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First total synthesis of 11-oxa steroids

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Abstract

The first total synthesis of 11-oxa steroids was achieved via an intramolecular Diels–Alder cycloaddition of orthoquinodimethane as the key-step.

Steroids continue to be one of the most intriguing classes of biologically active compounds.[1] In particular, heterosteroids have recently received much attention. Indeed, the replacement of one or more carbon atoms of a steroid molecule by heteroatoms brings about notable modifications of its biological activity.[2] Engel and colleagues have found that replacement of the 11-carbon atom of the pregnane skeleton resulted in interesting modifications of the biological activities.[3] For example, it was found that 11-oxaprogesterone synthesized from hecogenin presents a significantly higher ovulation-inhibiting activity in comparison with progesterone.[4]

In connection with our interest in steroid synthesis, we recently described a novel strategy for the synthesis of 12-oxa steroids.[5] To the best of our knowledge, there is no total synthesis described in the literature concerning the elaboration of the 11-oxa steroid structure. In this paper, we report a total synthesis of 11-oxa steroids based on an intramolecular Diels–Alder cycloaddition of orthoquinodimethane.[6] The key reactions leading to those compounds are schematically depicted in Scheme 1.

The condensation of BISTRO **1** with anhydride **2** led to *dl*-2,5-divinylcyclopentan-1-ol **3** which is treated by MeONa to give epoxide **4** in good yield. Acid treatment of epoxide **4** led to diol **5** which is alkylated by iodobenzocyclobutenes to give *dl*-benzocyclobutenes **6**.

Thermolysis[7] of **6** afforded a mixture of two oxa steroids **7a** and **7b** in 55% yield and a 80:20 ratio, which were separable by chromatography on silica gel. The steroids **7a** and **7b** have, respectively, a *trans–anti–trans* and a *trans–anti–cis* ring fusion.[8] Interestingly, the main product **7a** matches the *trans–anti–trans* ring fusion configuration of the natural products.

Wacker-type oxidation[9] of the vinyl group of **7a** led to the corresponding ketone **8a** and aldehyde **9a** resulting from an anti-Markovnikov hydroxypalladation, in a 4:1 ratio and 70% overall yield (Scheme 2).

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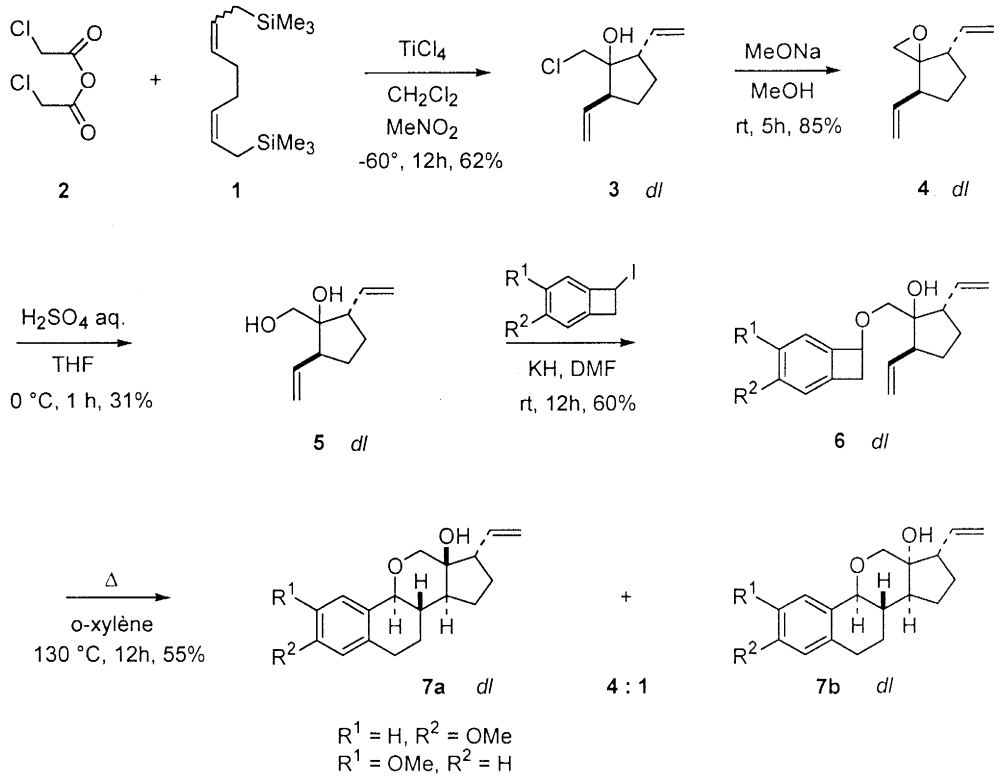
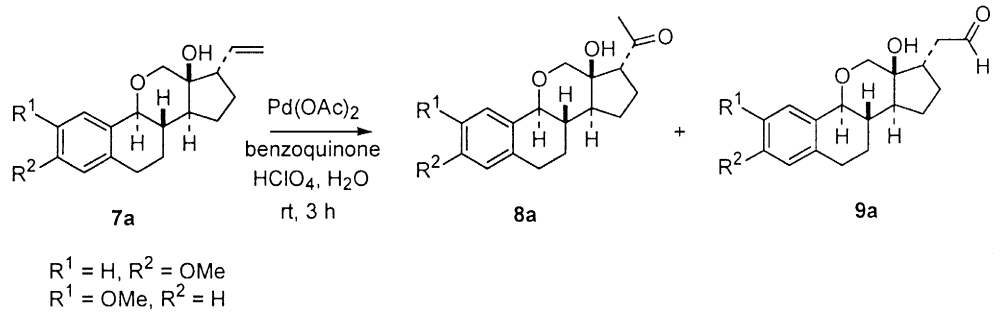


Scheme 1.



Scheme 2.

In conclusion, we have described the first short and efficient synthesis of 11-oxa steroids from BISTRO and chloroacetic anhydride. The possibility to change the nature of the substituent of the aromatic ring enhances the synthetic versatility of our methodology.

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7. The typical procedure of thermolysis is as follows: A solution of **6** (0.4 g, 1.33 mmol) in 20 mL of *o*-xylene was stirred under argon at 130°C for 12 h. After cooling, the solvent was removed under reduced pressure (0.2 mmHg). The resulting oil was purified by flash chromatography on silica gel (9:1 EP:EE) to afford compound **7a** (0.17 g, 42.5%) and compound **7b** (0.05 g, 12.5%).
8. The configuration of the different steroids was established by analysis of their ^{1}H, ^{13}C, COSY and NOESY NMR 400 MHz spectra. Selected spectral data are as follows. Compound **7a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50–2.00 (m, 8H), 2.20 (m, 1H), 2.56 (s, 1H), 2.70 (m, 1H), 2.79 (m, 2H), 3.57 (d, *J*=11.3 Hz, 1H), 3.96 (d, *J*=9.3 Hz, 1H), 4.01 (d, *J*=11.3 Hz, 1H), 4.94–5.09 (m, 2H), 5.53–5.71 (m, 1H), 6.73 (dd, *J*=2.4, 8.2 Hz, 1H), 6.97 (d, *J*=8.2 Hz, 1H), 7.09 (d, *J*=2.4 Hz, 1H). Compound **7b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50–2.20 (m, 9H), 2.76 (m, 2H), 2.94 (m, 1H), 3.54 (d, *J*=11.3 Hz, 1H), 3.76 (s, 3H), 4.01 (d, *J*=11.3 Hz, 1H), 4.11 (d, *J*=9.3 Hz, 1H), 4.94–5.09 (m, 2H), 5.53–5.71 (m, 1H), 6.74 (dd, *J*=2.4, 8.2 Hz, 1H), 6.98 (d, *J*=8.2 Hz, 1H), 7.09 (d, *J*=2.4 Hz, 1H).
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