

ALL-TRANS-1-ACYLOXY-1,3-PENTADIENE-5-OLS AS REACTIVE DIENES
IN NEW INTRAMOLECULAR DIELS-ALDER REACTIONS

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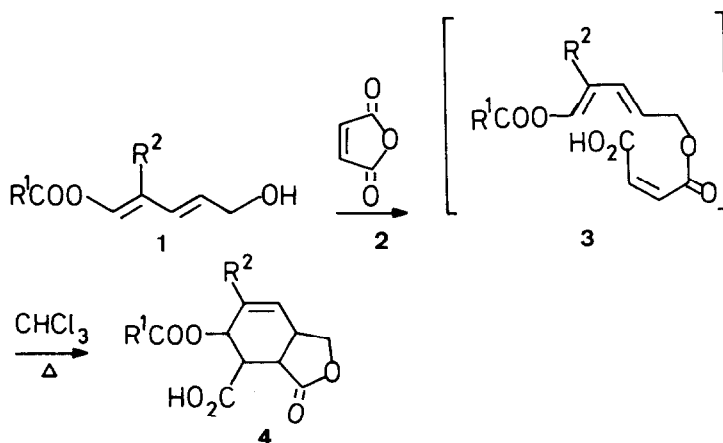
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Abstract: The high reactivity of the all-trans-1-acyloxy-1,3-pentadiene-5-ols as dienes in intramolecular Diels-Alder reactions with maleic anhydride and fumaric acid ethylester monochloride is discussed.

The utilization of the IMDA-reaction (Intramolecular Diels-Alder reaction) is an elegant and valuable synthetic strategy for the construction of complex natural compounds¹.

A usable IMDA-reaction depends on the easy access to compounds which contain a diene and a dienophile moiety within the same molecule. The all-trans-1-acyloxy-1,3-pentadiene-5-ols (1) are readily prepared in few steps from simple and inexpensive pyridines². Diels-Alder reactions with the dienes 1 have not been investigated previously. These dienes appeared as promising candidates for new IMDA-reactions for the following reasons: i; The acyl-enol structure activates the diene system and should therefore facilitate an IMDA-reaction, thus leading to compounds with kinetically controlled stereochemistry³. ii; The all-trans-diene system in compounds 1 prevents the possibility of a 1,5-hydrogen shift which is often observed in IMDA-reactions of dienes with cis-configuration⁴. iii; In the present example a number of suitable dienophiles can in our case easily be connected to the pentadienols 1, thus making it possible in a convergent route to prepare diene and dienophile separately followed by ester bond formation prior to IMDA-cyclisation. iv; The expected IMDA-reaction products in this reaction will contain differently protected hydroxy-groups suited for further selective transformations.

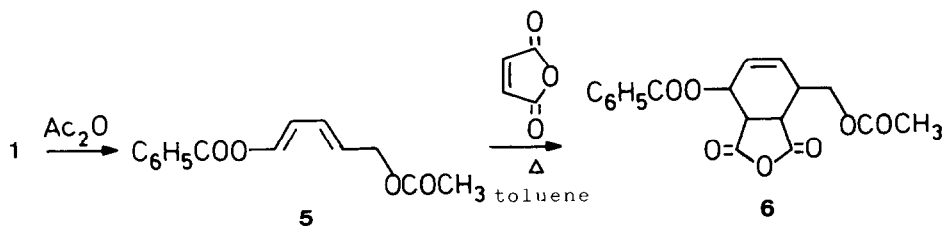
Thus reflux of 1 ($R^1 = C_6H_5$, $R^2 = H$) and maleic anhydride in chloroform (0.01 mol in 100 ml) give the α, β -annellated γ -butyrolactone 4a as a single isomer (TLC, ¹³C-NMR and ¹H-NMR). The lactones 4 usually precipitate as colourless crystals from the reaction medium almost analytically pure and in fair yields:



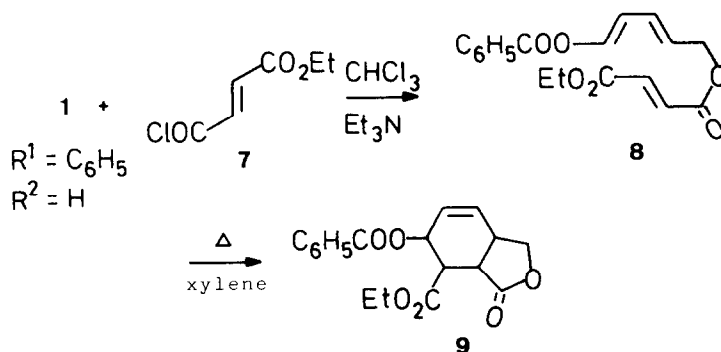
| R^1 | R^2 | Yield % | m.p. °C | compound |
|-----------------|--------|---------|----------------------|------------------------|
| C_6H_5 | H | 72 | 186-187 ^a | <u>4a</u> ^e |
| C_6H_5 | CH_3 | 67 | 198-200 ^b | <u>4b</u> ^f |
| C_2H_5O | H | 63 | 145-146 ^c | <u>4c</u> ^e |
| $C_6H_5CH = CH$ | H | 80 | 195-193 ^d | <u>4d</u> ^e |

a) Ethylacetate, cyclohexane. b) Toluene, ethylacetate. c) Ethylacetate. d) Toluene.
 e) Chloroform, reflux 2-3h. f) Toluene, reflux 5h.

The reaction probably proceeds intramolecularly via the intermediate half ester 3, since the acetate 5 of the pentadienol 1 ($R^1 = C_6H_5$, $R^2 = H$) only gives the expected IMDA-reaction product 6 at elevated temperature (toluene, reflux 4 hours, yield 60%):

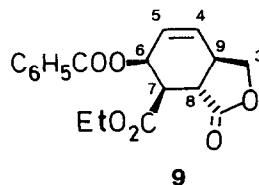
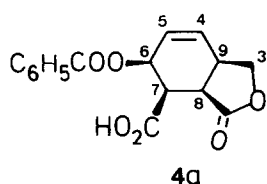


with fumaric acid ethylester monochloride 7 as the dienophile the mixed ester 8 can be isolated (m.p. 78°C, yield 80%).



The ester **8** could only be cyclised after prolonged refluxing in xylene (b.p. 140°C) to yield the butyrolactone **9** as a single isomer m.p. $172\text{--}173^\circ\text{C}$ (toluene); (TLC, ^{13}C -NMR and ^1H -NMR). Structure of the new IMDA-reaction products was assigned from the analytical and spectroscopic data. Related Diels-Alder products prepared by White and Sheldon⁵ showed corresponding ^{13}C -NMR and ^1H -NMR values. The mass spectra of compounds **4a** showed $m/e = 302$, M^+ and loss of benzoyl $m/e = 105$ resulting in the ion at $m/e = 197$.

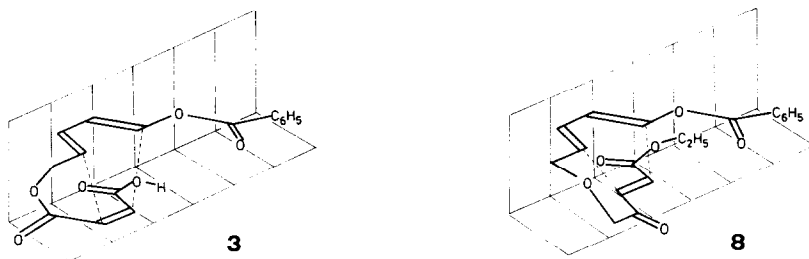
The stereochemistry of the isomeric butyrolactones **4** and **9** is assigned as depicted below according to the ^1H -NMR spectral data (CDCl_3 , 270 and 300 MHz) as well as the ^{13}C -NMR data (DEPT GL spectral editing⁸).



| | 4a <u>cis</u> | 9 <u>trans</u> |
|----------------------|---|--|
| ^1H -NMR | $J_{4,5} = 9.9$, $J_{5,6} = 5.6$ | $J_{4,5} = 9.8$, $J_{5,6} = 3.9$ |
| J in Hz | $J_{4,9} = 2.9$, $J_{6,7} = 4.0$ | $J_{4,9} = 1.4$, $J_{6,7} = 5.4$ |
| | $J_{3,9} = 1.8$ and 9.2 | $J_{3a,9} = 6.5$, $J_{3a,3b} = 8.1$ |
| | $J_{7,8} = 4.8$, $J_{8,9} = 8.5$ | $J_{7,8} = 11.7$, $J_{8,9} = 13.3$ |
| ^{13}C -NMR | $\text{C}^1 = 165.11$, $\text{C}^3 = 70.08$ | $\text{C}^1 = 165.20$, $\text{C}^3 = 69.64$ |
| δ in ppm | $\text{C}^4 = 125.44$, $\text{C}^5 = 132.67$ | $\text{C}^4 = 128.12$, $\text{C}^5 = 133.47$ |
| | $\text{C}^6 = 63.44$, $\text{C}^7 = 40.19$ | $\text{C}^6 = 67.31$, $\text{C}^7 = 44.88$ |
| | $\text{C}^8 = 35.90$, $\text{C}^9 = 35.87$ | $\text{C}^8 = 40.80$, $\text{C}^9 = 40.04$ |
| | $\text{HOOC} = 169.58$, $\text{ROOC} = 175.82$ | $\text{EtOOC} = 168.11$, $\text{ROOC} = 173.07$ |
| | $\text{C}_6\text{H}_5 = 128\text{--}133$ | $\text{C}_6\text{H}_5 = 129\text{--}130$, $\text{CH}_3 = 14.00$, $\text{CH}_2 = 61.39$ |

The different stereochemistries observed in the IMDA-reaction products using maleic anhydride and fumaric ester chloride probably reflect different transition states. Thus the transition state **3** leading to compounds **4** with maleic anhydride as the dienophile has both

carbonyl groups in the endo orientated conformation:



In contrast the trans-annulated butyrolactone 9 can only be derived from the transition state 8 in which the linking estercarbonyl group in the chain is in an exo orientated configuration while the terminal carbonyl group can adopt the energetically favoured endo orientation. It should be noted, however, that intermediate 3 has a carboxylic function in the dienophile part, while 8 has an ester function at this position. This difference could therefore also play a role for the outcome of the reaction. Different stereochemistry in the IMDA-reaction of an acid and of the corresponding ester in a related system has been reported by White *et al.*⁶.

The new cis- and trans-annulated butyrolactones 4 and 9 contain two differently protected hydroxy groups (ester and lactone) as well as two differently protected carboxyl groups (lactone and acid in 4, lactone and ester in 9) well suited for further transformation into compounds related to natural products. The majority of known α,β -annulated γ -butyrolactones exists in the thermodynamically more stable cis-configuration. The IMDA-reaction products 9 give access to otherwise difficult obtainable butyrolactones with trans-configuration⁷.

The use of this new IMDA-reaction for the synthesis of compounds related to natural products is currently under investigation.

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