The Chemistry of Vicinal Tricarbonyls and Related Systems

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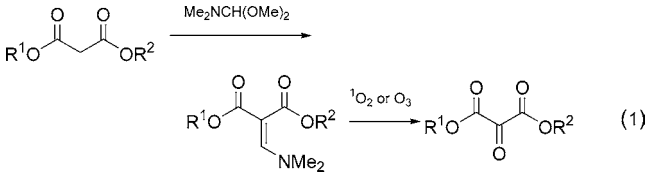
ABSTRACT

In this Account, we survey our work on the chemistry of vicinal tricarbonyls and cyano analogues. Methods of preparing the vicinal functionalities are reviewed as well as the use in organic synthesis of these strongly electrophilic aggregates, readily available from carboxylic acids. By attaching neighboring electrophilic groups to the vicinal tricarbonyl, we have developed polyelectrophilic systems, which may be added to di- and trinucleophiles to create novel types of multistep reactivity. Application of tricarbonyl chemistry in synthesis is illustrated by the formation of various natural products or their precursors including fused-ring β-lactams, indole alkaloids, marine metabolites, enzyme inhibitors containing α-keto amides, and bioactive depsipeptides incorporating hydrated tricarbonyl units.

Introduction

The functional unit consisting of three carbonyl groups located in a vicinal relationship has been known in organic chemistry since the preparation of diphenyl triketone was reported in 1890.[1] The central carbonyl group in the unit is a strongly electrophilic entity, accounting for the fact that tricarbonyls are hydrated at this site, and one might have expected that this functional array would represent fertile territory for investigation by organic chemists interested in synthetic applications of a powerful electrophilic species. However, despite the relatively straightforward availability of these aggregates, they received little attention as reagents in organic synthesis until late in the 20th century.[2a,b]

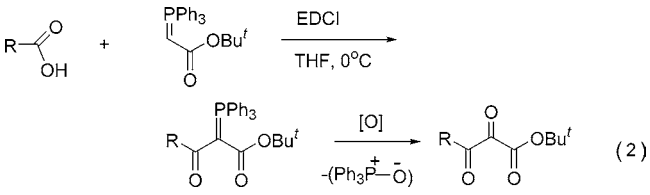
A possible reason for the reluctance of chemists to work with this system may be connected with the tendency of the tricarbonyls to form hydrates. Chemists looking for purity in starting materials and products tended to ascribe unsatisfactory carbon and hydrogen analytical results to impurities in the form of hydration. For this reason, they may have avoided dealing with vicinal tricarbonyls despite the fact that pure products such as oxomalonic ester hydrate and ninhydrin hydrate have long been known to be stable reactants of proven value in synthesis and analysis.[3a,b] Our work in this area had its origins in our discovery that tricarbonyl esters could be prepared easily as pure monohydrates by the reaction of dimethylformamide dimethylacetal with β-keto esters, followed by oxidative cleavage of the carbon nitrogen double bond with singlet oxygen (eq 1).[4] This Account reviews our studies



(1)

on vicinal tricarbonyl and related cyano derivatives during the past 20 years.

As is covered in the recent excellent comprehensive review by Rubin and Gleiter,[2a] the vicinal tricarbonyl (VTC) system may be prepared in high purity by a variety of procedures. Our contributions to this methodology are outlined in several communications.[5a−g] We draw particular attention to the ease of forming these systems from carboxylic acids. One such process utilizing a coupling reaction with ylide $Ph_3P(CH)COOBu^t$ is summarized in eq 2. In solution, the hydrates are in equilibrium with the



(2)

parent tricarbonyls, and in this form, they undergo reactions with a broad range of nucleophiles. More recently, we found that the cyanophosphorane $Ph_3P(CH)$-CN provides an alternative, more reactive carboxylate derivative. In either case, the ylide intermediates are quite stable and may act as protecting groups for the tricarbonyls and the related very labile α,β-diketo nitriles.

Early studies on addition reactions of the tricarbonyl system focused on the enhanced electrophilic activity of the central carbonyl group associated with the destabilization of the ground state of the carbon−oxygen double

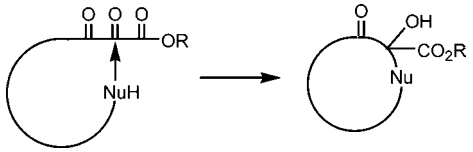


FIGURE 1.

Harry H. Wasserman received a B. S. degree from MIT in 1941 and then began graduate work at Harvard under the supervision of Professor R. B. Woodward. In 1942, he joined the Army Air Force, serving as the Chemical Officer of the Africa-Middle East Division of the Air Transport Command until late 1945 when he left the service to join the Woodward OSRD team, working on the synthesis of penicillin. From 1946 to 1948, he completed his doctoral studies at Harvard and accepted a faculty position in Yale's Chemistry Department. At Yale, he rose through the ranks to become Eugene Higgins Professor of Chemistry in 1983. He is a member of the American Academy of Arts and Sciences and the National Academy of Sciences. In his research, he has used natural products synthesis as a matrix for the discovery of new methodology.

Jonathan Parr received his Ph.D. (1989) working with Prof. Dennis Evans at Imperial College. Postdoctoral positions at the Universite Louis Pasteur, Yale University, and Imperial College preceded his appointment as an Associate Research Scientist and Lecturer in the Department of Chemistry, Yale University.

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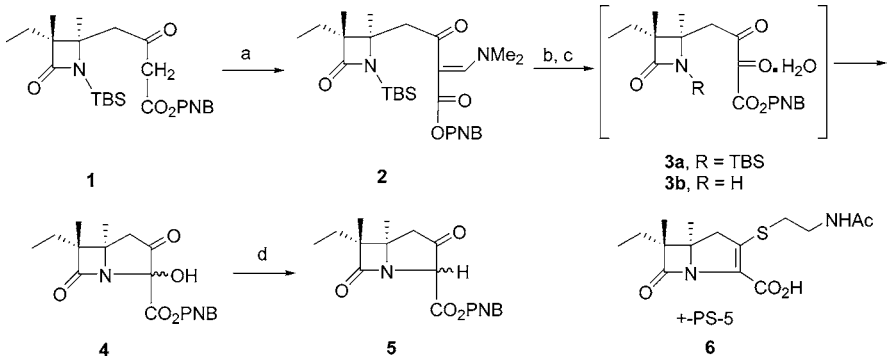
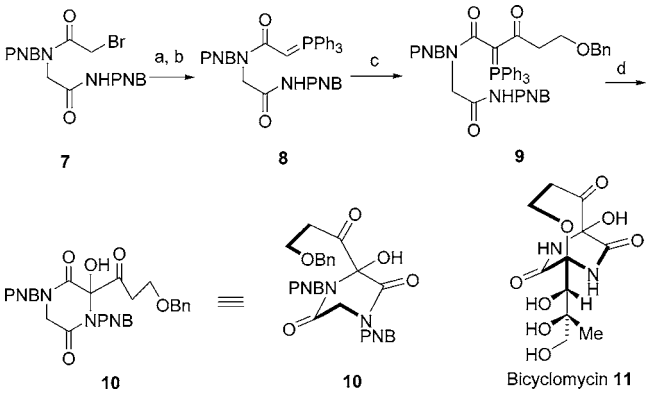
Scheme 1. Partial Synthesis of Antibiotic (±)-PS-5[a]



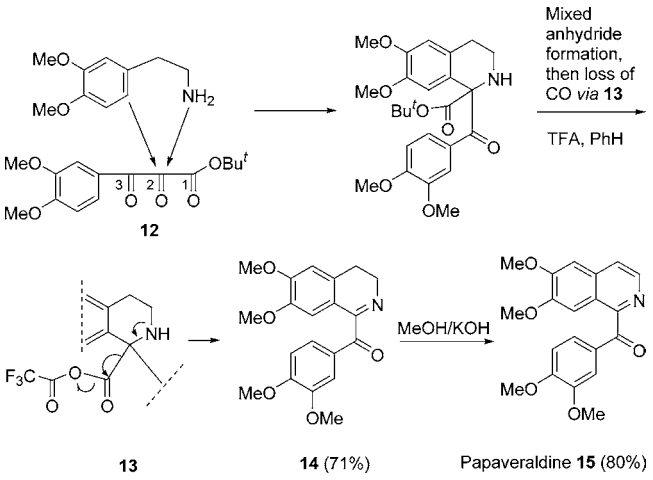
[a] Reagents and conditions: (a) $Me_2NCH(OMe)_2$ (87%); (b) $^1O_2$ (92%); (c) HF·py; (d) TMSI (30%).

Scheme 2. Synthesis of a Bicyclomycin Precursor[a]



[a] Reactions and conditions: (a) PPh_3 (98%); (b) NaOH (quant); (c) $BnO(CH_2)_2COCl$, BSA (88%); (d) O_3, −78 °C (54%).

Scheme 3. Synthesis of Papaveraldine



bond. In this setting, ready addition of donor reagents such as water, alcohols, amines, and mercaptans is favored, and these reactions made up much of the early literature of tricarbonyl reactivity.[2a] In our studies on synthetic applications, we were interested in intramolecular versions of this type of addition. As pictured (Figure 1), we expected that such reactions would be driven by the interaction of the strongly electrophilic central carbonyl with a suitably located nucleophilic group.

An early use of tricarbonyl systems in intramolecular reactions is found in the fusion of β-lactam nuclei to the five- and six-membered rings of penams and cephams, as illustrated in the partial synthesis of the penam antibiotic (±)-PS-5 (Scheme 1).[6] The *N*-silylated β-keto ester **1** was converted to the enamine **2** and then, by photooxidation, to the tricarbonyl **3a**. Desilylation yielded **3b**, which underwent immediate cyclization to the fused ring system **4**. Reduction then yielded the PNB ester **5**, identical with the product converted by Kametani to (±)-PS-5 (**6**).[7]

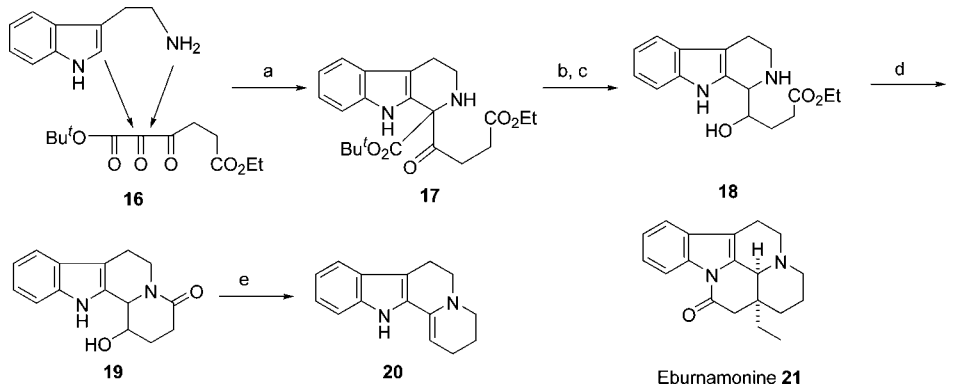
In a related intramolecular reaction of an α,β-diketo amide, we were able to prepare an intermediate in the Yoshimura synthesis of bicyclomycin (**11**).[8] The sequence in Scheme 2 illustrates the conversion of the diamide **7** to the ylide **8**, which could be further transformed to the diacyl ylide **9**. On ozonolytic cleavage, **9** yielded a key precursor **10** to the natural product **11**.[9]

Syntheses of Isoquinoline and Indole Frameworks

Other reactions involving 2-fold intramolecular addition to the central carbonyl led to novel syntheses of the isoquinoline alkaloids, papaveraldine, hydrastine, and cordrastine.[10] Scheme 3 shows a flexible route to papaveraldine (**15**) based on the reaction of a substituted vicinal tricarbonyl **12** with 3,4-dimethoxyphenethylamine. Here, the C-2 carbonyl of **12** provides the acceptor site for bond formation with both the primary amino group and the aromatic ring. The C-1 carboxyl, which initially acts as an activating group, was removed by strong acid to yield the imino product **14** most probably by a decarbonylation process through the mixed anhydride **13**.[11,48] The C-3 carbonyl of **12** thus became the ketone group of papaveraldine (**15**) following aromatization in methanolic potassium hydroxide.

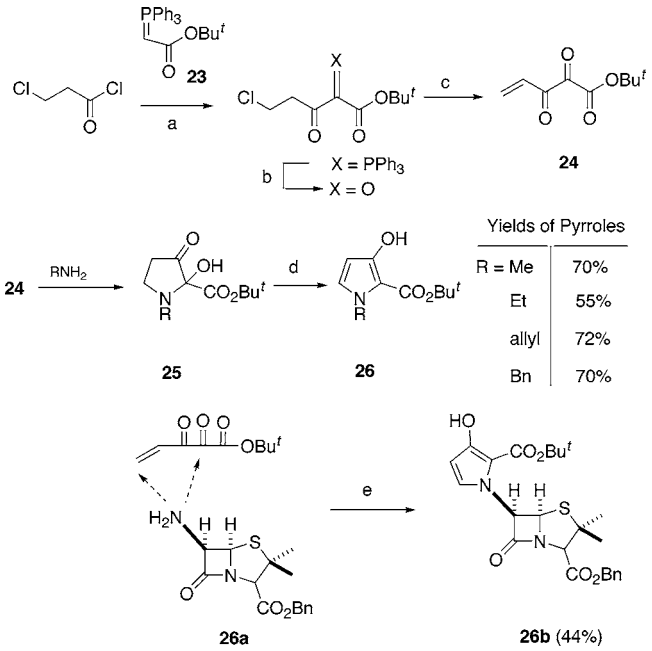
Use of tryptamine as the dinucleophilic donor in reaction with a substituted tricarbonyl **16** was key to a synthesis of the indole alkaloids, eburnamonine and tacamonine.[12] Scheme 4 illustrates the attack of both primary amino and indolo nucleophilic centers at the same carbonyl site forming **17**, followed by the steps leading to **20** through **18** and **19**. Compound **20** was previously converted by Martel to eburnamonine (**21**) by standard enamine coupling reactions.[13]

Scheme 4. Partial Synthesis of Eburnamonine[a]



[a] Reagents and conditions: (a) $CHCl_3$, 65 °C, 17−26 h (65%); (b) mixed anhydride formation with 98% HCO_2H, then loss of CO as in Scheme 3; (c) $NaBH_3CN$ (45% for steps b and c); (d) EtOH, 78 °C, 16 h (83%); (e) $LiAlH_4$ (75%), then 48% HBr (83%).

Scheme 5. Formation of Vinyl VTC: Conversion to Pyrroles[a]



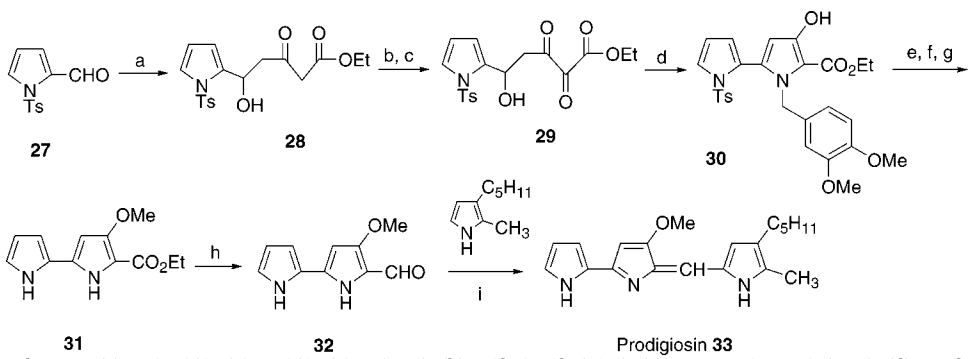
[a] Reagents and conditions: (a) BSA; (b) O_3; (c) $NaHCO_3$ (60%); (d) SiO_2; (e) CH_2Cl_2, then SiO_2.

Vinyl, Alkenyl, and Acetylenic Groups as Partners in Electrophilic Addition to VTC Esters

Novel polyelectrophiles were generated by substituting the vicinal tricarbonyl group with a neighboring electrophilic unit such as an olefinic, an acetylenic, a carbonyl, or an epoxide group. When such aggregates were treated with di- and trinucleophilic reactants, new types of tandem reactivity were observed. One such dielectrophile that opened up a broad range of transformations is the vinyl vicinal tricarbonyl (vinyl VTC) derivative **24**. This *tert*-butyl ester was easily prepared (Scheme 5) from β-chloropropionyl chloride by coupling with the phosphoranylidene ester **23** using BSA, followed by ozonolysis and dehydrohalogenation.[5a,14] Reaction of **24** with primary amines yielded hydroxy pyrrolidone carboxylates **25** by Michael attack along with carbonyl addition. The pyrrolidones underwent ready dehydration on silica gel, yielding 3-hydroxy pyrroles **26**.[15a] The generality of this reaction is shown in the formation of the pyrrole **26b** from 6-APA benzyl ester (**26a**).[15b]

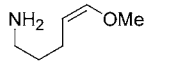
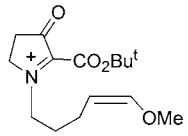
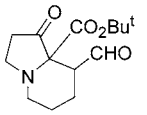
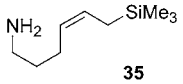
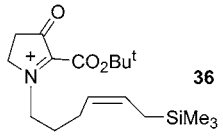
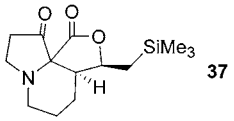
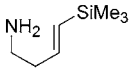
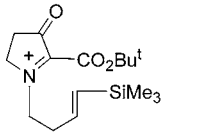
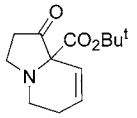
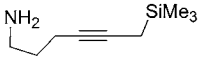
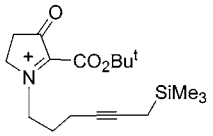
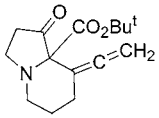
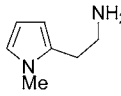
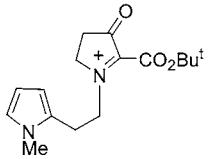
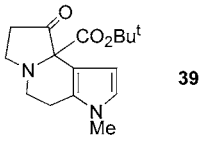
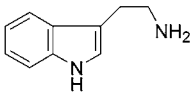
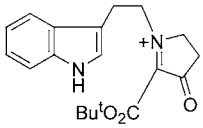
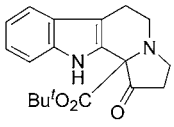
A timely application of this type of pyrrole formation involved synthesis of the bacterial metabolite prodigiosin (**33**),[5b] analogues of which have shown immunosuppressant and other biological activity.[16] Starting with the protected pyrrole-2-aldehyde **27**, reaction with the dilithium salt of ethyl acetoacetate led to **28** (Scheme 6). After dehydration of **28**, oxidation[17,18] yielded the alkenyl VTC ethyl ester **29**. Conversion of **29** to a hydroxypyrrole **30** with 3,4-dimethoxybenzylamine was followed by methylation and deprotection, yielding **31**. Reduction of **31** to the methoxy bipyrrole aldehyde **32** was followed by acid-catalyzed coupling of this prodigiosin precursor with methylamyl pyrrole to yield prodigiosin (**33**).[5b]

Scheme 6. Synthesis of Prodigiosin[a]

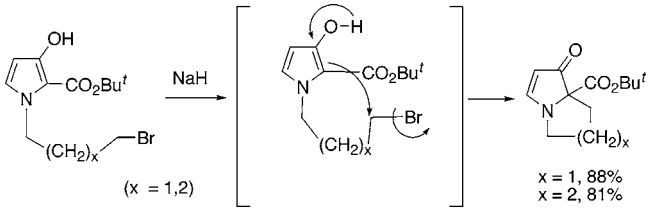


[a] Reagents and conditions: (a) $H_2C{=}C(OLi)CH{=}C(OLi)OEt$ (75%); (b) HCl, $CHCl_3$ (58%); (c) 4-NMe_2-C_6H_4NO (70%); (d) 3,4-dimethoxybenzylamine (23%); (e) NaH, Me_2SO_4 (77%); (f) 5% H_2SO_4, TFA, anisole (62%); (g) NaOH, EtOH (65%); (h) McFadyen−Stevens reduction (33%); (i) HBr catalysis (50%).

Table 1. The Reaction of Trinucleophiles with Vinyl VTC 24[21]

Amine	Intermediate	Product	Yield
			45%
 **35**	 **36**	 **37**	45%
			42%
			64%
 **38**		 **39**	90%
			73%

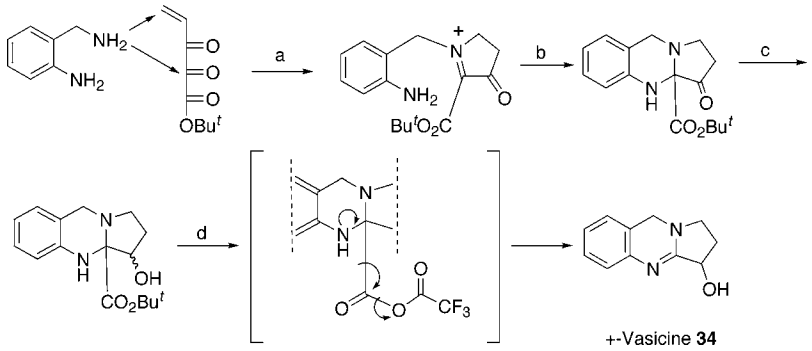
Scheme 7. Intramolecular Alkylation Reactions of 3-Hydroxy Pyrroles



The 3-hydroxypyrrole-2-carboxylates could be used in the formation of pyrrolizidine and indolizidine alkaloids (Scheme 7). In this process, incorporation of a bromo leaving group in the framework of the amino nucleophile provided an opportunity for intramolecular alkylation.[19]

The hydroxypyrrolidone precursor to the pyrroles may react by a different pathway under more strongly acidic conditions through an iminium ion, which can take part in a further intramolecular addition. This outcome is shown in the synthesis of the medicinal agent vasicine (**34**) (Scheme 8)[20] and in the transformations listed in Table 1. In these reactions, the primary amino group behaved as the dinucleophilic agent, and the third-stage nucleophilic attack took place at the iminium site with a variety of donor groups, including an aromatic amine,

Scheme 8. Decarbonylation[48] in the Synthesis of (±)-Vasicine[a]



[a] Reagents and conditions: (a) $CHCl_3$, 20 °C, 2 h; (b) SiO_2 (68%); (c) $NaBH_4$ (82%); (d) TFA, 40 °C (48%).

Table 2. The Reactions of Amino Amides with Vinyl VTC 24[22]

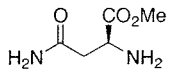
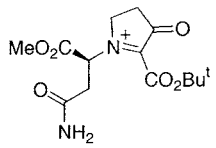
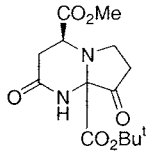
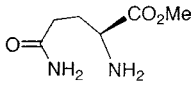
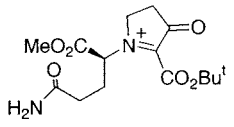
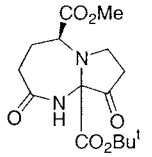
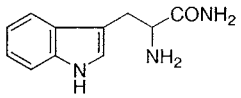
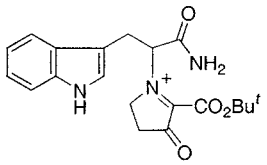
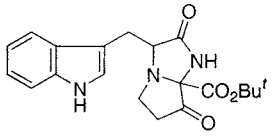
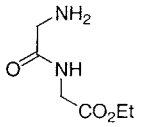
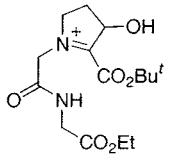
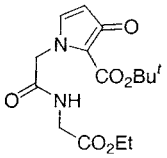
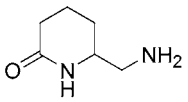
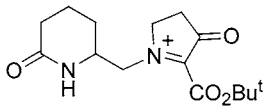
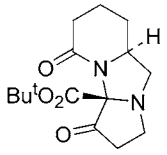
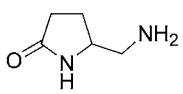
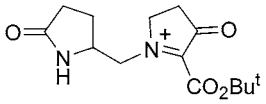
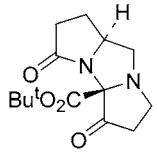
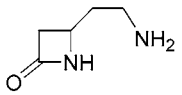
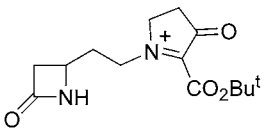
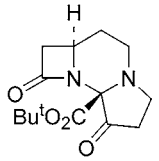
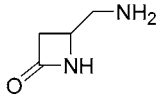
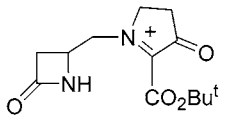
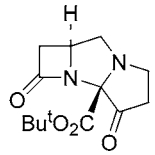
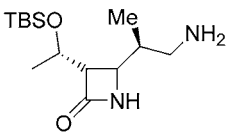
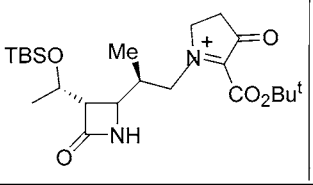
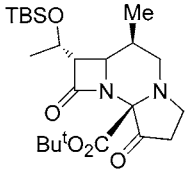
Amine	Intermediate	Product	Yield
			81%
			33%
			68%
			38%

Table 3. The Reactions of Amino Lactams with Vinyl VTC 24[23]

Amine	Intermediate	Product	Yield
			84%
			76%
			72%
			30%
			41%

an enol ether, an allylic silane, an alkenyl silane, a propargyl silane, a pyrrole, and an indole. Interestingly, the product **37** from the allylsilane **35** involved the fragmentation of the intermediate **36** with loss of isobutylene.[21] The reaction with the aminoethyl pyrrole **38** yielded indolizidine **39**. Amino amides and amino lactams also took part in this sequence as illustrated in Tables 2[22] and 3.[23]

Other electrophilic substituents attached to the VTC contribute to di- and trielectrophilic behavior. Thus, the acetylenic derivative **40** underwent reaction with polynucleophilic reagents to form products as illustrated in Scheme 9 and Table 4.[24] In the acetylenic VTC reactions with polynucleophiles such as amino amides, third-stage processes through iminium ion intermediates did not take place. This is, most probably, a consequence of the high-energy antiaromatic nature to be expected of the cyclopentadienone-like iminium species.

Scheme 9. Reaction of Acetylenic VTC with Amines

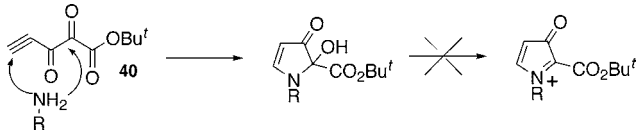
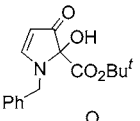
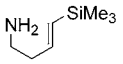
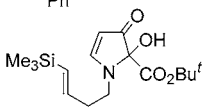
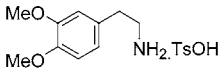
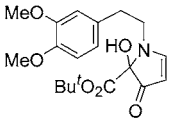
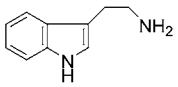
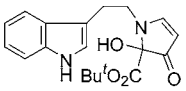
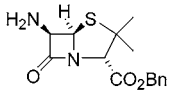
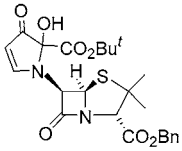


Table 4. Reactions of Acetylenic VTC 40

Amine	Product	Yield
$PhCH_2NH_2$		65%
		57%
		62%
		40%
		38%

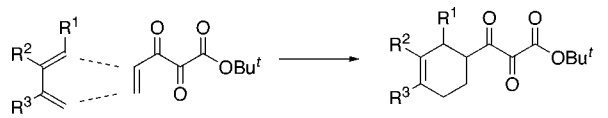
Diels–Alder Reactions with Vinyl VTC Derivatives

In early studies on vinyl and acetylenic derivatives of tricarbonyl compounds (**24** and **40**) with dinucleophiles, we explored the reactivity of the α,β-unsaturated double bond with dienes. As expected, Diels–Alder adducts were the major products (Scheme 10).

In the reaction of acylamino dienes **41** with the vinyl VTC **24**, the initial Diels–Alder addition product **42** underwent a second-stage cyclization involving addition of the Cbz-protected NH to the favorably located central carbonyl, as shown in Scheme 11. The resulting pyrrolidone **43** could then be converted to the tetrahydroindole **44** by H_2/Pd reduction and $N(Bu)_4F$ deprotection.

Similarly, the acetylenic VTC derivative **40** underwent reaction with dienes, yielding intermediates **45**, which could be converted by primary amines to dihydroindoles **46**. Oxidation of these to the corresponding indoles **47** took place with DDQ (Scheme 12).[25]

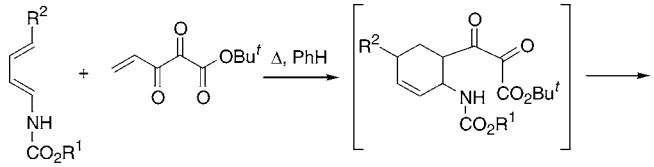
Scheme 10. Diels–Alder Reactions of Vinyl VTC



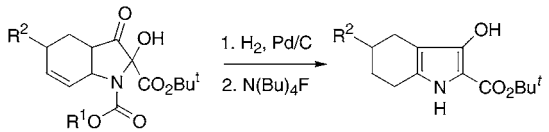
24

$R^1 = R^2 = R^3 = H$ (78%)
$R^1 = Me; R^2 = R^3 = H$ (60%)
$R^1 = H; R^2 = R^3 = Me$ (82%)

Scheme 11. Acyl Amino Dienes with Vinyl VTC



41 **24** **42**



43 **44**

$R^1 = CH_2Ph; R^2 = Me$ (77%)
$R^1 = (CH_2)_2SiMe_3; R^2 = H$ (75%)
$R^1 = (CH_2)_2SiMe_3; R^2 = Me$ (87%)

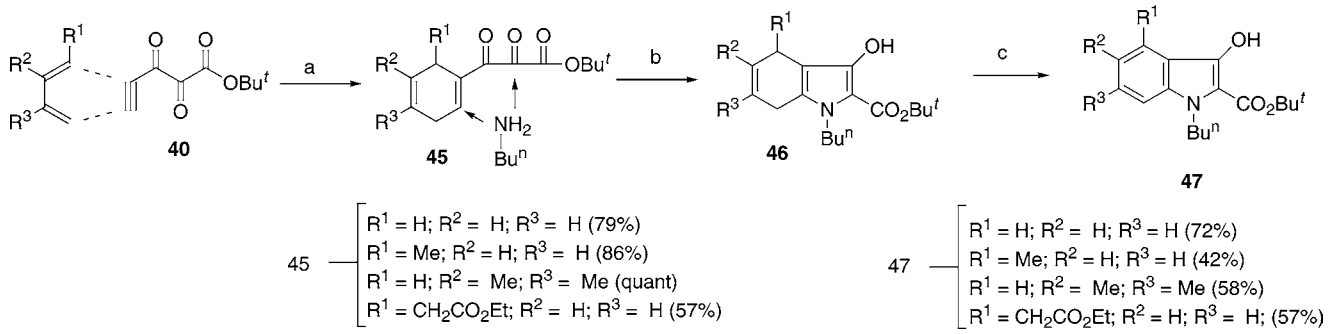
Formation of Hydroxy Furan Carboxylates using Tricarbonyls

Synthesis of novel furan derivatives started with tricarbonyl precursors such as **48**, which were converted to lithio derivatives **49** (Scheme 13). Aldol reactions of the enolates **49** with aldehydes yielded alcohols such as **50**, which on ozonolysis underwent intramolecular reaction with the tricarbonyls, forming the dihydrofuranone carboxylates, **51**. These products could be converted to the furans **52** by *p*-toluenesulfonic acid.[26,27]

Tricarbonyls Derived from Carboxylic Acids in Peptides

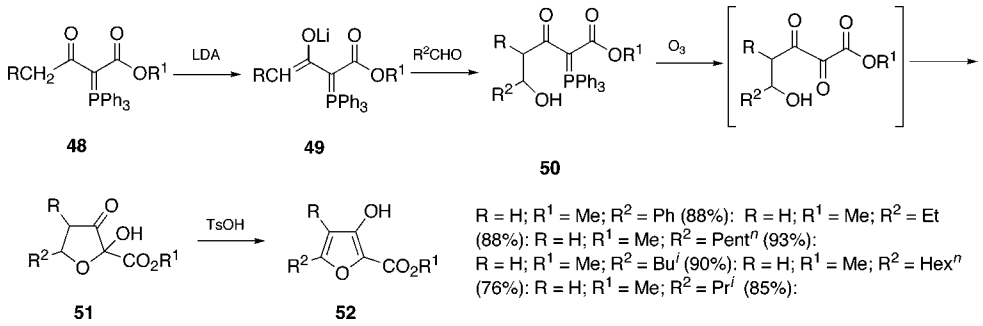
As part of our investigation into the electrophilic behavior of VTC derivatives, we prepared a series of tricarbonyls from protected peptidic carboxylic acids. Coupling of the acids with benzyl(triphenylphosphoranylidene)acetate in the presence of EDCI followed by oxidation with ozone yielded the peptidyl tricarbonyls **53** (Scheme 14). These modified dipeptides listed in Table 5 showed activity as inhibitors of human neutrophil elastase (HNE), porcine pancreatic elastase (PPE), and α-chymotrypsin comparable to the activity of trifluoromethyl ketone serine

Scheme 12. Diels–Alder Reaction of Aceylenic VTC[a]



[a] Reagents and conditions: (a) PhH, 60 °C; (b) mild acid; (c) DDQ.

Scheme 13. Synthesis of Substituted Furans



Scheme 14. Synthesis of Peptidic VTCs

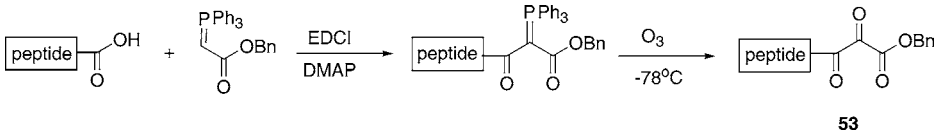
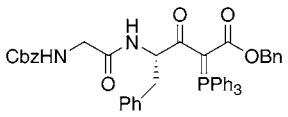
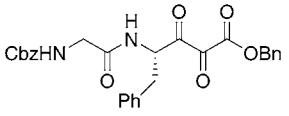
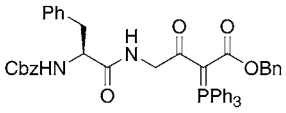
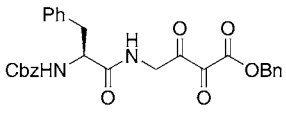
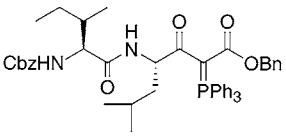
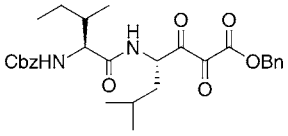
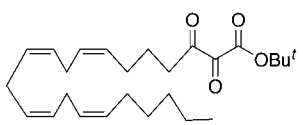


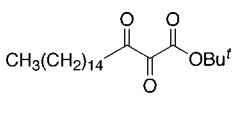
Table 5. Peptidic Tricarbonyls

Peptide	Ylide	Tricarbonyl	Yield
Cbz-HN-Gly-Phe			67%
Cbz-HN-Phe-Gly			58%
Cbz-HN-Ile-Leu			68%

protease inhibitor analogues.[28] In related studies, tricarbonyl derivatives of palmitic and arachidonic acids, **54** and **55**, showed phospholipase inhibitory activity, though somewhat less effectively than the corresponding trifluoromethyl ketones.[29]



54

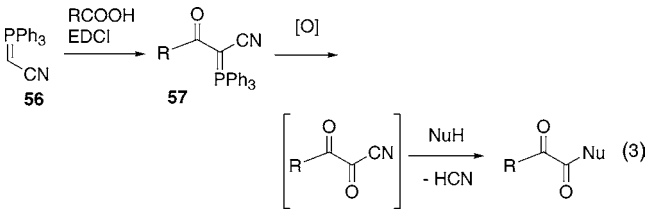


55

α-Keto and α-Hydroxy Amide Synthesis

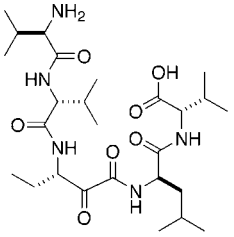
In extending our studies to cyano analogues, we used (cyanomethylene)triphenyl-phosphorane (**56**) in the formation of stable acyl cyanophosphorane intermediates **57**.

These could be oxidized (O_3) at low temperature to labile α,β-diketo nitriles, which undergo rapid reaction in situ with nucleophiles such as alcohols and amines (eq 3) to yield α-keto esters or α-keto amides.[30,31]

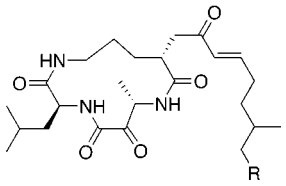


(3)

This acyl cyanophosphorane procedure was utilized in the synthesis of a series of natural products containing α-keto amide linkages, such as the prolyl endopeptidase inhibitors poststatin (**58**) and eurystatin (**59**), as well as

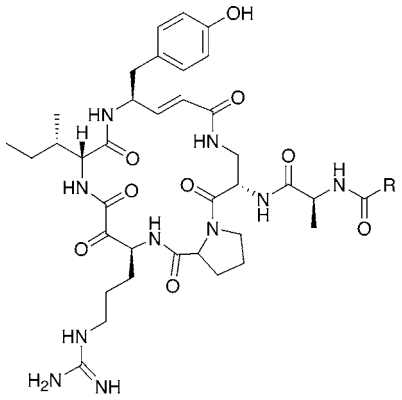


Poststatin **58**



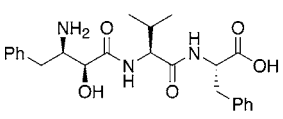
R = H, Eurystatin A (**59a**)
R = Me, Eurystatin B (**59b**)

the serine protease inhibitors cyclotheonamides E_2 and E_3 (**60a**,**b**). Likewise, the aminopeptidase inhibitors,

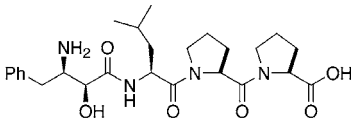


R = C_6H_5, Cyclotheonamide E_2 (**60a**)
R = $CH_2CH(CH_3)_2$, Cyclotheonamide E_3 (**60b**)

phebestin (**61**) and probestin (**62**) containing α-hydroxy



Phebestin **61**



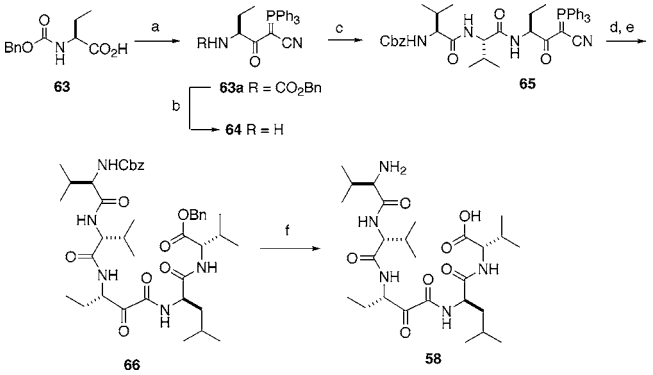
Probestin **62**

amide linkages were formed by stereocontrolled reduction of initially formed α-keto amides to the corresponding α-hydroxy amides.[31]

Poststatin

The acyl cyanophosphorane **63a** formed by the EDCI coupling of Cbz-protected (*S*)-(+)-2-aminobutanoic acid (**63**) with (cyanomethylene)triphenylphosphorane was deprotected by hydrogenolysis, Scheme 15. The free amine **64** was treated with Cbz-protected valylvaline under standard peptide-coupling conditions, yielding the tripeptide **65** as the sole epimer. Ozonolytic cleavage of the carbon−phosphorus double bond in **65** generated a labile α,β-diketo nitrile, which was allowed to react in situ with D-leucylvaline *O*-benzyl ester, forming the protected pentapeptide **66**. Hydrogenolysis of the benzylic groups of **66** yielded poststatin (**58**).[31]

Scheme 15. Synthesis of Poststatin[a]



[a] Reagents and conditions: (a) PPh_3CHCN, EDCI (88%); (b) H_2, Pd/C (69%); (c) Cbz-Val-Val-OH (69%); (d) O_3, −78 °C; (e) H-D-Leu-Val-OBn; (f) H_2, Pd/C (73%).

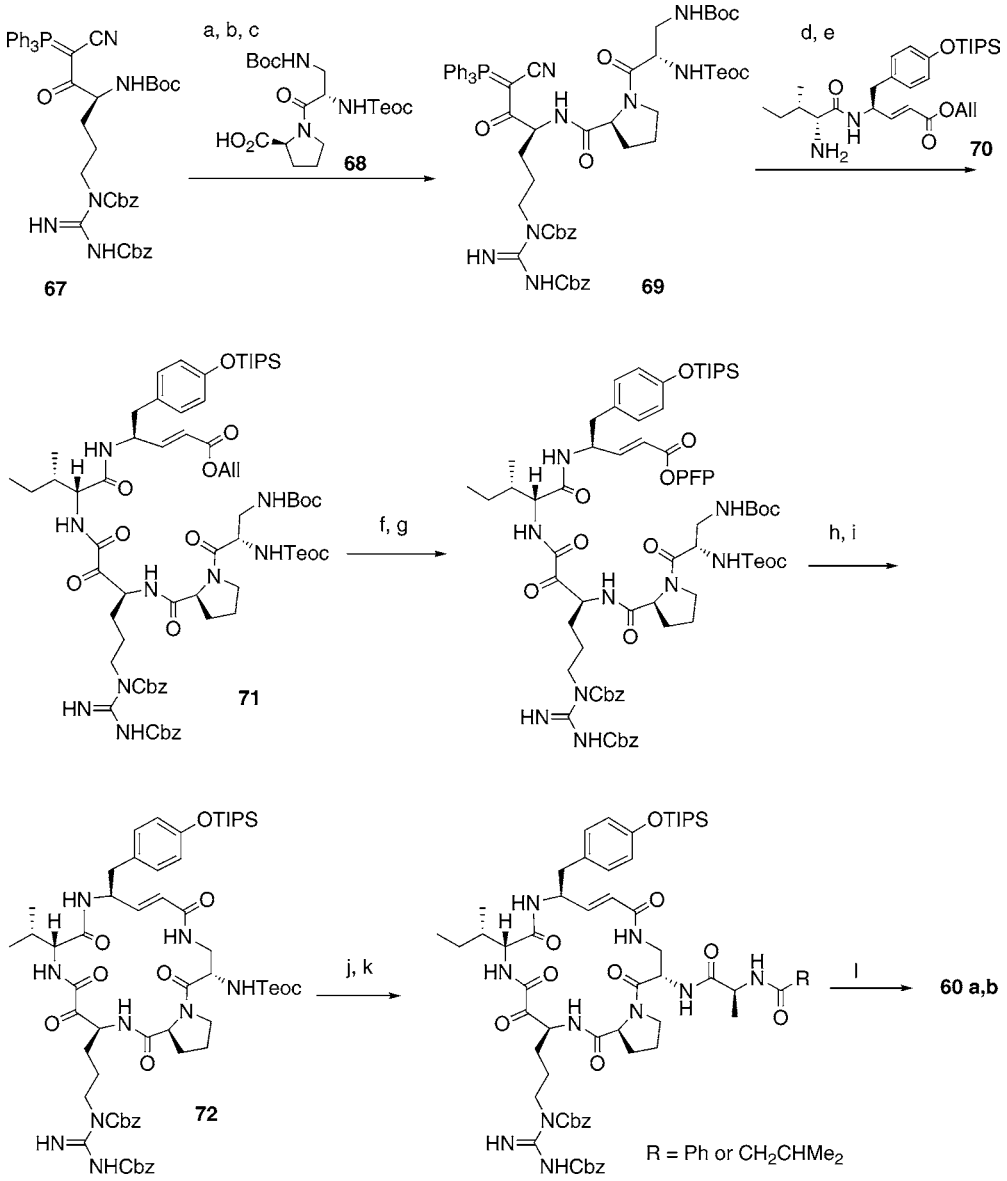
Synthesis of Cyclotheonamides E_2 and E_3

Our synthesis of the cyclotheonamides[32,33] (**60a**,**b**) incorporated features of special interest in connection with the formation of the α-keto amide linkage. Generation of this key unit at an early stage avoided problems found in previous syntheses associated with the use of α-hydroxy amide precursors, requiring subsequent operations with mixtures of diastereomers. In our procedure, outlined in Scheme 16, the ylide **67**, formed from triply protected arginine, was treated with trifluoroacetic acid (TFA) and coupled with protected dipeptide **68** to form **69**. Ozonolysis of **69** yielded the α,β-diketo nitrile for in situ coupling with the dipeptide **70**, leading to the complete pentapeptidic framework **71**. This pentapeptide could then be transformed to lactam **72** by changing protecting groups and DMAP, $NaHCO_3$ cyclization. The TFA deprotection, incorporation of the side chains, and final HF-pyridine conversion to **60a**,**b** took place in excellent yields.

Phebestin

We illustrate the methodology used in the synthesis of natural α-hydroxy amides with the synthesis of phebestin, outlined in Scheme 17. *N*-Boc-D-phenylalanine was coupled with (cyanomethylene)triphenylphosphorane **56** to form the acyl cyanophosphorane **73**. Ozonolysis of **73** was followed by coupling with the benzyl ester of L-valine to yield the α-keto amide **74**. We then explored reduction procedures for the diastereoselective conversion of **74** to **75**. Among reductants examined, including complexes of rhodium with chiral ligands, Dip-Cl, DIBAL-H, zinc borohydride, L-Selectride, K-Selectride, and $(BuO)_3BH-Li$, we found that zinc borohydride[34] gave the highest diastere-

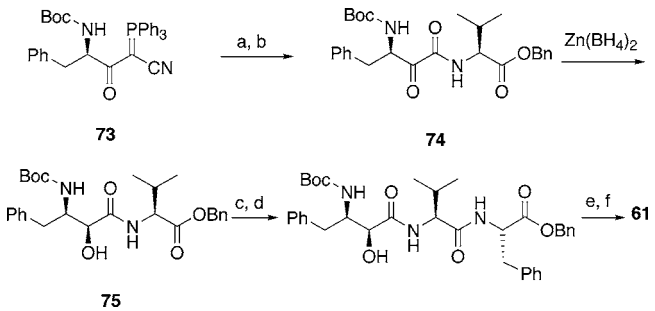
Scheme 16. Synthesis of Cyclotheonamides E_2 and E_3[a]



[a] Reagents and conditions: (a) TFA; (b) EDCI, HOBt (78%, two steps); (c) **68** (88%); (d) O_3, −78 °C; (e) **70** (75%, two steps); (f) $Pd(PPh_3)_4$, $PhSiH_3$ (86%); (g) DCC, PFP-OH (88%); (h) HCl in Et_2O; (i) DMAP, $NaHCO_3$ (61%, two steps); (j) TFA; $NaHCO_3$; (k) EDCI, HOBt, *N*-benzoylalanine (83%) or isovaleryalanine (85%) two steps; (l) HF·py (70−72%).

omeric selectivity (92:8) in reduction of the ketone **74** to the alcohol **75**. The further conversion of **75** to phebestin is shown in Scheme 17.[31]

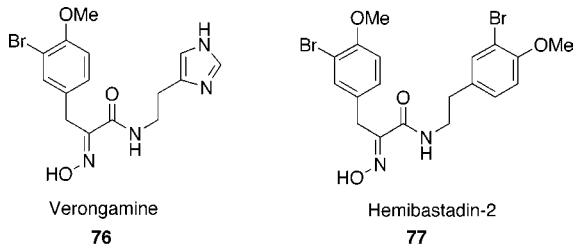
Scheme 17. Synthesis of Phebestin[a]



[a] Reagents and conditions: (a) O_3, −78 °C; (b) L-Val-OBn (62%); (c) H_2, Pd/C, MeOH; (d) EDCI, HOBt, Et_3N, L-Phe-OBn (83%); (e) H_2, Pd/C; (f) TFA (80%).

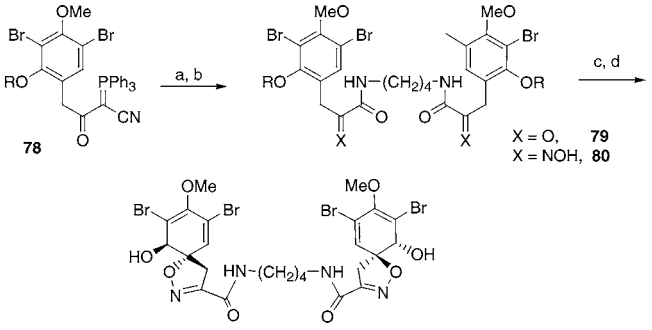
Marine Metabolites

In work on derivatives of α-keto amides, we examined a family of antibiotic marine metabolites. These alkaloids, including verongamine (**76**), hemibastadin-2 (**77**), and



aerothionin (**81**), contain vicinal dicarbonyl linkages in the form of α-oximino amides. Syntheses of these products employed the same acyl cyano phosphorane methodology

Scheme 18. Synthesis of Aerothionin[a]

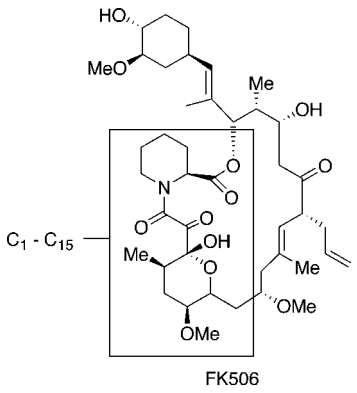


[a] Reagents and conditions: (a) O_3, −78 °C; (b) 1,4-diaminobutane (64%); (c) $NH_2OH{\cdot}HCl$, NaOAc, EtOH (95%); (d) 2,4,4,6-tetrabromo-2,5-cyclohexadienone (70%), then $NaCNBH_3$, TFA (25%).

described above. Scheme 18 illustrates the formation of aerothionin in which the bis α-keto amide (**79**, R = PNB) formed by the reaction of 1,4-diaminobutane with the ozonolysis product of **78** was converted to the bis α-oximino derivative **80** (R = PNB). After deprotection and subsequent oxidation[35a] and reduction steps,[35b] **80** (R = H) yielded the bis spiro oxazoline system containing the desired trans/trans stereochemistry of the natural product **81**.

Synthesis of Tricarbonyl-Containing Protease Inhibitors, YM-47141 and YM-47142, *Scheme 19*

Interest in the chemistry of tricarbonyls has recently been heightened by the isolation of biologically active natural products containing a tricarbonyl aggregate precursor in macrocyclic lactones and depsipeptides. In FK-506 (**82**),

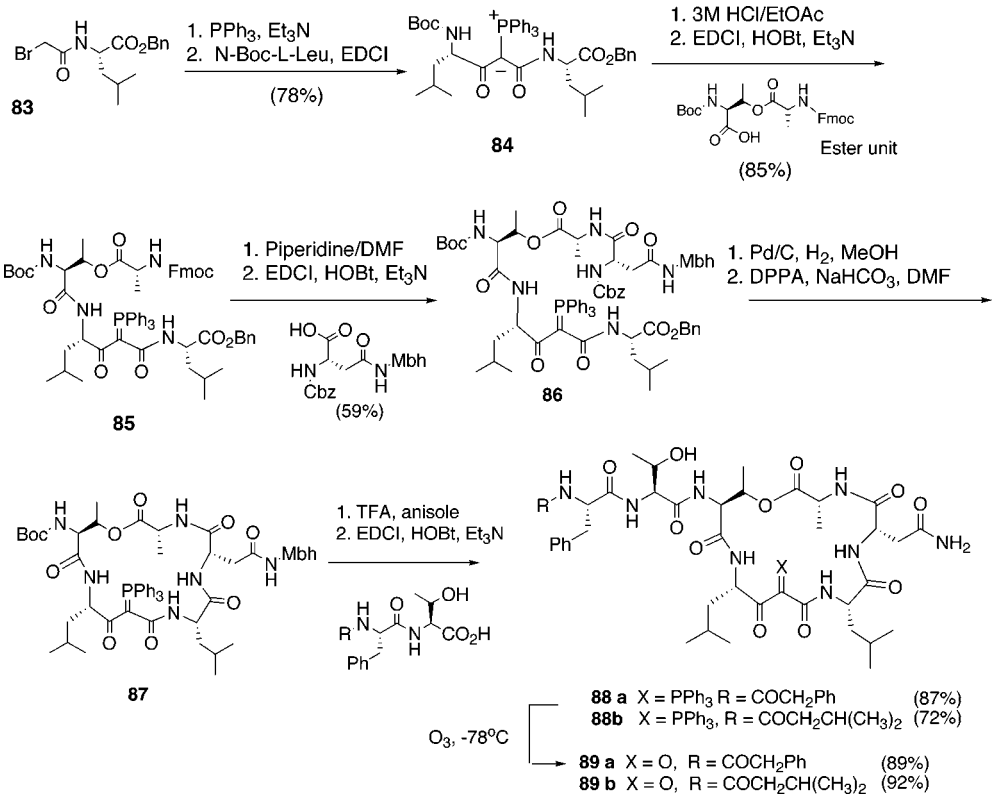


82

a potent immunosuppressant, and the related antifungal antibiotics rapamycin and 29-demethoxy rapamycin, vicinal tricarbonyls occur in the form of hemiketal linkages with neighboring alcohol functions.[36]

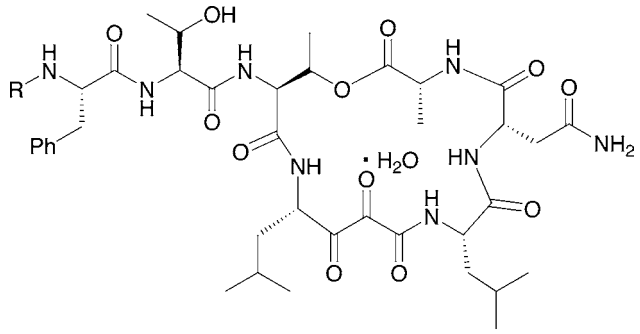
We had previously shown how the C_1−C_{15} diketo amide function in FK-506 may be prepared using the ylide coupling, ozonolysis sequence.[5c] More recently, the isolation of the protease inhibitors YM-47141 and YM-47142 (**89a**,**b**) by Japanese investigators provided the first examples of natural products containing the tricarbonyl unit in hydrated form.[37] These depsipeptides offered challenging synthetic targets to test our ylide protection and activation procedures as outlined in our total synthesis of **89a**,**b** described below.[38]

Scheme 19. Synthesis of YM-47141 and YM-47142



An important element in planning this synthesis centered on the role played by the diketo ylide **84** as a stabilized dipeptidic scaffold for generating the differentially protected precursor **88a**,**b** containing the complete depsipeptidic framework, which could be transformed to the products **89a**,**b** in the final step.[38] We began by coupling L-leucine benzyl ester with bromoacetic acid to form **83**, convertible to the ylide **84** by formation of the phosphonium salt followed by reaction with triethylamine and then EDCI coupling with *N*-Boc-L-leucine. Further steps to the macrocycle (Scheme 19) involved the reaction of the depsipeptide ester unit with **84** to form **85** and the coupling of **85** with Mbh-protected *N*-Cbz-asparagine yielding **86**. The debenzylation of **86** and cyclization with DPPA formed lactam **87**, which was then coupled with the substituted phenylalanylthreonines to yield the diacyl ylides **88a**,**b** as the penultimate products.

Throughout the above process, the ylide group served to protect the incipient central carbonyl. In the last step (**88a**,**b** to **89a**,**b**), ozonolysis at low temperature formed the hydrated vicinal tricarbonyl aggregate in excellent yields. This protective feature of the synthesis is important since the highly electrophilic 1,2,3-tricarbonyl system, generated only at the end of the sequence, is known to undergo cleavage or rearrangement under hydrolytic conditions.[39]

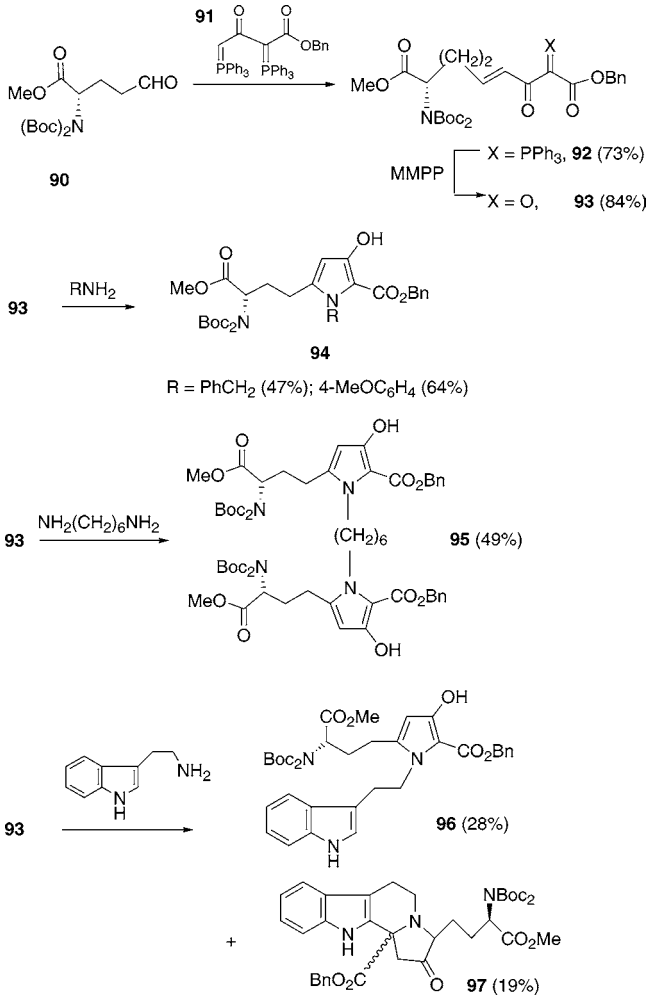


89 a R = $COCH_2Ph$
89 b R = $COCH_2CH(CH_3)_2$

Incorporation of Heterocyclic Systems into α-Amino Acids Using Vicinal Tricarbonyls and Cyano Analogues

There has been continued recent interest in the synthesis of unnatural amino acids prompted by the biological and toxicological activity observed with representatives of this group. In one class of modified α-amino acids, VTC units have been incorporated by Baldwin[40] into the amino acid backbone, and these units have been transformed into heterocyclic derivatives, offering possibilities for new types of chemical and biological reactivity. This work has shown how monocarboxylic acid derivatives of protected aspartic and glutamic acids could be transformed into tricarbonyl esters using the cyano ylide procedures described above. The substituted amino acids were then converted to novel heterocyclic products by reactions with aromatic diamines or other dinucleophiles.

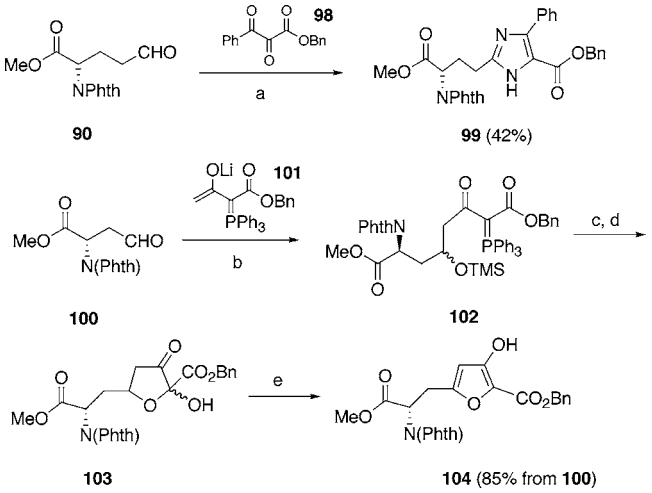
Scheme 20. Pyrrole- and Indole-Substituted Amino Acids



Pyrrole Derivatives of Amino Acids

Our related recent studies on the use of tricarbonyl chemistry to introduce heterocyclic systems into α-amino acids made use of monoaldehydes formed by selective reduction of *N*,*N*-di-Boc dimethyl esters of aspartic and glutamic acids. Our sequence began[41] with aldehyde **90** prepared by the lithium triethylborohydride reduction of the corresponding di-*N*-Boc-protected glutamic acid dimethyl diester.[42] Wittig reaction of **90** with the known bis phosphorane **91**[43] yielded the α,*β*-unsaturated keto ylido ester **92**, which was then oxidized with magnesium monoperphthalate (MMPP) to yield alkenyl tricarbonyl **93**. As in our synthesis of prodigiosin,[5b] we treated **93** with primary amines, such as benzylamine and *p*-anisidine, forming *N*-substituted pyrroles **94** (Scheme 20). Similar reactions were carried out using aspartic acid as the starting material and DMDO as the oxidant. As illustrated, 1,6-diaminohexane underwent bis-addition to **93** yielding the alkyl-bridged bipyrrole **95**. With tryptamine, the reaction took place through the typical pyrrole-forming route yielding **96** along with the iminium ion adduct **97**.

Scheme 21. Imidazole- and Furan-Substituted Amino Acids[a]



[a] Reagents and conditions: (a) NH_4OAc, HOAc; (b) TMSCl; (c) mild acid; (d) O_3, −78 °C; (e) TsOH.

Imidazole and Furan Derivatives of Amino Acids

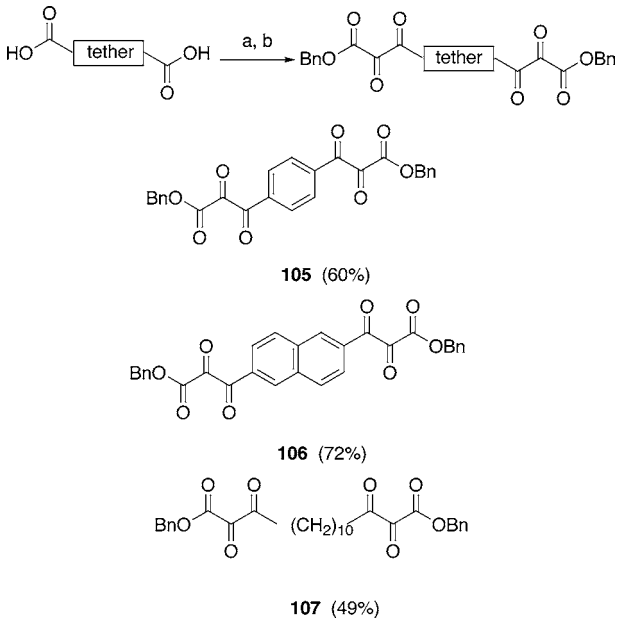
In a second phase of our work designed to prepare heterocyclic derivatives of amino acids, we studied the reaction of **90** with the tricarbonyl ester **98** in the presence of ammonium acetate leading to the imidazole carboxylate **99** (Scheme 21).[44] Based on procedures that we we have previously developed,[26] the aldehyde esters could also be employed in the formation of furan derivatives of α-amino acids. Thus, the phthalimide-protected aldehyde ester **100** derived from aspartic acid dimethyl ester underwent reaction with the lithiated tricarbonyl derivative **101** in the presence of tetramethylsilane chloride (TMS-Cl) to form a diasteromeric mixture of the TMS-protected alcohol **102**. Deprotection of the alcohol followed by ozonolysis yielded a tricarbonyl, which underwent cyclization to **103** and then TsOH-promoted conversion to the furan **104**.

The DNA Binding Properties of Dielectrophiles Incorporating Bis Vicinal Tricarbonyls[45]

We have described the finding that VTC systems may serve as versatile electrophilic reactants for the formation of heterocyclic products with a variety of primary amines. On the basis of this work, we investigated the possibility that two such electrophilic sites, incorporated into a single molecule and separated by a suitable tether, might react with the amino groups of DNA bases to provide interstrand DNA cross-links. Our studies on the synthesis of bis vicinal tricarbonyls and their DNA binding properties are summarized below.

The bis tricarbonyl derivatives were prepared from readily available dicarboxylic acids or their diacid chloride analogues. The EDCI coupling of the diacids or diacid chlorides with benzyl(triphenylphosphoranylidine)acetate was accomplished using our earlier procedures (Scheme 22). Oxidative cleavage of the carbon−phosphorus double bonds was conducted utilizing either ozone or Oxone to provide the bis tricarbonyls as hydrates. The products thus generated contained either benzene **105**, naphthalene **106**, or decane **107** as the tethers. The agents were each incubated with FCX174 *Pst*I-linear double-stranded DNA (pH 7.1, 5386 base pairs, 1×10^{-8} M) for 24 h at 37 °C. The reaction samples were then denatured (100 °C, 3 min) and loaded onto a denaturing agarose gel (0.7% agarose with 0.03 M NaOH, 5 h, 50 V). Cross-linking was detected by fluorescence visualization of a substantially more slowly moving band, compared to the fast moving band associated with the lower molecular weight single-stranded DNA. As shown in Figure 2, **105** was effective at generating cross-linked DNA at 5 and 1 mM (lanes 1 and 2). This activity is not apparent at lower concentrations of **105** (0.5 mM, lane 3). Lane 4 shows a faster moving band (single-stranded DNA) corresponding to the incubation of the DNA without added agent. For a positive cross-linking comparison (lane 5), a control experiment was carried out employing psoralen-induced DNA cross-links. Although the 1,4-benzene derivative **105** was the most effective of the bis dielectrophiles used, each of the bis tricarbonyls shown in Scheme 22 brought about cross-linkages in the DNA at concentrations of 5 mM. Derivatives **106** and **107** were slightly less effective. In other experiments, we

Scheme 22. Bis-VTC Derivative Hydrates in DNA Cross-Linkage[a]



[a] Reagents and conditions: (a) $PPh_3C(H)CO_2Bn$, EDCI; (b) O_3, −78 °C.

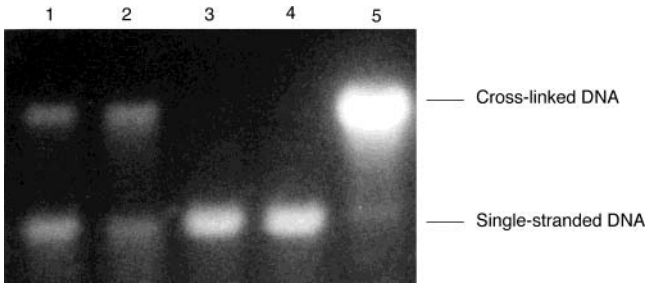


FIGURE 2. Cross Linking Assay: lane 1, 5 mM **105**; lane 2, 1 mM **105**; lane 3, 0.5 mM **105**; lane 4, untreated DNA; lane 5, 10 mM psoralen.

showed that these bis-VTC agents were also effective in cleaving supercoiled DNA.[45]

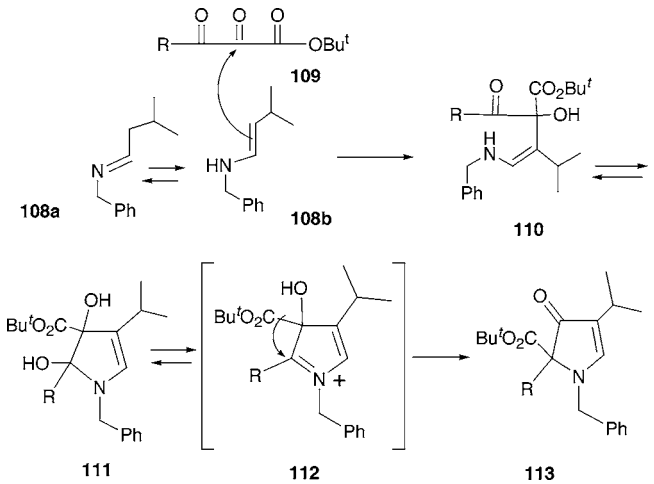
Highlights and Sidelights

The vicinal tricarbonyl grouping contains a highly reactive electrophilic central carbonyl. Until recently, this functional array has been largely overlooked by the community of synthetic organic chemists despite the potential for its use in a wide range of transformations. We found that when we coupled the reactivity of the central carbonyl with that of neighboring electrophilic units such as the vinyl or acetylenic group, we observed novel multistage reactions of these partnership derivatives with di- and trinucleophilic systems.

An example of one such four-step transformation is the acid-catalyzed reaction of the vinyl VTC with an aminoethyl pyrrole **38** leading to the substituted indolizidine **39** through the iminium intermediate shown in Table 1 (90% overall yield). The foregoing addition−cyclization process, along with the examples reported in Tables 1−3, highlight the role of intermediate iminium ions in the reactions of vinyl and acetylenic VTCs with donor reagents.

In addition, we have discovered other examples of the reactivity of this unique carbonyl. A notable case involves the reaction of VTC ester **109** with the Schiff base derived from the addition of benzylamine to isovaleraldehyde (**108a**). As shown below, treatment of **109** with the enamine **108b** yielded pyrrolinones **113** as the final products, most probably by the route illustrated in Scheme 23. We propose that the initial addition of the enamine to the central carbonyl yields product **110**, which is in equilibrium with the carbanolamine **111** and the iminium hydroxide **112**. A benzilic acid-like rearrangement of **112** then takes place forming the products **113**. The assigned pyrrolinone structure was confirmed by X-ray crystallographic analysis of **113**, R = p-tolyl.[46]

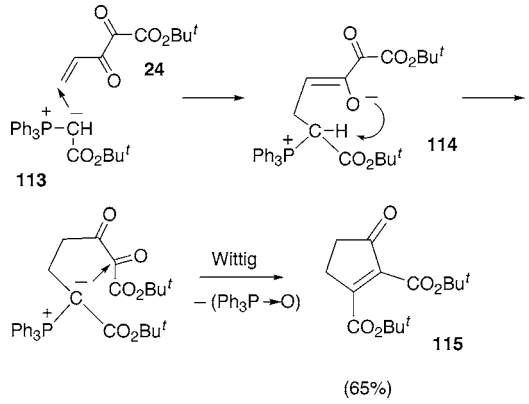
Scheme 23. The Reaction of Vicinal Tricarbonyls with Enamines[a]



[a] R = Ph (59%), 4-MeC_6H_4 (54%), 4-$MeOC_6H_4$ (63%), 4-$Me_2NC_6H_4$ (61%), 2-$MeOC_6H_4CH$=CH (53%), or Bu^t (58%).

Finally, as an interesting sidelight, Scheme 24 illustrates an unprecedented reaction between the stabilized ylide **114** and the vinyl VTC **24** whereby the initial Michael addition is followed by an intramolecular Wittig reaction yielding the substituted cyclopentenone **115**.[47]

Scheme 24. Addition of Ylide to VTC



Conclusion

The vicinal tricarbonyl and related α,β-diketo nitrile aggregates are powerful electrophiles with widespread application in organic synthesis. These systems are readily available from carboxylic acids by a simple peptide-like coupling process with a carboalkoxy or cyano ylide followed by mild oxidation. Our work, outlined above, illustrates the application of VTC and cyano analogues in the synthesis of alkaloid-related heterocyclic systems including a diverse range of natural products. We have also demonstrated the utility of this chemistry in the formation of α-keto amides and α,β-diketo amides found in many important bioactive systems.

We hope that the explorations and new methodology reviewed here will stimulate further investigation into imaginative applications of these unique electrophilic systems in organic synthesis.

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References

(1) de Neufville, R.; von Pechmann, H. Ueber das Diphenyltriketon. *Ber.* **1890**, *23*, 3375−3387.
(2) (a) Rubin, M. B.; Gleiter, R. The Chemistry of Vicinal Polycarbonyl Compounds. *Chem. Rev.* **2000**, *100*, 1121−1164. (b) Rubin, M. B. The Chemistry of Vicinal Polyketones. *Chem. Rev.* **1975**, *75*, 177−202.
(3) (a) Schönberg, A.; Singer, E. Die Chemies des Ninhydrins und Anderer Cyclischer 1,2,3-Tricarbonylverbindungen. *Tetrahedron* **1978**, *34*, 1285−1300. (b) Joullié, M. M.; Thompson, T. R.; Nemeroff, N. H. Ninhydrin and Ninhydrin Analogues. Syntheses and Applications. *Tetrahedron* **1991**, *47*, 8791−8830.
(4) Wasserman, H. H.; Han, W. T. Vicinal Tricarbonyl Products from Singlet OxygenReactions. Application to the Synthesis of Carbacephams. *Tetrahedron Lett.* **1984**, *25*, 3743−3746.
(5) (a) Wasserman, H. H.; Fukuyama, J.; Murugesan, N.; Van Duzer, J.; Lombardo, L.; Rotello, V.; McCarthy, K. The Chemistry of Vicinal Tricarbonyls. A Stable Vinyl Tricarbonyl Hydrate as a Di- and Trielectrophile. *J. Am. Chem. Soc.* **1989**, *111*, 371−372. (b)

Wasserman, H. H.; Lombardo, L. J. The Chemistry of Vicinal Tricarbonyls. A Total Synthesis of Prodigiosin. *Tetrahedron Lett.* **1989**, *30*, 1725−1728. (c) Wasserman, H. H.; Rotello, V. M.; Williams, D. R.; Benbow, J. W. Synthesis of the "Tricarbonyl" Region of FK-506 Through an Amidophosphorane. *J. Org. Chem.* **1989**, *54*, 2785−2786. (d) Wasserman, H. H.; Kelly, T. A. The Chemistry of Vicinal Tricarbonyl Compounds. Short Syntheses of Eudistomins T, I and M. *Tetrahedron Lett.* **1989**, *30*, 7117−7120. (e) Wasserman, H. H.; Vu, C. B. Formation of Vicinal Tricarbonyl Compounds by Selective Oxidation of Ylides Using Potassium Peroxymonosulfate. *Tetrahedron Lett.* **1990**, *31*, 5205−5208. (f) Coats, S. J.; Wasserman, H. H. The Conversion of α-Bromo-β-Dicarbonyls to Vicinal Tricarbonyls Using Dimethyldioxirane and Base. *Tetrahedron Lett.* **1995**, *36*, 7735−7738. (g) Wasserman, H. H.; Baldino, C. M.; Coats, S. J. Selective Oxidation of Phosphorus Ylides by Dimethyldioxirane. Application to the Formation of Vicinal Tricarbonyls. *J. Org. Chem.* **1995**, *60*, 8231−8235.

(6) Wasserman, H. H.; Han, W. T. A Synthesis of Antibiotic (±)-PS-5. *Tetrahedron Lett.* **1984**, *25*, 3747−3750.

(7) Kametani, T.; Honda, T.; Nakayama, A.; Sasaki, Y.; Mochizuki, T.; Fukumoto, K. A Short and Stereoselective Synthesis of the Carbapenem Antibiotic PS-5. *J. Chem. Soc.*, *Perkin Trans. 1* **1981**, 2228−2232.

(8) Wasserman, H. H.; Rotello, V. M.; Krause, G. B. Oxidation of α-Ylido, β-Keto Amides to Vicinal Tricarbonyls. Synthesis of a Diketopiperazine Precursor of Bicyclomycin. *Tetrahedron Lett.* **1992**, *33*, 5419−5422.

(9) Yamaura, M.; Suzuki, T.; Hashimoto, H.; Yoshimura, J.; Shin, C. A Convenient Synthesis of 6-Hydroxy-7,9-bis(para-methoxybenzyl)-5-methylene-2-oxa-7,9-diazabicyclo[4.2.2]decane-8,10-dione. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2812−2820.

(10) Wasserman, H. H.; Amici, R.; Frechette, R.; Van Duzer, J. H. The Chemistry of Vicinal Tricarbonyl Compounds. Applications in the Synthesis of Isoquinoline Alkaloids. *Tetrahedron Lett.* **1989**, *30*, 869−872.

(11) We originally suggested that **14** was formed by decarboxylation in strong acid followed by air oxidation. With further study on related systems, we now picture the process as a decarbonylation of an intermediated mixed anhydride as shown. Other examples of this type of decarbonylation in strong acid were observed in related syntheses of the vincamine alkaloid eburnamonine (**21**) and vasicine (**34**) as well as in other work cited in ref 48.

(12) (a) Wasserman, H. H.; Kuo, G.-H. The Chemistry of Vicinal Tricarbonyl Compounds. Applications in the Synthesis of Vincamine-Related Alkaloids. *Tetrahedron Lett.* **1989**, *30*, 873−876. (b) Wasserman, H. H.; Kuo, G.-H. Oxidation of Ylide Precursors to Vicinal Tricarbonyls. Application in Vincamine Alkaloid Synthesis. *Tetrahedron* **1992**, *48*, 7071−7082.

(13) Martel, J.; Toromanoff, E.; Buendia, J.; Costerousse, G. Synthese Totale Stereospecifique de la (−) Eburnamonine: Acces a un Intermediaire Clé. *Bull. Soc. Chem. Fr. II* **1978**, 355−360.

(14) Wasserman, H. H.; Ennis, D. S.; Blum, C. A.; Rotello, V. M. The Conversion of Carboxylic Acids to Keto Phosphorane Precursors of 1,2,3-Vicinal Tricarbonyl Compounds. *Tetrahedron Lett.* **1992**, *33*, 6003−6006.

(15) (a) Wasserman, H. H.; Cook, J. D.; Fukuyama, J. M.; Rotello, V. M. The Chemistry of Vicinal Tricarbonyls. Use of Vinyl Tricarbonyl Esters in the Formation of 3-Hydroxypyrrole-2-Carboxylates. *Tetrahedron Lett.* **1989**, *30*, 1721−1724. (b) Wasserman, H. H.; Niu, C. Pyrrole Derivatives of 6-APA and 7-ACA. Oxygenation by Singlet Oxygen. *Biomed. Chem. Lett.* **1992**, *2*, 1101−1104.

(16) (a) D'Alessio, R.; Bargiotti, A.; Carlini, O.; Colotta, F.; Ferrari, M.; Gnocchi, P.; Isetta, A.; Mongelli, N.; Motta, P.; Rossi, A.; Tibolla, M.; Vanotti, E. Synthesis and Immunosuppressant Activity of Novel Prodigiosin Derivatives. *J. Med. Chem.* **2000**, *43*, 2557−2565. (b) D'Alessio, R.; Rossi, A. Short Synthesis of Undecyl Prodigiosine. A New Route to 2,2′-Bipyrrole-pyrromethene Systems. *Synlett*, **1996**, *6*, 513−514. (c) For a recent review of work on the synthesis of naturally occurring tripyrromethenes in the prodigiosin family, see: Fürstner, A. Chemistry and Biology of Roseophilin and the Prodigiosin Alkaloids: A Survey of the Last 2500 Years. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582−3603.

(17) This mild method of forming the tricarbonyl system using 4-(NMe_2)C_6H_4NO reported earlier by Sachs (ref 18) was used here because it avoided reagents (O_3, $^1O_2$, etc.) that could have oxidized the pyrrole ring.

(18) Sachs, F.; Harold V. Ueber Triketone IV. *Ber.* **1907**, *40*, 2714−2730.

(19) Wasserman, H. H.; Cook, J. D.; Vu, C. B. Intramolecular Alkylation of 3-Hydroxypyrrole-2-carboxylates. Formation of 5/5, 5/6, and 5/7 Ring Systems Related to Pyrrolidine Alkaloids. *Tetrahedron Lett.* **1990**, *31*, 4945−4948.

(20) Wasserman, H. H.; Kuo, G.-H. The Chemistry of Vicinal Tricarbonyls. An Efficient Synthesis of (±)-Vasicine. *Tetrahedron Lett.* **1991**, *32*, 7131−7132.

(21) (a) Wasserman, H. H.; Cook, J. D., Vu, C. B. The Chemistry of Vicinal Tricarbonyls. New Routes to Indolizidines. *J. Org. Chem.* **1990**, *55*, 1701−1702. (b) Wasserman, H. H.; Vu, C. B.; Cook, J. D. Vicinal Tricarbonyls in Synthesis. New Routes to Indolizidines. *Tetrahedron* **1992**, *48*, 2101−2112.

(22) Wasserman, H. H.; Henke, S. L.; Nakanishi, E.; Schulte, G. K. Addition of Amino Amides to Vinyl Vicinal Tricarbonyls. Formation of Tricyclic 3-Azadethiacephams. *J. Org. Chem.* **1992**, *57*, 2641−2645.

(23) Wasserman, H. H.; Henke, S. L.; Luce; P.; Nakanishi, E. Addition of Amino Lactams toVinyl Vicinal Tricarbonyls. Formation of Tricyclic 2-Azadethiapenams and 3-Azadethiacephams. *J. Org. Chem.* **1990**, *55*, 5822−5823.

(24) Wasserman, H. H.; Frechette, R.; Oida, T.; Van Duzer, J. H. The Chemistry of Vicinal Tricarbonyls. Preparation and Reactions of Acetylenic Tricarbonyls. *J. Org. Chem.* **1989**, *54*, 6012−6014.

(25) Wasserman, H. H.; Blum, C. A. The Chemistry of Vicinal Tricarbonyls. Use of Vinyl and Acetylenic Derivatives in the Synthesis of Substituted Indoles. *Tetrahedron Lett.* **1994**, *35*, 9787−9790.

(26) Wasserman, H. H.; Lee, G. M. The Chemistry of Vicinal Tricarbonyls. A New Synthesis of Substituted Furans. *Tetrahedron Lett.* **1994**, *35*, 9783−9786.

(27) Unlike the related conversion to pyrroles, the dihydrofuranone intermediates resisted dehydration with weaker acids.

(28) Wasserman, H. H.; Ennis, D. S.; Power, P. L.; Ross, M J.; Gomes, B. Synthesis and Evaluation of Peptidyl Tricarbonyl Monohydrates as Inhibitors of Hydrolytic Enzymes. *J. Org. Chem.* **1993**, *58*, 4785−4787.

(29) Conde-Frieboes, K.; Reynolds, L. J.; Lio, Y.-C.; Hale, M. R.; Wasserman, H. H.; Dennis, E. A. Activated Ketones as Inhibitors of Intracellular Ca^{2+}-Dependent and Ca^{2+}-Independent Phospholipase A_2. *J. Am. Chem. Soc.* **1996**, *118*, 5519−5525.

(30) Wasserman, H. H.; Ho, W.-B. (Cyanomethylene)phosphoranes as Novel Carbonyl 1,1-Dipole Synthons: An Efficient Synthesis of α-Keto Acids, Esters, and Amides. *J. Org. Chem.* **1994**, *59*, 4364−4366.

(31) Wasserman, H. H.; Petersen, A. K.; Xia, M. Application of Acyl Cyanophophorane Methodology to the Synthesis of Protease Inhibitors: Poststatin, Eurystatin, Phebestin, Probestin and Bestatin. *Tetrahedron* **2003**, *59*, 6771−6784.

(32) Wasserman, H. H.; Zhang, R. Application of Cyano Ylide Methodology to the Synthesis of Cyclotheonamides E_2 and E_3. *Tetrahedron* **2002**, *58*, 6277−6283.

(33) For references to earlier syntheses of cyclotheonamides, see papers cited in ref 32.

(34) Rappe, C. Cis-α,β-unsaturated Acids. Isocrotonic Acid. *Org. Synth.* **1973**, *53*, 123−127.

(35) (a) Forrester, A. R.; Thomson, R. H.; Woo, S.-O. Intramolecular Cyclisation of Phenolic Oximes III. A synthesis of *cis*,*cis*-Aerothionin. *Justus Leibigs Ann. Chem.* **1978**, 66−73. (b) Wasserman, H. H.; Wang, J. Syntheses of the Marine Metabolites Verongamine, Hemibastadin-2, and Aerothionin Using the Cyano-Ylide Coupling Methodology. *J. Org. Chem.* **1998**, *63*, 5581−5586.

(36) For leading references on the isolation, characterization, and synthesis of these molecules, see cited papers in ref 32.

(37) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. Structure of FK-506: A Novel Immunosuppressant Isolated from Streptomyces. *J. Am. Chem. Soc.* **1987**, *109*, 5031−5033.

(38) Wasserman, H. H.; Chen, J.-H.; Xia, M. The Chemistry of Vicinal Tricarbonyls: Total Syntheses of Elastase Inhibitors YM-47141 and YM-47142. *Helv. Chim. Acta* **2000**, *83*, 2607−2616.

(39) Fisher, M. J.; Chow, K.; Villalobos, A.; Danishefsky, S. J. On the Remarkable Propensity for Carbon−Carbon Bond Cleavage Reactions in the C_8−C_{10} Region of FK-506. *J. Org. Chem.* **1991**, *56*, 2900−2907.

(40) Adlington, R. M.; Baldwin J. E.; Cutterick, D.; Pritchard, G. J. A Versatile Synthetic Route to Quinoxaline, Pyrazine and 1,2,4-Triazine Substituted α-Amino Acids from Vicinal Tricarbonyls. *J. Chem. Soc.*, *Perkin Trans. 1* **2000**, 299−302.

(41) Wasserman, H. H.; Long, Y. O.; Zhang, R.; Parr, J. Alkenyl Tricarbonyl Derivatives of α-Amino Acids as Trielectrophiles. Formation of Heterocyclic-substituted Products. *Tetrahedron Lett.* **2002**, *43*, 3351−3353.

(42) Padron, J. M.; Kokotos, G.; Martin, S. J.; Markidis, T.; Gibbons, W. A.; Martin, V. S. Enantiospecific Synthesis of α-Amino Acid Semialdehydes: A Key Step for the Synthesis of Unnatural Unsaturated and Saturated α-Amino Acids. *Tetrahedron: Asymmetry* **1998**, *9*, 3381−3394.

(43) Chopard P. A. Acylation of Phosphine-Methylene Derivatives. Preparation and Properties of Mixed Phosphorane-Phosphonium Salts. *J. Org. Chem.* **1966**, *31*, 107−111.

(44) Brackeen, M. F.; Stafford, J. A.; Feldman, P. L.; Kavanewsky, D. S. An Efficient and Mild Synthesis of Highly Substituted Imidazoles. *Tetrahedron Lett.* **1994**, *35*, 1635−1638.
(45) Wasserman, H. H.; Baldino, C. M. The Synthesis and Investigation of the DNA Binding Properties of Dielectrophiles Incorporating Bis-Vicinal Tricarbonyls. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 3033−3038.
(46) Wasserman, H. H.; Ennis, D. S.; Vu, C. B.; Schulte, G. K. Benzilic Acid Rearrangements in the Reations of Aryl Vicinal Tricarbonyl Derivatives with Aldehyde Schiff Bases. *Tetrahedron Lett.* **1991**, *32*, 6039−6042.
(47) Wasserman, H. H.; Shiraishi, M.; Coats, S. J.; Cook, J. D. Cyclopentenones and Cyclopentanones from the Reactions of Vinyl Vicinal Tricarbonyls with Carbon Nucleophiles. *Tetrahedron Lett.* **1995**, *37*, 6785−6788.
(48) (a) Weinstein, B.; Craig, A. R. A Synthetic Approach to the Cephalotaxine Skeleton. *J. Org. Chem.* **1976**, *41*, 875−878. (b) Dean, R. T.; Padgett, H. C.; Rapoport, H. A High Yield Regiospecific Preparation of Iminium Salts. *J. Am. Chem. Soc.* **1976**, *98*, 7448−7449. (c) Wasserman, H. H.; Lipshutz, B. H.; Tremper, A. W.; Wu, J. S. Preparation of β-Lactams from Azetidine-2-carboxylic Acids and Esters. *J. Org. Chem.* **1981**, *46*, 2991−2999.

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