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THE SYNTHESIS OF MACROCYCLIC LACTONES

APPROACHES TO COMPLEX MACROLIDE ANTIBIOTICS

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INTRODUCTION

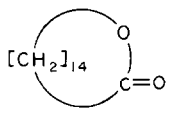
Medium and large rings contain 8–11 and 12 or more atoms respectively. The term "macrocyclic" most commonly refers to large-ring compounds, but in a broader sense sometimes denotes those with medium rings as well. The term "macrolide" has several connotations; in the classical sense it describes a class of antibiotics derived from species of Streptomyces which possess as characteristic features (a) a large lactone ring containing few double bonds and devoid of nitrogen and (b) one or more sugars which may be amino sugars, non-nitrogenous sugars or both.[1] Wider application of the term encompasses all other natural products with large lactone rings. In some cases, macrocyclic lactams such as the maytansinoids have also been described as macrolides.

The chemistry of macrocyclic compounds originated in 1926 with Ruzicka's structural elucidation of the musk components civetone and muscone, which were shown to be large-ring ketones.[2–4] This discovery revealed the inadequacies of the von Baeyer strain theory which had predicted that large-ring compounds would be too unstable to exist because of overextension of internal bond angles from the preferred tetrahedral geometry. In fact, large rings are virtually strain-free as a result of their flexibility and ability to adopt non-planar conformations.[5] Difficulties in their preparation stem from entropy factors associated with the required interaction of two remote groupings in a suitable acyclic precursor rather than from enthalpy considerations.

Shortly after Ruzicka's initial discovery, Kerschbaum[6] demonstrated the presence of pentadecanolide (exaltolide) **1** and Δ^7-hexadecenolide (ambrettolide) **2** in the vegetable musk oils of angelica root and ambrette seed respectively. Vigorous efforts to discover synthetic routes to these and related compounds ensued, prompted by the challenge of preparing the novel macrocyclic lactone structures and by their commercial importance in the fragrance industry.[7–9] Several preparative techniques were developed for this purpose, generally effecting cyclization of suitable bifunctional precursors by employing high dilution conditions. Although slow and awkward, such techniques permitted cyclization in lieu of polymerization of molecules with remote reactive ends.

Interest in large-ring lactones experienced a second quantum jump in the 1950s after Brockmann and Henkel[10] isolated the first macrolide antibiotic picromycin **3** from an Actinomyces culture.

Since then, a large number of macrolides possessing diverse biological activity has been isolated from natural sources, and many have proved of considerable importance clinically and as preservatives and supplements to animal feeds. New macrolides continue to be discovered at a rapid rate. The complexity of their structures has made the macrolide antibiotics challenging subjects for the scrutiny of organic chemists and consequently the chemical literature abounds with reports of their isolation, structural elucidation, stereochemistry and biosynthesis. Several reviews have appeared on these aspects of their chemistry.[11–18] Major contributions to their synthesis was however belated, despite the obvious scientific and commercial rewards arising from the success of such endeavours. Thus, at the time of



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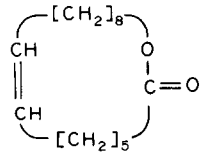

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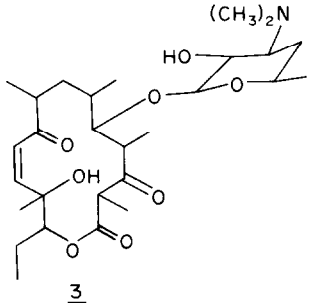

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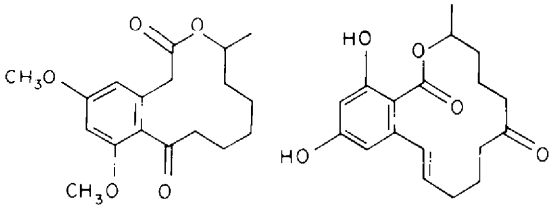
Keller-Schierlein's comprehensive review[16] of the chemistry of the macrolide antibiotics in 1973, only the relatively simple compounds di-O-methylcurvularin **4** and zearalenone **5** had been synthesized.



4 **5**

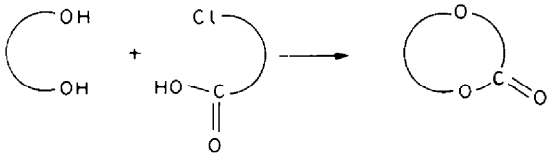
The complex stereochemistry and the number and lability of the substituents borne by their skeletons has generally precluded the synthesis of the macrolide antibiotics via the simple approaches which had been successful in preparing derivatives and homologues of musk lactones. Recently, however, the advent of several activation methods permitting the cyclization of bifunctional precursors under mild conditions has permitted rapid progress in the field, culminating in the total synthesis of several complex macrolides. In view of the expanding activity in this area, the present review was undertaken. Its objective is to outline available routes to macrocyclic lactones in general, and particularly to survey their application to the synthesis of complex macrolide antibiotics.

THE SYNTHESIS OF MACROCYCLIC LACTONES

I. *From ω-halocarboxylic acids*

The first[6] and one of the most direct syntheses of simple macrolides such as exaltolide **1**, ambrettolide **2** and related compounds results from the cyclization of the corresponding ω-bromo-[6,19–23] or iodo-[21,24] alkanoic acids. The acids were heated with silver oxide[6] or lactonized via their silver carboxylates.[6,20] Alternately, slow addition (e.g. 0.0066 mole/day/liter of solvent[21]) of the bromoacid to a solvent containing potassium carbonate[19–21,23] or hydroxide[22] afforded 10–18-membered lactones in good yield.

More recently, Russian workers obtained macrocyclic oxalactones in 35–38% yield by condensing diols with ω-chloroalkanoic acids.[25]

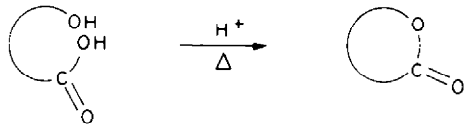


A kinetic study of the cyclization of ω-bromoacids was performed by Stoll *et al.*[26] in the case of 12 and 16-membered lactones, and by Illuminati *et al.*[27] in the range of 7 to 12-membered lactones. First order kinetics were observed at low concentrations, with the rate of ring-closure revealing a minimum for 8 and 9-membered rings.[27]

II. *From ω-hydroxycarboxylic acids*

ω-Hydroxycarboxylic acids are the most common starting materials for large-ring lactones because of their relative availability and due to the development of techniques for activation of the carboxyl group, the hydroxyl moiety or both functions simultaneously.

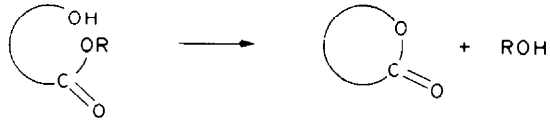
(i) *By direct esterification.* The most direct route to macrocyclic lactones involves the intramolecular esterification of ω-hydroxyalkanoic acids, as originally reported by Stoll and Rouvé.[28]



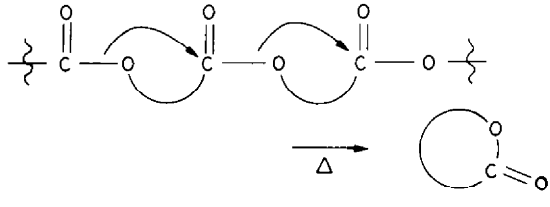
The use of dilute solutions (e.g. 0.0002–0.0008 M[28]) and catalysts such as benzenesulfonic[28–30] or *p*-toluenesulfonic acid[31] is essential. The synthesis of rings of up to 24 members has been accomplished.[30] Yields range from *ca.* 1% for nonanolide[30] to 87% for exaltolide.[28] Objections to this approach arise from its cumbersome execution as well as from concomitant formation of dimers,[28,30] trimers[30] and polymers.[28] A kinetic study of the internal esterification reaction has been made.[32] A recent variation was reported by Scott and Naples[33] who effected lactonization of ω-hydroxy acids in improved yield by using boron trifluoride etherate in the presence of unfunctionalized polystyrene beads as catalyst.

The method has been utilized in the synthesis of the Lythraceae alkaloids vertaline[34,35] **6**, decaline[36,37] **7**, decinine[38] **8** and the methyl ether **9** of the latter.[39–41] The success of the technique for these compounds, which were obtained in yields of 40–82%, is attributable to the rigidity of the acyclic skeleton which enables cyclization to compete successfully with intermolecular esterification.

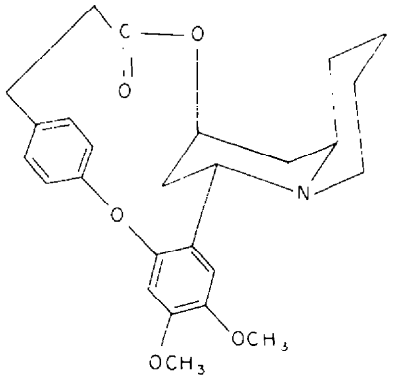
(ii) *By transesterification.* Macrocyclic lactones may be prepared by internal transesterification of esters of ω-hydroxy acids.



An early adaptation of this approach was discovered by Hill and Carothers,[42] who found that pyrolysis of linear polyesters in the presence of a catalyst under vacuum resulted in the distillation of monomeric (and dimeric) products, obtained through ester interchange.



Optimum temperatures of *ca.* 270° were required and a variety of catalysts was explored.[43] Polyesters of dibasic



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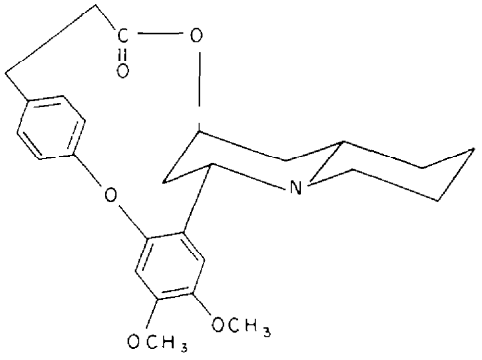

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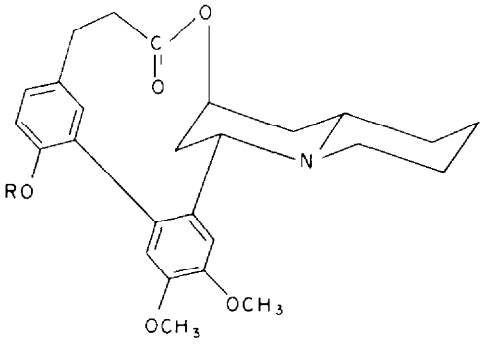
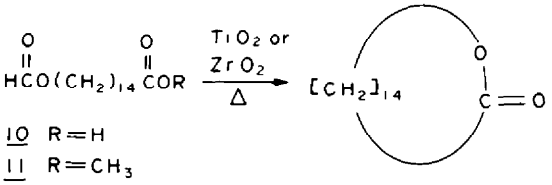


8 R = H
9 R = CH_3

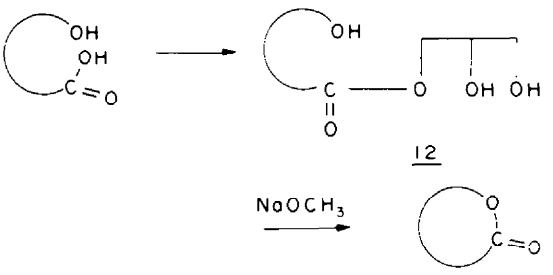
acids[42–44] as well as those of ω-hydroxyalkanoic acids[45] were treated in this manner. The latter compounds furnished lactones with 11 to 17-membered rings in yields ranging from a trace (14-membered) to 90% (15-membered). Awkward high dilution techniques could thus be avoided.

Stoll and Bolle[46] reported that vapours of the esters **10** and **11** generate pentadecanolide in yields of *ca.* 50% when passed over titanium or zirconium oxide at 250–320°. The authors postulated formation and subsequent depolymerization of polyesters on the catalyst surface.



10 R=H
11 R=CH_3

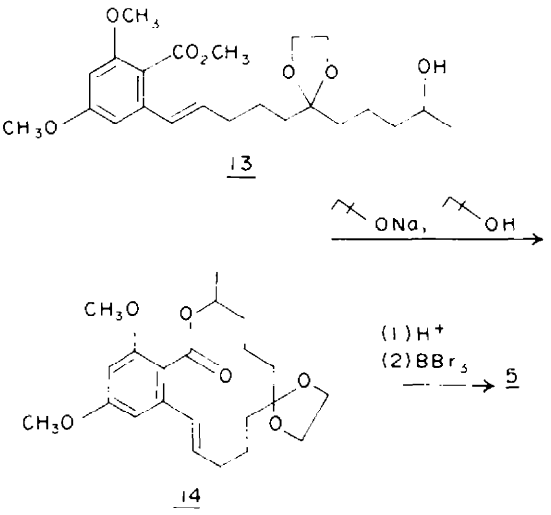
Collaud[47–49] demonstrated that internal transesterification of glycerides **12** of ω-hydroxycarboxylic acids in the presence of sodium methoxide affords the corresponding lactones in high yield. The products were distilled from the reaction mixture with excess glycerol.



12

Recent variations of these techniques have found application in the synthesis of macrocyclic musk lactones in the perfume industry.[7–9,50,51] However, the method offers limited scope for more complex substrates because of the required high temperatures.

The synthesis of zearalenone **5** by transesterification of the hydroxy methyl ester **13** has been reported.[52] Cyclization of the latter compound was achieved in low yield by treating it with a dilute toluene solution of t-amyl alcohol and sodium t-amylate. The by-product methanol was continuously removed by distillation to drive the reaction to completion. Removal of the ketal and methyl ether protecting groups from **14** completed the synthesis.



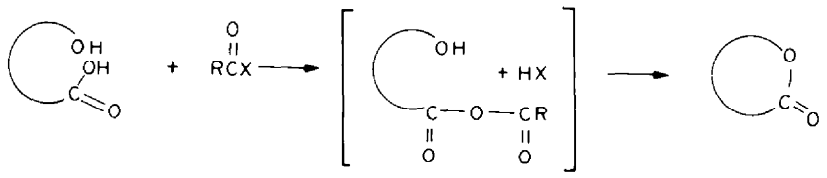
13

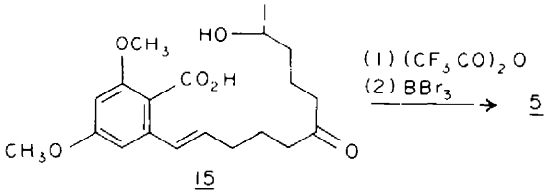
14

(iii) *Via mixed anhydrides.* The lactonization of ω-hydroxy acids has been achieved by their reaction with phosgene-triethylamine[53] or with trifluoroacetic anhydride. The formation of mixed anhydrides occurs[54,55] and these intermediates undergo intramolecular attack (in dilute solution) by the free hydroxyl function to afford the corresponding lactones. In this way, carboxyl activation permits the use of less forcing conditions.

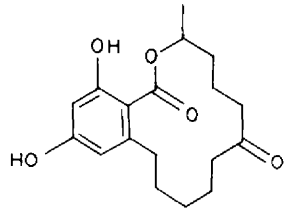
Trifluoroacetyl mixed anhydrides have been used to prepare zearalenone **5** from the hydroxy acid **15** in varying yield.[56–59]

This method was also employed in the synthesis of the related compounds zearalanone[60,61] **16** and zearalanol[61] **17**.





15 → 5



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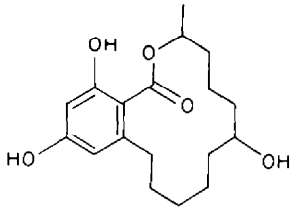
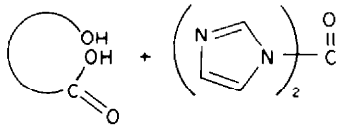


17

Two related techniques have also been reported. The synthesis of the 14-membered lactone **18** was achieved by cyclization of the corresponding hydroxy acid **19** with *p*-toluenesulfonyl chloride-triethylamine.[62] The product is a model compound of erythronolide B, the aglycone of the antibiotic erythromycin B (*vide infra*). Similarly, thionyl chloride was employed in the synthesis of decaline[37,63] **7** from the hydroxy acid **20**. A lower yield was obtained than by direct esterification.[37]

(iv) *Via N-acylimidazolides.* An alternate method for the activation of carboxylic acids for esterification is by their conversion to N-acylimidazolides by treatment with N,N'carbonyldiimidazole **21**.[64] Base-catalyzed internal alcoholysis of the imidazolides **22** provides access to the desired lactones.



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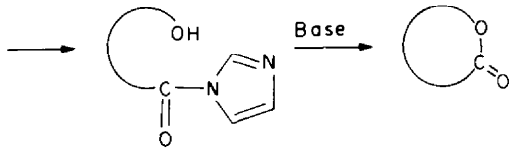

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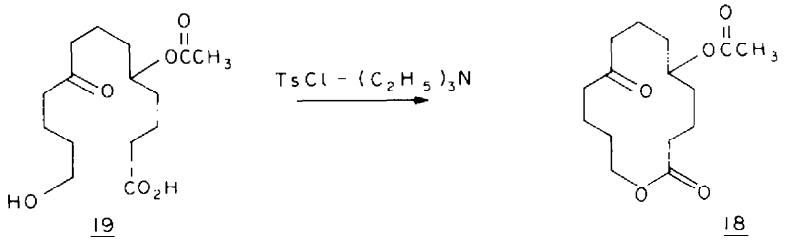
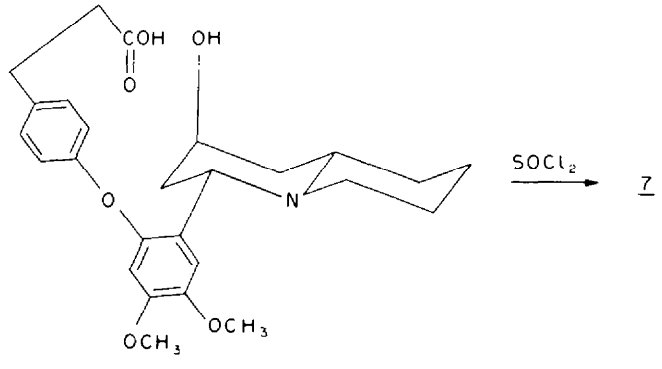
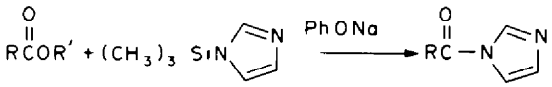
Masamune *et al.*[65] have also prepared acylimidazolides from phenyl or 2,2,2-trifluoroethyl esters by their reaction with N-trimethylsilylimidazole **23** in the presence of a catalytic amount of sodium phenoxide. Since alkyl, S-t-butylthiol and benzenethiol esters are inert to **23**, the method permits selective activation of one ester in the presence of others.



19 → 18



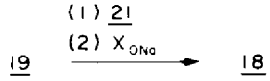
20 → 7



23

R = aryl, alkyl or cycloalkyl
R′ = Ph or CF_3CH_2

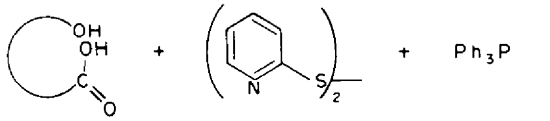
The tridecanolide **18** was obtained from **19** by treating the imidazolide with sodium t-amylate. The yield of **18** was slightly lower (40 vs 52%) with this method than with *p*-toluenesulfonyl chloride-triethylamine, although milder conditions were used.[62]



Carboxyl activation via imidazolide formation was also employed by Colvin, Purcell and Raphael[66,67] in their synthesis of (±)-pyrenophorin **24**. This antifungal and cytostatic dilactone was prepared from a diastereoisomeric mixture of the key intermediate E,E-diene **25**. Removal of the tetrahydropyranyl and 2-(*p*-tolysulfonyl)-ethyl protecting groups liberated the free hydroxy acid which was treated with N,N′-carbonyldiimidazole **21**. The resulting imidazolide **26** was cyclized to the dilactone **27** in the presence of a catalytic amount of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) at room temperature in a total yield of 60%. Finally, generation of the keto groups from **27** with N-chlorosuccinimide and silver nitrate provided a 1:1 diastereoisomeric mixture of the corresponding oxolactones which were chromatographically separated into racemic pyrenophorin and its meso isomer.

(v) *Via thiol esters.* The advantage of activating the carboxylic acid function prior to internal esterification of an ω-hydroxy acid is obvious. An even more expedient procedure involves simultaneous activation of both the hydroxyl and carboxyl groups. Such a technique permits milder conditions and more rapid cyclization, thereby providing access to complex, polyfunctional lactones. Corey *et al.*[68] found that such "double activation" was observed with 2-pyridinethiol esters **28** of ω-hydroxy acids. Proton transfer from the hydroxyl group to the carbonyl oxygen is possible through the formation of a dipolar intermediate **29**. Cyclization to **30** is thus facilitated, followed by elimination of 2-pyridinethione **31** to generate the desired lactone. Since the thione is the dominant tautomer of **31**, complications from the formation of a byproduct thiol are avoided.[69] The 2-pyridinethiol esters are readily prepared by the well-known oxidation-reduction condensation developed by Mukaiyama,[70,71] employing di(2-pyridyl) disulfide **32** in the presence of triphenylphosphine.

The lactonization reaction is generally performed in refluxing benzene or xylene. It is not catalyzed by acids, bases or co-products.[72] The intermediacy of a proton-



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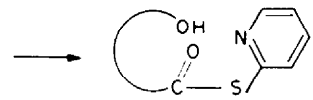

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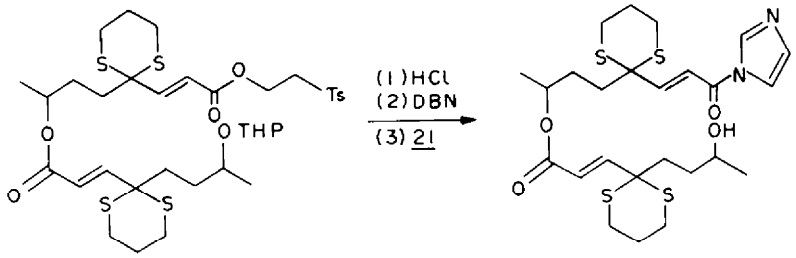

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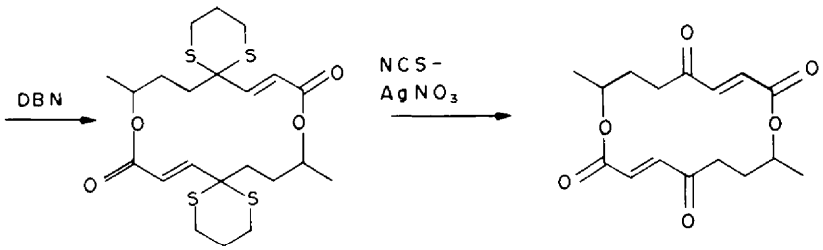
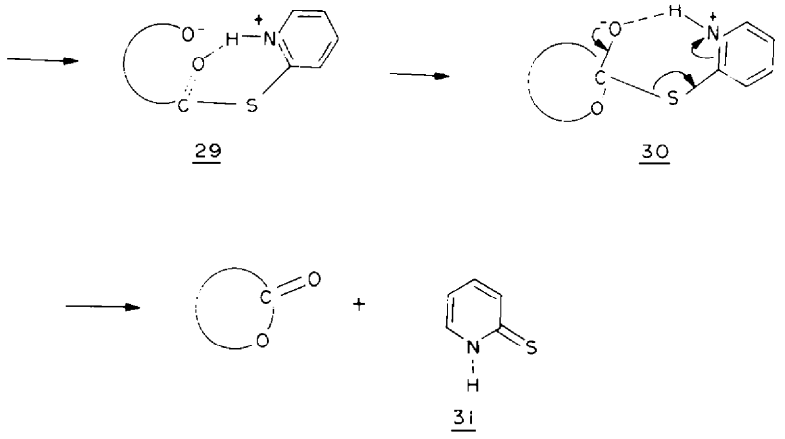
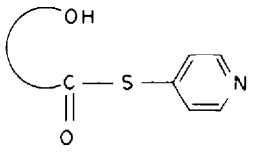


27 24



29 30 31

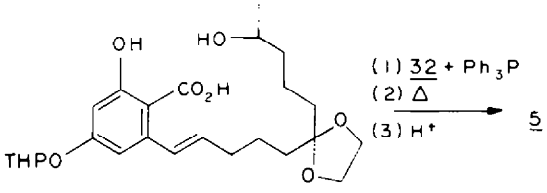
chelated species **29** is supported by the observation[72] that the reaction fails with benzenethiol or 4-pyridinethiol esters **33**.



33

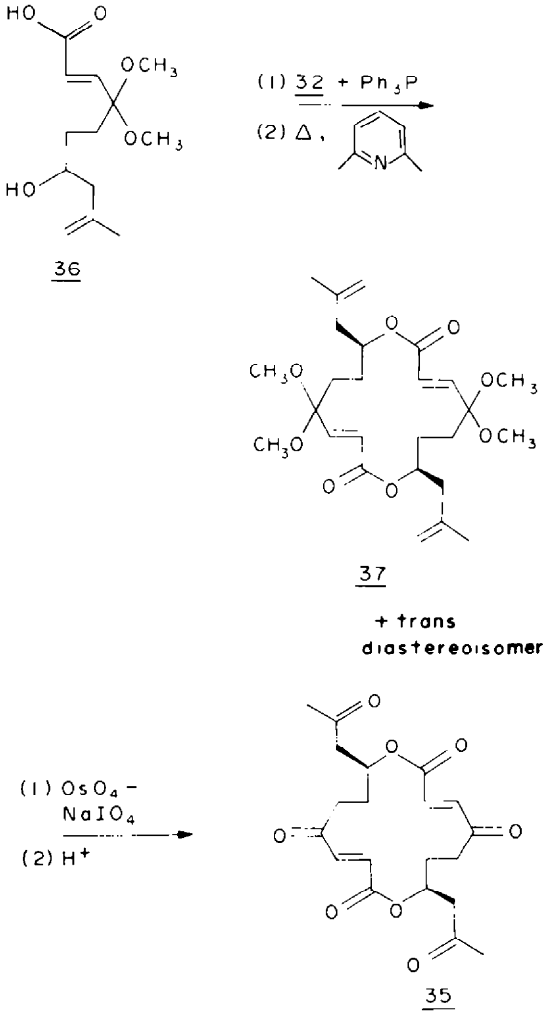
Macrocyclic lactones with 12 to 21-membered rings have been obtained by this method.[68,72] The rate of formation is slowest for the 12-membered and most rapid for the 16-membered lactone.[72] The acceleration of the lactonization process by Ag (I) has also been demonstrated.[73]

The utility of 2-pyridinethiol esters in the preparation of macrocyclic lactones was made evident by Corey *et al.* who, in recent years, have succeeded in the synthesis of several complex macrolides. Thus, racemic zearalenone **5** was obtained in 75% yield from the protected (±)-hydroxy acid **34**.[68]



34

Two macrocyclic dilactones were also prepared directly from their corresponding hydroxy acids. The antibiotic vermiculine **35** was synthesized[74] by a one-step dimerization of the hydroxy acid **36**. Conversion of the latter to the 2-pyridinethiol ester, followed by coupling in the presence of 2,6-lutidine (to neutralize acidic impurities) produced a 30% yield of a 1:1 mixture of the protected (±)-vermiculine derivative **37** and its *trans*-methallyl diastereoisomer. Generation of the side-chain keto functions with osmium tetroxide-sodium periodate and removal of the ketal groups afforded racemic vermiculine, chromatographically separable from the *trans* diastereoisomer. The authors point out that the undesirable formation of the latter compound would be avoided with the use of the optically pure hydroxy acid **36**.



36 37 + trans diastereoisomer 35

The dilactone carpaine **38** was obtained in a similar manner from N-benzyloxycarbonyl carpamic acid **39**.[75] One-step dimerization furnished the N-protected dilactone in 50% yield, with no concomitant formation of the monolactone. Subsequent hydrogenolysis afforded carpaine quantitatively. Since the carpamic acid precursor was in this case derived from naturally occurring car-

paine, the product was optically pure. The synthesis of (±)-carpamic acid has also been recently reported.[76]

The Corey synthesis of vermiculine and carpaine differ from that of pyrenophorin **24** in the direct formation of the dilactone moiety from a hydroxy acid. In contrast, the synthesis of **24** involved cyclization of an acyclic precursor containing a pre-formed ester linkage.

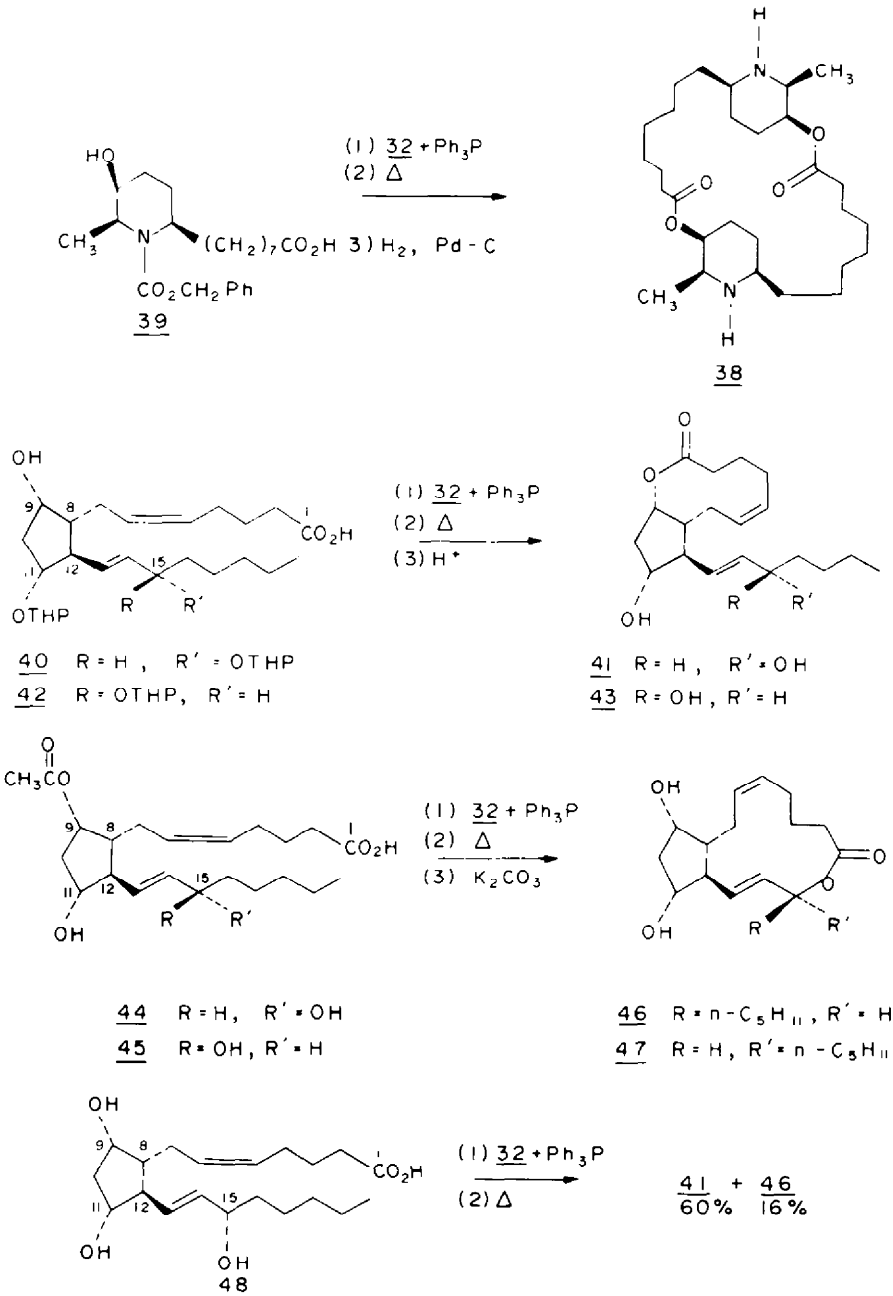
Corey *et al.* have also reported the application of this lactonization technique to hydroxy acids in the prostaglandin $F_{2\alpha}$ series.[77] The 11,15-bis(tetrahydropyranyl) derivative **40** underwent cyclization to furnish the 1→9 lactone of prostaglandin $F_{2\alpha}$ **41**, obtained in 81% overall yield after removal of the tetrahydropyranyl groups. Formation of lactone **41** was claimed to provide a useful means of protecting the parent hydroxy acid during further transformation. Similar treatment of **42**, the 15-R epimer of **40**, provided the corresponding 1→9 lactone **43** in 91% yield.

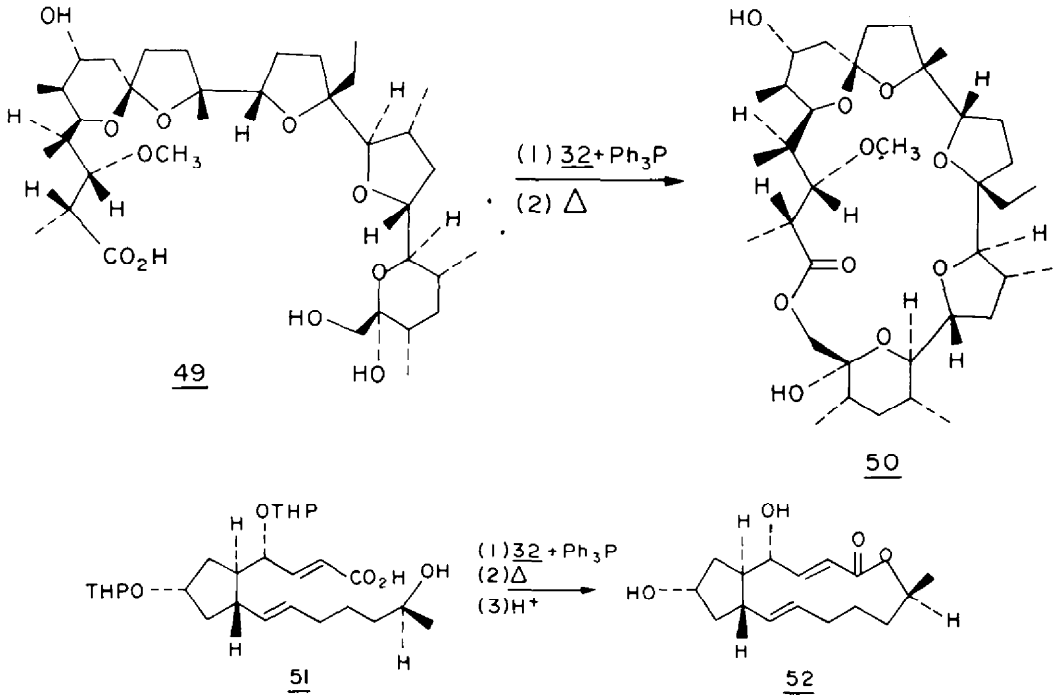
The 9-acetate of prostaglandin $F_{2\alpha}$ **44** and its 15-epimer **45** provided the corresponding 1→15 lactones **46** and **47** in good yield.[77]

The lactonization of the parent prostaglandin $F_{2\alpha}$ **48** via its 2-pyridinethiol ester gave a mixture of both the 1→9 and 1→15 lactones **41** and **46** in yields of 60 and 16% respectively.[77]

The antibiotic monensin **49** was converted to its cyclic form **50** in 95% yield by this method.[77] Reaction proceeded through the primary OH group.

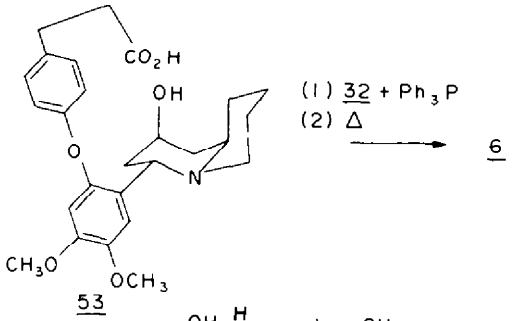
Several naturally occurring macrocyclic monolactones have also been synthesized by Corey *et al.*[75] Thus, the protected A-brefeldinoic acid **51** was converted to the corresponding lactone in 70% yield. Tetrahydropyranyl





ether cleavage afforded brefeldin A **52** in 97% yield.

Similarly, vertaline **6** was obtained in 67% yield from its hydroxy acid **53**.[75] The yield is higher with the 2-pyridinethiol ester method than by the direct, acid-catalyzed lactonization described previously.

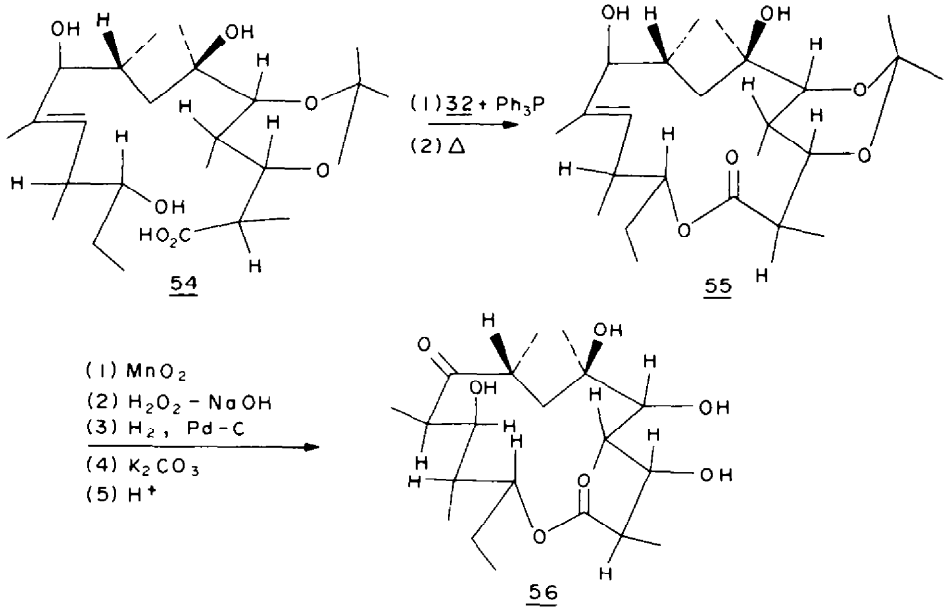


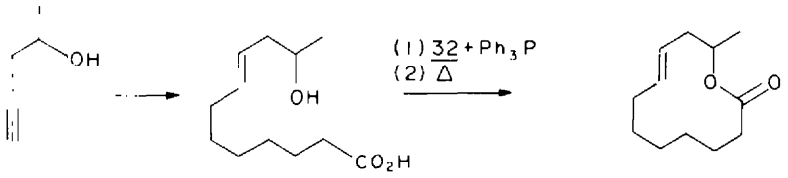
Furthermore, the hydroxy acid **54** was cyclized to the lactone **55** in 36% yield.[75] The latter compound was converted to erythronolide B **56**, the aglycone portion of the antibiotic erythromycin, by a five-step sequence.

The hydroxy acid precursors **51**, **53** and **54** were all derived from the naturally occurring macrolides by saponification.

The synthesis of (±)-11-methyl-*trans*-8-undecenolide **57**, a fungal metabolite of *Cephalosporium recifei*, has been reported.[78] The required hydroxy acid **58** was obtained by elaboration of the acetylene derivative **59**. Cyclization of its 2-pyridinethiol ester provided the desired macrolide in 52% yield.

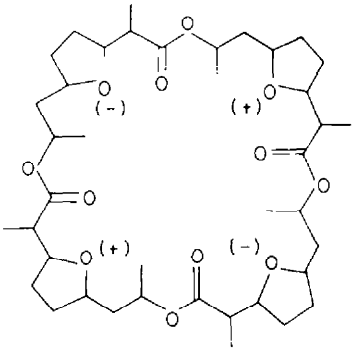
The 2-pyridinethiol ester cyclization method has also been employed in the synthesis of nonactin **60**, a 32-membered tetralactone (tetrolide). It consists of four





59 58 57

alternating units of levorotatory (2*R*, 3*R*, 6*S*, 8*S*) and dextrorotatory (2*S*, 3*S*, 6*R*, 8*R*)-nonactic acid **61**. The most obvious synthetic route to nonactin involves stepwise formation of the corresponding acyclic tetramer, followed by cyclization to the tetrolide.



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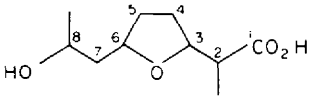


61

Two groups of workers have reported syntheses of nonactin. Gerlach *et al.*[79] coupled two nonactic acid residues protected as the t-butyl ester **62** and the benzyl ether **63** respectively, using mesitylenesulfonyl chloride-pyridine as coupling agent. The product dimer **64** was treated similarly to furnish the required tetramer **65**. Cyclization of the latter was accomplished by activation of its 2-pyridinethiol ester with Ag (I) to provide nonactin as well as two diastereoisomers.

Schmidt *et al.*[80–82] constructed the dimer **66** by treating the 8-epitosylate **67** with the carboxylate **68**. The desired stereochemistry at C-8 was obtained by means of the resulting Walden inversion. The tetramer **65** was prepared in a similar fashion[80,82] and cyclized by treatment of its 2-pyridinethiol ester with Ag(I). Alternately, the tetramer was obtained by dimerization of the free acid dimer with N,N'-carbonyldiimidazole **21**.[81]

It is clear that the stereochemical integrity of synthetic nonactin depends on the availability of optically pure nonactic acid. Partially stereoselective syntheses of the latter compound were reported by Beck and Henseleit[83] and independently by Gerlach and Wetter.[84] These preparations furnished racemic nonactic acid as well as other diastereoisomers. More recently, Schmidt *et al.*[85,86] reported highly stereoselective syntheses of optically pure nonactic acids from (−)-propylene oxide, in turn derived from (+)-lactic ester.[87]

The utility of heterocyclic disulfides other than di(2-pyridyl) disulfide was investigated by Corey and Brunelle.[88] Compounds **69–74** were less effective than the di-2-pyridyl derivative. Use of the imidazolyl disulfide **75** permitted rapid cyclization of 16-hydroxyhexadecanoic acid at 25°. However, the yield of the corresponding lactone was limited to 37%, owing to competing formation of the N-acyl derivative **76** at the expense of the required S-acyl lactone precursor **77**. The problem was circumvented by the use of the 4-t-butyl derivatives **78** and **79** in which N-acylation is sterically suppressed. The latter compounds have improved properties over di(2-pyridyl) disulfide **32** in macrocyclic lactone synthesis as increased reaction rates (and therefore lower temperatures) and higher yields are obtained.

Masamune *et al.* have demonstrated that t-butylthiol[89,90] and benzenethiol[91] esters of ω-hydroxy acids **80** and **81** provide an attractive means for protecting and subsequently activating the carboxyl group.

The thiol esters were prepared from the corresponding acid chlorides by reaction with thallous thiolates[89,90] **82**, or by treatment of the acids with diethyl phosphorochloridate **83**, followed by reaction with the thiolate salts **82**. The latter procedure[92] circumvents the need for the acid chloride and the intermediate **84** is inert to unmasked hydroxyl functions.

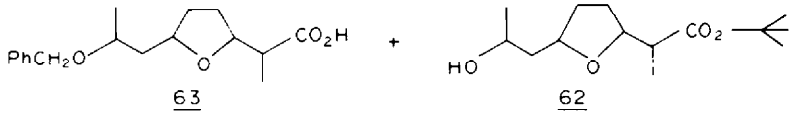
Thiolysis of imidazolides **22** also afforded the desired thiol esters.[65,91] The reaction of t-butylthiol[89,90] and benzenethiol[91] esters **80** and **81** with mercuric trifluoroacetate[89,90] or methanesulfonate[91] furnished the corresponding lactones under mild conditions.

Model studies of thiol ester **85** indicated that mercuric trifluoroacetate-mediated alcoholysis may proceed via an intermediate **86** or through the conventional mixed anhydride **87**, depending on the nature of the alcohol.[90]

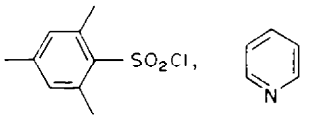
The utility of this technique has been elegantly demonstrated in the synthesis of several complex macrolides by Masamune *et al.*

The protected zearalenone **14** was prepared[90] in 90% yield by lactonization of the t-butylthiol ester **88** with mercuric trifluoroacetate under mild conditions.

The complex macrolide antibiotic methymicin **89** was successfully synthesized using Hg (II)-mediated lactonization of a hydroxy t-butylthiol ester as a key step. The precursors for the synthesis were the optically pure epoxyaldehyde[93] **90** and the racemic lactonic acid[93] **91**. The t-butylthiol ester **92** of the latter compound was converted to the Wittig reagent **93** via a five-step sequence.[89] Condensation with the aldehyde **90** afforded a mixture of diastereoisomers which, upon acid-catalyzed epoxide ring-opening, provided the hydroxy t-butylthiol ester **94**. Separation of diastereoisomers was effected at the lactonization stage. Oxidative thiol ester activation of compound **94** with *m*-chloroperbenzoic acid failed to effect lactonization.[89] Oxidative hydrolysis to the free acid, followed by cyclization via the triflu-



63 62



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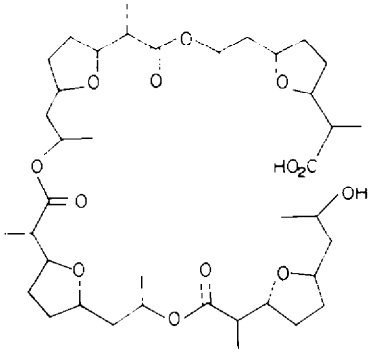
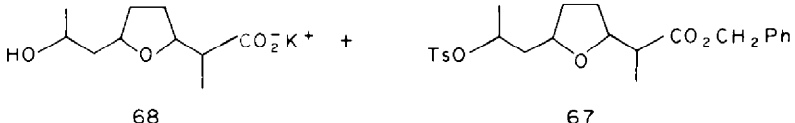


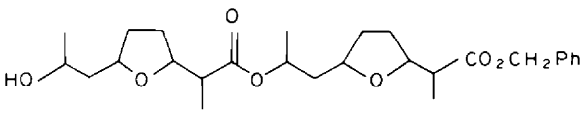
65

(1) 32 + Ph_3P
(2) Ag (I)

60

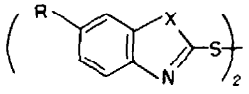


68 67

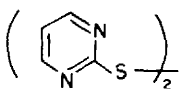


66

65 (1) 32 + Ph_3P (2) Ag (I) 60



69 X = NCH_3, R = H
70 X = O, R = H
71 X = S, R = H
72 X = S, R = NO_2



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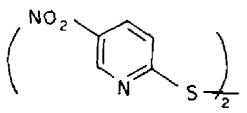

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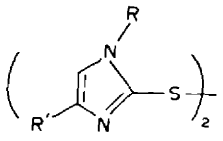
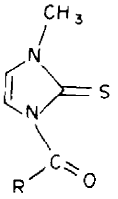


75 R = CH_3, R' = H
78 R = CH_3, R' = t-C_4H_9
79 R = i-C_3H_7, R' = t-C_4H_9



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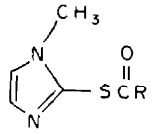
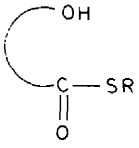
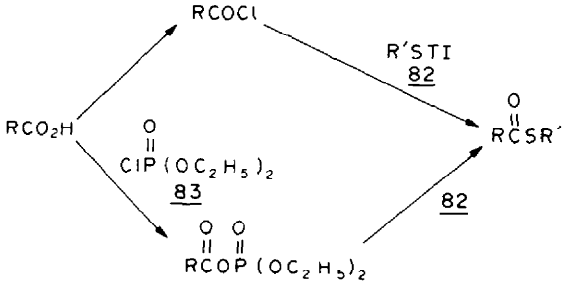


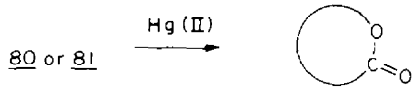
77

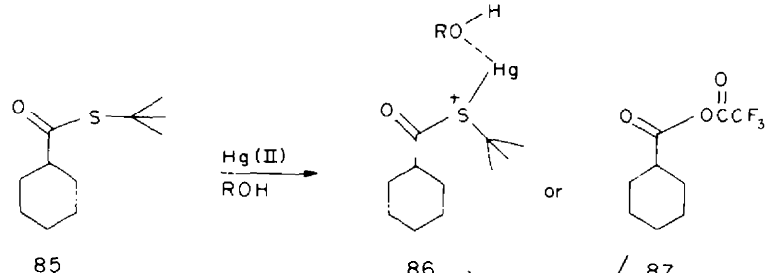
R = $+CH_2)_{15}$ OH

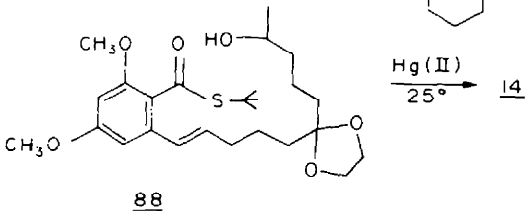


80 R = t-C_4H_9
81 R = Ph







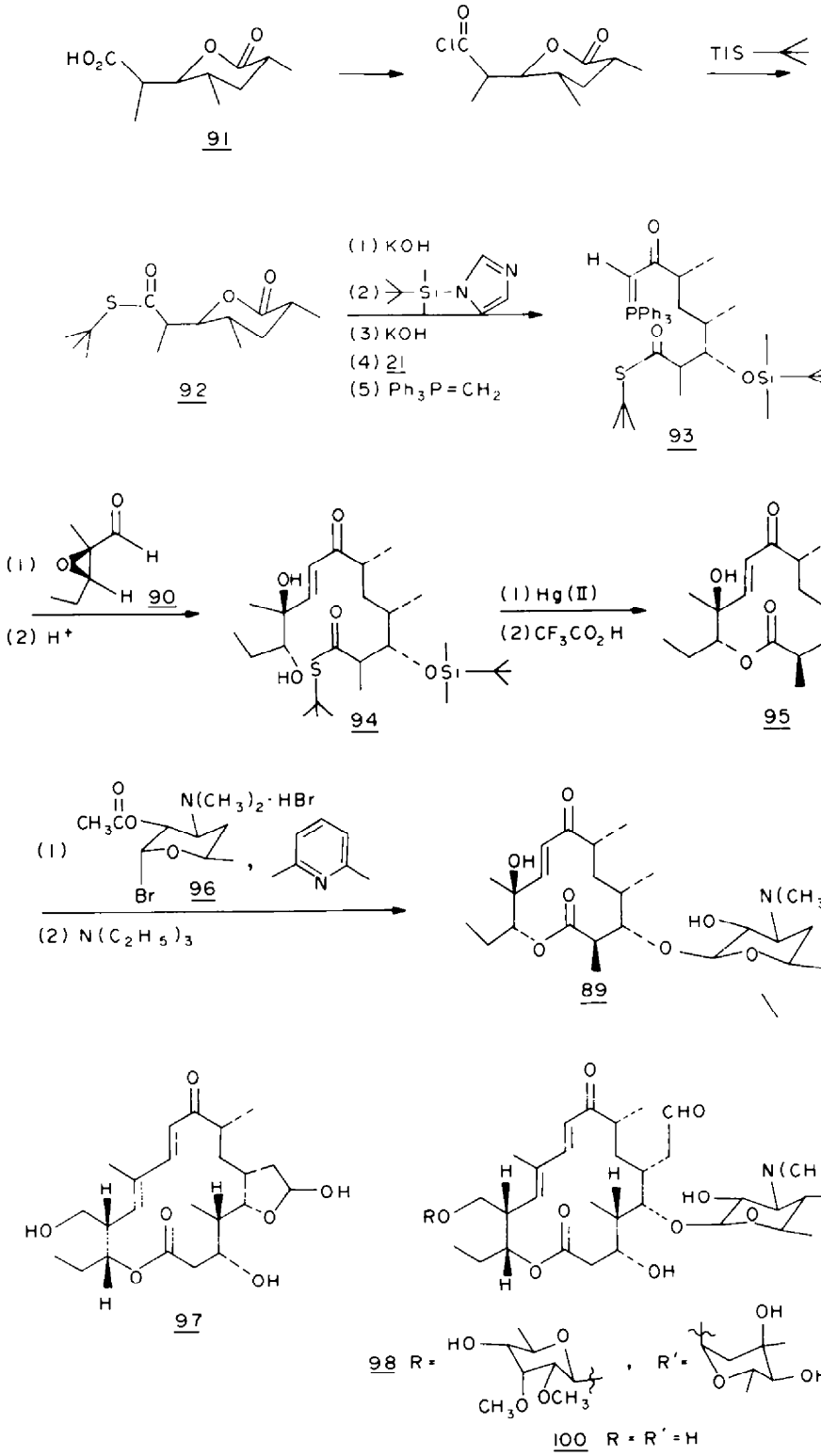


88

oroacetyl mixed anhydride afforded the lactone in erratic yields of up to 25%.[89] The best results were obtained by thiol ester activation with mercuric trifluoroacetate[89] and subsequent desilylation in trifluoroacetic acid to furnish methynolide **95**, the aglycone of methymicin in yields of up to 30%. Finally, glycosylation of **95** with 1-α-bromo-2-acetyldesosamine hydrobromide **96** and deacetylation completed the synthesis of the desired antibiotic **89**.

A partial synthesis of tylonolide hemiacetal **97**, the aglycone moiety of the complex macrolide tylosin **98** was reported.[91]

The hydroxy acid **99**, obtained from O-micaminosyl tylonolide **100**, was converted to the benzenethiol ester **101** via thiolysis of the corresponding imidazolide and reaction with manganese dioxide (to generate the 9-keto function). Cyclization of **101** with mercuric methanesul-

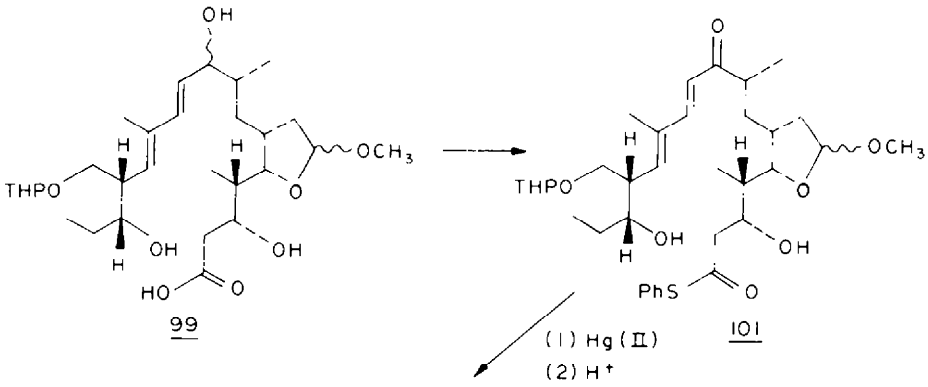


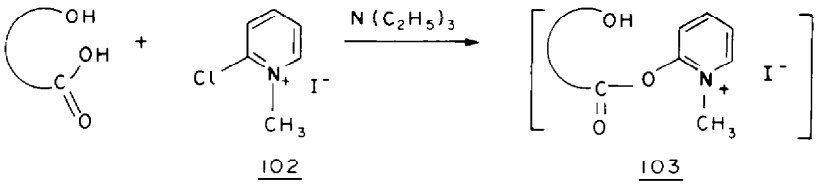
fonate followed by acid hydrolysis afforded **97** in 17% yield. It is worthy of note that the formation of the 16-membered lactone was favoured over that of the β-lactone derived from interaction of the 3-hydroxyl group of **101** with the thiol ester moiety.

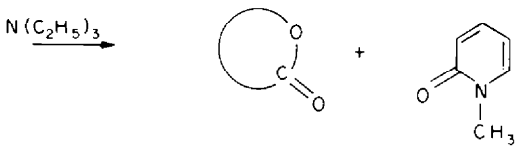
(vi) *Via 2-chloropyridinium and 2-chlorobenzothiazolium salts.* Lactonization of ω-hydroxycarboxylic acids was accomplished by carboxyl activation with 1-methyl-2-chloropyridinium iodide **102** in the presence of triethylamine. The reaction proceeds via the pyridinium intermediate **103**, in which nucleophilic attack by the OH group generates the lactone and the 2-pyridone **104**. Mukaiyama[94] prepared several large-ring lactones of up to 16 members in refluxing methylene chloride or acetonitrile.

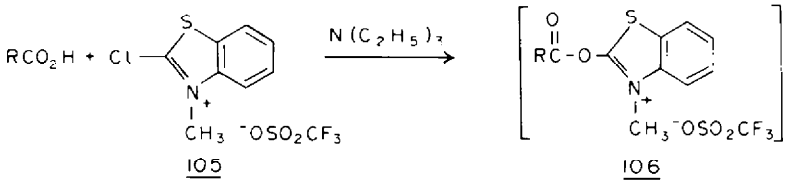
Carboxylic acids may also be treated with 2-chloro-N-methylbenzothiazolium trifluoromethanesulfonate **105** and triethylamine.[95] The intermediates **106** produce acid chlorides and anhydrides. Ester formation from the latter is sluggish, but thiolysis proceeds smoothly. Thus, indirect access to lactones is provided via thiol esters (*vide supra*).

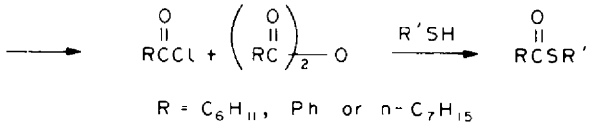
(vii) *By hydroxyl activation.* A "reverse activation" technique for ring-closure of ω-hydroxy acids was reported by Mitsunobu *et al.*[96] wherein the OH group is activated and the carboxylate anion functions as the





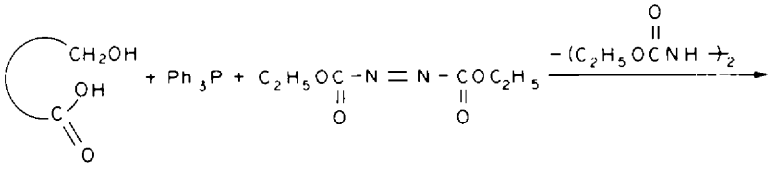


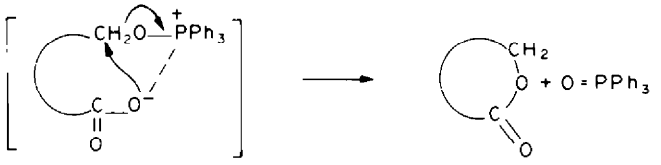




nucleophile. Thus, reaction of the hydroxy acid with triphenylphosphine and diethyl azodicarboxylate at room temperature effects ring-closure via an alkoxyphosphonium carboxylate **107**.

White *et al.*[97] applied this technique to the synthesis of (±)-vermiculine **35**. The intermediate **108** was subjected to lead tetraacetate oxidation and acid hydrolysis to provide the hydroxy acid **109**. Cyclization of the latter with triphenylphosphine and diethyl azodicarboxylate provided vermiculine in 15% yield. This intramolecular cyclization contrasts with the dimerization technique employed by Corey's group in their synthesis of vermiculine (*vide supra*).





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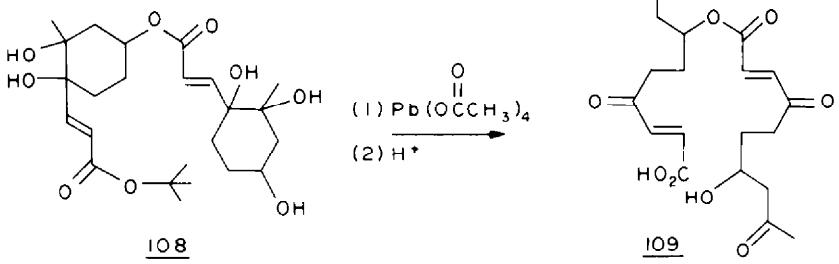
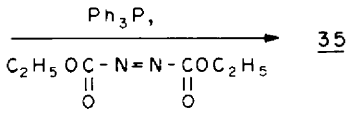


108 109



35

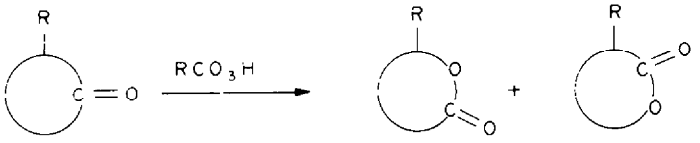
III. *From cycloalkanones by Baeyer–Villiger oxidation*

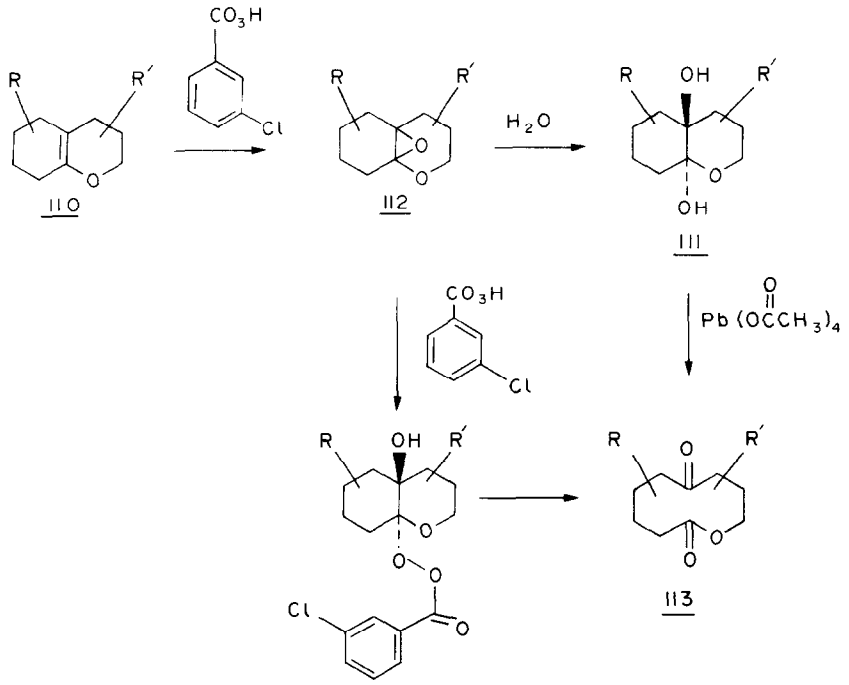
In cases where macrocyclic ketones are readily available, the corresponding lactones may be obtained via the Baeyer–Villiger reaction.[98–100] The efficacy of peracetic acid-boron trifluoride etherate has been particularly recommended for this purpose.[100] It is evident that when an unsymmetric ketone is employed, two products are possible, thereby reducing the scope of this technique.

IV. *By fusion-bond cleavage of bicyclic compounds*

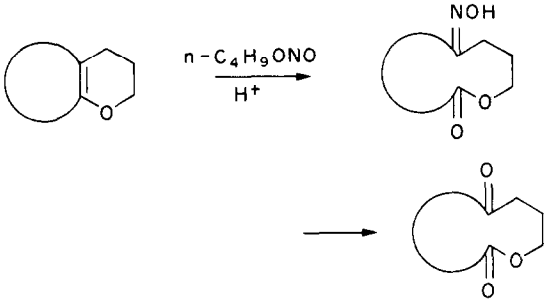
Enol ethers in which the C=C linkage forms the fusion-bond of a bicyclic structure undergo oxidative cleavage to form ketolactones. Thus, Borowitz *et al.* found that tetrahydrochromans **110** furnished nonanolides upon oxidation with excess *m*-chloroperbenzoic acid.[101–103] The presence of moisture led to formation of *trans*-glycols **111** in lieu of lactones. The glycols may be further oxidized to ketolactones **113** with lead tetraacetate[102] or *m*-chloroperbenzoic acid.[103] These results are rationalized by invoking the formation of an intermediate epoxide **112**, which is regio- and stereospecifically quenched by excess peracid or water.[102,103]

Similarly, 11-,[103,104] 12-,[103,104] 13-,[105] 14-[105] and 16-[105] membered ketolactones have been synthesized as well as benzo- and naphthoketolactones[106] and certain resorcylic acid lactones[107] related to zearalanone **16**. Oxidants other than *m*-chloroperbenzoic acid include chromic acid (or anhydride),[103,108–110] t-butyl or cumene hydroperoxide in the presence of molybdenum hexacarbonyl,[111] ozone,[110,112,113] hydrogen peroxide[114] and n-butyl nitrite.[115] Mahajan *et al.* found that the latter reagent

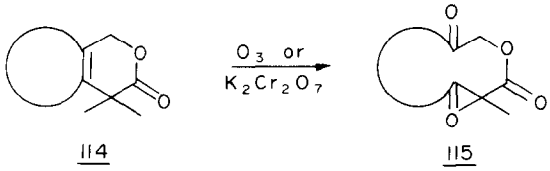




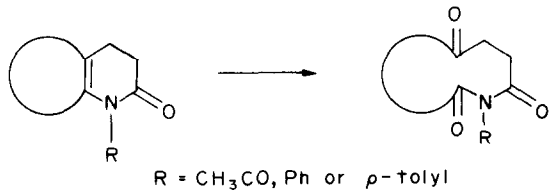
produced oximino lactones which were converted to the corresponding keto derivatives by hydrolysis[115] or by oxidative deoximation.[116]



Cleavage of the non-activated fusion-bond of compounds **114** with ozone or potassium dichromate was reported[117] to provide diketolactones **115**.



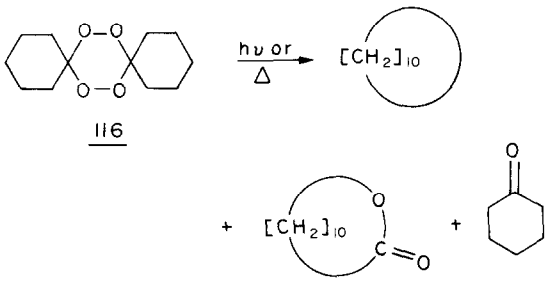
Macrocyclic ketolactams were prepared in a similar way by oxidative fusion-bond cleavage of bicyclic enamides with n-butyl nitrite,[118] ozone,[119] *m*-chloroperbenzoic acid[119] or sodium periodate.[120]



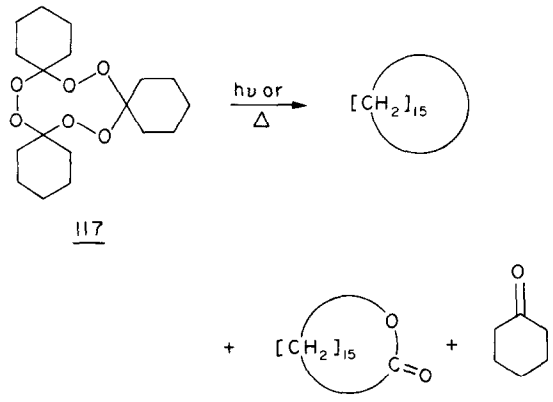
R = CH_3CO, Ph or *p*-tolyl

V. *From cycloalkanone di- and triperoxides*

Story *et al.* demonstrated that cyclohexanone diperoxide **116** undergoes pyrolysis or photolysis to furnish a mixture of cyclodecane, undecanolide and cyclohexanone.[121]

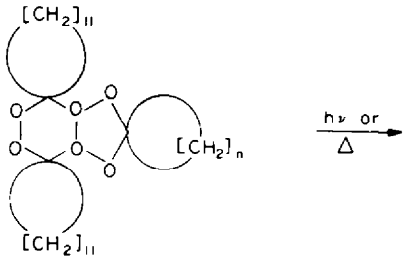


The triperoxide **117** behaved in a similar manner, generating cyclopentadecane, hexadecanolide and cyclohexanone.[121]



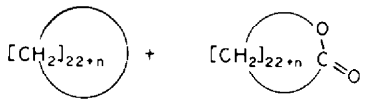
A variety of other cycloalkanone di- and tri-peroxides reacted in this was.[121–124] They were conveniently prepared by hydrogen peroxide oxidation of the parent

cycloalkanones.[122,123] The scope of the peroxide route to macrocyclic lactones was recently extended by a procedure permitting the synthesis of mixed peroxides **118**.[124] On the other hand, the explosive nature of peroxides and the multiplicity of products obtained from their decomposition limits the utility of this method.



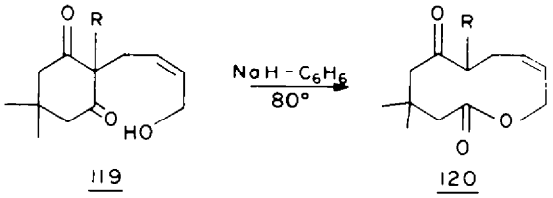
118

n = 4-7



VI. *By reverse Dieckmann reaction*

Mahajan[125] recently reported that the reverse Dieckmann reaction of the 2,2-dialkylcycloalkane-1,3-diones **119** provides entry to the ketolactones **120**. The precursors are in turn readily obtained by alkylation of the parent cycloalkane-1,3-diones.

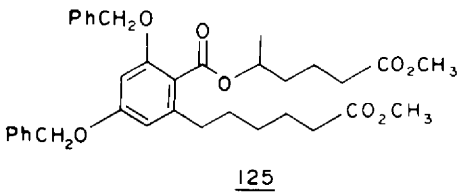


119 **120**

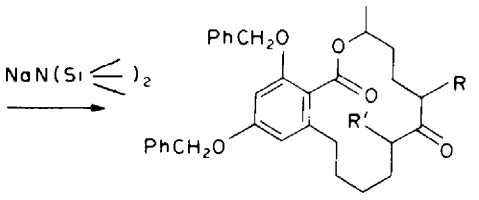
R = $PhCH_2$, $CH_2=CHCH_2$, CH_3

VII. *From acyclic esters*

Another approach to the synthesis of macrocyclic lactones employs an acyclic precursor with two reactive ends capable of ring-closure and an internal ester function which remains intact during the process.

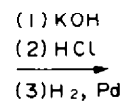


125



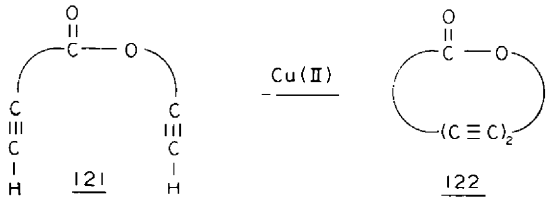
126 R = CO_2CH_3, R' = H

127 R = H, R' = CO_2CH_3



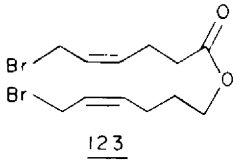
16

(i) *Via ω,ω'-diacetylenic esters.* Oxidative coupling of ω,ω'-diacetylenic esters **121** by cupric ion provided the corresponding diynolides **122** in good yield.[126-128]

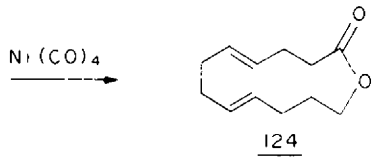


121 **122**

(ii) *Via allylic dibromides.* Corey and Kirst[129] reported that cyclization of the allylic dibromide **123** to the diene lactone **124** was effected by nickel tetracarbonyl in 70–75% yield.



123



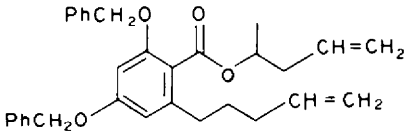
124

Diynes **122** and diene **124** provided saturated lactones when hydrogenated under standard conditions.

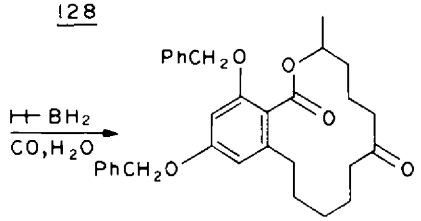
(iii) *By intramolecular Dieckmann condensation.* Hurd and Shah[130,131] reported that triester **125** undergoes internal Dieckmann condensation in the presence of sodium bis(tri-methylsilyl)amide in dilute ether solution to afford a mixture of the 14-membered lactones **126** and **127** in 77% yield. The possible formation of two products curtails the general applicability of the method. In this case however, the mixture was saponified, decarboxylated and hydrogenolyzed to furnish (±)-zearalanone **16** in high yield. Thorpe–Ziegler condensation of the analogous dinitrile did not provide **16**.[130]

The preparation of other potential precursors of zearalanone derivatives was also reported by these authors.[132,133]

(iv) *Via diene esters.* An alternate synthesis of (±)-zearalanone **16** employed the hydroboration-carbonylation of the resorcylate diene **128** with thexylborane and carbon monoxide to give O-dibenzylzearalanone **129**.[134]



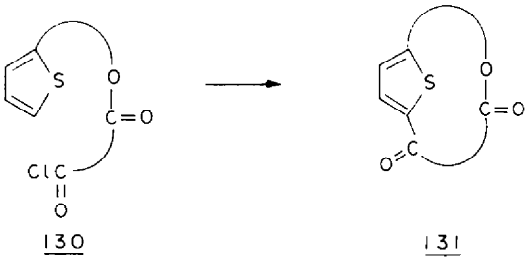
128



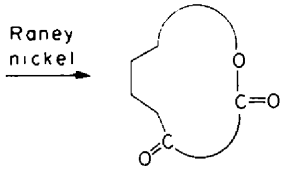
129

The synthesis of various other derivatives and precursors of zearalenone has also been widely reported in the patent literature.[135,136]

(v) *By intramolecular aromatic acylation.* Intramolecular acylation of the thiophene moiety of compounds **130** was claimed to furnish macrocyclic lactones **131** in yields of 47.5–68%.[137] Dilactones were obtained as byproducts. Reductive desulfurization with Raney nickel converted the compounds **131** to the corresponding ketolactones.[138]



130 131



Intramolecular acylation of compound **132** in a mixture of trifluoroacetic acid and anhydride was employed in the synthesis of (±)-di-O-methylcurvularin **4**.[139] It was obtained in 15% yield by this method while efforts to prepare it by lactonization of the hydroxy acid **133** failed.[139,140]

Note added in Proof. Several new developments in the synthesis of macrocyclic lactones have been reported subsequent to the literature survey originally conducted for this Report.

A number of macrocyclic polyether-esters have been prepared by condensing bifunctional acyl chlorides with diols[141–143] or by an adaptation of the Hantzsch condensation.[144]

The following macrolides were prepared by cyclization of ω-hydroxy acids via their 2-pyridinethiol esters: brefeldin A,[145] 21,22-dihydroisocytochalasin A,[146] diplodialide A,[147] and 11-methyl-*trans*-8-undecenolide.[148] Activation by Ag(I) was employed in the synthesis of the latter compound.

The dilactones pyrenophorin and vermiculine were obtained by dimerization of the corresponding hydroxy acid monomers via the azodicarboxylate-triphenylphosphine ("reverse activation") method.[149]

An alternate approach to macrolide synthesis employed the Pd(O) catalyzed cyclization of an acyclic precursor containing a vinyl group and a sulfone ester moiety at opposite ends of the molecule, as well as an internal ester function which remained unreacted. Interaction of the terminal functions was induced by sodium hydride. The method afforded 14 and 16-membered lactones in 49–69% yield.[150]

The kinetics of the cyclization of ω-bromoalkanoic acids in basic media was recently extended to cover the formation of lactones containing from 3 to 23-membered rings.[151] Activation parameters were determined.

An independent review of the synthesis of macrolides has recently appeared.[152]

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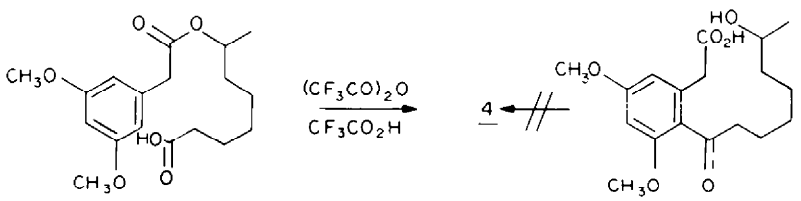
REFERENCES

[1]R. B. Woodward, *Angew. Chem.* **69**, 50 (1957).
[2]L. Ruzicka, *Helv. Chim. Acta* **9**, 230 (1926).
[3]L. Ruzicka, *Ibid.* p. 715.
[4]L. Ruzicka, *Ibid.* p. 1008.
[5]E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis*, Chap. 4. Wiley, New York (1967).
[6]M. Kerschbaum, *Ber. Dtsch. Chem. Ges.* **60B**, 902 (1927).
[7]S. Abe, *Koryo*, **96**, 19 (1970).
[8]S. Abe, T. Eto and Y. Tsujito, *Ibid.* **101**, 53 (1972).
[9]S. Abe, T. Eto and Y. Tsujito, *Cosmetics and Perfumery* **88**, 67 (1973).
[10]H. Brockmann and W. Henkel, *Naturwissenschaften* **37**, 138 (1950).
[11]M. Berry, *Quart. Rev.* **17**, 343 (1963).
[12]W. Keller-Schierlein and H. Gerlach, *Fortschr. Chem. Org. Naturstoffe* **26**, 161 (1968).
[13]W. D. Celmer, *Pure Appl. Chem.* **28**, 413 (1971).
[14]K. L. Rinehart, Jr., *Acc. Chem. Res.* **5**, 57 (1972).



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[15]M. Binder and C. Tamm, *Angew. Chem.* Internat. Edit. **12**, 370 (1973).
[16]W. Keller-Schierlein, *Fortschr. Chem. Org. Naturstoffe*, **30**, 313 (1973).
[17]G. M. Purandare and B. B. Bannur, *Hindustan Antibiotics Bull.* **16**, 149 (1974).
[18]S. Omura and A. Nakagawa, *J. Antibiotics* **28**, 401 (1975).
[19]H. Hunsdiecker, *Naturwissenschaften* **30**, 587 (1942).
[20]P. Baudart, *C. R. Acad. Sci.* **221**, 205 (1945).
[21]H. Hunsdiecker and H. Erlbach, *Chem. Ber.* **80**, 129 (1947).
[22]M. Stoll, *Helv. Chim. Acta* **30**, 1393 (1947).
[23]S. T. Tong, *Soap, Perfum. Cosmet.* **27**, 58 (1954).
[24]P. C. Mitter and B. K. Bhattacharyya, *J. Ind. Chem. Soc.* **19**, 69 (1942).
[25]S. A. Voitkevich, N. P. Solov'eva, L. P. Kizyakova and A. G. Belfer, *Maslo-Zhir. Prom.* **10**, 29 (1973).
[26]A. G. Davies, M. Davies and M. Stoll, *Helv. Chim. Acta* **37**, 1351 (1954).
[27]C. Galli, G. Illuminati and L. Mandolini, *J. Am. Chem. Soc.* **95**, 8374 (1973).
[28]M. Stoll and A. Rouvé, *Helv. Chim. Acta* **17**, 1283 (1934).
[29]M. Stoll and R. E. Gardner, *Ibid.* **17**, 1609 (1934).
[30]M. Stoll and A. Rouvé, *Ibid.* **18**, 1087 (1935).
[31]W. H. Carothers and J. W. Hill, *U.S. Pat.* 2,163,268 (1939).
[32]M. Stoll, A. Rouvé and G. Stoll-Comte, *Helv. Chim. Acta* **17**, 1289 (1934).
[33]L. T. Scott and J. O. Naples, *Synthesis* 738 (1976).
[34]M. Hanaoka, N. Ogawa and Y. Arata, *Chem. Pharm. Bull.* **22**, 973 (1974).
[35]M. Hanaoka, N. Ogawa and Y. Arata, *Ibid.* **24**, 1045 (1976).
[36]M. Hanaoka, N. Ogawa and Y. Arata, *Tetrahedron Letters* 2355 (1973).
[37]M. Hanaoka, N. Ogawa and Y. Arata, *Chem. Pharm. Bull.* **23**, 2140 (1975).
[38]I. Lantos and B. Loev, *Tetrahedron Letters* 2011 (1975).
[39]B. Loev, I. Lantos and H. Van Hoeven, *Ibid.* 1101 (1974).
[40]M. Hanaoka, H. Sassa, C. Shimezawa and Y. Arata, *Chem. Pharm. Bull.* **22**, 1216 (1974).
[41]M. Hanaoka, H. Sassa, C. Shimezawa and Y. Arata, *Ibid.* **23**, 2478 (1975).
[42]J. W. Hill and W. H. Carothers, *J. Am. Chem. Soc.* **55**, 5031 (1933).
[43]E. W. Spanagel and W. H. Carothers, *Ibid.* **57**, 929 (1935).
[44]E. W. Spanagel and W. H. Carothers, *Ibid.* p. 935.
[45]E. W. Spanagel and W. H. Carothers, *Ibid.* **58**, 654 (1936).
[46]M. Stoll and P. Bolle, *Helv. Chim. Acta* **31**, 98 (1948).
[47]C. Collaud, *U.S. Pat.* 2,234,551 (1941).
[48]C. Collaud, *Helv. Chim. Acta* **25**, 965 (1942).
[49]C. Collaud, *Ibid.* **26**, 849 (1943).
[50]F. Takahashi, T. Kawanobe and K. Hayashi, *Japan. Pat.* 7,225,071 (1972).
[51]T. Yasukawa, S. Abe and T. Eto, *Japan. Pat.* 7,328,488 (1973) and 7,328,491 (1973).
[52]I. Vlattas, I. T. Harrison, L. Tokés, J. H. Fried and A. D. Cross, *J. Org. Chem.* **33**, 4176 (1968).
[53]H. L. Wehrmeister and D. E. Robertson, *Ibid.* **33**, 4173 (1968).
[54]T. B. Windholz, *Ibid.* **25**, 1703 (1960).
[55]W. D. Emmons, K. S. McCallum and A. F. Ferris, *J. Am. Chem. Soc.* **75**, 6047 (1953).
[56]D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber and N. L. Wendler, *Chem. Comm.* 225 (1967).
[57]N. N. Girotra and N. L. Wendler, *Chem. Ind.* 1493 (1967).
[58]D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber and N. L. Wendler, *Tetrahedron* **24**, 2443 (1968).
[59]C. A. Peters and R. N. Hurd, *J. Med. Chem.* **18**, 215 (1975).
[60]W. H. Urry and G. T. Mullenbach, *U.S. Pat.* 3,810,918 (1974).
[61]R. D. Hoffsommer and D. Taub, *U.S. Pat.* 3,860,616 (1975).
[62]J. D. White, S. N. Lodwig, G. L. Trammell and M. P. Fleming, *Tetrahedron Letters* 3263 (1974).
[63]J. T. Wrobel and W. M. Golebiewski, *Ibid.* 4293 (1973).
[64]H. A. Staab, *Angew. Chem.* Internat. Edit. **1**, 351 (1962).
[65]G. S. Bates, J. Diakur and S. Masamune, *Tetrahedron Letters* 4423 (1976).
[66]E. W. Colvin, T. A. Purcell and R. A. Raphael, *Chem. Comm.* 1031 (1972).
[67]E. W. Colvin, T. A. Purcell and R. A. Raphael, *J. Chem. Soc.* Perkin I, 1718 (1976).
[68]E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.* **96**, 5614 (1974).
[69]T. Mukaiyama, R. Matsueda and M. Suzuki, *Tetrahedron Letters* 1901 (1970).
[70]T. Mukaiyama, *Synthetic Comm.* **2**, 243 (1972).
[71]T. Mukaiyama, *Angew. Chem.* Internat. Edit. **15**, 94 (1976).
[72]E. J. Corey, D. J. Brunelle and P. J. Stork, *Tetrahedron Letters* 3405 (1976).
[73]H. Gerlach and A. Thalmann, *Helv. Chim. Acta* **57**, 2661 (1974).
[74]E. J. Corey, K. C. Nicolaou and T. Toru, *J. Am. Chem. Soc.* **97**, 2287 (1975).
[75]E. J. Corey, K. C. Nicolaou and L. S. Melvin Jr., *Ibid.* **97**, 654 (1975).
[76]E. Brown and A. Bourgouin, *Tetrahedron* **31**, 1047 (1975).
[77]E. J. Corey, K. C. Nicolaou and L. S. Melvin, Jr., *J. Am. Chem. Soc.* **97**, 653 (1975).
[78]E. J. Corey, P. Ulrich and J. M. Fitzpatrick, *Ibid.* **98**, 222 (1976).
[79]H. Gerlach, K. Oertle, A. Thalmann and S. Servi, *Helv. Chim. Acta* **58**, 2036 (1975).
[80]J. Gombos, E. Haslinger, H. Zak and U. Schmidt, *Tetrahedron Letters* 3391 (1975).
[81]J. Gombos, E. Haslinger, A. Nikiforov, H. Zak and U. Schmidt, *Monatsh. Chem.* **106**, 1043 (1975).
[82]U. Schmidt, J. Gombos, E. Haslinger and H. Zak, *Chem. Ber.* **109**, 2628 (1976).
[83]G. Beck and E. Henseleit, *Chem. Ber.* **104**, 21 (1971).
[84]H. Gerlach and H. Wetter, *Helv. Chim. Acta* **57**, 2306 (1974).
[85]H. Zak and U. Schmidt, *Angew. Chem.* Internat. Edit. **14**, 432 (1975).
[86]J. Gombos, E. Haslinger, H. Zak and U. Schmidt, *Monatsh. Chem.* **106**, 219 (1975).
[87]J. Gombos, E. Haslinger and U. Schmidt, *Chem. Ber.* **109**, 2645 (1976).
[88]E. J. Corey and D. J. Brunelle, *Tetrahedron Letters* 3409 (1976).
[89]S. Masamune, H. Yamamoto, S. Kamata and A. Fukuzawa, *J. Am. Chem. Soc.* **97**, 3513 (1975).
[90]S. Masamune, S. Kamata and W. Schilling, *Ibid.* **97**, 3515 (1975).
[91]S. Masamune, Y. Hayase, W. H. Chan and R. L. Sobczak, *Ibid.* **98**, 7874 (1974).
[92]S. Masamune, S. Kamata, J. Diakur, Y. Sugihara and G. S. Bates, *Can. J. Chem.* **53**, 3693 (1975).
[93]S. Masamune, C. U. Kim, K. E. Wilson, G. O. Spessard, P. E. Georghiou and G. S. Bates, *J. Am. Chem. Soc.* **97**, 3512 (1975).
[94]T. Mukaiyama, M. Usui and K. Saigo, *Chem. Letters* 49 (1976).
[95]F. Souto-Bachiller, G. S. Bates and S. Masamune, *J. Chem. Soc.* Chem. Comm. 719 (1976).
[96]T. Kurihara, Y. Nakajima and O. Mitsunobu, *Tetrahedron Letters* 2455 (1976).
[97]Y. Fukuyama, C. L. Kirkemo and J. D. White, *J. Am. Chem. Soc.* **99**, 646 (1977).
[98]L. Ruzicka and M. Stoll, *Helv. Chim. Acta* **11**, 1159 (1928).
[99]K. Kosswig, W. Stumpf and W. Kirchhof, *Ann. Chem.* **681**, 28 (1965).
[100]B. D. Mookherjee, R. W. Trenkle and R. R. Patel, *J. Org. Chem.* **37**, 3846 (1972).
[101]I. J. Borowitz and G. Gonis, *Tetrahedron Letters* 1151 (1964).
[102]I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp and G. J. Williams, *J. Org. Chem.* **31**, 3032 (1966).
[103]I. J. Borowitz, G. J. Williams, L. Gross and R. Rapp, *Ibid.* **33**, 2013 (1968).
[104]I. J. Borowitz, G. J. Williams, L. Gross, H. Beller, D. Kurland, N. Suciu, V. Bandurco and R. D. G. Rigby, *Ibid.* **37**, 581 (1972).
[105]I. J. Borowitz, V. Bandurco, M. Heyman, R. D. G. Rigby and S. Ueng, *Ibid.* **38**, 1234 (1973).
[106]J. R. Mahajan and H. C. Araújo, *Synthesis* 111 (1976).
[107]H. Immer and J. F. Bagli, *J. Org. Chem.* **33**, 2457 (1968).

[108]K. Schreiber and H. Ripperger, *Ann. Chem.* **655**, 114 (1962).
[109]R. G. Carlson and R. G. Blecke, *J. Org. Chem.* **32**, 3538 (1967).
[110]J. R. Mahajan and H. C. Araújo, *Synthesis* 54 (1975).
[111]R. D. Rapp and I. J. Borowitz, *Chem. Comm.* 1202 (1969).
[112]I. J. Borowitz and R. D. Rapp, *J. Org. Chem.* **34**, 1370 (1969).
[113]R. Hopp and K. Bauer, *German Pat.* 2,410,859 (1975).
[114]J. Becker and G. Ohloff, *Helv. Chim. Acta* **54**, 2889 (1971).
[115]J. R. Mahajan, G. A. L. Ferreira and H. C. Araújo, *J. Chem. Soc.* Chem. Comm. 1078 (1972).
[116]H. C. Araújo, G. A. L. Ferreira and J. R. Mahajan, *Ibid.* Perkin I, 2257 (1974).
[117]J. Falbe and F. Korte, *Chem. Ber.* **96**, 919 (1963).
[118]J. R. Mahajan, G. A. L. Ferreira, H. C. Araújo and B. J. Nunes, *Synthesis* 313 (1973).
[119]J. R. Mahajan, G. A. L. Ferreira, H. C. Araújo and B. J. Nunes, *Ibid.* 112 (1976).
[120]J. R. Mahajan, personal communication.
[121]P. R. Story, D. D. Denson, C. E. Bishop, B. C. Clark, Jr. and J. C. Farine, *J. Am. Chem. Soc.* **90**, 817 (1968).
[122]P. R. Story and P. Busch, *Adv. Org. Chem.* **8**, 67 (1972).
[123]J. R. Sanderson, K. Paul, P. R. Story, D. D. Denson and J. A. Alford, *Synthesis* 159 (1975).
[124]K. Paul, P. R. Story, P. Busch and J. R. Sanderson, *J. Org. Chem.* **41**, 1283 (1976).
[125]J. R. Mahajan, *Synthesis* 110 (1976).
[126]G. Eglinton and A. R. Galbraith, *J. Chem. Soc.* 889 (1959).
[127]J. Carnduff, G. Eglinton, W. McCrae and R. A. Raphael, *Chem. Ind.* 559 (1960).
[128]L. D. Bergelson, J. G. Moltkovsky and M. M. Shemyakin, *Ibid.* 558 (1960).
[129]E. J. Corey and H. A. Kirst, *J. Am. Chem. Soc.* **94**, 667 (1972).
[130]R. N. Hurd and D. H. Shah, *J. Org. Chem.* **38**, 390 (1973).
[131]R. N. Hurd and D. H. Shah, *J. Med. Chem.* **16**, 543 (1973).
[132]R. N. Hurd and D. H. Shah, *J. Org. Chem.* **38**, 607 (1973).
[133]R. N. Hurd and D. H. Shah, *Ibid.* p. 610.
[134]W. H. Urry and G. T. Mullenbach, *U.S. Pat.* 3,862,980 (1975).
[135]D. H. Shah and R. N. Hurd, *U.S. Pat.* 3,839,363 (1974).
[136]W. H. Urry and G. T. Mullenbach, *U.S. Pats* 3,852,307 (1974); 3,901,921 (1975); 3,901,922 (1975) and 3,903,115 (1975).
[137]Y. L. Gol'dfarb, S. Z. Taits, F. D. Alashev, A. A. Dudinov and O. S. Chizhov, *Khim. Geterotsikl. Soedin.* **1**, 40 (1975).
[138]S. Z. Taits, F. D. Alashev and Y. L. Gol'dfarb, *Izv. Akad. Nauk. S.S.S.R., Ser. Khim.* **3**, 566 (1968).
[139]P. M. Baker, B. W. Bycroft and J. C. Roberts, *J. Chem. Soc.* Part C, 1913 (1967).
[140]O. C. Musgrave, R. Templeton and H. D. Munro, *Ibid.* Part C, 250 (1968).
[141]J. S. Bradshaw, C. T. Bishop, S. F. Nielsen, R. E. Asay, D. R. K. Masihdas, E. D. Flanders, L. D. Hansen, R. M. Izatt and J. J. Christensen, *J. Chem. Soc.* Perkin I, 2505 (1976).
[142]S. E. Drewes and B. G. Riphagen, *Ibid.* 2574 (1976).
[143]R. M. Izatt, J. D. Lamb, G. E. Maas, R. E. Asay, J. S. Bradshaw and J. J. Christensen, *J. Am. Chem. Soc.* **99**, 2365 (1977).
[144]T. J. van Bergen and R. M. Kellogg, *J. Chem. Soc.* Chem. Comm. 964 (1976).
[145]E. J. Corey and R. H. Wollenberg, *Tetrahedron Letters* 4705 (1976).
[146]D. Scherling, I. Csendes and C. Tamm, *Helv. Chim. Acta* **59**, 914 (1976).
[147]T. Ishida and K. Wada, *J. Chem. Soc.* Chem. Comm. 337 (1977).
[148]H. Gerlach, K. Oertle and A. Thalmann, *Helv. Chim. Acta* **59**, 755 (1976).
[149]D. Seebach, B. Seuring, H.-O. Kalinowski, W. Lubosch and B. Renger, *Angew. Chem.* Internat. Edit. **16**, 264 (1977).
[150]B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.* **99**, 3867 (1977).
[151]C. Galli, G. Illuminati, L. Mandolini and P. Tamborra, *Ibid.* **99**, 2591 (1977).
[152]K. C. Nicolaou, *Tetrahedron* **33**, 683 (1977).