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FACILE SYNTHESIS OF SUBSTITUTED 1,5-CYCLODECADIENES EMPLOYING A PHOTOADDITION-THERMOLYSIS SEQUENCE

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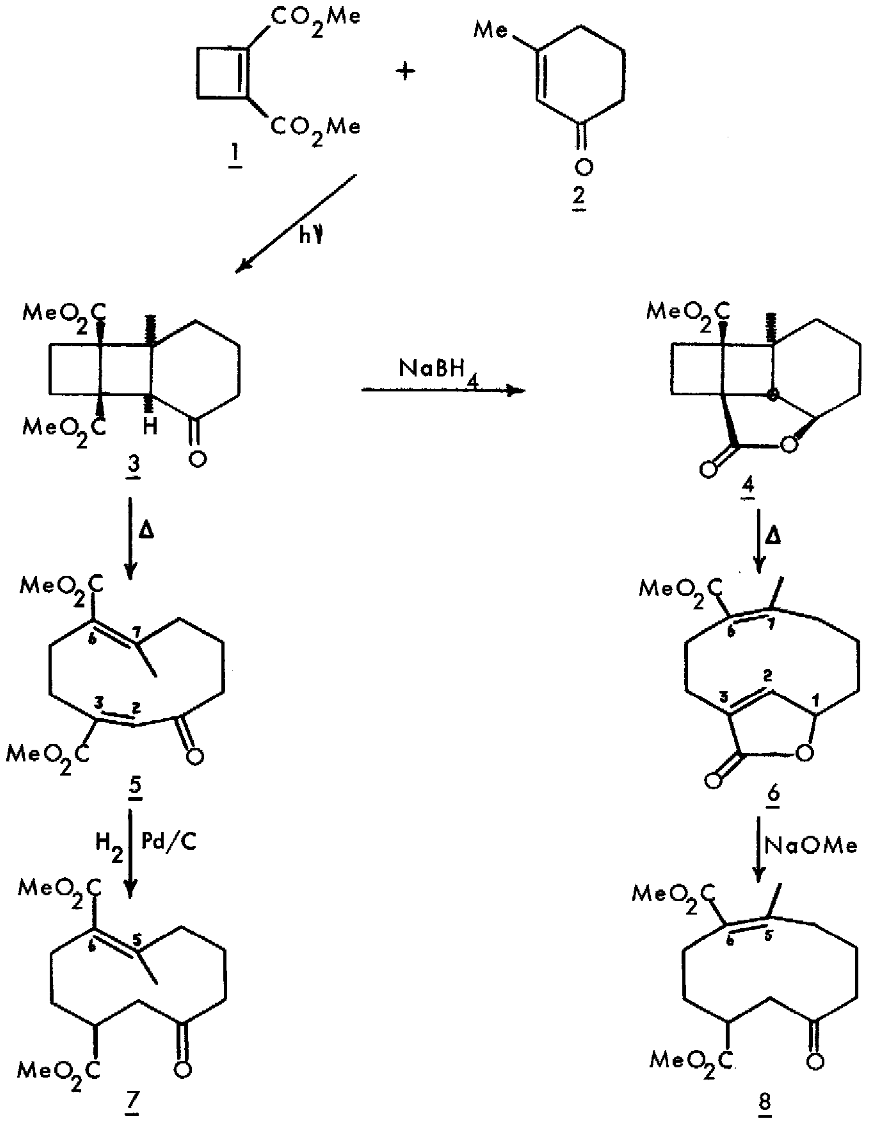
The germacranolides,[1] a class of sesquiterpenes which often possess a substituted 1,5-cyclodecadiene carbon skeleton to which is attached an alpha-methylene-gamma-lactone moiety, are gaining increasing importance as the anti-tumor activity of many of them is discovered.[2] A flexible approach to the synthesis of these dienes is essential if new and potentially more active derivatives are to be uncovered. We wish to report a new, efficient, and flexible approach to the preparation of substituted 1,5-cyclodecadienes.[3]

Our two-step approach involves a photochemical cycloaddition of a substituted cyclobutene to a 2-cyclohexenone to form a strained tricyclo[4.4.0.0^{2,5}]decane system, which upon thermolysis yields a 1,5-cyclodecadiene. In our initial attempts, the components chosen were dimethyl cyclobutene-1,2-dicarboxylate (1)[4] and 3-methyl-2-cyclohexenone (2). Irradiation[5,6,7] of equimolar amounts of the two compounds in benzene for 22 hrs with a 350-nm source resulted in the formation of an oily adduct 3 in 70% yield[8] (based on reacted 2[9]) as well as a small amount of the dimer of 1.[6,7] The spectral data for 3 were consistent with the structure proposed: ir (CCl_4) 1740, 1735, 1718 cm^{-1}; nmr (CCl_4) τ 6.40 (6H, s), 7.0-8.3 (11H, m), 8.67 (3H, s).

The geometry of the two ring fusions in 3 was established in the following manner. Treatment of an ether solution of 3 with basic alumina did not result in epimerization and thus the 4-6 ring fusion must be the more stable *cis* configuration.[10] Reduction of 3 with sodium borohydride gave as the major product (61%) a crystalline gamma lactone 4:[11] mp 100-101°; ir (CCl_4) 1780, 1735 cm^{-1}; nmr (CCl_4) τ 5.29 (1H, m), 6.33 (3H, s), 8.63 (3H, s), 7.1-8.9 (11H, m). The formation of 4 is readily explained by hydride attack of the ketone function in 3 from the less hindered alpha face to give the beta alcohol, which then spontaneously forms the lactone because of the close proximity of the ester group at the gamma position. This result firmly establishes the *cis,anti,cis* configuration for the ring fusions in adduct 3.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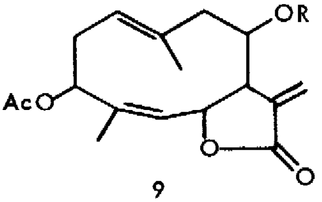
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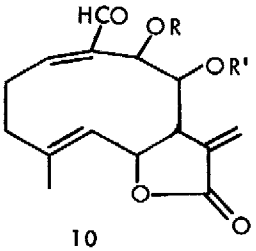
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The thermolysis reaction was investigated next as two compounds with the desired strained ring system, 3 and 4, now were readily available. Thermolysis of adduct 3 at 139° (refluxing *m*-xylene) for 6 hrs gave a 60% yield[12] of a crystalline diene 5: mp 72-73°; ir (CCl_4) 1720, 1710, 1690, 1640 cm^{-1}; uv max (EtOH) 225 nm (ϵ 9,100); nmr (CCl_4) τ 2.93 (1H, s), 6.23 (3H, s), 6.44 (3H, s), 8.29 (3H, s), 7.0-8.2 (10H, m). The data are consistent with the structure proposed for 5 but do not clearly establish the configuration at either double bond. Experiments described later in this letter will confirm the configuration as shown.

Thermolysis of lactone 4 for 2 hrs at 139° resulted in the formation of an oily diene 6 in 75% yield:[12] ir (CCl_4) 1768, 1720 cm^{-1}; uv max (EtOH) 215 nm (ϵ 13,000); nmr (CCl_4) τ 3.25 (1H, broad s), 4.93 (1H, broad d, J=7 Hz), 6.33 (3H, s), 8.12 (3H, s), 7.2-8.5 (10H, m). In addition, irradiation of the nmr resonance for the methyl group at C_7 resulted in an NOE of 16% enhancement for the vinyl hydrogen at C_2 and 12% enhancement for the carbinol hydrogen at C_1. Examination of molecular models indicates that these effects are only possible if the C_6-C_7 double bond is of the *cis* configuration. As the other double bond is necessarily *trans*, this completely establishes the structure of 6 as proposed. In support of these conclusions, a lactone similar to 4 but derived from the natural product isabelin, also gave upon thermolysis a *trans,cis*-cyclodecadiene as the major product.[13,14]

The following transformations were effected to establish the relationship between dienes 5 and 6. Selective hydrogenation of 5 with 5% Pd on charcoal gave the crystalline keto diester 7: mp 46-47°; ir (CCl_4) 1741, 1723, 1715 cm^{-1}; uv max (EtOH) 212 nm (ϵ 5,500); nmr (CCl_4) τ 6.32 (3H, s), 6.44 (3H, s), 8.41 (3H, s), 6.9-8.8 (13H, m); ms *m/e* 282 (M^+). Treatment of 6 with 1% sodium methoxide in methanol at room temperature for 24 hrs resulted in transesterification and migration of the C_2-C_3 double bond[15] to give the oily keto diester 8: ir (CCl_4) 1742, 1728, 1716 cm^{-1}; uv max (EtOH) 215 nm (ϵ 5,100); nmr (CCl_4) τ 6.33 (3H, s), 6.37 (3H, s), 8.23 (3H, s), 6.8-8.8 (13H, m); ms *m/e* 282 (M^+). As these two transformations resulted in the formation of different keto diesters,[16] the C_5-C_6 double bond in 7 must have the *trans* configuration.[17] Examination of the C_5 methyl resonances in the nmr spectra of 7 (τ 8.41) and 8 (τ 8.23) provides additional support for this conclusion. As expected, when the C_5 methyl group is oriented *cis* to the C_6 ester function as in 8, the methyl resonance is downfield relative to its position when the two groups are in a *trans* orientation as in 7.[18] As 7 was derived from 5, the C_6-C_7 double bond in 5 also must have the *trans* configuration. Finally, 5 was reduced with sodium borohydride in an attempt to obtain information on the configuration of the C_2-C_3 double bond. The resultant alcohol did not yield a lactone either upon heating or treatment with dilute acid. This result suggests that the C_2-C_3 double bond is of the *cis* configuration and that 5 is a *cis,trans*-2,6-cyclodecadienone.

Germacradienolides with both the *cis,trans*- (e.g. 5) and the *trans,cis*-1,5-cyclodecadiene (e.g. 6) configurations have recently been found in Nature. For example, provincialin (9),[2c] which exhibits cytotoxic properties, has the *cis,trans* configuration[19] (the heliangolide subgroup) while acanthospermal (10)[20] has the *trans,cis* configuration (the melampolide subgroup[21]). We are presently exploring the potential of this photoaddition-thermolysis sequence for the preparation of compounds more closely related to natural products and have found that the combination of cyclobutene 1-carboxylic acid and 2 yields an adduct and thermolysis products similar to those described in this letter.

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5. Irradiations were performed in uranium glass tubes (Corning No. 3320) with a Rayonet Model RPR 208 preparative reactor. In a typical run, a degassed solution of 0.25 g (1.5 mmol) of 1 and 0.33 g (3.0 mmol) of 2 in 15 ml of benzene was irradiated for 6 hrs, then an additional 0.25 g of 1 was added and the irradiation was continued a further 16 hrs.[6]
6. Formation of the dimer of 1 was reduced if 1 was added in two portions.
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   (b) I. Lantos and D. Ginsburg, Tetrahedron, 28, 2507 (1972).
8. The adduct was isolated by preparative tlc using silica gel and 25% ethyl acetate-benzene.
9. Consumption of 2 was followed by gc using a 6' X 0.25" 20% Carbowax 20M column at 190°.
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11. All new solid compounds gave C and H analyses within 0.3% of the calculated values.
12. In the thermolysis of either 3 or 4 no evidence was found for the formation of a substituted 1,2-divinylcyclohexane, a possible intermediate or product in these reactions.
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16. Compounds 7 and 8 were readily separated by silica gel tlc using 50% ether-petrol.
17. Treatment of 7 with 1% sodium methoxide in methanol did not give 8 and thus the possibility that the C_6-C_7 double bond in 6 was isomerized in going to 8 is eliminated.
18. In 3-methyl-2-butenoic acid the cis methyl resonance is found at τ 7.80 while the trans methyl is at τ 8.05: N.S. Bhacca, L.F. Johnson, and J.N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, California, 1961.
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21. Reference 20 cites several papers describing additional members of this subgroup.