# Naturally Occurring Tetramic Acids: Structure, Isolation, and Synthesis

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*Received February 3, 1995 (Revised Manuscript Received May 22, 1995)*

## Contents



## I. Introduction

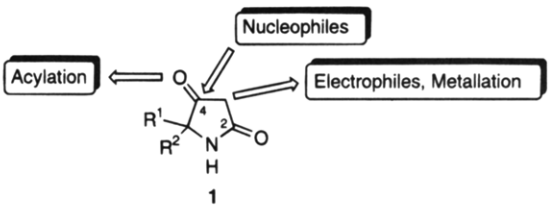
The tetramic acid (2,4-pyrrolidinedione) ring system has been known since the early twentieth century when the first simple derivatives were prepared. However, the true importance of this heterocycle was not realized until the 1960s when it was found to be a key structural unit in many natural products. The naturally occurring tetramic acids have attracted a great deal of interest not least because the majority of the compounds isolated to date exhibit some biological function—usually antibiotic or antiviral activity. The tetramic acid moiety, in most cases, is present as a 3-acyl derivative or, less commonly, as a 4-*O*-alkyl ether derivative. Thus the synthesis of such compounds represents a worthwhile and challenging goal for the organic chemist particularly as many of the target molecules are comprised of complex architectural frameworks and include several stereogenic centers; indeed, for these reasons, many members of this class have yet to be synthesized or have only been prepared as diastereomeric mixtures.

The spectrum of biological activity displayed by tetramic acid-containing natural products is remarkable in its diversity; it includes potent antibiotic, antiviral and antiulcerative properties, cytotoxicity and mycotoxicity, the inhibition of tumors (in mice and humans) as well as fungicidal action. Other members of this class are responsible for the pigmentation of certain molds and sponges. Synthetic analogues of certain tetramic acids have been the subject of clinical investigations, particularly in the antibiotic area, but so far these have not produced a proprietary drug.

Surprisingly, given the vast amount of work to have appeared in the literature, to date there has only been one review published on tetramic acids.[1]

Brodyck Royles, born in Edinburgh (April 20, 1965), received his Bachelors degree from Heriot-Watt University in 1987. He then moved to the University of Edinburgh where, under the guidance of Professor R. Ramage, he carried out research on the asymmetric synthesis of polyenoyltetramic acids which led to the award of his Ph.D. in 1991. In 1992 he was appointed to a post-doctoral research assistantship with Dr. D. M. Smith in the University of St. Andrews. For the first three years he was involved with the development of the "inverse electron-demand" Diels-Alder reaction as a potential novel route to poly(heteroaromatic) systems. He is currently (in conjunction with Drs. D. M. Smith and C. Glidewell) engaged in the synthesis of novel heterocyclic and polymeric systems that incorporate a ferrocenyl nucleus.

This primarily covered the reactions of the tetramic acid ring (**1**) itself which can be summarized as follows: (a) reaction with electrophilic species (*e.g.* aldehydes, bromine or nitrating agents) at C-3, (b) with nucleophilic species (*e.g.* hydrazine) at C-4, (c) acylation on O-4 or, under certain conditions, C-3, and (d) with organometallic bases (*e.g.* *n*-butyllithium) metallation occurs at C-3. This review includes sections concerning the synthesis of tetramic acids; however, the naturally occurring systems are only treated very briefly.




**1**

The present review is a survey of known natural products that contain a tetramic acid unit, with particular emphasis on their structural and biological characteristics. A description of the tautomeric behavior is included to familiarize the reader with the behavior of this ring system, in particular the differences which arise when C-3 carries an acyl substituent—as is the case in the majority of the natural product systems. The section on the synthe-

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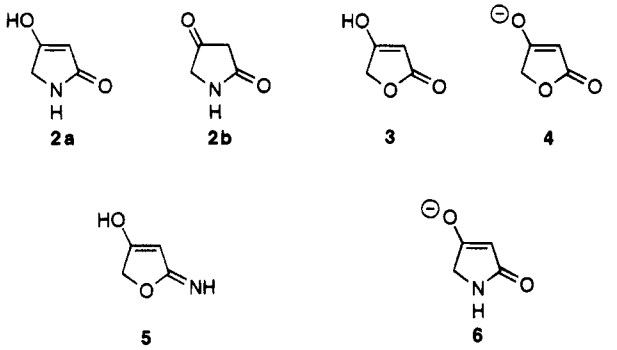



**Figure 1.**

sis of naturally occurring tetramic acids is concerned only with the actual methodology employed to construct the ring system itself. To include a broader section of this work would not only be outside the scope of the title, due to the magnitude and diversity of the range of synthetic methodology involved, but would encompass far too much material for a journal article.

## II. Structure of the Tetramic Acid Ring

Tetramic acids have traditionally been represented as derivatives of the enolic tautomer (4-hydroxy-3-pyrrolin-2-one) **2a** as opposed to the corresponding keto (pyrrolidine-2,4-dione) form **2b**. This was due to analogy with tetronic acid (**3**), the assumption being made that such derivatives would show similar physical and chemical properties. Tetronic acid was first prepared[2] in 1896 and is strongly acidic ($pK_a$ = 3.76) in aqueous solution.[3] The solid-state infrared spectrum[4] is consistent with the enolic structure **3** showing absorptions at 1690 (C=O) and 1635 (C=C) $cm^{-1}$ while the ultraviolet spectrum in aqueous ethanol shows absorptions ($\lambda_{max}$ 223 and 248 nm) due to the enol **3** and the enolate **4**, the proportion of each being pH dependent.[5]

Tetramic acid (**2**) was surprisingly not synthesized until 1972;[6] earlier attempts[7,8] were later shown to have resulted only in the formation of the isomer 2-iminotetronic acid (**5**).[9,10] It is a much weaker acid (with $pK_a$ = 6.4 in aqueous solution)[6] than its oxygen analogue **3** and consequently tetramic acid (**2**) is not highly enolized (it gives a negative ferric chloride test) but exists mainly in the 2,4-diketo form. The solid-state infrared spectrum shows absorptions at 3230 (NH stretch), 1696 (lactam C=O), 1670 (NH bend), and 1782 $cm^{-1}$ which is due to the C-4 (ketonic) carbonyl group. This band is also observed in the solution infrared spectrum, inferring that in the solid state the lactam group participates in hydrogen bonding. The ultraviolet spectrum shows a single absorption ($\lambda_{max}$ 260 nm) due to the enolate species **6** with the intensity being strongly pH dependent. This means, in aqueous solution, the ionized form **6** exists predominantly in equilibrium with the 2,4-diketo form **2b**, the enolic tautomer **2a** being absent (Figure 1).

Tetramic acids bearing acyl (**7**) or alkoxycarbonyl (**8**) substituents at the 3-position have similar acidity to the tetronic acids. The former have $pK_a$ values in the range 3.0–3.5[11,12] while the latter have values in the range 2.3–2.5.[3] Proton NMR spectra indicate the complete enolization of these systems although they are complicated by the presence of several tautomeric forms. The ultraviolet absorption spectra are very characteristic for **7** and similar systems,[12] with a red shift observed on conversion of the enol ($\lambda_{max}$ 220 and 277 nm) into the enolate form ($\lambda_{max}$ 240 and 279 nm). The tautomeric behavior of 3-acyltetramic acids has been explained using a similar mechanism to that which occurs in 2-acetylcyclopentane-1,3-diones (**9**)[13] and 3-acetyltetronic acids (**10**).[14,15] This involves two sets of rapidly interchanging internal tautomers {**11a** ⇌ **11b**} and {**11c** ⇌ **11d**}, where each set arises through proton transfer along the intramolecular hydrogen bond, together with two pairs of slowly interconverting external tautomers {**11a**, **11b**} ⇌ {**11c**, **11d**}, arising from the rotation of the acyl side chain (Figure 2). The internal tautomerization of these derivatives occurs too rapidly to be detected on the time scale of an NMR experiment; the external tautomerism, however, occurs at a rate which can be measured on the NMR time scale and this has provided an interesting insight into this dynamic equilibrium. The ratios of the external tautomers were determined by Steyn and Wessels[16,17] in a comprehensive analysis of the $^1H$ and $^{13}C$ NMR characteristics of 3-acyltetramic acids of type **12** and **13**. The observed chemical shifts and coupling constants represent the weighted population averages of the corresponding internal tautomers {**11a** ⇌ **11b**} and {**11c** ⇌ **11d**}.

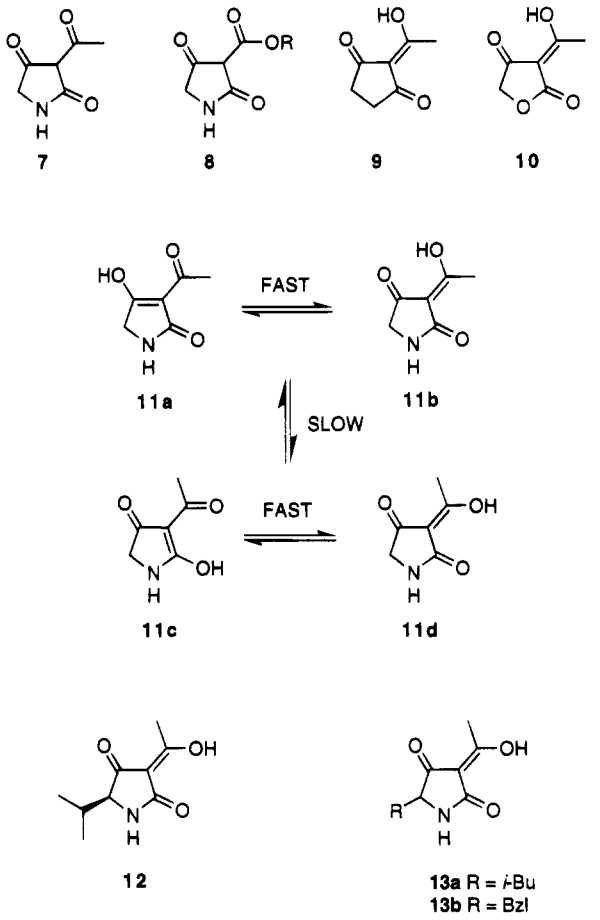
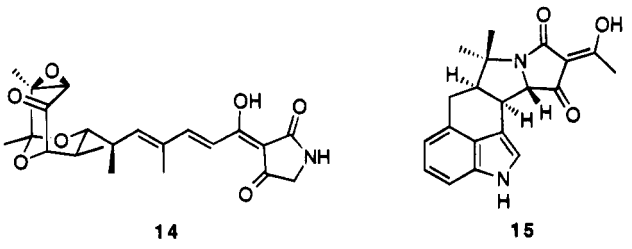



**Figure 2.**



14 15

**Figure 3.**

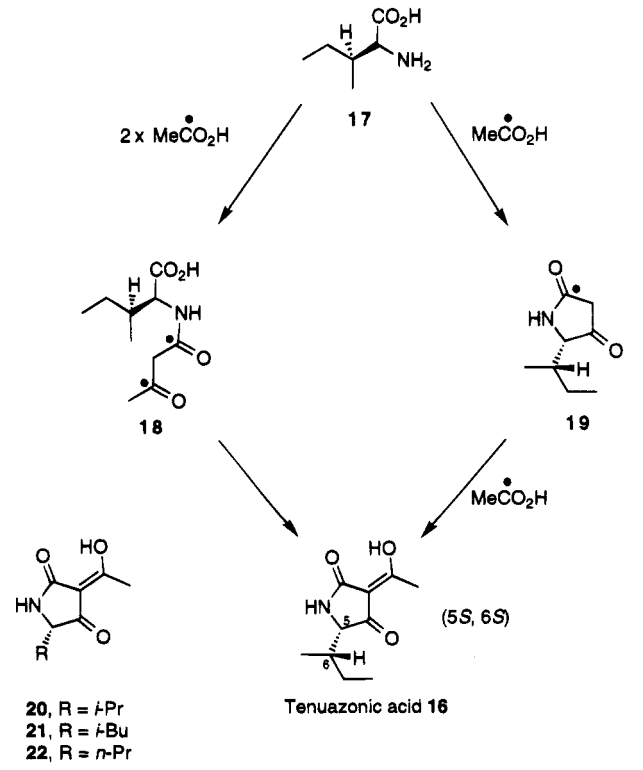
$^{13}C$ NMR spectroscopy proved to be more useful for the study of the tautomerization in tetramic acids[16,17] as the chemical shift of the $^{13}C$ nucleus depends on the hybridization of the carbon atom while being virtually unaffected by the anisotropy of neighboring functional groups. The carbon resonances were assigned using off-resonance proton-decoupled and single-frequency nuclear Overhauser effect (NOE) $^{13}C$ NMR spectra. The main tautomers were assigned with the help of some earlier work by Strothers and Lauterbur[18] which showed that enolic carbon atoms resonate at lower frequency than the corresponding keto carbons, and that hydrogen-bonded carbonyl carbon atoms resonate at higher frequency than the corresponding free carbonyl groups. The enolic forms **11b** and **11d** were deduced to be the main tautomers from the predominance of the lower frequency C-6 enolic carbon atom resonance. The predominance of the higher frequency C-2 hydrogen bonded carbonyl signal led to the conclusion that the *exo*-enol **11d** is the main tautomeric form. The approximate ratios of each of the tautomers was also calculated in the same study.[17] This gave the ratio of individual tautomers **11a**:**b**:**c**:**d** for simple 3-acyltetramic acids as 5:15:0:80 although this contradicted the results of Yamaguchi,[19] who (using electron density values from CNDO/2 calculations as an aid to interpretation of the $^{13}C$ NMR spectra) concluded that the main tautomers were **11a** and **11b**; the conclusions of Steyn and Wessels are supported by the X-ray crystallographic structure determination[17] of tetramic acid **12**, which was found to exist in the *exo*-enolic form **11d** (Figure 2). The same workers also studied[20] the tetramic acid antibiotic tirandamycin A (**14**)- and found it to exist predominantly as an *exo*-enol analogous to **11d**. Further evidence that **11d** is the principal tautomeric form of 3-acyltetramic acids is the X-ray crystal structure of α-cyclopiazonic acid (**15**). This shows[21] that the 3-acyltetramic acid subunit exists likewise in the *exo*-enolic form (Figure 3). Semiempirical SCF-MO methods (employing MNDO, AM1, and PM3 Hamiltonians) have been used to predict the most favorable tautomeric form.[22,23] These studies both concluded (from the calculated $\Delta H_f$ values) that **11d** is the thermodynamically most stable tautomer. A recent study of this equilibrium[24] showed (by $^{13}C$ NMR and X-ray crystallography) that when the ring nitrogen is acylated the major tautomer is **11a**. This difference was attributed to the possibility of hydrogen bonding with the C-4 carbonyl being increased as the nitrogen lone pair is no longer able to enhance the proton acceptor ability of the C-2 carbonyl. Throughout this review, for the sake of consistency, the tetramic acid rings are represented as derivatives of the *exo*-enol **11d**.

## III. Naturally Occurring Tetramic Acids

### A. Acyltetramic Acids

Pyrrolidine-2,4-diones bearing an acyl substituent at C-3 are the most commonly found tetramic acid derivatives in nature. Tenuazonic acid (**16**), the simplest compound of this type, was originally isolated by Stickings' group[25] from the culture filtrate of *Alternaria tenuis* auct. (strain nos. 430 and 628) and subsequently other species have also been found[26] to produce **16**. The structure of **16** was elucidated by the same group[12] who obtained L-isoleucine (**17**) after degradation of **16** by ozonolysis then acidic hydrolysis, thus establishing the absolute configuration as (5*S*,6*S*). Tenuazonic acid (**16**) exhibits[27] a low level of antibacterial activity and has an inhibitory effect[28] on several viruses (at high dose levels) including poliovirus MEF-1, ECHO-9, parainfluenza-3, vaccinia, and herpes simplex (HF). It also shows the ability[29] to inhibit human adenocarcinoma growing in the embryonated egg with the mode of action proposed[30] to involve the inhibition of amino acid incorporation into microsomal protein. Much interest has been focused[31-33] on tenuazonic acid (**16**) because of the broad spectrum of biological activity it displays but it has been of limited value due to its extreme toxicity. Biosynthetic studies[34] on **16** led to the isolation of radioactive *N*-acetoacetyl-L-isoleucine (**18**) from feeding experiments (using **17** and [1-$^{14}C$]-labeled acetate) and it was concluded[35,36] that, as none of the desacetyl species **19** was observed, the biosynthesis occurs via cyclization of **18** rather than by (C-3) acetylation of **19**. Feeding the appropriate microbes with L-valine, L-leucine,[37] or L-norvaline[26] results in production of the respective isopropyl (**20**), isobutyl (**21**), or *n*-propyl (**22**) tenuazonic acid analogues. These were found to have biological activity similar to, though less potent than, **16** itself (Scheme 1).

**Scheme 1**



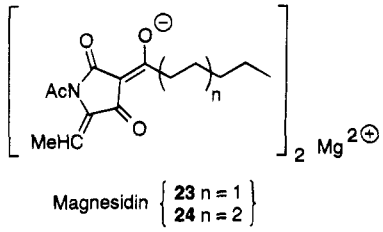



**Figure 4.**

Kohl and his colleagues isolated[38] the antibiotic magnesidin from *Pseudomonas magnesiorubra* nov. sp. (ATCC no. 21856) as a 1:1 mixture of the covalent magnesium chelates of the 3-hexanoyl (**23**) and 3-octanoyl (**24**) tetramic acid derivatives (Figure 4). In fact, since tenuazonic acid (**16**) has also been isolated[39] as a mixture of calcium and magnesium complexes, and is known readily to form[40] transition metal complexes (with $Cu^{II}$, $Ni^{II}$, and $Fe^{III}$) and previous isolation techniques[25] involve an acidification step, it can be hypothesized that the natural form of these compounds may well be as covalent metal chelates. The structures of **23** and **24** were determined[38] by degradation (deacylation gave hexanoic and octanoic acids respectively while ozonolysis afforded acetaldehyde) as well as ultraviolet, NMR, and mass spectroscopic evidence. Attempts were made to ascertain the configuration of the exocyclic ethylidene group using NOE experiments (on the *O*-methyl ethers of **23** and **24**); however, these were unsuccessful as no spatial interactions were observed between either the methoxy or *N*-acetyl groups and the vinylic proton of the ethylidene unit. Magnesidin inhibits various Gram-positive bacteria (MIC 2–7 mg $mL^{-1}$) and prevents the decay of foodstuffs caused by spore-generating organisms.[41]

The structurally interesting mycotoxin, α-cyclopiazonic acid (**15**), is produced by the fungus *Penicillium cyclopium* Westling; it was isolated by Holzapfel[42] who used proton NMR spectroscopy (of **15** and its degradation products) to assign the structure and relative stereochemistry. Recently the X-ray crystal structure of **15** has been obtained:[21] this confirmed the original assignment as well as proving the absolute configuration to be that shown (Figure 5). Investigation of the biosynthetic route[43–46] to **15** using $^{3}H$- and $^{14}C$-labeled L-tryptophan, mevalonic acid, and acetate showed that these are all precursors to β-cyclopiazonic acid (**25**) which then undergoes ring closure by way of a *syn* addition to form **15**.[47] The imino derivative **26** can also be obtained[43] from the same culture but it is unclear if this is an enzymic metabolite or arises through aminolysis of **15** (a known chemical process) due to the presence of ammonia in the fungus. α-Cyclopiazonic acid (**15**) possesses disparate biological effects; it is very toxic ($LD_{50}$ 2–6 mg $kg^{-1}$) which is of some concern as the producing organisms are found[48,49] in numerous agricultural commodities (*e.g.* cheeses, grain, and peanuts). Neurological action has been reported, the presence of **15** causing depression and immobility in cattle and humans because the levels of neurotransmitters (such as dopamine and 5-hydroxyindoleacetic acid) are drastically altered.[50] The cytotoxic effects of patulin (*i.e.* lipid peroxidation and abrupt calcium

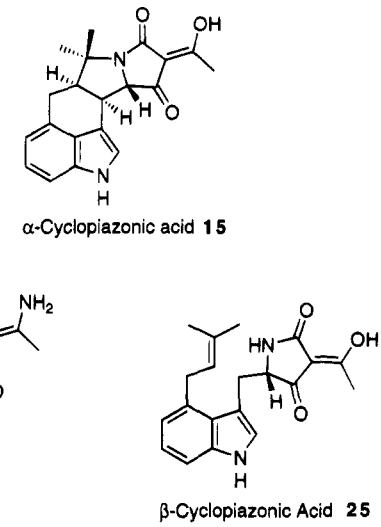
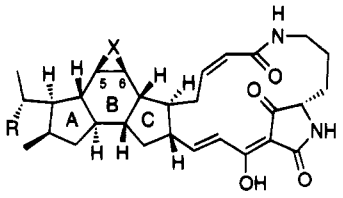


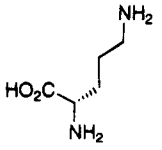

**Figure 5.**

influx) are suppressed by **15** which can act as an antioxidant.[51] α-Cyclopiazonic acid (**15**) is a potent inhibitor[52,53] of calcium uptake and $Ca^{2+}$ATP-ase activity in sarco- and endoplasmic reticulum—a vast amount of work is being published in the biological literature on this topic.

Ikarugamycin (**27**) was isolated[54] from the culture broth of *Streptomyces phaeochromogenes* var. ikaruganensis Sakai and shows strong specific antiprotozoal, *in vitro* antiamoebic, as well as some antibiotic activity (against Gram-positive bacteria). The use of **27** as an antiulcer agent has also been noted.[55] The structure and relative configuration of **27** were deduced by Ito and Hirata who carried out an exquisite structure proof,[11,56–58] utilizing NMR spectroscopy to identify the products of oxidative (chromic acid, ozone, hydrogen peroxide, and permanganate) degradation. They also prepared several cyclopentane subunits, derived from the carbocyclic portion of the molecule, as an aid to interpretation of the spectra from this region of the natural product.[59] Acidic hydrolysis gave L-ornithine (**29**) and the chromophore of the fully hydrogenated system was shown to be the same as that in tenuazonic acid (**16**). Ikarugamycin (**27**) has a very unusual molecular architecture; an enoyltetramic acid which is incorporated into a (16-membered) macrocyclic lactam and the *trans,anti,cis*-decahydro-*as*-indacene skeleton (rings A, B, and C). A strong tendency to encapsulate the sodium ion, almost irreversibly, was noted during the purification of synthetic material—so much so that contact with aqueous solutions containing $Na^{+}$ or chromatography on silica must be avoided.[60] In fact the related antifungal compound capsimycin (antibiotic N-461) (**28**), isolated from a *Streptomyces* strain,[61,62] is the only other known example containing both these features—however an antibiotic compound, catacandin A, that contains as part of its structure a similar macrocyclic lactam unit, has been isolated (from a fermentation broth of the bacterium *Lysobacter gummosus*)[63] but the full structure has not been reported in the literature. The absolute stereochemistry of **27** and **28** were assigned through determination of the respective X-ray crystal structures—which concomitantly showed that **28**



Ikarugamycin **27**; R = H, X = bond
Capsimycin **28**; R = OMe, X = O



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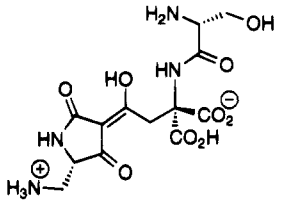


Malonomycin **30**

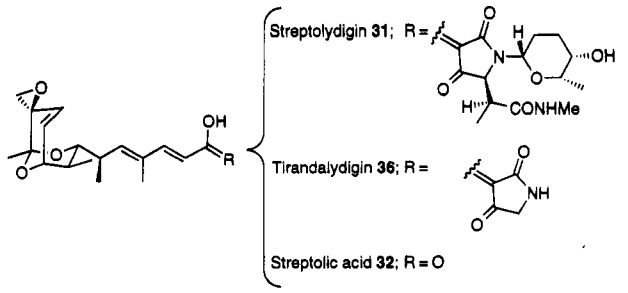
**Figure 6.**

differs from **27** only by the methoxy and 5,6-epoxy moieties (Figure 6).[64]

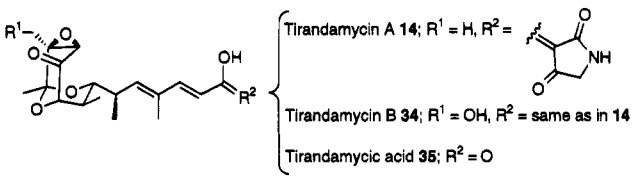
The antiprotozoal compound malonomycin (previously known as K-16) (**30**) was isolated from *Streptomyces rimosus* var. paromomycinus and has particularly potent activity against trypanosomes.[65] The molecular assemblage was deciphered by van der Baan and co-workers;[66,67] they were able to identify the unique aminomalonic acid unit (that forms part of the acyl side chain) as well as L-serine and racemic aspartic acid from the degradation of **30**. Monodecarboxylation of the aminomalonic acid function (by brief reflux in water) led to complete loss of biological activity.[66] Biosynthetic studies indicate that the aminomethyl substituent (at C-5) in **30** originates from L-2,3-diaminopropionic acid (Figure 6).[68]

## B. Dienoyltetramic Acids

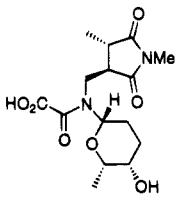
The first of the dienoyltetramic acids, that is to say those bearing a 1-oxopentadienyl substituent at C-3 in the ring, to be isolated was streptolydigin (**31**).[69] It was obtained from the culture filtrates of the actinomycete *Streptomyces lydicus*, and it is a potent inhibitor of terminal DNA transferase and bacterial RNA polymerase enzymes in addition to showing strong antibiotic activity against Gram-positive organisms (with the exception of micrococci).[70] Work on structure–activity relationships revealed that the 3-dienoyl unit of streptolydigin (**31**) is crucial for activity while the presence of 1- and 5-substituents, although not essential, does improve potency.[71] Elucidation of the structural makeup of **31** was acheived by Rinehart's group who used an elegant combination of chemical and spectroscopic techniques.[72–74] Detailed analysis of the proton NMR, UV, and mass spectra of the oxidative degradation products streptolic acid (**32**)[72] (from periodate treatment) and ydiginic acid (**33**)[73] (from ozonolysis), in conjunction with comparison of data from synthesized model subunits, confirmed the identities of these significant derivatives of streptolydigin (**31**). The chromophores of **31** and its fully hydrogenated (octahydro) derivative indicated the presence of a dienoyltetramic acid[74] and



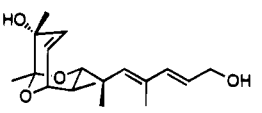
Streptolydigin **31**; R =
Tirandalydigin **36**; R =
Streptolic acid **32**; R = O



Tirandamycin A **14**; $R^1$ = H, $R^2$ =
Tirandamycin B **34**; $R^1$ = OH, $R^2$ = same as in **14**
Tirandamycic acid **35**; $R^2$ = O



Ydiginic acid **33**



**37**

**Figure 7.**

together with the degradation experiments led to the deduction that **31** was the correct molecular framework. The sugar component was later identified as 2,3,6-trideoxy-L-*threo*-aldohexose by comparison of authentic and synthetic material[75] which partially determined the absolute configuration of **31** (Figure 7). Feeding studies (using $^{14}C$-labeled compounds) indicate that acetate, propionate, D-glucose, and (±)-glutamic acid are all incorporated into **31**.[76]

A closely related substance tirandamycin A (**14**) was isolated from *Streptomyces tirandis*.[77] The biological activity was comparable to that of **31**,[78,79] although it is a less potent inhibitor of terminal DNA transferase.[71] The mode of action likewise involves the inhibition of chain initiation as well as elongation during the transcriptional process.[80,81] The structure was tentatively assigned through study and comparison of the proton NMR spectra with those of streptolic acid (**32**). An X-ray crystal structure was obtained for the *p*-bromophenacyl ester of tirandamycic acid (**35**) (obtained by periodate oxidation of **14** and then esterification) and this enabled the absolute configuration to be ascertained.[82] When, in the same investigation, streptolic acid (**32**) was reduced (with lithium aluminum hydride) to the allylic alcohol **37**, which was found to be identical to the product of two-stage reduction (hydrazine in acetic acid followed by lithium aluminum hydride) of tirandamycic acid **35**, the absolute configuration of **31** was thus explicated. Tirandamycin B (**34**), isolated from *Streptomyces flaveolus*, exhibited an analogous spectrum of biological activity to **14**.[83] Structurally it only differs from **14** by the presence of a hydroxyl group on the methyl function adjacent to the oxirane moiety. Comparison of the $^1H$ and $^{13}C$ NMR spectra with those of **14** proved their absolute configurations to be identical (Figure 7).

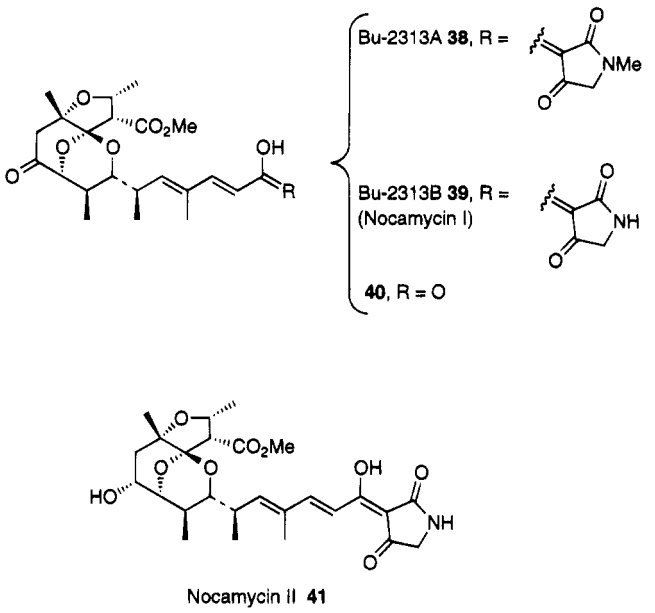



**Figure 8.**

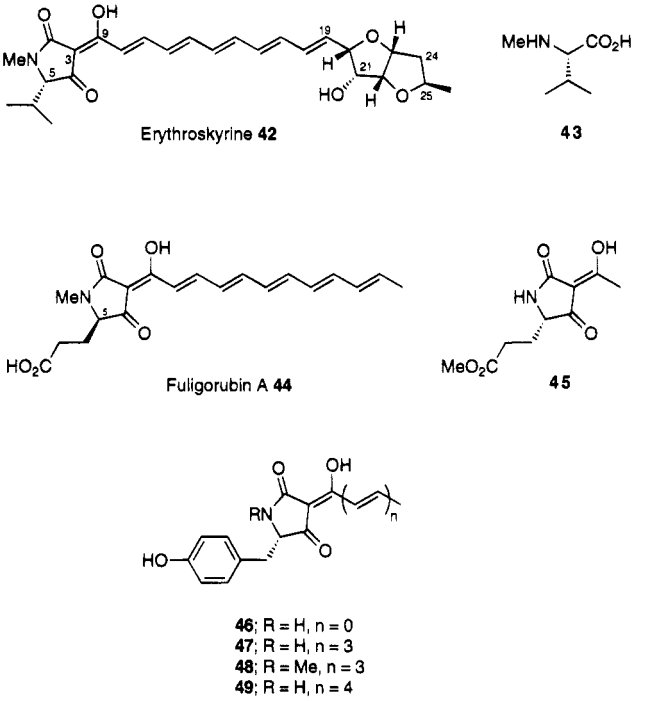



**Figure 9.**

A structural hybrid of **14** and **31** namely, tirandalydigin (**36**), was sequestered from the fermentation beers of *Streptomyces* sp. AB-1006A-9;[84] it showed an antimicrobial spectrum comparable with that of the other members of this series.[85] Structural assignment was carried out using two-dimensional NMR spectroscopic studies on **36** and comparing these to spectra of the related known systems.[84]

A family of metabolites closely related to **14**, **31**, and **36** was reported in the late 1970s. Japanese workers described the isolation[86,87] of two compounds Bu-2313A (**38**) and Bu-2313B (**39**), from an unidentified oligosporic actinomycete strain (no. E864-861). Both **38** and **39** are broad-spectrum antibiotics,[87] effective against Gram-positive and Gram-negative anaerobic bacteria as well as some aerobic bacteria such as *Streptococci* (with **39** being nearly twice as potent as **38**). Comprehensive analysis of the proton and carbon NMR spectra of **38** and **39** allowed elucidation of their respective structures—the only difference being the *N*-methyl group in **38**.[88] The absolute configuration was obtained from the X-ray crystal structure of the *p*-bromophenacyl ester of the acid **40**, which is a derivative obtained upon periodate oxidation of **38** or **39** (Figure 8).[86]

A Russian group concurrently reported two antibiotic compounds—nocamycins I and II.[89] The original structural assignment[90] for nocamycin I (previously known as nocamycin) was incorrect and this was revised to **39** (that is, the same as Bu-2313B).[91] Nocamycin II (**41**) was shown to be virtually identical to **39** (except for the carbonyl group) by spectroscopic methods.[91] The biological activity exhibited by **41** is, not surprisingly, identical to that reported for **39**;[90] indeed it has been postulated that a common biosynthetic pathway to all the dienoyltetramic acids may well exist (Figure 8).[84]

## C. Polyenoyltetramic Acids

The first of the so-called polyenoyltetramic acids to be obtained was erythroskyrine (**42**)—the principal pigment of *Penicillium islandicum* Sopp. which also demonstrated antibiotic action against some *Staphylococcus* species.[92] The structure was deduced by means of degradation studies[93] (acidic hydrolysis, hydrogenation and ozonolysis) with NMR spectroscopy employed to identify the structural subunits thus obtained. The only stereochemical assignment made was (5*S*) as L-(+)-*N*-methylvaline (**43**) was obtained during the degradation of **42** with ozone. Beutler and co-workers assigned the relative and absolute configuration[94] through detailed NMR experiments (using COSY, HETCOR, and INAPT pulse trains) on **42** and its two esters (of the C-21 hydroxyl group) derived from (*R*)- and (*S*)- mandelic acid (Figure 9). Feeding studies,[95] using sodium acetate and diethyl malonate both of which were labeled with $^{14}C$ at C-1 and C-2, showed that C-9 to C-24 are derived from malonate while C-25 and C-26 are acetate derived. The uptake of $^{14}C$-carboxyl-labeled L-valine indicated the origins of the tetramic acid ring. Attempts to determine the biosynthetic origin of the *N*-methyl group as well as C-2 and C-3 (in the tetramic acid) were inconclusive.

The yellow colored plasmodia of certain slime molds contain polyenoyltetramic acids. Steglich and his colleagues obtained fuligorubin A (**44**)[96] (from *Fuligo septica*) and found a family of compounds (derived from L-tyrosine) **46**–**49** in the slime mold *Leocarpus fragilis*.[97] Whether compounds of this sort play any biological role other than as colorants (*e.g.* photoreceptors or chelating agents for metal ions) remains to be investigated. Two-dimensional NMR (H–H COSY) spectroscopy was used to determine the structural identity of these compounds while a comparative study of the chiroptic properties of **45** and completely hydrogenated **44** (*i.e.* decahydrofuligorubin A **193**) led to the conclusion that the absolute configuration is 5*R*, the opposite to that found in most other naturally occurring tetramic acids (Figure 9).[96]

Oleficin (**50**), the first in a sequence of cognate polyenoyltetramic acid antibiotics, was separated

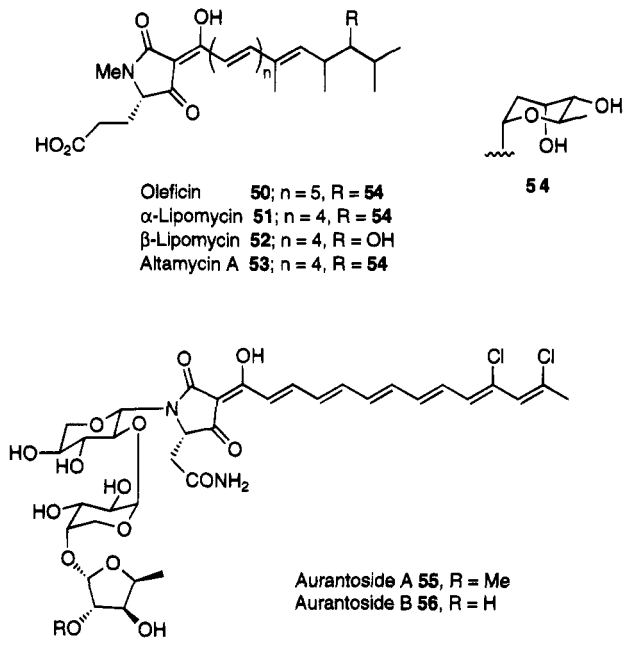



**Figure 10.**

from a strain of *Streptomyces* (no. A-461) related to *Streptomyces parvulus* as a dark red powder.[98] Shortly afterward α-lipomycin (**51**) was reported as a metabolite of *Streptomyces aureofaciens*.[99] Both compounds exhibit strong inhibitory activity against Gram-positive bacteria while being inactive against fungi.[98,99] Oleficin (**50**) also functions as an ionophore for $Mg^{2+}$ and $Ca^{2+}$ ions in isolated rat liver mitochondria,[100] and this can be attributed to the ability of the β-tricarbonyl moiety present in the acylated tetramic acid unit to form complexes with various metal ions. Indeed the complexation of metal ions is known for other 3-acyltetramic acid systems.[101,102] The structure of **51** was obtained[103] (before that of **50**) through spectroscopic analysis of the chemical degradation (hydrogenation, hydrolysis, and ozonolysis) products. This indicated the presence of acyltetramic acid, *all-trans*-tetradecapentaene units, and a β-anomeric linkage. The carbohydrate moiety was identified as the known desoxy sugar D-digitoxose (**54**) through comparison with authentic material.[104] L-*N*-Methylglutamic acid was obtained via ozonolysis and then acidic hydrolysis of the aglycon β-lipomycin (**52**); thus the configuration (5*S*) was assigned, however, the configuration of the remaining two stereogenic centers remains unknown as any asymmetry is lost upon oxidative degradation due to loss of carbon dioxide from the ensuing β-hydroxy acid. The structure of oleficin (**50**) was deduced[105] in a similar manner—the initial report being erroneous,[106] in that it was thought one of the methyl groups of the polyene side chain was part of the C-5 substituent of the tetramic acid, and again the two stereogenic centers at the end of the hexaene chain are of indeterminate configuration. A third member of this group of antibiotics, altamycin A (**53**), was acquired by Shenin from an actinomycete strain (LIA-0788).[107] The antibiotic spectrum is, as might be expected, in keeping with that of **50** and **51**.[108] Once more a similar procedure was employed to ascertain the structure[108] of **53**—only the length of the polyene chain being different (four double bonds). Shenin was likewise unable to assign the configuration of the asymmetric centers at the terminus of the olefinic chain—the same problems of amorphous parent compound and loss of stereochemical integrity (through decarboxylation occurring during degradation) being encountered (Figure 10).

## D. Other Tetramic Acid Natural Products

Marine sponge *Theonella* sp. contains the orange, chlorine-containing cytotoxic pigments aurantosides A (**55**) and B (**56**).[109] These were obtained by alcoholic extraction and proved to be strongly active against P388 and L1210 leukemic cell strains. The structures of **55** and **56** were elucidated through mass spectroscopy (FAB) and various correlation NMR (COSY, NOESY, HMBC, and HMQC) techniques—denoting the incidence of dichlorohexaenoyltetramic acid and trisaccharide portions. Absolute stereochemistry in the carbohydrate portion was determined as D-xylo-D-arabino-D-arabino by GC analysis of the hydrolyzed sugar while the (4*S*) configuration of the tetramic acid was ascertained because L-aspartic acid (identified by HPLC) was recovered from degradation (periodate/permanganate oxidation with subsequent hydrolysis) of **55** or **56** (Figure 10).

Equisetin (**57**), the principal toxic metabolite of the fungus *Fusarium equiseti*, was isolated by chromatography of a chloroform extract from the culture broth.[110-112] Such fungal species are believed to be leukemogenic as well as causing immunosuppression in guinea pigs.[113] Electronic and mass spectra revealed the presence of two domains, a tetramic acid and a bicyclic hydrocarbon, but unfortunately the $^1H$ NMR spectrum of **57** was not amenable to detailed analysis due to overcomplication by an equilibrium mixture of tautomers.[112] In order to circumvent this difficulty the same group prepared a phenylboronate ester derivative **58** (by reaction of **57** with phenylboronic acid) so effectively "freezing out" a single tautomer. This meant that the $^1H$ NMR spectra (COSY, NOE) of **58** could be used to assign the structure of **57** (Figure 11). The absolute stereochemistry of the tetramic acid portion was determined as 5′*S* by comparative analysis of the CD curves with those for tenuazonic acid (**16**). Once the configuration at C-5′ was established this was used to assign the configuration at C-2 in the bicyclic ring by relay of the asymmetry in the heterocyclic portion of **58** using NOE experiments and molecular mechanics calculations to ascertain the minimum-energy conformation.[112] The original assignments were concurrently proved to be correct through total synthesis of **57**.[114]

Lydicamycin (**59**) was the next tetramic acid compound isolated to possess an octahydronaphthalene skeleton.[115] It was obtained from the culture broth of an actinomycete *Streptomyces lydicus* and was found to be active against Gram-positive bacteria such as *Bacillus subtilis* and *Staphylococcus aureus* at reasonable concentration levels (MIC 1.5–6.2 μg $mL^{-1}$). The structure and relative stereochemistry of the bicyclic portion were worked out from two-dimensional NMR and high-resolution mass spectra; the stereochemistry of the polyol side chain and the

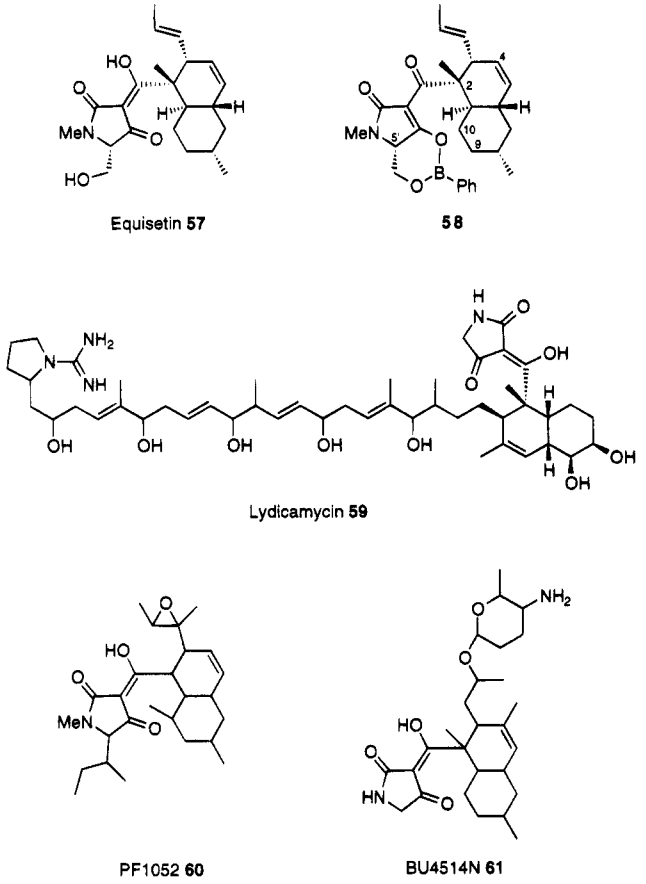



**Figure 11.**

overall absolute configuration remain unknown. Thus it was found that the bicyclic system is *cis* fused, unlike that of **57**, which permits the tetramic acid and polyol side chain to adopt an *anti* relationship and hence lie far apart in space and consequently avoid severe steric interactions (Figure 11).

PF1052 (**60**) an antibiotic compound with a very similar structure to **57** was the subject of a Japanese patent application.[116] It was separated from the culture of the microbe *Phoma* sp. PF1052 and shows good activity (MIC < 1 $\mu$g mL$^{-1}$) against *Streptococcus*, *Staphylococcus*, *Bacteroides*, and *Clostridium* bacteria. The structure of **60** was elucidated by spectroscopic means (NMR) although no information on the stereochemistry was presented; it may, of course, be likely the absolute configuration is the same as that of equisetin (**57**) as there is much homogeneity between the two molecules (Figure 11).

Another related compound, known as BU-4514N (**61**), was reported very recently.[117,118] Extracted from the fermentation broth of *Microtetraspora* sp. T689-92, it shows activity against Gram-positive bacteria as well as neuritogenetic behavior—it being significantly effective as a nerve growth factor mimic. The skeletal structure of **61** was derived from NMR data but no information on relative or absolute stereochemistry was presented (Figure 11).

Research workers at the Sankyo Co. Ltd. obtained apiodionen (**62**) from the acid-treated fermentation broth of *Apiosordaria effusa* SANK 15803.[119] Interestingly, **62** was not obtained if acid treatment of the broth prior to extraction was omitted suggesting that the organism actually produces an unidentified pre-

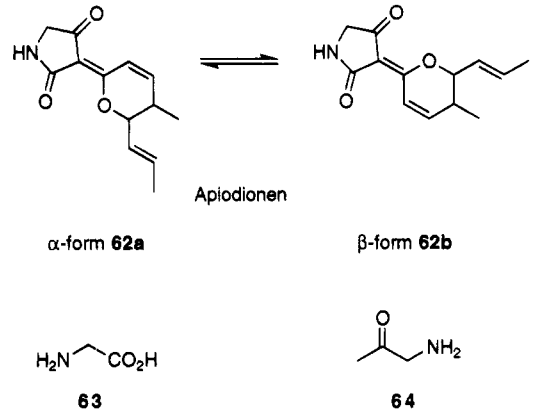


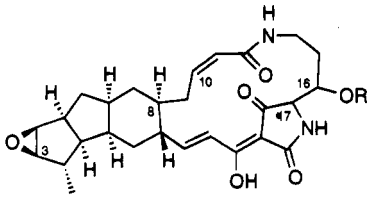

**Figure 12.**

cursor which cyclizes to give **62** under acidic conditions. Determination of the structural framework of **62** was achieved through identification of the hydrolytic degradation products **63** and **64** as well as NMR information. According to the NMR spectral evidence apiodionen (**62**) exists as an equilibrium mixture of $\alpha$- and $\beta$-forms (**62a** and **62b**) but the question of stereochemistry has yet to be tackled (Figure 12).[119]

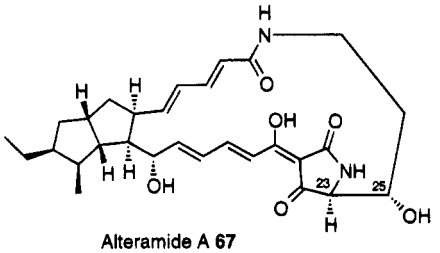
Lately a new family of tetramic acid-containing macrolactams has been detected in various marine sponges and in terms of this lactam unit they bear some resemblance to ikarugamycin (**27**) and capsimycin (**28**) (although these compounds are microbially derived). The first member of the group, discodermide (**65**), was obtained from the Caribbean sponge *Discodermia dissoluta* and was shown to inhibit *in vitro* proliferation of P388 murine leukemia cells in addition to the growth of *Candida* fungi.[120] The skeletal architecture and relative stereochemistry of the tricyclic hydrocarbon component were ascertained from extensive NMR experiments (COSY and NOE difference spectra) on **65** and its O-16 acetate counterpart **66**, however stereochemistry at C-16 and C-17 remains uncertain (Figure 13).

The next compound in this series to be reported was alteramide A (**67**), obtained from the bacterium *Alteromonas* sp. which itself was collected from the marine sponge *Halichondria okadai*.[121] The molecular composition was reasoned from H−H COSY and heteronuclear multiple-bond correlation (HMBC) NMR experiments while the relative configuration of the bicyclo[3.3.0]octane moiety was assigned from the NOESY spectrum of **68** (derived from the ozonolytic degradation of **67** employing a borohydride workup followed by acetylation). When an oxidative workup ($H_2O_2$/$HCO_2H$) is used for the ozonolysis of **67** the breakdown product is L-$\beta$-hydroxyornithine (**69**) hence establishing the configurations of both C-23 and C-25 as (*S*).[121] Perhaps not unexpectedly, alteramide A (**67**) undergoes an (allowed) intramolecular photochemical [4 + 4] cycloaddition, in sunlight, to afford the cyclooctadiene **70** which was shown to have a *cis* arrangement about both of the new carbon−carbon bonds (Figure 13).

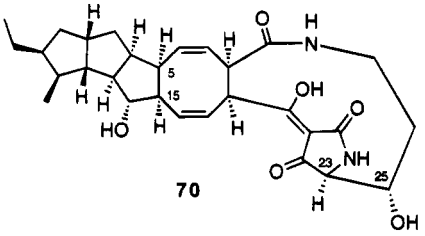
Cylindramide (**71**), the most recent metabolite in this class, was described by a Japanese group in 1993.[122] This substance exhibited cytotoxic action against melanoma cells with an $IC_{50}$ of 0.8 $\mu$g mL$^{-1}$. Once again the structure and relative configuration



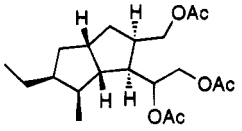
Discodermide **65**, R = H
**66**, R = $COCH_3$



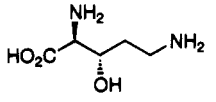
Alteramide A **67**



**70**

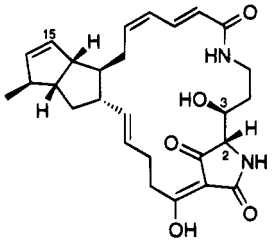


**68**



**69**

**Figure 13.**



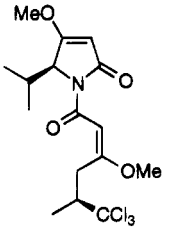
Cylindramide **71**

**Figure 14.**

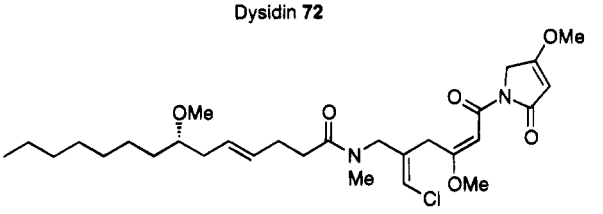
could be obtained from high-resolution two-dimensional NMR experiments. The absolute configuration is undetermined except at C-2 and C-3 which were both designated as (*S*) because L-$\beta$-hydroxyornithine (**69**) was obtained after oxidative ozonolysis of cylindramide (**71**) (Figure 14).

## E. *N*-Acyl-4-methoxy-3-pyrrolin-2-ones

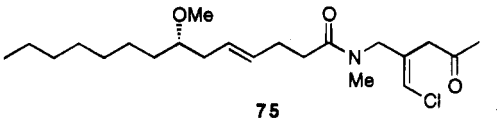
The final class of natural products to contain a tetramic acid component are the *N*-acyl-4-methoxy-3-pyrrolin-2-ones, in other words the 4-*O*-methyl ethers of *N*-acylated tetramic acids. The first metabolite of this type to be discovered was dysidin (**72**), a chlorine containing secondary metabolite of the Indo-Pacific sponge *Dysidea herbacea*.[123] The structure **72** was assigned from X-ray diffraction studies



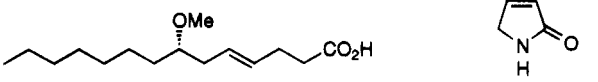
Dysidin **72**



Malingamide A **73**



**75**



*E*-(7*S*)-7-Methoxytetradec-4-enoic acid **76**

**74**

**Figure 15.**

which afforded the crystal structure; the absolute configuration was consequently revealed as (*S*) at both stereogenic centers (Figure 15).

Malingamide A (**73**), a more complex chlorine-containing compound, was isolated from the marine cyanophyte *Lyngbya majuscula* and as in the case of **72** no biological activity has been reported.[124] The structure was derived by degradative and spectral means. Alkaline hydrolysis of **73** produced tetramic acid methyl ether **74** while mild acidic hydrolysis gave the $\beta$-ketoalkenyl chloride **75**. NOE experiments were then used to work out the relative spatial arrangement of the structure and the absolute configuration of **73** was found to be (*S*) by comparison with the known (*E*,7*S*)-7-methoxytetradec-4-enoic acid (**76**) (Figure 15).

The same workers subsequently isolated a family of seven closely related nontoxic compounds from the same blue-green algae.[125,126] They all lacked the fatty acid side chain and chlorine atom of malingamide A (**73**) and were termed the pukeleimides (A, B, C, D, E, F, and G). Pukeleimide C (**77**) was crystallized, and an X-ray structure was obtained.[125] It is a largely planar molecule with the hydroxyl and methoxymethyl groups above and below the plane. Intriguingly it is a racemic compound. The other pukeleimides A (**78**), B (**79**), D (**80**), E (**81**), F (**82**), and G (**83**) were separated chromatographically then identified using NMR spectroscopy, although the stereochemistry of **80** has not been determined (Figure 16).[126]

Althiomycin (**84**) was isolated[127] from *Streptomyces althioticus* and has been the subject of attention for

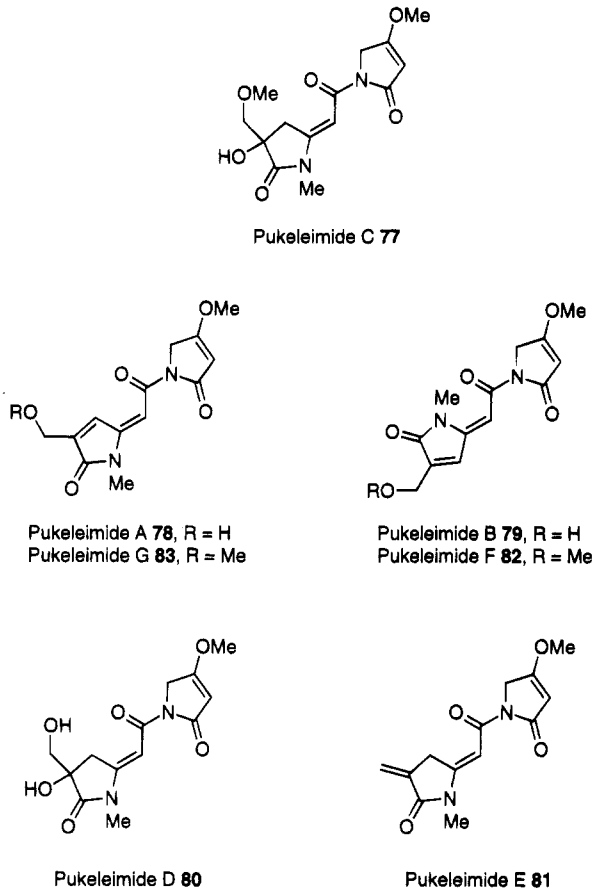



**Figure 16.**

several groups. Althiomycin (**84**) exhibits a broad spectrum of antibacterial activity, with low toxicity, against both Gram-positive and Gram-negative microorganisms through inhibition of protein synthesis.[128] Structural assignment was achieved by a combination of methods: the geometric configuration of the aldoxime was deduced to be (*E*) as this is the arrangement found[129] in the X-ray crystal structure of the methanolysis product **85**, and this was later confirmed by partial synthesis and an NOE study of the thiazole portion.[130] The absolute configuration in the thiazoline ring was proven to be (*S*) from crystallographic data;[131] however, the configuration of the center bearing the hydroxymethyl group is still unknown because althiomycin (**84**) is always isolated as a mixture of diastereoisomers containing both (*R*) and (*S*) arrangements about this stereogenic center. It is still unclear whether the natural material is a mixture or if racemization occurs during the isolation procedure (Figure 17).

One more peptidyl 4-methoxy-3-pyrrolin-2-one derivative has been obtained from the shell-less Western Indian Ocean mollusk *Dolabella auricularia* (1600 kg of mollusk yielded 6.2 mg!).[132] It has been named dolastatin 15 (**86**) and it is a potent cytostatic agent particularly against P388 leukemia cells. Originally the structure was derived by high-field two-dimensional NMR spectroscopy (COSY and HMBC) which gave the sequence of amino acid residues and identified the novel dolapyrrolidone (**87**) unit—a derivative of phenylalanine. Total synthesis of **86** using components possessing only the (*S*) configuration gave material that was identical with the natural

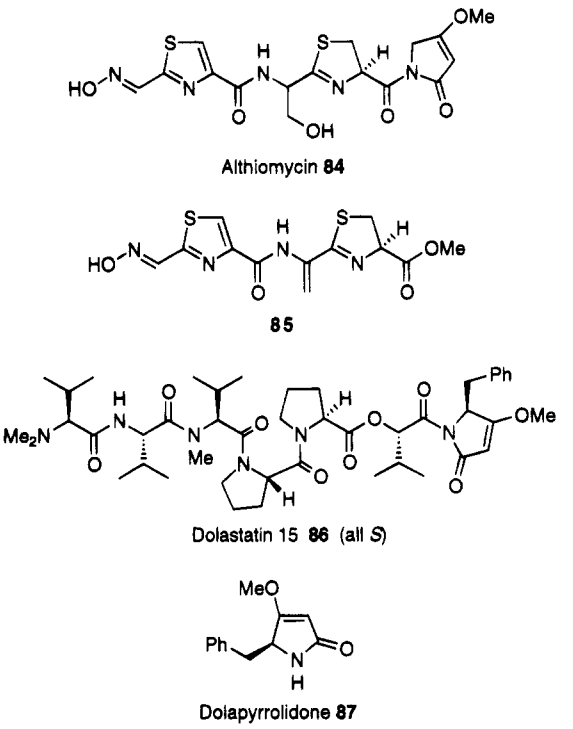



**Figure 17.**

**86**, so, from this, the *all*-(*S*) absolute configuration can be inferred (Figure 17).[133]

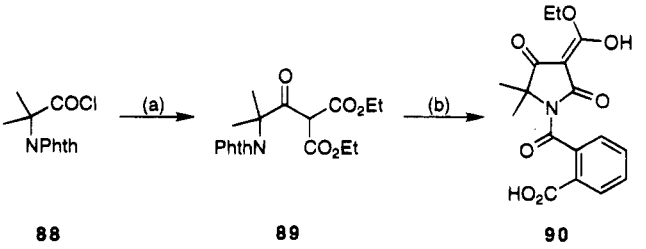
## *IV. Synthetic Routes to Tetramic Acid Natural Products*

### A. Racemic Syntheses

#### *1. Ring Closure by C–N Bond Formation*

Gabriel achieved the first reliable synthesis of a tetramic acid derivative in 1914.[134,135] Reaction of phthalimidoisobutyryl chloride (**88**) with diethyl sodiomalonate gave **89**, which on treatment with concentrated sulfuric acid cyclized to the 3-ethoxycarbonyl tetramic acid **90** (Scheme 2).

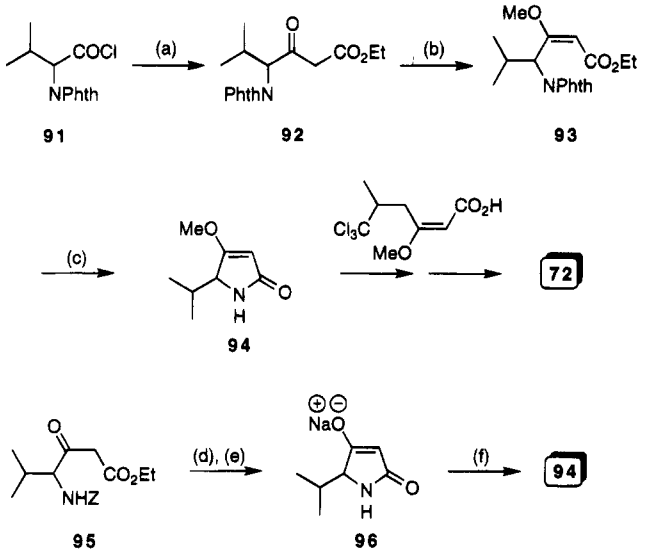
**Scheme 2**




(a) Diethyl sodiomalonate; (b) conc. $H_2SO_4$

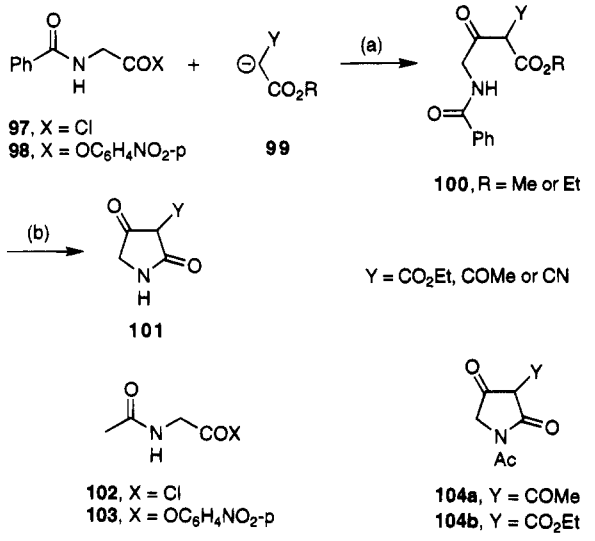
Similar methodology was applied to the total synthesis of dysidin (**72**).[136] The acid chloride of (±)-*N*-phthaloylvaline (**91**) was homologated to the keto ester **92** by reaction with the dilithium dianion of monoethyl malonate. *O*-Methylation of **92** was carried out with some difficulty (using potassium hydride and methyl fluorosulfonate) and the resultant enol ether **93** was treated with hydrazine to give the 4-*O*-methyltetramic acid **94**, which was then elaborated to dysidin (**72**) by *N*-acylation (Scheme 3). In an alternative preparation of dysidin (**72**) the prob-

**Scheme 3**



(a) Ethyl dilithiomalonate; (b) KH, $MeOSO_2F$; (c) hydrazine; (d) $H_2$, Pd-C; (e) $NaOC[Me]_2Et$; (f) $[MeO]_2SO_2$

**Scheme 4**

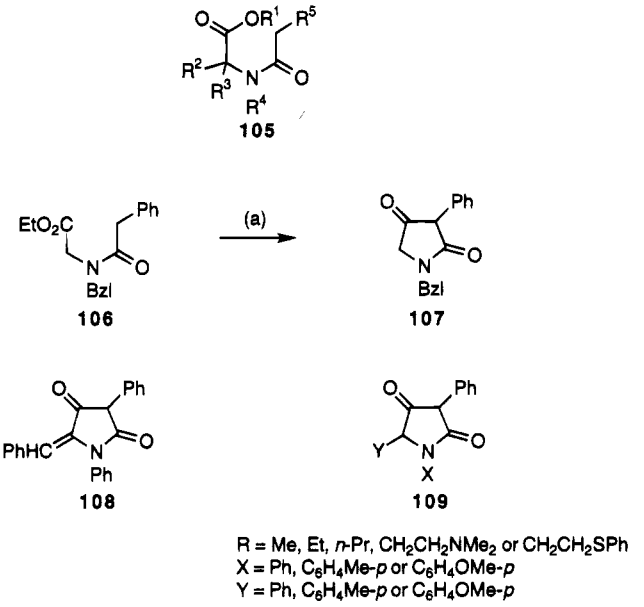


(a) *t*-BuOK [2 equiv.]; (b) NaOR

lem of difficult *O*-methylation at the β-keto ester stage was avoided by performing the methylation after ring closure had been accomplished. The removal of the urethane protecting group of valine derivative **95** was accompanied by cyclization to the sodium salt **96** (in the presence of sodium *tert*-pentyl oxide) which was then methylated using dimethyl sulfate to produce **94**.

The versatility of hippuric acid derivatives **97** and **98** as building blocks for the synthesis of 3-substituted tetramic acids has been demonstrated by research from a Greek laboratory.[137] Reaction of **97** or **98** with the anion of an active methylene compound **99** gave the corresponding (benzoylamino)-acetyl derivative **100** in reasonable yield. Cyclization of **100** was then performed using excess sodium alkoxide and was observed to proceed with simultaneous debenzoylation to result in formation of the corresponding 3-substituted tetramic acid **101**. The same group found that the aceturic acid derivatives

**Scheme 5**



(a) NaOEt

**102** and **103** also furnish 3-substituted tetramic acids **101** under analogous conditions, however reaction times are much shorter and the yields better.[138] The mechanism is believed to involve a two-step cyclization-deacetylation process as the *N*-acetyltetramic acids **104a,b** were also isolated and could be easily deacetylated in the presence of acid (Scheme 4).[138]

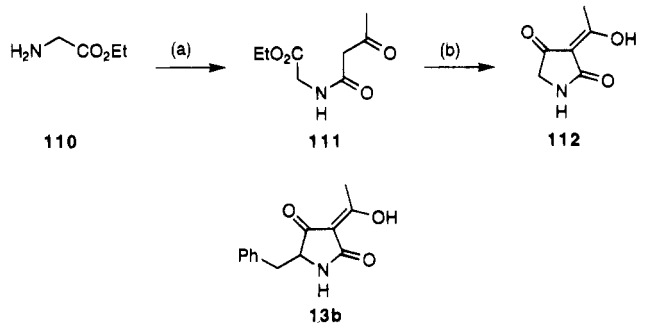
### *2. Formation of Tetramic Acids by Dieckmann Cyclization*

The so-called Dieckmann cyclization (a base-induced intramolecular Claisen condensation) of *N*-acyl-α-amino esters of the type **105**, offers a convenient route to tetramic acid rings which is potentially very versatile in terms of the possible substitution patterns available, and indeed this approach has seen some use. The formation of 1-benzyl-3-phenyltetramic acid **107** by treatment of **106** with sodium methoxide was reported[139] in 1950 and shortly afterward the benzylidenetetramic acid **108** was prepared in a cognate manner.[140] A series of 3-alkyl-1,5-diaryltetramic acids **109** with analgesic and antiinflammatory activity has likewise been prepared using this method (Scheme 5).[141]

### *3. 3-Acyltetramic Acids via Lacey's Modified Dieckmann Cyclization*

In 1954, Lacey reported a convenient two-step synthesis of 3-acyltetramic acids from readily available α-amino esters. This strategy has since become widely adopted in the construction of the tetramic acid ring and is undoubtedly the most common method employed in their preparation. The original method[142] involved condensation of an α-amino ester **110** with diketene to give the *N*-acetoacetyl-α-amino ester **111**, which cyclized to the 3-acyltetramic acid **112** upon exposure to sodium ethoxide (Scheme 6). This route has been used by other groups to prepare (a) tetramic acid (**2**) itself,[143] (b) the 4-methoxypyrrolin-2-one subunit **74** of althiomycin (**84**),[144–146] and (c) tenuazonic acid analogues (including **112** and **13b**),[101,147,148] from their respective *N*-acetoacetyl-α-amino ester precursors.

**Scheme 6**



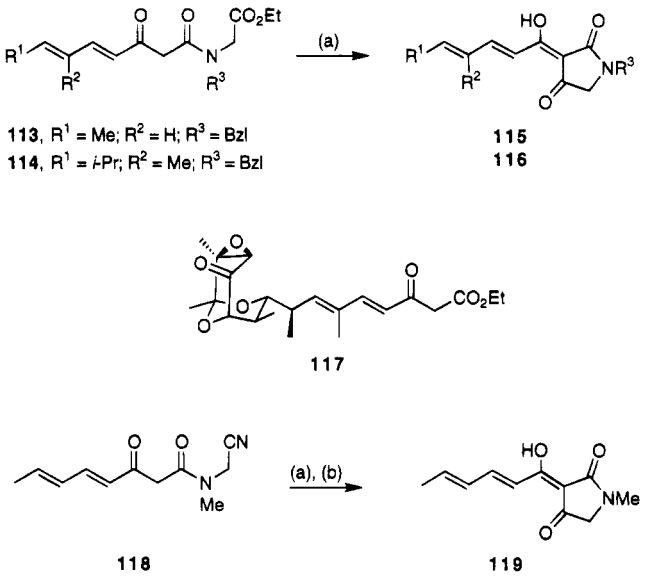
(a) Diketene; (b) NaOMe

This method is extremely flexible and can be used to a prepare 3-acyltetramic acids with a diversity of substituents, provided that the relevant *N*-acetoacetyl-α-amino ester precursor can be assembled. The only limitation is that the basic conditions required to bring about the cyclization obviously preclude the use of intermediates that are unstable in such media and can lead to racemization of stereogenic centers with acidic hydrogens. Tenuazonic acid **16** was prepared from ethyl L-isoleucinate and diketene by several groups, although as in previous examples, with racemization of the stereogenic center at C-5 occurring.[28,101,149] Rinehart has investigated the applicability of this methodology to the synthesis of 3-dienoyltetramic acids related to streptolydigin (**31**) and tirandamycin A (**14**).[150] Cyclization of the acetoacetamides **113** and **114**, prepared from ethyl *N*-benzylglycinate and the appropriate dienoylacetyl ester, with sodium ethoxide as the base afforded the corresponding dienoyltetramic acids **115** and **116**. Unfortunately, attempts to obtain the precursor to tirandamycin A (**14**) from β-keto ester **117** and ethyl *N*-benzylglycinate led solely to thermal decomposition of **117**.[150] An alternative approach described in the same article[150] involved the treatment of an α-(acylacetamido)acetonitrile **118** with sodium ethoxide: this gave rise to the dienoyltetramic acid **119** after an aqueous workup (Scheme 7). This approach was also used to prepare a range of streptolydigin analogues for investigation of structure–activity relationships in the inhibition of terminal DNA transferase.[71]

Kozikowski's group published a total synthesis of α-cyclopiazonic acid (**15**)[151] from indole-4-carboxaldehyde, in which the tetramic acid ring was formed by treatment of **120** with base. They obtained iso-α-cyclopiazonic acid (**121**) exclusively from the reaction mixture, indicating that epimerization of the ester-bearing stereogenic center had occurred. The isomerization of **15** to **121** had been reported[42] to take place only very slowly in aqueous alkali so this would seem to suggest, given the relative ease with which it had occurred in the formation of **121**, that epimerization precedes ring closure. α-Cyclopiazonic acid (**15**) was subsequently isolated by chromatographic separation of a 2.5:1 mixture of **15** and **121** obtained by treating the iso compound with triethylamine at high temperature (Scheme 8).

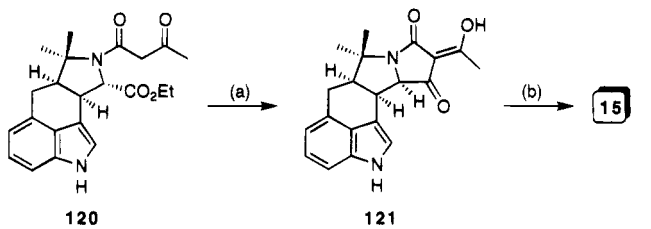
Racemic tirandamycin A (**14**) was synthesized through Lacey–Dieckmann cyclization of **124** and then removal of the *N*-protecting group, with the

**Scheme 7**



(a) NaOEt; (b) $H_2O$

**Scheme 8**



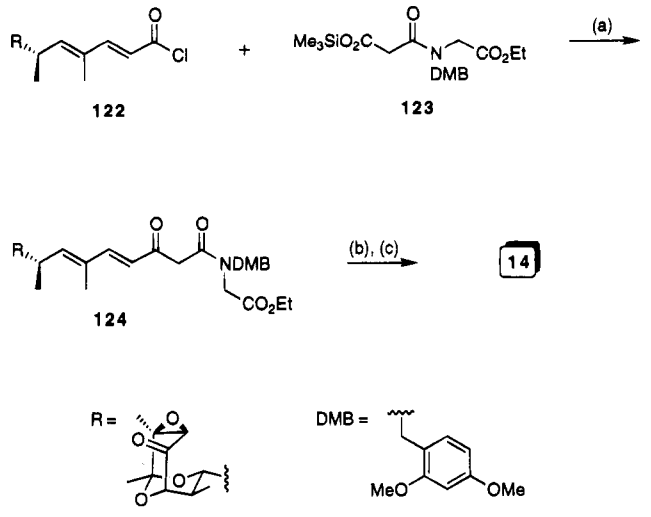
(a) NaOMe; (b) $Et_3N$, 100°

yield for the ring closure an excellent 95%.[152] The issue of decomposition during formation of the β-ketoacetyl-α-amino ester **124**, encountered in earlier cognate work,[150] was evaded by first making the amide bond to give malonamidate **123** and then acylating the latter with **122** (Scheme 9).

Efforts to prepare 3-acyltetramic acids having large and more complex side chains through Lacey–Dieckmann cyclization (at a late stage in the synthesis) were subject to the problems of capricious yields and/or decomposition of substrates. Thus an alternative strategy was evolved which entailed cyclization at an earlier stage with subsequent elaboration of the substituents on the tetramic acid ring.

Boeckman first reported the synthesis of a tetramic acid nucleus **128** with the 3-acetyl group suitably functionalized for further elaboration; it contained a phosphonate group thus activating the methyl terminus toward reaction with aldehydes.[153] This was prepared by Lacey–Dieckmann cyclization of the phosphonoacetoacetyl-α-amino ester **126** (obtained via ring opening of the 1,3-diox-5-en-4-one **125** with ethyl glycinate), giving rise to the sodium salt **127** which upon acidification afforded the free tetramic acid **128**; however, it was found to be better to store the phosphonoacetyl compound as its sodium salt **127**. Experimentally it was demonstrated that unless the ring nitrogen of the phosphonoacetyltetramic acid is alkylated the Horner–Wadsworth–Emmons

**Scheme 9**




(a) KO*t*-Bu, -78°; (b) KO*t*-Bu; (c) TFA

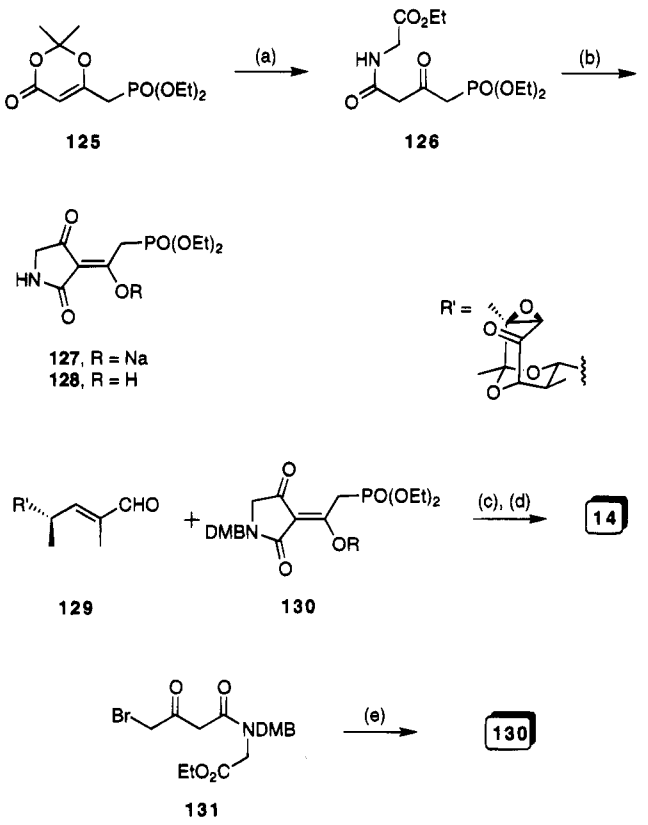
reaction with aldehydes, such as the intermediate **129** employed in the synthesis of (±)-tirandamycin A (**14**),[154] does not work well (if at all!). The requisite *N*-alkylated phosphonate **130** was therefore constructed in a similar fashion to **128** using the suitably protected glycine ester. This behaved as envisaged in the Horner–Wadsworth–Emmons reaction with (±)-**129**, yielding racemic **14** after deprotection of the ring nitrogen (Scheme 10). Schlessinger and his coworkers have also prepared and used the phosphonate **130** in the synthesis of complex tetramic acids.[155] They found that treatment of bromoacetoacetamido ester **131** with potassium diethyl phosphite (2.1 equiv) furnished **130** directly and in good yield.

Tetramic acid phosphonate **128** has also been prepared via an alternative route;[156] the isoxazolium salt **132** was treated with aqueous sodium bicarbonate to induce fragmentation into the same phosphonoacetoacetamide intermediate **126** used by Boeckman (probably via the nitrilium ion formed through deprotonation of **132** at C-3).[157] Again, this afforded the activated tetramic acid **128** on treatment with alkoxide and likewise (±)-tirandamycin A (**14**) was produced upon Horner–Wadsworth–Emmons reaction with the aldehyde **129**.[157] The generality of this approach was somewhat limited by the fact that the fragmentation step gave rise to the corresponding β-ketoacetamides for only a narrow range of substituents. Efforts to circumvent this by carrying out the fragmentation under anhydrous conditions failed, despite the appropriate amidines **134** being isolated, because hydrolysis of **134** did not produce the corresponding tetramic acids (Scheme 11).[158]

This methodology has also been utilized independently, by DeShong's and Rosen's laboratories, as the crucial step in the total synthesis of (±)-tirandamycin B (**34**)[159] and for preparing a series of aromatic dienoyltetramic acids as synthetic antibacterials.[160]

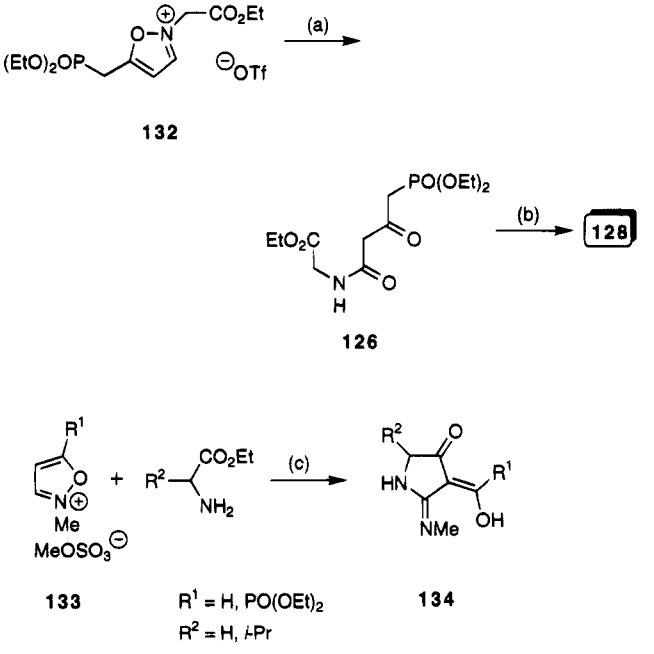
A novel entry to β-ketoacetamides **136** through zirconium(IV)-catalyzed coupling of aldehydes and α-diazoacetamides **135** constitutes a useful addition to the methodology available for constructing tetramic acids, particularly as the preparation of substituted β-ketoacetamides was previously not feasible.[161] The products of the coupling reaction were readily cyclized to the 3-acyltetramic acids **137** by standard methods (Scheme 12).

**Scheme 10**



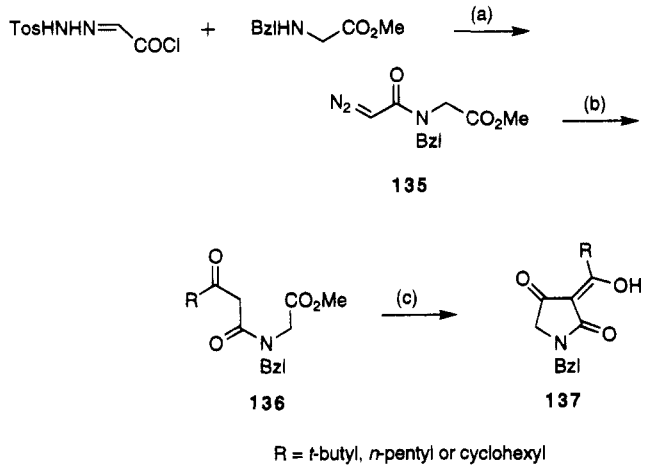

(a) $H_2NCH_2CO_2Et$, $PyH^+Tos^-$; (b) NaOMe; (c) KO*t*-Bu [2 equiv.]; (d) TFA; (e) $KPO(OEt)_2$ [2.1 equiv.]

**Scheme 11**



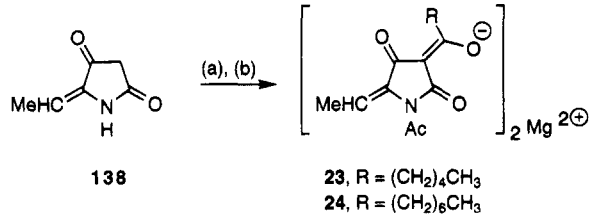

(a) aqueous $NaHCO_3$; (b) NaOEt; (c) KO*t*-Bu [2 equiv.]

**Scheme 12**




(a) $Et_3N$; (b) RCHO, $ZrCl_4$; (c) $n$-$Bu_4NF$

**Scheme 13**



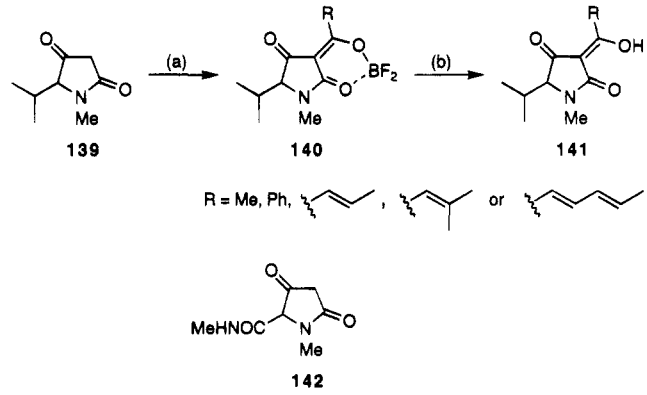

(a) RCOCl, $BF_3.OEt_2$; (b) $Ac_2O$, NaOAc, $MgCl_2$

### 4. Acylation at C-3

The acylation of pyrrolidine-2,4-diones, bearing no substituents at the 3-position, was regarded as a promising alternative means of access to complex naturally occurring tetramic acids, first in view of the ease with which the simple heterocycle can be made (through Lacey–Dieckmann cyclization) and second, because of the appearance of an acyl substituent at C-3 in many of the natural systems. Kohl was the first to use this strategy, in the synthesis of magnesidin (**23** and **24**).[38] Acylation of 5-ethylidenepyrrolidine-2,4-dione (**138**) was achieved through reaction with the appropriate acid chloride in the presence of boron trifluoride–etherate (Scheme 13).

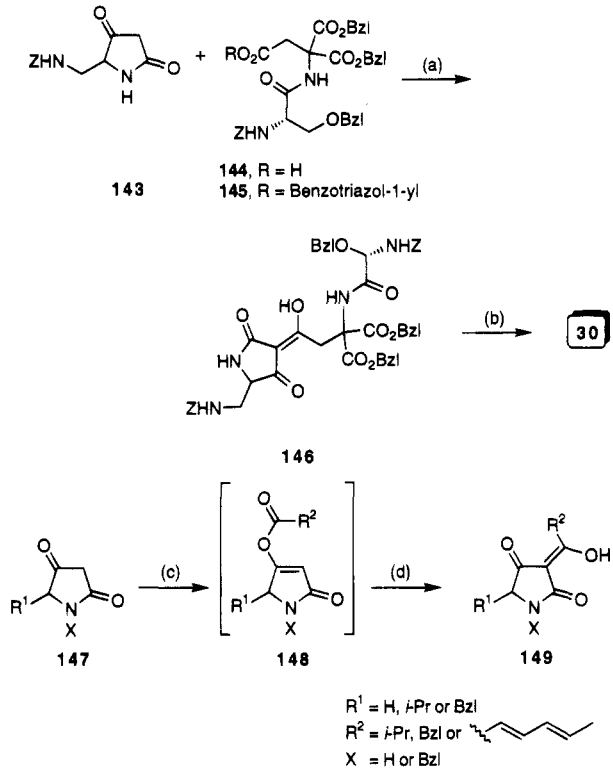
The viability of this strategy in the synthesis of models of the complex naturally occurring 3-polyenoyltetramic acids was further investigated by Jones and colleagues. Initial results were not encouraging as the yields were poor (when the Lewis acid was $TiCl_4$) or the product was being lost during the basic workup required for the Lewis acid-mediated ($BF_3$·$OEt_2$) acylation.[162] This problem was overcome by using neutral workup conditions and isolating the 3-acyltetramic acid products as their boron difluoride complexes **140**; these were obtained in 50–78% yields via acylation of the pyrrolidine-2,4-dione **139**.[163,164] The 3-acyltetramic acids **141** were liberated by simple treatment of complexes **140** with methanol (Scheme 14). In a preliminary study of the total synthesis of streptolydigin (**31**), thallium-mediated acylations of **142** had to be abandoned because the major products were due to *O*-acylation at the C-4 carbonyl (in the case of acid chlorides) and acylation

**Scheme 14**




(a) RCOCl, $BF_3.OEt_2$; (b) MeOH

**Scheme 15**

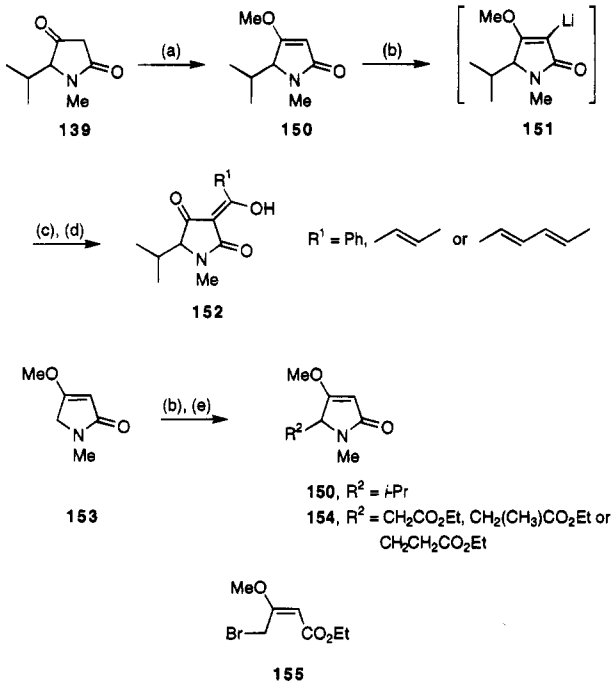



(a) HOBT, DCC then $Et_3N$; (b) $H_2$, Pd-C; (c) $R^2CO_2H$, DCC, DMAP; (d) $Et_3N$

of the exocyclic nitrogen (for acid fluorides)—the only successful reaction was that of the thallium(I) enolate derived from **142** with acetyl fluoride.[150]

A mild base-induced acylation was developed and applied to the synthesis of malonomycin (**30**).[68] Coupling of **143** and **144** could only be accomplished via *in situ* formation of the benzotriazolyl ester **145** with triethylamine present; under harsher (Lewis acid) conditions the delicate malonamide moiety was destroyed and no **146** isolated (Scheme 15). Hydrogenolysis of **146** gave rise to malonomycin (**30**) contaminated with only a trace of the decarboxylated material. Yoshii described an associated base-induced "one pot" acylation technique which gave the 3-acyltetramic acids in excellent yield (*ca.* 95%).[165] Thus tetramic acids **147** were acylated on O-4 and the resultant *O*-esters **148** were exposed directly to triethylamine which brought about rearrangement to the required 3-acyltetramic acids **149**. Usefully,

**Scheme 16**



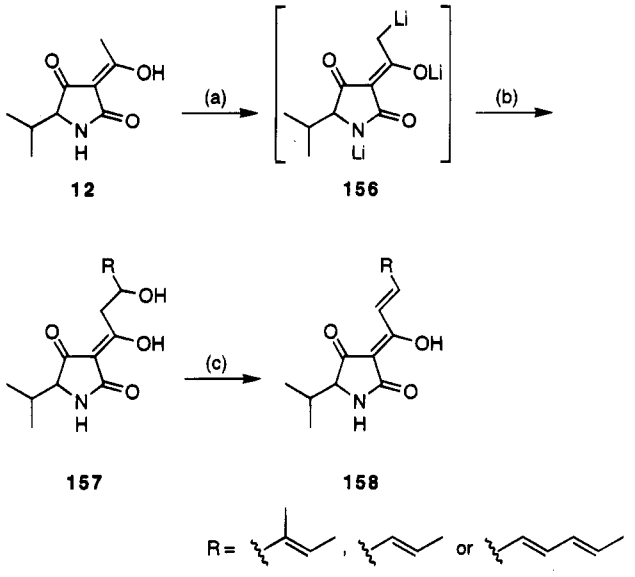

(a) $n$-$Bu_4NOH$, $[MeO]_2SO_2$; (b) $n$-BuLi, -78°; (c) $R^1CHO$, -78°; (d) $MnO_2$; (e) $R^2Br$, -78°

the phosphonate activated tetramic acid **128**, described earlier, was produced by this method in higher yield than previously possible.

Metalation and, in particular, lithiation of methyl tetramates of the type **150** has been thoroughly investigated and provides a convenient way to acylate such heterocycles.[166-168] The action of $n$-butyllithium on **150** causes deprotonation at C-3 and the ensuing lithio species **151** reacts, at low temperature with aldehydes to furnish, after oxidation, the 3-acylated substances **152**. An advantageous feature of this scheme is that 5-unsubstituted tetramates **153** undergo deprotonation, under identical conditions, at C-5 thereafter giving rise to the 5-alkylated tetramates **154** upon reaction with alkyl halides. The diversity of the range of 3-acyltetramic acids available by these means is consequently extended as compounds of type **154** may obviously be elaborated, by further metalation, into the corresponding 3-acyltetramic acids **152** (Scheme 16). Methyl tetramates like **153** are obtained directly from ethyl 4-bromo-3-methoxy-2-butenoate (**155**) by reaction with methylamine[169-171] but substituted systems **150**, however, are not easy to make in this way due to steric interactions at the cyclization stage.[168]

The discovery was later made that 3-acetyltetramic acids, the most readily accessible compounds of this type (via Lacey–Dieckmann cyclization of the $N$-acetoacetyl-α-amino esters), were deprotonated rapidly at both the nitrogen and enol oxygen but more slowly at the acetyl methyl group.[172,173] More importantly the (presumed) trilithio derivative **156** obtained on kinetic deprotonation of **12** with $n$-butyllithium (3.5 equiv) reacted rapidly (at the acetyl methyl carbon) with aldehydes to afford the aldol adducts **157** which were dehydrated to the 3-enoyltetramic acids **158** (Scheme 17).[172] This represents a concise means of incorporating a tetramic acid nucleus into a large

**Scheme 17**




(a) $n$-BuLi, -78° [3 equiv.]; (b) RCHO, -78°; (c) HCl

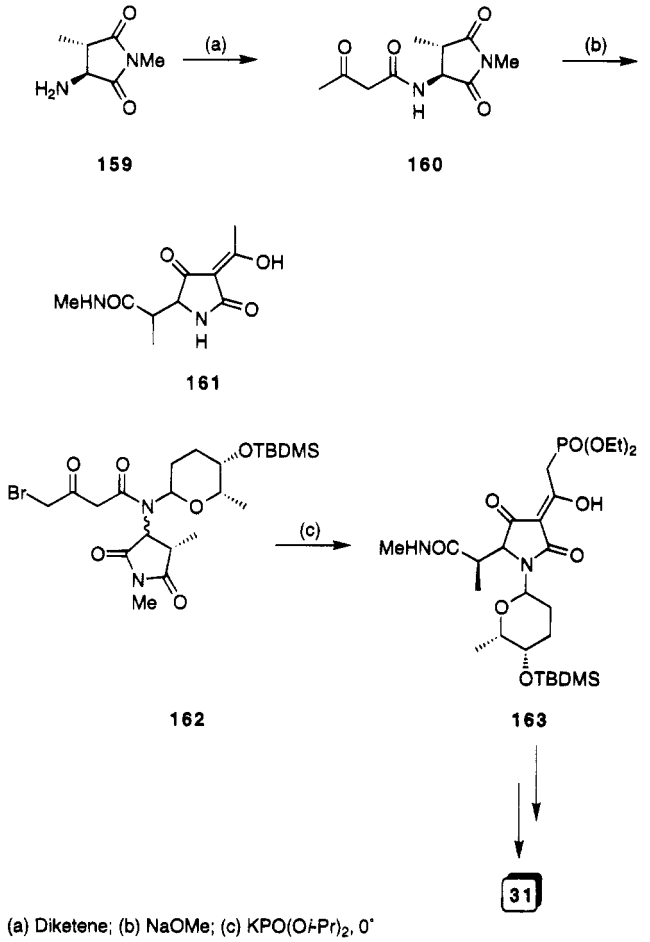
molecule during a convergent synthesis although its applicability to complex chiral targets may be limited by modest yields and the requirement for gaseous hydrogen chloride to effect the dehydration step.

### 5. Other Stratagems

The tetramic acid unit **161**, akin to the one found in streptolydigin (**31**), was found to be accessible from intramolecular rearrangement of the $N$-acetoacetylaspartimide **160**.[174] Reaction of **159** (prepared in the usual way from DL-*threo*-β-methylaspartic acid) and diketene resulted in the formation of **160** which, upon treatment with base, underwent a Dieckmann-type ring closure (on to the amidic carbonyl group next to the amidic nitrogen) with concomitant opening of the imide to yield tetramic acid **161** (Scheme 18). Efforts directed toward the extension of the methodology to a total synthesis of **31** proved fruitless. Schlessinger, however, reported by a very similar route the synthesis of phosphonoacetyltetramic acid **163** which was successfully attenuated to **31**.[175] Again the key step in the formation of the tetramic acid **163** was a base-induced rearrangement of the aspartimide **162**, which by using sufficient potassium diisopropylphosphite (as the base) gave the phosphonate directly—apparently as a single compound although this was not rigorously determined (Scheme 18).

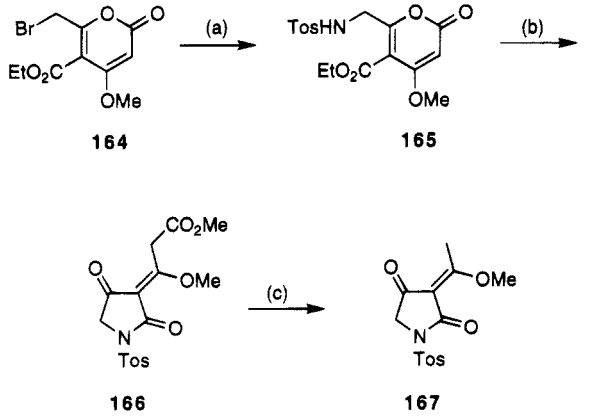
A novel route to 3-acyltetramic acids involving the ring opening of an α-pyrone system was described in 1989 by Jones.[176] Treatment of (bromomethyl)-pyrone **164** (derived from the parent methyl compound) with sodium $p$-toluenesulfonamide afforded **165** which, when exposed to sodium methoxide, led to the formation of the carbomethoxy-substituted tetramic acid **166**. The 3-acyltetramic acid **167** was easily obtained via alkaline hydrolysis of **166** followed by decarboxylation (Scheme 19). Elaboration of the alkyl substituent in pyrone **164** can be easily achieved through metalation of the methyl group (in the parent system); this leads to the formation of more complex 5-substituted tetramic acids and therefore

**Scheme 18**



(a) Diketene; (b) NaOMe; (c) $KPO(O\text{-}i\text{-}Pr)_2$, 0°

**Scheme 19**

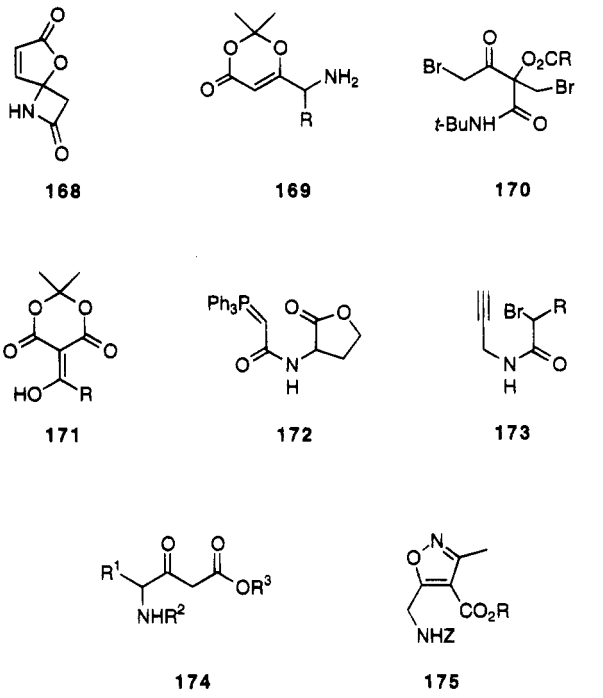


(a) TosNHNa; (b) NaOMe, 65°; (c) NaOH

this strategy shows promise as a viable entry to tetramic acid natural products.

A number of other synthetic routes to simple pyrrolidine-2,4-diones have been published over the years, namely: base-induced rearrangement of spiro β-lactams **168**,[177] intramolecular thermal rearrangement of 6-(aminoalkyl)-1,3-diox-5-en-4-ones **169**,[178] fluoride ion-promoted cyclization of 4-bromobutanamides **170**,[179] ring opening of Meldrum's acid derivatives **171** by aminoacetonitrile,[180] intramolecular Wittig reaction of γ-acylphosphonium ylides **172**,[181] radical cyclization of propargyl bromoamides **173**,[182] cyclization of γ-amino-β-keto esters **174**,[183] and finally

**Scheme 20**



the cyclization of isoxazole-4-carboxylates **175** followed by hydrogenolysis,[184] but as none of these are readily extended to more complex systems, and therefore have received little or no attention from those working in the natural product area, they have only been mentioned in passing (Scheme 20).

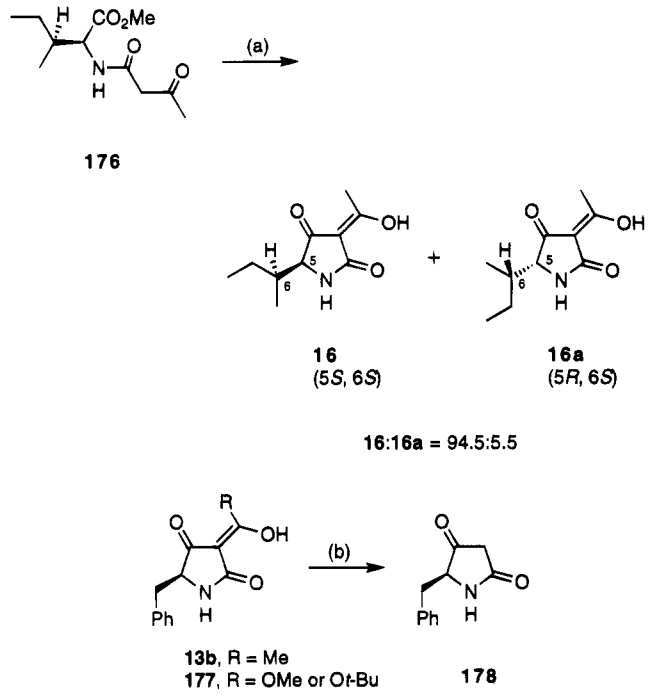
## B. Enantioselective Syntheses

### *1. Enantioselective Lacey–Dieckmann Cyclizations*

The tremendous advances which have been made in asymmetric methodology mean that the enantioselective synthesis of molecules containing many stereogenic centers is now feasible. Most of the natural products discussed earlier fall into this category with a single diastereoisomer responsible for their biological activity. Routes to optically pure materials are consequently becoming increasingly important; the syntheses of (−)-dysidin (**72**)[185] and (−)-tirandamycin A (**14**)[155] have been achieved, but of course, both of these contain tetramic acid units that do not possess a stereogenic center and thus the methodologies involved are not of direct relevance to this section.

The principal method used for preparing chiral tetramic acids has been, like that for racemic or achiral examples, the Lacey–Dieckmann cyclization. This procedure so easily lends itself to use in an enantioselective synthesis as chiral amino acids may be used to introduce asymmetry, of either absolute configuration, into the requisite *N*-(β-ketoacetyl)-α-amino ester precursors. The base-induced cyclization has to be cautiously executed in order to avoid epimerization of the stereogenic center, which is α to an ester, making its proton relatively acidic. A careful study of the occurrence of racemization during Lacey–Dieckmann cyclizations revealed, first, that partial loss of stereochemical integrity was encountered under the controlled conditions used and, second, that the diastereomer ratio was dependent

**Scheme 21**

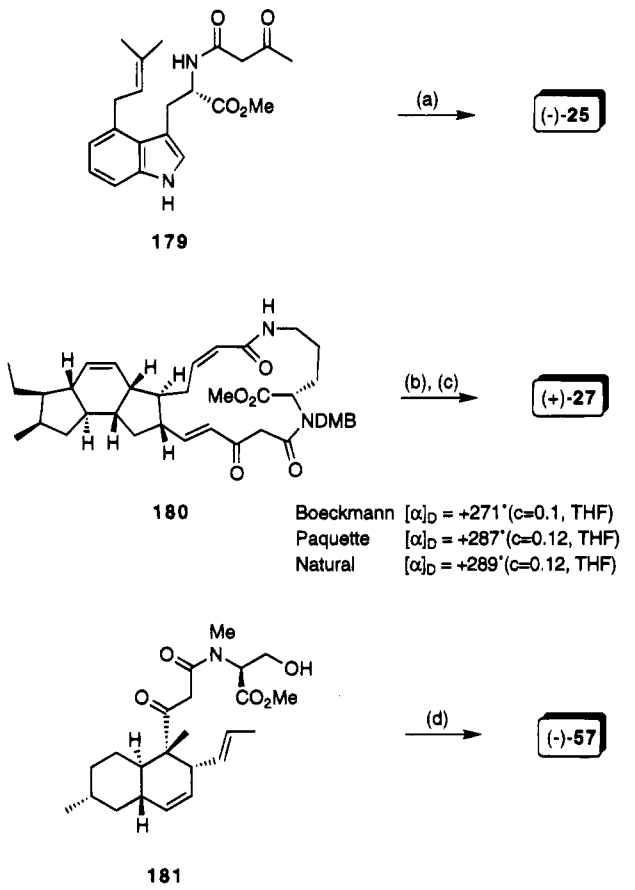



(a) NaOMe [0.9 equiv.]; (b) $H_2SO_4$ [aqueous, 25mM] or TFA

upon base concentration and reaction time.[186] Hence when the (2*S*,3*S*)-isoleucinate derivative **176** was treated with sodium methoxide for 2 h at reflux tenuazonic acid (**16**) and its C-5 epimer **16a** were isolated (the major epimer being **16a**) in a ratio of 94.5:5.5 by $^1$H NMR (Scheme 21). Some of the contributors to this work had previously reported that this route gave **16** which was identical in all respects to material from natural sources.[32] Investigation into the hydrolytic deacetylation of **13b** and decarboxylation of **177** indicated that **178** was not obtained as a single enantiomer, between 10 and 30% of the C-5 epimer being obtained in each attempt (Scheme 21).[186]

Notwithstanding the above, an almost identical process has been used to successfully prepare β-cyclopiazonic acid (**25**), in optically pure form, through exposure of **179** to methoxide (3.6 equiv) in refluxing benzene for 10 h.[187] The CD spectra of synthetic and natural material were identical thus demonstrating that stereochemical integrity was not lost during the base-induced ring closure (Scheme 22). An enantioselective Lacey–Dieckmann cyclization was employed in the landmark syntheses of (+)-ikarugamycin (**27**) by Boeckman,[188] Paquette,[60,189] and their coworkers; furthermore, the optical rotation of the synthetic material was either in excellent agreement[188] or virtually identical[60] to that of the natural samples. Both laboratories obtained **180**, using phosphonate **125** as means of introducing the key γ,δ-unsaturated-β-keto amide functionality, and then performed the cyclization using potassium *tert*-butoxide (2.0 equiv, 0 °C, 15 min;[188] or 1.0 equiv, room temperature, 10 min[60,189]) followed by deprotection with TFA to yield (+)-**27** (Scheme 22). The mild temperatures as well as the brief reaction times employed in all these reports are obviously important in minimizing the likelihood of racemization while

**Scheme 22**

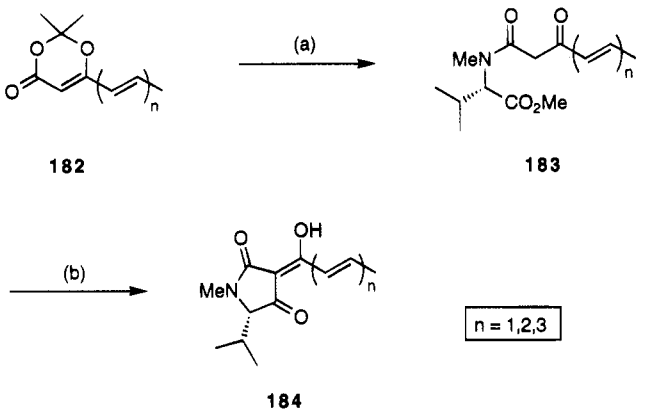



(a) NaOMe; (b) KO*t*-Bu; (c) TFA, 10 min.; (d) NaH, 0°, 30 min.

the steric bulk of the base may also be a significant factor as the stereogenic center concerned is somewhat hindered compared with the active methylene group. Similarly, the action of excess sodium hydride (5.6 equiv) on **181** furnished (−)-equisetin (**57**) as a single diastereoisomer with $[\alpha]_D = -253°$.[114] This is approximately 100° more negative than that measured for a natural sample, the difference being attributed to the presence of hydrocarbon impurities in the natural substance[190] which cause a reduction in magnitude of the optical rotation (Scheme 22). More recently Jones[191] applied a very similar strategy (to those of Boeckman[188] and Paquette[189]) in the synthesis of compounds related to erythroskyrine (**42**). Acid-mediated thermolysis of dioxenones **182** (prepared from **125**) in the presence of methyl *N*-methyl-L-valinate generated the unsaturated β-ketoacetamides **183** in high yield. These upon treatment with potassium *tert*-butoxide (room temperature, 45 min) were converted into the corresponding 3-enoyltetramic acids **184** without loss of stereochemical integrity (Scheme 23).

Ley and his colleagues described what is probably the most significant advancement of the Lacey–Dieckmann protocol in the context of forming chiral tetramic acids.[192] Their strategy is centered on *tert*-butyl 3-oxobutanethioate (**185**) and its 4-diethylphosphono derivative **186** which allows a wide range of sensitive β-keto amides **188** to be made under very mild conditions. Horner–Wadsworth–Emmons reaction of **186** with aldehydes and ketones

**Scheme 23**




(a) Methyl *N*-methyl-L-valinate.HCl, $Et_3N$ then $PyH^+Tos^-$ [1.0 equiv.], PhMe, reflux;

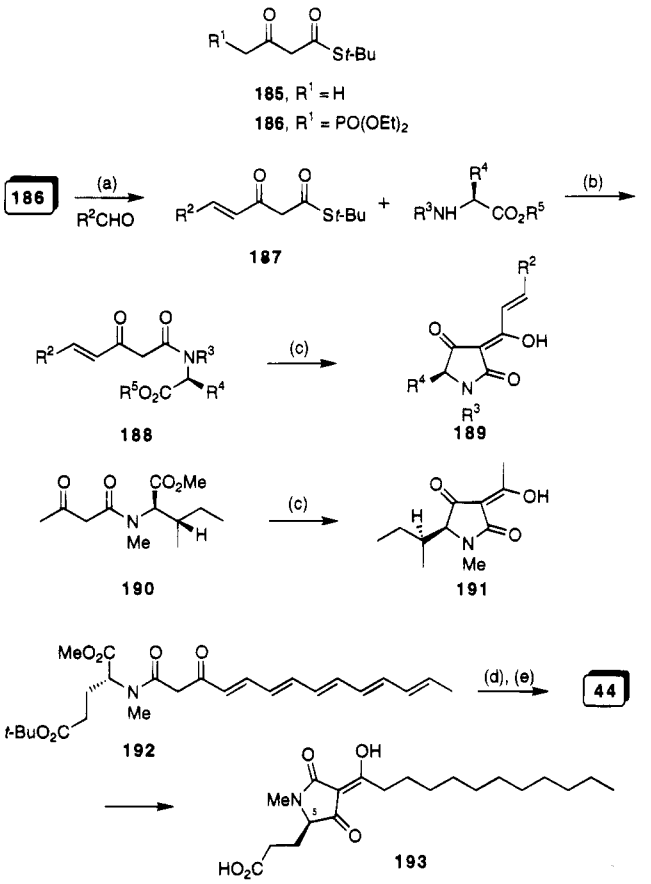
(b) KO*t*-Bu, *t*-BuOH, RT, 45min.

proceeds rapidly at ambient temperature giving rise to the (*E*)-alkene products **187** almost exclusively. Conversion of the β-keto thioesters **185** or **187** into the corresponding β-keto amides is accomplished by reaction with an amine or α-amino ester in the presence of silver(I) trifluoroacetate. The innocuous nature of these steps means that systems of types **187** and **188** containing stereogenic centers as well as sensitive functionality (present via the carbonyl or α-amino ester moieties) can be obtained without any racemization or decomposition occurring in either step. Cyclization of the β-keto amides **188** using TBAF or *tert*-butoxide produced the tetramic acids **189** with complete retention of configuration. By way of a test case enantiomerically pure **190** was subjected to a variety of cyclization conditions: (i) TBAF, room temperature, THF, 5 min; (ii) sodium methoxide, MeOH, room temperature, 5 min; (iii) potassium *tert*-butoxide, *tert*-butyl alcohol, room temperature, 5 min; (iv) as in ii except reaction time of 24 h; (v) as in iii except reflux for 24 h; (vi) sodium methoxide, benzene–methanol, reflux, 3 h—in i, ii, and iii the resultant tetramic acid **191** was obtained with complete retention of configuration whereas in all other cases some degree of racemization had taken place (*N.B.* in all cases the yields were >74%). This demonstrates nicely that the Lacey–Dieckmann cyclization is a viable means of preparing chiral tetramic acids so long as the cyclization is performed briefly at ambient temperature (Scheme 24).

Final evidence of the capability of this technique was the total synthesis of fuligorubin A (**44**) as a single enantiomer.[192,193] Thus cyclization of **192** was effected by *tert*-butoxide over 10 min which afforded **44** as a single enantiomer identical in every way, including optical rotation, to a natural specimen. The decahydro derivative **193** was prepared (by catalytic hydrogenation) from synthetic fuligorubin A (**44**) and this again was found to be identical to **193** derived from natural **44** (Scheme 24).[192]

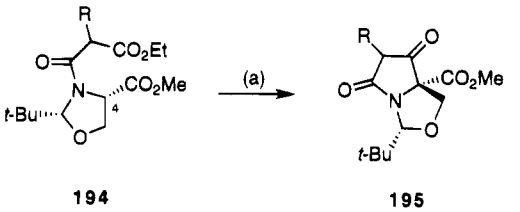
An account of the synthesis of enantiomerically pure tetramic acids from *N*-acyloxazolidines **194** derived from L-serine appeared recently.[194] Deprotonation of **194** (with *tert*-butoxide or methoxide) at the most acidic site does not lead to cyclization

**Scheme 24**




(a) NaH, 0°; (b) $AgO_2CCF_3$; (c) TBAF; (d) *t*-BuOK, 5 min.; (e) $HCO_2H$

**Scheme 25**



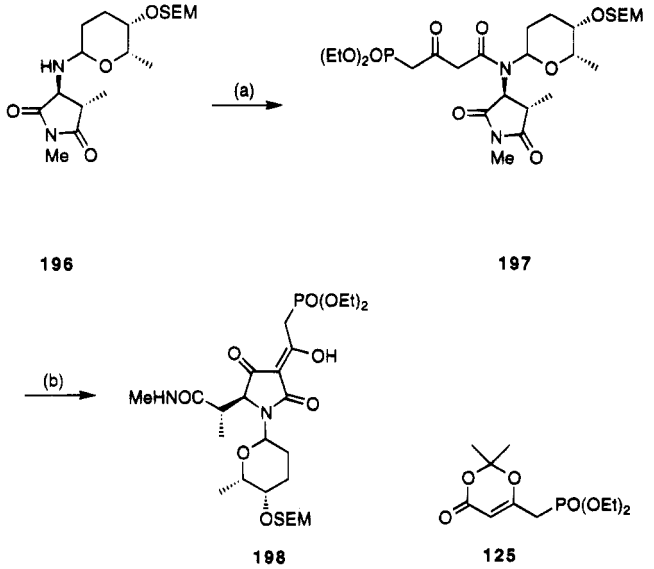

(a) KO*t*-Bu

products as one might expect; this is strongly disfavored because this pathway results in the *tert*-butyl group being on the sterically crowded *endo*-face of the bicyclic product. The tetramic acids **195** which are obtained, with an enantiomeric excess of 96% in favor of the (*R*) enantiomer (*i.e.* inversion of configuration), are formed by deprotonation at C-4 in the oxazolidine ring then cyclization of this anion on to the ester of the nitrogen substituent (Scheme 25). This method only provided a limited range of tetramic acids; the possible cleavage of the oxazolidine ring did not receive any attention and this could prove to be a major drawback for the route.

### *2. Other Enantioselective Methods*

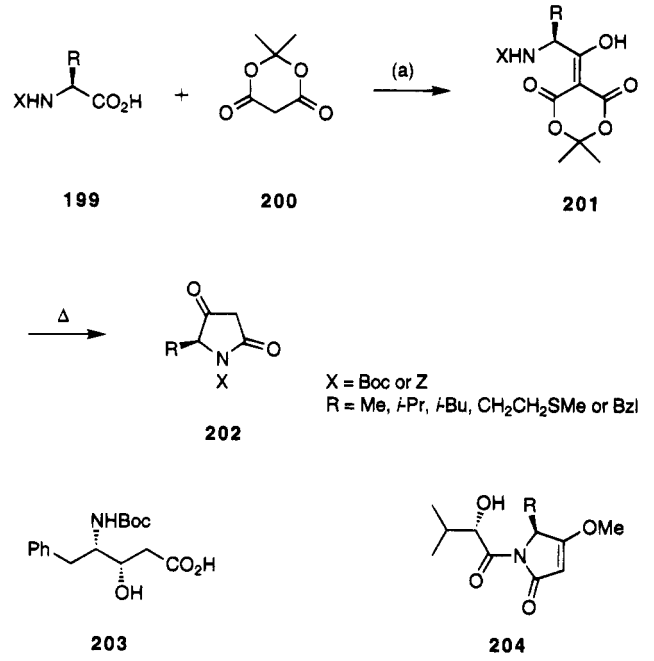
Aspartimide rearrangement of the ydiginic acid derivative **197** with *tert*-butoxide gave the protected phosphonate-activated tetramic acid building block **198** for streptolydigin (**31**).[195] Phosphonate **197** was

**Scheme 26**




(a) **125**; (b) KO*t*-Bu

**Scheme 27**

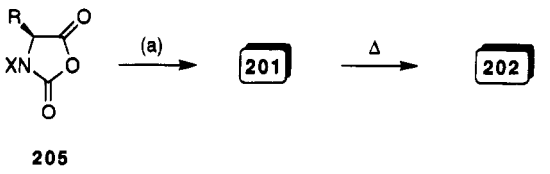



(a) Isopropenyl chloroformate, DMAP

prepared from **196** by reaction with **125**—the protected ydiginate **196** was itself obtained from enantiomerically pure (−)-ydiginic acid (**33**), nevertheless, the stereochemical integrity of the antecedent compounds must be viewed with some trepidation as no firm evidence of their optical purity was presented (Scheme 26).

Optically pure 5-substituted tetramic acids **202** are available through thermal rearrangement of the Meldrum's acid derivatives **201**.[196] The condensation of protected chiral amino acids **199** with Meldrum's acid **200** in the presence of isopropenyl chloroformate and DMAP afforded **201** without racemization. The enantiomeric purity of the tetramic acids **202** was unequivocally established by making the known statine derivative **203**, through hydrogenation then hydrolysis, which had an optical rotation identical

**Scheme 28**




(a) **200**, DMAP, $Et_3N$

to the literature value (Scheme 27). The tetramic acid subunit **204** of dolastatin 15 (**86**) was later synthesized enantioselectively by Pettit[197] using this technique.

A variant of the above protocol has appeared which uses urethane-*N*-carboxy anhydrides **205** (derived from the corresponding amino acids) instead of amino acids in the condensation with Meldrum's acid **200**.[198] The condensation products **201** give rise to enantiomerically pure tetramic acids **202** exactly as before. The main advantage of this route is that the condensation reaction is (reportedly) much more reliable as well as occurring in a matter of a few minutes; the overall yields of the tetramic acids (from **205**) are in excess of 60%, making this method a very attractive way of producing chiral 5-substituted tetramic acids (Scheme 28).

## V. Summary

A comprehensive survey of known natural products which contain as part of their structure the tetramic acid (pyrrolidine-2,4-dione) or 4-*O*-methyltetramate ester (4-methoxy-3-pyrrolin-2-one) heterocycles has been presented. They have been arranged according to similarities in structural characteristics and their biological significance, where applicable, has been adumbrated. Synthetic routes to such systems have been examined and the advantages, scope, as well as limitations of each method in terms of expediency, flexibility, and stereoselectivity was described. The review incorporates the relevant literature up to the end of 1994 enabling the reader, first, to appreciate the need and scope for innovative research in this area—particularly in enantioselective total synthesis and preparation of analogues as potential proprietary medicines, and, second, to recognize the fact that as tetramic acid natural products continue to be discovered great interest in the field is certain to be maintained for the foreseeable future.

*Acknowledgments.* The author thanks Professor Robert Ramage for providing the opportunity to work in such a stimulating area of organic chemistry as well as the Science and Engineering Research Council (now the Engineering and Physical Sciences Research Council) for generous financial support. He also expresses his appreciation of the encouragement and invaluable advice given by Dr. David M. Smith throughout the preparation of this manuscript.

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CR9401735