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Diastereoselective synthesis of 5-hydroxy-3-methylalkane-1,6-diones from ketones and acetylene in two atom-economic steps

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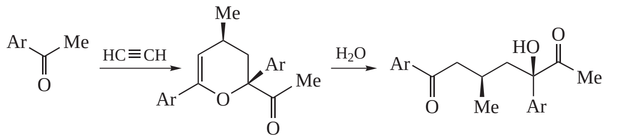
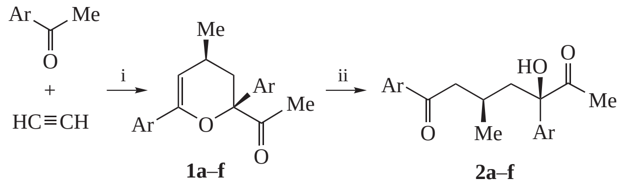
(2*R,4*R**)-2-Acetyl-2,6-diaryl-4-methyl-3,4-dihydropyrans (diastereoselectively synthesized from acetylene and ketones in one synthetic operation) undergo ring opening by aqueous NH_4Cl (MeCN, 80 °C, 8 h) to afford diastereomerically pure 5-hydroxy-1,6-diketones in 48–89% yields.**



6 examples

1,6-Diketones are widely employed in organic synthesis for construction of biologically active carbo- and heterocycles.[1] Whereas many ring closing reactions of 1,6-diketo derivatives have been reported,[1,2] much less works are focused on their synthesis. Among the approaches to 1,6-diketones are oxidative cleavage of cyclohexanone,[3] decomposition of peroxycycloalkanols[4] or siloxycyclopropanes,[5] reaction of α-bromo ketone, malononitrile and α,β-enones,[6] double lithiation/alkylation of benzotriazole ethers.[7] However, most of these syntheses involve multistep procedures, require inaccessible starting materials and suffer from disadvantages in terms of selectivity and efficiency.

In this paper, we describe a simple two-step transition from ketones and acetylene to hardly accessible rare substituted 1,6-diketones with the hydroxyl functionality. The starting dihydropyrans **1a–f** were assembled as single diastereomers according to an original approach (Scheme 1) from ketones and acetylene in one synthetic operation.[8]

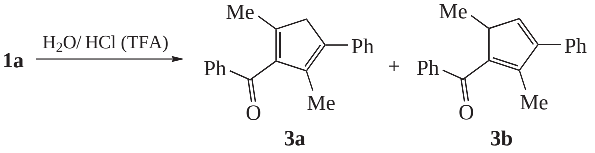


	Ar	Isolated yield of **2** (%)
a	Ph	74
b	4-MeC_6H_4	71
c	4-PhC_6H_4	75
d	4-ClC_6H_4	83
e	3-$MeOC_6H_4$	48
f	1-Naphthyl	89

Scheme 1 *Reagents and conditions*: i, KOH, DMSO, then HCl; ii, H_2O, NH_4Cl, MeCN, 80 °C, 8 h.

It turned out that dihydropyrans **1a–f** upon treating with 2 equiv. of aqueous amonium hydrochloride in acetonitrile can be diastereoselectively transformed into 5-hydroxy-1,6-diketones **2a–f**. After special optimization of the synthesis conditions (80 °C, 8 h), we managed to reach the yields of diketones **2a–f** ranging 48–89% (see Scheme 1).[†]

Surprisingly, if hydrolysis of the dihydropyrans is carried out in aqueous TFA or under the action of aqueous HCl in dioxane, isomeric cyclopentadienes **3a**,**b** (1:1 ratio) are formed in 69 and 63% total yield, respectively (in Scheme 2 it is shown on the example of dihydropyran **1a**).



Scheme 2

Recently, the selective synthesis of cyclopentadienes of the type **3** by acid-catalyzed rearrangement of 7-methylidene-6,8-dioxabicyclo[3.2.1]octanes (*via* dihydropyrans **1**) under anhydrous conditions has been described.[9]

The structure of 1,6-diketones **2** and configuration of two asymmetric carbon atoms unambiguously follow from the single-

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[†] The IR spectra were recorded on a Bruker IFS25 spectrophotometer. The NMR spectra were recorded on Bruker DPX-400 and AV-400 spectrometers (400.1 MHz for ^{1}H and 100.6 MHz for ^{13}C) in $CDCl_3$. The assignment of signals was made using COSY, NOESY, ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC experiments.

1,6-Diketones **2** *(typical procedure)*. A mixture of dihydropyran **1** (0.5 mmol), water (83 mmol, 1.5 g), NH_4Cl (1 mmol, 53.5 mg) in MeCN (8 ml) was stirred at 80 °C for 8 h. The reaction mixture was poured into Et_2O (20 ml) and dried over K_2CO_3. The solvents were evaporated, and the crude products **2** were eluted with CCl_4–$CHCl_3$ (gradient from 1:0 to 0:1) from the SiO_2-packed column.

(3R,5R*)-5-Hydroxy-3-methyl-1,5-diphenylheptane-1,6-dione* **2a**: yield 115 mg (74%), colorless oil. ^{1}H NMR, δ: 7.91–7.89, 7.55–7.53, 7.46–7.42, 7.36–7.32, 7.27–7.26 (m, 10 H, Ph), 4.94 (s, 1H, OH), 3.18 (dd, 1H, ^2J 16.7 Hz, ^3J 6.3 Hz), 2.28 (dd, 1H, ^2J 16.7 Hz, ^3J 6.8 Hz) [C^2H_2], 2.43–2.37 (m, 1H, C^3H), 2.29–2.27 (m, 2 H, C^4H_2), 2.18 (s, 3 H, C^6Me), 1.08 (d, 3 H, C^3Me, ^3J 6.7 Hz). ^{13}C NMR, δ: 209.9 (C^6), 200.5 (C^1), 141.6, 136.9, 133.1, 128.5, 128.4, 128.2, 128.1, 127.7, 125.9, 125.1, 124.4 (12 C, Ph), 82.9 (C^5), 46.9 (C^2), 43.8 (C^4), 25.6 (C^3), 24.1 (C^6*Me*), 21.9 (C^3*Me*). IR (film, ν/cm^{-1}): 3445, 2956, 2929, 2251, 1708, 1679, 1596, 1493, 1449, 1361, 1279, 1212, 1182, 1128, 1071, 1006, 939, 912, 758, 733, 700, 590. Found (%): C, 71.36; H, 7.10. Calc. for $C_{20}H_{22}O_3$ (%): C, 77.39; H, 7.14.

For characteristics of compounds **2b–f**, see Online Supplementary Materials.

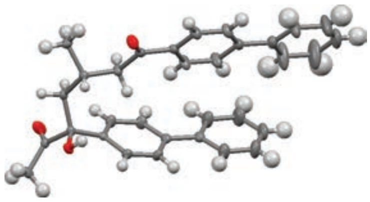
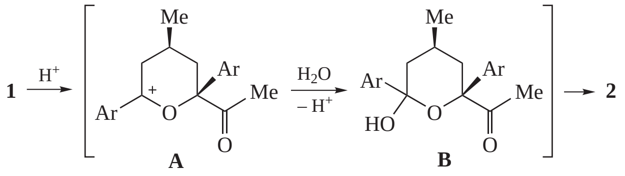


Figure 1 X-ray structure of **2c**. Thermal ellipsoids set at 50% probability level.

crystal X-ray diffraction analysis of compound **2c** (Figure 1).[‡] ^{1}H, ^{13}C NMR, 2D NOESY, and HMBC spectra of diketones **2a–f** are in full agreement with their structures.

A likely pathway of formation of 1,6-diketones **2** is shown in Scheme 3. The process starts with addition of water at the enol moiety of dihydropyrans **1** to deliver hemiacetals **B** (*via* carbocation **A**), which decompose with the ring-opening to give 5-hydroxy-1,6-diketones **2**. This mechanism accounts for diastereoselectivity of the process as the chiral centres in all the intermediates remain intact.



Scheme 3

The approach developed possesses the following advantages: atom economy, efficiency, diastereoselectivity, mild reaction conditions, two synthetic operations, thus fairly meeting the requirements of PASE (pot, atom, step economy) paradigm.[10] The starting compounds employed in this synthesis are diastereomerically pure 2-acetyl-3,4-dihydropyrans (versatile substrates in the synthesis of complex molecules),[11] which are readily available from ketones and acetylene.[8] The 5-hydroxy-1,6-diketones synthesized represent a novel so far inaccessible family of building blocks for wide applications in organic synthesis.

The spectral data were obtained with the equipment of the Baikal Analytical Center for collective use, Siberian Branch of the Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.01.004.

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[‡] *Crystal data for* **2c**. $C_{32}H_{30}O_3$, $M = 462.56$, triclinic, space group P-1, approximate dimensions 0.08 × 0.12 × × 0.38 mm, $a = 5.954(16)$, $b = 7.88(2)$ and $c = 26.30(7)$ Å, $Z = 2$, $V = 1231(6)$ Å^3, $d_{\text{calc}} = 1.248$ g cm^{-3}. The data collection was performed on a Bruker D8 VENTURE PHOTON 100 CMOS diffractometer with MoKα radiation ($\lambda = 0.71073$ Å) at 100.0(2) K using the ω–φ scan technique. Data were corrected for absorption effects using the multi-scan method (SADABS). The structure was solved and refined using the SHELXTL Software Package.[12] The final anisotropic full-matrix least-squares refinement on F^2 with 321 variables converged at $R_1 = 0.0484$, for the observed data and $wR_2 = 0.1304$ for all data.

CCDC 1852181 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.