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The use of vicinal tricarbonyl derivatives in alkaloid synthesis

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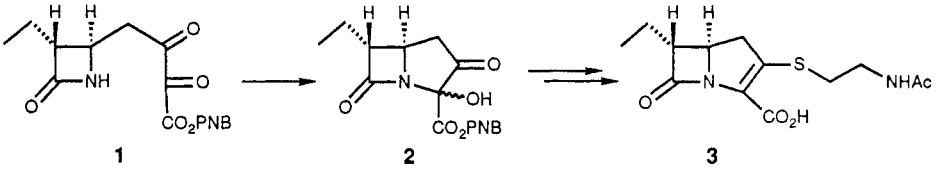
Abstract - We have recently shown that 1,2,3-vicinal tricarbonyl derivatives may serve as potent electrophiles in synthetic operations. When generated as substituents on β-lactam rings, they have served as acceptor centers for the construction of the fused 4,5-bicyclic systems of carbapenams and penems. In combination with neighboring ester, or vinyl groups, they have taken part in cyclization reactions leading to vincamine, erythrina, and phthalideisoquinoline alkaloids. Other applications involve the synthesis of hydroxypyrroles and indolizidines.
A particularly useful intermediate prepared in this series of investigations has been the vinyl tricarbonyl ester which has served as a versatile dielectrophile for the tandem addition of primary amines to the α,β-unsaturated ketone as well as to the central carbonyl group. In addition, related acetylenic derivatives may be used to extend this methodology, providing polyelectrophiles of unusual potential. Natural products which we have synthesized using tricarbonyl reactivity in key steps include prodigiosin, 3-demthoxy-erythratidinone, vasicine, eburnamonine and the C_1-C_{15} segment of antibiotic FK506. Progress in the synthesis of the tricyclic nucleus of bicyclomycin is also reported.

The powerful electrophilicity of 1,2,3-vicinal tricarbonyls has been known to organic chemists for many decades. These systems are prone to react readily at the central electron-deficient site with donor reagents such as water, alcohols, and amines. It is therefore not surprising that these functional group aggregates exist primarily in the form of adducts such as the hydrates of ninhydrin and oxomalonic ester.[1] Despite the potential for exploiting the electrophilic reactivity of tricarbonyls, they have found relatively little use by organic chemists in synthetic operations. Thus a recent review by Rubin[1] describes Diels-Alder reactions at the central carbonyl, as well as reactions with water, alcohols, thiols, amines, active methylene compounds, and diazo compounds. However, it is clear from this account that little attention has been given to the use of these aggregates in synthetically-directed bond formation.

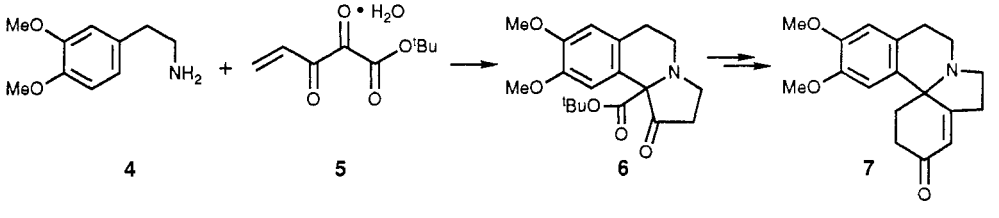
We have recently found that these systems, either partially or fully hydrated, may react with nucleophiles in varied molecular settings, and have sought to utilize this reactivity in the synthesis of alkaloids and other natural products. Our present work has been oriented in two directions. One pursuit aims to incorporate the tricarbonyl into a key intermediate such as **1** so that, in a subsequent step attack at the central ketonic residue by a nucleophile would result in bond formation. This is illustrated in the formation of the carbapenem system **2** in our synthesis of the antibiotic PS-5, **3** (Scheme 1).[2] Other natural products made in this way have been prodigiosin,[3] members of the vincamine,[4] and isoquinoline alkaloid families,[5] and vasicine.[6] Another general pathway involves the use of the vinyl tricarbonyl reagent **5** [7]as a polyelectrophile is illustrated in the synthesis of (±)-3-demethoxyerythratidinone **7**[8] (Scheme 2) and by the formation of the indolizidine derivative **33**[9] from an aminopyrrole (Scheme 7).

Scheme 1



1 **2** **3**

Scheme 2

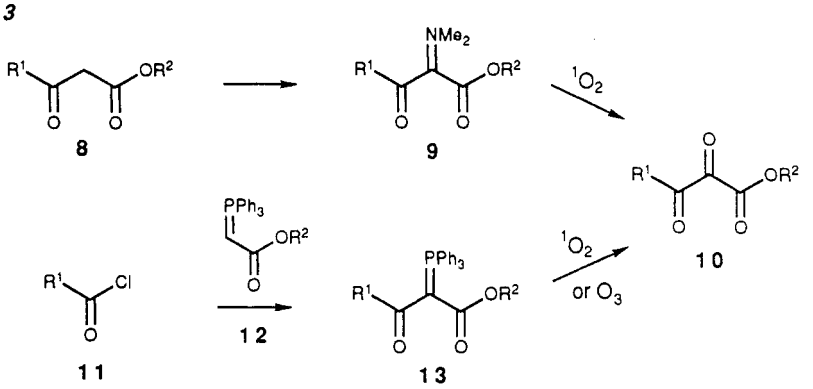


4 **5** **6** **7**

The following discussion will outline the use of tricarbonyl chemistry in the formation of cordrastines,[5] eudistomins,[10] and the C_1 to C_{15} fragment of FK-506.[11] We also describe a novel and efficient method for the formation of indolizidines[9] and carbazole derivatives[12] through this route.

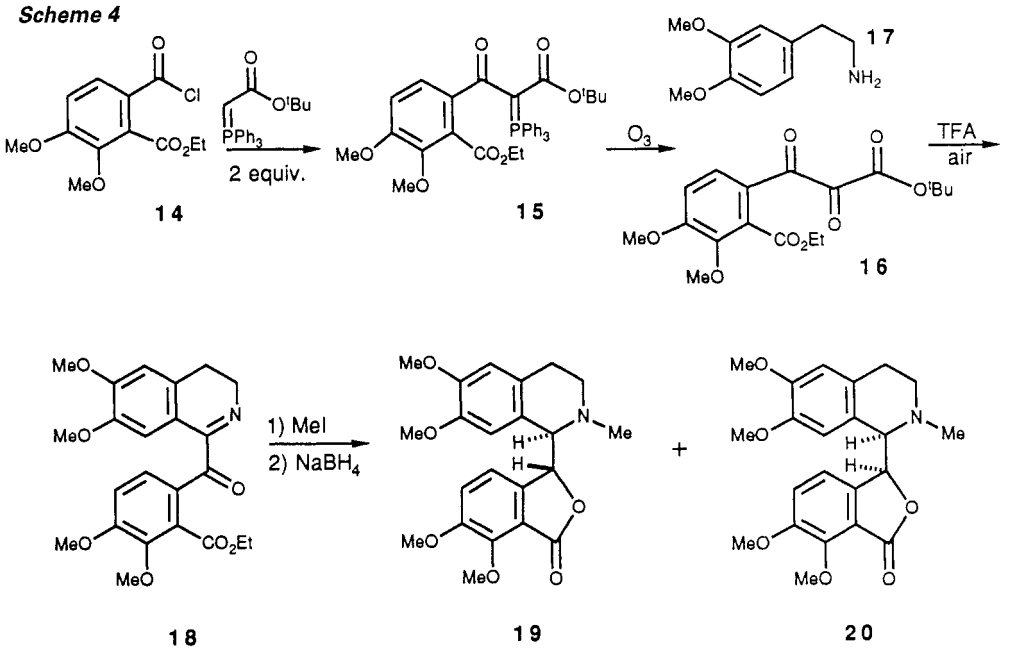
One method for forming the required tricarbonyl unit **10** involves the singlet oxygen cleavage of enamines **9** as shown in Scheme 3. A second method makes use of the condensation of an acid chloride **11** with the ylide **12**. In the next step, singlet oxygen or ozone can be use to generate **10** from the derivative **13** (Scheme 3).

Scheme 3



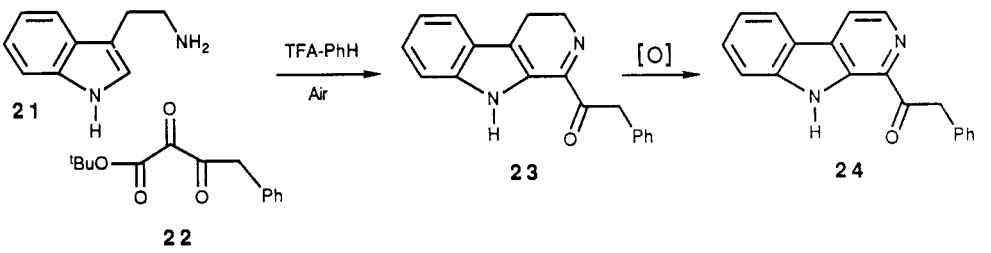
In our synthesis of the cordrastines,[5,13] we employed the tricarbonyl derivative **16** (Scheme 4). This, in turn, was conveniently prepared by the condensation of the acid chloride **14** with t-butyl (triphenylphosphoranylidine)acetate. Ozonolysis of **15** gave the tricarbonyl compound **16** (67%) as the monohydrate. Reaction of **16** with the phenethylamine derivative **17** afforded the keto-imine **18** (61%). 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 oxidative decarboxylation of the resulting β-keto-ester. Methylation (80%), and subsequent hydride reduction (72%) led directly to the cordrastines (diastereomeric ratio of 1:2 in favor of **20**).

Scheme 4



For our synthesis of the eudistomins,[10] members of a family of marine alkaloids possessing antiviral activity, a similar strategy was employed. As shown in the synthesis of eudistomin T (**24**) (Scheme 5), the tricarbonyl derivative **22** was mixed with tryptamine in excess trifluoroacetic acid (TFA) to give **23** (76%). Refuxing **23** in CCl_4 for three days produced the natural product **24** in high yield (88%).

Scheme 5



The above procedure for forming tricarbonyl derivatives was also applied successfully in the formation of the C_1-C_{15} α,β-diketo amide subunit of FK-506[11] (Figure 1). Our synthesis began with the condensation of the

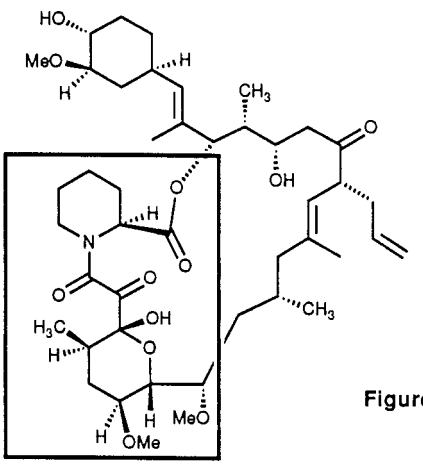
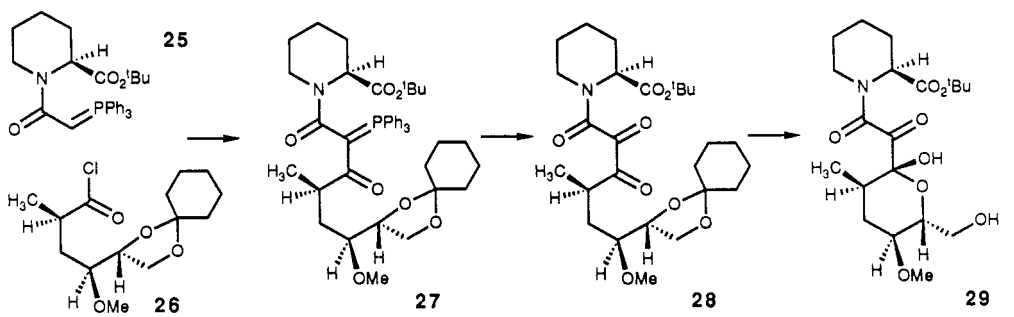


Figure 1

ylide **25** with the William's acid chloride **26**[14] in the presence of BSA to yield the keto ylide intermediate **27** (91%). Oxidative cleavage of **27** using ozone (88%) or singlet oxygen (69%) yielded the α,β-diketo amide **28**. The tricarbonyl **28** was then readily converted in dilute acid to the hemiketal **29**.

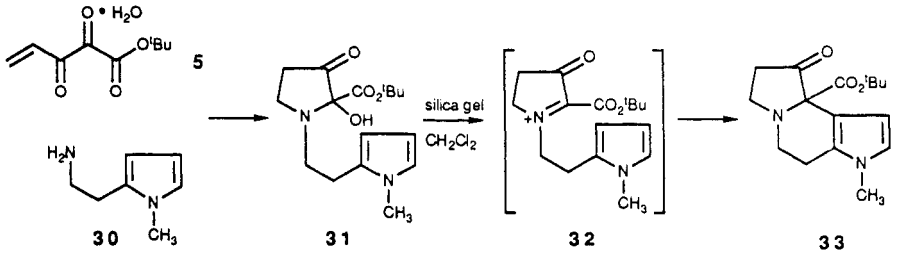
Scheme 6



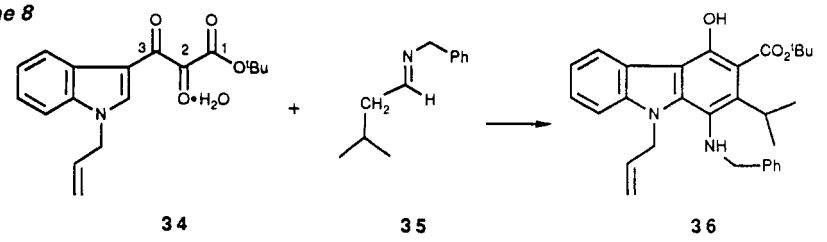
To prepare indolizidine derivatives,[9] we exploited the capability of the vinyl tricarbonyl ester **5** to act as a trielectrophile. The aminopyrrole **30** took part in a two-fold addition to the α,β- unsaturated ketone and the central carbonyl group generating a hydroxypyrrolidinone carboxylate **31** (Scheme 7). Under mild acid conditions (silica gel) this intermediate formed an iminium salt which acted as an acceptor for a third stage nucleophilic attack of the pyrrole to form the tricyclic system **33** (90%).

We have recently found that treatment of the indole tricarbonyl **34** with an excess of the Schiff base **35** resulted in a facile transformation to the *N*-benzylamino-4-hydroxycarbazole carboxylate **36** [12] (Scheme 8).

Scheme 7

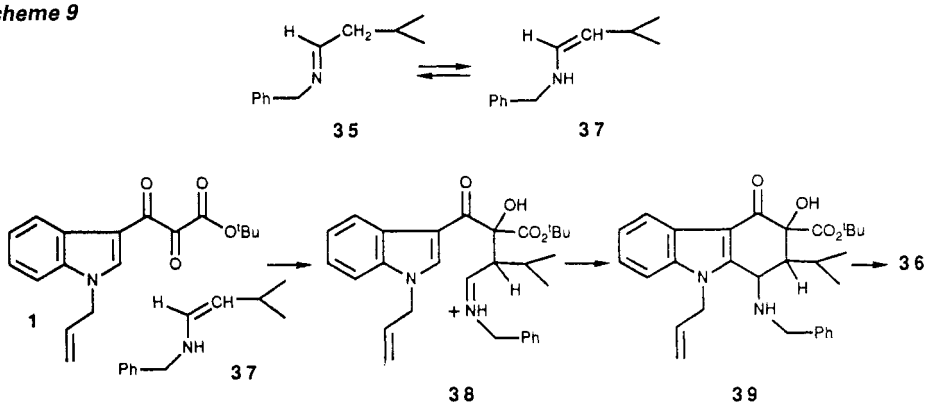


Scheme 8



We picture the transformation of **34** to **36** according to the sequence outlined in Scheme 9. Tautomerization of the imine **35** to the enamine **37** provides the donor species which initiates the addition leading to **38**. Intramolecular cyclization to **38** is then followed by dehydration and aromatization to **36**.

Scheme 9



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