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New domino transposition/intramolecular Diels–Alder reaction in monocyclic allenols: a general strategy for tricyclic compounds

Benito Alcaide,* Pedro Almendros,* Cristina Aragoncillo and María C. Redondo
Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense, 28040-Madrid, Spain. E-mail: alcaideb@quim.ucm.es; palmendros@quim.ucm.es

Received (in Cambridge, UK) 17th April 2002, Accepted 23rd May 2002
First published as an Advance Article on the web 7th June 2002

A novel and direct synthetic strategy to prepare fused tricycles has been developed from monocyclic allenols, masked functionalized dienes, which underwent a domino allenol transposition/intramolecular Diels–Alder reaction.

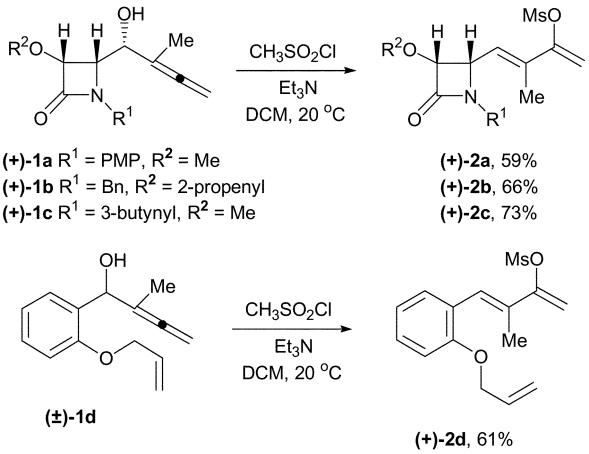
In view of the importance of ring structures in essentially all classes of natural products, the construction of rings represents a central theme in organic synthesis. The tandem or domino reactions are versatile methods for constructing complex structures in one step, offering an efficient way to prepare desired organic molecules.[1] It is obvious that this type of reaction would be more economic by requiring fewer reagents, solvents, adsorbents as well as less energy and labour together with a reduction of waste and thus preserve our environment. Domino reactions based on Diels–Alder chemistry are important examples for such sustainable methodologies.[2] However, the intricate access to the appropriate functionalized 1,3-dienes often is the major drawback to a practical use of these reactions.

Herein we report an efficient strategy for the one-step stereoselective synthesis of tricycles—found in many biologically active natural products such as β-lactams, cromenes, and pyrrolizidines—from monocyclic α-allenic alcohols. The ready availability of allenols, such as by the Barbier-type reaction in aqueous media between carbonyls and propargyl bromides,[3] makes such strategy very attractive. This unprecedented domino sequence represents a practical opportunity to connect the rapidly expanding fields of environmentally benign chemistry[4] and multiple bond-forming processes.

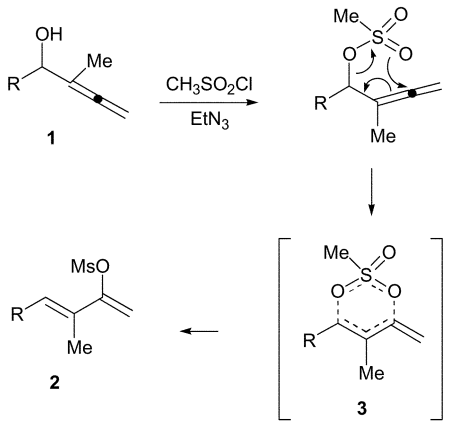
In continuation of our program directed toward the synthesis of potentially bioactive products,[5] we initiated a study into the use of allene substrates in organic synthesis. Allylic and propargylic alcohols react with metal complexes to form 1,3-transposition products. However, the corresponding rearrangement of allenyl alcohols has been virtually ignored.[6] Interestingly, during our work on this subject, we have noted the unexpected production of 2,3-difunctionalized diene (+)-**2a** in good yield and total stereoselectivity just by the addition of methanesulfonyl chloride and triethylamine to a dichloromethane solution of α-allenyl alcohol (+)-**1a**.[7] There was no significant solvent effect on the observed yield or stereoselectivity when a few other solvents (tetrahydrofuran or toluene) were also screened. This transposition was extended to various allenols including aromatic allenic alcohols (Scheme 1). Total *E*-stereoselectivity was observed when different α-allenyl alcohols were used.[8] In most cases these 2,3-difunctionalized dienes are unstable under prolonged storage at 20 °C.

This transformation might be tentatively explained through a migration of the methanesulfonyl group in the initially formed α-allenic methanesulfonate to give the corresponding mesyloxy-diene counterpart **2**. The high selectivity observed in the formation of dienes **2** may point to a concerted pathway. According to this idea, the 1,3-mesyloxy-group migration may follow a concerted mechanism *via* a rearrangement involving the six-membered cyclic transition structure **3** (Scheme 2).

Encouraged by these results, we decided to attempt a novel method for the straightforward synthesis of functionalized polycyclic compounds from monocyclic aldehydes. Our approach relied on the regioselective condensation of aldehydes with propargyl bromides to give allenols, masked functionalized dienes, which underwent a domino allenol transposition/intramolecular Diels–Alder reaction upon treatment with methanesulfonyl chloride. Thus, we subjected α-allenyl alcohols **1** bearing allyl or propargyl tethers to methanesulfonyl chloride–triethylamine treatment at 190 °C.† The expected products, fused tricycles **4**, were formed in moderate yields (35–54%) and good or total stereoselectivity (Scheme 3).‡



Scheme 1

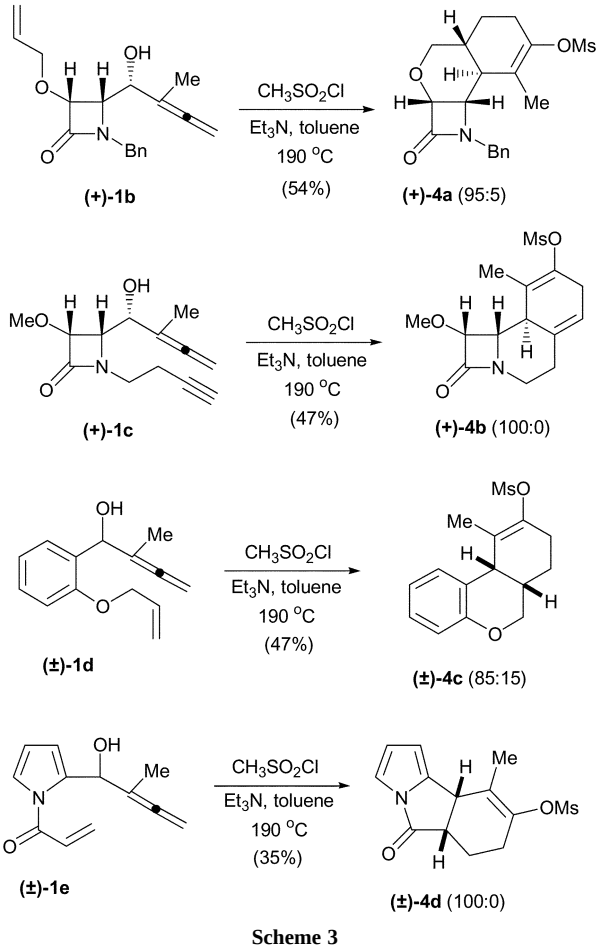


Scheme 2

In conclusion, we have presented a new straightforward methodology in a highly atom economic fashion for the synthesis (racemic or asymmetric) of naturally occurring fused tricycles. Studies towards this end, involving the use of different enantiopure aldehydes are currently under investigation in our laboratory.

We would like to thank the DGI-MCYT (Project BQU2000-0645) for financial support. C. Aragoncillo thanks the DGI (CEC-Comunidad de Madrid-Spain) for a fellowship.

DOI: 10.1039/b203450f



Scheme 3

Notes and references

† *Representative experimental procedure* for the synthesis of fused tricycles **4**. Methanesulfonyl chloride (1.10 mmol) and triethylamine (1.20 mmol) were sequentially added dropwise to a solution of the corresponding α-allenyl alcohol **1** (1.0 mmol) and hydroquinone (cat.) in toluene (10 mL). The resulting solution was heated in a sealed tube at 190 °C. The reaction mixture was allowed to cool to room temperature, and the solvent was removed under reduced pressure. Chromatography of the residue eluting with dichloromethane–ethyl acetate or hexane–ethyl acetate mixtures gave analytically pure fused tricycles **4**.

‡ All new compounds were fully characterised by spectroscopic data and microanalysis and/or HRMS.

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5 For reviews, see: B. Alcaide and P. Almendros, *Chem. Soc. Rev.*, 2001, **30**, 226; B. Alcaide and P. Almendros, *Synlett*, 2002, 381.

6 In the route to aldol-type products, the formation of an intermediate involving the 1,3-transposition of α-allenic alcohols has been postulated: B. M. Trost, C. Jonasson and M. Wuchrer, *J. Am. Chem. Soc.*, 2001, **123**, 12736.

7 α-Allenic alcohols **1** were prepared in aqueous media using propargyl bromides *via* metal-mediated Barbier–type carbonyl allenylation of the appropriate aldehyde. See ref. 3.

8 The geometry of the double bonds was determined on performing NOE experiments.