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SYNTHESIS OF 4-(ALKENYL)-3-METHYL-2-CYCLOHEXEN-1-ONES

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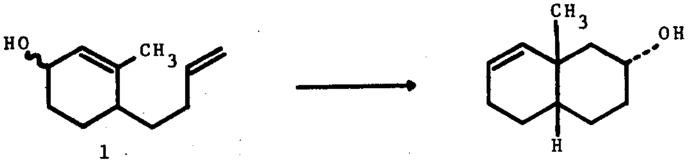
The stereoselective synthesis of polycyclic compounds from appropriately substituted cyclohexenols, e.g. **1**→**2**, has been demonstrated in a variety of systems.[1,2] Synthetic schemes based upon such reactions require the availability of simple synthetic routes to the requisite cyclohexenols.

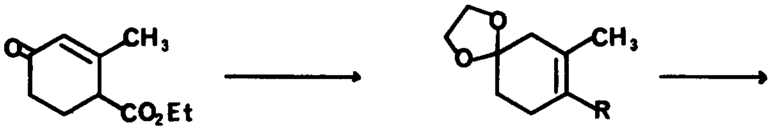


1 **2**

Previous synthesis of 4-(3-butenyl)-3-methyl-2-cyclohexen-1-ol (**1**) and related compounds involved Birch reduction and hydrolysis of anisole derivatives followed by reduction of the resulting cyclohexenone.[3] Such syntheses, although noteworthy with respect to synthetic design,[4] are lengthy and include experimental problems in the synthesis and reduction of the anisole derivatives.

This communication reports an improved synthetic route to 4-alkenyl-3-methyl-2-cyclohexen-1-ones based on the precursor **5**. The readily available 4-carbethoxy-3-methyl-2-cyclohexen-1-one (**3**) appeared ideally suited as a starting material; extension of the sidechain at C-4 might be accomplished in a variety of ways.

Treatment of keto ester **3** (Hagemann's ester) with ethylene glycol and p-toluenesulfonic acid (0.01 equivalents) in refluxing benzene gave the ketal **4**[5,6] in 96% yield after bulb-to-bulb distillation at 125° (0.5 mm). Ketal 4 was reduced by lithium aluminum hydride in ether at 0° to afford alcohol 5[6,7] in 96% yield after bulb-to-bulb distillation at 120° (0.14 mm). Alcohol 5 was converted to chloride 6 with hexamethylphosphorous triamide and carbon tetrachloride in ether.[8] The crude chloride was found to be very sensitive to exposure to oxygen and so was used directly in subsequent reactions.



3

4 R = CO_2Et
5 R = CH_2OH
6 R = CH_2Cl
7 R = $CH_2P^{\oplus}Bu_3$
8 R = $CH(\overset{\oplus}{P}Bu_3)CH_2CH=CH_2$
9 R = $CH_2CH_2C\equiv CH$
10 R = $CH_2CH_2C\equiv CCH_2OH$

11 R = H
12 R = CH_2OH

13 R = H

When treated with allylmagnesium chloride in tetrahydrofuran-hexamethylphosphoric triamide,[9] chloride 6 was converted to the alkylated ketal 11 which was hydrolyzed with dilute hydrochloric acid in ethanol-water.[1c] Bulb-to-bulb distillation of the product gave the known ketone 13 (dinitrophenylhydrazone: m.p. 115-116.5°) in 60% yield from alcohol 5.

Ketone 13 was also prepared by an alternative route.[10] Treatment of chloride 6 with tributylphosphine in acetonitrile gave, after chromatography on silica gel, the phosphonium salt 7. The phosphorous ylid, formed by the addition of phenyl lithium to the phosphonium salt in tetrahydrofuran at -76°, was alkylated with allyl bromide to give the substituted phosphonium salt **8**. Cleavage of the carbon-phosphorus bond with lithium in ethylamine at -76° gave the ketal **11**, which was converted as above to ketone **13** (41% overall yield from alcohol **5**). This latter synthetic route promises to be of use for the synthesis of ketones with more complex sidechains and is currently being investigated for this purpose.

Extension of the sidechain of chloride **6** to give ketal **12** was also accomplished. Treatment of the chloride with excess propargylmagnesium bromide in ether at 0°[11] gave a mixture of acetylene **9** and the corresponding terminal allene.[12] This mixture was treated with methylithium, followed by paraformaldehyde, to give alcohol **10**.[6] This alcohol, contaminated by allenes, was treated directly with lithium aluminum hydride[13] in refluxing tetrahydrofuran to afford the desired trans alkenyl alcohol **12**[6] in 13% yield from alcohol **5**. This alcohol has been used to prepare cyclohexenones with even larger sidechains through further alkylation reactions.[14]

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