Very Mild and Efficient One-pot Access to the Valuable 2-Hydroxybicyclo[3.2.1]octan-8-one Ring System

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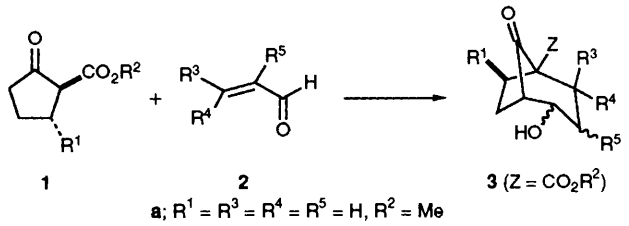
Cyclic β-ketoesters undergo, in a one-pot process, a facile tandem Michael addition–regioselective aldol cyclization with α,β-unsaturated aldehydes in acetone at room temperature in the presence of 1.5 equiv. of K_2CO_3 to afford 2-hydroxybicyclo[3.2.1]octan-8-ones in synthetically useful yields.

In the course of our studies on the stereoselective synthesis of the naturally occurring Prelog–Djerassi lactone we found a very useful base-catalysed diastereoselective three-centre Michael addition of chiral β-ketoesters **1** to prostereogenic α,β-unsaturated carbonyl compounds **2**.[1] In this paper, we describe a mild and general one-pot high yield preparation of synthetically valuable hydroxybicyclo[3.2.1]octanones **3** by a slight modification of our initial conditions for the Michael addition.

It is of interest to note that the bicyclo[3.2.1]octane ring system is an important skeleton in organic synthesis since it represents the basic framework of many diterpenoids such as gibberellanes and kauranes.[2] Furthermore, it has been shown recently that these bicyclic derivatives are involved as intermediates in the ring expansion of cyclopentanones to seven-membered rings.[3] A fragmentation reaction of related compounds, leading to *trans*-hydroazulenes, has also been published recently.[4]

In spite of the synthetic usefulness of this system, only a few reports have appeared on the direct preparation of these bicyclic intermediates starting from simple β-ketoesters and α,β-unsaturated compounds.[5] The use of high pressure with α,β-unsaturated ketones[6] and the two-step annulation of β-keto thioesters[7] constitute the two major synthetic applica-



1 2 3 (Z = CO_2R^2)

a; $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Me$
b; $R^1 = R^3 = R^4 = H$, $R^2 = R^5 = Me$
c; $R^1 = R^4 = R^5 = H$, $R^2 = R^3 = Me$
d; $R^4 = R^5 = H$, $R^1 = R^2 = R^3 = Me$
e; $R^1 = R^5 = H$, $R^2 = R^3 = R^4 = Me$
f; $R^4 = R^5 = H$, $R^1 = R^3 = Me$, $R^2 = Bu^t$
g; $R^4 = R^5 = H$, $R^1 = R^3 = Me$, $R^2 = Bn$

Scheme 1 *Reagents and conditions*: 1.5 equiv. K_2CO_3, acetone, room temp., 15–30 h, 25–96%

tions of this process. Moreover, to our knowledge, there is no successful example of the direct construction of a bicyclo-[3.2.1]octane derivative, starting with simple α,β-unsaturated aldehydes and β-ketoesters,[8] probably due to the difficulty in controlling the Michael addition.[9]

Our one-pot condensation–cyclization takes place under very mild conditions with α,β-unsaturated aldehydes **2** in acetone at room temperature in the presence of 1.5 equiv. of K_2CO_3 (Scheme 1). The method has been applied to several α,β-unsaturated aldehydes, and the results are summarized in Table 1. All reactions are unoptimized but give reproducible results under the conditions reported above.†

The reaction is quite general and proceeds smoothly to give good yields of hydroxybicyclo[3.2.1]octanones **3**, except in the case of **2e** in which, as expected, the β-disubstitution influences the course of the reaction.[8] The use of K_2CO_3 is crucial as shown by the rapid polymerization observed for example with Cs_2CO_3 or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the inefficiency of Na_2CO_3 and Li_2CO_3.[10] Ketols **3**‡ are

† All new compounds gave satisfactory analytical and/or spectral data.

‡ For example: *exo*-**3a**: colourless oil, R_f = 0.17 (diethyl ether); IR (neat) ν/cm^{-1} 3480, 2960, 2890, 1760, 1730; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.69 (2H, m), 2.00 (5H, m), 2.54 (2H, m), 3.71 (3H, s), 4.28 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.3, 25.4, 25.8, 33.9, 52.1, 52.3, 57.4, 77.4, 171.7, 212.1; *endo*-**3a**: white crystals, m.p. = 64 °C, R_f = 0.25 (diethyl ether); IR (neat) ν/cm^{-1} 3480, 2950, 2880, 1755, 1720; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.68 (1H, m), 1.96 (6H, m), 2.55 (2H, m), 3.71 (3H, s), 4.04 (1H, dt, *J* 5.6, 3.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.2, 26.3, 27.0, 31.1, 52.4, 54.1, 56.8, 73.4, 171.8, 211.2.

Table 1 Synthesis of hydroxybicyclo[3.2.1]octanones

β-Ketoester	Aldehyde	*t*/h	Product	Yield (%)
1a	**2a**	15	**3a**	96
1b	**2b**	24	**3b**	78
1c	**2c**	20	**3c**	90
1d	**2d**	22	**3d**	92
1e	**2e**	30	**3e**	25
1f	**2f**	30	**3f**	76
1g	**2g**	30	**3g**	53

obtained as a separable mixture of isomers having predominantly the *exo* configuration with respect to the hydroxy substituent. The stereochemistry of this condensation–cyclization is determined by the stereoselectivity of the Michael addition,[1] which constitutes the first step of the overall process and allows the preparation of highly substituted, stereodefined and optically active hydroxybicyclo[3.2.1]octanones such as **3d**, **f** and **g**.[1,10]

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