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THE CHEMISTRY OF VICINAL TRICARBONYLS
A TOTAL SYNTHESIS OF PRODIGIOSIN

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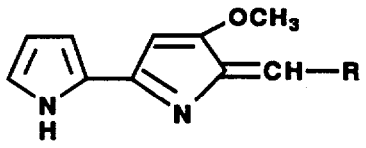
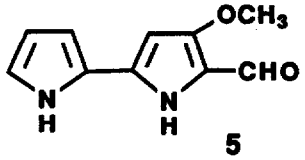
Summary: The addition of primary amines to alkenyl vicinal tricarbonyls leads to 5-substituted-3-hydroxypyrroles. This reaction has been employed in a synthesis of the 2-formyl-3-methoxy-α,α'-bipyrrole precursor of the prodigiosin family of natural products.

Prodigiosin[1-5], in the form of the methyl amyl derivative **1**,[1] is the parent member of a group of naturally-occurring pyrryldipyrrylmethenes. These include, among other analogs,[6] undecylprodigiosin **2**,[7] metacycloprodigiosin **3**,[8] and cycloprodigiosin **4**,[9] which possess potent antibacterial and antifungal activity.[4] A key intermediate in the biosynthesis[5] and in the synthesis[2-4,7-9] of these derivatives is the methoxybipyrrole aldehyde **5** which can be isolated from a mutant strain of *Serratia marcescens*.[5] We now report a total synthesis of the aldehyde **5** by an application of the chemistry of alkenyl vicinal tricarbonyl compounds.



1, R=a **3, R=c**
2, R=b **4, R=d**



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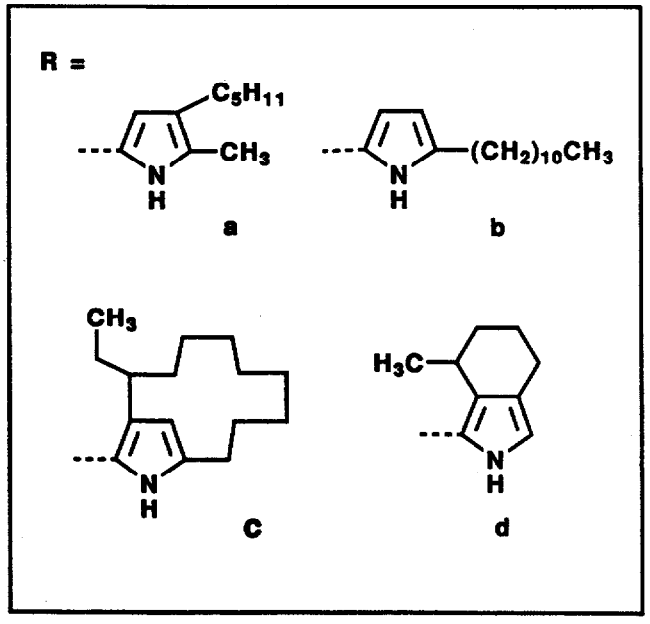
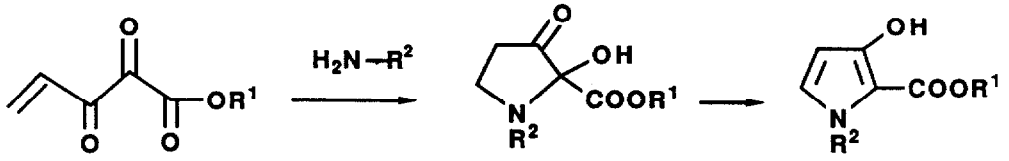


We have recently shown that vinyl vicinal tricarbonyls **6** are converted to 3-hydroxypyrrole-2-carboxylates **7** by the double addition of primary amines to the two acceptor sites in the polyfunctional system.[10,11] When the double bond is conjugated with a pyrrole ring as in **8**, this type of reaction may be used for the formation of substituted α,α'-bipyrroles, and particularly, for the synthesis of **5**. This precursor may be readily transformed by acid-catalyzed condensation with suitable pyrroles to the dipyrromethenes **1**,**2**,**3** and **4**.



6 **7**

The required unsaturated 1,2,3-tricarbonyl intermediate **12** was formed by the procedure outlined in Scheme 1. Pyrrole-2-carboxaldehyde **8**, protected as the 1-*p*-toluenesulfonyl derivative **9**, was treated with the dianion of ethyl acetoacetate **10** in THF at 0° C. The resulting alcohol **11** was dehydrated with gaseous HCl in $CHCl_3$ at -5° C to yield the enone **12**. Our earlier method for forming tricarbonyls from β-keto esters by generating an enamine with DMF acetal followed by cleavage with singlet oxygen[12] was not applicable here due to competing oxidation of the pyrrole ring. We therefore oxidized the active methylene group in **12** according to the method of Sachs[13] using N,N-dimethyl-p-nitrosoaniline in ethanolic NaOH followed by acid hydrolysis, generating the tricarbonyl derivative **13** as a stable hydrate.

Coupling of **13** with 3,4-dimethyoxybenzylamine yielded a mixture of products from which the intermediate hydroxypyrrolidone carboxylate could be separated and dehydrated (HOAc) to the bipyrrole ester **14**. Alternatively, the conversion of **13** to **14** could be accomplished directly on warming **13** with 3,4-dimethoxybenzylamine in glacial acetic acid. This product could then be converted to the methyl ether with dimethyl sulfate. Removal of the dimethoxybenzyl group was accomplished by an adaptation of Evans' oxidative procedure using sulfuric acid/trifluoroacetic acid.[14] Detosylation took place cleanly in ethanolic NaOH providing the known bipyrrole ester **16**. As reported earlier,[3,4] McFayden-Stevens reduction of **16** yielded the methoxy bipyrrole derivative **5** identical in all respects to the naturally occurring aldehyde formed from the mutant strain of *Serratia*. The further conversion of **5** to prodigiosin and analogues by coupling with methylamyl pyrrole or other substituted pyrroles has been reported in earlier communications.[2-4,7-9]

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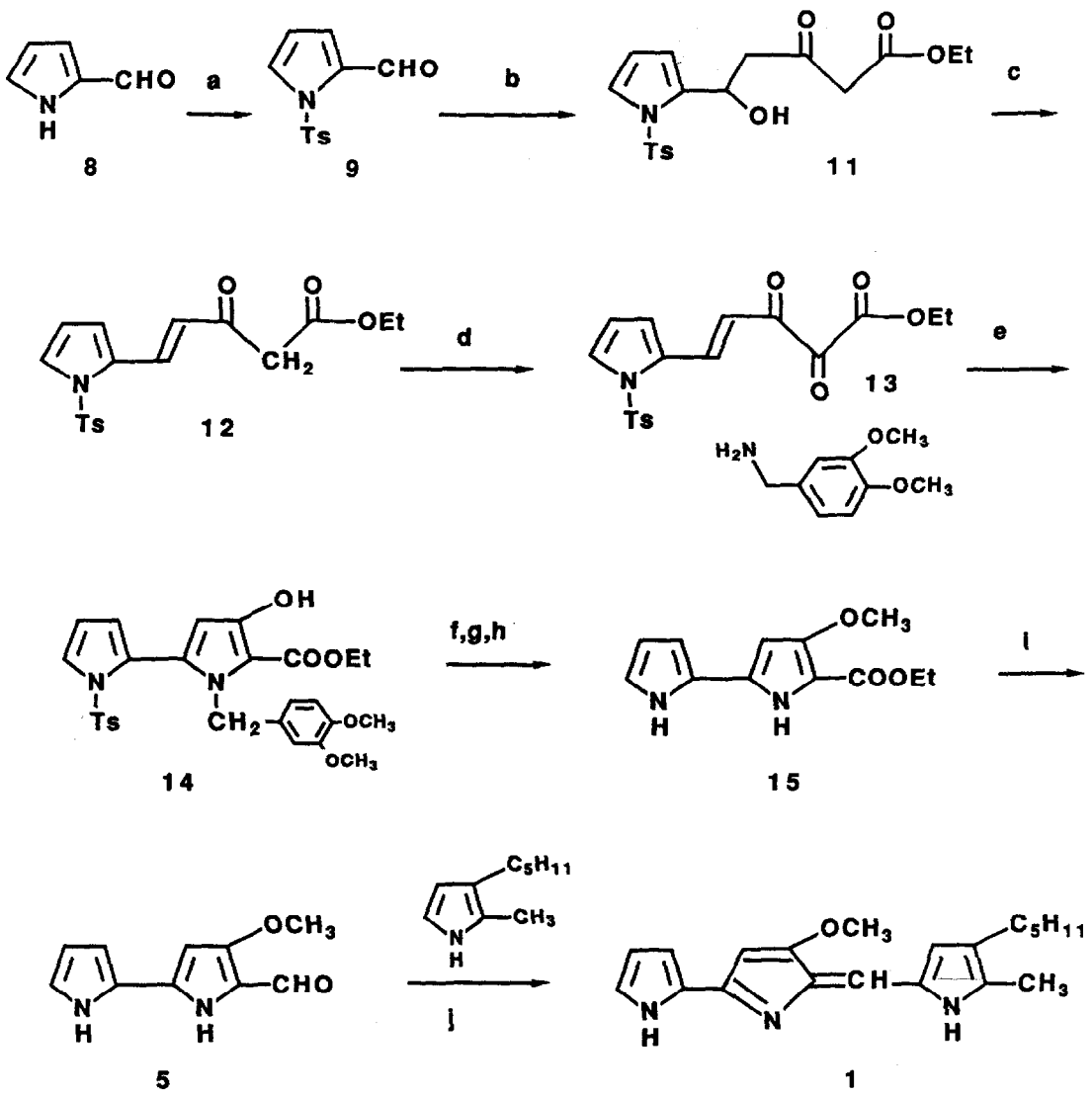

(a) NaH, *p*-TsCl, THF (93%); (b) $H_2C{=}C(OLi)CH{=}C(OLi)OEt$ **10**, THF (75%); (c) HCl(g), $CHCl_3$, -5° C (58%); (d) *p*-Me_2N-C_6H_4-NO, NaOH, EtOH; 1NHCl, THF, 0° C (70%); (e) 3,4-dimethoxybenzyl amine, HOAc(glacial), 60° C (23%); (f) NaH, Me_2SO_4, THF (77%); (g) 5% H_2SO_4, TFA, anisole (62%); (h) NaOH, EtOH, Δ, (65%); (i) 98% H_2NNH_2 (95%); *p*-TsCl, pyridine (75%); Na_2CO_3, $HOCH_2CH_2OH$, 170° C (33%); (j) catalytic HBr, (50%).

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1. The product of the bacterium *Serratia marcescens*, prodigiosin makes its appearance in the form of tiny blood red droplets on suitable growth media. When, in the Middle Ages, it appeared on white, unleavened bread, its presence formed the basis for the "Miracle of the Bleeding Host." Isolation, characterization and early references: Wrede, F.; Rothhass, A.Z. *Physiol. Chem.* **1934**, *226*, 95.

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