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A New Approach to Pyrrolophenanthridone Alkaloids via Allene Intramolecular Cycloaddition: Total Synthesis of Hippadine

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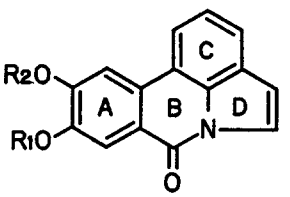
Abstract: Combination of the indole synthesis (C-D ring) via intramolecular Diels-Alder reaction of 3-substituted allenic dienamide (5) and base-catalyzed intramolecular N-acylation (B ring formation) provides a simple route to pyrrolophenanthridone alkaloids such as hippadine (1).

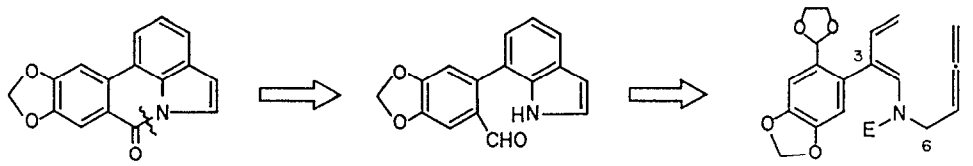
Recently, a series of pyrrolophenanthridone alkaloids, such as hippadine (1),[1] pratorimine (2),[2] and pratorinine (3),[3] have been isolated from the bulbs of several Crinum species (Amaryllidaceae), collected at flowering time, though these are present only in traces in the resting bulbs.[2,3] These new class of alkaloids, identified by spectroscopic methods,[1-3] the X-ray structural analysis,[4] and synthesis,[5] are characterized by the presence of an indole moiety (C-D ring). Moreover, recent studies have shown that hippadine (1) produces reversible inhibition of fertility in male rats with a remarkable decrease both in the testicular weight and in DNA content, but no anti-mitotic activity, suggesting the exertion of its effect at the genetic level.[6] These interesting biological activities have motivated exploration of general synthetic routes to this class of compounds. We now report a new facile synthesis of 1, a representative of pyrrolophenanthridone alkaloids, based on the strategy of initial indole construction (C-D ring) followed by the intramolecular N-acylation (B-ring formation) as outlined retrosynthetically in Scheme 1.



(1) $R_1, R_2 = -CH_2-$

(2) $R_1 = H$, $R_2 = Me$

(3) $R_1 = Me$, $R_2 = H$



(1) (4) (5)

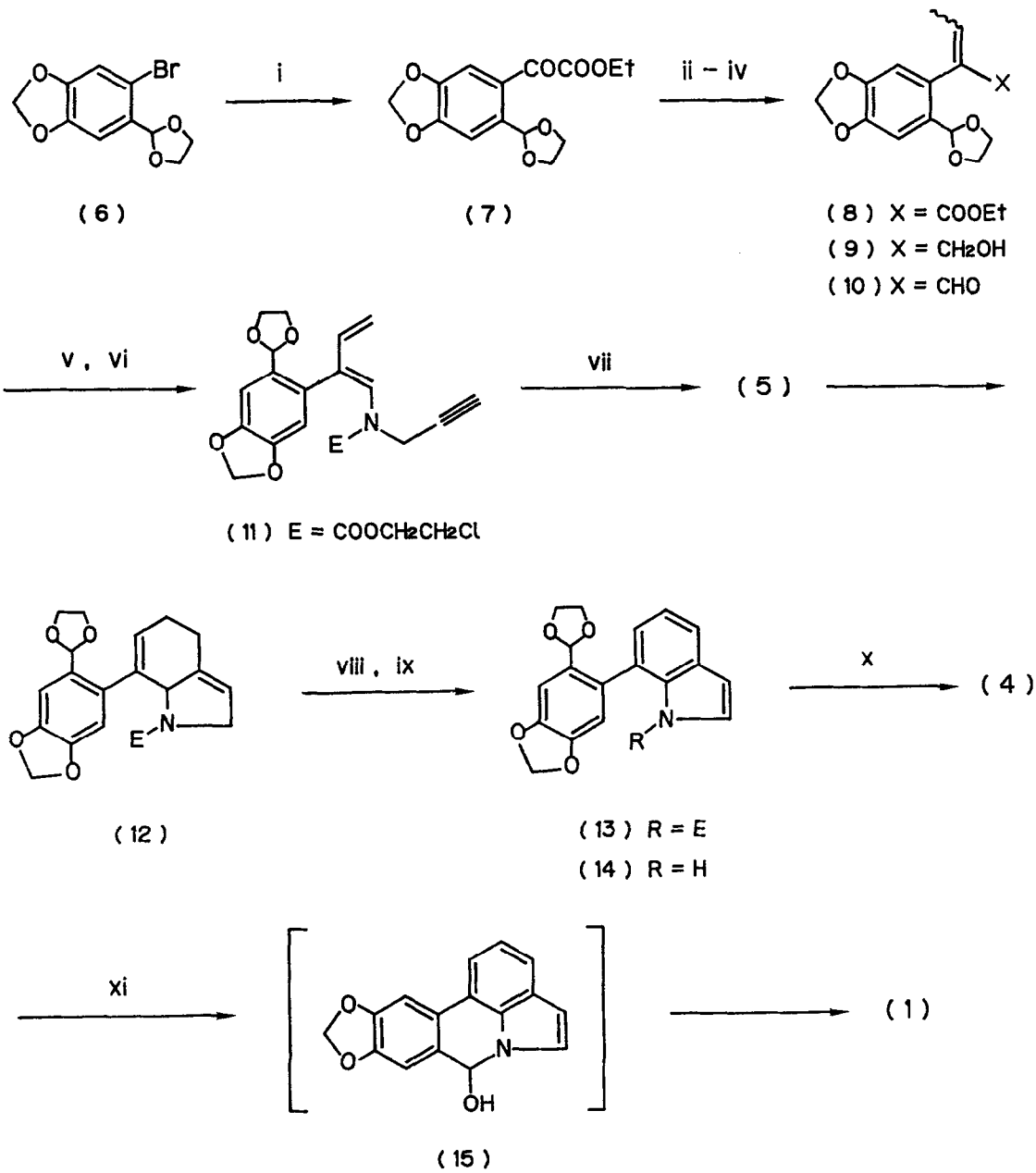
Scheme 1

Previously, we reported a new indole synthesis via the intramolecular Diels-Alder (D.A.) reaction of allenic dienamide (ex., 5), wherein the 3- and 6-substituents remarkably accelerated the cycloaddition.[7] This substituent effect might fairly profit our strategy of pyrrolophenanthridone skeleton synthesis through allene intramolecular cycloaddition[8] (Scheme 2). The requisite propargyl dienamide (11), a precursor of allenic dienamide (5), was prepared as shown in Scheme 2. The bromide (6), readily obtainable from piperonal,[9] was converted into 7[10] in 87% yield by the reported procedure.[11] The Wittig reaction with ethylidene phosphorane gave the ester (8)[10] as an easily separable 3:2 mixture of (E)- and (Z)-isomers in 85% yield, which was directly reduced by DIBAH to afford the corresponding mixture of the alcohol (9)[10] in 83% yield. After oxidation of 9 (E/Z- mixture) to the aldehyde (10),[10] successive treatment with propargyl amine and 2-chloroethyl chloroformate in the presence of diethylaniline by Oppolzer's method[12] afforded the dienamide (11)[10] in 34% overall yield from 9.

When 11 was subjected to homologative allenylation at 100 °C (Crabbé's method),[13] the resulting allene (5) was found to undergo spontaneously the D.A. reaction to give directly the adduct (12)[10] as the sole product in 56% overall yield, which was in turn dehydrogenated by DDQ to produce the indole (13)[10] (48%). The alkaline hydrolysis of 13 to 14[10] followed by deprotection of the acetal group provided the key compound (4)[10] in 79% yield. Finally, treatment of 4 with NaH in THF resulted in the smooth ring closure to give 15 which underwent the air oxidation during the work-up to afford 1, m.p. 217-218°C (lit[2] m.p. 213-215°C), in 43% yield. The synthetic 1 was identical with the natural product[2] in all spectroscopic aspects.

The successful application of allene intramolecular cycloaddition to synthesis of 1 may indicate that this methodology provides a general synthetic route to pyrrolophenanthridone alkaloids like 2 and 3.

We are grateful to Professor A. W. Frahm for identification of 1 with authentic sample by spectral comparison.



Scheme 2. Reagents and Conditions: i, n-BuLi, ether, 78°C, then $(COOEt)_2$, 87%; ii, $Ph_3P^+CH_2CH_3Br^-$, n-BuLi, ether, 25°C, 85%; iii, DIBAH, ether, -40°C, 83%; iv, DMSO, trifluoroacetic anhydride, CH_2Cl_2, -78°C, then Et_3N; v, propargylamine, 4A molecular sieves, toluene, 25°C; vi, 2-chloroethyl chloroformate, diethylaniline, toluene, 25°C, 34% from 9 ; vii, 35% HCHO, i-Pr_2NH, CuBr, dioxane, 100°C, 56%; viii, DDQ, benzene, 80°C, 48%; ix, KOH, MeOH, H_2O, 70°C, 88%; x, HCl, THF, H_2O, 25°C, 90%; xi, NaH, THF, 25°C, 43%.

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10. All new compounds gave satisfactory analytical and spectral data. **11**; i.r., ν_{max} (neat) 3260, 2090, and 1700 cm^{-1}; ^1H n.m.r., δ ($CDCl_3$) 7.10 (s, 1H), 6.81 (s, 1H), 6.64 (s, 1H), 6.59 (dd, J 17.4 and 9.6 Hz, 1H), 6.00 (s, 2H), 5.57 (s, 1H), 5.06 (d, J 9.6 Hz, 1H), 4.74 (d, J 17.4 Hz, 1H), 4.44 (t, J 6.0 Hz, 2H), 4.23-3.71 (m, 6H), 3.71 (t, J 6.0 Hz, 2H), 2.12 (t, J 2.4 Hz, 1H). **13**; i.r., ν_{max} ($CHCl_3$) 1730 cm^{-1}; ^1H n.m.r., δ ($CDCl_3$) 7.65 (d, J 3.6 Hz, 1H), 7.59-7.08 (m, 3H), 7.26 (s, 1H),6.69 (s, 1H), 6.67 (d, J 3.6 Hz, 1H), 6.00 (s, 2H), 5.42 (s, 1H), 4.30-3.91 (m, 2H), 4.03 (t, J 6.0 Hz, 2H), 3.91-3.69 (m, 2H), 3.52 (t, J 6.0 Hz, 2H). **4**; i.r., ν_{max} ($CHCl_3$) 3480 and 1675 cm^{-1}; ^1H n.m.r., δ ($CDCl_3$) 9.58 (s, 1H), 8.12 (br s, 1H), 7.71 (dd, J 7.2 and 1.8 Hz, 1H), 7.51 (s, 1H), 7.41-7.05 (m, 3H), 6.97 (s, 1H), 6.63 (dd, J 3.6 and 2.4 Hz, 1H), 6.09 (s, 2H).
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