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THE HIGH PRESSURE MEDIATED INTRAMOLECULAR DIELS-ALDER REACTION OF FURAN DIENES: A SYNTHETIC APPROACH TOWARDS DAPHNANES.

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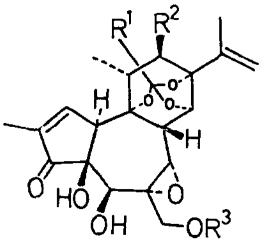
ABSTRACT: Furan 2 undergoes intramolecular Diels-Alder reaction when subjected to high (14kbar) pressures to give a mixture of endo and exo adducts in which the exo adduct is formed as the kinetic product, at variance with the expected course of events.

The daphnanes 1 are a class of tricyclic diterpenes, obtained from extracts of seeds and sap of *Euphorbia* species.[1] Several members of this group of compounds have been shown to demonstrate cytotoxic activity[2] and are responsible for the extreme toxicity of principles derived from the shrubs.



1

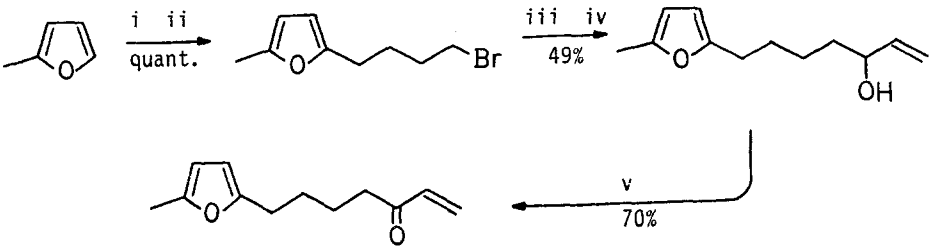
Compound	R^1	R^2	R^3	Botanical Source	Activity
Daphnetoxin	C_6H_5-	H	H	*Daphne mezereum*	toxic
Gnididin	C_6H_5-	$CH_3(CH_2)_4(CH{=}CH)_2COO$-	H	*Gnidia lamprantha*	antileukaemic
Gniditrin	C_6H_5-	$CH_3(CH_2)_2(CH{=}CH)_3COO$-	H		
Gnidicin	C_6H_5-	$C_6H_5CH{=}CH\ COO$-	H		
Gnidilatidin	$CH_3(CH_2)_4(CH{=}CH_2$-	C_6H_5COO-	H	*Gnidia latifolia & Gnidia glaucus*	toxic
Gnidiglaucin	$CH_3(CH_2)_8$-	CH_3COO-	H		
Huratoxin	$CH_3(CH_2)_8(CH{=}CH)_2$-	H	H	*Hura crepitens*	toxic

Recently we have been investigating the intramolecular Diels-Alder reaction of furan dienes (IMDAF) with the aim of applying this reaction to the construction of medium rings fused to a functionalised 6-membered ring in order to assess its potential in a synthetic approach towards the daphnane skeleton.[3] (Scheme 1)

Scheme 1

Whilst the literature contains examples of 5- and 6-membered ring closures via the IMDAF[4], attempts to prepare 7-membered carbocycles have been unsuccessful.[5] This failure is presumably a combination of the reversibility of Diels-Alder reactions involving furans[6] and entropic factors concerned with the closure of the larger ring. However, 7-membered cyclic amides have been prepared via an IMDAF[5] and we reasoned that the desired carbocycle construction might be feasible if the IMDAF could be carried out under milder reaction conditions than those used previously. The intermolecular high pressure Diels-Alder reaction of furans[7] has been shown to proceed efficiently at room temperature and, prompted by earlier work[8] on an intramolecular example, we decided to study the model substrate 2 under such conditions.

Enone 2 was synthesised in a straightforward manner by a three step sequence from 2-methylfuran (Scheme 2) in 34% overall yield.



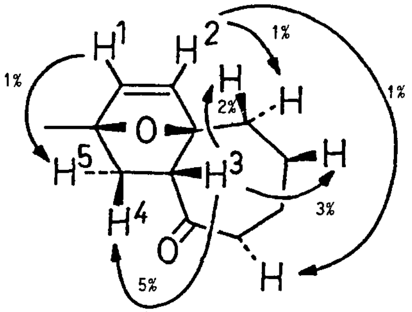
2

Reagents: i n-BuLi, THF, -20°C → 0°C, 6 h; ii $Br(CH_2)_4Br$; iii Mg,Et_2O; iv $CH_2=CHCHO$, 0°C; v CrO_3- C_6H_5N, CH_2Cl_2

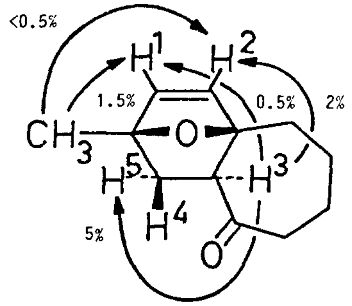
Scheme 2

Heating 2 under various conditions and treatment with several Lewis acids, previously shown to be of use in promoting Diels-Alder reactions of furans, (ZnI_2[10]; $AlCl_3$/-78°C[11]) did not lead to the isolation of any new identifiable material.

However, a solution of 2 in dichloromethane, on being subjected to 14kbar pressure at room temperature, produced two new products. Rapid chromatography enabled the products to be isolated in the pure form and each was shown to possess the 7-oxabicyclo [2.2.1.] hept-2-ene structure by 500 MHz n.m.r.[12] Both products reverted to starting material at atmospheric pressure. Unexpectedly, the more stable isomer ($t_{\frac{1}{2}}$= 1100 min./40°C) was shown to have the endo structure 3a on the basis of n.O.e. difference experiments[12]. Likewise, the less stable adduct ($t_{\frac{1}{2}}$= 90 min./40°C) was found to be the exo epimer 3b. The key features in assigning structure 3a to the more stable product were the enhancement of H^5 on irradiating H^1 and the enhancement of H^4, together with the absence of any enhancement of H^1 or H^2 on irradiating H^3. (Figure 1) Structure 3b was assigned on the basis of enhancement of H^2, H^1 (to a smaller extent) and H^5 on irradiating H^3 and the enhancement of H^1 to a much greater extent than H^2 on irradiating the methyl group protons.



3a



3b

Figure 1

N.m.r. analysis of the evolution of the reaction with time demonstrated that the endo adduct 3a was the thermodynamically favoured product and the exo adduct 3b was the kinetically formed product at high pressure. (Figure 2)

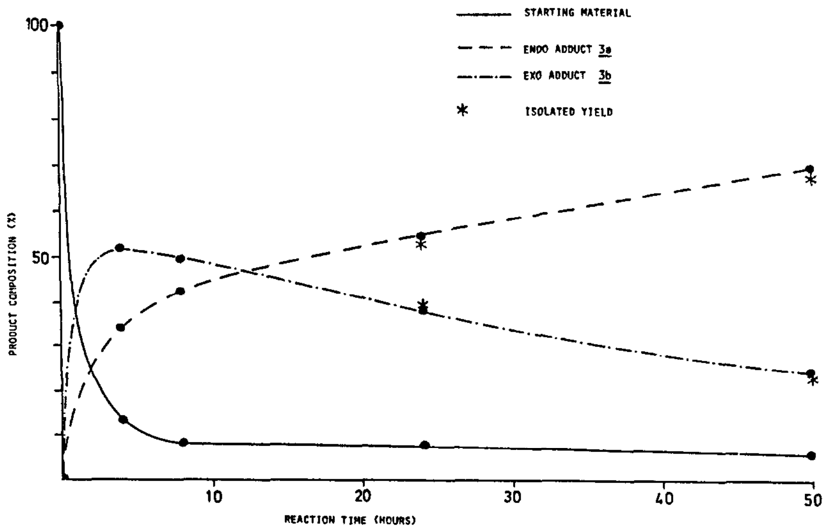


Figure 2

This constitutes a complete reversal of the usual stereochemical course of Diels-Alder cycloadditions and is also at variance with work of Kotsuki[13] who has clearly demonstrated the irreversibility of the high pressure intermolecular Diels-Alder reaction of furans. Work is now underway to determine the origin of this divergence which may lie in the intramolecular nature of the reaction, together with the size of the ring being generated, or in the relative activation volumes of the transition states leading to the adducts.

We have thus demonstrated that the high pressure mediated IMDAF provides a novel and efficient means of generating 7-membered carbocycles, suitable for further elaboration towards our synthetic goal, *via* novel kinetic *exo* adduct formation.

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