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The Torgov Reaction as a Short Cut to Kametani's Synthesis of (±)14α-Hydroxyestrone and Derivatives

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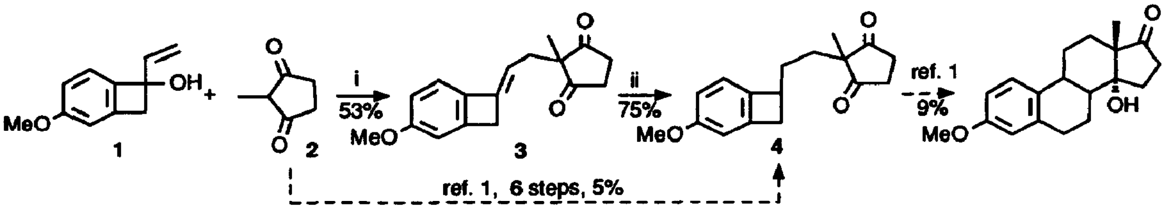
Key Words: 14α-hydroxyestrone; Torgov reaction; *o*-quinodimethane.

Abstract: A key intermediate in Kametani's synthesis of 14α-hydroxyestrone is prepared in two steps via a Torgov like reaction of 2-methylcyclopentane-1,3-dione with a vinylbenzocyclobutenyl alcohol.

The benzocyclobutenylethyl-2-methylcyclopentane-1,3-dione 4 has been used as a key intermediate in Kametani's synthesis of (±)14α-hydroxyestrone and its derivatives[1] *via* the intramolecular cyclisation of a thermally generated *o*-quinodimethane.

The main advantage of this approach is to give the correct relative stereochemistry for the four centres 8,9,13 and 14 in the cyclisation step[2].



Reagents and conditions: i, H_2O, 4 days; ii, H_2, Pd/C, THF, 3h.

However the published route from 2-methylcyclopentanedione 2 to the intermediate 4 requires a quite lengthy multi-step sequence (6 steps) involving protection and deprotection of the carbonyl groups in dione 2, resulting in a 5% overall yield[1].

We have now found that this sequence can be greatly shortened by the use of a Torgov-like reaction[3] as the key step.

Thus, condensation of the readily obtained[4] vinylic alcohol **1** with the dione **2** in water[6] (four days) afforded the alkene **3** in 53% yield[7]. Further catalytic hydrogenation of **3** over 10% Pd/C in THF solution[8] gave directly the sought intermediate **4**[9] (75% yield).

The whole sequence requires thus two steps with a 40% overall yield. This result may give a renewed interest in the Kametani's approach to 14α-hydroxyestrone and its derivatives.

References and Notes

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4. The vinylic alcohol **1** was obtained in essentially quantitative yield by condensation of a two-fold excess of vinyl magnesium bromide at -20°C on the known, readily available, corresponding ketone[5].
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6. The Torgov reaction is usually conducted in alcoholic medium (see ref. 3); we used here water conditions, described for some Michael reactions of dione **2**, for convenience. Hajos, Z.G.; Parrish, D.R. *J. Org. Chem.*, **1974**, , *39*, 1612-1613.
7. Alkene **3** had: m.p. (isopropanol) 98°C; δ_H (200 MHz, $CDCl_3$) 1.13 (s,3H,Me); 2.39 (d, J 8.1 Hz, 2H); 2.68 (apparent d, J 1.5 Hz, 4H); 3.44 (s,2H); 3.75 (s, 3H, OMe); 5.29 (t, J 8.1 Hz, 1H) and 6.67-6.93 ppm (m, 3H). δ_C (50 MHz) 18.9; 35.6; 35.8; 36.3; 55.5; 57.2; 108.2; 108.9; 114.3; 119.6; 136.7; 140.3; 145.5; 160.8 and 216.8 ppm. The presence of a second isomer (*ca.* 1%) could be noticed in the ^1H nmr spectrum.
8. The reduction time should not exceed 3 hours to avoid over-reduction of the aromatic ring.
9. Compound **4** had: m.p. (isopropanol) 81.5 °C (this compound was reported as an oil[1]); δ_H (200 MHz, $CDCl_3$) 1.09 (s, 3H, Me); 1.38-1.79 (m, 4H); 2.56-2.72 (m, 5H); 3.13-3.23 (m, 2H); 3.73 (s, 3H, OMe) and 6.61-6.92 ppm (m, 3H); δ_C (50 MHz) 19.1; 29.5; 30.6; 35.2; 35.3; 42.2; 55.5; 56.5; 109.1; 113.3; 122.9; 140.2; 144.3; 159.8 and 216.5 ppm.

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