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THE SYNTHESIS OF EUDISTOMINS S AND T:ß-CARBOLINES FROM THE TUNICATE EUDISTOMA OLIVACEUM

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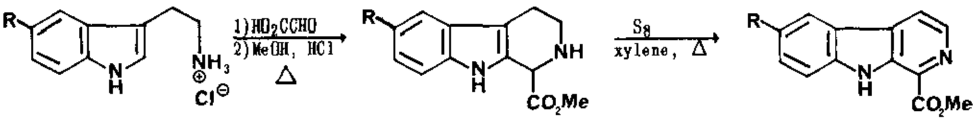
Abstract – The syntheses of two ß-carbolines, eudistomins S and T, have been accomplished from tryptamine precursors.

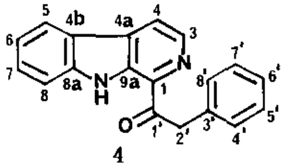
Since the first reported activity against Herpes simplex virus, type 1 (HSV-1), by the tunicate (ascidian) organism Eudistoma olivaceum,[1] and the subsequent characterization and structural elucidation of fifteen components of the organism by Rinehart et al.[2,3] in 1984, there has been widespread interest in the structure[4] and synthesis[5] of these antiviral ß-carboline derivatives, collectively referred to as eudistomins, as well as closely related compounds such as eudistomidin-A.[6] Recently, the identification of three new members of the eudistomin series, eudistomins R, S, and T, was reported by Kinzer and Cardellina.[7] We now wish to report the total synthesis of eudistomin T($C_{19}H_{14}N_2O$)4 and one of its closely related bromo-analogues, eudistomin S($C_{19}H_{13}BrN_2O$)5.



1a, R = H
b, R = Br

2a, R = H(71%)
b, R = Br(65%)

3a, R = H(92%)
b, R = Br(96%)



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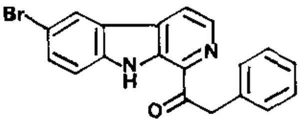

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The starting materials for the synthesis of eudistomins T and S, outlined above, were tryptamine and 5-bromotryptamine,[8] respectively. Pictet-Spengler condensation of the tryptamine with glyoxylic acid[9] produced, after esterification, the tetrahydro-ß-carbolines (2a,b). Dehydrogenation to the ß-carboline system could not be effected with palladium in the presence of the bromo-substituent and we have found elemental sulfur in refluxing xylene[10] to be the reagent of choice for this transformation. The final step was achieved in each case by a modified Grignard reaction[11] on the esters 3a,b, providing 4 and 5, in isolated yields of 59% and 40% respectively. Only minor amounts of tertiary alcohol are formed under our conditions. The use of alkyllithiums for the generation of hydroxy-ketones from γ-lactones has been reported[12] and lithium salts have been reported recently to assist the reaction of organomanganese bromide reagents with acid chlorides and anhydrides.[13] The role of the lithium salts in the conversion of 3a, b ⟶ 4 and 5 above is clearly crucial, but as yet unexplained. We are presently exploring the generality of this simple ester to ketone interconversion.

Eudistomins S and T prepared in this way[14] were identical in all respects (ir, uv, ^{1}H nmr, and mass spectral fragmentation pattern) with the data reported by Kinzer and Cardellina.[7,15] The synthetic route described here is direct, efficient and appears quite capable of extension to the synthesis of eudistomin R and other potentially interesting analogues of this class of compound.

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11. Benzylmagnesium chloride (2.05 equiv.), LiCl (8.0 equiv.), in refluxing diethyl ether, 25 min.
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14. Both eudistomins have been obtained as (yellow) crystalline compounds for the first time; eudistomin T(4), mp 160–161°C (MeOH) and eudistomin S(5), mp 168°C (MeOH).
15. ^{13}C Nmr data, (below) are recorded for **4** and 5 (Varian XL 400, 21°C); (4) δ(CDCl$_3$):43.8(C-2'), 111.8(C-8), 119.1(C-4), 120.4(C-4b), 120.6(C-6), 121.7(C-5), 126.7(C-6'), 128.4(C-5', C-7'), 129.1(C-7), 130.0(C-4', C-8'), 131.4(C-4a), 135.0, 135.2, 135.8(C-3', C-8a, C-9a), 138.1(C-3), 140.9(C-1), 202.1(C-1'); (5) δ(CDCl$_3$):43.8(C-2'), 113.3(C-8), 113.5(C-6), 119.2(C-4), 122.3(C-4b) 124.5(C-5), 126.8(C-6'), 128.5(C-5', C-7'), 130.0((C-4', C-8'), 130.4(C-4a), 132.0(C-7), 134.8, 135.6, 136.0(C-3', C-8a, C-9a), 138.5(C-3), 139.5(C-1), 202.2(C-1').

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