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A New Approach to the Synthesis of AntitumourAlkaloids with the Lycorane Skeleton

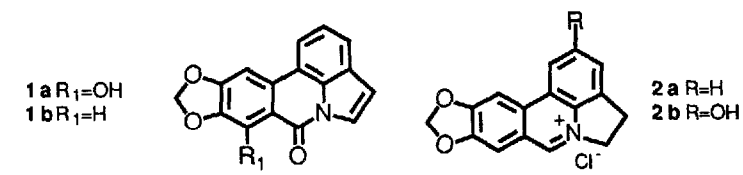
Dolores Pérez, Enrique Guitián and Luis Castedo

Dpto. Química Orgánica , Univ. Santiago and Sección de Alcaloides, CSIC. 15706 Santiago de Compostela, Spain.

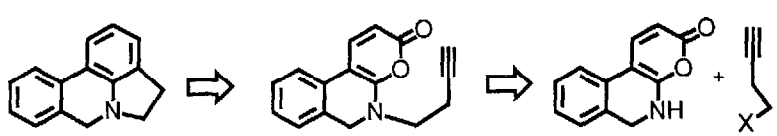
Key Words: Pyrone-alkyne intramolecular cycloaddition, Lycorane-type Alkaloids.

Abstract: A new approach to the synthesis of lycorane-type alkaloids is described. The key step is intramolecular cycloaddition between an α-pyrone and an alkyne.

Kalbretorine **1a**, hyppadine **1b**, anhydrolycorinium chloride **2a** and ungeremine **2b** are Amaryllidaceae alkaloids[1] with a lycorane-type skeleton and very interesting pharmacological properties. Anhydrolycorinium chloride has *in vitro* and *in vivo* antileukaemic activity in test P388,[2] kalbretorine has antitumour activity[3], ungeremine is active against some types of carcinoma[4] and hyppadine reversibly inhibits fertility in male rats.[5] Although there are several procedures for the synthesis of these alkaloids[1], they have poor versatility and/or low overall yields.

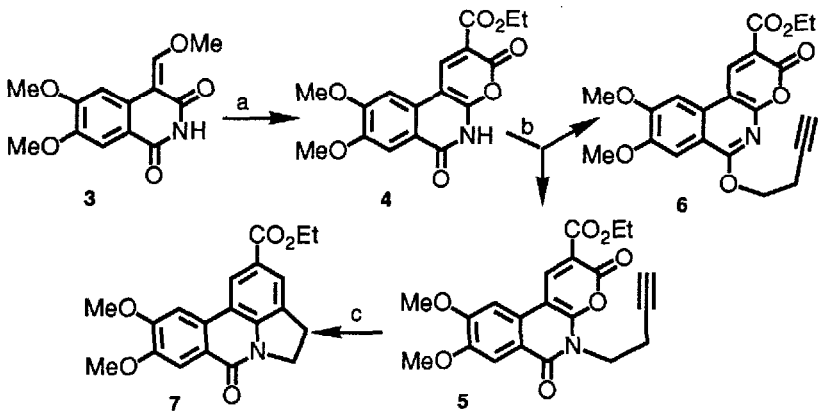


In connection with work on the synthesis of antitumour benzophenanthridine alkaloids[6] we became interested in the cycloaddition reactions of α-pyrones. It is known that α-pyrones react with alkynes and arynes to afford an adduct which loses CO_2 by retro Diels-Alder reaction to yield a benzene derivative[7]. In view of this, we devised the retrosynthetic path from the basic skeleton of compounds **1-2** that is shown in Scheme 1. We report here the preliminary results of pursuing this path in the synthetic direction.



Scheme 1

Pyrone **4** was prepared by the procedure described for certain of its analogues[8]: condensation of 4,5-dimethoxyhomophthalimide with trimethylorthoformate in Ac_2O/DMF afforded **3**,[9] which by treatment with ethyl cyanoacetate and NaOMe yielded, after acidic work-up, the pyrone **4**.



a) $NCCH_2CO_2Et$, NaOMe, 72%; b) $HCCCH_2CH_2OTS$, t-BuOK, DMF, 93%; c) $O_2NC_6H_5$, 210 °C, 95%

Scheme 2

Alkylation of **4** under unoptimized conditions with 3-butyn-1-tosylate led to an equimolar mixture of **5** and **6** in 93% overall yield. After separation, the O-alkylated product **6** was hydrolyzed to **4** and recycled. Heating the N-alkylated pyrone **5** in refluxing nitrobenzene to force the intramolecular cycloaddition of the pyrone and alkyne components afforded the adduct **7** in 95% yield.[9] Further studies are in course to optimize the yield of the N-alkylation of pyrone **4** and to apply this method to the synthesis of antitumour alkaloids.

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9. All new products afforded correct spectroscopic data. **7**: ^1H NMR ($CDCl_3$), δ : 8.57 (s, 1H); 7.96 (s, 1H); 7.92 (s, 1H); 7.60 (s, 1H); 4.53 (t, J=8.2 Hz, 2H); 4.42 (q, J= 7.1 Hz, 2H), 4.12 (s, 3H); 4.05 (s, 3H); 3.46 (t, J=8.2 Hz); 1.45 (t, J= 7.1 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$), δ : 166.75; 160.01; 153.42; 150.22; 142.84; 131.08; 128.25; 125.68; 124.49; 122.50; 121.41; 116.10; 108.92; 103.31; 61.13; 56.38; 56.27; 46.94; 27.03; 14.40 ppm. MS m/z (%) : 353 (M^+, 100), 308 (23).

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