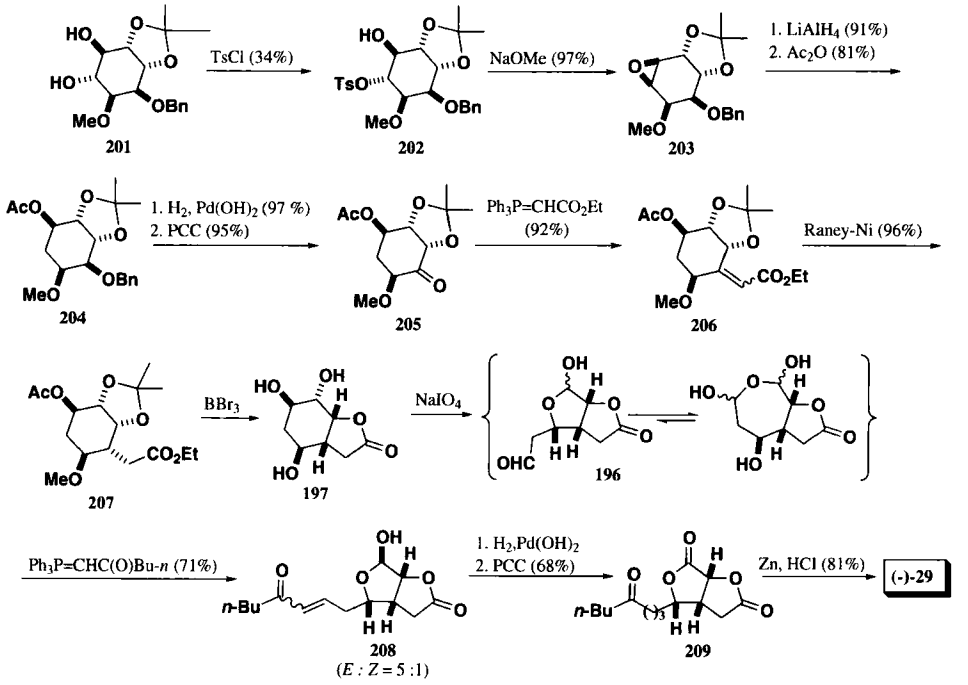
Scheme 40. Masamune *et al.* Approach to the Synthesis of Isoavenaciolide

Cyclitols have not been widely used for the synthesis of enantiomerically pure natural products in spite of their abundance in nature. The syntheses of isoavenaciolide (**3**) and ethisolide (**4**) reported by Ogawa *et al.*[72] are based on the use of the natural enantiomer of L-quebrachitol (**200**), a cyclitol available from the serum of the rubber tree.[73] As usual, the bislactones **29** can be considered to be the direct predecessors of the natural products. In both cases, and considering the length of the hydrocarbon chain, the same precursor **196** could be a common precursor. This acetal could be formed *via* the oxidative cleavage of a diol such as **197**. The synthesis of the γ-lactone moiety could arise from an α,β-unsaturated ester such as **198** *via* a ketone **199** by a Wittig-type reaction. Considering the carbon framework and substituents, quebrachitol could be envisioned as a suitable starting material selective by a series of selective protections and functional group interconversions.



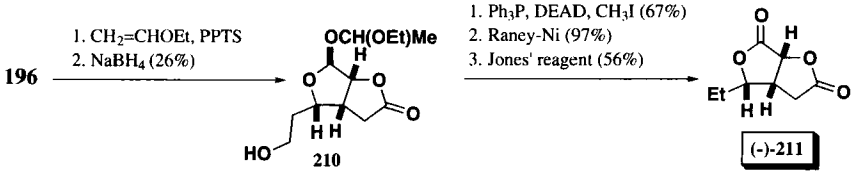
The diol **201**, prepared from **200** in three steps,[73b] was selectively tosylated to **202**. Base treatment of **202**, followed by reduction of the resulting epoxide **203**, gave **204** after acetylation. Debenzylation and subsequent oxidation afforded the ketone **205**, whose Wittig reaction with a stabilized phosphorane gave an inseparable mixture of *E*- and *Z*-unsaturated esters **206**. Hydrogenation of

the double bond proceeds stereoselectively, obtaining almost exclusively the epimer **207**. Treatment of **207** with strong Lewis acid caused deprotection of the methyl, acetyl and ketal groups, as well as lactonization, to give the γ-lactone **197**, which was purified as the triacetate. Acid hydrolysis regenerated the triol **197**, which was submitted to periodate fragmentation to afford the hemiacetal aldehyde **196** that, without purification, was homologated with a stabilized Wittig reagent to a mixture of *E*- and *Z*-isomers **208**. Saturation of the double bond and oxidation provided the bislactone **209**. Finally, reduction of the ketone carbonyl group in **209** by modified Clemmensen reaction[74] gave the precursor of natural isoavenaciolide **29**.



Scheme 41. Ogawa *et al.* Approach to the Synthesis of (-)-Isoavenaciolide

Alternatively, the protection as ethoxy ethyl ether of **196** provided the corresponding acetal-aldehyde that without purification was reduced to the primary alcohol **210**. Iodination, subsequent hydrogenolysis and further Jones oxidation gave the intermediate for ethisolide **211** in enantiomeric form.



Scheme 42. Ogawa *et al.* Approach to the Synthesis of (-)-Ethisolide

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ABBREVIATIONS

AIBN	2,2'-Azobisisobutyronitrile
BBN	9-Borabicyclo[3.3.1]nonane
Bpy	2,2'-Bipyridyl
COD	Cyclooctadiene
CSA	Camphorsulfonic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DET	Diethyl tartrate
DHP	Dihydropyran
DIBAL	Diisobutylaluminum hydride
DIPT	Diisopropyl tartrate
HMPA	Hexamethylphosphoramide
Im	Imidazole
m-CPBA	*m*-Chloroperbenzoic acid
MoOPH	Diperoxo-oxohexamethylphosphoramidomolybdenum(VI)
MPM	*p*-Methoxyphenylmethyl
Ms	Methanesulfonyl
NMO	4-Methylmorpholine *N*-Oxide
PCC	Pyridinium chlorochromate
PPTS	Pyridinium *p*-toluenesulfonate
Py	Pyridine
TBAB	Tetrabutylammonium bromide
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butyl hydroperoxide
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Ts	*p*-Toluenesulfonyl

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3. In order to simplify the discussion, the numbering of atoms in structure **1** is employed throughout the schemes and does not correspond to systematic nomenclature for all intermediates. In the case of avenaciolide, the systematic name corresponds to: (3a*R*, 4*R*, 6a*R*)-3-methylene-4-octyl-dihidro-furo[3,4-*b*]furan-2,6(*3*H, *4*H)-dione.

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