Preparation of β-Substituted α-(Acetoxymethyl)cyclohex-2-en-1-ones†

J. Chem. Research (S), 1999, 576–577†

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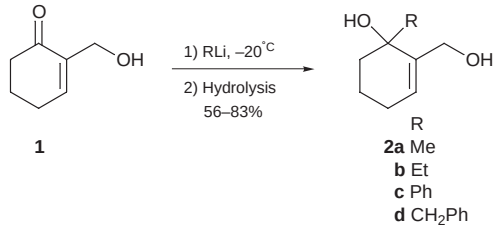
An effective three-step sequence for the preparation of β-substituted 2-(acetoxymethyl)cyclohex-2-en-1-ones **4**, *via* oxydative allylic transposition of the corresponding allylic alcohols **3**, is reported.

β′-Functionalized cyclohex-2-en-1-ones are useful intermediates in organic chemistry[1–4] and for biologically active products.[5,6] Several methods have been reported[7,8] to obtain these compounds. In connection with our interest in the functionalization of cyclic α,β-enones, we[9] have recently reported a simple procedure for the preparation of a variety of 2-(hydroxymethyl)cyclohex-2-en-1-ones from the corresponding α,β-enones. Unfortunately, this method is not suitable when the starting cyclohex-2-en-1-ones are β-substituted. In continuation of our previous work, we report here, an indirect method allowing access to a variety of 2-(acetoxymethyl)cyclohex-2-en-1-ones **4**,[10] starting from 1,2-addition of organolithium compounds to enone **1**.

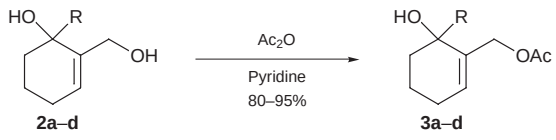
An excess of organolithium reagent (2.5 equiv.), reacted at −20 °C with 2-(hydroxymethyl)cyclohex-2-en-1-one **1** in diethyl ether to give regioselectively diols **2a–d**, after hydrolysis in satisfactory yields (Scheme 1).



Scheme 1

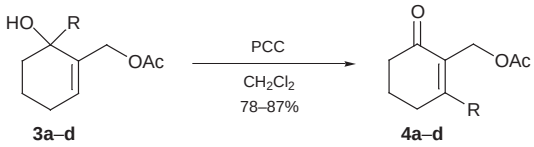
Further monoacetylation of diols **2a–d** with acetic anhydride, in anhydrous pyridine at room temperature, afforded primary acetates **3a–d**, in good yields (Scheme 2).

Finally, allylic transposition–oxidation[11] of **3a–d** with a suspension of pyridinium chlorochromate (PCC)[12,13] in anhydrous dichloromethane, led to the required β-substituted α-(acetoxymethyl)cyclohex-2-en-1-ones **4a–d** in good yields (Scheme 3).



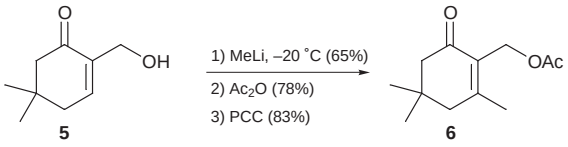
Scheme 2

The reaction sequence described above for the preparation of cyclohex-2-en-1-one derivatives **4a–d** was successfully extended to 2-(hydroxymethyl)-5,5-dimethylcyclohex-2-en-1-one **5** and allowed access to 2-(acetoxymethyl)-isophorone **6** in good yield (Scheme 4). To our knowledge, this polyfunctional synthon has not been previously described and could be used for the preparation of various β′-functionalized-cyclohex-2-en-1-ones.



Scheme 3

In summary, a general preparation of various 2-(acetoxymethyl)cyclohex-2-en-1-ones **4** has been achieved in a three-step sequence, in fair to good yields. These acetates are synthetically useful intermediates, *via* replacement of acetoxy group, for the preparation of allylic amines and products having biological activities.[8,9]



Scheme 4

Experimental

All reactions progress was monitored by thin-layer chromatography (TLC) analysis (Merck Kieselgel 60 F254) (eluent: hexane–ethyl acetate, 1:1). All compounds were purified by chromatography column (Silica gel 60, 70-230 mesh ASTM). IR spectra were recorded on Perkin-Elmer model FT PARAGON 1000 PC. ^{1}H NMR (60 or 300 MHz) and ^{13}C NMR (75 MHz) were recorded on JEOL-CHL 60 or Bruker AC 300 spectrometers using tetramethylsilane (TMS, $\delta = 0$) as internal standard. Mass spectra were recorded on a Hewlett-Packard instrument (70 eV).

General Procedure for the Preparation of Diols **2a–d**.—The preparation of **2a** from **1** serves to illustrate the general procedure utilized: a dry four-necked flask fitted with a nitrogen inlet, a mechanical stirrer, a thermometer and a pressure-equalizing dropping funnel was charged with methyllithium (1.6 M, 100 mmol, 62.5 mL) in anhydrous diethyl ether. Enone **1** (5.04 g; 40 mmol) in anhydrous ether (50 mL) was added dropwise at −20 °C. The reaction mixture was stirred at −20 °C for 3 h. The mixture was quenched with saturated NH_4Cl, and the aqueous layer extracted several times with dichloromethane. The combined organic phases were dried over $MgSO_4$. Removal of the solvents *in vacuo* and purification of the crude product by chromatography column (diethyl ether–dichloromethane, 1:1) afforded compound **2a**, as a yellow oil.

2-*(Hydroxymethyl)*-1-*methylcyclohex*-2-*en*-1-*ol* **2a**: yield = 83%; viscous oil; IR(CCl_4) ν/cm^{-1}: 3400, 1670; δ_H(60 MHz, CCl_4) 5.58 (m, 1H), 4.17 (m, 2H), 2.17–1.43 (m, 6H), 1.30 (s, 3H); δ_C (75 MHz, $CDCl_3$) 19.5, 23.4, 26.3, 32.3, 64.1, 70.4, 129.4, 136.9; MS (EI) *m/z* 79(74), 93(69), 107(100), 123(56), 142(M^+, 2%).

1-*Ethyl*-2-*(hydroxymethyl)cyclohex*-2-*en*-1-*ol* **2b**: yield = 74%; solid, mp 48–50 °C; IR ($CHCl_3$) ν/cm^{-1}: 3470, 1660; δ_H(60 MHz, CCl_4) 5.68 (m, 1H), 4.00 (AB, J = 12 Hz, 2H), 2.14–1.40 (m, 8H), 0.80 (t, J = 6 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 8.2, 18.7, 25.4, 32.0, 34.2, 65.5, 73.0, 129.7, 139.4; MS (EI) *m/z* 79(61), 93(79), 107(30), 139(M − 17, 100%).

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† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

2-*(Hydroxymethyl)*-*1-phenylcyclohex*-2-*en*-1-*ol* **2c**: yield = 63%; solid, mp 150–152 °C; IR ($CHCl_3$) ν/cm^{-1}: 3480, 1670, 1600; δ_H(60 MHz, $CDCl_3$) 7.50–7.17 (m, 5H), 5.98 (m, 1H), 3.93 (m, 2H), 2.46–1.33 (m, 6H); δ_C(75 MHz, $CDCl_3$) 18.7, 25.3, 40.8, 65.2, 75.2, 125.4, 126.4, 127.8, 129.8, 138.5, 146.8; MS (EI) *m/z* 77(35), 91(12), 105(85), 158(100), 186(23), 204(M^+, 2%).

1-*Benzyl*-2-*(hydroxymethyl)cyclohex*-2-*en*-1-*ol* **2d**: yield = 56%; solid, mp 132–134 °C; IR ($CHCl_3$) ν/cm^{-1}: 3500, 1610; δ_H(60 MHz, $CDCl_3$) 7.20 (s, 5H), 5.70 (m, 1H), 4.26 (AB, J = 12 Hz, 2H), 2.90 (AB, J = 10 Hz, 2H), 2.20–1.37 (m, 6H), δ_C (75 MHz, $CDCl_3$) 19.1, 25.3, 35.1, 44.8, 65.4, 73.2, 126.5, 128.2, 129.3, 130.6, 136.9, 140.0; MS (EI) *m/z* 79(10), 91(100), 129(8), 141(6), 182(12), 200(M − 18, 12%).

General Procedure for the Preparation of Acetates **3a**–**d**.—The preparation of **3a** from **2a** serves to illustrate the general procedure utilized: a mixture of diol **2a** (4.69 g, 33 mmol), anhydrous pyridine (4.5 mL) and acetic anhydride (10 mL, 99 mmol) was stirred at room temperature for 12 h. The mixture was quenched with water and extracted with dichloromethane. The combined organic phases were washed successively with aqueous 1.5 M NaOH and with brine, then dried and concentrated *in vacuo*. The purification of the residue by chromatography column (eluent: diethyl ether) afforded pure **3a**.

2-*(Acetoxymethyl)*-1-*methylcyclohex*-2-*en*-1-*ol* **3a**: yield = 95%; oil; IR ($CHCl_3$) ν/cm^{-1}: 3480, 1730, 1670; δ_H(60 MHz, $CDCl_3$) 5.67 (m, 1H), 4.53 (m, 2H), 2.13–1.90 (m, 2H), 2.00 (s, 3H), 1.80–1.50 (m, 4H), 1.27 (s, 3H); δ_C(75 MHz, $CDCl_3$) 19.5, 21.4, 25.8, 27.7, 39.4, 65.3, 69.7, 130.2, 137.3, 171.3; MS (EI) *m/z* 81(71), 96(35), 109(100), 124(29), 169(M − 15, 54%).

2-*(Acetoxymethyl)*-1-*ethylcyclohex*-2-*en*-1-*ol* **3b**: yield = 80%; oil; IR ($CHCl_3$) ν/cm^{-1}: 3480, 1730; δ_H(60 MHz, $CDCl_3$) 5.73 (m, 1H), 4.50 (m, 2H), 2.20–1.90 (m, 2H), 2.00 (s, 3H), 1.80–1.46 (m, 6H), 1.83 (t, J = 7 Hz, 3H); δ_C(75 MHz, $CDCl_3$) 8.3, 18.7, 21.1, 25.6, 32.0, 34.3, 65.0, 71.7, 131.1, 136.4, 170.9; MS (EI) *m/z* 81(46), 109(100), 127(7), 169(M − 29, 38%).

2-*(Acetoxymethyl)*-1-*phenylcyclohex*-2-*en*-1-*ol* **3c**: yield = 83%; oil; IR ($CHCl_3$) ν/cm^{-1}: 3480, 1735, 1670; δ_H(60 MHz, $CDCl_3$) 7.50–7.10 (m, 5H), 6.03 (m, 1H), 4.40 (AB, J = 13 Hz, 2H), 2.40–1.80 (m, 6H), 1.77 (s, 3H); δ_C(75 MHz, $CDCl_3$) 18.3, 20.4, 25.2, 40.4, 65.2, 73.9, 125.5, 126.4, 127.6, 131.2, 135.7, 146.1, 171.0; MS (EI) *m/z* 77(33), 91(11), 105(88), 158(100), 168(20), 186(25), 246(M^+, 2%).

2-*(Acetoxymethyl)*-1-*benzylcyclohex*-2-*en*-1-*ol* **3d**: yield = 86%; oil; IR ($CHCl_3$) ν/cm^{-1}: 3500, 1760, 1660, 1610; δ_H(60 MHz, $CDCl_3$) 7.13 (s, 5H), 5.73 (m, 1H), 4.58 (s, 2H), 2.83 (AB, J = 14 Hz, 2H), 2.13–1.93 (m, 2H), 2.00 (s, 3H), 1.83–1.67 (m, 4H); δ_C(75 MHz, $CDCl_3$) 18.8, 20.9, 25.2, 35.1, 44.8, 64.4, 71.6, 126.2, 127.9, 130.4, 136.87, 136.90, 170.8; MS (EI) *m/z* 81(45), 91(36), 109(100), 169(M − 91, 60%).

General Procedure for the Preparation of Enones **4a**–**d**.—The preparation of **4a** from **3a** serves to illustrate the general procedure utilized: to a suspension of PCC (3.23 g, 15 mmol) in anhydrous dichloromethane (20 mL) was added rapidly at 0 °C, **3a** (1.84 g, 10 mmol) dichloromethane (20 mL). The mixture was stirred at room temperature for 5 h. After evaporation of the solvent, the mixture was flash-chromatographed over silica gel using diethyl ether as eluent to give **4a** as a yellow oil.

2-*(Acetoxymethyl)*-3-*methylcyclohex*-2-*en*-1-*one* **4a**: yield = 85%; oil; IR ($CHCl_3$) ν/cm^{-1}: 1760, 1670, 1635; δ_H(60 MHz, $CDCl_3$) 4.63 (s, 2H), 2.57–2.07 (m, 6H), 2.0 (s, 3H), 1.93 (s, 3H), δ_C(75 MHz, $CDCl_3$) 20.9, 21.4, 21.7, 33.1, 37.4, 57.0, 130.3, 162.8, 171.0, 197.4; MS (EI) *m/z* 77(11), 97(7), 112(14), 125(8), 139(M − 43, 100), 182(M, 1%).

2-*(Acetoxymethyl)*-3-*ethyl*-2-*cyclohexenone* **4b**: yield = 87%; oil; IR ($CHCl_3$) ν/cm^{-1}: 1760, 1670, 1630; δ_H(60 MHz, $CDCl_3$) 4.73 (s, 2H), 2.60–2.00 (m, 8H), 1.97 (s, 3H), 1.10 (t, J = 7 Hz, 3H), δ_C(75 MHz, $CDCl_3$) 12.7, 21.0, 22.1, 28.2, 30.4, 37.5, 56.6, 129.4, 167.9, 170.9, 197.7; MS (EI) *m/z* 79(13), 93(10), 111(15), 125(10), 153(M − 43, 100).

2-*(Acetoxymethyl)*-3-*phenylcyclohex*-2-*en*-1-*one* **4c**: yield = 85%; oil; IR ($CHCl_3$) ν/cm^{-1}: 1735, 1675, 1620; δ_H(60 MHz, $CDCl_3$) 7.70–7.17 (m, 5H), 4.56 (s, 2H), 2.90–2.03 (m, 6H), 1.97 (s, 3H); δ_C(75 MHz, $CDCl_3$) 20.9, 22.2, 33.2, 37.5, 58.7, 126.8, 128.4, 128.8, 130.5, 139.5, 163.2, 170.5, 197.9; MS (EI) *m/z* 77(21), 91(20) 184(100), 201(M − 43, 75); 245(M + 1, 14%).

2-*(Acetoxymethyl)*-3-*benzylcyclohex*-2-*en*-1-*one* **4d**: yield = 78%; oil; IR ($CHCl_3$) ν/cm^{-1}: 1730, 1675; δ_H(60 MHz, $CDCl_3$) 7.20 (s, 5H), 4.82 (s, 2H), 3.60 (s, 2H), 2.60–2.20 (m, 4H), 2.60–1.93 (m, 2H), 1.90 (s, 3H); δ_C(75 MHz, $CDCl_3$) 20.4, 21.5, 30.2, 37.0, 40.2, 56.3, 126.3, 128.2, 128.3, 130.4, 136.8, 163.2, 170.3, 197.1; MS (EI) *m/z* 77(39), 91(83) 141(79), 167(79), 182(100), 196(M − 62, 72%).

2-*(Acetoxymethyl)*-3,5,5-*trimethylcyclohex*-2-*en*-1-*one* **6**: yield = 83%; oil; IR ($CHCl_3$) ν/cm^{-1}: 1730, 1670, 1640; δ_H(60 MHz, $CDCl_3$) 4.70 (s, 2H), 2.33–2.17 (m, 4H), 2.00 (s, 3H), 1.95 (s, 3H); 1.00 (s, 6H); δ_C(75 MHz, $CDCl_3$) 20.7, 21.3, 28.0, 32.5, 46.9, 50.6, 56.7, 129.0, 159.9, 170.8, 197.5 (Found: C, 68.7; H, 8.5. $C_{12}H_{18}O_3$ requires C, 68.57; H, 8.57%).

Received, 27th April 1999, Accepted, 8th June 1999
Paper E/9/03349A

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