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THE INFLUENCE OF SIDECHAIN SUBSTITUENTS IN THE INTRAMOLECULAR DIELS-ALDER REACTION

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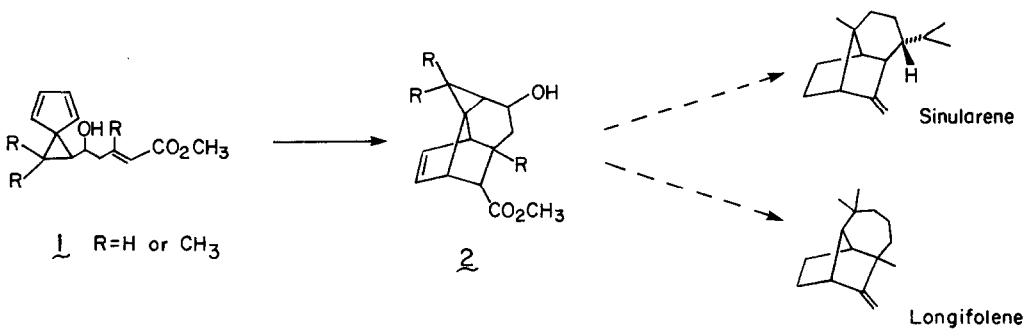
Summary: The intramolecular Diels-Alder reactivity of a series of methyl 5-(spiro[2.4]hepta-4,6-dien-1-yl)-2-pentenoates is described. A sidechain oxygen substituent is essential for cyclization and the ^{1}H nmr chemical shift of the β-dienophilic hydrogen provides a useful diagnostic guide to their cycloaddition potential.

There is considerable current interest in the intramolecular Diels-Alder reaction and it has been applied to a number of synthetic objectives with notable success.[1] The strategic advantage of confining the diene and dienophile to the same molecule facilitates the construction of complex natural product skeletons in a predictable fashion with a high degree of regio- and stereochemical control. In spite of recent studies[2] many facets of this cycloaddition are still imperfectly understood and to be synthetically useful one must be able to predict the feasibility of the cyclization with various substitution patterns in both the reacting units themselves and the sidechain connecting them.



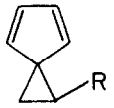
1 R=H or CH_3 2

We are developing general intramolecular routes, in which the diene component is a substituted cyclopentadiene, to diverse terpenoids. This has resulted in the total synthesis of cedrol and cedrene,[3] and work is in progress toward sinularene, 12-acetoxysinularene, and longifolene.[4] The latter syntheses proceed via a bicyclo[2.4]heptadiene of type 1 to the tetracyclic adduct 2 followed by controlled cyclopropane ring opening. In the course of this research we have studied several spiro-trienes 10, 11, 14, 15, 18, 19 and discovered a remarkable influence of sidechain oxygen substituents.

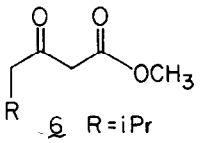
The triene 10, prepared by alkylation of the dianion derived from 6[5] with bromide 4[6] followed by $NaBH_4$ reduction and dehydration, refused to cyclize under thermal or Lewis acid catalyzed conditions without decomposition of the sensitive spiro-cyclopentadiene moiety. It had been anticipated that the desired epimer might cyclize preferentially since the non-bonded interactions between the developing exo hydrogen and the isopropyl substituent are reduced in structures of type 23 compared to 22. It appeared that adverse steric crowding inhibited cycloaddition and thus triene 11, lacking the isopropyl function, was synthesized in analogous fashion (4 plus 7) but it also showed no inclination to cyclize and after 65 h (195°, toluene, sealed tube) was recovered unchanged.

In marked contrast the hydroxytriene 14, from condensation of the Grignard reagent of 8 with aldehyde 5,[6] cyclized smoothly (180°, 6 h, p-dichlorobenzene, 60%) to 16. Why does 14 cyclize while 10 and 11 do not? Apparently alcohol 14 prefers a conformation in which the dienophile is folded underneath the cyclopentadiene ring in an alignment which approximates that required for cycloaddition. This contention is supported by the ^1H nmr spectra of the different trienes. Normally the β-hydrogen on a conjugated double bond has a chemical shift between δ 6.5 - 7.5 but for 14 these olefinic protons fall together (δ 5.0, m) as a consequence of shielding by the cyclopentadiene. The dienophilic protons for 10 and 11 appear as separate signals (β-H's at δ 6.55 and 6.75) and thus are not shielded significantly. The beneficial influence of the oxygen substituent is not dependent upon hydrogen bonding since the triene acetate 15 cyclized (175°, 4.5 h, toluene, sealed tube, 66%) as expected (β-H at δ 4.9). In addition, cycloaddition proceeded readily under catalytic conditions with $AlCl_3$ (23°, 3 h, CH_2Cl_2, 75%).

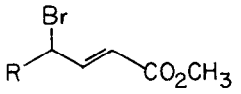
These results imply that triene 18, which contains both the requisite sidechain, hydroxyl function, and an isopropyl substituent should exist preferentially in a folded conformation and undergo intramolecular cyclization. The ^1H nmr spectrum of 18 (derived from 5 and the Grignard reagent of 9) contained a multiplet at δ 5.2 - 5.5 due to the dienophilic hydrogen. The four C_4C_5 diasteroimers were separated and heated individually but only the R,R and S,R isomers (82% of coupled product) cyclized (180°, 24 h, ~10%, extensive decomposition) indicating that the interactions depicted in 22 play a dominant role in the other cases. The acetates 19 were more thermally stable and cyclized cleanly (180°, 24 h, p-dichlorobenzene, 62%) providing material for further synthetic study. Although polymerization competes, the acetate cycloadditions may be catalyzed with $AlCl_3$ (1.1 eq., 23°, CH_2Cl_2, 25%) under mild conditions



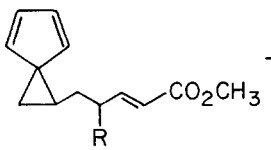
3 R=CH_2OH
4 R=CH_2Br
5 R=CHO



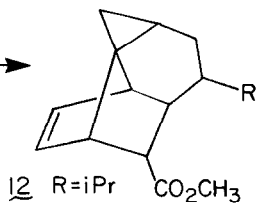
6 R=iPr
7 R=H



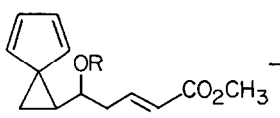
8 R=H
9 R=iPr



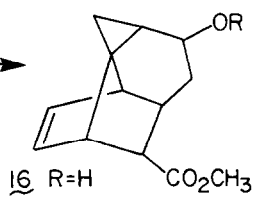
10 R=iPr
11 R=H



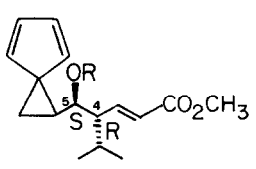
12 R=iPr
13 R=H



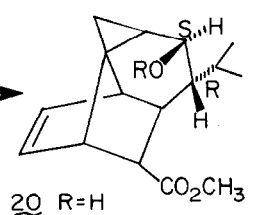
14 R=H
15 R=Ac



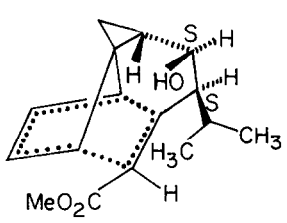
16 R=H
17 R=Ac



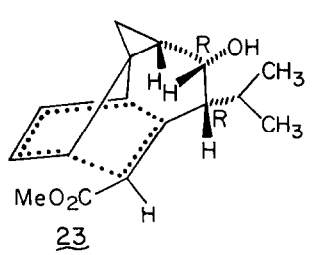
18 R=H
19 R=Ac



20 R=H
21 R=Ac



22



23

to the diesters 21 thus adding to the growing number of intramolecular Diels-Alder reactions which may be catalyzed with Lewis acids.[7] Unfortunately, in our cases, other catalysts ($EtAlCl_2$, $SnCl_4$, $FeCl_3$, $BF_3.Et_2O$, -78° to 23°) promoted decomposition rather than cyclization.

In conclusion, a C_5-oxygen substituent is essential for successful cyclization of these trienes. The chemical shift of the β dienophilic hydrogen provides a reliable diagnostic guide to the relative ease of internal cycloaddition and this observation may be of predictive benefit in other series as well. These concepts are currently being extended to an asymmetric synthesis of longifolene from ascorbic acid and the total synthesis of sinularene and 12-acetoxysinularene.

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