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PALLADIUM (0) MEDIATED β-CARBOLINE SYNTHESIS: PREPARATION OF THE CDE RING SYSTEM OF LAVENDAMYCIN

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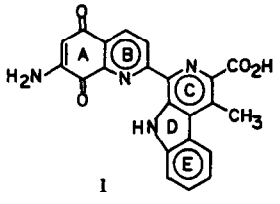
Summary: A five-step approach to the preparation of the β-carboline CDE ring system of lavendamycin is detailed and is based on: (1) thermal cycloaddition of 3,5,6-tricarbomethoxy-1,2,4-triazine with the pyrrolidine enamine of o-bromopropiophenone followed by (2) implementation of a newly developed palladium (0) mediated β-carboline synthesis.

A recent search of the broth of Streptomyces lavendulae resulted in the detection and isolation of lavendamycin (**1**),[2] a potent antitumor-antibiotic[3] which is structurally and biogenetically related to streptonigrin (**2**). The initial structure identification of lavendamycin rested on extensive, comparative spectroscopic studies and biosynthetic considerations[2] and recent synthetic efforts[4] have verified the proposed structure **1**.



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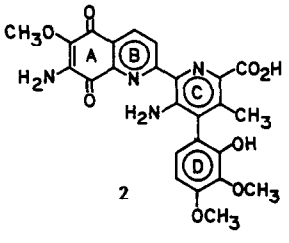

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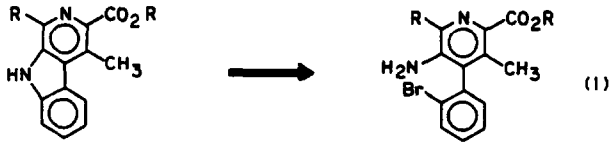
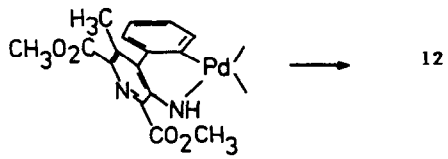
In recent efforts we have shown that the inverse electron demand Diels-Alder reaction of appropriately substituted, electron-deficient 1,2,4-triazines with α-aryl enamines, electron-rich olefins, provide a useful entry into the preparation of substituted 4-aryl pyridines[5a] and further demonstrated the utility of this process in a formal total synthesis of streptonigrin.[5b] Herein we describe extensions of this study, a synthesis of the lavendamycin CDE ring system from the readily available 4-aryl pyridines, which utilizes a newly developed palladium (0) mediated β-carboline preparation, equation 1.



(1)

Two-step conversion of commercially available o-bromobenzaldehyde (**3**) to o-bromopropiophenone (**5**) and subsequent pyrrolidine enamine formation[6] afforded **6**. Inverse electron demand Diels-Alder reaction of **6** with 3,5,6-tricarboethoxy-1,2,4-triazine (**7**)[7] completed the preparation of the pentasubstituted 4-aryl pyridine **8** (45 - 60 %, **8**:regioisomer, 5 - 6:1). Exhaustive ester hydrolysis of triester **8** to the triacid **9** followed by selective Fisher esterification of the two unhindered carboxylic acids afforded the dimethyl ester mono-acid **10**. Modified Curtius rearrangement utilizing diphenylphosphoroazidate[8] gave **11** directly from **10** and allowed introduction of the required pyridyl 3-amine. All attempts to effect D-ring closure on **11** to afford the β-carboline **12** utilizing existing methods[9] were unsuccessful. This can be attributed to the non-coplanarity of the biaryl ring system which prevents or retards the N-C bond formation and five-membered ring closure. In contrast, a palladium (0) mediated cyclization[10] of the amino bromide **11** afforded **12**[11] sucessfully completing the β-carboline synthesis and provided the carbon skeleton of the lavendamycin CDE ring system. Table I details representative results of the investigation of this cyclization process. The success with the palladium (0) mediated cyclization of **11** to **12** may be attributed to the mild, accessible formation of the six-centered intermediate **I** which would be expected to precede reductive elimination with β-carboline formation.



12

Application of this work in a total synthesis of lavendamycin (**1**) is in progress.

Table I. Palladium (0) mediated conversion of **11** to **12**

Conditions Equiv $(Ph_3P)_4Pd$, solvent, Temp °C(time h)	% Yield[a]
1.0, tetrahydrofuran, 80(20)[b]	50 %
1.2, tetrahydrofuran, 80(21)[b]	81 %
1.5, tetrahydrofuran, 80(21)[b]	84 %
1.2, dioxane, 100(20)	50 %
1.5, dioxane, 100(24)	73 - 80 %
1.2, toluene, 100(24)	43 %
0.01, tetrahydrofuran, 80(24)[b]	0 %

(a) All yields are based on pure material isolated by chromatography (SiO_2).
(b) The reactions were run in a resealable Kontes vial.

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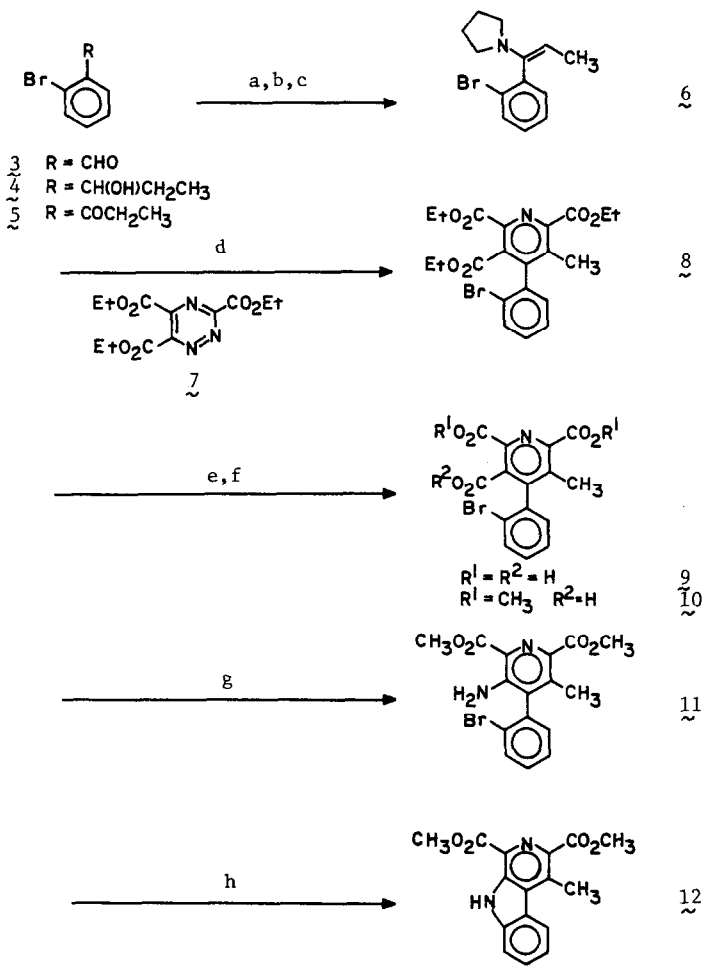
Scheme I[a]



(a) 1.2 Equiv EtMgBr, THF, -78 to 25°C, 3.5 h. (b) 2.0 Equiv H_2CrO_4, 25°C, 3 h, 94% from **3**. (c) 6 Equiv pyrrolidine, 0.5 equiv $TiCl_4$[6], Et_2O, 0-25°C, 12-16 h, 80-88%. (d) 1.5 Equiv **6**, $CHCl_3$, 45-50°C, 12-24 h, 45-60%, 5-6:1 **8** :regioisomer. (e) 15 Equiv LiOH, THF:CH_3OH:H_2O (3:2:1), reflux, 28-30 h. (f) 10% HCl/CH_3OH, 25°C, 18-20 h, 65% from **8**. (g) 2.2 Equiv $(PhO)_2P(O)N_3$[8], 2.2 Equiv Et_3N, C_6H_6, reflux, 2.5 h; H_2O, reflux, 1 h, 71%. (h) Table I.

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10. We are not aware of reports of related palladium (0) mediated dihydroindole or β-carboline syntheses. The success reported herein with **11**, which apparently involves a rare heteroatom - palladium (II) reductive elimination, can be attributed to the reduced nucleophilicity of the aryl amine, the result of carbomethoxy delocalization, and a weakened N-Pd coordination. For example, see: Hegedus, L. S.; McKearin, J. M. J. Am. Chem. Soc. **1982**, 104, 2444; Venanzi, L. M.; Pugin, B. J. Organomet. Chem. **1981**, 214, 125.
11. For **12**: M.P. 219°C (EtOH); ^{1}H-NMR ($CDCl_3$) δ 10.17 (1H, br s, -NH), 8.35 (1H, d, J = 8 Hz, aromatic), 7.68 - 7.40 (3H, m, aromatic), 4.11 (3H, s, $-CO_2CH_3$), 4.04 (3H, s, $-CO_2CH_3$), 3.22 (3H, s, $ArCH_3$); ^{13}C NMR ($CDCl_3$) δ 166.8 and 165.2 (two s, $-\underline{C}O_2CH_3$), 141.5 (C-8), 137.3 (C-2), 135.8 (C-3), 132.8 (C-6), 129.8 (C-4), 128.6 (C-10), 128.4 (C-3), 123.6 (C-12), 123.4 (s, C-7), 120.7 (C-11), 113.1 (C-9), 52.1 and 52.08 ($-CO_2\underline{C}H_3$), 16.3 ($-CH_3$); IR ($CHCl_3$) ν_{max} 3422 (NH), 3005, 2928, 1723, 1700, 1590, 1490, 1458, 1438, 1342, 1297, 1272, 1241, 1098, 1062, cm^{-1}; mass spectrum m/e (rel. intensity) 298 (M_+, 65), 208 (base); high resolution mass spectrum, $C_{16}H_{14}N_2O_4$ requires m/e 298.0953, Found 298.0939.

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