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INTRAMOLECULAR DIELS-ALDER ADDITION OF CITRACONATE ESTERS. STEREOSELECTIVE REACTION VIA ENDO AND EXO MODES

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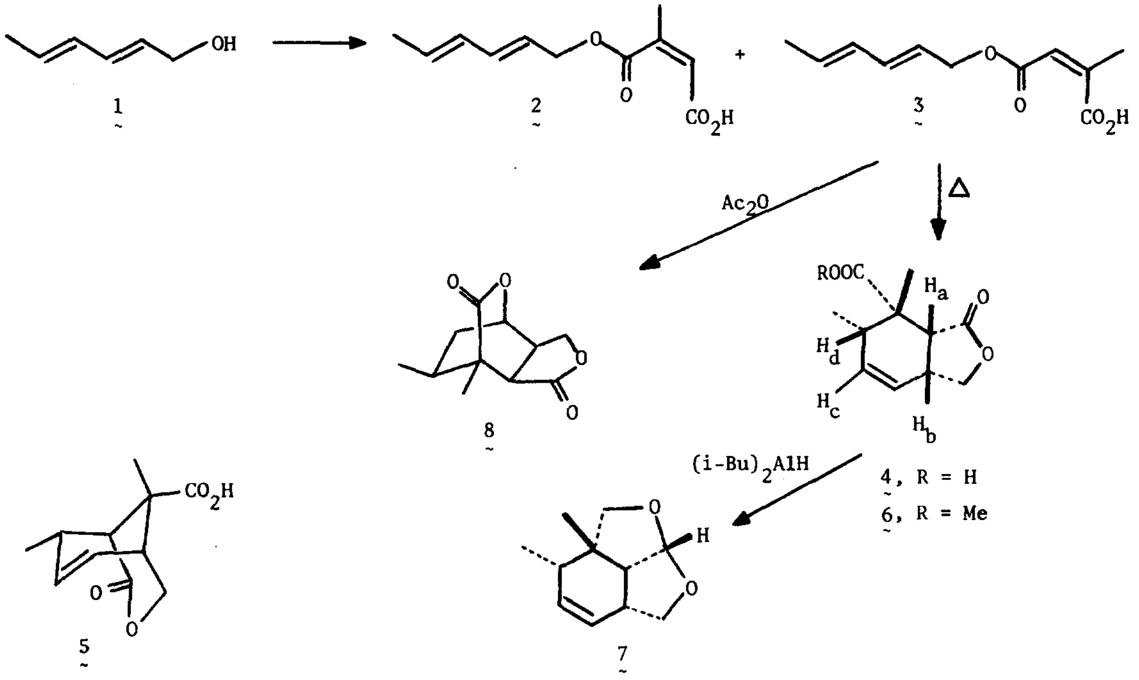
Intramolecular variants of the Diels-Alder reaction and other cycloadditions[3] afford a powerful method for the stereocontrolled synthesis of polycylic structures.[4] The pioneering study in this field by House and Cronin[5] explicitly defined those geometrical and conformational factors by which the stereochemical outcome of the intramolecular (4 + 2) cycloaddition is determined, and demonstrated that constraints imposed by the linkage between diene and dienophile can lead to formation of a bicyclic adduct from acyclic precursor with high stereochemical precision. In extending these ideas to carbocyclic systems suitable for elaboration towards certain diterpenoids, we have encountered remarkable and divergent stereoselectivity associated with the intramolecular cycloaddition of citraconate esters.

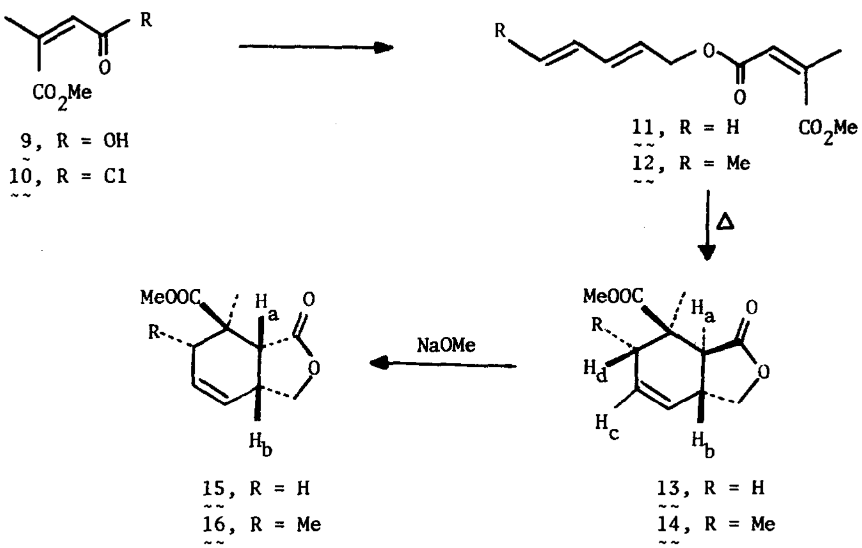
Sorbyl alcohol (1) reacts with citraconic anhydride in benzene containing an equivalent of pyridine and a trace of 2,6-di-t-butyl-p-cresol (50°C, 6 h) to give a mixture of half esters 2 and 3 in 60% yield. Separation of these regioisomers is unnecessary since, upon heating (xylene, reflux, 15 h), only 3 undergoes intramolecular cycloaddition, leading stereospecifically to lactone 4 (mp 170-172°C) in good yield. The formation of fused bicycle 4 rather than the alternate bridged structure 5, is apparent from the presence of a γ-lactone (1765 cm^{-1}). The configuration of the four, newly generated chiral centers of 4 can be deduced from careful analysis of the NMR spectrum of its methyl ester 6 (CH_2N_2, Et_2O, 0°C), and also from the further transformation of 6 to a tricyclic acetal 7 upon treatment with diisobutyl aluminum hydride, which thereby defines the cis relationship of the three oxygenated substituents.[6] Thus, a coupling constant of 9 Hz between H_a (δ 3.05, d) and H_b (δ 3.20, m) of 6 implies a cis ring fusion,[7] while the appearance of H_c (δ 5.80) as a triplet of doublets with J = 2,4,10 Hz indicates a dihedral between this proton and H_d consistent with a pseudoequatorial disposition of the secondary methyl group. This configuration was, in fact, fully confirmed by means of an X-ray crystallographic analysis of the parent acid 4.[8]

Interestingly, when the mixture of 2 and 3 was exposed to acetic anhydride (reflux, 6 h), a different product containing both a γ- and δ-lactone (1778, 1743 cm^{-1}) was produced. This was shown to be 8, formed via a subsequent lactonization of the Diels-Alder adduct 4. Thus, in both acetic anhydride and xylene media the acid 3 undergoes intramolecular cycloaddition exclusively via the endo mode.



Since separation of the isomeric acylation products 2 and 3, as well as their methyl esters, proved difficult, a regiocontrolled route to these systems was sought. The half ester 9 of citraconic acid[11] was converted to its chloride 10 ((COCl)$_2$, C$_6$H$_6$, 50°C, 1 h), which was then used to esterify both 1 and 2,4-pentadienol, affording 12 and 11 respectively. Surprisingly, when 12 was heated in xylene it gave, not 6, but an isomeric γ-lactone 14 (mp 94-96°C, 1775, 1735 cm^{-1}) as the sole product in 40% yield. An analogous cycloadduct 13 (mp 96-98°C, 1775, 1735 cm^{-1}) was derived by similar treatment of 11. That both of these intramolecular adducts were trans-fused lactones was apparent from the 14 Hz coupling constant between H$_a$ and H$_b$ in each case.[7] Both 13 and 14 exhibit a sharp 2H singlet for the vinylic protons, indicating that the vicinal coupling of H$_c$ with H$_d$ is ~ 0 Hz. A Dreiding model of 14, besides revealing that this structure is conformationally quite rigid, protracts a dihedral of 90° between these two protons, so that the secondary methyl must be pseudoequatorial and hence cis to its neighbor.[12] A further consequence of the trans fusion in 13 and 14 is that these lactones embody a greater measure of strain than is present in the cis fused structure 6. An opportunity for epimerization would thus lead to a new stereoisomer[13] and, indeed, treatment of 13 and 14 with sodium methoxide gave in each case a different γ-lactone, 15 and 16. The cis coupling between H$_a$ and H$_b$ in these isomers was obscured by the similarity in chemical shift of these protons, but it was apparent that, in the course of both epimerizations, H$_a$ had shifted downfield by > 1 ppm, consistent with its new orientation on the same side of the cyclohexene as the carbomethoxyl group.

The implication from these experiments is that, whereas the carboxylic acid 3 undergoes intramolecular Diels-Alder addition via the endo mode A, its ester 12 (and, analogously, the pentadienyl ester 11) accomodates only the exo configuration via B. Examination of the transition states of these cycloadditions suggests that relatively straightforward steric effects could provide an explanation for this reversal, although the possibility that secondary orbital over-



9, R = OH

10, R = Cl

11, R = H

12, R = Me

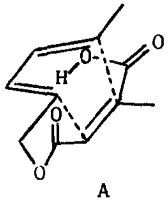
13, R = H

14, R = Me

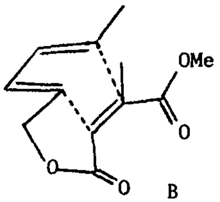
15, R = H

16, R = Me

lap may play a role cannot be excluded. Thus, the intramolecular hydrogen bond in 3 permits a sterically undemanding orientation of the dienophile in the endo mode (see A), whereas esters 11 and 12 would need to tolerate a substantial compression of the carboxyl groups as the cis fusion develops. Even though the alternative exo transition state B generates torsional strain as bonding toward the trans fusion proceeds, this is evidently compensated by the diminished interaction of carboxyl residues along the reaction profile.

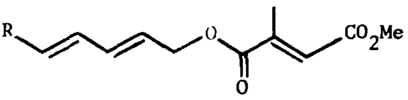


A



B

In spite of this clear-cut divergence in the directing influence of a carboxyl group versus its methyl ester, it is not obvious why the alternate citraconate half ester 2 and also the mesaconate esters 17 and 18 fail to undergo internal cycloaddition even at 180°C. Further studies



17, R = H

18, R = Me

may reveal why the placement of a methyl substituent at C-3 rather than C-2 of the dienophile suppresses this reaction; in any case, it is evident that this intramolecular Diels-Alder reaction is sensitive to extraordinarily subtle substituent effects.

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(8) Crystals of 4 formed in the monoclinic crystal class. Accurate cell constants, determined by a least-squares fit of fifteen moderate angle, diffractometer measured 2θ values, were a = 8.845(4), b = 6.534(3), c = 18.411(7) Å and β = 83.98(3)°. Systematic absences were consistent with the uniquely determined space group $P2_1/c$ and a calculated (z=4) and observed (floatation) density of $\sim$1.3 g/cc indicated one unit of composition $C_{11}H_{14}O_4$ formed the asymmetric unit. All unique diffraction maxima with $\theta \leq 57^{\circ}$ were collected on a fully automated diffractometer with graphite monochromated CuKα (1.54178Å) radiation and a variable speed ω-scan technique. Of the 1668 reflections surveyed in this manner, 1405 (84%) were judged observed ($I \geq 3\sigma(I)$) after correction for Lorentz, polarization and background effects. Structure solution by a multiple solution sign determining procedure[9] was straightforward. A plausible nine atom fragment was found and the remaining nonhydrogen atoms were found in an electron density synthesis.[10] Hydrogen atoms were located on subsequent difference electron density syntheses. Full matrix least squares refinements have converged to a final crystallographic residual of 0.045 for the observed data. All bond distances and angles agree well with generally accepted values. There were no abnormally short intermolecular contacts or high residual peaks in a final difference synthesis.

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