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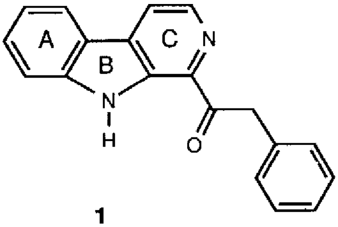
The Chemistry of Vicinal Tricarbonyl Compounds. Short Syntheses of Eudistomins T, I and M

Harry H. Wasserman* and Terence A. Kelly

Department of Chemistry, Yale University, New Haven, Connecticut 06511 USA

Abstract: The formation of three novel 1,2,3-tricarbonyl compounds and their use in the total syntheses of eudistomins T, I and M is described.

In earlier work we have shown that vicinal tricarbonyl compounds may be used effectively for the formation of products in the isoquinoline,[1] indole,[2] and erythrina[3] alkaloid series. In this communication we show how these derivatives may be used in short, efficient syntheses of eudistomins T (**1**), I (**2**) and M (**3**), members of a family of marine alkaloids possessing antiviral activity.



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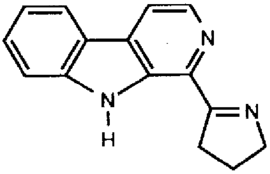

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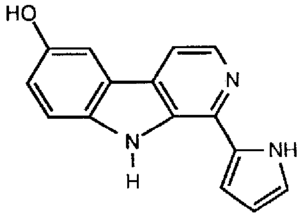
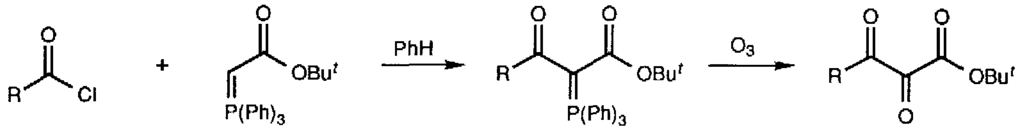


3

Since the recent discovery of the eudistomins by Rinehart[4] and Cardellina,[5] more than twenty members of this class have been isolated and a number of total syntheses have been reported.[6] In our work, the carbonyl groups at the 1 and 3-positions of the 1,2,3-tricarbonyl component each play a dual role in the alkaloid synthesis (Scheme 2). Initially, they serve to activate the central carbonyl for the Pictet-Spengler condensation. In the next phase of the same step, the ester carbonyl takes part in hydrolysis and oxidative decarboxylation, setting the stage for the subsequent facile aromatization, while the carbonyl group at position-3 remains as the ketone group in eudistomin T, and the precursor to the pyrroline or pyrrole groups in eudistomin I or M.

The syntheses of the three required tricarbonyl derivatives are shown in Scheme 1. Condensation of the appropriate acid chloride[7] with two equivalents of *t*-butyl triphenylphosphorylidene acetate (**5**)[8] produced the ylids **6a-c** in excellent yields.[9] Ozonolysis in a 4:1 solution of methylene chloride and methanol to a Sudan-III endpoint furnished the tricarbonyls **7a-c**.[10]

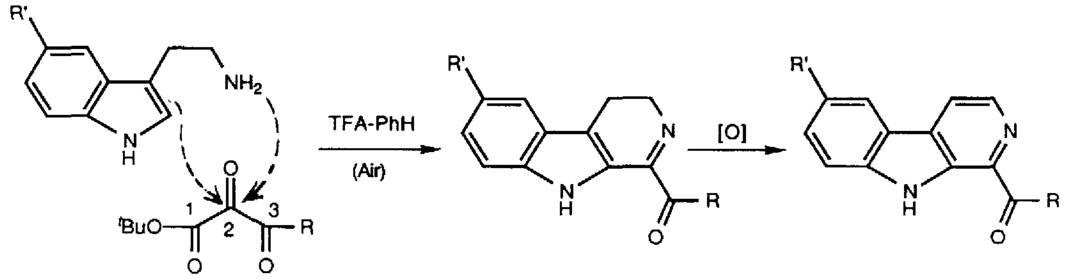
Scheme 1



4		5	6	7
a	R = $CH_2C_6H_5$		94%	64%
b	R = $(CH_2)_3NPht$		96%	78%
c	R = $(CH_2)_2CO_2Et$		96%	84%

The formation of eudistomin T (**1**) illustrates the standard procedure used in this work (Scheme 2). The tricarbonyl **7a** was mixed with a slight excess of tryptamine in benzene. After 15 min., a large excess of trifluoroacetic acid (TFA) was added and the mixture was stirred for 12 h. The solvents were evaporated and the residue dissolved in CH_2Cl_2. The solution was then washed with aqueous sodium bicarbonate, dried and chromatographed, yielding the dihydro β-carboline **9a** (76%).[11]

Scheme 2

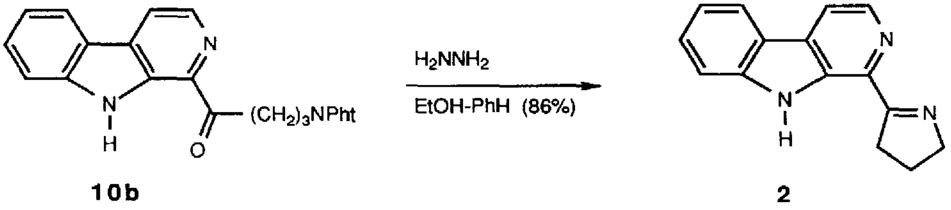


8	7	9	10
R' = H	7a	9a (76%)	1 (88%)
R' = H	7b	9b (82%)	10b (83%)
R' = OMe	7c	9c (84%)	10c (88%)

As expected, the introduction of unsaturation into the C-ring served to facilitate oxidation to the fully aromatized species. In fact, simply refluxing **9a** in CCl_4 for three days produced high yields (83 - 88%) of the natural product. This process could be accelerated by using catalytic amounts of palladium on charcoal or elemental sulfur.[12] It is interesting to contrast these results with the more difficult aromatization steps reported in cases where the C-ring is fully saturated.[6d,e]

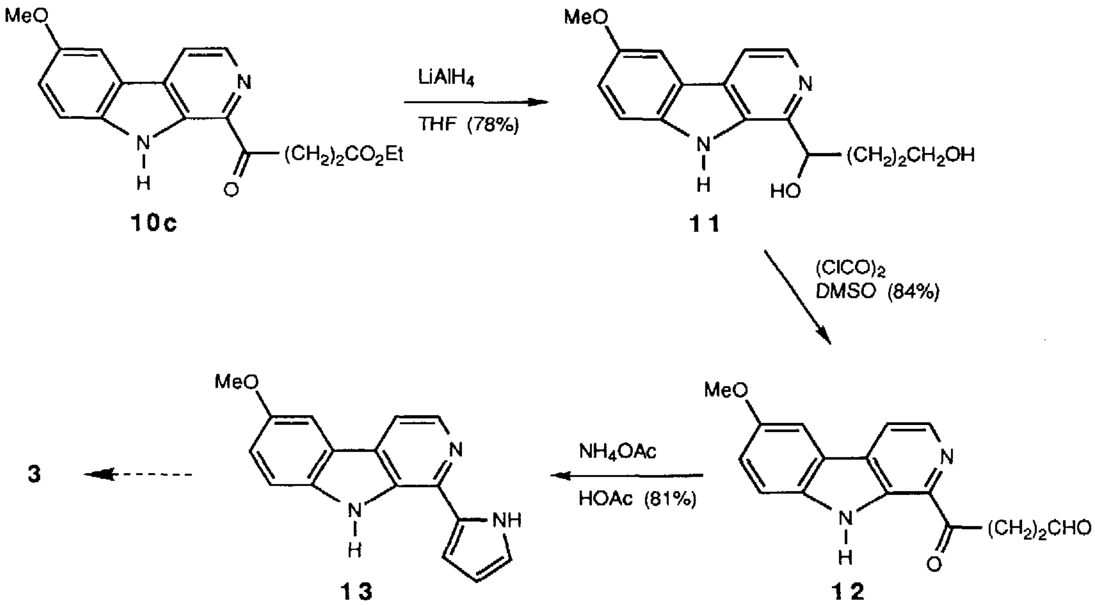
To form eudistomin I, the β-carboline **10b**, generated as outlined above, was treated with hydrazine in a 9:1 mixture of benzene and ethanol (Scheme 3).[13] Removal of the volatiles and chromatography yielded the natural product (86%).

Scheme 3



The synthesis of eudistomin M is outlined in Scheme 4. We used the ester-adduct **10c** as a precursor of the aldehyde **12** since ketal protecting groups did not survive the acidic conditions (TFA) used in the condensation. Reduction of **10c** with $LiAlH_4$ followed by a double Swern oxidation produced the desired γ-ketoaldehyde. This compound was then transformed into the pyrrole **13** by standard cyclization with ammonium acetate in acetic acid.[14] The demethylation of compound **13** to form eudistomin M has already been reported.[4]

Scheme 4



The method outlined above for the formation of the 1,2,3-tricarbonyl components allows for the incorporation of side chains with a wide variety of functional arrays. Additionally, the tricarbonyl aggregate appears to undergo reaction in a predicable sequence allowing orderly coupling with different donor groups. Further investigations are in progress on the application of these processes to alkaloid synthesis.

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