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SHORT, EFFICIENT SYNTHESES OF THE ANTIBIOTIC EUDISTOMINS I AND T

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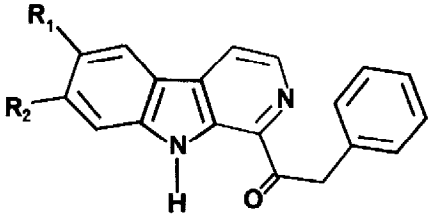
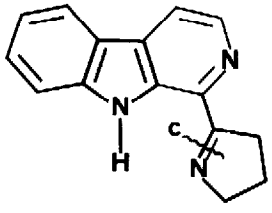
Summary - Simple, concise syntheses of eudistomins I and T, ß-carboline antibiotics from the tunicate Eudistoma olivaceum, have been achieved. The route utilized is an attractive alternative to traditional ß-carboline syntheses and is amenable to preparation of a wide range of analogs.

Not long ago, we reported the isolation of seven ß-carbolines from the Bermudian tunicate Eudistoma olivaceum, among them the unprecedented eudistomins R, S and T (**1-3**).[1] The very small quantities of these metabolites available from the ascidian precluded any biological testing. Reports of antimicrobial[2,3] and antiviral[3] activity in the other eudistomins[1-3] stimulated us to synthesize eudistomin T for pharmacological and agrochemical testing. Herein we describe concise synthetic approaches to eudistomins T, **3**, and I, **4**.



1 R_1=H, R_2=Br
2 Br H
3 H H



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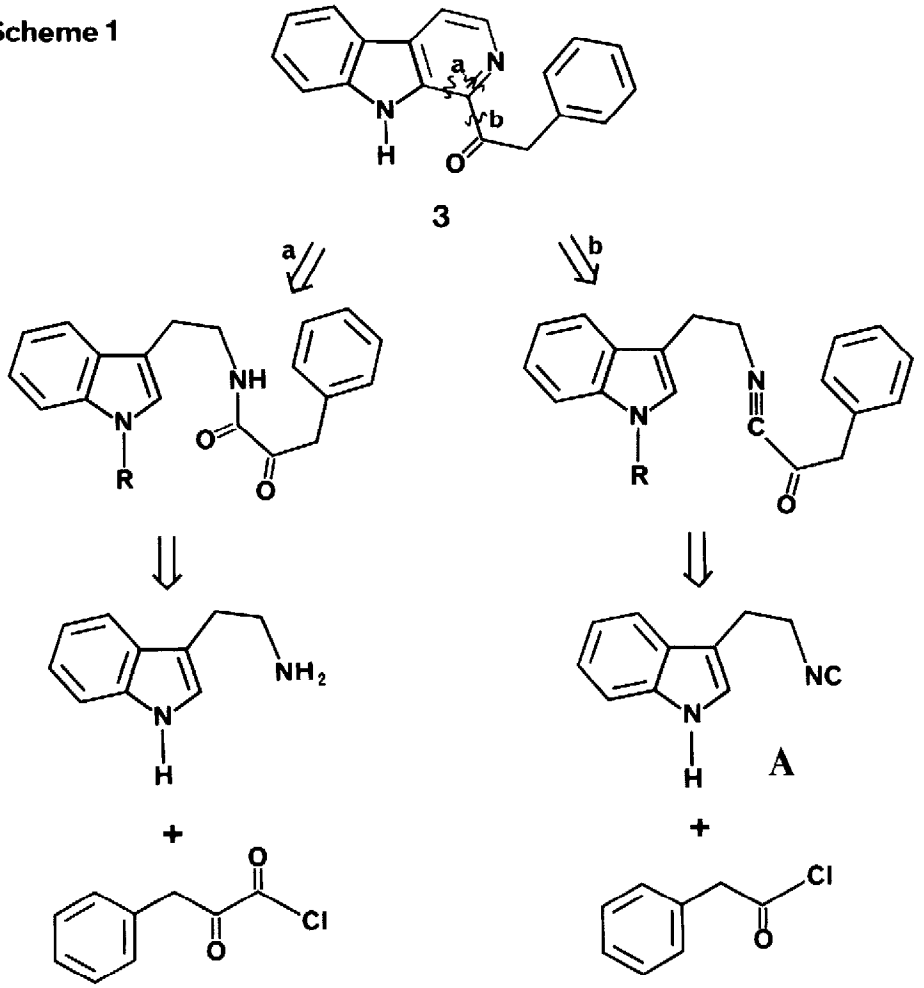
A prospective synthetic approach employing the traditional Bischler-Napieralski cyclization[4] (bond disconnection "a", Scheme 1) would involve condensation of tryptamine with a phenyl pyruvyl halide, followed by cyclization and aromatization. Predicted[5] and realized[6] difficulties in condensing tryptamine with a variety of protected or masked phenyl pyruvic acid halides led us to consider an alternative approach, characterized by bond dissection "b" in Scheme

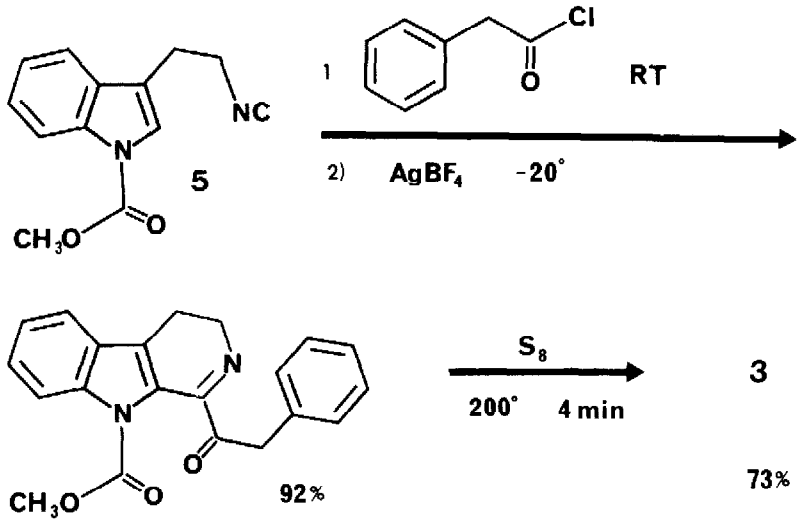
Scheme 1



1. This approach, developed by the Livinghouse group[7], hinges upon the silver ion mediated cyclization of α-ketoimidoyl chlorides, which can be prepared by acylation of the isonitrile **A** by an acyl chloride. The dihydro ß-carbolines thus obtained would then be dehydrogenated and deprotected to afford the target compounds.

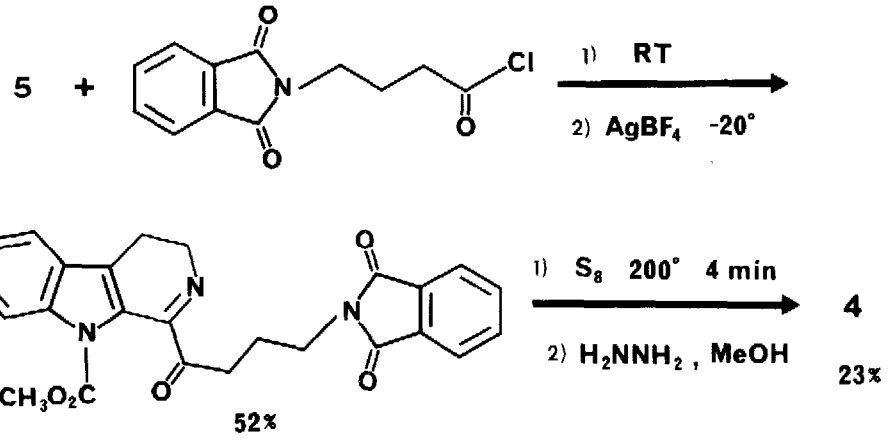
For the synthesis of eudistomin T (**3**), the N-protected indole isonitrile **5**[7b] was acylated with phenylacetyl chloride; the reaction mixture was exposed to silver tetrafluoroborate to afford the dihydro-ß-carboline **6** in 92% yield. A number of common dehydrogenation methods (Pd/C[8], DDQ[9], and ϕ_3PRhCl[10]) were explored, but mediocre yields and complex purification problems resulted in each case. The most expedient route proved to be treatment of **6** with elemental sulfur at 200° for 4 minutes[11]; both dehydrogenation and deprotection were accomplished in one step, providing eudistomin T (**3**)[12] in 73% yield.

Preparation of eudistomin I (**4**) by this method would require assembly of the



pyrrolidine ring subsequent to the acylation/cyclization step and protection during the aromatization. Dissection of the imine bond ("c" in **4**) suggested that a suitably protected γ-aminobutyric acid, condensed with the isonitrile **5**, could lead to **4**. Treatment of the isonitrile **5** with 4-phthalimidobutyryl chloride, followed by silver tetrafluoroborate gave the dihydro-ß-carboline **7** in 52% yield. Exposure of the intermediate **7** to elemental sulfur at 200° for 4 minutes provided **8**; hydrolysis of **8** with methanolic hydrazine[13] resulted in cleavage of the protecting groups and cyclization to eudistomin I, **4**,[14] in 23% yield.

Preliminary biological testing of eudistomin T revealed antimicrobial activity (inhibition of Aspergillus terreus, Staphylococcus aureus, Bacillus cereus and Corynebacterium michiganense), but no phytotoxicity toward johnsongrass or



activity against the tobacco hornworm. A report on the synthesis of a series of analogs of **3** and their pharmacological and agrochemical profiles will be presented elsewhere.

The simplicity and versatility of this approach to ß-carbolines complements the Bischler-Napieralski reaction and should find numerous applications in the synthesis of members of this important class of pharmacologically active compounds.

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12. Eudistomin T(**3**): λ_{max} (CH_2Cl_2) 380 nm (ε = 7000), 280(56100), 227(24100); ν_{max}($CDCl_3$): 3440, 3065, 3035, 2930, 1672, 1627, 1597 cm^{-1}; MS: m/z 286.1085 (calc'd for $C_{19}H_{14}N_2O$ - 286.1106) 286(65), 256(39), 195(20), 167(100), 140(37), 91(36); ^{1}H-NMR($CDCl_3$): δ 10.3(1H,s), 8.58(1H, d, J=5), 8.14(1H, d, J=5), 8.12(1H, d, J=8), 7.51(1H, t, J=8), 7.55(1H, d, J=8), 7.39(1H, t, J=8), 7.40 - 7.25(5H,m), 4.74(2H,s).
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14. Eudistomin I(**4**): λ_{max}(CH_2Cl_2) 368 nm(ε=5700) 282(11300), 227(14500); ν_{max}($CDCl_3$): 3370, 3065, 3035, 2930, 1630, 1607, 1435 cm^{-1}; MS: m/z 235.1117 (calc'd for $C_{15}H_{13}N_3$ - 235.1047) 235(100), 206(33), 193(44), 167(15); ^{1}H-NMR($CDCl_3$): δ 10.9(1H, s), 8.49(1H, d, J=5), 8.12(1H, d, J=8), 7.99(1H, d, J=5), 7.55(1H, dd J=5.5, 5), 7.51(1H, d, J=5), 7.31(1H, dd, J=8, 5.5), 4.25(2H, m), 3.33(2H, m), 2.07(2H, m).

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