



## A Diels-Alder reaction / oxa-Michael addition / acyloin rearrangement cascade on tropolonic substrates



Macarena Eugui<sup>a</sup>, Katerine Rasquin<sup>a</sup>, Andrés López Radcenco<sup>a</sup>, Leopoldo Suescun<sup>b</sup>, Guillermo Moyna<sup>a,\*</sup>

<sup>a</sup>Departamento de Química del Litoral, CENUR Litoral Norte, Universidad de la República, Ruta 3 Km 363, Paysandú 60000, Uruguay

<sup>b</sup>Crysmat-Lab / Cátedra de Física / DETEMA, Facultad de Química, Universidad de la República, Avenida General Flores 2124, Montevideo 11800, Uruguay

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### ABSTRACT

We describe a novel pericyclic/anionic cascade reaction on tropolonic substrates that combines a Diels-Alder reaction, an oxa-Michael addition, and an acyloin rearrangement to afford tricyclic  $\alpha$ -hydroxy- $\beta$ -methoxyketones. Spectroscopic, crystallographic, and mechanistic studies indicate that the process requires stabilization of reaction intermediates through intramolecular H-bonding to take place, and suggest that the conjugate addition step involves a catalytic cycle with initial formation of an ammonium enolate and sustained by an alkoxide ion pair. Given the rich functionality and structural complexity generated in a single step, the process could be exploited in the preparation of natural product-like compound libraries.

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The *de novo* preparation of natural products and their analogs depends on concise synthetic strategies that can yield significantly complex structures in which both the regio and stereochemistry of all the intermediate products can be controlled.<sup>1</sup> One of such approaches involves the use of domino or cascade reactions, chemical processes with good atom economy that combine two or more sequential transformations, and in which downstream transformations rely on the chemical functionality created in the upstream steps.<sup>2–4</sup> This methodology is, in addition, amenable for use in the preparation of natural product-like compound libraries, and applications in this area are well documented.<sup>5–8</sup> Although a cascade process can combine a variety of reactions types, those incorporating pericyclic transformations as key steps, and in particular Diels-Alder cycloadditions, are commonly encountered.<sup>4</sup>

As part of our efforts towards the preparation of biologically active natural product-like compounds, we recently reported on a novel approach for the synthesis of bicyclo[4.1.0]heptane, or norcarane, scaffolds through phototransformation of the Diels-Alder adducts formed between tropolone (**1**) or methyltropolone (**2**) and different dienophiles (Fig. 1).<sup>9</sup>

Based on literature reports for these systems,<sup>10</sup> we surveyed a variety of Lewis acid/base catalysts in an attempt to better control the rate, regio, and stereoselectivity of the cycloaddition reaction. As expected, our preliminary results were mostly in line with those

obtained earlier by Okamura and coworkers.<sup>10</sup> Nevertheless, we found that when the cycloadditions were carried out on non-alkylated tropolonic substrates in methanolic solution using Et<sub>3</sub>N as a catalyst, the Diels-Alder adducts suffered the incorporation of a solvent molecule. As described in the following sections, spectroscopic, crystallographic, and mechanistic studies allowed us to determine that in addition to the cycloaddition reaction, the process involves an oxa-Michael addition catalytic cycle followed by an acyloin rearrangement, can be classified as a pericyclic/anionic cascade, and only takes place when reaction intermediates are stabilized through intramolecular H-bonds.

As stated above, treatment of a methanolic solution of **1** with *N*-methylmaleimide in the presence of a catalytic amount of Et<sub>3</sub>N yields a product with [M+H]<sup>+</sup> and [M+Na]<sup>+</sup> peaks at *m/z* 266.1025 and 288.0846 in the HR-ESIMS spectrum, respectively, which correspond with the hydromethoxylation of *ENDO* Diels-Alder adduct **3** (Scheme 1).<sup>9</sup> Taking also into account that cursory inspection of the NMR data reveals only one unsaturation in the final product, we initially envisioned that a conjugate addition had occurred across the  $\alpha,\beta$ -unsaturated ketone chromophore of intermediate **3**, and, as shown in Scheme 1, assigned the structure of the new compound as that of  $\beta$ -methoxyketone **4**.

However, the proposed structure was inconsistent with several experimental observations. First, the addition product did not afford any of the expected phototransformation products upon irradiation under conditions developed by us for similar compounds (*vide supra*).<sup>9,11</sup> These photochemical conversions are

\* Corresponding author.

E-mail address: [gmoyna@fq.edu.uy](mailto:gmoyna@fq.edu.uy) (G. Moyna).

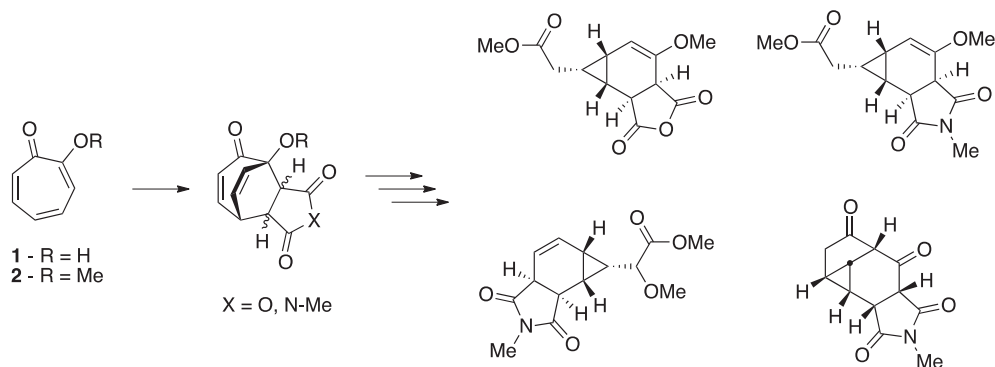
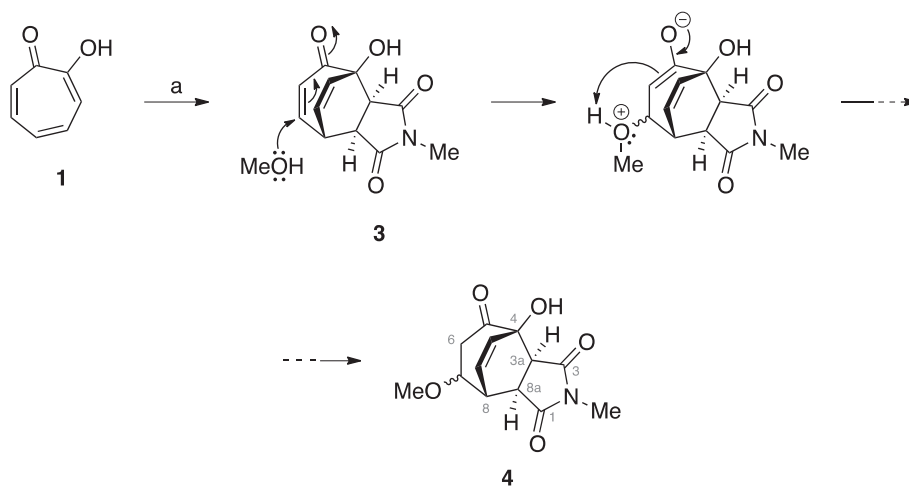


Fig. 1. Preparation of norcarane scaffolds through phototransformation of tropolone-based Diels-Alder adducts.



Scheme 1. Proposed mechanism for the conversion of tropolone (1) into  $\beta$ -methoxyketone 4. (a) *N*-Methylmaleimide (1.5 equiv),  $\text{CH}_3\text{OH}$ ,  $\text{Et}_3\text{N}$  (0.1 equiv),  $60^\circ\text{C}$ .

initiated through a Norrish type I homolysis of a  $\beta,\gamma$ -unsaturated ketone chromophore,<sup>12</sup> and it is therefore unlikely that this functional group is present as depicted in compound 4. Furthermore, a vicinal coupling constant of 5.1 Hz was measured between the protons on the C-8 and C-8a positions when the  $^1\text{H}$  spectrum of the addition product was recorded in  $\text{CD}_3\text{OD}$ . Similarly, and although the signal for the proton on the C-8 position is part of a second order system, a value of 5.3 Hz for this coupling constant was estimated when the data was obtained in  $\text{CDCl}_3$ . These do not compare well with the  $^3J_{\text{H8H8a}}$  values computed for the two possible diastereomers that can be obtained for compound 4, which include products where the methoxy group at position C-7 is in either  $\alpha$  or  $\beta$  configuration (see Supplementary data). After resorting to X-ray diffraction studies, we established that the structure of the addition product corresponds to that of tricyclic  $\alpha$ -hydroxy- $\beta$ -methoxyketone 5 (Fig. 2 and Scheme 2). Not surprisingly, vicinal coupling constants computed using dihedral angles measured from this X-ray structure, presented as Supplementary data, correlate well with experimental values.

Interestingly, the methoxy group in compound 5 appears to have added across the non-conjugated olefin of the Diels-Alder intermediate and not through a 1,4-addition. This seemingly anomalous product can be readily explained taking into account that intermediate adduct 3 can undergo a reversible acyloin rearrangement.<sup>9,10</sup> As shown in Scheme 2, initial attack of methanol on the  $\beta$ -carbon of the  $\alpha,\beta$ -unsaturated ketone moiety leads to an enolate that is potentially stabilized through intramolecular H-bonding. Instead of only protonating at the  $\alpha$ -position to afford

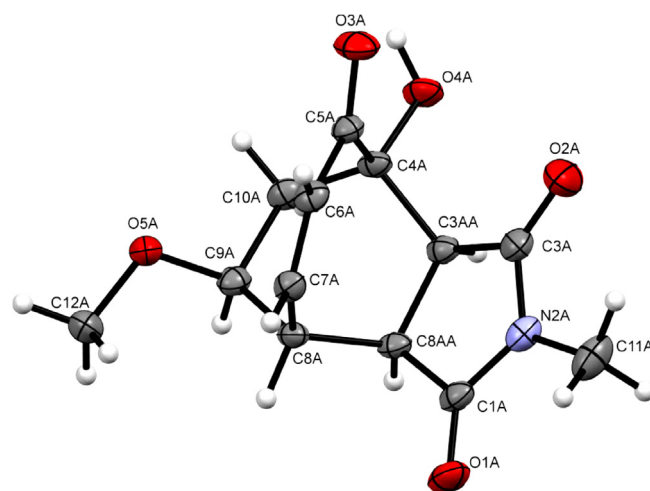


Fig. 2. ORTEP representation of the X-ray crystal structure of compound 5.

the originally proposed 1,4-addition product 4, this intermediate rearranges first to yield compound 5.

In order to assess the importance of the H-bonded intermediate in the outcome of the cascade reaction, we substituted 1 for methyltropolone (2) as starting material. As expected, the lack of a H-bond donor in the C-2 position of 2 precludes the oxa-Michael addition step, and only a Diels-Alder adduct previously described by us was obtained (compound 6, Scheme 3).<sup>9</sup> This finding, which

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