# AN IMPROVED SYNTHESIS OF 4-METHYLENE-2-CYCLOHEXEN-1-ONE

Michael E. Jung[*][1] and Heather L. Rayle[2]

Department of Chemistry and Biochemistry, University of California,
Los Angeles, California 90024

Abstract: An improved synthesis of 4-methylene-2-cyclohexen-1-one (1) is
described, which involves four steps from commercially available starting
materials and proceeds in 65-75% overall yield.

During studies in our laboratory which required the preparation of 4-
substituted cyclohexenones, we developed a novel synthesis of 4-methylene-2-
cyclohexen-1-one (1), which utilizes clean, high-yielding reactions. Compound 1
and its simple derivatives are valuable organic building blocks. In addition, by
carrying out a 1,6-Michael addition to the exocyclic double bond, 4-substituted 3-
cyclohexenones and, by isomerization,[3] 2-cyclohexenones are also available.
This mode of reactivity has been exploited in a synthesis of the antibiotic
anticapsin.[4] We now report our high-yielding four-step synthesis of 1.

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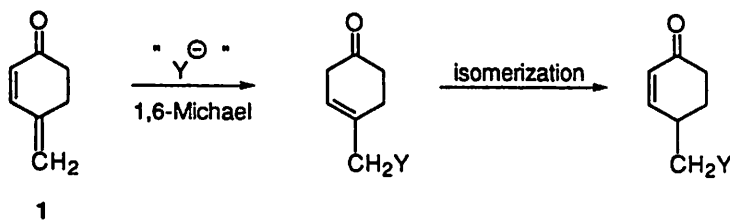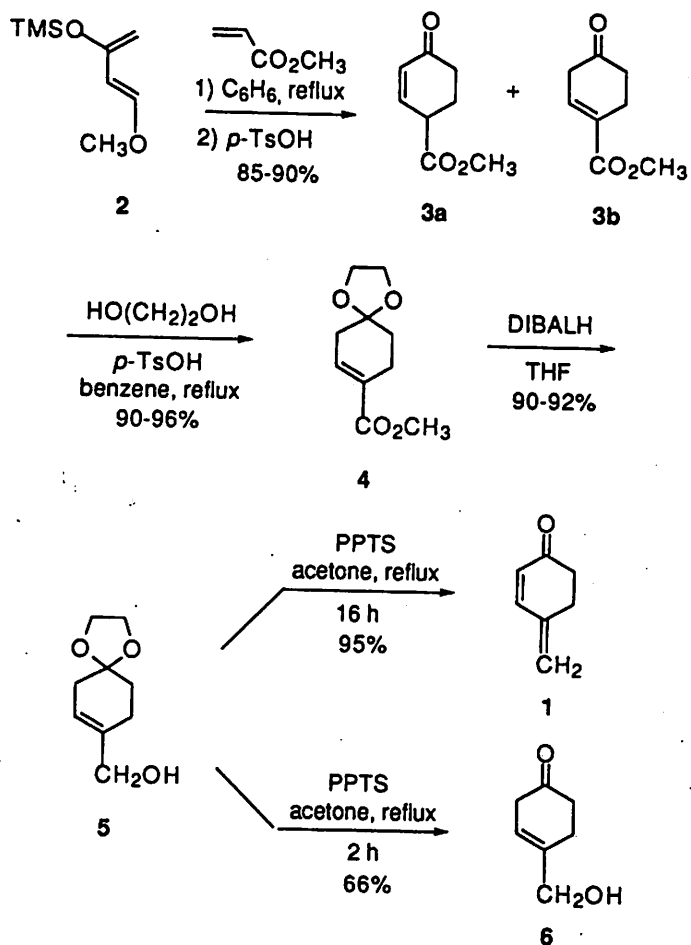
Only one synthesis of 1 has been reported to date.[5] The procedure requires a Birch reduction of 4-methoxybenzyl alcohol, affording a mixture of the expected 1-(hydroxymethyl)-4-methoxy-1,4-cyclohexadiene and 1-methoxy-4-methyl-1,4-cyclohexadiene resulting from deoxygenation by reductive fission.[5,6] In our hands, acidic hydrolysis produced a mixture of products, with 1 being obtained in 35-40% overall yield.

Our new route to 1 begins with the Diels-Alder reaction of Danishefsky's diene 2 with methyl acrylate, followed by normal acidic hydrolysis of the β-methoxy silyl enol ether, to afford the keto esters 3 in 85-90% yield. The crude product consisted predominately of the 2-cyclohexenone 3a, which isomerized during column chromatography to a 3:1 mixture favoring 3b. Ketalization with ethylene glycol and p-toluenesulfonic acid completed double bond isomerization and provided 4 (90-96%); both steps may be performed in a one-pot reaction with no loss in yield.[7,8] Reduction of the ester with DIBALH produced 5 (90-92%). This ketal, a useful intermediate in various syntheses,[6,9,10] has been prepared to date from the Birch reduction product of 4-methoxybenzyl alcohol, the disadvantages of which are described above. Our method also provides an improved preparation of this compound. Ketal deprotection with pyridinium p-toluenesulfonate (PPTS) in refluxing acetone for 16 h effected both ketal hydrolysis and dehydration of the allylic alcohol to afford 1 in 95% yield. Alternatively, brief treatment with mild acid provided the keto alcohol 6 in good yields. This improved procedure affords the dienone 1 in 65-75% overall yield from commercially available Danishefsky's diene 2.

Experimental Section

Nuclear magnetic resonance spectra (^{1}H, ^{13}C NMR) were acquired on a Bruker AM-360 spectrometer. Resonances are reported in ppm (δ) downfield from tetramethylsilane. Infrared spectra were recorded using a Nicolet 510 spectrometer. Mass spectra were recorded on a VG Autospec mass spectrometer.

All reactions were performed in oven-dried glassware under an argon atmosphere. Tetrahydrofuran was distilled from sodium benzophenone ketyl; all other solvents were distilled from calcium hydride. Column chromatography[11]

was performed using Merck silica gel 60 (70-230 mesh); thin-layer

chromatography was performed using Merck 60 F_{254} plates.

Methyl 4-oxocyclohex-2-enecarboxylate (3a) and methyl 4-oxocyclohex-1-enecarboxylate (3b).[12] To a stirred solution of Danishefsky's diene 2 (1.2 g, 6.96

mmol) in 5 mL of benzene was added 1.25 mL methyl acrylate (1.2 g, 13.92

mmol). The solution was heated at reflux for 48 h. p-Toluenesulfonic acid (100

mg) was added to the cooled reaction, which was stirred until hydrolysis was

complete as determined by TLC. Solvent and excess acrylate were removed by

evaporation under reduced pressure. The crude product consisted primarily of 3a;

the residue was then chromatographed (50% ethyl acetate/hexanes) to give 0.94 g

(87%) of a 3:1 mixture of the keto esters 3b and 3a as a pale yellow oil. For 3a:

^{1}H NMR (CDCl$_3$) δ 7.03 (1H, dd, J = 10.2, 3.2 Hz), 6.04 (1H, dd, J = 10.2, 2.5

Hz,), 3.74 (3H, s), 3.42-3.36 (1H, m) and 2.6-2.15 (4H, m). ^{13}C NMR (CDCl$_3$) δ

198.9, 172.7, 147.0, 131.4, 53.2, 42.2, 37.0, 26.2. IR (neat) 1752, 1680, 1645 cm⁻

[1]. For 3b: ^{1}H NMR (CDCl$_3$) δ 6.97 (1H, bt, J = 3.9 Hz), 3.73 (3H, s), 3.05 (2H,

bd, J = 3.9 Hz), 2.8-2.3 (4H, m). ^{13}C NMR (CDCl$_3$) δ 208.8, 167.2, 136.4, 131.1,

52.7, 40.2, 38.7, 24.9. IR (neat) 1720 (br), 1670 cm⁻¹. For both isomers: high-

resolution MS, m/e 154.0636, calcd for C$_8$H$_{10}$O$_3$ 154.0630.

Methyl 1,4-dioxaspiro-[4.5]dec-7-ene-8-carboxylate (4).[7,8] Ethylene glycol

(0.15 mL, 2.6 mmol) was added to the mixture of keto esters 3a and 3b (0.20 g,

1.3 mmol) and 25 mg p-toluenesulfonic acid in 2 mL benzene. The reaction was

refluxed with azeotropic removal of water for 12 h. After cooling, benzene was

added and the reaction mixture was washed with water and brine. The resulting

solution was dried over anhydrous sodium sulfate and the solvent was evaporated

to give 0.25 g of 4 (94%). The crude product was sufficiently pure for use, but

could be distilled using a Kugelrohr apparatus (bp 92-93°/0.8 mm Hg). ^1H NMR (CDCl$_3$) δ 6.85 (1H, t, J = 3.7 Hz), 3.97 (4H, s), 3.71 (3H, s), 2.52 (2H, t, J = 6.5 Hz), 2.43 (2H, d, J = 3.7 Hz), 1.79 (2H, t, J = 6.5 Hz). ^{13}C NMR (CDCl$_3$) δ 168.0, 137.3, 130.5, 107.9, 65.2 (2C), 52.4, 36.9, 31.4, 24.3. IR (neat) 1717, 1653, 1260, 1119 cm^{-1}. High-resolution MS, m/e 198.0900, calcd for $C_{10}H_{14}O_4$ 198.0890.

The ketal was also prepared in one step by addition of ethylene glycol and p-toluene-sulfonic acid to the reaction mixture containing the silyl enol ether of 3; refluxing was continued for 16 h and the product was isolated as above in a 75% yield.

1,4-Dioxaspiro-[4.5]dec-7-ene-8-methanol (5).[6,9,10] The ketal ester 4 (0.14 g, 0.70 mmol) was added to a solution of DIBALH (1.75 mL of a 1M solution in hexane) in 4 mL THF. The solution was stirred for 2 h and quenched with water. Magnesium sulfate was added to the residue, which was stirred for 0.5 h.[13] Filtration and thorough washing of the aluminum salts with ether afforded pure 5 (0.11 g, 92%). The crude product was used for subsequent reactions. ^1H NMR (CDCl$_3$) δ 5.56 (1H, t, J = 1.3 Hz), 3.97 (2H, s), 3.95 (4H, s), 2.27 (1H, bs), 2.25 (2H, d, J = 1.3 Hz), 2.22 (2H, t, J = 6.5 Hz), 1.76 (2H, t, J = 6.5 Hz). ^{13}C NMR (CDCl$_3$) δ 138.0, 120.5, 108.9, 67.2, 65.1 (2C), 36.1, 31.5, 25.5. IR (neat) 3434 (br), 1680, 1113, 1059 cm^{-1}. High-resolution MS, m/e 170.0938, calcd for $C_9H_{14}O_3$ 170.0943.

4-(Hydroxymethyl)-3-cyclohexen-1-one (6). The ketal 5 (0.10 g, 0.58 mmol) was refluxed with pyridinium p-toluenesulfonate (20 mg) in wet acetone for 2 h. Dichloro-methane was added, and the organic layer was washed with water and dried over Na$_2$SO$_4$. After evaporation of the solvent, the residue was

chromatographed (40% ethyl acetate/hexanes) to afford 48 mg of 6 (66%). No
attempts at yield optimization were made. ^{1}H NMR (CDCl$_3$) δ 5.76 (1H, bs),
4.12 (2H, s), 2.90 (2H, bs), 2.51 (4H, m), 1.71 (1H, bs). ^{13}C NMR (CDCl$_3$) δ
211.1, 138.8, 120.1, 66.7, 40.0, 39.1, 26.5. IR (CHCl$_3$) 3455, 1713-1674 (br) cm$^-$
[1]. High-resolution MS, m/e 126.0683, calcd for C$_7$H$_{10}$O$_2$ 126.0681.

4-Methylene-2-cyclohexen-1-one (1). The ketal 5 (0.86 g, 0.50 mmol) was
refluxed with pyridinium p-toluenesulfonate[14] (30 mg) in wet acetone for 16 h.
Ether was added to the cooled reaction, which was washed with water and brine to
give pure 1 (52.4 mg, 96%) as a colorless oil. Further purification was
unnecessary; analytical samples were purified by flash chromatography (40%
ethyl acetate/hexanes). ^{1}H NMR (CDCl$_3$) δ 7.07 (1H, d, J = 9.9 Hz), 5.94 (1H, d,
J = 9.9 Hz), 5.31 (1H, bs), 5.27 (1H, bs), 2.73 (2H, t, J = 6.8 Hz), 2.50 (2H, t, J =
6.8 Hz). ^{13}C NMR (CDCl$_3$) δ 199.8, 148.1, 141.3, 128.8, 120.1, 37.9, 29.8. IR
(neat) 3030 (w), 1673 (s), 1626 cm^{-1}. High-resolution MS, m/e 108.0577, calcd
for C$_7$H$_8$O 108.0577.

Acknowledgment:

<div align="center">References and Notes</div>

(1)   UCLA McCoy Award recipient, 1991-92; UCLA Hanson-Dow Teaching
       Award recipient, 1992. To whom correspondence should be addressed.

(2)   National Science Foundation Fellow, 1989-92.

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(13) Though convenient, addition of sodium potassium tartrate solution to dissolve the aluminum salts followed by a standard extractive workup consistently afforded lower product yields. Addition of $MgSO_4$ to the precipitated salts facilitated filtration.

(14) Some aromatization to *p*-methylphenol occurred when 5 was treated with stronger acid (*p*-TsOH), although 1 was still obtained as the major product. No aromatization occurred when PPTS or oxalic acid was used.