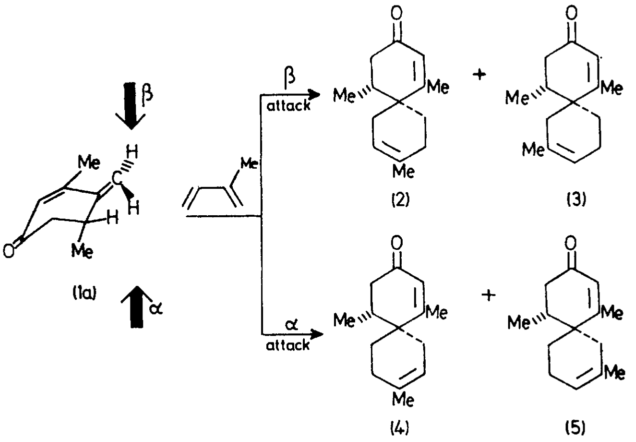
Regio- and Stereo-specificity in the Diels–Alder Reaction of a Lewis Acid-complexed 4-Methylenecyclohex-2-enone

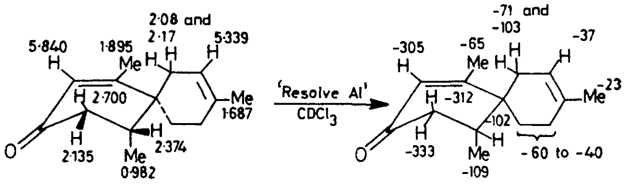
By Patrick M. McCurry, Jr.* and Rajendra K. Singh
(*Chemistry Department, Carnegie-Mellon University, Pittsburgh, Pennsylvania* 15213)

Summary Spiro[5.5]undeca-1,8-dien-3-ones were prepared by the reaction of the title compounds with dienes in the presence of Lewis acids.

Spiroannelation and the Lewis acid-catalysed Diels–Alder reaction have been subjects of continuing interest. We now report a synthetically useful reaction, the Diels–Alder cycloaddition to a 4-methylenecyclohexenone. To our knowledge this is the first reported example[1] of its kind.



The reaction we investigated was between 3,5-dimethyl-4-methylenecyclohex-2-enone (**1**)[2] (a double tautomer of 3,4,5-trimethylphenol) and isoprene. This pair of reactants was chosen because there are eight theoretical 1 : 1 adducts. In fact, when (**1**) was treated with 0·3 equiv. of $AlCl_3$† and 1·5 equiv. of isoprene in chloroform (3 h; 25 °C) a 60—70% yield of semicrystalline material was obtained (b.p. 120—130 °C at 0·1 mmHg). The 250 MHz spectrum of the crude product mixture showed the presence of two products in a 95:5 ratio. One recrystallization from cold pentane afforded a crystalline 1:1 adduct [mp. 61—62·5 °C, M^+ 204·1514 ($C_{14}H_{20}O$)]. Addition of isoprene to the α–β linkage was precluded on the basis of the i.r. (λ_{max} 6·00 μm) and n.m.r. (see below) spectra. Four possibilities, (**2**)–(**5**) then exist for the structure of the major product. Compounds (**2**), (**3**) and (**4**), (**5**) each represent a pair of *para,meta*-isomers resulting from addition of isoprene to the β and α faces, respectively, of the dienone (**1**) in the conformation (**1a**) drawn. The 95:5 ratio of isomers is in accord with published regiochemical results[3] in the acid-catalysed Diels–Alder reaction of enones with isoprene.[4] Compounds (**2**) and (**3**) are the structures of the major and minor products, respectively, on the basis of the arguments summarized below.



(A) (B)

Figure. (A): Proton chemical shifts (250 MHz; δ values downfield from Me_4Si). (B): Resonance shifts (at 250 MHz in Hz with 'Resolve Al' added).

The reaction of (**1**) with the symmetrical diene 2,3-dimethylbutadiene afforded a single crystalline compound (m.p. 104—106 °C). This result strongly suggests that the two isomers in the isoprene reaction arise from lack of regio- rather than stereo-specificity. The secondary methyl group in the major isomer is in an axial conformation in that it appears at δ 0·982 as a doublet of doublets [$|J(\text{CH–Me})|$ 6·89 Hz, $|J_W|$ 0·63 Hz]. The W coupling was shown by double resonance to be with the *trans* diaxial proton at C-4 (δ 2·700, $|J_{gem}|$ 16·9 Hz, $|J_{vic}|$ 5·02 Hz, J_W 0·63 Hz). Furthermore, irradiation of the olefinic proton in the methyldialkylcyclohexene ring (δ 5·339, m) showed it to be adjacent to a neopentyl methylene group, displaying AB resonances centred at δ 2·08 and 2·17. Finally, addition of *ca.* 0·20 equiv. of shift reagent (Aldrich 'Resolve Al')

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† This reaction was initially carried out using BF_3–Et_2O (1 equiv.) in acetone. The conditions above result in a more rapid, cleaner reaction.

shifted the neopentyl methylene resonances significantly further downfield than any other peaks assigned to the methylcyclohexene ring (see Figure for assignments), thus indicating its pseudo-axial and hence *trans* relationship to the secondary methyl group in the enone ring, and confirming structure (**2**) as the major product from (**1**) and isoprene.

The 250 MHz spectra were recorded at the N.I.H. Facility for Biomedical Studies at Carnegie-Mellon University.

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[1] For the *in situ* generation and thermal Diels–Alder trapping of a 4-methylenecyclohexa-2,5-dienone see: S. Mazza, S. Danishefsky, and P. McCurry, *J. Org. Chem.*, **1974, 39,** 3610.

[2] M. Mongrain, J. Lafontaine, A. Bélanger, and P. Deslongchamps, *Canad. J. Chem.*, 1970, **48**, 3273.

[3] E. F. Lutz and G. H. Bailey, *J. Amer. Chem. Soc.*, 1964, **86**, 3899.

[4] For a recent non-stereospecific use of a substituted 2-methylenecyclopentanone in a Diels–Alder approach to spirosesquiterpenes, see J. N. Marx and L. R. Norman, *J. Org. Chem.* 1975, **40**, 1602.