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SYNTHESIS OF EITHER THE GERMACRANE OR THE CADINANE CARBON SKELETON FROM A SINGLE PHOTOADDUCT

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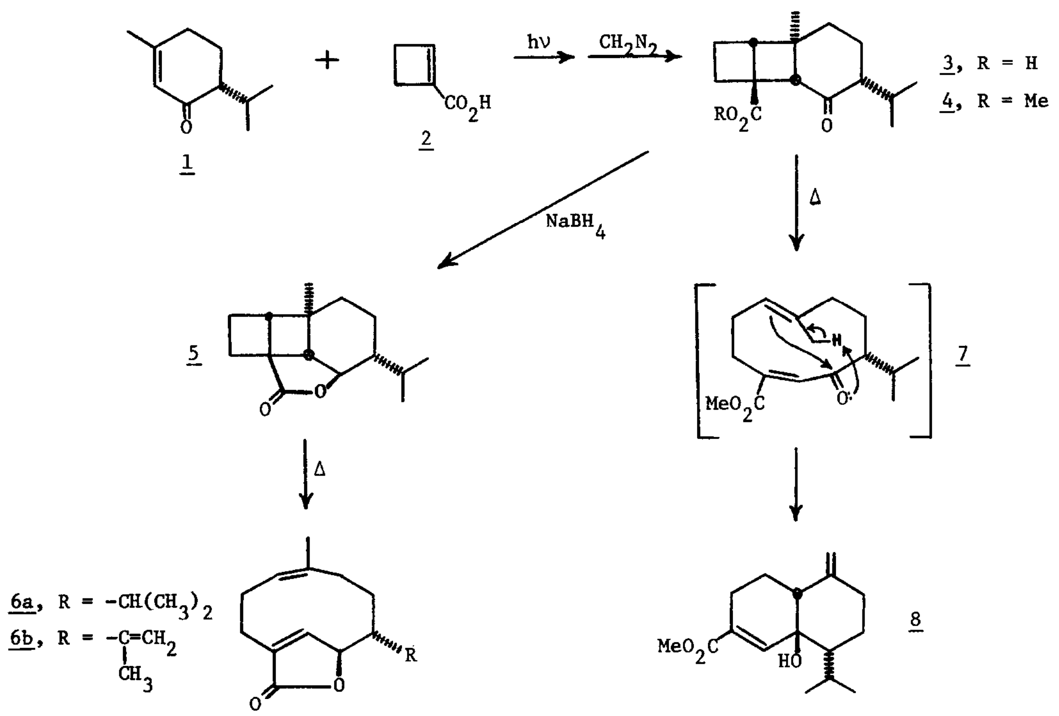
The anti-tumor activity of a number of germacranolides[1] has sparked interest in developing approaches to the synthesis of these sesquiterpenes. Two groups have described[2,3] a photoaddition-thermolysis sequence for the preparation of 1,5-cyclodecadienes, the ring system present in most of these natural products. The sequence involved photoaddition of a 2-cyclohexenone to a substituted cyclobutene to give a strained tricyclo[4.4.0.$0^{2,5}$]decane which upon thermolysis yielded a *cis,trans*-1,5-cyclodecadiene. In this letter we report the synthesis from a single photoadduct, of optically active dienes possessing either the germacrane or the cadinane carbon skeleton.

Irradiation of (-)-piperitone (1),[4] $[\alpha]_D^{20}$ -44° (lit.[5] -51°), and an excess of cyclobutenecarboxylic acid (2) in benzene with a 350-nm source gave adduct 3,[6] mp 134.0-135.5°, which upon esterification with diazomethane gave in 52% overall yield[7] keto ester 4:[8] mp 58-60°; $[\alpha]_D^{20}$ +130°. Sodium borohydride reduction (3 hrs., 0°) of 4 gave in 50% yield[7] the γ-lactone 5: mp 78-80°; $[\alpha]_D^{20}$ +90°; ir (CCl_4) 1770 cm^{-1}; nmr (CCl_4) δ 4.58 (1H, d, J=9 Hz), 1.1-2.9 (12H, m), 1.25 (3H, s), 1.00 (6H, m). Thermolysis of 5 in refluxing decane (bp 174°) for 4 hrs. gave in 73% yield[7] a dihydroisoaristolactone[9] 6a: mp 85-87°; $[\alpha]_D^{20}$ -192°; ir (CCl_4) 1770, 1660 cm^{-1}; nmr (CCl_4) δ 7.19 (1H, br. s), 5.0-5.3 (2H, m), 1.61 (3H, s), 1.1-2.6 (10H, m), 1.08 (6H, m); uv max (EtOH) 217.5 nm (ε 8800) and strong end absorption. The *cis,trans* configuration of the diene was anticipated as a result of previous investigations.[2,3] This assignment was also supported by comparison of the nmr spectrum of 6a with that of isoaristolactone (6b),[9] particularly the chemical shift of the vinyl methyl group (δ 1.61 in 6a and 1.59 in 6b[10]). The sequence described illustrates the utility of this approach in the synthesis of sesquiterpenes with the germacrane skeleton.

Thermolysis of 4 in refluxing decane for 10 hrs. gave in quantitative yield[11] the diene 8: $[\alpha]_D^{20}$ -193°; ir (CCl_4) 3620, 3090, 1725, 1655, 900 cm^{-1}; nmr (CCl_4) δ 7.25 (1H, br. s), 4.98 (1H, br. s), 4.71 (1H, br. s), 3.79 (3H, s), 1.4-2.6 (11H, m), 1.35 (1H, s, disappears on addition of D_2O), 0.94 (6H, d, J=7 Hz); uv max (EtOH) 213 nm (ε 7200). We suggest that the initially formed diene 7[12] is further transformed to 8 via a transannular ene type reaction[13] as indicated. Molecular models reveal that the six atoms involved are ideally situated for such a transformation. Thus, thermolysis of 4 provides a novel entry into the cadinane family of sesquiterpenes.



References and Notes

1. E. Rodriquez, G. H. N. Towers, and J. C. Mitchell, Phytochemistry, 15, 1573 (1976).
2. G. L. Lange, M.-A. Huggins, and E. Neidert, Tetrahedron Letters, 4409 (1976).
3. P. A. Wender and J. C. Lechleiter, J. Am. Chem. Soc., 99, 267 (1977).
4. All structures depict absolute configurations. For absolute configuration of (-)-piperitone see: W. Klyne and J. Buckingham, "Atlas of Stereochemistry," Chapman & Hall, London, 1974, p 78.
5. "Handbook of Chemistry and Physics," Chemical Rubber Co., Cleveland, Ohio, 1976, p C443.
6. All new compounds gave spectral and analytical data consistent with their structures.
7. This product was purified by prep. tlc using silica gel GF-254 and 1% ethyl acetate/chloroform.
8. Racemic 4, mp 61-62°, was recently prepared by photoaddition of (±)-piperitone to methyl cyclobutenecarboxylate: P. A. Wender and J. C. Lechleiter, J. Am. Chem. Soc., 100, 4321 (1978).
9. M. Martin-Smith, P. de Mayo, S. J. Smith, J. B. Stenlake, and W. D. Williams, Tetrahedron Letters, 2391 (1964) and references cited therein.
10. In aristolactone[9] this double bond has the trans or E configuration and the resonance for the methyl group appears at δ 1.48.
11. The crude product exhibited only one spot on tlc analysis and the nmr spectrum of this crude product was essentially the same as that of a sample purified by prep. tlc.
12. See reference 2 for an analogous thermolysis.
13. For related ene type reactions see: E. G. Scovell and J. K. Sutherland, Chem. Commun., 529 (1978) and references cited therein.
14. The authors acknowledge the financial assistance of the National Research Council of Canada.

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