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The Ene Reaction as a Route to 3-Hydroxycyclopentanone Derivatives. Application to the Prostaglandins.

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and the effect of "hiding" the developing cationic orbital between (or inside) the "cage" and CF$_3$SO$_2$.

These data alone do not clarify why antiperiplanar Cs migration is so dominant over synperiplanar H migration. Influential factors may include substituent geometry, ring structure, and destabilization of charge on C3 if H migration were to occur. Pyridine buffer and product structural features do not accommodate an addition-rearrangement-elimination structure, and destabilization of charge on C3 if H migration were to occur. Pyridine buffer and product structural features do not accommodate an addition-rearrangement-elimination mechanism, which, moreover, is practically unknown in related neutral media solvolyses.

A preliminary search for the independent or interconverting primary and secondary vinyl carbenium ions was inconclusive. Mixing either Ia or IvA with SbF$_5$-SO$_2$ClF at -80 °C gave an orange solution which showed only broad, partially resolved proton NMR absorptions between 2 and 5 ppm (6). Neither mixture showed significant NMR change upon warming to -10 °C.

Experiments are planned to determine activation parameters, and if the carbon-bound oxygen atom in IvA is different from that in Ia, whether Cs undergoes inversion during the Ia to IvA rearrangement, and if the photolysis of I (R$_1$ = iodine) will be a source of "free" 4-homoadamant-4-yl carbenium ion.

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References and Notes

3. 4-Homoadamanalone, from adamantane and diazomethane, is converted to liquid IvA (> 90%) (silica gel-pentane; M$, 296. Anal. Calcd for C$_8$H$_{12}$F$_2$OS: C, 48.65; H, 5.08. Found: C, 48.62; H, 5.08. NMR (6), 6.1 d (1 H, vinyl), 1.7-2.7 (14 H) by the method of ketones. P. Stang and T. Dueber, Org. Synth., 54, 79 (1974).
4. An authentic sample of liquid IvA (silica gel-pentane elution before Ia) was prepared from adamantane-2-carboxylic acid (J. Sharp, H. Wynberg and J. Strang, Rec. Trav. Chim. Pays-Bas, 88, 16 (1970); or, in our hands from adamantane reacting with the Wittig reagent of CH$_2$OCH$_2$Cl followed by HCIS by the silyl ether method for aldehydes. P. Stang, M. Mangum, D. Fox, and P. Haag, J. Am. Chem. Soc., 96, 4552 (1974)); M$, 296. Anal. Found: C, 48.71; H, 5.10. NMR (6), 6.5 s (1 H, vinyl), 3.1 m (C$_2$-H), 2.45 m (C$_3$-H), 1.7-2.2 (12 H).
5. All reactions were carried out in a glass-lined, stainless steel reactor sealed with Teflon gaskets. Product mixtures were monitored by thermal conductivity VPC.

(7) Authentic IvA was not available. Our liquid IvA analyzed as follows: M$, 246; NMR (6), 8.0 s (1 H, vinyl), 4.1 t (2 H, 3.1 m (C$_3$-H), 2.3 m (C$_2$-H), 1.7-2.2 (12 H)); VPC I$\beta$RivA > I$\alpha$ on OV-275 at 140 °C.

(10) See ref 9b and L. Radom, P. Harisaran, J. Pople, and P. v. R. Schleyer, ibid., 95, 8531 (1973).
(12) This has been shown to be the most desirable geometry for vinyl carbenium ion stabilization: Z. Rappoport and Y. Apeloig, J. Am. Chem. Soc., 98, 6428 (1976); D. Kelsey and R. Bergman, ibid., 92, 228 (1970).
(13) This experiment was suggested and performed by Dr. David Forsyth. Further work is in progress.

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The Ene Reaction as a Route to 3-Hydroxycyclopentanone Derivatives. Application to the Prostaglandins

Sir:

We have previously demonstrated an efficient route to the prostaglandins via 2-methylenecyclopentanone (1) which were synthesized by formaldehyde trapping of the proper regio-specifically generated enolate. The thermal ene reaction of an appropriate acyclic enyne (e.g., 2 - 3).

We now wish to report an entirely different approach to 1: the thermal ene reaction of an appropriate acyclic enyne (e.g., 2 - 3).

We were encouraged to examine the possibility of this transformation because arrays such as 2 are now easily accessible: the vinyllogous aldo$^4$ 4 was protected as its tert-butylimidethylsilyl$^5$ derivative which was then submitted to the kinetic aldo reaction$^6$ with propional. The usefulness of the

Communications to the Editor
kinetic aldol process is well illustrated by this example which, in spite of the acidity of the acetylene hydrogen, gives acceptable (60–70%) yields of 5.

Simultaneous cyanohydrin formation and protection of the two free hydroxyls as their trimethylsilyl ethers was achieved conveniently by reaction of 5 with trimethyl silyl cyanide (catalytic amount of potassium cyanide and dicyclohexyl-18-crown-6 in carbon tetrachloride at 75 °C) to yield, in quantitative yield 6, (mixture of diastereoisomers: δ 3.4–6.5 (m; trans HC≡C–CH=CH2), 4.4–4.9 (m; Me3SiO(CH3)2), 6.5–7.0 (m; C≡N–CH≡C–), 7.25–7.65 (m; trans HC≡C–CH=CH2)) (ratios 1:3, 1:4, 1:7, 1:10, 1:7, and 1:3 for compounds 5, 7, 9, 10, and 11, respectively). The mass spectra referred to are chemical ionization spectra.

Transformation to the desirable 2-methylenecyclopentanone (acetic anhydride–pyridine) was followed by treatment with sodium borohydride in methanol and protection of the new hydroxyl as its tert-butyl dimethylsilyl ether which gave 8 in 50% yield from 7. In this molecule, the important trans relationship between the vinyl carbinal and the adjacent cyclopentanol hydroxyl (C11 and C12 of the eventual prostaglandins) has been established stereoselectively by taking advantage of the expected formation of a trans-2-alkylocyclopentanone in the reduction of a 2-alkylocyclopentanone with sodium borohydride. The cyclopentanone function required for this operation was generated in situ, under the conditions of the borohydride reduction, from the silylated cyanohydrin which thus allowed the survival of a latent carbonyl function in what would otherwise have been an incompatible environment.

Acetylation of the newly liberated hydroxyl (acetic anhydride–pyridine) was followed by treatment with sodium borohydride in methanol and protection of the new hydroxyl as its tert-butyl dimethylsilyl ether which gave 8 in 50% yield from 7. In this molecule, the important trans relationship between the vinyl carbinal and the adjacent cyclopentanol hydroxyl (C11 and C12 of the eventual prostaglandins) has been established stereoselectively by taking advantage of the expected formation of a trans-2-alkylocyclopentanone in the reduction of a 2-alkylocyclopentanone with sodium borohydride. The cyclopentanone function required for this operation was generated in situ, under the conditions of the borohydride reduction, from the silylated cyanohydrin which thus allowed the survival of a latent carbonyl function in what would otherwise have been an incompatible environment.

Transformation to the desirable 2-methylenecyclopentanone system and confirmation of the stereoselectivity of the borohydride reduction were carried out by deacetylation of 9 (catalytic amount of potassium cyanide and dicyclohexyl-18-crown-6 in carbon tetrachloride at 75 °C) to yield, in quantitative yield, 11 (mixture of diastereoisomers: δ 6.0–6.15 (dd, 1 H, H1C=C–C=O), 5.75 (m, 2 H), 5.1–5.25 (m, 1 H), 3.9–4.35 (m, 2 H), 3.1–3.4 (m, 1 H), 1.7 (m, C≡N–CH≡C–), 1.95–2.8 (m, 2 H, O=C–CH2CHO–), δ 1740, 1642.

The structure and stereochemistry of 9 were corroborated by correlation with the previously synthesized methylene cyclopentanone 11. This was achieved by protection of the alcohol function of 7 (ethyl vinyl ether), borohydride reduction and benzylation (benzyl iodide on lithium salt) to 10 followed, after desilylation, by introduction of the requisite benzyloxy-

methyl group on the side chain hydroxyl and, finally, by Jones oxidation (–20 °C). Chromatography on silica gel (1:3 ether–pentane) easily separated the desired 11 from its cis isomer (ratio ~3:5:1). The more rapidly eluted methylene cyclopentanone 11 had an identical NMR spectrum as that of the substance prepared previously.

The ene reaction would seem to be an excellent route to 2,3-disubstituted-4-hydroxycyclopentanones in general, and prostaglandins in particular.

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References and Notes

(3) The formation of a methylene cyclopentanone system by the thermal cyclization of 6-octen-1-yne has been described by W. D. Huntman and R. P. Hall, J. Org. Chem., 27, 1989 (1962).
(7) The mass spectra referred to are chemical ionization spectra.
(9) The sealed tube was previously washed with pyridine.
(10) The slower hydrolysis of the silylated cyanohydrin may reflect either sterically hindered hydrolysis or a rate-determining oxygen protonation step in this case, or both.
(12) This compound is actually a mixture of "C15"-epimers (prostaglandin numbering, as are all the other "15"-hydroxy compounds.

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Austin, a Novel Polysiprenoid Mycotoxic from Aspergillus ustus

Sir,

The discovery of the highly toxic and carcinogenic aflatoxins has generated considerable interest in other toxins produced by fungi contaminating stored foodstuffs. Steyn has reported austamide and substances biogenetically related to it as toxic metabolites from a strain of Aspergillus ustus. Vleeghaar, Steyn, and Nagel have described austidiol as the major toxin from the same source. We now report the highly unusual structure 1 for the major toxin elaborated by a strain of A. ustus found on stored black-eyed peas (Vigna sinensis).

We propose the trivial name austin for this metabolite.