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# Substituted Hydrazulenones via Cyclopropanone Addition, Cyclopropanol Rearrangement, and a Retroaldol/Re-aldol Sequence

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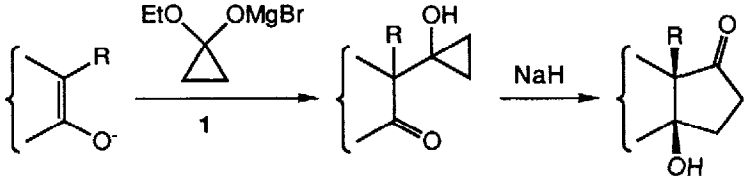
Summary: 2-Substituted cycloheptanone enolates add to cyclopropanone to give adducts that undergo base-promoted rearrangement followed, in most cases, by a retroaldol/re-aldol sequence to give conjugated hydrazulenones that are substituted at a position γ to the carbonyl group.

Previous reports from this laboratory have demonstrated the synthetic applications of adducts obtained from ketone enolates and cyclopropanone.[1,2] Among the applications of these species is a new cyclopentanone annulation procedure based upon the use of the hemiacetal derivative **1** as a source of cyclopropanone[3,4] (eq 1). Similar reports have come from the laboratory of Narasimhan.[5]




(1)

We now wish to report a very direct route to regiospecifically substituted hydrazulenones based upon this same type of annulation but also involving a surprisingly substrate-dependent retroaldol/re-aldol pathway.

Enolates derived from 2-substituted cycloheptanones undergo reaction with cyclopropanone formed from hemiacetal derivative **1** to give the adducts **2** (eq 2) in the low to modest yields seen previously. Treatment of these cyclopropanol derivatives with sodium hydride affords the expected fused hydróxycyclopentanone **3** only in the case of the methyl-substituted adduct **2a** (eq 3). In all other cases studied to date in which the substituent is larger than a methyl group, the observed products are the unexpected hydrazulenones **4** (eq 4). Our results are summarized in the table below.

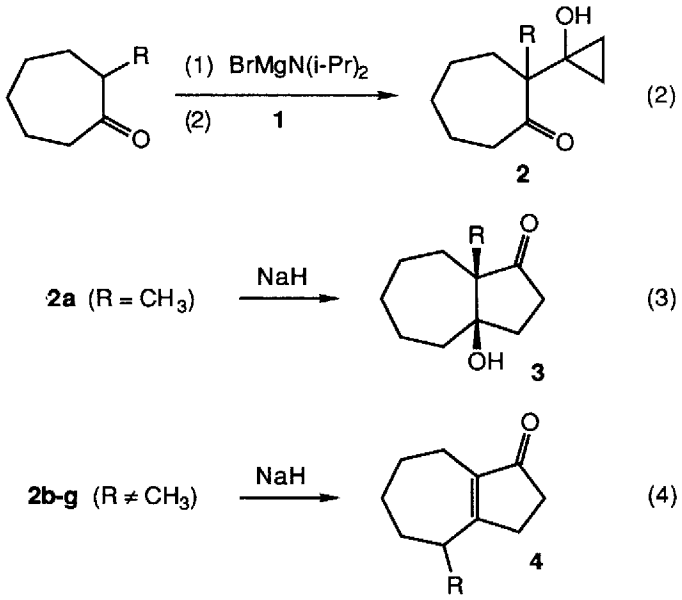


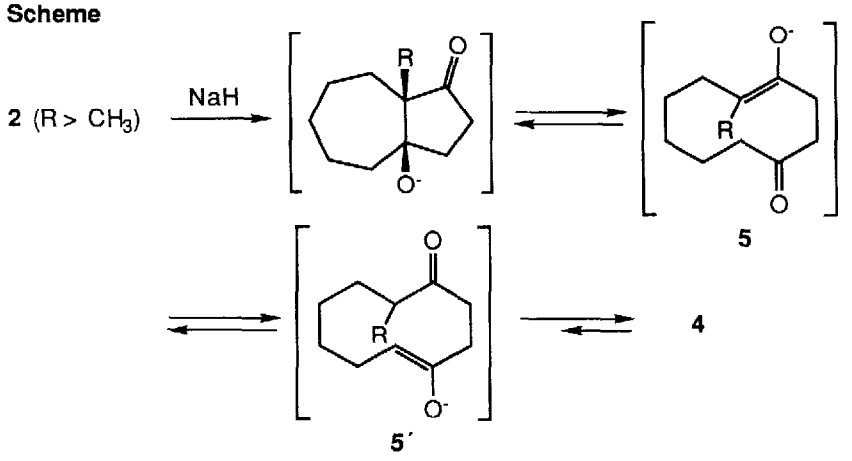

Table. Preparation and Rearrangement of Cyclopropanols **2.**

| Entry | R | Products and Yields (%) | | | |
|---|---|---|---|---|---|
| **a** | $CH_3$ | **2a** | (26) | **3a** | (90) |
| **b** | $CH_2CH_3$ | **2b** | (26) | **4b** | (82) |
| **c** | $CH_2CH_2CH_3$ | **2c** | (28) | **4c** | (80) |
| **d** | $CH_2CH{=}CH_2$ | **2d** | (24) | **4d** | (88) |
| **e** | $CH_2CH(CH_3)_2$ | **2e** | (26) | **4e** | (86) |
| **f** | $CH_2Ph$ | **2f** | (16) | **4f** | (86) |
| **g** | $CH_2CH_2CH{=}CH_2$ | **2g** | (27) | **4g** | (80) |

A likely pathway for formation of the hydrazulenones **4** is retroaldol cleavage of the initially formed, fused hydroxycyclopentanone to give the cyclodecan-1,4-dione **5** followed by enolate equilibration and re-aldol ring closure (see Scheme below). Indeed, when the rearrangements of the cyclopropanols **2** ($R \neq CH_3$) are monitored by GC, an initial product, presumably **3**, builds up in concentration for *ca.* one hour as **2** disappears, but then the initial product decreases in concentration as the final product **4** appears. Obviously, a delicate balance exists between **3** and **4** whereby **3** is formed as the only product (within the limits of detection) even after prolonged reaction times when the substituent R is a methyl group, but **4** is formed when R is larger than a methyl group.

Differences in steric requirements for the range of alkyl groups that we have studied may not be adequate to explain these results, but we are not able to put forth any other explanation at this time.

**Scheme**




The products **4** are potentially very valuable intermediates in the synthesis of hydrazulene terpenoids and other related systems. Note that the products are formed as fused, cyclic enone derivatives having alkyl substituents at a carbon atom $\gamma$ to the carbonyl group, a position at which direct introduction of substituents is normally difficult.

Further work is obviously required to improve the efficiency of the initial cyclopropanone additions in order to make the overall transformation of cycloheptanones to hydrazulenones more synthetically useful.

A representative procedure follows for the preparation of **4d**.

**2-(1-Hydroxycyclopropyl)-2-allylcycloheptanone (2d)**. A solution of bromomagnesium 2-allylcycloheptanone enolate was first prepared by addition of methylmagnesium bromide (4.2 mmol) to diisopropylamine(4.2 mmol) in ether (25 mL) at 0 °C over 10 min, followed by warming to 25 °C over 5 min, stirring for 18 h, heating at reflux for 2 h, cooling to 0 °C, dropwise addition of 2-allylcycloheptanone (4 mmol) over 10 min, warming to 25°C over 5 min, and stirring for 30 min. As a separate preparation, a solution of cyclopropanone ethyl hemiacetal (8 mmol) in anhyd ether (15 mL) was added to methylmagnesium bromide (8 mmol) in ether (80 mL) over 10 min at 0 °C under nitrogen, and this mixture was stirred for 1 h at 0 °C. To this mixture was then added the solution of the enolate from above with a cannula over 30 min. The reaction mixture was then warmed to 25 °C over 5 min and stirred for 1 h. Saturated aq. $NH_4Cl$ (30 mL) was added, the layers were separated, and the organic phase was washed with water (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The remaining yellow oil was flash chromatographed on silica gel (7/3 hexanes/ether) to give 0.20 g (24%) of a clear oil: Rf = 0.30 (7/3 hexanes/ether); IR (neat/NaCl) 3500 (O-H), 3070 (cyclopropane and ethylenic C-H), 2920 (C-H), 1685 (C=O), 1635 $cm^{-1}$ (C=C); CI-MS, m/e (rel intensity) 210 (15%, M + 2), 209 (100%, M + 1), 208 (9%, M), 191 (15%, M + 1 - $H_2O$), 153 (56%, M + 2 -

$C_3H_4OH$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.81-5.69 (m, 1 H, C<u>H</u>=$CH_2$), 5.08-5.01 (m, 2 H, CH=C<u>H</u>$_2$), 3.95 (s, 1 H, O<u>H</u>), 2.72-2.57 (m, 2 H, O=C-C<u>H</u>$_2$), 2.23-2.15 (m, 2 H, C<u>H</u>$_2$-CH=$CH_2$), 2.10-1.44 (m, 8 H, cycloheptyl C<u>H</u>$_2$), 0.88-0.71 and 0.45-0.32 (m, 2 H, cyclopropyl C<u>H</u>$_2$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 218.63 (s, <u>C</u>=O), 136.18 (d, <u>C</u>H=$CH_2$), 116.29 (t, CH=<u>C</u>H$_2$), 57.69 (s, <u>C</u>-OH), 56.80 (s, O=C-<u>C</u>-), 51.15 (t, <u>C</u>H$_2$-C=O), 34.46 (t, <u>C</u>H$_2$-CH=$CH_2$), 29.35, 27.84, 27.13 and 26.06 (t, cycloheptyl <u>C</u>H$_2$), 13.96 and 10.78 (t, cyclopropyl <u>C</u>H$_2$).

**2-Allylbicyclo-[5.3.0]-dec-1(7)-en-8-one (4d).** A solution of 2-(1-hydroxycyclopropyl)-2-allylcycloheptanone (**2d**) (0.48 mmol) in an ether-hexane mixture (1:1 by volume, 2 mL) was added over 5 min to oil-free sodium hydride (0.96 mmol) in an hexane-ether mixture (1:1 by volume, 2 mL) at 0 °C under nitrogen. The reaction mixture was then warmed to 25 °C over 20 min and stirred for 4 h. Ether (10 mL) and water (10 mL) were added, the layers were separated, and the organic phase was dried ($MgSO_4$) and concentrated in vacuo. The resulting crude yellow oil was flash chromatographed on silica gel (1:1 ether/hexanes) to give 80 mg (88%) of a clear oil; Rf = 0.39 (1:1 ether/hexanes); IR (NaCl cell) 3090 (=C-H), 2920 (C-H), 1695 (C=O), 1638 (C=C), 910 and 990 $cm^{-1}$ (vinylic C-H); CI-MS, m/e (rel intensity) 192 (18%, M + 2), 191 (100%, M + 1), 190 (11%, M), 149(18%, M - 41 (allyl)); $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.80-5.63 (m, 1 H, C<u>H</u>=$CH_2$), 5.08-4.98 (m, 2 H, CH=C<u>H</u>$_2$), 2.61-2.54 (m, 1 H, C<u>H</u>-CH$_2$CH=$CH_2$), 2.54-2.50 (m, 2 H, O=C-C<u>H</u>$_2$), 2.50-2.44 (m, 1 H, O=C-CH$_2$-C<u>H</u>$_2$), 2.44-2.38 (m, 1 H, C<u>H</u>$_2$-C-C=O), 2.38-2.28 (m, 2 H, C<u>H</u>$_2$-CH=$CH_2$), 2.28-2.20 (m, 1 H, O=C-CH$_2$-C<u>H</u>$_2$), 2.20-2.05 (m, 1 H, C<u>H</u>$_2$-C-C=O), 1.83-1.70 (m, 2 H, C<u>H</u>$_2$ cycloheptyl), 1.70-1.58 (m, 2 H, C<u>H</u>$_2$ cycloheptyl), 1.37-1.15 (m, 2 H, $CH_2$ cycloheptyl); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 208.98 (s, <u>C</u>=O), 179.10 (s, O=C-C=<u>C</u>), 141.61 (s, O=C-<u>C</u>=C), 136.29 (d, <u>C</u>H=$CH_2$), 116.65 (t, CH=C<u>H</u>$_2$), 42.53 (d, <u>C</u>H-C=C), 35.24 (t, O=C-CH$_2$-<u>C</u>H$_2$), 34.25 (t, <u>C</u>H$_2$-C=C), 30.19 (t, O=C-<u>C</u>H$_2$), 29.80 (t), 26.45 (t), 26.33 (t) and 22.63 (t, <u>C</u>H$_2$, cycloheptyl).

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