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PHOTOANNELATIONS WITH α-FORMYL KETONES. A FACILE SYNTHESIS OF THE CIS-9,10-DIMETHYLDECALIN RING SYSTEM OF THE VALERANE SESQUITERPENES

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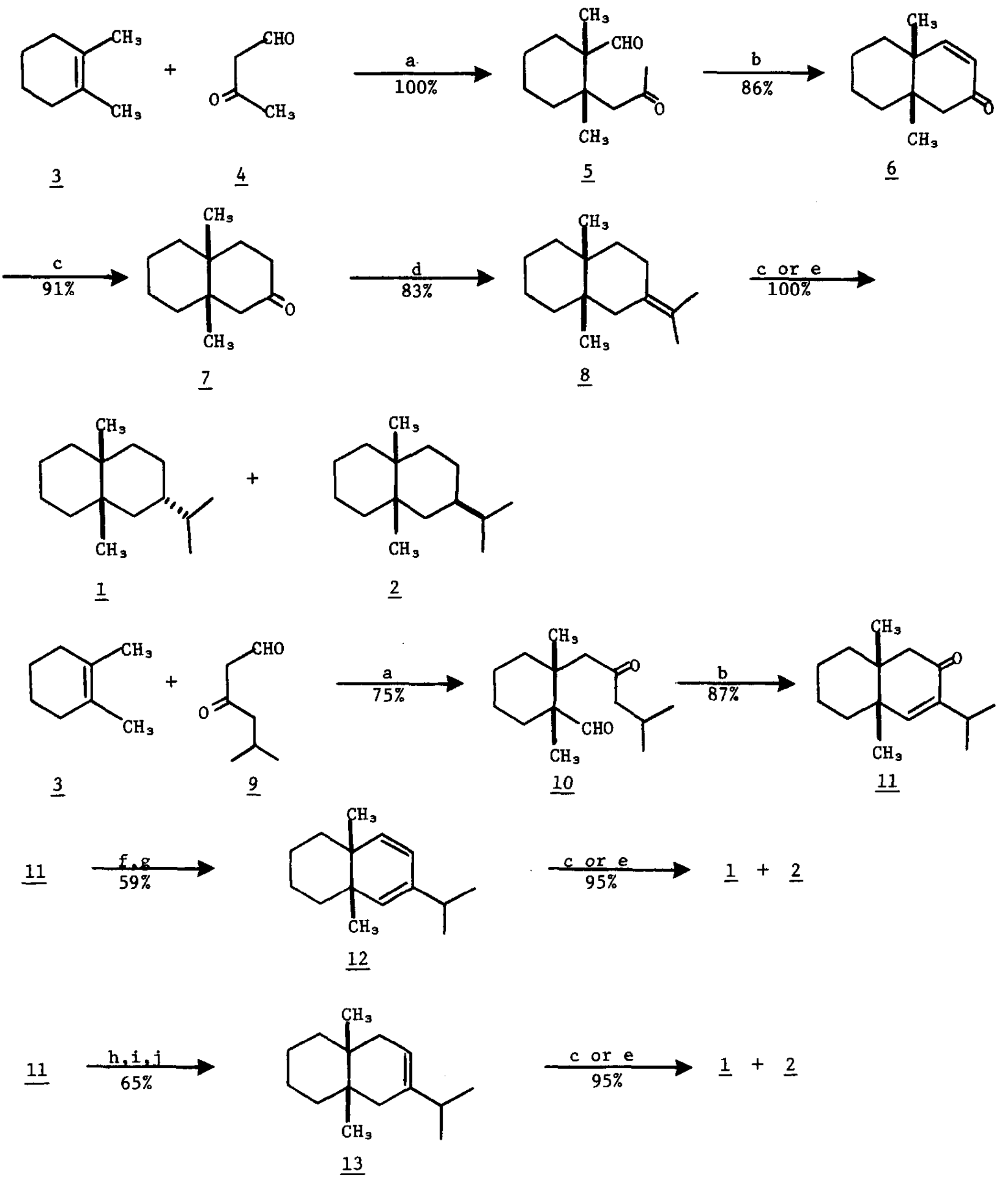
Recently we reported the enol-specific photochemical cycloaddition of α-formyl ketones to symmetrical alkenes.[2] In our note we suggested that this reaction would provide a powerful annelation tool when coupled to an aldol cyclization of the crude photoproduct. We now wish to report an application of the above reaction to the synthesis of the cis-9,10-dimethyldecalin moiety of the valerane sesquiterpenes, specifically valerane (1) and isovalerane (2). Although other syntheses of the valerane skeleton have been reported,[3] it is our opinion that the preparations described herein are sufficiently novel to merit mention.

The primary challenge in valerane syntheses has been the construction of the cis-9,10-dimethyldecalin group. No completely general and efficient route to this system has yet emerged. To this end it seemed likely that the photochemical addition of an α-formyl ketone (or other active enone) to 1,2-dimethylcyclohexene (3) would occur so as to generate the desired cis relationship of the angular methyl groups.[4] This has been verified as shown below.

Irradiation of a pentane solution of formylacetone (4)[5] and 1,2-dimethylcyclohexene (3)[6] afforded keto aldehyde 5 in high yield. A singlet at δ 9.82 (-CHO) in the nmr spectrum indicated that the photoaddition had occurred via the aldehyde enol tautomer, as expected.[7] Acid catalyzed cyclization of the crude material then gave cis-9,10-dimethyl-3-octal-2-one (6) in 86% yield for the two steps. Compound (6) was identical in all respects with an authentic sample prepared by the method of Marshall,[8] thus verifying that the initial photochemical reaction had been cis with respect to the alkene. It was then possible to convert 6 to a mixture of valerane (1) and isovalerane (2) in three steps. Catalytic hydrogenation of 6

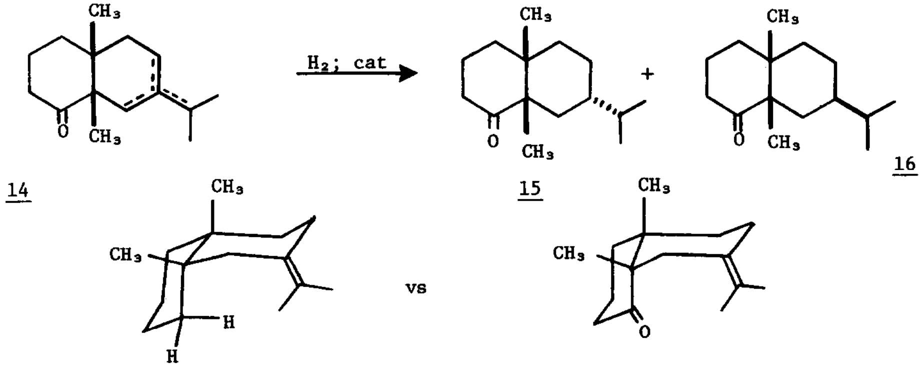


[a] hν. [b] H^+. [c] H_2; Pd/C. [d] $(C_6H_5)_3PC(CH_3)_2$. [e] H_2; Pt. [f] $TsNHNH_2/EtOH$. [g] CH_3Li/Et_2O.
[h] Li/NH_3/t-BuOH. [i] $ClPO(OEt)_2$/THF/TMEDA. [j] $Li/EtNH_2$.

produced 7 in good yield, again identical with an authentic sample.[8] The isopropylidene group of 8,[9] formed by the reaction of 7 with isopropyltriphenylphosphorane, was then reduced catalytically to give 1 in a ratio of ∿40/60.[10]

It was also possible to incorporate the valerane isopropyl group directly in the initial photochemical step. Thus irradiation of 4-isopropylformylacetone (9)[11] in the presence of 3 afforded keto aldehyde 10 (δ 9.65, singlet, -CHO) which was directly cyclized to octalone 11 as a single homogeneous compound (66% for the two steps). The conversion of 11 to valerane and isovalerane was accomplished in two ways. First the tosylhydrazone of 11 was treated with methyl lithium[12] to afford diene 12 which was then catalytically hydrogenated yielding 1 and 2 in a ratio of 40/60. Alternatively Birch reduction of 11, quenching of the derived enolate with diethylchlorophosphate, followed by reductive cleavage of the enol phosphate with $Li/EtNH_2$[13] gave alkene 13. Catalytic hydrogenation of 13 afforded 1 and 2 in the same 40/60 ratio.

The nearly complete lack of selectivity in the hydrogenation of alkenes 8, 12, and 13 is of interest. Previous workers have noted that catalytic reduction of olefin mixture 14 affords the two isopropyl isomers 15 and 16 in a ratio of 20/80, although the exact composition of 14 was not specified.[14] Our results, which show a slight increase in the amount of α-isopropyl isomer (40/60 vs 20/80), are consistent with an alkene in which the α face in one conformation is slightly less accessible to the catalyst surface than is 14 by virture of the additional α-hydrogen at C-1. We have not explored alternative methods for rendering this final step more stereoselective.



The results presented here demonstrate the synthetic potential of photoannelations with α-formyl ketones. The complex valerane ring system has been produced efficiently in as few as five steps from readily available starting materials. The photochemical production of 5 and 10 provide further confirmation of the enol specificity of the photoaddition and also indicate that the reaction with 1,2-dimethylcyclohexene occurs in a *cis* fashion.

Footnotes

1. (a) Financial support from the U.S. Public Health Service (Grant No. 1 R01 GM20790-01) is gratefully acknowledged; (b) we are indebted to Dr. David Rosenthal and Mr. Fred Williams of the Research Triangle Institute for Mass Spectrometry (supported by NIH grant RR 00330) for mass spectral determinations.

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3. (a) D. J. Dawson and R. E. Ireland, *Tetrahedron Lett.*, 1899 (1968); (b) G. H. Posner, C. E. Whitten, J. J. Sterling, C. M. Lentz, and D. J. Brunelle, *J. Amer. Chem. Soc.*, **97**, 107 (1975); (c) J. A. Marshall, W. I. Fanta, and G. L. Bundy, *Tetrahedron Lett.*, 4807 (1965); (d) E. Wenkert and D. A. Berges, *J. Amer. Chem. Soc.*, **89**, 2507 (1967); (e) J. A. Marshall, G. L. Bundy, and W. I. Fanta, *J. Org. Chem.*, **33**, 3913 (1968).

4. The formation of the *trans* product, although considered unlikely cannot be ruled out without experimental verification. For two examples of the generation of *trans* products at the alkene in photocycloadditions see (a) A. Cox, P. de Mayo, and R. W. Yip, *JACS.*, **88**, 1043 (1966); and (b) L. Duc, R. A. Mateer, L. Brassier, and G. W. Griffin, *Tetrahedron Lett.*, 6173 (1968).

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7. Had the alternate enol tautomer been involved, the aldehyde region of the nmr spectrum would have included a triplet.

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9. All new compounds gave satisfactory elemental and spectral analyses.

10. The two isomers were separated by preparative glc (OV-17) and identified by a detailed comparison of their nmr spectra with published spectra. P. N. Rao, *J. Org. Chem.*, **36**, 2426 (1971).

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