Tetrahedron Vol. 33, pp. 683 to 710 Pergamon Press 1977. Printed in Great Britain

TETRAHEDRON REPORT NUMBER 27

SYNTHESIS OF MACROLIDES

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(*Received in the UK for publication* 19 *November* 1976)

Abstract—The biologically important macrolide class of natural products, although known for some time, has until recently received little synthetic attention. This was primarily due to the lack of general synthetic methodology and the complex structures involved, but in recent years has changed with the development of new experimental techniques. The recent synthetic advancements in this area, reported from the laboratories of Prof. E. J. Corey of Harvard University were undoubtedly the most powerful single thrust that brought these medicinally useful molecules into focus and propelled them into the forefront of organic synthesis. Following a brief introduction into the macrolide structural spectrum, the general methodology for macrolide synthesis is discussed in detail with several illustrative applications. A number of total syntheses of macrolides is then detailed with particular emphasis on the key macrolide ring-forming reactions.

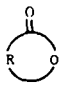
CONTENTS

1. Introduction and structures of macrolides
2. General methodology for the synthesis of macrolides
2.1 Methods involving C=C fusion bond cleavage
2.2 Methods involving C–O bond formation
2.3 Methods involving C–C bond formation
2.3.1 Acetylene coupling
2.3.2 Allylic dibromide—nickel carbonyl coupling
2.3.3 Intramolecular Diels–Alder reaction
2.3.4 Dieckmann condensation
2.3.5 Intramolecular photolytic oxetane formation
2.3.6 Decomposition of cycloalkanone peroxides
2.4 Methods involving C(=O)–O bond formation (Lactonization methods)
2.4.1 The Corey–Nicolaou method
2.4.2 The Masamune method
2.4.3 The Makaiyama method
2.4.4 Miscellaneous methods involving carboxyl activation
3. Total syntheses of macrolides
3.1 Zearalenone
3.2 Pyrenophorin
3.3 Vermiculine
3.4 Methymycin
3.5 Recifeiolide
3.6 Vertaline
3.7 Nonactin
3.8 Brefeldin A
4. Conclusion and future outlook
5. Addendum

1. INTRODUCTION AND STRUCTURES OF MACROLIDES

The macrolide structural spectrum is perhpaps one of the richest in natural product chemistry. It embraces a wide variety of molecules whose number and structural type has grown enormously during the last quarter of a century, and the trend is certain to continue in view of the continuous development in fermentation, isolation and structural elucidation techniques.

Generally, a macrolide is defined as a molecule containing a large ring lactone in its structure (general formula **1**). In principle, the macrolides **1** can be considered to be derived from the corresponding hydroxy-acids **2** by internal esterification. Macrocyclic structures with more than one ester linkage are also



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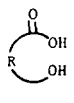

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classified as macrolides. Some of the most important therapeutic agents of our time belong to this class of compounds, while the biological and physiological activities of other members of the macrolide group are currently under intense investigations and have potential, as possibly useful drugs.

Below, a number of molecules from the macrolide field of natural products, representing a wide range of structural type, are briefly discussed in order to introduce the reader into this relatively unexplored continent of organic chemistry. This brief tour into the macrolide structures should also serve to bring into focus the various problems associated with the synthesis of such complex molecules, a task that until recently seemed so far beyond the reach of the synthetic chemist.

The macrolide antibiotics,[1] numbering in the hundreds, are of course, of immense pharmacological importance. Their structures feature a macrocyclic lactone, usually 12- to 16-membered ring with numerous substituents asymmetrically placed on the periphery of the ring including one to three glycoside units. Examples of 14-membered ring macrolide antibiotics are the erythromycins A and B and oleandomycin, shown in Fig. 1, all of which are used in medicine today. Figure 2 shows some important representatives of the 16-membered ring subclass of macrolide antibiotics.[1] These include leucomycin A_3, a clinically useful substance and carbomycins A and B (magnamycins A and B).

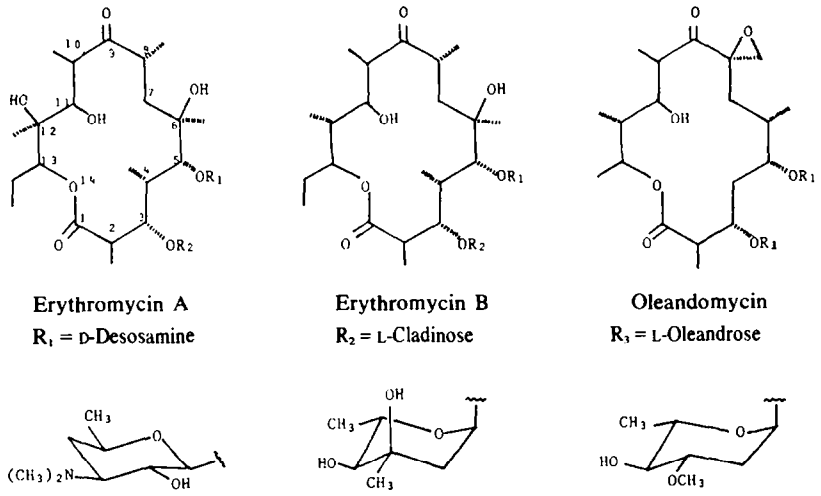
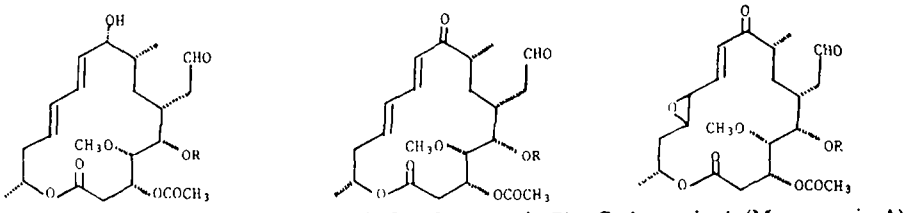


Fig. 1. Structures of some erythromycin and oleandomycin macrolide antibiotics.



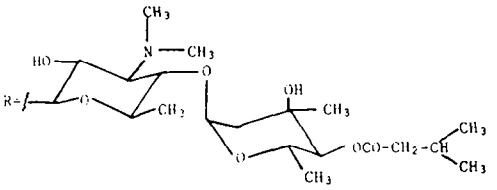
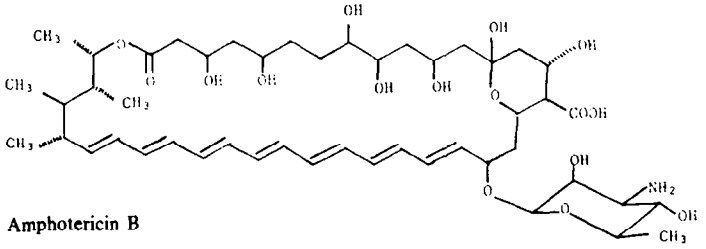


Fig. 2. Structures of some 16-membered ring macrolide antibiotics.

The polyene macrolide antibiotics[2] are a group of compounds which are characterized by strong antifungal activity. These rather complex substances, some of which are under clinical use, are characterised by larger rings, and distinct hydrophilic (polyhydroxy) and hydrophobic (polyene) zones. They may or may not have sugars attached onto the macrocyclic ring. Amphotericin B,[3] a 38-membered ring macrolide and chainin,[4] a substance containing a 28-membered macrolide ring, both of which are shown in Fig. 3, are examples of polyene macrolide antibiotics.

A rather fascinating class of active metabolites, the



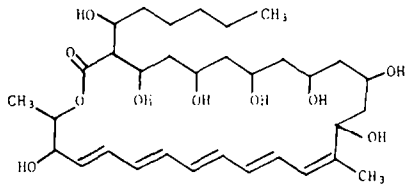


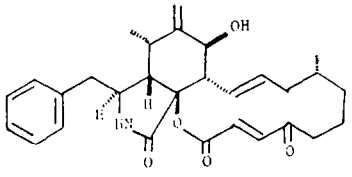
Fig. 3. Structures of some polyene macrolide antibiotics.

cytochalasans,[5] have been discovered in recent years. Some of these macrocyclic substances, such as cytochalasans A and B, shown in Fig. 4, contain lactone functionality in the macrocycle, and are therefore classified as macrolides. These and other cytochalasans have attracted considerable attention worldwide due to their novel and potentially useful biological properties. Among other biological activities, for example, they show antibiotic, antitumor and cytostatic action, and induce ejection of the cell nucleus, production of polynuclear cells and platelet aggregation. Their structures, complex as they are, present the synthetic chemist with a formidable academic challenge.

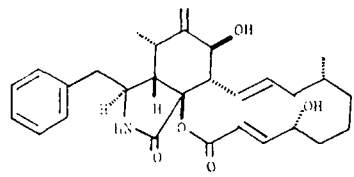
Macrodilides and macrotetrolides, structures with two and four ester linkages respectively, in the macrocyclic ring are also known to occur in nature. Examples of dilides are the antibiotics pyrenophorin[6] and vermiculine[7,8] shown in Fig. 5, both of which have been recently synthesized (*vide supra*). Boromycin,[9] one of the rare boron containing natural products, shown in Fig. 5, is an antibiotic first described in 1967. This unusual structure is the D-valine ester of a boric acid complex with a 28-membered ring macrodilide. A number of 32-membered ring tetrolides[10] with antibiotic and ionophoric properties are known, an example of which is nonactin (Fig. 5), the total synthesis of which has recently been accomplished and will be discussed later in this report.

Zearalenone[11] and radicicol,[12] the structures of which are shown in Fig. 6, are two examples of the β-resorcylic acid macrolide group of antibiotics. Zearalenone, due to its pronounced anabolic and uterotrophic activities, has attracted considerable interest in recent years and a number of syntheses leading to this molecule or derivatives of it have been reported (*vide supra*).

A number of alkaloids contain macrocyclic lactones in their structures and can, therefore, be considered as

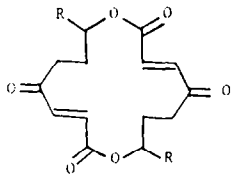


Cytochalasan A

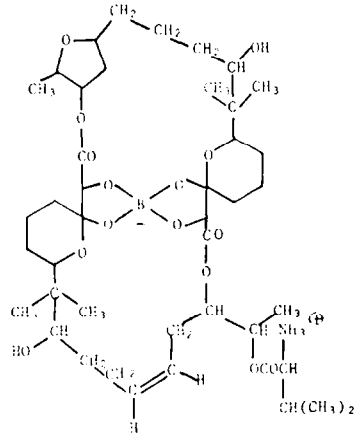


Cytochalasan B

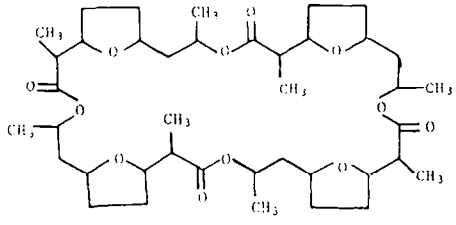
Fig. 4. Structures of some macrolide cytochalasans.



Pyrenophorin, R = CH_3
Vermiculine, R = CH_2COCH_3

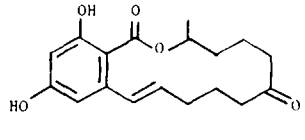


Boromycin

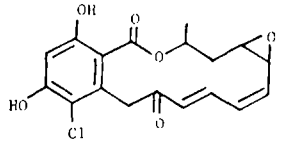


Nonactin

Fig. 5. Structures of some macrodilide and macrotetrolide antibiotics.

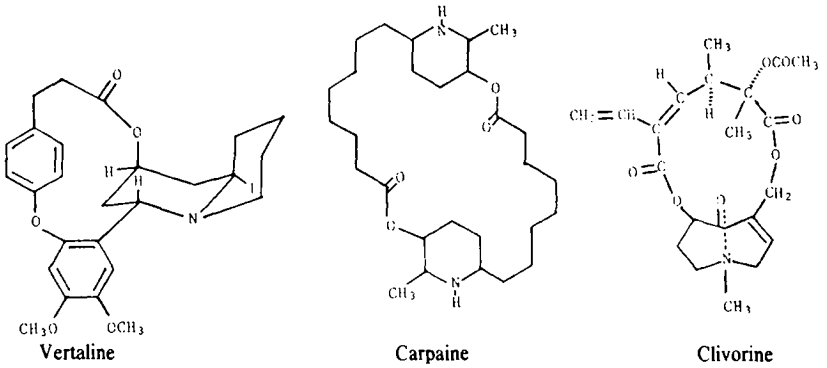


Zearalenone



Radicicol

Fig. 6. Structures of some β-resorcylic acid macrolide antibiotics.



Vertaline Carpaine Clivorine

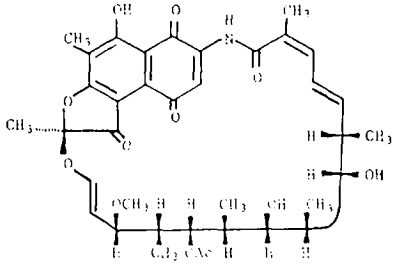
Fig. 7. Structures of some alkaloid macrolides.

macrolides. Figure 7 shows some structures representing three families of alkaloids. Carpaine,[13] representing its own family (carpaine alkaloids), is a symmetrical 26-membered ring macrodilide. Vertaline[14] is a member of the Lythraceae family and has a 14-membered ring lactone in its structure, whereas clivorine,[15] from the Senecio family of alkaloids,[16] is characterized by a 12-membered ring macrolide structure.

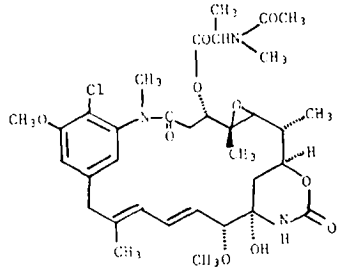
Macrocyclic lactams such as the immensely important *ansa* macrolides, streptovaricins,[17] rifamycins,[17] and maytansenoids,[18] are also rather loosely included into the macrolide field. Rifamycin S, a useful drug for the treatment of tuberculosis, and maytansine,[19] a highly promising antitumor agent under clinical trial, are shown in Fig. 8.

2. GENERAL METHODOLOGY FOR MACROLIDE SYNTHESIS

The construction of macrocyclic structures is a frequent and challenging problem in synthetic organic chemistry. The advances made in the synthesis of annulenes,[20] crown ethers,[21] and macrocyclic natural products illustrate the difficulties and illustrate some of the ingenious ways by which this problem has been attacked and solved by synthetic chemists. In principle, macrocyclic systems can be generated by cyclization of open, long chain precursors or by cleavage of internal bonds in polycyclic systems. However, in the former case, which is the most general one, the ring closure is disfavored entropically, due to the loss of entropy associated with the formation of the usually more rigid, cyclic structure. Furthermore, polymerization due to intermolecular rather than intramolecular interactions is often a serious problem, although subject to experimental control. Despite the severe problems, however, recent interest in the chemistry of macrolide antibiotics and other biologically active macrolactones and macrolactams resulted in the discovery and development of several new synthetic methods for macrolide formation. This new exciting methodology together with the early methods for the synthesis of macrolides will be discussed below according to the type of bond cleaved or formed in the key macrocyclic ring-forming reaction.



Rifamycin S



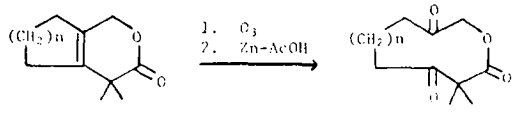
Maytansine

Fig. 8. Structures of some naturally occurring macrolactams.

2.1 *Methods involving* C=C *fusion bond cleavage*

The concept of cleaving fusion bonds of bicyclic structures to create larger rings[22] has been applied with some success to the synthesis of macrocyclic lactones.

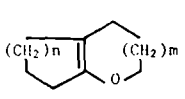
Falbe and Korte[23] demonstrated that medium size ring diketone lactones (**4**, n = 1–3) could be obtained in good yields (50–62%) from bicyclic olefins (**3**, n = 1–3) by ozonolysis of the fusion double bond followed by reductive (Zn–AcOH) work-up. Chromic acid was also reported to give similar results in the case of the 10-membered ring, although in lower yield.



3 (n = 1–3) **4** (n = 1–3)

A reaction that generates a large ring from a bicyclic system and at the same time creates a lactone functionality is the oxidative cleavage of bicyclic enol ethers with the double bond at the ring fusion. This idea has been extensively utilized by Borowitz and his group, Mahajan, and by Immer and Bagli. Borowitz and his collaborators[24] reported the synthesis of several rather simple ketolactones **6** of various sizes ranging from 10- to 16-membered from the enol ethers **5** in synthetically useful yields. *m*-Chloroperbenzoic acid, ozone followed by zinc-acetic acid, or chromic acid, were used to effect the cleavage of **5** to **6**. The same cleavage of **5** to **6** (n = m = 1) was effected according to Mahajan[25] by treatment with *n*-butyl nitrite

to afford the oximelactone **7**, which on acid hydrolysis gave the ketolactone **6** (n = m = 1) in high yield.



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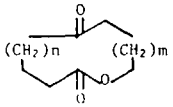

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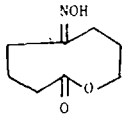

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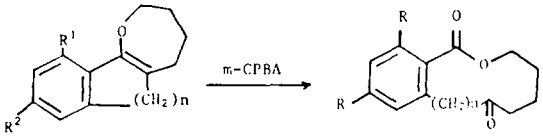
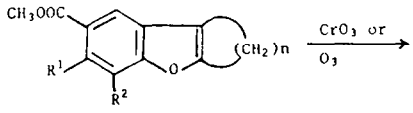
Immer and Bagli[26] have prepared a number of medium ring (10- to 12-membered) lactones of substituted benzoic acids resembling somewhat the β-resorcylic acid lactone structures occurring in nature (e.g. zearalenone and radicicol). Thus, *m*-chloroperbenzoic acid (*m*-CPBA) oxidation of various substituted enol ethers **8** (n = 1–3) produced lactones **9** (n = 1–3) in most instances in satisfactory yields.

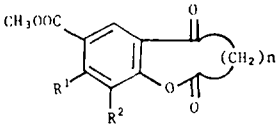


8 **9**

Similarly, the benzo- and naphthofurans **10** and **11** suffered oxidative cleavage (chromic anhydride or ozone) to furnish medium to large ring lactones **12** and **13** respectively.[27] The analogous pyran derivatives **14** and **15** were also converted to the macrocyclic lactones **16** by *m*-chloroperbenzoic acid in reasonable yields.[28]



10: $R^1 = R^2 = H$ n = 4–6,10
11: $R^1 = R^2 = CH{=}CH{-}CH{=}CH$



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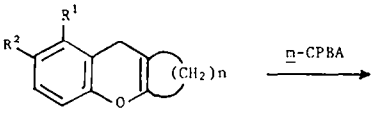
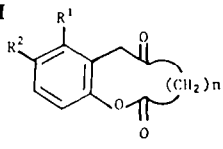


14: $R^1 = R^2 = H$ n = 4–6,10
15: $R^1 = R^2 = CH{=}CH{-}CH{=}CH$



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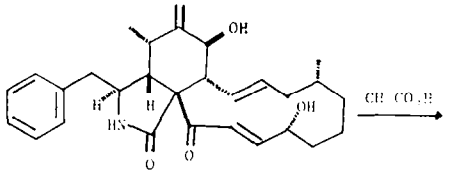
2.2 *Methods involving* C–O *bond formation*

The Baeyer–Villiger reaction was used as early as 1929 by Ruzicka and Stoll[29] in the preparation of simple macrocyclic lactones from the corresponding cyclic ketones. Although this method is perhaps the simplest way to prepare several simple macrocyclic lactones whenever the requisite ketones are available, serious limitations exist for its application to the field of complex naturally occurring substances due to interference from other functionalities and regiospecificity problems. However, a rather interesting application of the Baeyer–Villiger reaction involving a complex molecule has been reported by Binder and Tamm[30] who claimed conversion, in low yield, of deoxyphomin **17** to phomin **18** along with several other products using peracetic acid and *p*-toluenesulfonic acid as catalyst.



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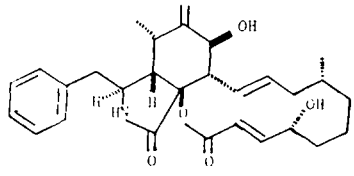
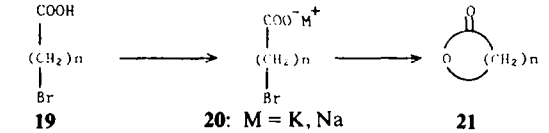


18

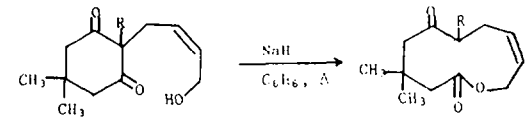
Internal nucleophilic displacement by carboxylate anion has been applied on ω-bromocarboxylic acids **19** (n = 8–16) to form macrocyclic lactones **21** (n = 8–16) via the potassium carboxylates **20** (M = K) by Hunsdiecker and Elbach[31] and by Stoll.[32] The former authors report good to excellent yields of 10- to 18-membered ring lactones when the carboxylates **20** (M = K; generated



19 **20**: M = K, Na **21**

from the acids **19** and potassium carbonate) are refluxed in 2-butanone under high dilution conditions.[32a] Rate studies of this reaction have been carried out by Stoll *et al.*[33] on a limited number of cases (n = 10, 14) and by Illuminati *et al.*[34] who reported a systematic kinetic study on the lactone formation in the medium ring size range (n = 5–10). In the latter report, the lactonizations were effected employing the sodium salts **20** (M = Na) in dilute dimethyl sulfoxide-water (DMSO–H_2O; 90:1) solution at 50° in good to excellent yields. The results show considerably slower rates in the case of the 8-, 9- and 10-membered rings as expected from ring strain considerations.

An interesting, base induced, intramolecular rearrangement of hydroxydiketones of type **22** (R=CH_3, $CH_2CH{=}CH_2$, $CH_2C_6H_5$) has recently been reported to lead to 11-membered ring lactones **23** in good yields.[35]

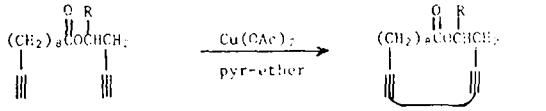


22 **23**

2.3 *Methods involving C–C bond formation*

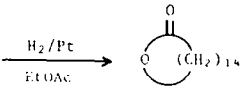
Open, long chain structures with ester linkages have been cyclized by C–C bond formation to macrocyclic lactones by a variety of techniques. The most prominent of these macrocyclic forming reactions are acetylene coupling, allylic dibromide-nickel carbonyl coupling, intramolecular Diels–Alder reaction, Dieckmann condensation intramolecular photolytic oxetane formation, and decomposition of cycloalkanone peroxides. These methods are separately discussed in brief below.

2.3.1 *Acetylene coupling.* Oxidative coupling of *ω,ω'*-diacetylenic esters (**24** and **25**) with cupric acetate in pyridine-ether under high dilution conditions afforded lactones (**26** and **27**) in high yields.[36,37] Catalytic, full hydrogenation of **26** gave the saturated 16-membered ring lactone **28**, a natural product known as exaltolide (*Angelica, archangelica officinalis*).[36,37]



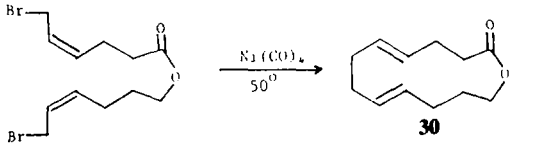
24: R = H
25: R = CH_3

26: R = H, (88%),[37] (80%)[36]
27: R = CH_3, (65%)[37]



28

2.3.2 *Allylic dibromide-nickel carbonyl coupling.* Nickel carbonyl has been found to be an excellent reagent for effecting cyclization of allylic dibromides to carbocycles of various sizes.[38–40] Corey and Kirst[41] reported in 1972 the successful application of this coupling reaction to the synthesis of macrocyclic lactones. Thus, the unsaturated lactone **30** was obtained as the major product (70–75%) upon slow addition of the allylic dibromide **29** to a *ca.* 0.2M solution of nickel carbonyl (6 equivalents) in N-methylpyrrolidone at 50°. Hydrogenation of **30** over palladium on charcoal in ethanol gave quantitatively the fully saturated 13-membered ring lactone **31**.

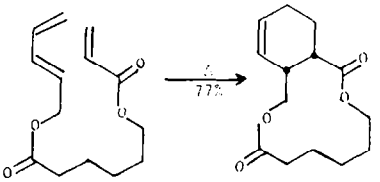


29

30

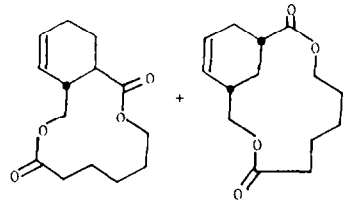
31

2.3.3 *Intramolecular Diels–Alder reaction.* The intramolecular version of the Diels–Alder reaction was utilized by Corey and Petrzilka[42] in the construction of bicyclic macrolactones. Thus, slow addition of the open chain diester **32** to refluxing benzonitrile resulted in the formation (77% yield) of a mixture of three intramolecularly formed Diels–Alder products **33**, **34** and **35** in *ca.* 6.2:6.8:1 ratio, the structures of which were deduced from degradation studies. As a further example of this approach, substrate **36**, similarly underwent the desired intramolecular Diels–Alder reaction in refluxing benzonitrile under high dilution conditions to furnish, in 80% yield, a mixture of four isomeric lactones **37a**, **37b**, **38a** and **38b** in a ratio of *ca.* 7:3:4:1. These results are of some interest, although the high temperatures employed (*ca.* 190°) and the non-stereoselective nature of the reaction are serious limitations of this method for the construction of complex, naturally occurring macrolides.



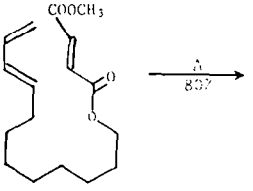
32

33 (6·2)

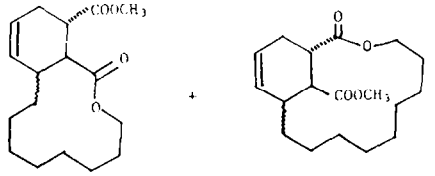


34 (6·8)

35 (1)



36



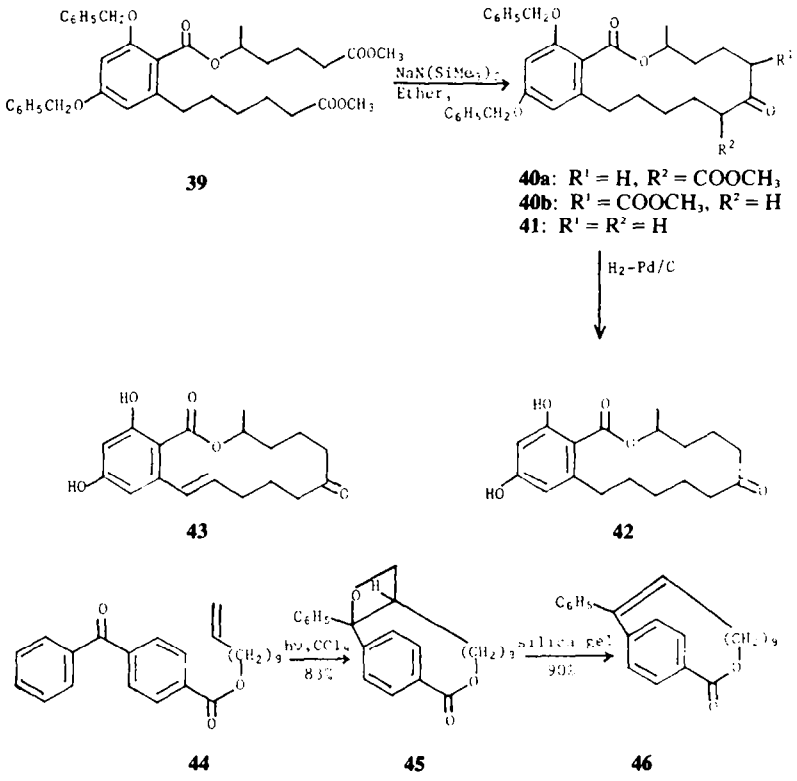
37a, **37b** (7:3)

38a, **38b** (4:1)

2.3.4 *Dieckmann condensation.* The application of the Dieckmann condensation to the formation of large ring lactones, namely derivatives of the macrolide antibiotic zearalenone **43** has been described by Hurd and Shah.[43,44] The diester **39** on exposure to sodium bis(trimethylsilyl)amide [$NaN(SiMe_3)_2$] in refluxing ether under high dilution conditions afforded a mixture of the two expected products **40a** and **40b** in 77% yield. Selective basic hydrolysis of the methylester function in **40a** and **40b** followed by decarboxylation of the resulting acids gave the dibenzyl ether **41**. Hydrogenolysis of **41** (EtOAc–Pd/C) gave racemic zearalanone **42** which showed comparable uterotrophic activity to zearalenone **43** itself.[44]

2.3.5 *Intramolecular photolytic oxetane formation.* A reaction resulting in macrolide formation based on the remote oxidation concept[45] was developed by Bichan and Winnik.[46] This novel approach involves a photochemically induced oxetane formation as a key ring-forming reaction. Photolysis of the unsaturated benzophenone ester **44** in dilute carbon tetrachloride solution, afforded stereospecifically, the oxetane **45** in 83% yield, which on exposure to silica gel was cleanly transformed to the lactone **46** (90% yield).

2.3.6 *Decomposition of cycloalkanone peroxides.* Story *et al.* reported in 1968[47] that the photochemical or thermal decomposition of cycloalkanone di- or triperoxides, such as **47** and **49**, produces macrocyclic compounds including



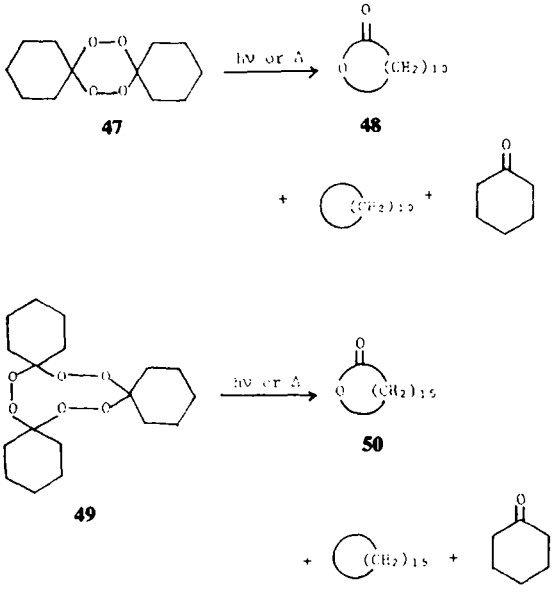
39

40a: $R^1 = H$, $R^2 = COOCH_3$
40b: $R^1 = COOCH_3$, $R^2 = H$
41: $R^1 = R^2 = H$

43 42

44 45 46

lactones in respectable yields. The cyclic peroxides **47** and **49** are readily available from cyclohexanone and hydrogen peroxide under acid catalysis.[47,48] The reaction is quite general and a variety of macrolactones (and cycloalkanes) used in perfumery have been produced by this method by varying the size and the substitution of the starting cycloalkanone. However, the application of this method in the synthesis of sensitive complex molecules has severe limitations.



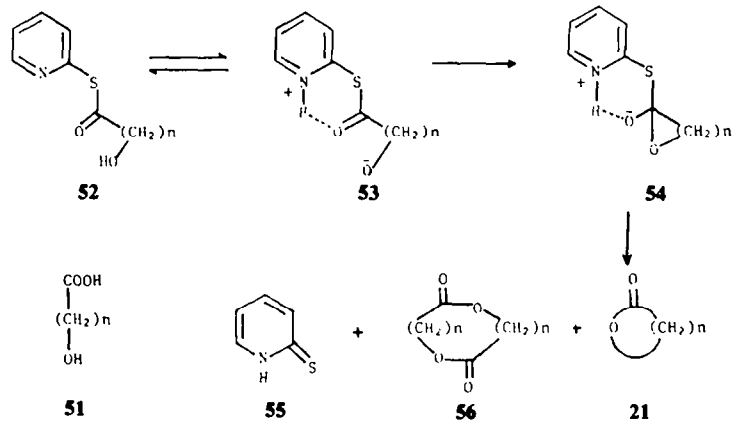
47 48

49 50

2.4 *Methods involving* $\overset{O}{\overset{\|}{C}}$–O *bond formation (lactonization methods)*

Of all macrolide-forming reactions, the lactonization of long open-chain hydroxy acids is the most direct and general method. It is not, therefore, surprising that most of the existing methodology for macrolide synthesis involves $\overset{O}{\overset{\|}{C}}$–O bond formation by internal esterification of hydroxy acid precursors. This, as was mentioned earlier, is not always on easy task since both entropy and polymerization factors tend to disfavor it. In the following section, a number of methods in this category involving activation of one or both interacting groups of the hydroxy acid precursor are discussed and their efficiency illustrated by examples from the natural and "unnatural" product fields.

2.4.1 *The Corey–Nicolaou method (double activation method).* A highly efficient method for the synthesis of macrocyclic lactones has been discovered recently by Corey and Nicolaou.[49] This procedure for internal esterification of hydroxy acids has been proven to be highly effective and mild enough to be useful in the field of complex natural products, and numerous applications in the partial and total synthesis of biologically active molecules have already appeared in the literature. The development of this cyclization procedure was guided by the following considerations: (A) Since lactone formation becomes relatively slow in going from common to large rings, undesirably high temperatures and/or excessively and inconveniently high dilutions would be required unless some means were to be found to activate the reacting groups. (B) One way of simultaneously activating both the carboxyl and hydroxyl groups for mutual interaction would be the utilization of a carboxylic derivative which would favor proton transfer from the hydroxyl to the carboxylic oxygen. This idea is illustrated for the specific case of 2-pyridinethiol esters **52** of the hydroxyacids **51** in Scheme 1. The proton transfer from hydroxyl to carbonyl in **52** is clearly



Scheme 1.

facilitated by the basic nitrogen of the pyridine nucleus present in the thioester. The mechanism of this "double activation" reaction is envisioned as follows: The dipolar intermediate **53** (or its hydrogen bonded equivalent) generated by internal proton transfer in **52**, could reasonably be expected to enter into a facile, electrostatically driven cyclization to **54** which then would collapse yielding lactone **21** and 2-pyridthione **55**. Although a comparable path can be followed by two molecules of **52** reacting intermolecularly, this was found to be subject to experimental control using high dilution techniques. The cyclization of 2-pyridinethiol esters was tested and in fact, found to be an extremely useful method.

Thus, a number of ω-hydroxy acids **51** (n = 5,7,10,11,12 and 14) were utilised in the initial cyclization studies. These substances were converted to their 2-pyridinethiol esters **52** (n = 5,7,10,11,12 and 14) by reaction in concentrated xylene solution with 2,2'-dipyridyl disulfide and triphenylphosphine according to Mukaiyama *et al.*[50] The thiol esters so obtained, without isolation, were subjected to lactonization by refluxing in xylene under high dilution conditions. The corresponding lactones (**21**; n = 5,7,10,11,12 and 14) were obtained in good to excellent yields together with varying amounts of the corresponding dilides **56** as indicated in Table 1.

Recently, relative rates of formation of a series of lactones **21** (n = 10–19) in benzene solution at 80°, obtained from the 2-pyridinethiol esters **52** (n = 10–19) of the corresponding ω-hydroxyalkanoic acids **51** were published,[51] and are presented here in Table 2. Of interest are the maximum in rate occurring at ring size sixteen and the rate alternation appearing in the 18- to 21-membered range. However, factors other than ring size (e.g. substituents, heteroatoms, multiple bonds) are expected to influence the cyclization rate even more strongly than the ring size.

Table 2. Relative rates of formation of $(CH_2)n-C(=O)-O$ from 2-pyridinethiol esters in benzene at 80°

Ring size (n + 2)	Relative rate
12	0.2
13	0.36
14	1.0 Standard
15	1.0
16	2.5
17	1.9
18	1.35
19	0.55
20	1.55
21	0.6

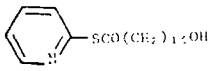
Also, in the same report,[51] support was gathered for the "double activation" mechanism proposed earlier and indicated in Scheme 1. Thus, the rate of cyclization of 16-hydroxyhexadecanoic acid thiolester **57** to hexadecanolide in refluxing benzene was not influenced by the addition of triphenylphosphine, triphenylphosphine oxide, triethylamine, triamylamine, 2-pyridthione or acetic acid. This result indicated the absence of catalysis by acid, base or any of the contaminants present in the reaction mixture. Furthermore, the thiolesters **58** or **59** which have no opportunity to form hydrogen bonded intermediates of types **53** did not cyclize on heating in

Table 1. Formation of lactones and dilides by cyclization of 2-pyridinethiol esters of ω-hydroxy carboxylic acids **51** (n = 5,7,10,11,12,14)

		Lactone			Dilide	
n	Solvent	Ring size	GLC yield (%)	Isolated yield (%)	Ring size	Isolated yield (%)
5[a]	Benzene	7	87	71	14	7
7[b]	Xylene	9	25	8	18	41
10[c]	Xylene	12	64	47	24	30
11[a]	Xylene	13	76	66	26	7
12[a]	Xylene	14	79	68	28	6
14[a]	Xylene	16	88	80	32	5

Slow addition of thioate to refluxing solvent was followed by [a]10 hr at reflux, [b]30 hr at reflux, [c]20 hr at reflux.

the absence or presence of base.[53] The above results are consistent with the proposed "double activation" mechanism, or a closely related variant in which some synchronization exists between the proton transfer and the nucleophilic attack on the carbonyl, although a clear distinction is not possible at the present time.



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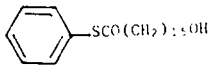

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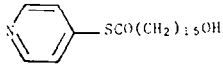
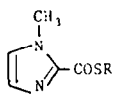


59

In an effort to maximize the efficiency of the double activation method for the formation of macrocyclic lactones, Corey *et al.* investigated a series of heterocyclic disulfides which in principle are capable of reacting in the same way as 2,2'-dipyridyl disulfide (DPDS) **60** (Scheme 2). 5,5'-Dinitro-2,2'-dipyridyl disulfide **61**, although effective in simple cases, was found to be less satisfactory in sensitive, polyfunctional systems.[52,53]

Bis-1-methyl-2-imidazolyl disulfide **62** showed exceptional promise since lactonization employing this reagent could be effected even at room temperature, although the yields were not satisfactory. The low yields were attributed to the partial conversion of the thiolester **65** to the isomeric species **66** which was shown incapable of cyclizing although it reacted with aniline to form the anilide in high yield. This observation led to the expectation that the disulfides **63** and **64**, with a *t*-butyl group strategically placed in a position to disfavor the formation of the N-acyl derivative **66**, due to steric hindrance, might furnish better results. Indeed, **63** and more so, **64** were found[53] to be superior to all reagents so far tested for the formation of simple lactones from ω-hydroxyalkanoic acids. In general, lower temperatures may be used and higher yields are obtained. For example,[53] the following lactones were obtained in refluxing benzene in the yields indicated: dodecanolide (87%), tetradecanolide (90%), hexadecanolide (96%). The application of these new reagents in the synthesis of



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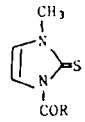


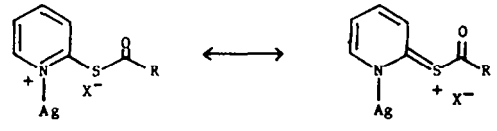
66

sensitive polyfunctional molecules offers exciting prospects and should result in significant improvements.

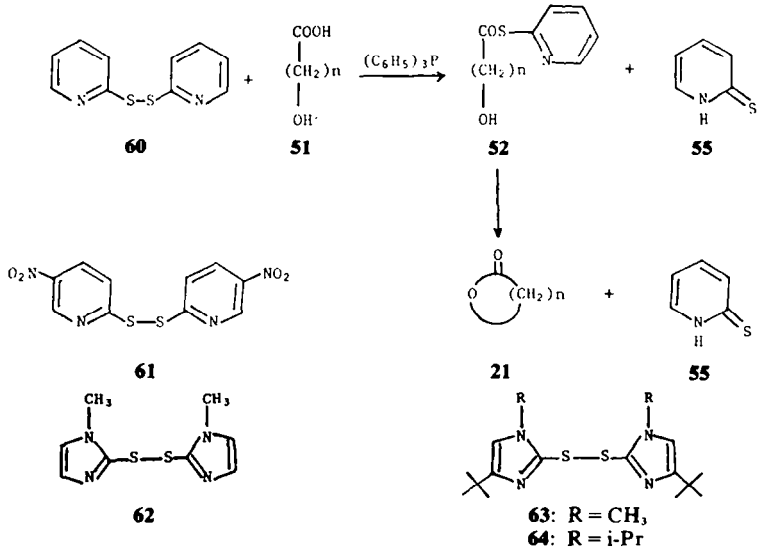
A modification of the Corey-Nicolaou lactonization method is due to Gerlach and Thalmann,[54] who used silver ion[55] ($AgClO_4$ or $AgBF_4$) to activate the 2-pyridinethiolesters by complexation as shown in Scheme 3. The activated ω-hydroxyalkanoic acid thiolesters [e.g. R=$(CH_2)_{14}OH$, Scheme 3] undergo cyclization at room temperature in benzene solution, whereas in the absence of internal hydroxyl and in the presence of alcohol (*i*-PrOH, R=$CH_2CH_2C_6H_5$) esterification takes place in high yield. This important modification has found applications in the total synthesis of nonactin **238**[92] and recifeiolide **211**,[88] both of which will be discussed later.

The synthetic utility of the neutral, "double activation" lactonization method soon became apparent by its extraordinary success in the synthesis of both naturally occurring substances and of novel potentially useful macrolide structures derived from complex biologically active non-macrocyclic hydroxyacids. A number of partial syntheses utilizing this methodology are discussed below, whereas total syntheses featuring this procedure in the key lactonization step (e.g. vermiculine, recifeiolide) will be dealt with later under the section of total synthesis of macrolides.

(±)-Zearalenone **43** was synthesized from the protected (±)-hydroxy acid **67**, obtained from the natural product by degradation, by refluxing in dilute benzene solution the 2-pyridinethiolester **68**, obtained in the usual way, and subsequent removal of the protecting groups



Scheme 3.



60 51 52 55

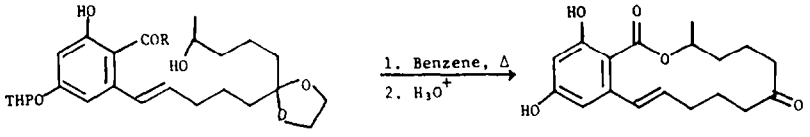
61 21 55

62

63: R = CH_3
64: R = i-Pr

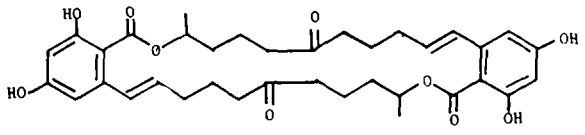
Scheme 2.

under acid conditions in 75% overall yield.[56] The novel dimer of zearalenone **69** was also isolated in lower yields and characterized by spectroscopic means.[52]



67: R = OH
68: R = S

43



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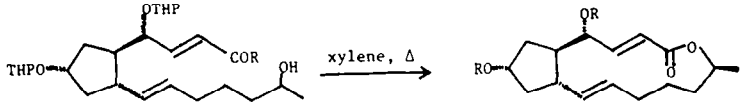
The bistetrahydropyranyl ether of A-brefeldenoic acid **70**, available from brefeldin A **73** by protection and base

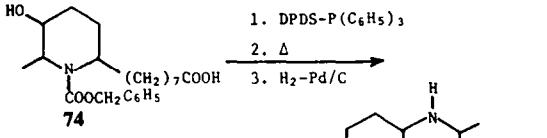


70: R = OH
71: R = S

72: R = THP
73: R = H

hydrolysis, was converted to brefeldin A **73** in good yield in two steps.[56] The 2-pyridinethiol ester **71** was prepared from **70** by reaction with 2,2'-dipyridyl disulfide (DPDS) and triphenylphosphine in concentrated xylene solution at 25° and cyclized in refluxing xylene under high dilution conditions to furnish the brefeldin A derivative **72** in 70% yield. Removal of the protecting groups from **72** afforded brefeldin A **73** in quantitative yield.

Similarly, N-benzyloxycarbonyl carpamic acid **74**, obtained from carpaine **75** by sequential protection and basic hydrolysis, when subjected to the "double activation" cyclization procedure, yielded, after hydrogenolysis of the benzyloxycarbonyl groups, carpaine **75** in over 50% overall yield.[56] The preferential formation of this dilide is a consequence of the severe steric interactions that would be present in the corresponding monomeric lactone which was not detected in the reaction mixture.



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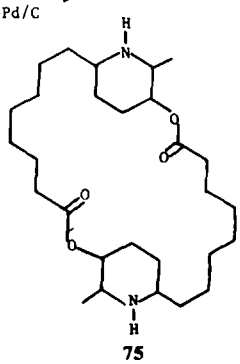
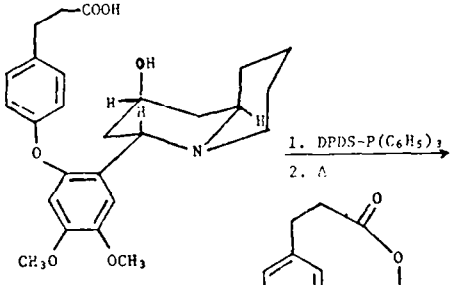


75

Another alkaloid macrolide, partially synthesized from its hydroxy acid was vertaline **77**. The hydroxy acid **76**, obtained from **77** by basic cleavage of the lactone, was converted to its 2-pyridyl thiol ester and cyclized by refluxing in xylene under high dilution conditions to vertaline **77** in 67% yield.[56] The cyclization of this type of hydroxy acids to *Lythraceae* alkaloids has also been achieved in lower yields by employing benzenesulfonic acid as catalyst and will be discussed later.



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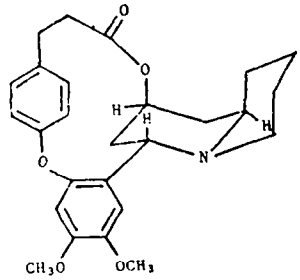
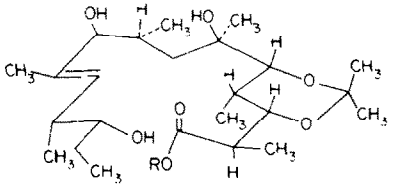


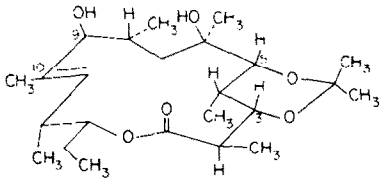
77

Perhaps one of the most severe tests of the "double activation" lactonization process was the formation of the erythromycin B skeleton.[56] Erythronolide B **82**, the aglycon of the macrolide antibiotic erythromycin B, has been synthesized from the protected acyclic hydroxy acid **78** by application of the "double activation method" as follows. The hydroxy acid **78**, obtained from natural erythronolide B **82** by protection and degradation, was converted to its 2-pyridinethiol ester **79**, which upon isolation (88%) and refluxing in dilute xylene solution, afforded in 36% yield the erythronolide B derivative **80**.

The conversion of **80** to erythronolide B **82** was completed by the following sequence: (1) selective oxidation of the allylic alcohol with manganese dioxide to form the $\Delta^{10,11}$-en-9-one (98%); (2) epoxidation of the resulting enone, 3,5-acetonide, $\Delta^{10,11}$-en-9-one, by basic hydrogen peroxide to form the 10(*R*), 11(*S*)-epoxide (100%); (3) reduction of the epoxyketone (H_2–Pd/C, CH_3OH. $NaHCO_3$) to yield the 3,5-acetonide of 10-*epi*-erythronolide B **81** (77%); (4) epimerization of **81** at C-10 (K_2CO_3–CH_3OH); and (5) removal of the acetonide by acid hydrolysis. This partial synthesis, which represented the first report of a successful cyclization to an erythromycin aglycon system simplifies considerably the formidable task of the total synthesis of this class of extremely important antibiotics.



78, R = OH
79, R = S



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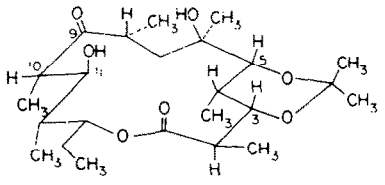

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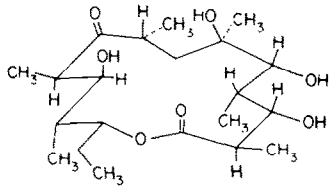
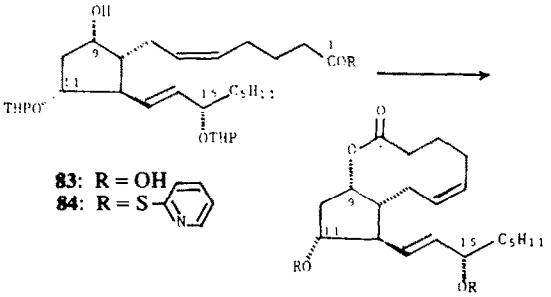


82

The extraordinary efficiency of the 2-pyridinethiolester method which operates without the need for basic or acidic catalysts opened up for the first time the possibility of synthesizing a wide variety of complex and highly functionalized macrocyclic lactones. These included not only natural macrolides such as the ones described above, but also novel substances derived from biologically active hydroxy-acids or other biologically active macrolides. Examples are the macrocyclic lactones derived from prostaglandins, the polyether antibiotic monensin and cytochalasan B.

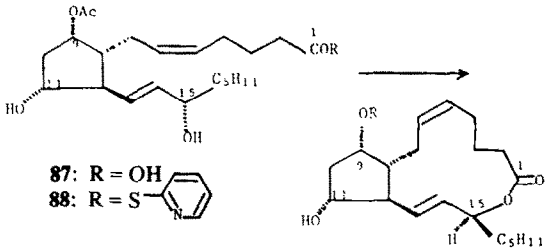
In the prostaglandin series, Corey *et al.*[57] reported the synthesis of both the 1→9 and the 1→15-lactones of $PGF_{2\alpha}$ **86** and **90**. Prostaglandin $F_{2\alpha}$ - 11,15 - bis(tetrahydropyranyl) (THP) ether **83**, after transformation to the 2-pyridylthiolester **84** in the usual way and refluxing in dilute xylene solution, yielded in 90% yield the protected derivative **85** of the 1→9-lactone. Acid hydrolysis of the protecting groups afforded the 1→9-lactone of prostaglandin $F_{2\alpha}$ **86** in 92% yield. This internally protected form of $PGF_{2\alpha}$ could be a potentially useful substance with regard to biological activity and further chemical transformations.

The 1→15-lactone of $PGF_{2\alpha}$ **90** was also synthesized, utilizing the 9-actoxy derivative **87**. Conversion of **87** to the thiolester **88** followed by cyclization in the usual manner afforded the 9-acetoxy lactone **89** in 74% yield contaminated with small amounts of what was presumed to be the 9-acetoxy 1→11-lactone. Selective removal of the acetate (K_2CO_3–CH_3OH, 25°) furnished (67%) the crystalline 1→15-lactone of $PGF_{2\alpha}$ **90**, a potentially useful intermediate. The 15-(*R*) epimers of both **86** and **90** were also prepared accordingly.[57]



83: R = OH
84: R = S

85: R = THP
86: R = H

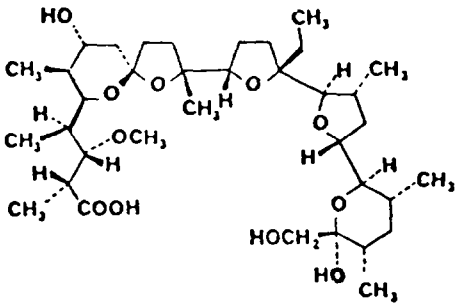


87: R = OH
88: R = S

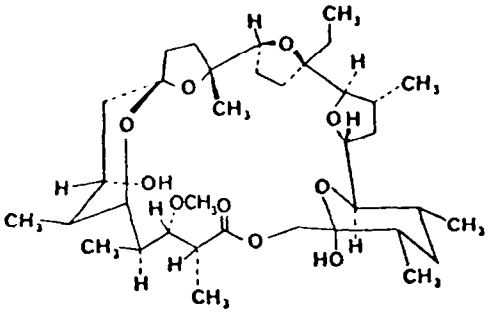
89: R = Ac
90: R = H

As an illustration of the applicability of their macrolactonization method in an even more complex case, Corey *et al.*[57] chose the naturally occurring polyether antibiotic monensin **91** for cyclization studies. Thus, the monensin free acid **91** was treated with 2,2'-dipyridyldisulfide (DPDS) and triphenylphosphine in concentrated benzene solution followed by dilution with benzene and refluxing to afford the cyclic molecule **92** in 95% yield, the structure of which was substantiated by spectroscopic and chemical means.

The novel iso-cytochalasan B structure **98** has been prepared[52] by the cyclization of the 20-*t*-butyldimethylsilyl ether hydroxy acid **93** [derived from cytochalasan B **99**] via the 2-pyridinethiolester **94**. When the thiolester **94** is heated in xylene under reflux, preferential cyclization takes place at the C-7 rather than the C-9 hydroxyl giving rise to the new cytochalasan B lactone derivative **97**, from which the interesting iso-cytochalasan B **98** was

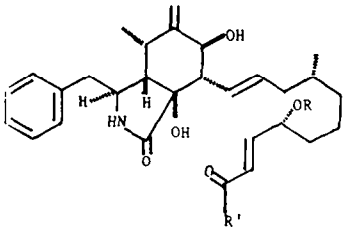


91



92

obtained in good yield. Similar observations were recently reported by Tamm *et al.*[58] who observed that the thiolester **96** of the unprotected (cytochalasan B derived) hydroxy acid **95**, on refluxing in xylene, afforded the 21,22 - dehydro - iso - cytochalasan A **100**.

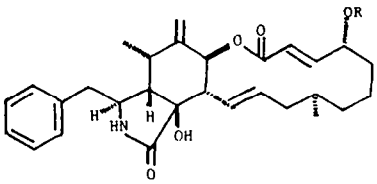


93: R = Si^{t}Bu(CH$_3$)$_2$, R′ = OH

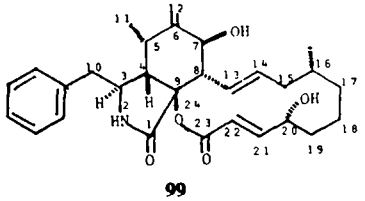
94: R = Si^{t}Bu(CH$_3$)$_2$, R′ = S

95: R = H, R′ = OH

96: R = H, R′ = S 



97: R = Si^{t}Bu(CH$_3$)$_2$
98: R = H



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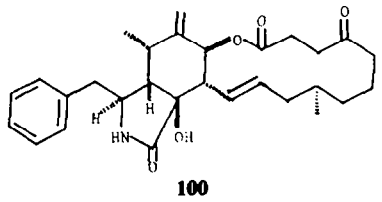


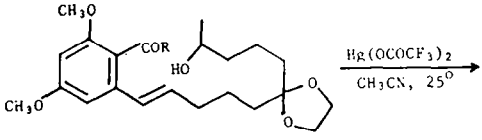
100

2.4.2 *The Masamune method.* In connection with the total synthesis of the macrolide antibiotic methymycin **174**, Masamune *et al.*[59a–c] have developed a new synthetic method for the construction of macrocyclic lactones which is also efficient for the preparation of esters.[59c] This procedure employs S-*t*-butyl thiolesters **103** of hydroxy acids and mercuric trifluoroacetate as an activating reagent. The lactonization proceeds rapidly in dilute acetonitrile solution at room temperature. The required S-*t*-butyl thiolesters **103** can be prepared in high yields from the corresponding acids and thallous 2 - methylpropane - 2 - thioate [Tl^{I}SC(CH$_3$)$_3$] via the acid chlorides **101**[59c] or the phosphorous containing mixed anhydrides **102**[60] according to eqns (1) and (2) respectively. The later method[60] appears to be milder and more general, being applicable in the preparation of a variety of thiolesters including the versatile 2-pyridinethiolesters.

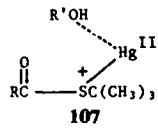
$$\text{RCOOH} \longrightarrow \underset{\mathbf{101}}{\text{RCOCl}} \xrightarrow{\text{Tl}^{\text{I}}\text{SC(CH}_3)_3} \underset{\mathbf{103}}{\text{RCOSC(CH}_3)_3} \qquad (1)$$

$$\text{RCOOH} \xrightarrow[\text{Et}_3\text{N, THF}]{(\text{BtO})_2\overset{\text{O}}{\overset{\|}{\text{P}}}\text{Cl}} \underset{\mathbf{102}}{\text{RCOO}\overset{\text{O}}{\overset{\|}{\text{P}}}(\text{OEt})_2} \xrightarrow{\text{Tl}^{\text{I}}\text{SC(CH}_3)_3} \underset{\mathbf{103}}{\text{RCOSC(CH}_3)_3} \qquad (2)$$

An illustration of the effectiveness of this method is the cyclization of (+)-dimethylzearalenone seco-acid ketal **104**, the thiolcarboxylate **105** of which, upon treatement with two equivalents of mercuric trifluoroacetate in dilute acetonitrile solution at 25° afforded the zearalenone derivative **106** in 90% yield in 5 min. The question of whether the reaction proceeds via the suggested mercury complex **107**, or through the intermediacy of a mixed trifluorocetic anhydride **108**, or both, has not been fully clarified. The application of the *S-t*-butyl thiolcarboxylate group for the protection of carboxylic acids and the use of this cyclization method in the total synthesis of methymycin **174** will be discussed in detail in a later section.



104: R = OH
105: R = SC(CH$_3$)$_3$



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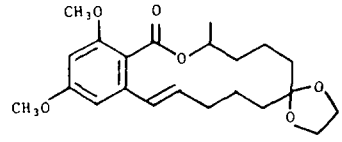

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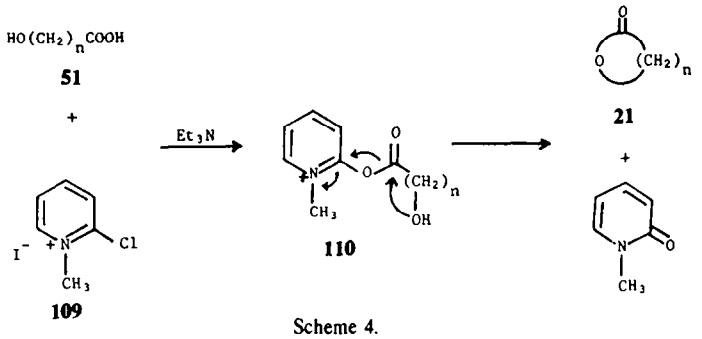
108



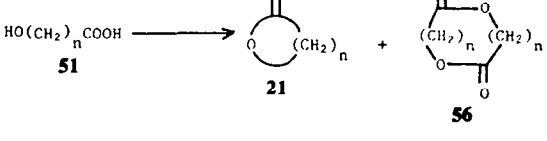
Scheme 4.

2.4.3 *The Mukaiyama method.* Closely related to the "double activation" method for the formation of macrocyclic lactones is a method developed by Mukaiyama *et al.*,[61] who introduced 1 - methyl - 2 - chloropyridinium iodide **109** as an effective cyclization reagent. According to this method a series of ω-hydroxyalkanoic acids (**51**; n = 5,6,7,10,11 and 14) were cyclized by slow addition to reagent **109** in the presence of triethylamine in refluxing methylene chloride or acetonitrile. The reaction proceeds according to Scheme 4 via the reactive species **110** which entropically favors the desired cyclization. Medium to large ring lactones together with varying amounts of their dilides are formed in good yields as indicated in Table 3. Although no applications of this methodology in the synthesis of complex natural products have appeared, the procedure seems very attractive and promising for future operations.

Table 3. Lactonization of ω-hydroxyacids $HO(CH_2)_nCOOH$ with 1-methyl-2-chloropyridinium iodide

			Lactone		Dilide	
n	Solvent	Time (hr)	Ring size	Yield	Ring size	Yield
5	CH_2Cl_2	7.5	7	89	14	0
6	CH_3CN	7.5	8	0	16	93
7	CH_3CN	8	9	13	18	34
10	CH_3CN	9	12	61	24	24
11	CH_3CN	8	13	69	26	14
14	CH_3CN	8.5	16	84	32	3

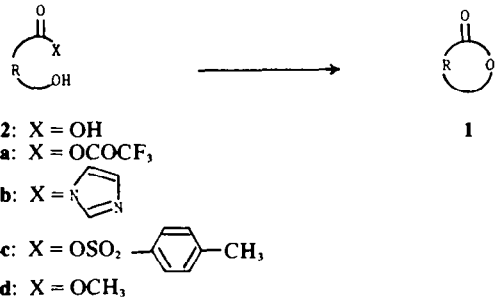
2.4.4 *Miscellaneous methods involving carboxyl activation.* Acid catalysis has been employed by Stoll and Rouvé,[62] who reported a large number of simple macrocyclic lactones **21** and their dimers **56** in good yields by cyclizing the corresponding acids **51** with benzenesulfonic acid in refluxing benzene for long periods of time. This lactonization method using acid catalysis has been successfully applied in recent years to the synthesis of *Lethraceae* alkaloids (*vide supra*).



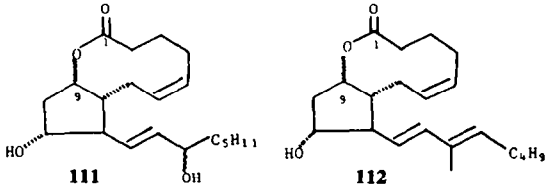
Thermal catalytic ($MgCl_2$) depolymerization of a variety of polyesters had been demonstrated by Spanagel and Carothers[63] to afford simple lactones in good yields. More recently,[64] dialkyltin or lead oxides have been used as catalysts in the thermal depolymerization of polyesters to form lactones.

Heterogeneous gas-phase thermal reaction of the formate esters of ω-hydroxypentadecanoic acid and its methylester over TiO_2 afforded pentadecanolide in *ca.* 50% yield.[65]

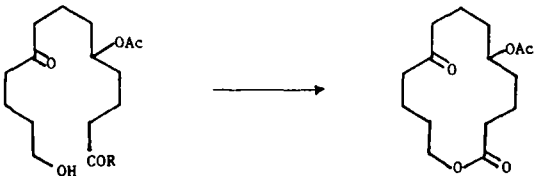
A variety of other methods for the lactonization of long chain hydroxy acids depending on the principle of carboxyl activation have been reported. These include mixed trifluoroacetic acid anhydride formation, imidazolide formation, mixed sulfonic acid anhydride formation and simple methyl ester formation. Brief discussion of these techniques follows, whereas their application as key reactions in the synthesis of naturally occurring macrolides will be described under the section of total synthesis of macrolides.



The mixed trifluoroacetic acid anhydride method of carboxyl activation has been introduced for the first time in the construction of the macrocyclic ring of macrolides by the Merck group[66] for the total synthesis of zearalenone **43**. It has also been applied subsequently by other groups in the construction of (*R*)-zearalenone[67] [the enantiomer of the natural (*S*)-zearalenone] and methymycin **174**.[59b] The mixed anhydride **2a** is usually prepared in benzene solution from the hydroxy acid **2** and the cyclization takes place at relatively low temperatures. Thus the novel 1→9-prostaglandin lactones **111**[68] and **112**[69] were prepared in good yields from the appropriate hydroxy acids and trifluoroacetic anhydride in benzene solution at room temperature. However, the yields generally obtained by this procedure are rather low and the strong acidic conditions (CF_3COOH) employed make this method not a very attractive one.



The excellent properties of the imidazolide moiety as an activating group of acids[70,77] have been utilized by Raphael *et al.*[71] in their total synthesis of pyrenophorin **161** for forming the final ester linkage of this 16-membered ring macrolide antibiotic. According to this method, the imidazolide derivative **2b** is prepared from hydroxy acid **2** by treatment with carbonyldiimidazole and treated with catalytic amounts of a strong base (DBN or sodium *t*-amylate) in benzene to form the macrocyclic lactone **2**. An example of a simple 14-membered ring lactone formed in this way was offered by White *et al.*[72] who converted the hydroxy acid **113** via its imidazolide derivative **114** to the lactone **116** in benzene solution under the influence of catalytic amounts of sodium *t*-amylate in 40% yield. However, the strong basic conditions required for this cyclization impose some limitations for applications in the field of sensitive polyfunctional molecules.



113: R = OH **116**

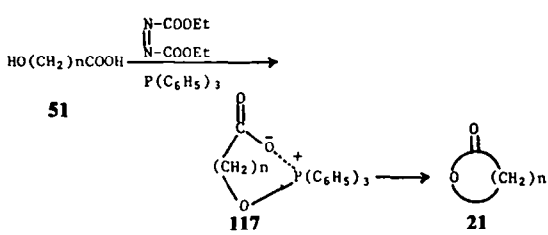
114: R = 

115: R = OSO_2—  —CH_3

The activation of the acid function of hydroxy acids **2** as mixed sulfonic acid anhydrides **2c** as a method for the formation of simple macrocyclic lactones **1** had been demonstrated by White *et al.*[72] As an example, they lactonized the model hydroxy acid **113** via its mixed sulfonic anhydride **115** (tosyl chloride-triethylamine-benzene) under carefully controlled conditions to lactone **116** in 52% yield.

Activation of the carboxyl group by esterification was utilized by the Syntex group[73] in the synthesis of zearalenone **43** and requires treatment of a methyl ester **2d** with sodium amylate at elevated temperatures. The strongly basic conditions employed and the low yields obtained make this a rather poor procedure.

Recently, Japanese workers reported[74] yet another rather general method for the synthesis of simple macrocyclic lactones **21** from ω-hydroxyalkanoic acids **51** by using as a cyclization reagent triphenylphosphine in combination with diethyl azodicarboxylate. The intermediacy of the dipolar species **117** was postulated in this reaction and it implies that the "double activation" mechanism might be operating in this case also. The report[74] describes the formation, at room temperature in benzene or THF solution, of a number of macrocyclic lactones **21** and their corresponding dilides in low to moderate yields depending on the ring size and the exact experimental conditions.



51 **117** **21**

3. TOTAL SYNTHESES OF MACROLIDES

Although macrolide structures have been known for some time, synthetic work in the area did not start until recently. The complexity of these substances is perhaps the primary reason why synthetic chemists have ignored them for so long. Efforts directed toward the total synthesis of members of this class of natural products began in the late 1960s and intensified in the 1970s. Among the problems associated with the synthesis of macrolides, the most formidable are the formation of the macrocyclic ring, the building of the correct stereochemistry, and the creation and preservation of the various functionalities present in the molecule. The discovery of efficient new synthetic methodology for the cyclization of long open-chain hydroxy acids certainly simplified the problem to a considerable extent. The most important total syntheses of natural macrolides reported to date are individually discussed below.

3.1 *Zearalenone* 43

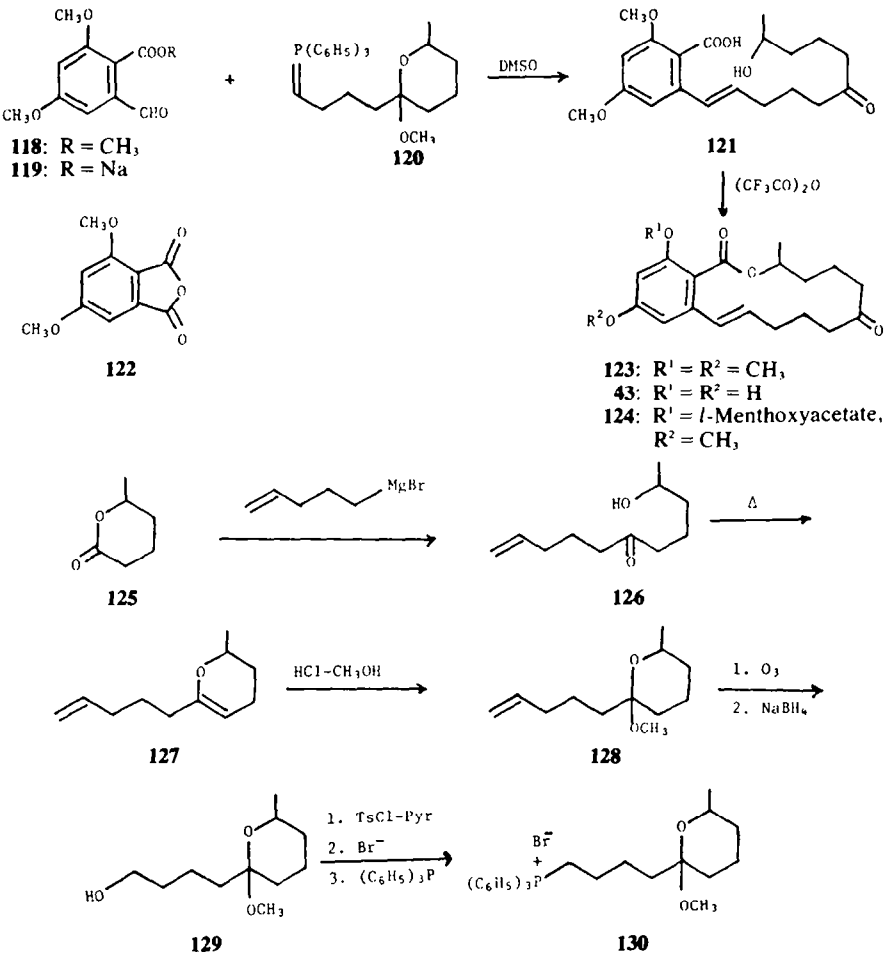
Zearalenone **43**,[11] an antibiotic with anabolic and uterotrophic activity, was perhaps the first naturally occurring macrolide to be synthesized. The biological importance of this substance prompted both the Merck and the Syntex groups to develop synthetic routes leading to this and related systems.[74a]

As a prelude to a total synthesis of zearalenone[66] **43**, the Merck group sought to answer the critical questions of whether the macrocyclic ring could be formed by internal esterification of the corresponding hydroxy acid **121** and whether the natural product could be generated from its dimethyl ether **123**. In order to test out these possibilities, the zearalenone *seco*-acid derivative **121** was prepared from natural zearalenone **43** by methylation of both phenolic groups and subsequent saponification. Preliminary experiments led to the realization that, indeed, zearalenone could be obtained from the acyclic precursor **121** by lactonization followed by removal of the protecting groups.

After securing the final stages of the synthesis the Merck chemists embarked on the construction of fragments **119** and **120** which were destined to be joined by a Wittig reaction to furnish the hydroxy acid **121** (Scheme 5).

The aromatic segment as the sodium salt **119** was obtained from 2,4-dimethoxyphthalic anhydride **122** by partial reduction with lithium tri-*t*-butoxyaluminum hydride followed by diazomethane treatment to afford methyl ester **118**, which was converted to the salt **119** with dimsyl sodium in dimethyl sulfoxide (DMSO).

The aliphatic portion as the phosphorane **120** was synthesized from lactone **125** in the following way: condensation of **125** with 1-pentenylmagnesium bromide followed by distillation of the product and exposure to methanolic hydrogen chloride afforded the ketal **128** via intermediates **126** and **127**. Reductive ozonolysis of the double bond of **128**, tosylation of the resulting alcohol **129**, displacement of the tosylate with bromide ion and heating with triphenylphosphine gave the phosphonium salt **130**. On generation of the ylide **120** with dimsyl sodium and condensation with the aldehyde **119** in dimethyl sulfoxide (DMSO), the hydroxy acid **121** was obtained after work up in 55–60% yield. Cyclization of **121** was effected in low yield by exposure to trifluoroacetic anhydride in dilute benzene solution. Liberation of the 2-phenolic group using boron trichloride at −28° and utilization of this



Scheme 5. The Merck synthesis of zearalenone.

group as a handle to resolve the racemate **43** as 2-*l*-menthoxyacetate **124** gave natural zearalenone **43** after removal of the menthoxyacetate (aqueous base) and the methyl ether (BBr_3).

A second total synthesis of (±)-zearalenone was reported in 1968 by a Syntex group.[73] This synthesis (Scheme 6) involves coupling of the aromatic aldehyde **131** with the ylide **132** followed by elaboration of the resulting product to the hydroxy ester **137** which was converted to zearalenone by cyclization and removal of the protecting groups. The details of the synthetic route are discussed below.

The aromatic fragment **131** was readily obtained from the O-orsellinate **133**[74] by oxidation with chromium trioxide in acetic acid-acetic anhydride to the tetraacetate **134** and subsequent methylation after acid hydrolysis.

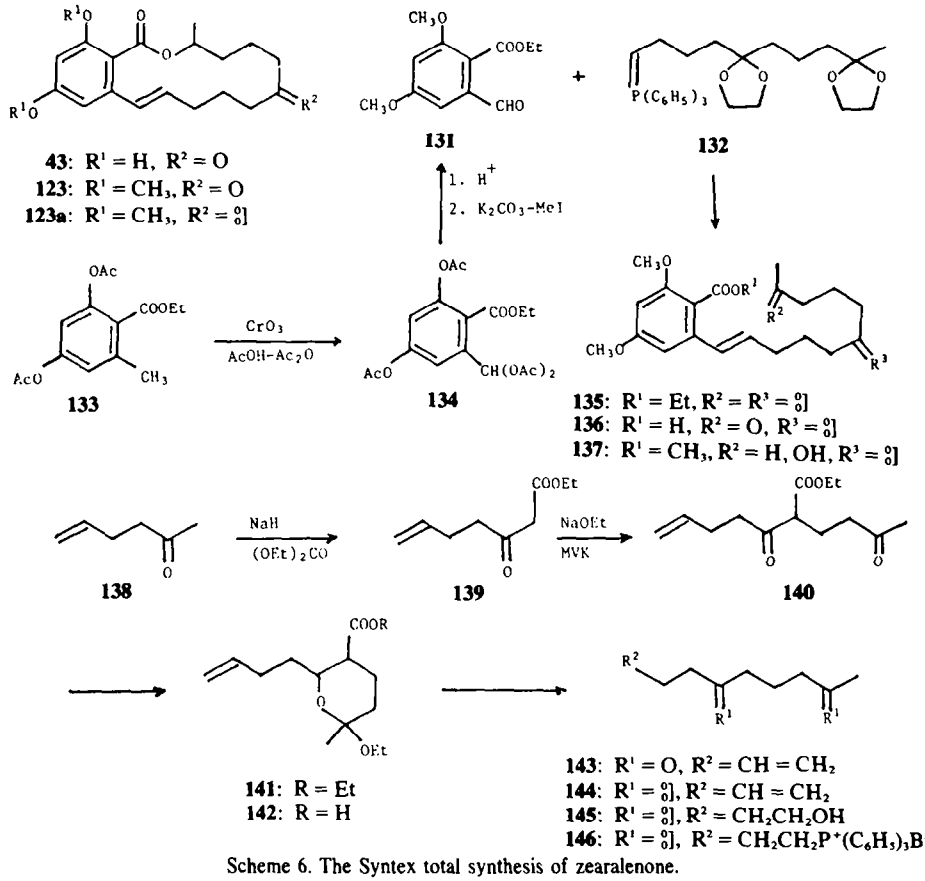
The aliphatic fragment **132** was synthesized starting from 1 - hexen - 5 - one **138**. Sodium hydride treatment of **138** followed by addition of diethylcarbonate gave the β-ketoester **139**, the enolate (NaOEt) of which added to methyl vinyl ketone in a 1,4-fashion to yield **140**. Ethyl orthoformate under acidic conditions converted **140** to the cyclic intermediate **141** from which the acid **142** was generated by aqueous base. Decarboxylation and hydrolysis of the ketal under acid conditions afforded the diketone **143** which was protected as the diethylene ketal **144**. Hydroboration of the olefin **144** led smoothly to the alcohol **145**. The phosphonium salt **146** was obtained from the corresponding bromide prepared (LiBr-acetone) from the tosylate (TsCl-pyridine) of **145**.

The ylide **132** generated from the phosphonium salt **146** and potassium *t*-butoxide in dimethyl sulfoxide (DMSO) reacted with the aldehyde **131** to afford **135**. Saponification of the ester function in **135** followed by treatment with *p*-toluenesulfonic acid in aqueous acetone proceeded selectively to furnish the monoketal acid **136**. Esterification with diazomethane and reduction with sodium borohydride gave the hydroxy ester **137**, cyclization of which was effected in rather low yield (8%) with sodium *t*-amyloxide in *t*-amyl alcohol to furnish the dimethyl ether **123a**. Removal of the ketal function under acidic conditions followed by cleavage of the methyl ethers with boron tribromide completed the synthesis of (±)-zearalenone **43** via **123**.

3.2 *Pyrenophorin*

The total synthesis of the macrolide antibiotic pyrenophorin[6] **161** as a racemate was reported by Raphael *et al.*[71] in 1972. The synthesis involves stepwise formation of the ester linkages of the 16-membered macrolide, the final closure being achieved via carboxyl activation employing the imidazolide of the appropriate hydroxy acid. The chemistry involved illustrates the effective use of various protective groups in the construction of complex molecules.

The route is summarized in Scheme 7. The lactol **148**



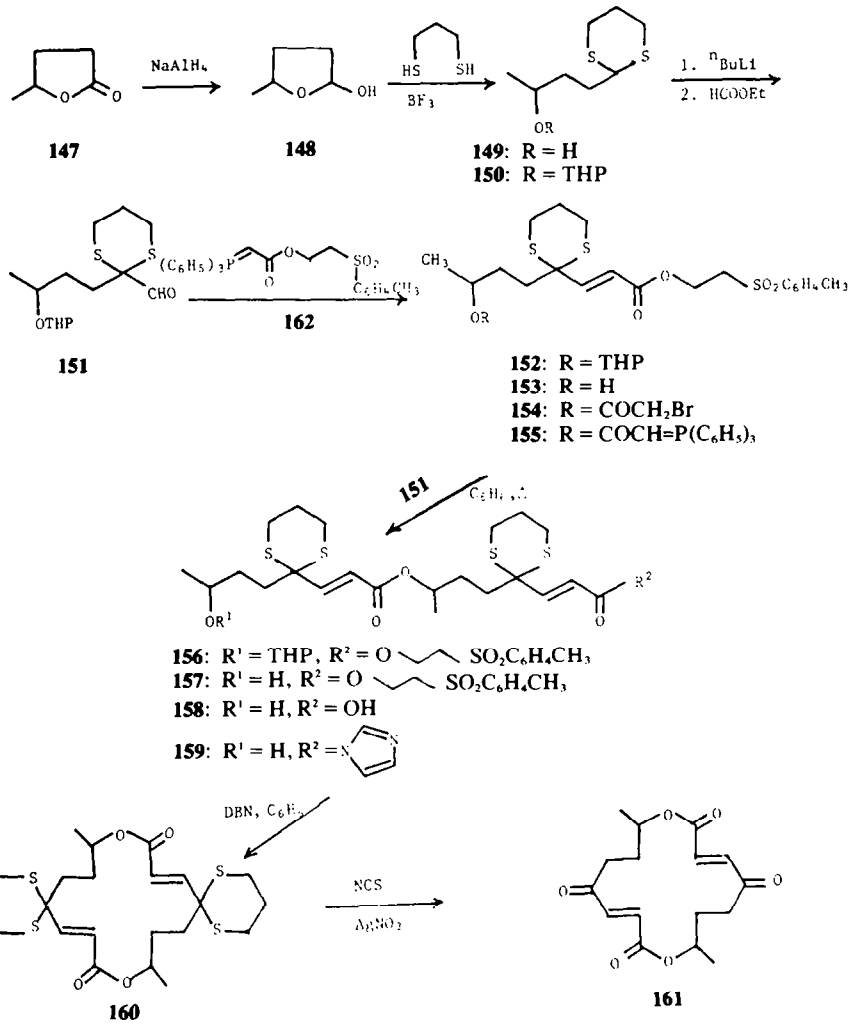
Scheme 6. The Syntex total synthesis of zearalenone.

was obtained by reduction of δ-valerolactone **147** with sodium aluminum hydride and was transformed to the dithiane derivative **150** by sequential treatment with propane - 1,3 - dithiol in the presence of boron trifluoride etherate (to give **149**) and dihydropyran under acid catalysis. Exposure of **150** to *n*-butyllithium followed by ethyl formate[76] gave the aldehyde **151** which on condensation with the ylide **162**, derived from the bromoacetate of toluene-*p*-sulphonylethanol, furnished the olefin **152** exclusively. Removal of the tetrahydropyranyl ether under acidic conditions afforded the alcohol **153** whose bromoacetate **154** on treatment with triphenylphosphine (to give the phosphonium salt) followed by aqueous sodium hydroxide was converted to the stabilized ylide **155**. Condensation of **155** with the aldehyde **151** in hot benzene gave the all-*trans* diene **156** as the only product. Acid hydrolysis of **156** afforded the alcohol **157** from which the toluene-*p*-sulphonylethyl protecting group was quantitatively removed at 25° employing 1,5 - diazabicyclo[4.3.0]non - 5 - ene (DBN) in benzene to give the key intermediate for the synthesis of pyrenophorin, hydroxy acid **158**. The choice of the toluene-*p*-sulphonylethyl protecting group and the conditions for its removal proved to be crucial for the success of the synthesis. The imidazolide **159** was prepared from the hydroxy acid **158** by the method of Staab.[70,77] Treatment of **159** with catalytic amounts of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in dilute benzene solution resulted in the formation of a mixture (1 : 1) of the pyrenophorin derivative **160** and its *trans*-diastereomer in a total yield of 60%. Removal of the thioketals from **160** by reaction with N-chlorosuccinimide in the presence of silver nitrate[78] gave (±)-pyrenophorin **161** together with its *trans* (*meso*) diastereomer from which it was separated by chromatography.

3.3 *Vermiculine*

Vermiculine **173**[7,8] a close relative of pyrenophorin **161**[6] has recently been synthesized in the racemic form by Corey *et al.*[79] following an elegant, short pathway. The ten-step synthesis summarized in Scheme 8 features several functionally selective reactions and reagents and the application of the "double activation" method[49] to generate both ester linkages of the macrocycle in a single operation.

The readily available dimethyl - 2,2 - dimethoxyglutarate **163**,[80] upon controlled treatment with di-isobutylaluminum (DIBAL) hydride in methylene chloride at −78° for 1 h, afforded the pure aldehyde **164** in 50% yield. Coupling of **164** with dimethylallylcadmium in ether at −78° for 1 h gave the alcohol **165** which without purification was treated with tribenzylchlorosilane in the presence of imidazole in dimethylformamide at 25° for 15 h to form the corresponding silyl ether **166** in 70% yield from **164**. Reduction of **166** with di-isobutylaluminum (DIBAL) hydride in methylene chloride at −78° produced the aldehyde **167** which was condensed with the sodium salt of diethylethoxycarbonyl methanephosphonate in tetrahydrofuran at 25° to furnish the *trans* - α,β - unsaturated ester **168** in 94% overall yield. The hydroxy acid **169** was prepared from **168** quantitatively by hydrolysis with dilute lithium hydroxide in aqueous methanol at 25° for 24 h. The 2-pyridinethiolester **170**, obtained by reaction of the hydroxy acid **169** with



Scheme 7. Total synthesis of pyrenophorin.

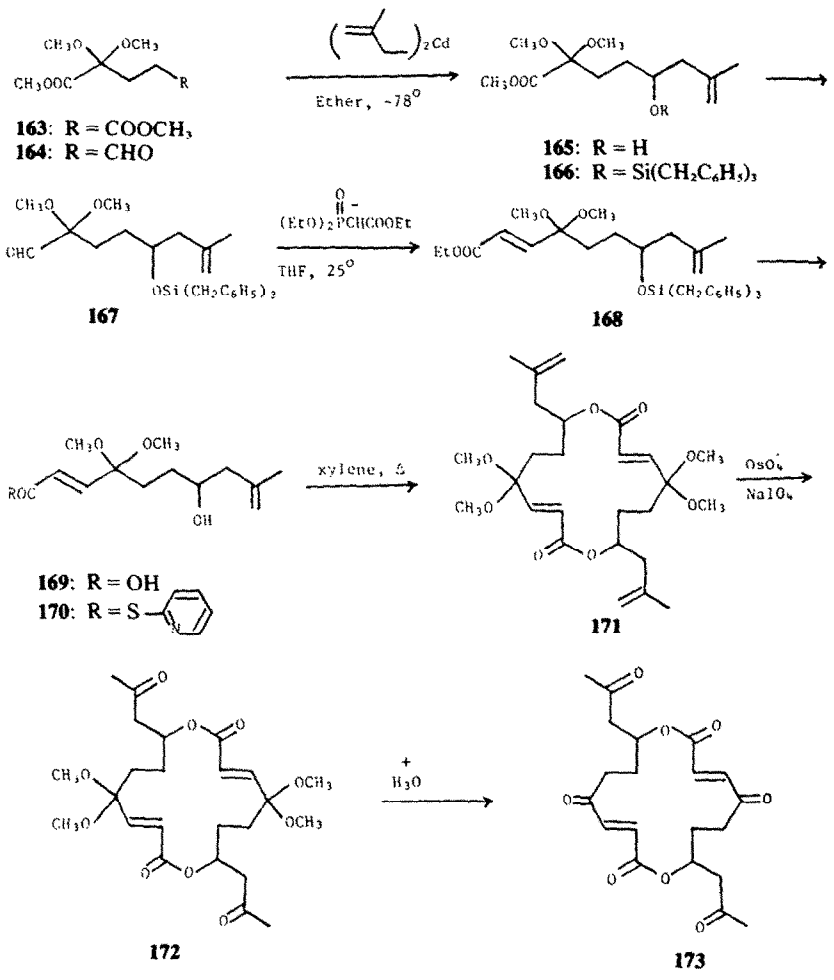
2,2-dipyridyl disulfide (DPDS) and triphenylphosphine in concentrated xylene solution at 0°, was purified by chromatography on silica gel (77% yield). Heating of **170** (0.1M solution) in oxygen-free xylene at reflux in the presence of 2,6-lutidine, produced in 30% yield, a mixture (1:1) of the desired vermiculine derivative **171** and its diastereomer, having a *trans* arrangement of the two methylallyl groups. The mixture was converted without separation to the keto ketal lactone **172** by reaction with osmium tetroxide (0.1 equivalent) and sodium periodate (6 equivalents) in aqueous *t*-butanol at 25° for 1 h in 70% yield, and thence quantitatively to a mixture of (±)-vermiculine **173** and its *trans*-diastereomer by treatment with acetic acid–water–tetrahydrofuran (3:1:1) at 45° for 1 h. Finally, chromatography on silica gel afforded pure racemic vermiculine **173** and its *trans* (*meso*) diastereomer as crystalline solids.

3.4 *Methymycin*

The total synthesis of methymycin **174**[81] by Masamune *et al.*[59a,b] represents the first synthesis of a "genuine" macrolide antibiotic; that is one with a sugar linkage. Masamune's elegant synthesis involves condensation of the major building blocks **176** (C-9 to C-11 fragment) and **177** (C-1 to C-8 fragment) in a Wittig reaction followed by elaboration of the product to the dihydroxy *t*-butylthiolester **178** which was cyclized, employing mercuric trifluoroacetate to induce lactonization,[59b,c] and converted to methynolide **175**. Finally, the synthesis was completed by attachment of the sugar desosamine to the C-3 hydroxyl group of methynolide **175**. The detailed pathway to methymycin is discussed below and shown in Scheme 9.

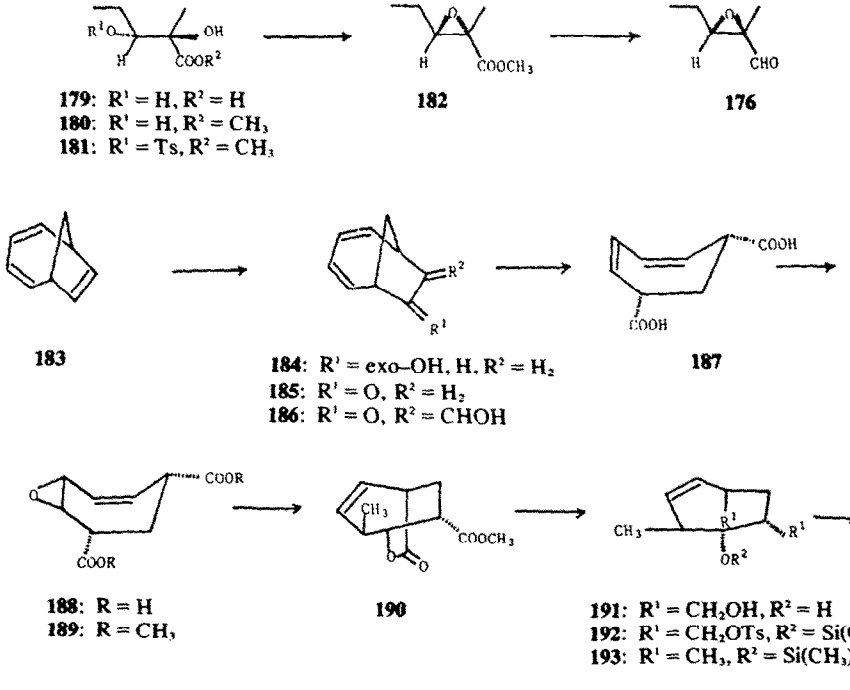
The aldehyde **176** (C-9 to C-11 fragment) was prepared in optically pure form from (+) - *erythro* - 2,3 - dihydroxy - 2 - methylvaleric acid **179** by sequential conversion to the methyl ester **180**, monotosylation to **181**, treatment with triethylamine to give epoxide **182** and finally reduction of the methyl ester with di-isobutylaluminum (DIBAL) hydride (75% yield).

The C-1 to C-8 fragment was synthesized starting with the readily available bicyclo[4.2.1]nona - 2,4,7 - triene **183**.[82] Hydroboration of **183** with bis - (3 - methyl - 2 - butyl)borane followed by oxidative workup gave the *exo*-hydroxy compound **184** in 75–80% yield. Oxidation of **184** with 4-benzoquinone and aluminum tri-*t*-butoxide afforded ketone **185** (75–81% yield), and formylation of **185** gave compound **186** in 85–90% yield. Sodium metaperiodate treatment of **186** led to the dicarboxylic acid **187** (100%) which was epoxidized with *m*-chloroperbenzoic acid (*m*-CPBA) to give predominantly *cis*-epoxydiacid **188** together with its *trans* isomer (7:3

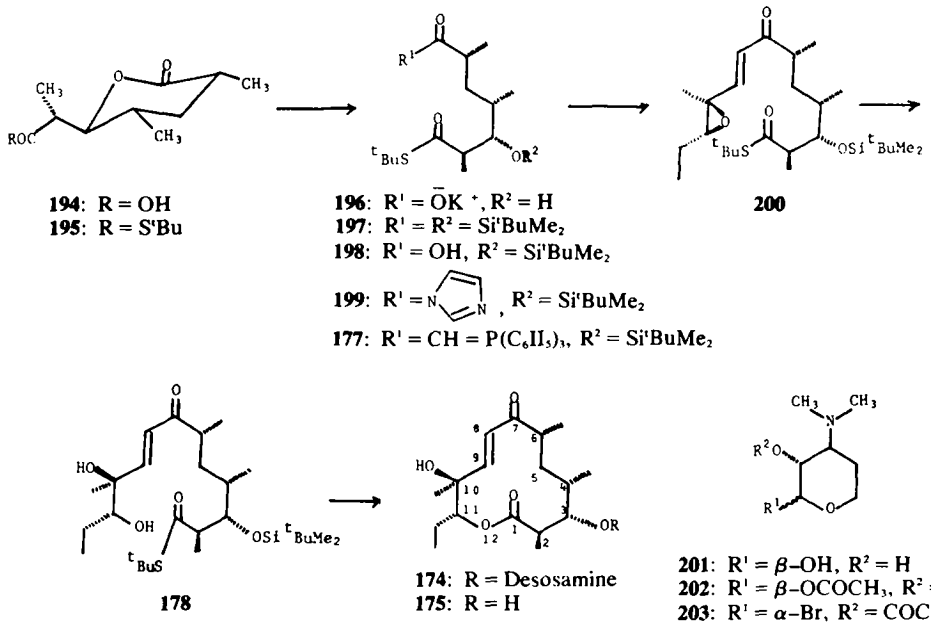


163: R = $COOCH_3$
164: R = CHO
165: R = H
166: R = $Si(CH_2C_6H_5)_3$
167
168
169: R = OH
170: R = S
171
172
173

Scheme 8. Total synthesis of vermiculine.



179: R^1 = H, R^2 = H
180: R^1 = H, R^2 = CH_3
181: R^1 = Ts, R^2 = CH_3
182
176
183
184: R^1 = exo-OH, H, R^2 = H_2
185: R^1 = O, R^2 = H_2
186: R^1 = O, R^2 = CHOH
187
188: R = H
189: R = CH_3
190
191: R^1 = CH_2OH, R^2 = H
192: R^1 = CH_2OTs, R^2 = $Si(CH_3)_3$
193: R^1 = CH_3, R^2 = $Si(CH_3)_3$



Scheme 9. Total synthesis of methymycin.

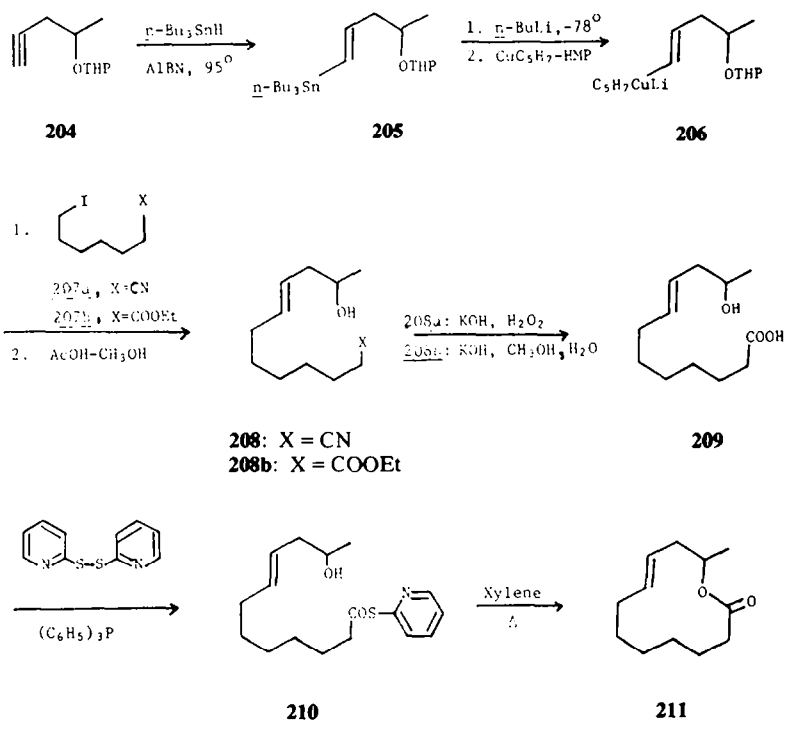
ratio). Without purification **188** was transformed to its methyl ester **189** and alkylated with lithium dimethylcuprate to furnish the lactone **190** in 30% overall yield from the diacid **187**. Lithium aluminum hydride (LAH) reduction converted **190** to the triol **191**, the primary hydroxyl groups of which were tosylated and the secondary trimethylsilylated to afford **192**. Lithium dihydrocuprate ($LiCuH_2$)[83] was used to smoothly remove the tosylates, and the cycloheptene **193** so obtained was cleaved according to Lemieux and Rudloff[84] ($KMnO_4$–$NaIO_4$) to produce directly (by concomitant removal of the trimethylsilyl ether and subsequent lactonization), the racemic Prelog–Djerassi[85] lactone **194** in 70% overall yield from **190**. Treatment of the acid chloride of **194** with thallous 2 - methylpropane - 2 - thiolate provided quantitatively the thioate **195**, which was converted to the potassium carboxylate **196** on treatment with 0.95 equiv potassium hydroxide. The bis (*t*-butyldimethylsilyl) derivative **197** was obtained by exposure to excess *t*-butyldimethylsilylimidazole and subsequently converted to the silyloxycarboxylic acid **198** by partial basic hydrolysis (KOH) in 90% overall yield from **194**. Conversion of the acid **198** to its imidazolide derivative **199** followed by refluxing in benzene solution with one equivalent of triphenylmethylenephosphorane, led to phosphorane **177** (C-1 to C-8 fragment) in 95% yield overall.

Condensation of aldehyde (+)-**176** with the stable Wittig reagent **177** was successfully carried out in refluxing toluene to afford a diastereomeric mixture (1:1) of epoxythiolcarboxylates **200** in 60% yield. Mild acid treatment of **200** resulted in the formation of the methynolide *seco*-acid derivative **178** (mixture of diastereomers) in 80% yield. Cyclization of **178** was effected by exposure to mercuric trifluoroacetate in acetonitrile at 25° to afford, after removal of the *t*-butyldimethylsilyl protecting group, methynolide **175** in 20–30% yield (based on the amount of the correct diastereomer of **178** estimated at 50%). The cyclization produces exclusively methynolide, the fate of the other diastereomer of the thiolcarboxylate **178** not being defined. Thus, resolution of the fragment (±)-**177** was achieved using optically active fragment **176** and the lactonization procedure.

The final stage of the synthesis involves glycosylation of methynolide **175** with the sugar desosamine **201**. Treatment of 1β,2-diacetyldesosamine **202** hydrochloride with hydrogen bromide in acetic acid-acetic anhydride (5:1) at room temperature gave 1 - α - bromo - 2 - acetyldesosamine **203** hydrobromide, three equivalents of which were treated with one equivalent of methynolide **175** in chloroform in the presence of lutidine at 50°. The product (50% yield) was treated with triethylamine in methanol to remove the acetyl group from the sugar to furnish a 5:1 mixture of β- and α-glycosides from which methymycin **174** (β-glycoside) was isolated by chromatography.

3.5 *Recifeiolide* (11-*hydroxy*-trans-8-*dodecenoic acid lactone*)

This naturally occurring macrolide isolated from the fungus *Cephalosporium recifei*,[86] has been synthesized in its racemic form by the Corey group[87] following a stereoselective route featuring the "double activation" procedure[49] for the lactonization of the key intermediate, 11 - hydroxy - *trans* - dodecenoic acid **209**. The synthesis proceeds according to Scheme 10. The acetylenic tetrahydropyranyl ether **204** was prepared from 4 - pentyn - 2 - ol in 99% yield by reaction with dihydropyran in methylene chloride containing catalytic amounts of *p*-toluenesulphonic acid at 25°. Hydrostannation of **204** with tri-*n*-butyltin hydride at 95° in the presence of catalytic amounts of azobisisobutyronitrile (AIBN) gave stereoselectively the vinylstannane **205** containing a small amount (15%) of its *Z*-isomer. Treatment of **205** (as a mixture with its *Z*-isomer) sequentially with *n*-butyllithium at −78° to −10° and pentynylcopperhexamethylphosphorous triamide (HMP) complex at −78° to −45° gave the cuprate **206** (containing its *Z* isomer). Coupling of the cuprate **206** with either 7-iodoheptanonitrile **207a** or ethyl 7-iodoheptanoate **207b** at −78° to 25° afforded, after removal of the tetrahydropyranyl protecting group, alcohols **208a** or **208b** in 54–56% yield



Scheme 10. The Corey synthesis of (±)-recifeiolide.

from the vinylstannane **205**. Alcohols **208a** and **208b** were obtained as 85:15 mixtures of *E*:*Z* isomers. Isomerically pure (±) - 11 - hydroxy - *trans* - 8 - dodecenoic acid **209** was obtained by saponification of the pure *trans* ethyl ester **208b** (KOH–H_2O–CH_3OH; 98%). Basic hydrogen peroxide converted the nitrile **208a** (mixture of *E*:*Z* isomers) to the same hydroxy acid **209** containing 15% of its *Z*-isomer. The thiolester **210**, prepared in high yield from the hydroxy acid **209**, 2,2'-dipyridyl disulfide (DPDS) and triphenylphosphine in concentrated xylene solution, was heated under high dilution conditions to afford, after chromatography, (±)-recifeiolide **211** in 52% yield.

A second total synthesis of recifeiolide **211** is due to Gerlach *et al.*[88] who prepared this 12-membered ring lactone in its optically active form. This synthesis, summarized in Scheme 11, starts with the (*R*)-enantiomer of 1,3-butane diol **212** (obtained by resolution), which is converted to the phosphonium salt **214** via the iodide **213**. The phosphorane, derived from **214** and *n*-butyllithium in ether, was condensed with the aldehyde **217**, obtained from 1-methoxycyclooctene **216** by ozonolysis, to form a mixture of *cis* and *trans* olefins (3:7 ratio). Isomerization to a 17:83 (*cis*:*trans*) mixture was achieved by irradiation with UV light in the presence of diphenyldisulfide, and separation of the isomers was performed chromatographically to give **215**. After removal of the methyl ester from **215** under basic conditions, the 2-pyridinethiolester of the acid **209** was prepared using 2,2'-dipyridyldisulfide (DPDS) and triphenylphosphine. Finally, cyclization was induced by further activation of the thiolester employing silver perchlorate to afford (*R*)-recifeiolide **211** in 75% overall from **209**.

3.6 *Vertaline*

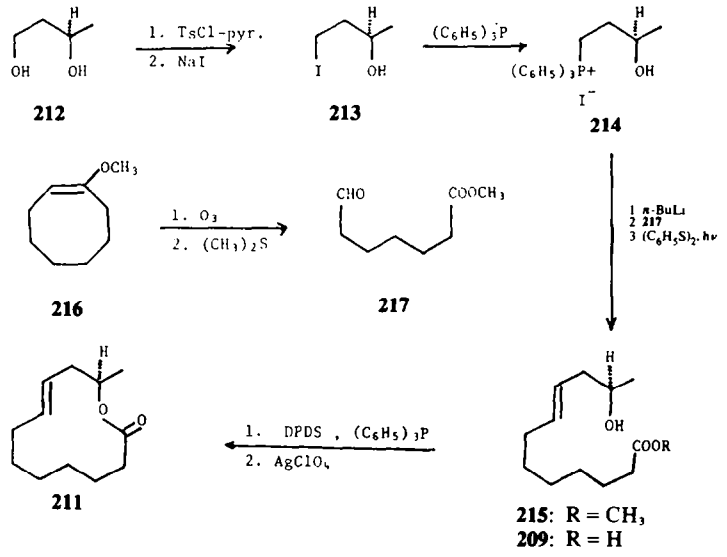
Vertaline **77**,[14] a member of the *Lythraceae* family of alkaloids with a *cis*-fused quinolizidine ring and a 14-membered ring lactone, has been synthesized by Japanese workers[89] according to the route shown in Scheme 12. Condensation of isopelletrierine **218** with 6-bromoveratraldehyde **219** under basic conditions (NaOH–THF–H_2O) afforded the *cis*-quinolizidine **220** together with its 10-epimer (3:2 ratio) in 42% yield. Reduction of **220** with sodium borohydride in methanol followed by acetylation gave the axial acetate **221** contaminated with its 2-epimer (3:1 ratio) in 96% yield. The acetate **221** underwent Ullmann condensation with methyl 4-hydroxyhydrocinnamate (pyridine-copper oxide) to furnish, after hydrolysis of the ester groups, the hydroxy acid **222** in 28% yield. Finally, the lactone ring closure was effected by refluxing in benzene with catalytic amounts of *p*-toluenesulfonic acid under high dilution conditions, producing (±)-vertaline **77** in 41% yield. Several other members of this family of alkaloid macrolides have been synthesized following similar methodology.[90]

3.7 *Nonactin*

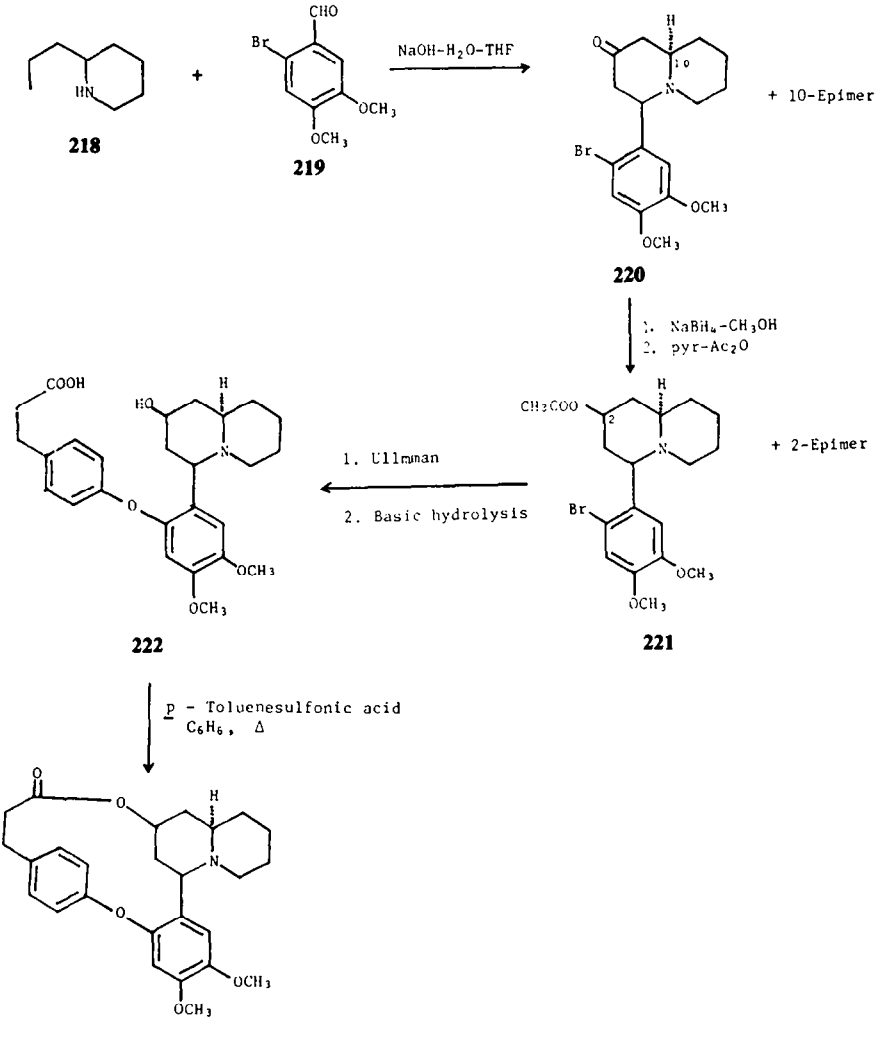
Nonactin **238**, a macrotetrolide antibiotic, has recently been constructed from four molecules of nonactic acid **229** by Gerlach and his collaborators.[91,92] The first objective was to synthesize the building block **229** (nonactic acid), a task that was accomplished by two different routes as shown in Scheme 13.

In the first synthesis, Gerlach *et al.*[91] started with 2-acetonylfuran **223**, which on treatment with the α-chloronitrone **224** in the presence of silver fluoroborate underwent electrophilic substitution to furnish **225**.

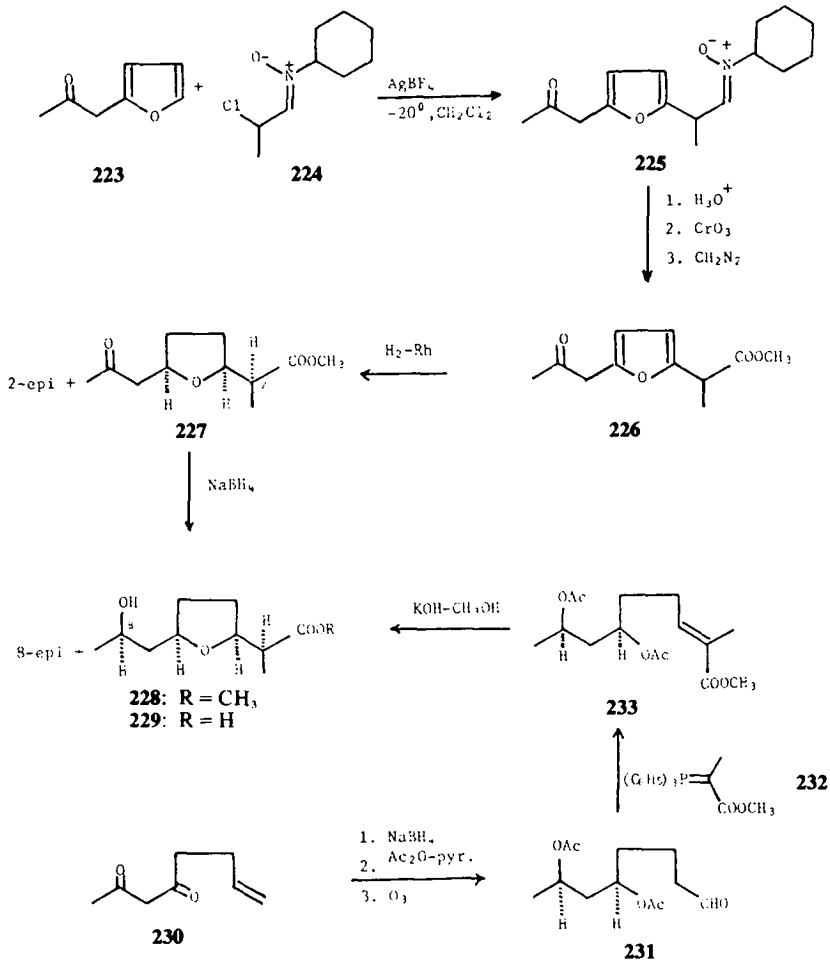
Acid hydrolysis to the aldehyde, followed by oxidation and esterification with diazomethane gave the methyl ester **226**. Catalytic hydrogenation of **226** over rhodium resulted in **227** with the correct *cis* stereochemistry of the



Scheme 11. The Gerlach synthesis of (*R*)-recifeiolide.



Scheme 12. The synthesis of vertaline.



Scheme 13. The Gerlach synthesis of nonactic acid.

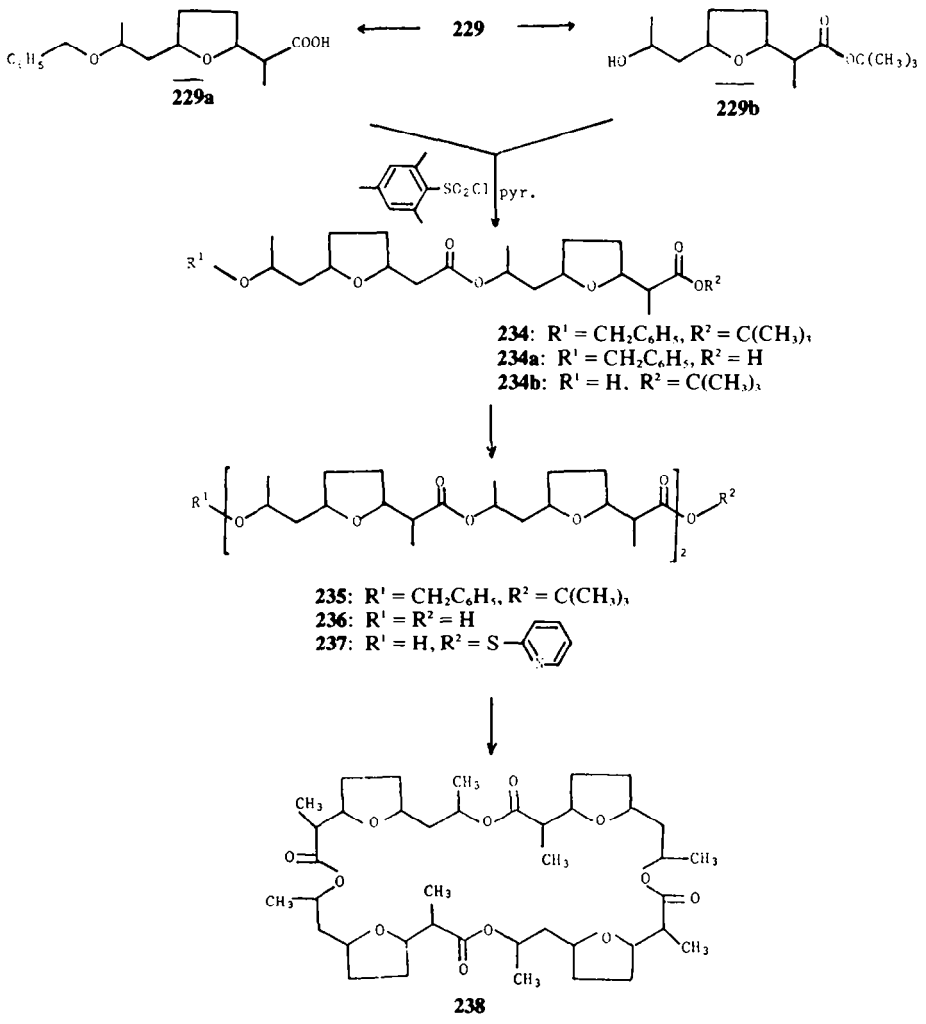
ring substituents but as a mixture with its 2-epimer. Sodium borohydride reduction of **227** yielded alcohol **228** together with its 8-epimer. Finally, base hydrolysis of **228** produced nonactic acid **229**.

The second synthesis of nonactic acid **229** according to Gerlach *et al.*[91] utilized the diketone **230** obtained by condensation of the dianion of acetylacetone (KNH_2-liquid NH_3) with allyl bromide. Sodium borohydride reduction of **230**, (non-stereospecific) followed by acetylation and ozonolysis, gave the aldehyde **231**, condensation of which with the Wittig reagent **232** formed **233** (contaminated with 15% of its *cis* isomer). Methanolic potassium hydroxide removed the acetates from **233** and induced cyclization to the methyl ester **228** as the major product.

The macrotetrolide was built from nonactic acid **229** by stepwise formation of the ester linkages[92] (Scheme 14). Thus, the benzyl ether **229a** and the *t*-butyl ester **229b** were prepared following conventional methods, and condensed, after activating the carboxylic acid using 2,4,6-trimethylbenzenesulfonyl chloride and pyridine (to form the mixed sulfonic anhydride). The ester **234** was transformed to acid **234a** by acid hydrolysis and to alcohol **234b** by hydrogenolysis. Coupling of **234a** and **234b**, employing the same esterification technique, afforded the triester **235** which on deprotection furnished the hydroxy acid **236**. Closure of the 32-membered ring was achieved via the 2-pyridinethiol ester **237** by silver perchlorate treatment.[49,54] In benzene solution at 25° (0.5h) a 20% yield of tetramers was obtained, whereas the yield rose to 35–40% in acetonitrile at 80° (1h). From the four possible tetrameric diastereoisomers (starting with racemic nonactic acid) only three were observed. Nonactin **238**, comprising 25% of the mixture, was finally isolated by chromatography.

Independently, and at about the same time, Schmidt *et al.*[93–96] synthesized nonactin **238**, starting with nonactic acid **229** of the correct configuration. The synthesis proceeds as shown in Scheme 15 starting from (−)-propylene oxide[93,94,96] which reacted with 2-lithiofuran to give alcohol **239**. Acetylation of **239** gave **240** which underwent Vilsmeyer reaction to afford **241** the conversion of which to **242** was realized by a Wittig reaction. Hydroformylation of **242** employing a rhodium-trialkylphosphine complex resulted in the formation of **243** which was converted to the acid **244** upon silver oxide oxidation. Hydrogenation over rhodium on alumina gave a mixture of four diastereoisomers **245** which on removal of the acetate resulted in **229**.

After the diastereoisomers were separated chromatographically, the tetrameric structure of nonactin, with alternate (+) and (−)-nonactic acid units, was built stepwise from (−)- and 8-epi-(+)-nonactic acids **229a** and **229b** by suitable protecting and coupling operations.[95,96] Thus, the benzyl ester tosylate **246** of 8-epi-nonactic acid **229b** was coupled with the potassium carboxylate **247a** of (−)-



Scheme 14. The Gerlach synthesis of nonactin.

nonactic acid **229a** in DMSO to furnish the (−)-nonactinyl-(+)-nonactic acid derivative **248a** (note inversion of configuration at C-8 in this S_N2 reaction). Similar coupling of the tosylate **246** with the salt **247b** of 8-epi-(−)-nonactic acid **229b** gave 8 - *epi* - (−) - nonactinyl - (+) - nonactic acid benzyl ester **248b**. Conversion of **248b** to the tosylate **249** and of **248a** to the carboxylate **250** followed by coupling of these two fragments accompanied by inversion of configuration of C-8, afforded (−)-(+)-(−)-(+)-hydroxy benzyl ester **251** which was transformed to the immediate precursor of nonactin, hydroxy acid **236**. Formation of the 32-membered ring was accomplished in 20% yield via the thioester **237**[49] which cyclized under silver ion catalysis[54] to give natural nonactin **238**.

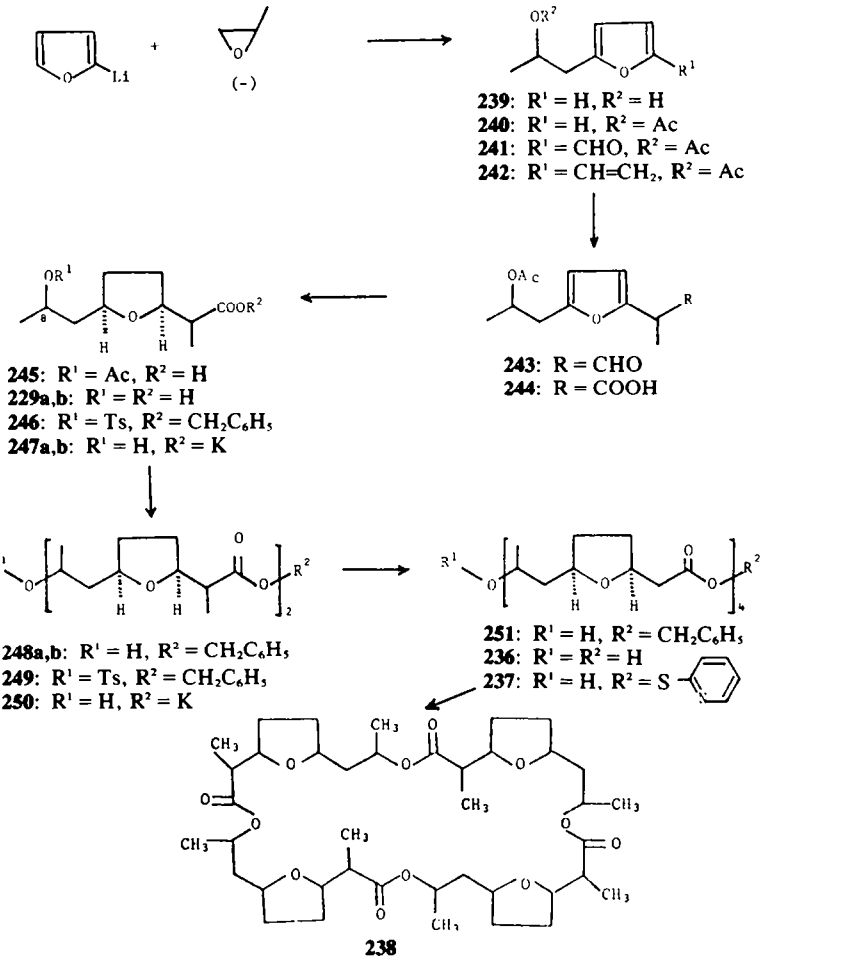
Several other non-stereoselective routes to nonactic acid have also been reported.[97,98]

3.8 *Brefeldin A*

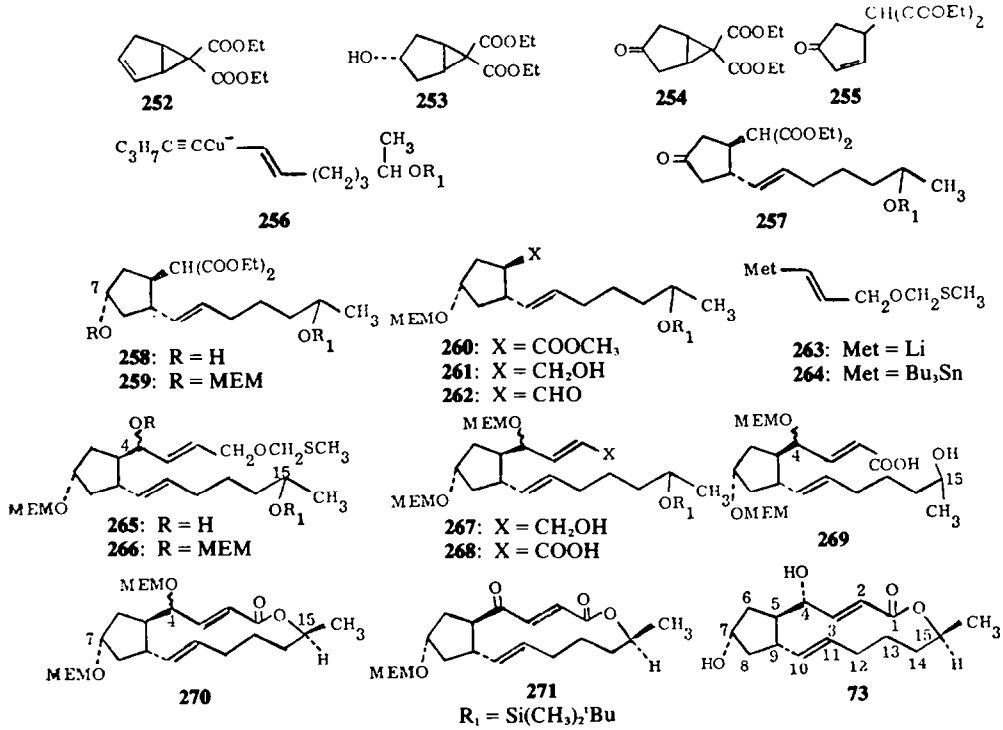
The total synthesis of brefeldin A **73**,[102] a biologically active[103] macrolide, has recently been accomplished by the Corey group.[104] The strategy for this synthesis was based on results obtained previously regarding the lactonization of derivatives of A-brefeldenoic acid[56,104] and on some interesting selective transformations observed in the brefeldin A series.[104] The outline of the synthesis is shown in Scheme 16.

Hydroboration of the bicyclic diester **252** with borane in tetrahydrofuran (THF) at −50° followed by alkaline hydrogen peroxide treatment afforded the alcohol **253** (50–80%) which was oxidized with chromic acid to the ketone **254** in 98% yield. Exposure of **254** to triethylamine gave the enone **255** in 88% yield. The sodio malonate derivative of **255** (formed using NaH) reacted with the vinyl cuprate reagent **256** at −78° in THF to furnish the conjugate adduct **257** stereospecifically in 82% yield.

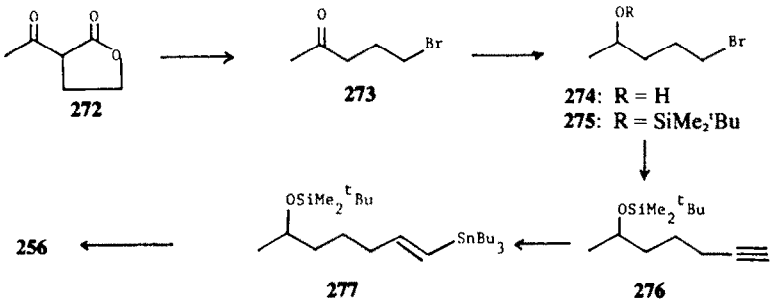
Reduction of ketone **257** with lithium borohydride in methanol at −78° gave the desired hydroxy compound **258** as the major product (80%) contaminated with its 7-epimer (20%) from which it was readily separated chromatographically. The alcohol **258** was then protected as the methoxyethoxymethyl (MEM) ether,[105] hydrolized to the corresponding diacid, α-hydroxylated (*n*-butyl-lithium-O_2-$(MeO)_3P$), and oxidatively decarboxylated (aqueous sodium periodate buffered with a little pyridine) to afford after exposure to diazomethane and chromatography the ester **260** in 60% yield. Treatment of **260** with excess diisobutylaluminum (DIBAL) hydride at −78° gave the alcohol **261** (97%) which was oxidized with Collins reagent to the aldehyde **262** (98%). Reaction of **262** with the lithium reagent **263** (prepared from the organotin compound **264**[106] and *n*-butyl-lithium) afforded the expected alcohol **265** which was converted to the MEM ether **266** in



Scheme 15. The Schmidt synthesis of nonactin.



Scheme 16. Total synthesis of brefeldin A.



the usual way[105] (82% from **262**). The methylthiomethyl protecting group was removed from **266** ($HgCl_2$–$CaCO_3$–CH_3CN–H_2O)[106b] and the resulting alcohol **267** was oxidized sequentially by Collins reagent and silver oxide to form the acid **268** in 48% overall yield. Disilylation of **268** using fluoride ion proceeded quantitatively to give the requisite hydroxy acid **269** (mixture of diastereoisomers relative to C-4 and C-15). The conversion of **269** to (±)-brefeldin A **73** was accomplished using the double activation method[49] for macrolide formation as follows.

The 2-pyridinethiol ester of **269**[56,104] prepared in the usual way[49] was subjected to lactonization in refluxing xylene for 8 h to form preferentially the 13-membered ring **270** having the desired β-orientation of methyl at C-15. The other C-15 diastereoisomers remain uncyclized and can be recovered as hydroxy acid upon aqueous treatment. Removal of the MEM groups ($TiCl_4$–CH_2Cl_2, 0°) to form the 4,7-diol followed by selective oxidation at C-4 (MnO_2–CH_2Cl_2) and etherification at C-7 with MEM–Cl[105] afforded **271**. Reduction at C-4 with sodium borohydride in methanol at −78° led to the 4α-alcohol (>95% selectivity) which after deprotection ($TiCl_4$–CH_2Cl_2, 0°) furnished (±)-brefeldin A **73** spectroscopically and chromatographically identical to the natural product.

The synthesis of the Gilman reagent **256** was accomplished from 5 - bromo - 2 - pentanone **273**, prepared by the action of hot hydrobromic acid on α-acetyl γ-butyrolactone **272**, as follows. Reduction of the carbonyl group with lithium aluminum hydride in ether at −78° formed the alcohol **274** which was silylated to afford the bromo *t*-butyldimethylsilyl ether **275**. Displacement of bromine with ethynyl was successfully carried out by reaction with lithium acetylide-ethylene diamine complex in dimethyl sulfoxide to afford the acetylene **276** (97%). Regioselective hydrostannation of **276** with tri-*n*-butyltin hydride at 90° in the presence of azoisobutyronitrile as initiator furnished the organotin compound **277** in high yield. Conversion to the cuprate reagent **256** was accomplished by treatment with *n*-butyllithium in THF at −78° (10 min), 25° (50 min), cooling to −78° and adding 1-pentynylcopper and stirring at −78° for 1 h.

4. CONCLUSION AND FUTURE OUTLOOK

The total synthesis of natural products with medicinally useful biological activities has always been a primary target of synthetic chemists. The steroids, the penicillins, the tetracyclines and the prostaglandins are distinct examples of such classes of compounds that have received so much synthetic attention as to be considered more or less exhausted areas of synthetic research, although, undoubtedly, they continue to be of considerable interest due to their medicinal importance. Similarly to the above mentioned classes of natural products, the biological properties of the macrolides brought them in recent years into the forefront of synthetic chemical research. From recent trends and reports, it seems rather conclusive that the synthesis of macrolides has already acquired considerable momentum and that the synthetic era of the macrolide antibiotics and antitumor agents has begun.

It is very much hoped that this review will serve as a platform from which the synthetic chemist can put past work in this area into perspective, familiarize himself with the current state of the synthesis of macrolides, and most importantly be stimulated and view the future with imagination and creativity.

The erythromycins,[56,99] the cytochalasans,[99,100] the rifamycins[99] and maytansine[99,101] are examples of macrolide molecules, the synthesis of which can reasonably be expected in the not-too-distant future and will certainly stand as outstanding achievements of human ingenuity.

5. ADDENDUM

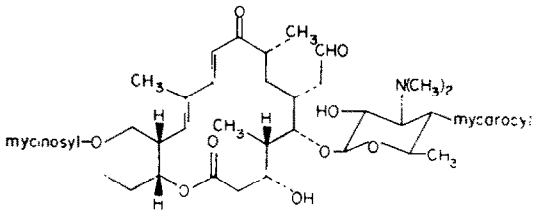
Since the preparation of the original manuscript the following significant developments in the macrolide field appeared in the literature.

Masamune and his collaborators have recently reported[107] the preparation of tylonolide (**279**), the aglycon of tylosin (**278**) a sixteen membered macrolide antibiotic by careful removal of the sugars from the natural product. Tylonolide was converted to an open chain hydroxy acid which was lactonized back to the cyclic product thus representing a partial synthesis of tylonolide.

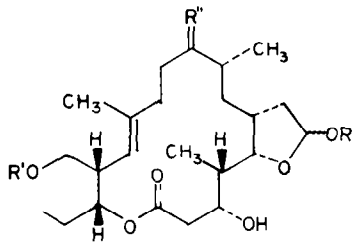
Thus the methyl ether obtained from tynolide (**279**) and trinethyl orthoformate was protected at the primary hydroxyl group as the tetrahydropyranyl (THP) ether (**280**), reduced with $NaBH_4$ to **281** (mixture of isomers) and saponified (1N NaOH, 60°C) to the hydroxy acid **282**. Conversion to the benzenethiol ester via the imidazolide, followed by MnO_2 oxidation afforded **283** which on exposure to mercury (II) methanesulfonate in the presence of Na_2HPO_4, and subsequent acid treatment furnished 17% yield of tylonolide (**279**)

A second total synthesis of (±)-vermiculine (**173**) has been reported in 1977 by White *et al.*[108] This synthesis which involves stepwise formation of the ester linkages of the macrolide is shown in Scheme 17.

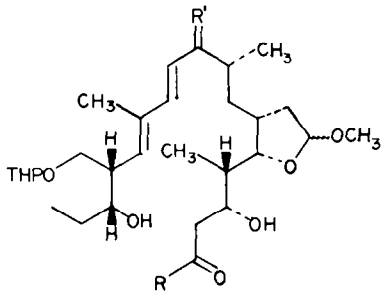
The dienol acetate **285**, obtained from the ester **284** and isopropenyl acetate under acidic conditions, was reduced



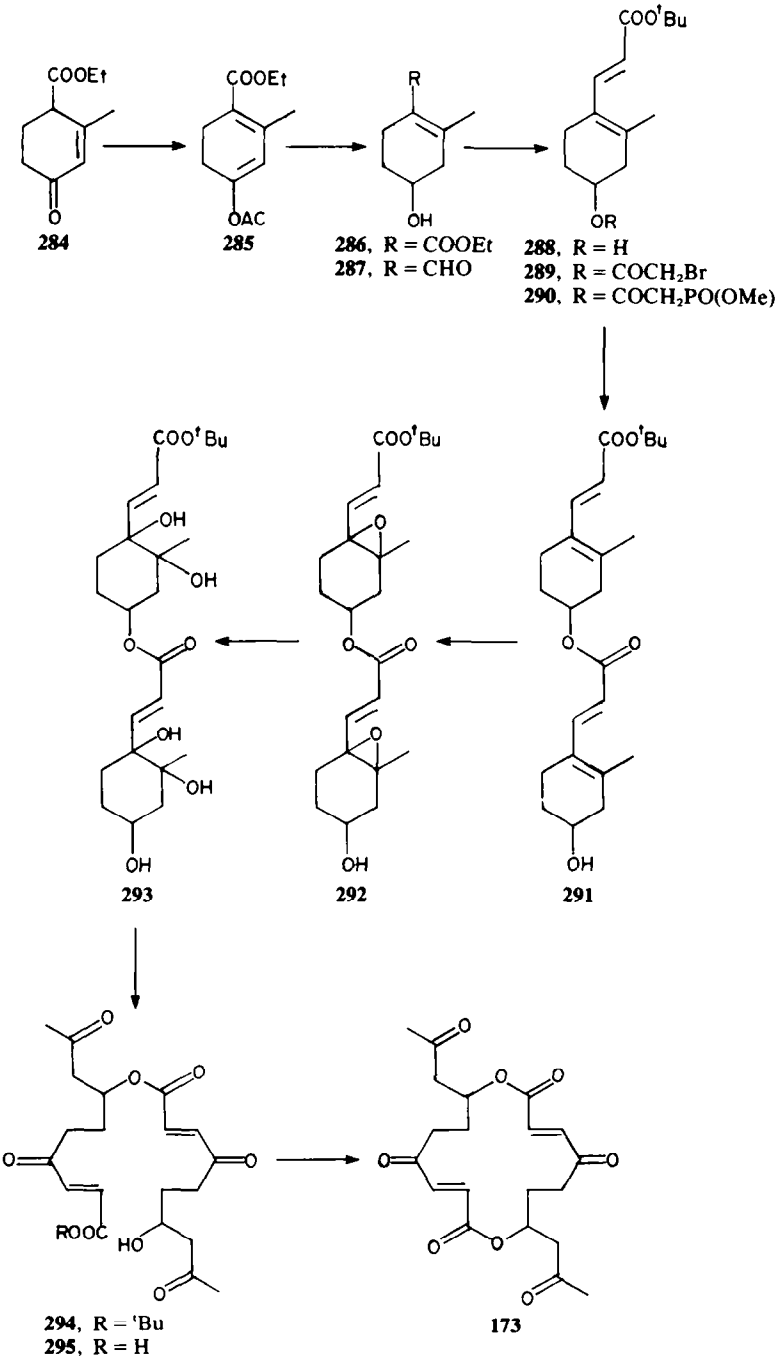
278



279, R = R′ = H, R″ = O
280, R = CH_3, R′ = THP, R″ = O
281, R = CH_3, R′ = THP, R″ = OH, H



282, R = OH, R′ = OH, H
283, R = SC_6H_5, R′ = O



284 **285** **286**, R = COOEt **287**, R = CHO **288**, R = H **289**, R = $COCH_2Br$ **290**, R = $COCH_2PO(OMe)$

293 **292** **291**

294, R = 'Bu
295, R = H

173

Scheme 17. The White total synthesis of (±)-vermiculine

with $NaBH_4$ to the hydroxy ester **286** (68%) which upon further reduction with $LiAlH_4$ followed by MnO_2 oxidation furnished aldehyde **287**. Condensation of this aldehyde with the phosphonate derived from $(MeO)_2POCH_2COO^t$-Bu and NaH in THF gave the diene ester **288** (82%). Transformation to the bromide **289** (bromoacetyl bromide) and then to the phosphonate **290** (trimethyl phosphite) followed by condensation with aldehyde **287** produced the ester **291** as a 1:1 mixture of diastereoisomers. Selective epoxidation of the γ,δ double bonds in **291** proceeded smoothly with *m*-chloroperbenzoic acid to afford **292** which was converted to the pentaol **293** with 8% perchloric acid in THF. Lead tetraacetate cleavage of **293** afforded **294** which was hydrolysed to the hydroxy acid **295**. The final cyclization step was achieved by treatment with triphenylphosphine in benzene followed by diethyl azodicarboxylate[74] at 25° to furnish (±)-vermiculine (**173**) in 15% yield.

Acknowledgements—The author wishes to thank sincerely his teachers in organic chemistry, Profs. P. J. Garratt, F. Sondheimer, T. J. Katz and E. J. Corey for their invaluable guidance and enthusiastic encouragement and support. In particular, the author wishes to express his deepest gratitude and appreciation to Professor E. J. Corey who "baptized" him into the natural product area of synthesis and whose brilliant and never-ending flow of ideas are in large part, responsible for some of the most elegant work described in this article. Many thanks also to J. Edward Semple and Zenon Lysenko for reading the manuscript and making valuable comments.

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[104]I am grateful to Prof. E. J. Corey for communicating these results to me prior to publication. Manuscripts describing this work have been submitted to *Tetrahedron Letters* (1976).
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