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INTRAMOLECULAR ARYNE CYCLOADDITION. A NEW APPROACH TO AMARYLLIDACEAE ALKALOIDS.

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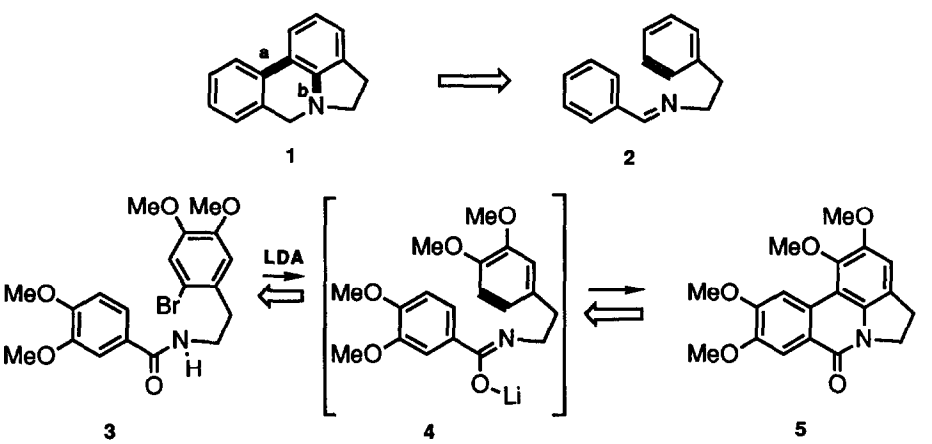
Summary. The synthesis of a compound closely related to Amaryllidaceae alkaloids by intramolecular aryne cycloaddition is described.

The intermolecular benzyne cycloaddition methodology that we have developed in recent years for the synthesis of isoquinoline alkaloids has been successfully applied to the preparation of aporphinoids[1], protoberberines[2] and benzophenanthridines[3]. Recently, we began to study a complementary strategy based on intramolecular aryne cycloaddition[4]. We describe here the preliminary results obtained on the synthesis of Amaryllidaceae alkaloids using this Intramolecular Aryne Cycloaddition approach. It is worth noting that some members of this group of alkaloids have antitumour activity[5].



Scheme 1

Our experience with aryne cycloadditions led us to consider the retrosynthetic analysis of the Amaryllidaceae skeleton shown in Scheme 1, where the key step is the simultaneous disconnection of the strategic bonds **a** and **b**. In the synthetic direction, it was thought that the simultaneous (but not necessarily synchronous) formation of bonds **a** and **b** might be achieved by an intramolecular Diels-Alder reaction between the aryne and azadiene components contained in compound **2**.

The amide **3**[6], which is easily prepared by condensation of bromo-homoveratrylamine and veratric acid chloride, was chosen as a test compound. When **3** was treated with two equivalents of LDA (THF, -78°C--->RT), we obtained as only detected products (tlc) the adduct **5** (isolated in 25% yield) and starting material **3**. Modification of the experimental procedure (stepwise addition at 0°C of 16 eq. of LDA to a solution of compound **3** in THF, 24 h stirring at room temperature) improved the yield of adduct **5** to 74% (90% based on recovered **3**).

Further work is in progress to optimize the experimental procedure and apply this method to the synthesis of Amaryllidaceae alkaloids with antitumour activity.

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6.- All new compounds afforded correct spectrocopic data.
5. Mp. 228-230 °C (EtOH). UV λ_{max} (EtOH): 252, 280 nm. IR (KBr) : 1630 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 3.38 (t, J= 8.3 Hz, 2H), 3.94 (s, 3H), 3.98 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 4.49 (t, J= 8.3 Hz, 2H), 7.02 (s, 1H), 7.99 (s, 1H), 8.56 (s, 1H). MS , m/e (%) : 341 (100, M^+), 326 (98).

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