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# DIELS-ALDER REACTION OF SUBSTITUTED MALEIC ANHYDRIDES WITH 1-VINYLCYCLOHEXENE AN APPROACH TO THE SYNTHESES OF CLERODANE DITERPENES

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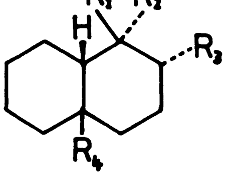
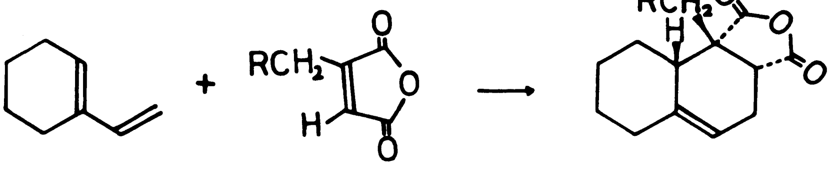
In an attempt to construct stereospecifically the clerodane skeleton, the Diels-Alder reactions of 1-vinylcyclohexene with aconitic, citraconic and chloromethylmaleic anhydrides have been undertaken and the configurations of the adducts are deduced. The product from the reaction with the last compound is found to be a potential intermediate for the syntheses of clerodane diterpenes.

Clerodane diterpenes are an unique class of compounds which have rearranged labdane skeleton. Now a number of the members have been known[2] and some of them are found to show interesting physiological activities[3]. However the synthetic route to this type of diterpenes seems to remain unexplored. In this communication we report the result of Diels-Alder reactions of substituted maleic anhydrides with 1-vinylcyclohexene, which would be expected to introduce stereoselectively the three asymmetric centers (C-8, C-9 and C-10) of clerodane skeleton 1.



1 ($R_4$= α or β)



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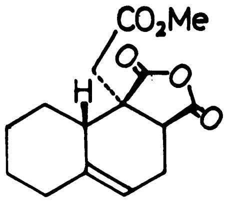
The reaction of aconitic anhydride (2, R = $CO_2H$) with 1-vinylcyclohexene at 95 -105° for 23 hr and subsequent methylation with diazomethane afforded the methyl ester 3[4], m.p. 172-173°, of an adduct in 26% yield as sole isolable product[5]. Performic acid oxidation of 3 followed by the treatment with 2N NaOH and the methylation led to the formation of a hydroxy-γ-lactone 4, $\nu_{max}$ 3440, 1770, 1730 $cm^{-1}$, which, on acetylation with acetic anhydride and pyridine, yielded an acetate 5, m.p. 120-121°, $\nu_{max}$ 1780, 1735, 1720 $cm^{-1}$. The nmr signals due to the protons on the carbon atoms bearing the secondary carbomethoxy and acetoxy groups in 5 are found both as double doublets at $\delta$ 3.92(J = 6,12 Hz) and 4.86 (J = 2,4 Hz) respectively, which indicate the presence of axial and equatorial protons respectively. This fact substantiates that 3 is a product formed by the normal orientation in the Diels-Alder addition, but the discrimination between the stereoisomers 5 and 5a was not possible in this stage.

In order to define the stereochemistry of 3 and to test a possibility of further structural conversion necessary for the syntheses of clerodane diterpenes, 3 was transformed to the unsaturated γ-lactone 6. Partial hydrolysis of the trimethyl ester 7, obtained from 3 by the treatment with aq. $NaHCO_3$ and subsequent methylation with diazomethane, gave 8. Selective reduction of 8 with sodium trimethoxyborohydride, after acid treatment of the product, afforded a hydroxy-γ-lactone 9, $\nu_{max}$3450, 1770 $cm^{-1}$ in 75% yield, which was converted in a good yield to 6, m.p. 86-87° by a sequence of reactions: mesylation, iodine substitution (NaI-acetone) and reduction (Zn-AcOH). In the nmr spectrum 6 exhibits signals at $\delta$ 0.98 (3H, d, J = 6 Hz, $-\overset{|}{C}HCH_3$), 2.22, 2.66 (2H, AB quartet, J = 18 Hz, $-CH_2CO_2-$), 4.02, 4.20 (2H, AB quartet, J = 10 Hz, $-CH_2OCO-$), 5.34 (1H, br. s, $-\overset{|}{C}=CH-$). On exposure to performic acid, 6 produced a secondary formate 10, m.p. 185°, $\nu_{max}$3440, 1760, 1720 $cm^{-1}$, $\delta$ 4.72 (1H, br. s, $-C\underline{H}OCHO$), 8.14 (1H, s, $-CHOC\underline{H}O$), which was hydrolyzed to a *trans*-diol 11. Provided that the peroxide attack occurs from the convex side of 6 and the intermediary epoxide 12 undergo *trans*-diaxial opening, the tertiary hydroxyl and formyloxy groups in 10 must have the conformation depicted in 10a. The configuration of the spiro-lactone ring is deduced from the nmr data of 10. The AB quartet (centered at $\delta$ 2.42) due to the methylene adjacent to the carbonyl group shifts to higher field by 0.02 ppm than that in 6, while the AB quartet (centered at $\delta$ 4.32) due to the methylene group attached to the potential hydroxyl group shifts by 0.23 ppm to lower field than that in 6. This fact indicates a 1,3-diaxial relationship between the tertiary hydroxyl group at angular position and the methylene group adjacent to the ether oxygen of the lactone ring[6]. In contrast the *cis*-diol 13, m.p. 128-128.5°, obtained by osmium tetroxide oxidation of 6, exhibits the corresponding signals of 6. 11 and 13 gave the same ketol 14 on oxidation with Jones' reagent. The conformation of 6, thus revealed, is ascertained by the synthesis of 6 by another route. Dien reaction of 1-vinylcyclohexene with *trans*-crotonic aldehyde at 130-140° yielded an adduct 15, which, on alkylation with ethyl bromoacetate ($Ph_3CK$) and subsequent hydrogenation with sodium borohydride afforded the lactone 6 in lower yield. It is worth to note that 6 has the reversed stereochemistry as predicted from Alder rule[8].

Subsequently Diels-Alder reactions of 1-vinylcyclohexene with chloromethylmaleic anhydride (2, R = $-CH_2Cl$) and citraconic anhydride (2, R = $CH_3$) have been studied. The reactions at 65° formed the adducts 16, m.p. 112-113° (71.5% yield) and 17, m.p. 98-99° (50% yield) respectively. The gross structures of 16 and 17 are verified by their nmr spectra: 16, $\delta$ 3.45, 4.05 (AB quartet, J = 12 Hz, $-CH_2Cl$), 3.64 (1H, dd, J = 2,9 Hz, $-CH_2C\underline{H}CO-$), 5.37 (1H, m, $-\overset{|}{C}=CH-$); 17, $\delta$ 1.43 (3H, s, $-\overset{|}{C}CH_3$), 2.92 (1H, dd, J = 2,8 Hz, $-CH_2C\underline{H}CO-$), 5.37 (br. d, J = 4 Hz, $-\overset{|}{C}=CH-$). In order to investigate the stereochemistry, 16 and 17 were converted by osmium tetroide oxidation to the diols 18, m.p. 155-156° and 19, m.p. 156-157°. In the nmr of 18, the center of the AB quartet due to the chloromethyl group appears at lower field by 0.78 ppm compared as that of 16[9]. This fact indicate the chloromethyl group in 16 is located at the same side of the molecule with the tertiary hydroxyl group and hence the adduct 16 has exactly the same configuration as predicted from Alder rule. Similar change in the chemical shift is observed between those of the methyl singlets of 17 and 19 ( $\Delta\delta$ = 0.33 ppm)[9], again showing 17 is the adduct with the configuration consonant to Alder rule. The reduction of 16 (NaI-Zn-AcOH) afforded 17.



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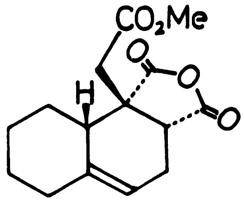
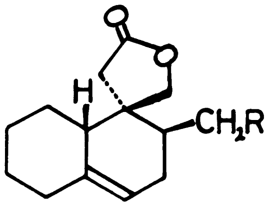
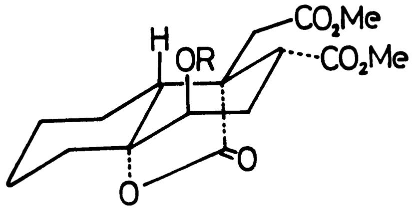


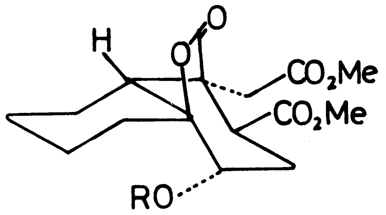
3a



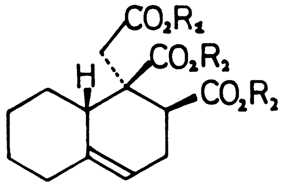
6 (R=H)
9 (R=OH)



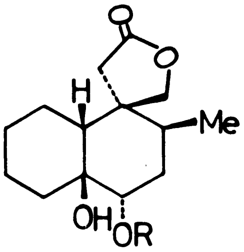
5a(R=Ac)



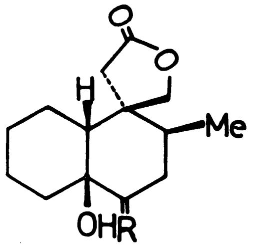
4 (R=H)
5 (R=Ac)



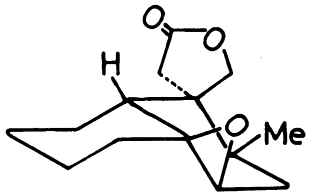
7 ($R_1=R_2=Me$)
8 ($R_1=H, R_2=Me$)



10 (R=CHO)
11 (R=H)



13(R=α-H, β-OH)
14(R=O)



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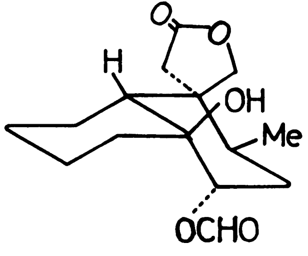
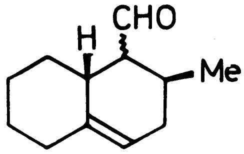


10a



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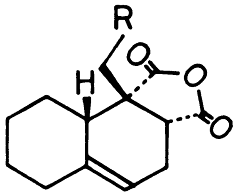
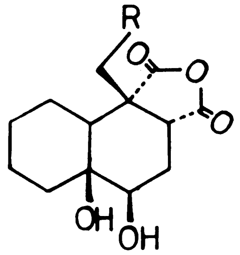


16(R=Cl)
17(R=H)



18 (R=Cl)
19(R=H)

It is remarkable that quite contrasting results are obtained in the Diels-Alder reaction of 1-vinylcyclohexene with the substitited maleic anhydrides studied. Although simple mechanistic interpretation would not be possible only from these data, our results are interesting in view of the fact that currently a number of proposals have been made on the stereospecificity of Diels-Alder reaction[10] and our case would deserve further investigations. Eventually the adduct 16 would be a useful intermediate for the syntheses of clerodane type diterpenes, having the functionalities appropriate for further elaboration of the molecules. The works in this line are in progress.

## REFERENCES AND NOTES

1) To whom the all correspondance should be adressed.
2) Chemical Society Special Periodical Reports, Terpenoid and Steroid, Vol. 1, p.128-130 (1971); Vol. 2, p.128 (1972).
3) S. Yamazaki, S. Tamura, F. Marumo and Y. Saito, Tetrahedron Lett., 1541 (1969); C. Nishino, K. Kawazu and T. Mitsui, Tetrahedron Lett., 1541 (1971); N. Kato, S. Shibayama, K. Munakata and C. Katayama, Chem. Comm., 1632 (1972).
4) Satisfactory analyses and spectral data were obtained for all crystalline compounds. Nmr spectra were measured in deuterochloroform solutions, if otherwise stated, on JEOL PS-100 spectrometer.
5) Chromatographic studies of the uncrystallized part showed that it did not contain the compounds of comparable polarity with 3, but mostly consisted of a polymeric material.
6) H. Wollweber in "Methoden der Organischen Chemie (Houben-Weyl), Bd. 5/1c, p.1007, Georg Thieme Verlag, Stuttgart (1970).
7) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd. ed., p.81, Pergamon Press, Oxford (1969).
8) ref.6, p.985.
9) The nmr data in deuteropyridine solutions were compared.
10) J. G. Martin and R. K. Hill, Chem. Rev., 61, 537 (1961); W. C. Herndon and L. H. Hall, Tetrahedron Lett., 3095 (1967); K. N. Houk, Tetrahedron Lett., 2621 (1970); R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", p.145, Academic Press, New York (1970); Y. Kobuke, T. Fueno and J. Furukawa, J. Am. Chem. Soc., 92, 6548 (1970).

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