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A STEREOSELECTIVE HYDROAZULENE SYNTHESIS

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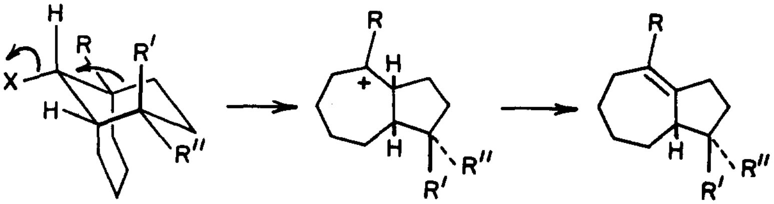
An interest in synthetic approaches to certain naturally occurring hydroazulenes[1] prompted our exploration of new stereoselective routes to substituted bicyclo[5.3.0]decanes.[2] The conformational uncertainties inherent in such ring systems[3] led us to consider schemes which employ rate-controlled reactions to construct the required derivatives. This report describes some progress toward this end along the general lines shown below.[4]



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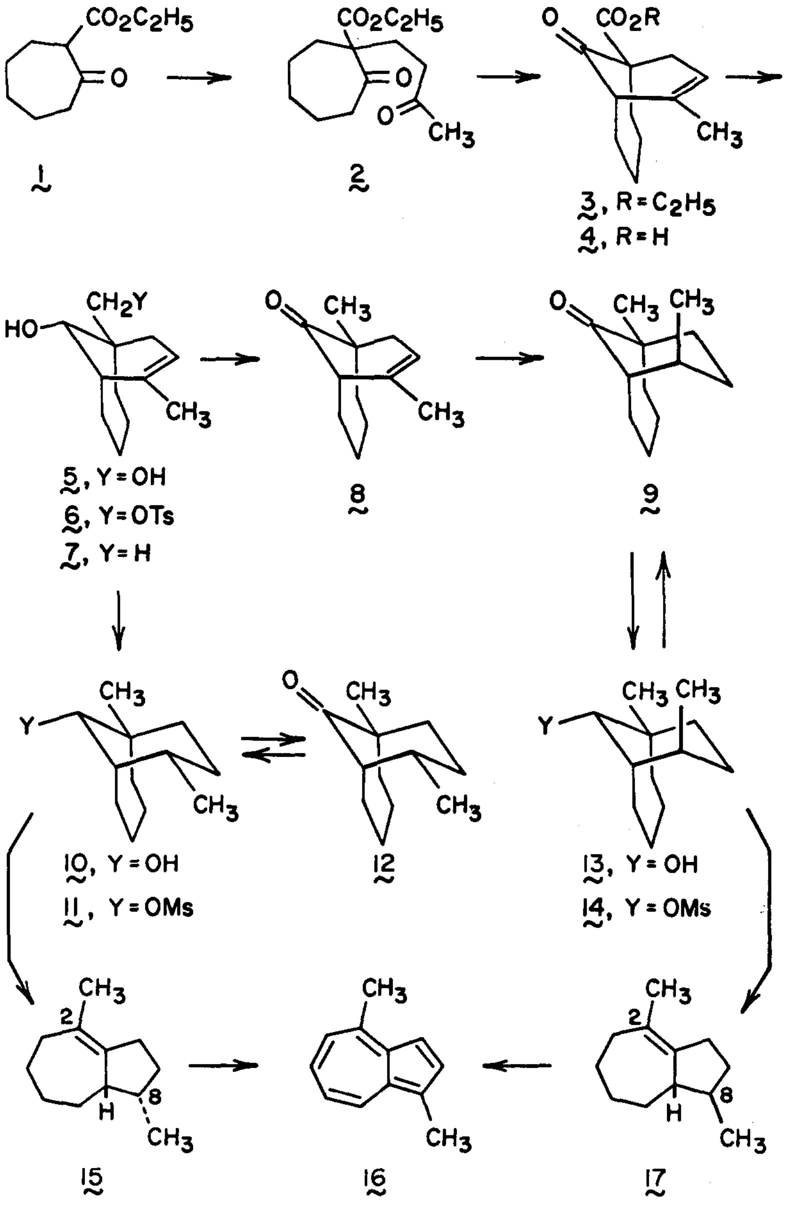
Ethyl 2-oxo-1-(3-oxobutyl)cycloheptanecarboxylate (2), the adduct of ethyl 2-oxocycloheptanecarboxylate (1) and methyl vinyl ketone, smoothly afforded ethyl 7-methyl-10-oxobicyclo[4.3.1]dec-7-enecarboxylate (3) upon treatment with sulfuric acid at 0° for 1 hr.[5] The corresponding acid (4, m.p. 173-173.5°; lit.[6] m.p. 174°), when reduced with lithium aluminum hydride in 1,2-dimethoxyethane, gave diol 5 92% yield, m.p. 95.5-96.0°; λ_{max}^{KBr} 3.00 (OH), 9.20, 9.82, 9.94, 10.43, 11.55, and 12.30 μ]. This diol with 1.2 equivalents of p-toluenesulfonyl chloride in pyridine for 48 hr. yielded mainly toluenesulfonate 6, which was directly reduced by lithium aluminum hydride to alcohol 7 [80% yield, b.p. 53-55° (0.1 mm.); λ_{max}^{film} 2.90 (OH), 9.22, 9.59, 10.18, 10.44, 10.92, 11.54, and 12.32 μ] and diol 5 (20% yield). Models show that approach to the C-10 carbonyl grouping of keto acid 4 (or a carboxy-reduced derivative thereof) by the hydridic reducing agent should be less hindered on the side of the three-carbon bridge and the stereochemistry of diol 5 is assigned accordingly. Ketone 8 [b.p. 45-55° (bath temperature) at 0.1 mm.; λ_{max}^{film} 5.83 (CO), 8.24, 8.62, 8.80, 9.84, 10.08, 10.60, 10.88, 11.43, 11.97, 12.18, and 12.44 μ], obtained by treating alcohol 7 with chromic acid reagent,[7] likewise afforded alcohol 7 in high yield upon reduction with lithium aluminum hydride.


1
2
3, R = C_2H_5
4, R = H
5, Y = OH
6, Y = OTs
7, Y = H
8
9
10, Y = OH
11, Y = OMs
12
13, Y = OH
14, Y = OMs
15
16
17

Ketone 9 [b.p. 52-53° (bath temperature) at 0.1 mm.; λ_{max}^{film} 5.87 (CO), 8.32, 8.90, 9.70, and 10.90μ; $\delta_{TMS}^{CCl_4}$ 0.98 (C-1 CH_3), and 0.94 ppm (C-7 CH_3 doublet, J = 8 cps)] was secured through hydrogenation of unsaturated ketone 8 over platinum in ethanol. Ketone 12 [b.p. 45-55° (bath temperature) at 0.1 mm.; λ_{max}^{film} 5.88 (CO), 8.93, 10.60, 10.90, and 11.09 μ; $\delta_{TMS}^{CCl_4}$ 0.98 (C-1 CH_3), and 0.97 ppm (C-7 CH_3 doublet, J = 6 cps)], an isomer of 9, was formed *via* hydrogenation of unsaturated alcohol 7 over platinum in acetic acid followed by oxidation of the resulting saturated alcohol 10 [b.p. 60-62°(0.1 mm.); λ_{max}^{film} 2.91 (OH), 9.17, 9.71, 9.98, 10.30, 10.68, and 11.00; $\delta_{TMS}^{CCl_4}$3.46 (H-10 doublet, J = 4.5 cps), 1.81 (OH), 1.00 (C-1 CH_3), and 0.93 ppm (C-7 CH_3 doublet, J = 5 cps)] with chromic acid reagent.[7] Each of the ketones 9 and 12 contained about 20% of its respective C-7 epimer as judged by gas chromatography.

As shown above, unsaturated alcohol 7 and unsaturated ketone 8 both undergo stereoselective hydrogenations giving dihydro compounds of opposite C-7 configuration. We base these stereochemical assignments upon a competitive hydrogenation experiment in which a 1:1 mixture of the epimeric ketones 9 and 12 was stirred with platinum in acetic acid under one atmosphere of hydrogen for two hours. Under these conditions, ketone 12 was completely reduced to alcohol 10 whereas over 90% of ketone 9, the more hindered of the two isomers, was recovered unchanged. Ketone 9 gave alcohol 13 [b.p. 58-60°

at 0.1 mm.; λ_{max}^{film} 2.98 (OH), 9.32, 9.62, 9.74, 10.30, 10.63, and 10.98 μ; $\delta_{TMS}^{CCl_4}$ 3.68 (H-10 doublet, J = 5 cps), 1.78 (OH), 1.02 (C-7 CH_3 doublet, J = 7 cps), and 1.01 ppm (C-1 CH_3)] upon reduction with sodium in alcohol.[8] Surprisingly, we obtained this same alcohol by treating ketone **9** with ethereal lithium aluminum hydride.[9] Evidently the cycloheptane ring effectively hinders bottom-side approach* of hydridic reducing agents to the carbonyl grouping of ketones **9** and **12**. The foregoing observations seem best reconciled by a twist-boat conformation for the cycloheptane ring in ketones **9** and **12**, and a twist-chair conformation[3] in the corresponding alcohols. The stereoselective hydrogenations of unsaturated ketone **8** and unsaturated alcohol **7** can be similarly explained.

The synthetic objectives of this study were realized through the solvolysis of methanesulfonates **11** and **14**. The former, upon treatment with acetic acid-sodium acetate at 118° for 3 hr., afforded a mixture of olefins in 96% yield with hydroazulene **15** [b.p. 100-120° (bath temperature) at 16 mm.; λ_{max}^{film} 7.23, 8.63, 9.35, 9.62, 12.33, and 12.64 μ; $\delta_{TMS}^{CCl_4}$ 1.58 (C-2 CH_3 doublet, J = 1 cps), and 0.83 ppm (C-8 CH_3 doublet, J = 7 cps)] comprising 80% (g.c. analysis) of this mixture. Methanesulfonate **14** afforded the isomeric meric hydroazulene **17** [b.p. 100-120° (bath temperature) at 16 mm.; λ_{max}^{film} 7.24, 8.63, 9.30, 9.46, 10.95, 11.43, 12.11,

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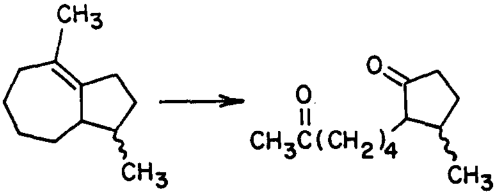
*Relative to the perspective formulas shown in the flow chart. No conformational implications are intended for the cycloheptane ring in these drawings.

and 12.80 μ; $\delta_{TMS}^{CCl_4}$ 1.64 (C-2 CH_3 doublet. J = 1 cps), and 1.02 ppm (C-8 CH_3 doublet, J = 5 cps)] in comparable yield. Both isomers gave 1,4-dimethylazulene (16)[10] upon dehydrogenation with sulfur. The placement of the double bond in hydroazulenes 15 and 17 follows from the fact that neither showed vinyl hydrogen absorption in its nmr spectrum and both gave diones upon ozonolysis which displayed peaks at 5.76 (cyclopentanone CO) and 5.84 μ (aliphatic CO) in the infrared and 2.04 ppm (CH_3CO) in the nmr spectra.



Under equilibrating conditions (p-toluenesulfonic acid--acetic acid at 118°), both 15 and 17 afforded the same mixture of hydrocarbons containing 15 (2%), 17 (20%), and three as yet unidentified compounds X (3%), Y (22%), and Z (53%). Their gas chromatographic retention times suggest that X, Y, and Z are isomers of 15 and 17. These equilibration experiments clearly demonstrate that hydroazulenes 15 and 17 are formed under kinetic conditions. Furthermore, the equilibrium ratio of 15 to 17 (1:10) lends support to their assigned stereochemistry since steric interactions between C-6 and the C-8 methyl grouping should be more severe in the former vs. the latter isomer.

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