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Application of the Chemistry of Vicinal Tricarbonyl Compounds in the Synthesis of Products of Biological Interest

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1   Introduction

It is well-known that the reactivity of carbonyl groups is enhanced by the presence of vicinal electron-attracting groups, as evidenced by the ready formation of hydrates in the cases of chloral, oxomalonic ester and ninhydrin (1). This heightened reactivity must be associated with the destabilization of the ground state of the carbonyl group due to the location of positive centers close to the electron-deficient carbon atom. Despite the recognition of this effect, very little use has been made of the powerful electrophilic reactivity of the 1,2,3-vicinal tricarbonyl unit in synthetic operations.

In this report, we explore some of the applications of vicinal tricarbonyl compounds in the synthesis of products of biological interest. Our work was stimulated, in part, by the discovery of new methods for the formation of these functional group aggregates by the singlet oxygen cleavage of enamines and ylides.

1.1   Singlet Oxygen Cleavage of Enamines

In early work, we demonstrated the use of singlet oxygen for the formation of carbonyl groups as a part of a general method for the introduction of a ketone function α-to a carbonyl group (2). The method involves conversion of the starting ketone, lactone, ester, amide, or lactam to the corresponding α-enamino derivative, followed by oxidative cleavage of the enamine double bond by singlet oxygen (Scheme 1).

Scheme 1
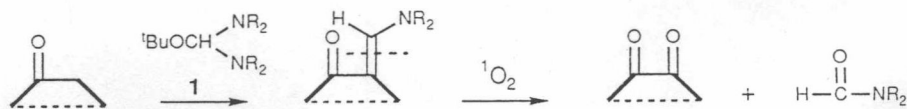
The formation of the α-enamino derivative involves the use of Bredereck's reagent **1** or other derivatives of dimethylformamide (DMF). During the photooxygenation process, the α-enamino ketone reacts with singlet oxygen to form dioxetane intermediates such as **A** which decompose with cleavage of the carbon-carbon bond yielding α-dicarbonyls and formamides (Scheme 2). This

<p align="center">**Scheme 2**</p>
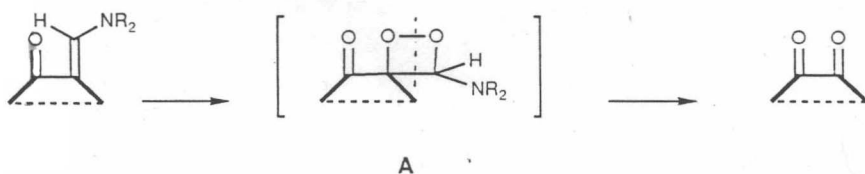
method can be further extended to the generation of vicinal tricarbonyl systems **4** from the corresponding β-dicarbonyl precursors **2** according to the general reaction in Scheme 3 (3).

<p align="center">**Scheme 3**</p>
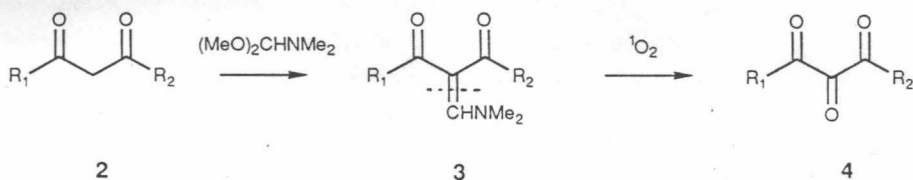
1.2 Carbacephams, Carbapenams and Penems

The above procedure for the *in situ* generation of vicinal tricarbonyl systems had an early application in our synthesis of a carbacepham (3). The silylated β-lactam derivative **5** was treated with *N,N*-dimethylformamide dimethyl acetal (DMF acetal) to form the enamine ketone **6** (79%) (Scheme 4). Oxidation of **6** with singlet oxygen gave the vicinal tricarbonyl derivative **7**. Under appropriate desilylation conditions, cyclization occurred to give a separable mixture of two isomers **8** (32% and 36%). Reduction of either of the isomers **8** with trimethylsilyl iodide resulted in a single product **9**, which, upon treatment with triethylamine and *p*-toluenesulfonyl anhydride gave the enol tosylate **10**, an intermediate used in the preparation of homothienamycin (4).

This method of ring fusion was also utilized in the synthesis of antibiotic PS-5, **16** (5). As outlined in Scheme 5, the active methylene group in compound **11** was converted to an enamino

Scheme 4

5   **6**   **7**

8   **9**   **1 0**
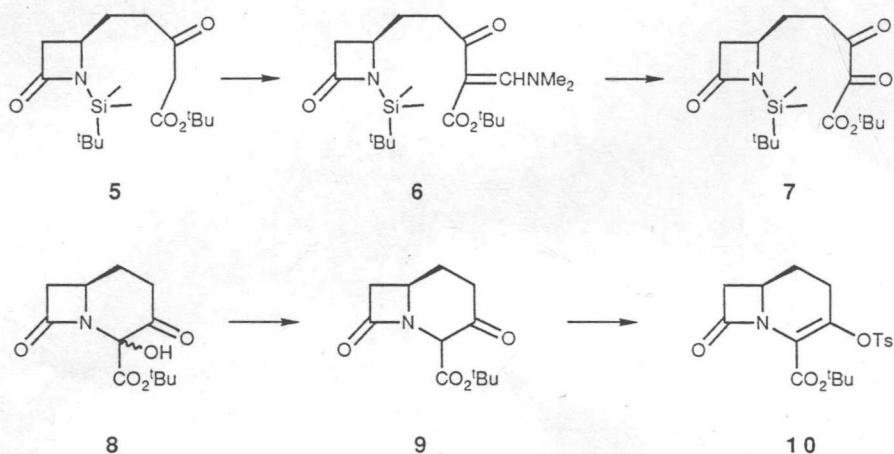
function **12** using DMF acetal (89%), and this product was subjected to photooxidative cleavage to give the hydrated tricarbonyl **13** (42%). After desilylation with HF-pyridine, the carbinolamide **14** was obtained (93%). Reduction with trimethylsilyl iodide then yielded the carbapenam **15** (30%). Compound **15** has been converted to the *p*-nitrobenzyl ester derivative of (±)-PS-5 by Kametani (6), and in its chiral form, **15** has been converted to (+) -PS-5 by Favara (7).

Scheme 5

1 1   **1 2**   **1 3**

1 4   **1 5**   **1 6**
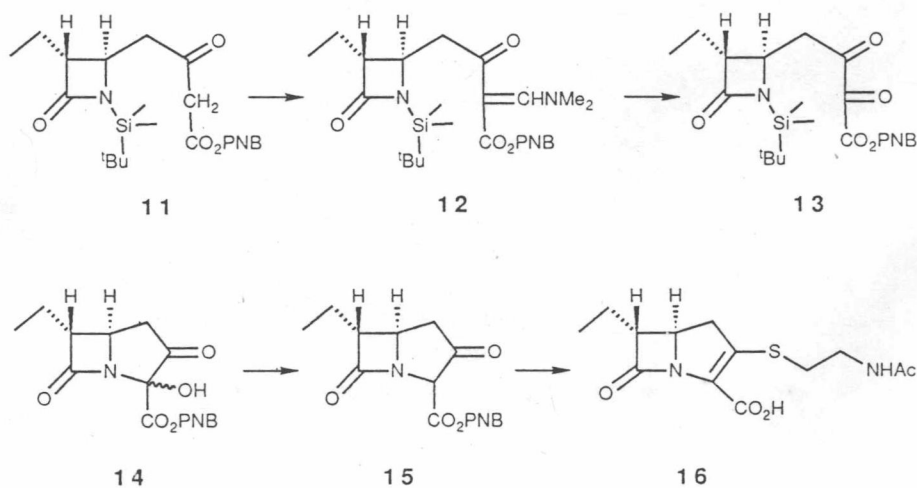
Tricarbonyl reactivity played a key role in a synthesis of the penem system. In this work, C_3-N bond formation was achieved using the powerful electrophilic nature of the central carbonyl in a vicinal tricarbonyl system as shown in **23** (Scheme 6) (8). The reaction sequence began with azetidinone **17** which was allowed to react with dimethylthioacetone dicarboxylate and sodium bicarbonate yielding **18** (60%). Protection of the NH group with t-BuMe$_2$SiCl afforded **19** (90%). Compound **19** was then ozonized in CH$_2$Cl$_2$ at -78° C, followed by reductive workup with dimethyl sulfide to form **20** (40%). Treatment of **20** with N,N-dimethylformamide dimethyl acetal gave the enamino derivative **21** (84%), which was subjected to photooxidation in CDCl$_3$ to afford the partially hydrated vicinal tricarbonyl **22** (76%). Desilylation with HF-pyridine led directly to the bicyclic system **24**, presumably through **23** (54% from **22**). Compound **24**, a mixture of isomers differing in the hydroxyl orientation at the 3-position, was reduced to **25** (51%) by conversion of the OH to Cl with SOCl$_2$/pyridine, followed by treatment with aqueous Zn-acetic acid. On treating **25** with diazomethane, the penem **26** was obtained (56%).

Scheme 6
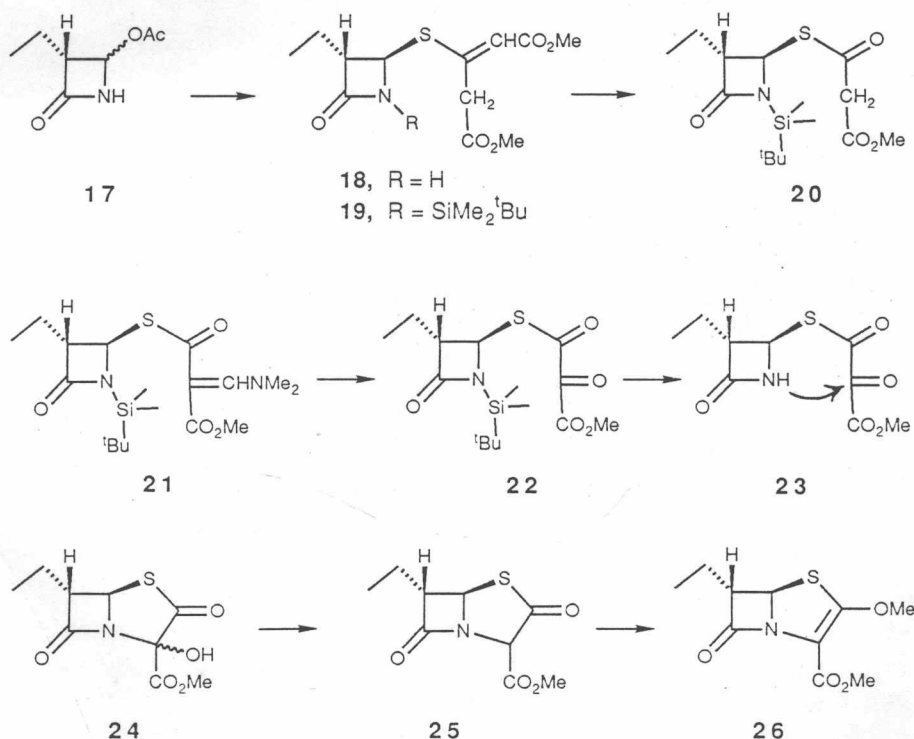
1.3 Ylide Route to Tricarbonyls

Having demonstrated the utility of the vicinal tricarbonyl unit as a powerful electrophile in synthesis, we sought a more generally applicable procedure for the formation of this functional group aggregate. The following procedure made use of the condensation between an ester ylide such as **28** and an acid chloride to give a keto ylide (Scheme 7) (9-11). In the next step, ozone or singlet oxygen could be used to generate the desired vicinal tricarbonyl unit. Using this method, a number of tricarbonyl derivatives have now been prepared and used as key intermediates in the synthesis of a variety of natural products as outlined below.

Scheme 7
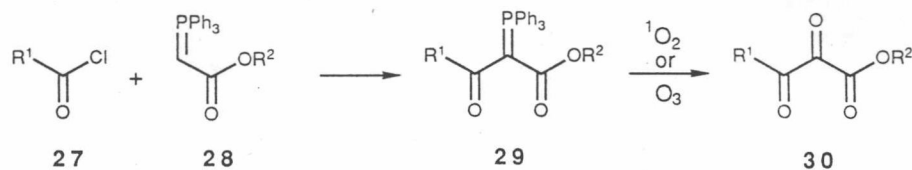
1.4 Isoquinoline Alkaloids

The structurally diverse isoquinoline alkaloids and their derivatives are of special interest in connection with their unique pharmacological properties (12-13). In our synthesis of papaveraldine **36** (10) the commercially available acid chloride **31** was reacted with 2 equivalents of t-butyl (triphenylphosphoranylidine)acetate to generate the corresponding keto-ylide **32** (93%) (Scheme 8). Ozonolysis of **32** proceeded smoothly to give the tricarbonyl monohydrate (85%). In our procedure, the C-2 carbon of **33** acts as the acceptor site for bond formation with both the primary amino group and the aromatic ring of a substituted phenylethylamine. The C-1 carboxyl function, which serves as the activating group in the first step, may be removed by decarboxylation, and the C-3 carbon then becomes the ketone group of papaveraldine. In practice, a benzene solution of **33** was combined with 2-(3,4-dimethoxyphenyl)ethylamine **34** and treated with trifluoroacetic acid to give **35** as the only isolable product (71%). This reaction appeared to take place by initial formation of a Schiff base at the central carbonyl, followed by a Pictet-Spengler cyclization and rapid decarboxylation of the resulting β-keto-ester. Air oxidation appeared to occur under the reaction conditions forming the conjugated keto-imine **35**. Papaveraldine was then obtained by dehydrogenation of **35** with methanolic potassium hydroxide (80%).

Scheme 8
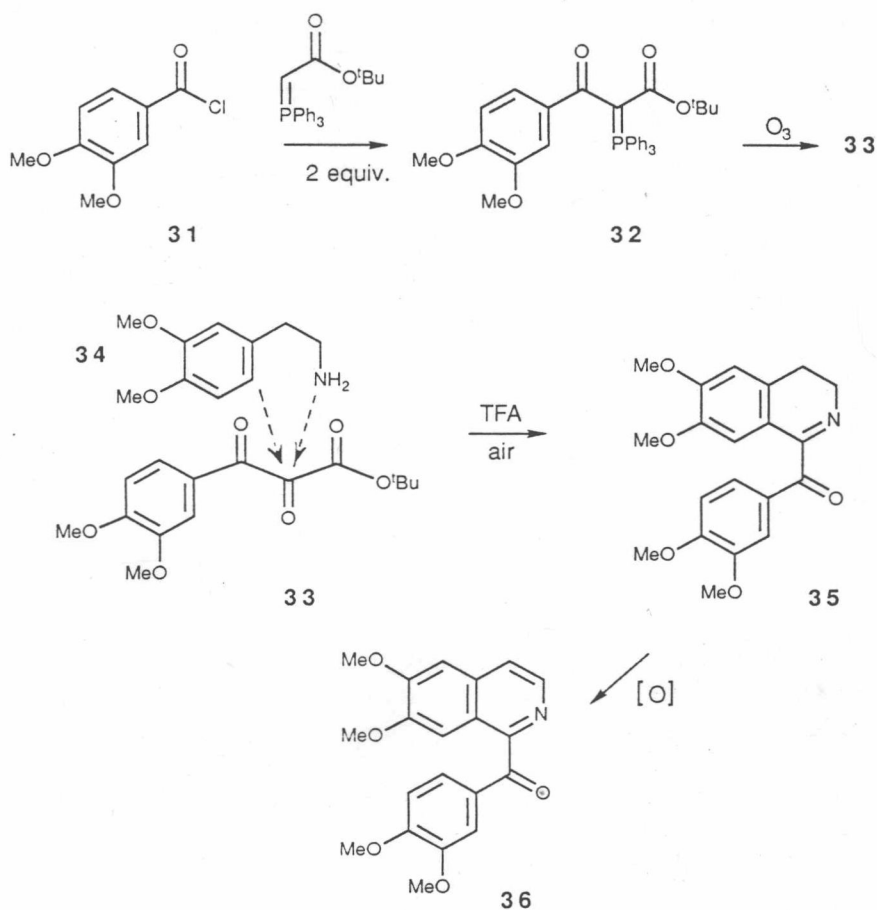
### 1.5 Vincamine-Related Alkaloids

In the synthesis of vincamine-related alkaloids (11), a suitably incorporated tricarbonyl unit as shown in **39** took part in reaction with the primary amino group of tryptamine **40**. The iminium salt thereby generated underwent cyclization at the 2-position of the indole ring to form **41** (Scheme 9). Following decarboxylation with formic acid, and *in situ* reduction with sodium cyanoborohydride, **42** was obtained as a mixture of diastereomers. Refluxing **42** in ethanol then led to the desired tetracyclic lactam **43**. Reduction of **43** with LiAlH₄ gave the amino alcohol **44** which could be dehydrated with 48% HBr to form the enamine **45**. This intermediate has previously been transformed into eburnamonine **46** by Martel (14).

Scheme 9
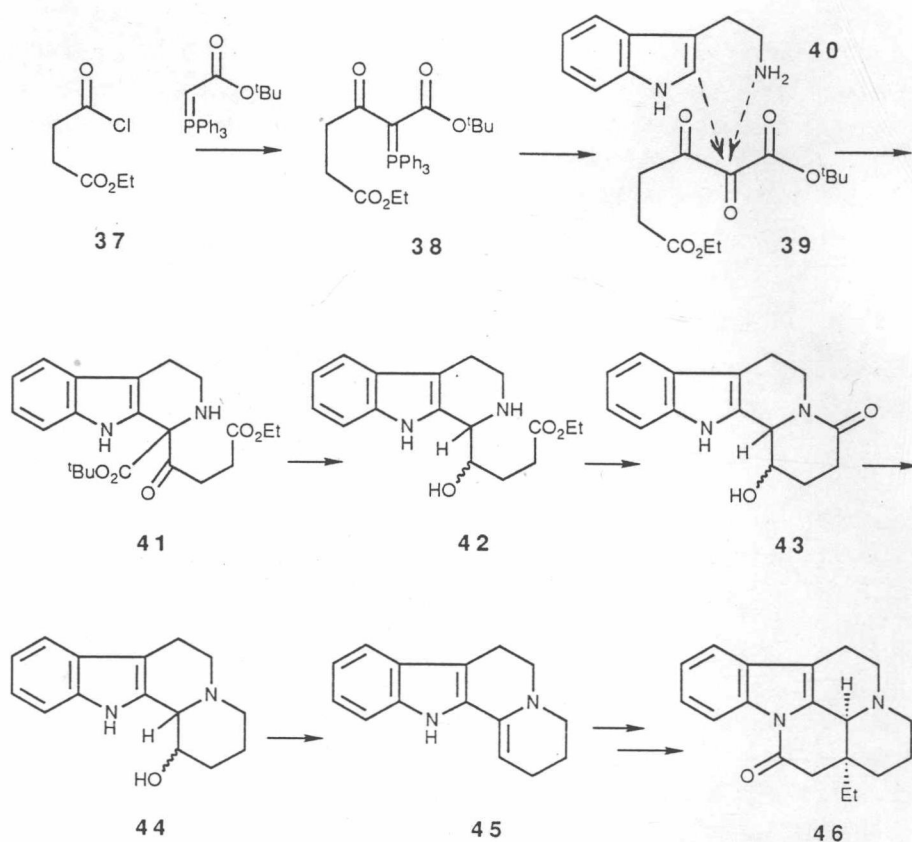
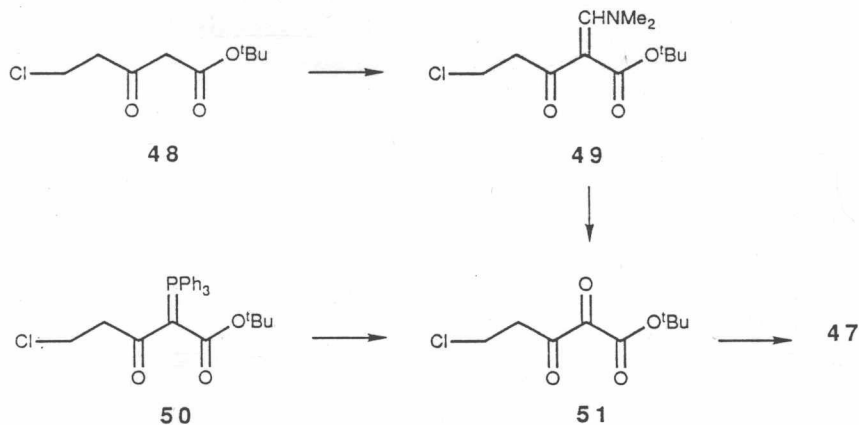### 1.6 The Vinyl Tricarbonyl Reagent

A synthon which has proved to be quite useful in our recent work is the vinyl tricarbonyl system **47** (9). This aggregate of reactive functional groups, acting as a di- or trielectrophile, has allowed efficient formation of a variety of heterocyclic systems of synthetic interest. A starting

4 7
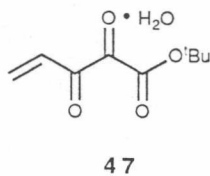
material for the preparation of **47** was t-butyl-5-chloro-3-oxopentanoate **48** which underwent ready reaction with *N,N*-dimethylformanide dimethyl acetal to form the enamino derivative **49** (Scheme 10). Treatment of the chloro enamine with singlet oxygen or ozone, followed by dehydrohaloge-

Scheme 10

48

49

50

51

47

nation with bicarbonate, gave the vinyl tricarbonyl **47** as the monohydrate. Alternatively, the chloro ylide **50**, reported earlier by Cooke (15-16) could be oxidized with ozone or singlet oxygen to give **51**. Dehydrohalogenation with saturated aqueous bicarbonate yielded **47** (60% form the chloro ylide) as a monohydrate. The structure **47** was confirmed by an X-ray crystallographic determination (Figure 1).
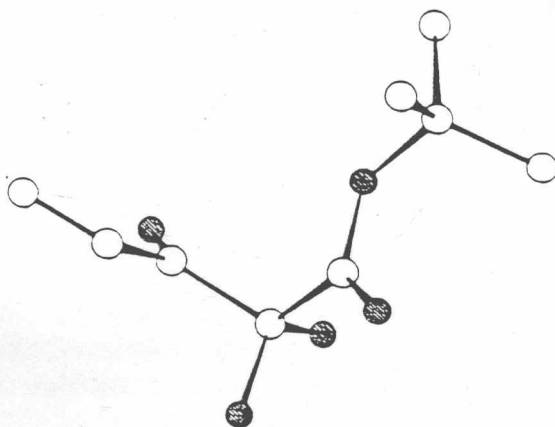

Figure 1. UPLOT drawing of the vinyl tricarbonyl hydrate **47**.

1.7 Pyrrole Formation

An example of the use of **47** as a dielectrophile could be found in its reaction with amines such as benzylamine (Scheme 11) (17). The primary amine, having two-fold nucleophilic capability, underwent conjugate addition to the α,β-unsaturated ketone in **47** with concomitant attack at the central carbonyl group to form the hydroxy pyrrolidinone carboxylate **52** (93%). Conversion of **52** to the hydroxy pyrrole **54** occurred readily with dehydrating reagents such as silica gel, presumably through the iminium ion **53**. This reaction has now been developed into a general method for forming hydroxypyrroles related to **54** .

Scheme 11

5 2

5 3

5 4
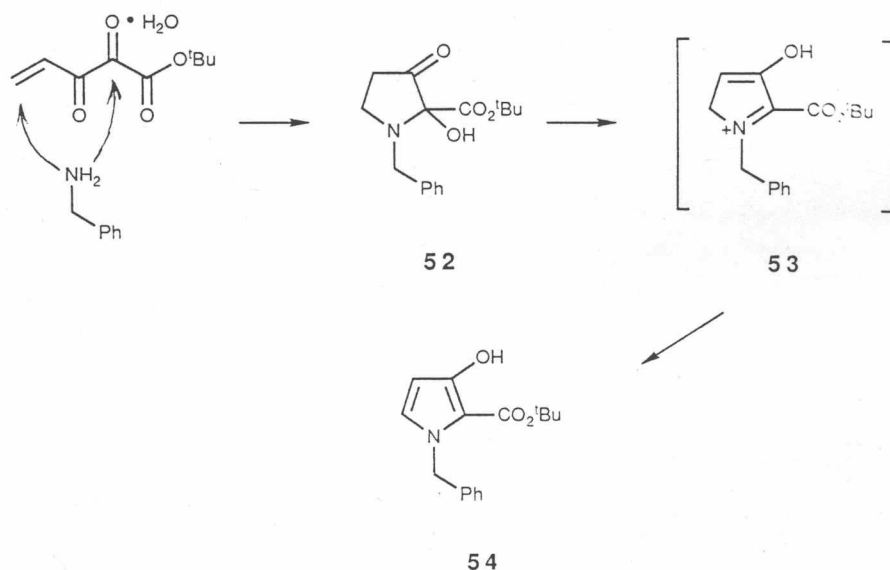
1.8 Indole Derivatives

The ability of **47** to react as a trielectrophile was illustrated in its reaction with tryptamine (Scheme 12). The carbinolamine **55** was initially formed by a double addition of the primary amine to the α,β-unsaturated ketone and the central carbonyl group. Treatment of **55** with BF₃·OEt₂ gave the tetracyclic system **57** rather than a pyrrole, presumably through an addition to the iminium ion **56** (73% from the vinyl tricarbonyl).

Scheme 12

55

56   **57**
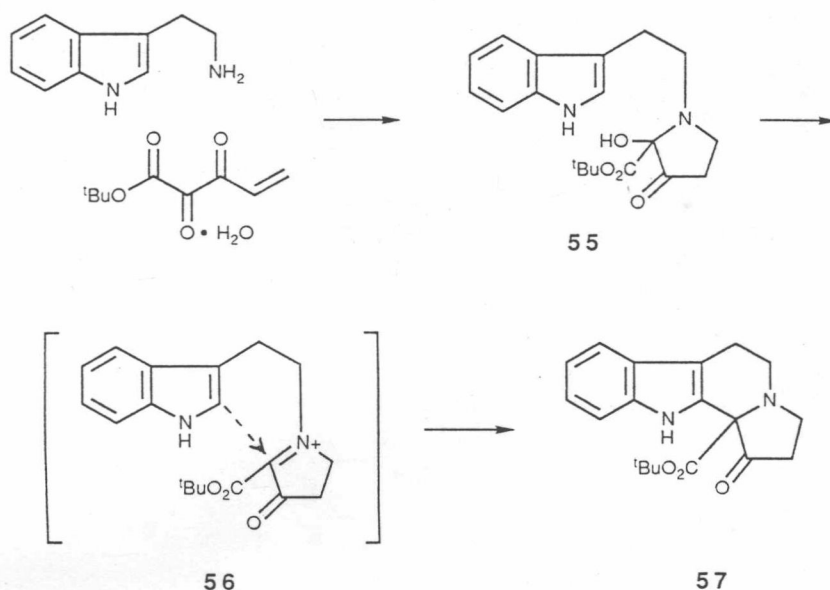
1.9 Total Synthesis of (±)-3-Demethoxyerythratidinone

An interesting use of the vinyl tricarbonyl reagent **47** could be found in the total synthesis of (±)-3-demethoxyerythratidinone **67** (18). When 2-(3,4-dimethoxyphenyl)ethylamine **34** was reacted with **47**, followed by treatment with a Lewis acid (POCl₃), the tricyclic system **58** was obtained (41%) (Scheme 13). In our synthetic sequence, the two carbonyl groups at C-1 and C-3 in **47**, which serve as activating groups in the reaction of **34** with **47**, remain favorably disposed for further elaboration into the diketone **66**. The natural product, **67**, could be obtained by a process involving an intramolecular aldol condensation of **66** followed by dehydration. In order to generate the required intermediate for the addition of a three-carbon fragment to **58**, a reduction of this compound with sodium cyanoborohydride in acetic acid was first carried out to give a diastereomeric mixture of the alcohols **59** (83%, ca 1:1 ratio). Treatment of each isomer under benzylation conditions (NaH, PhCH₂Br) resulted in a single diastereomer of the benzyl ether **60** (85% and 70%). The t-butyl ester **60** was then reduced to the aldehyde **61** with excess lithium aluminum hydride (89%). Horner-Emmons reaction of **61** with the anion of 2-oxopropyldimethyl phosphonate gave the trans-enone **62** (73%). Removal of the enone functionality and the benzyl protecting group gave the keto alcohol **63** (90%), which existed predominantly in the hemiketal form **64** (1:4 ratio of

Scheme 13

34   47   58

59   60   61

62   63   64
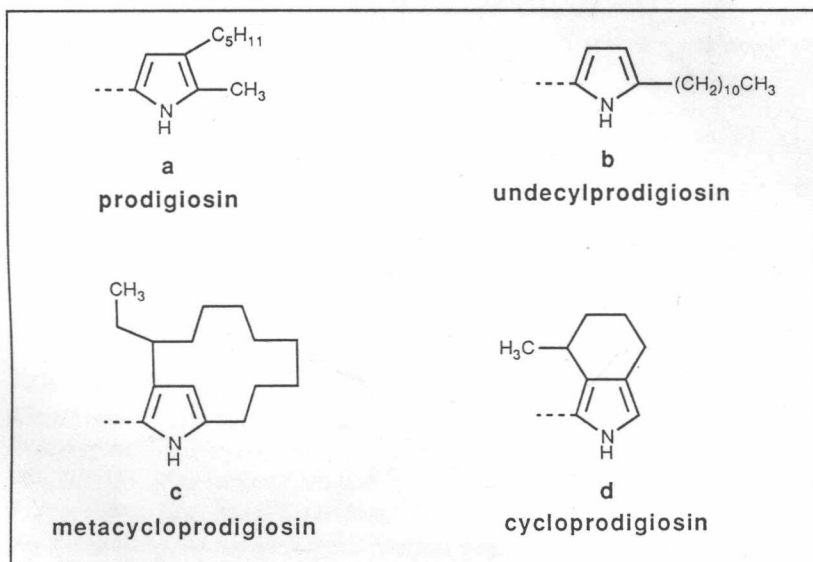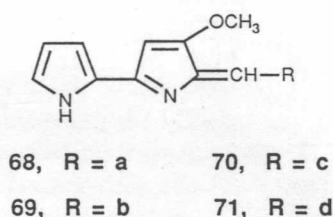
65   66   67
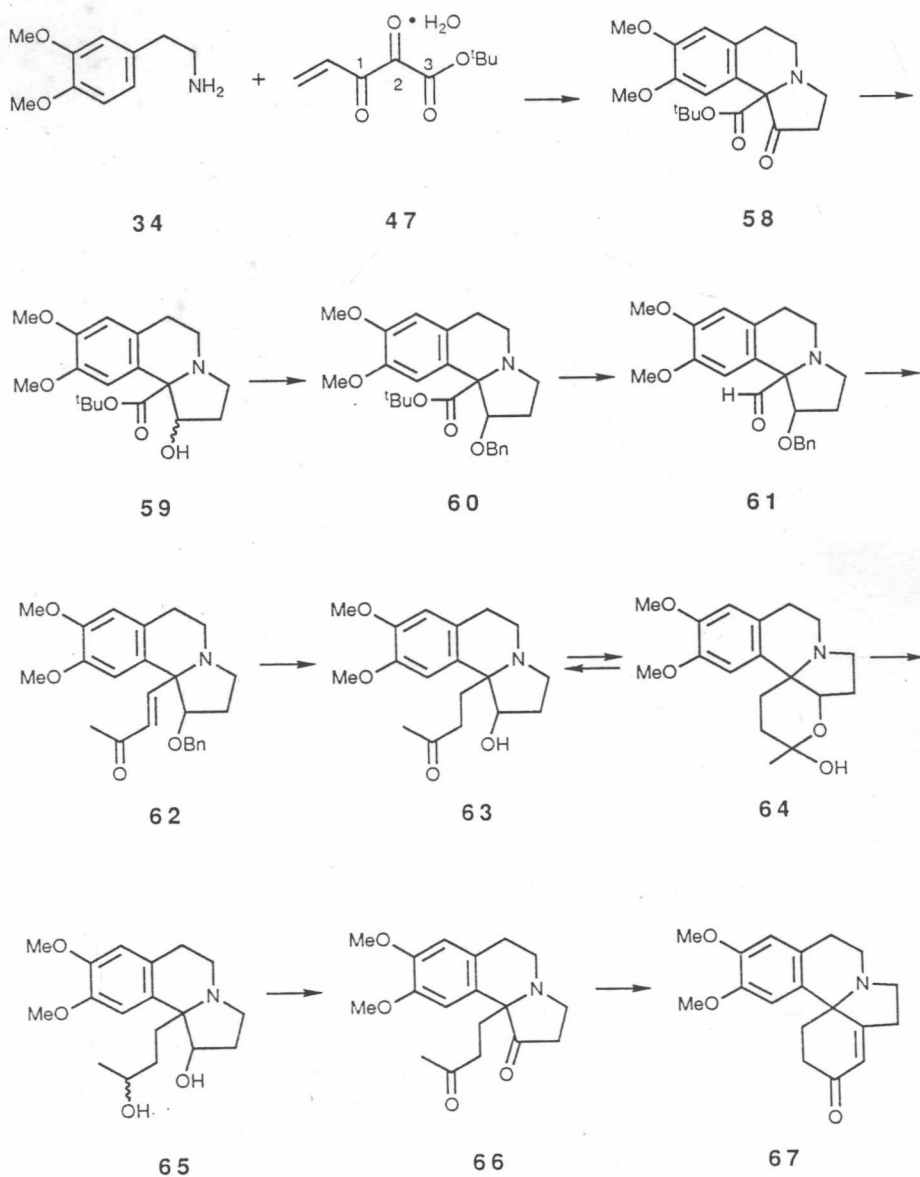
63:64). Reduction of this species with sodium borohydride in methanol gave the diol **65**, which was then oxidized with excess Swern reagent to yield the diketone **66**. Treatment of **66** with sodium hydroxide in refluxing methanol gave (±)-3-demethoxyerythratidinone **67** (41%).

2 Synthesis of Prodigiosin

As mentioned earlier, **47** could serve as a dielectrophile in the reaction with primary amines to form 3-hydroxypyrrole-2-carboxylates. These systems are of special interest because of their occurrence in heterocyclic units found in natural products such as the prodigiosins (19) (Figure 2).

Figure 2

68, R = a   **70, R = c**

69, R = b   **71, R = d**

a
prodigiosin

b
undecylprodigiosin

c
metacycloprodigiosin

d
cycloprodigiosin

For our synthesis of the methoxybipyrrole aldehyde **79** (19), a key intermediate in the biosynthesis (20) and in the synthesis of prodigiosin derivatives (21-26), we employed compound

75, an alkenyl vicinal tricarbonyl conjugated to a pyrrole ring (Scheme 14). The protected pyrrole derivative **72** was condensed with the anion of ethyl acetoacetate to give **73** (75%). Upon treatment with gaseous HCl, the enone derivative **74** was obtained (58%). The active methylene group was oxidized to the tricarbonyl derivative **75** using Sachs' procedure involving N,N-dimethyl-p-nitrosoaniline and acid hydrolysis (70%). The desired bipyrrole unit was obtained upon coupling of **75** with 3,4-dimethoxybenzylamine **76** in glacial acetic acid (23%). After the hydroxypyrrole was converted to the methyl ether (77%), the protecting groups were removed, and the resulting compound **78** was subjected to a McFayden-Stevens reduction to yield **79** (22). The condensation of **79** with methylamylpyrrole in the presence of acid then yielded prodigiosin (21-22).

Scheme 14
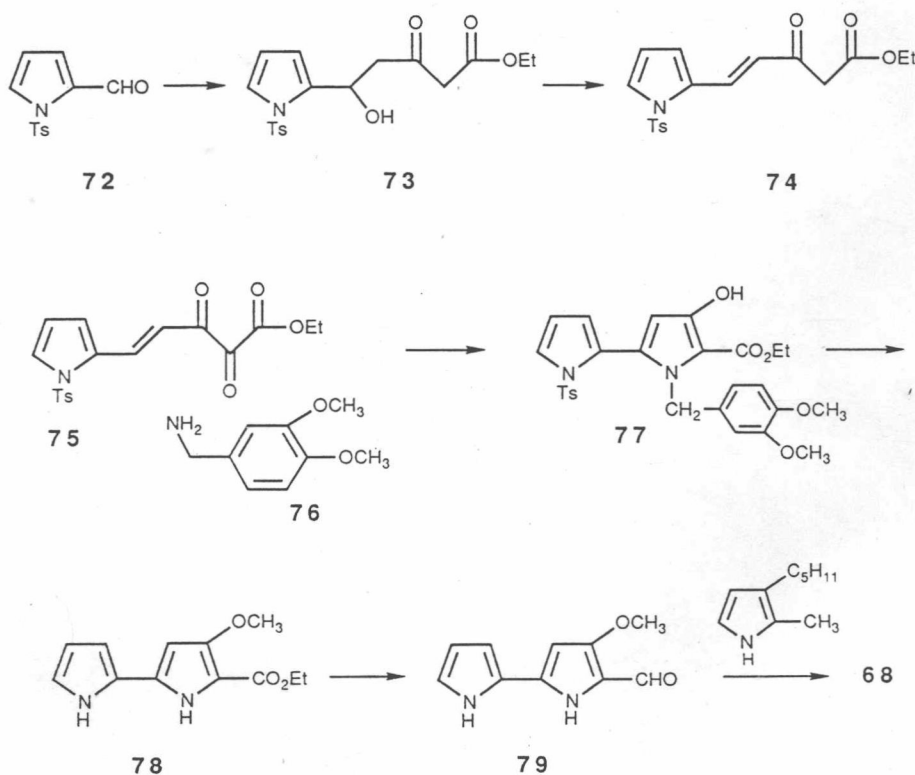
The investigations outlined here represent some recent applications of vicinal tricarbonyl compounds in synthesis. We have also made other uses of this reactive unit in the synthesis of natural products such as vasicine (27) and the eudestomins (28), as well as key structural elements of compound FK-506 (29) and bicyclomycin (30).

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