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A new efficient synthesis of 11-aza steroids

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Abstract—The total synthesis and stereochemistry of new 11-aza steroids are reported. Our strategy involves an intramolecular Diels–Alder cycloaddition of *o*-quinodimethanes which are generated by thermal ring opening of a benzocyclobutene.

In recent years, considerable interest has been evinced in the total synthesis of steroids. The major emphasis has been directed towards the synthesis of unnatural steroids. Heterosteroids have recently received much attention for pharmacological interest[1] and their structures have been widely studied.[2,3] Moreover, some of them present interesting chemical and physical properties. So, these results have encouraged organic chemists to get new compounds having the potential of providing some useful drugs.

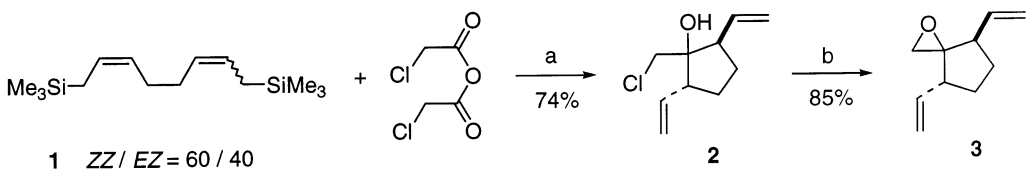
We described previously the first total synthesis of 11-thia[4] and 11-oxa[5] steroids based on our general strategy for elaborating the steroid skeleton.[6] We were now interested by the synthesis of aza derivatives of steroid in which the nitrogen atom occupies a position of established biological importance. It is well known today that the 11-position of aza steroids has a biological significance, primarily with respect to gluco-corticoid activity.[7]

The preparation of steroids containing nitrogen in the ring system has been reported by several groups, but reports concerning the synthesis of 11-aza steroids were limited.[8] The synthesis of 11-oxa and 11-aza steroids has been reported by Engel et al.[9] and also by Badanova and Pivnitskii.[10] In general hecogenin was selected as starting material.

In this paper, we describe a further application of our method to the synthesis of new aza steroids. We thus show that it may be applicable not only to the synthesis of oxa or thia steroids. It may complement or replace some of the earlier methods that have been used for synthesising these classes of heterosteroids.

The starting compound **3** was easily accessible by a procedure reported by us recently[11] via a basic treatment of (*d*,*l*)-2,5-divinylcyclopentan-1-ol **2**, prepared by condensation of BISTRO **1** with chloroacetic anhydride (Scheme 1).[4]

Ring opening of the epoxide **3** was done by heating this latter with ammonia in a pressure Schlenk tube for 18 h at 100°C under a pressure of 46 bars. Condensation of 5-methoxybenzocyclobutenone[12] with **4**, followed by treatment with $NaBH_3CN$[13,14] gave **5** in 75% overall yield. A direct thermolysis of **5** did not allow the



Scheme 1. Reaction conditions: (a) $TiCl_4$, CH_3NO_2, CH_2Cl_2, 12 h, −60°C; (b) *t*-BuOK, EtOH, 0°C, 2 h.

Keywords: aza steroids; divinylcyclopentanes; thermolysis.

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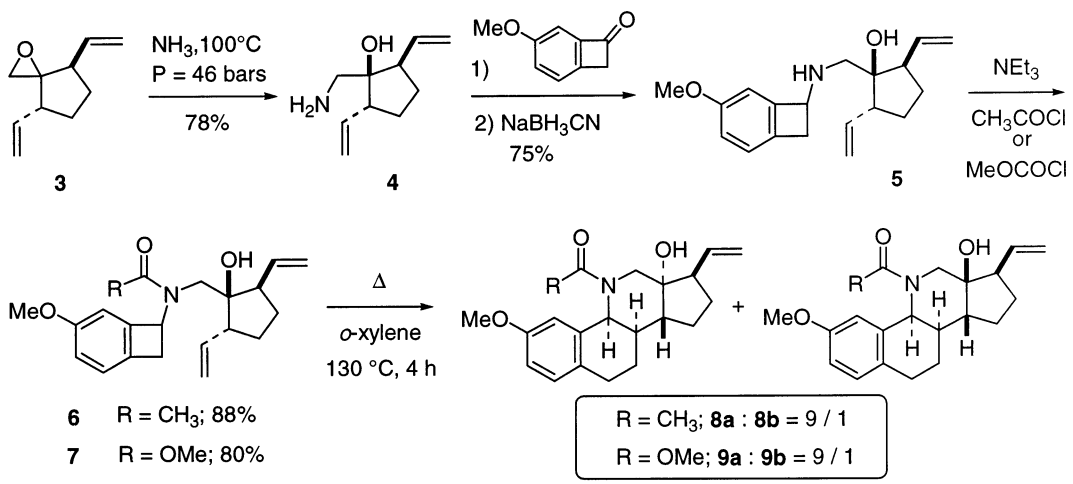

Scheme 2.

achievement of the Diels–Alder reaction. So, we decided to protect the nitrogen atom either by formation of an amide or of a carbamate.[15] Thus, **6** was isolated in 88% yield by treatment of **5** with acetyl chloride, and **7** was obtained in 80% yield by using methyl chloroformate. Thermolysis[16] of **6** or **7** at 130°C in *o*-xylene afforded in the two cases a 9:1 mixture of diastereoisomers **8a**–**b** or **9a**–**b** (Scheme 2). The Diels–Alder cycloaddition was *quasi*-quantitative and the isomers were easily separated by flash chromatography over silica gel.

The relative stereochemistry of the steroids **8a**–**b** and **9a**–**b** was determined by a series of 1D NMR, COSY and NOESY experiments (400 MHz). The structure of **8a** was confirmed unambiguously by the NOE effects and by an X-ray structure determination (Fig. 1).

It is worth pointing out that in contrast with what we have previously described and observed for their analogous 11-oxa[4] and 11-thia steroids,[5] the introduction of a nitrogen atom at the same position led to the formation of the major cycloadduct having a *cis–anti–trans* ring fusion configuration accompanied by the presence of a minor product matching a *cis–anti–cis* ring fusion. The *cis* relationship between H-(8) and H-(9) was confirmed by the vicinal coupling constant $J = 4.8$ Hz for **8a** and **9a** (δ (H-9) = 5.8 ppm for **8a** and δ (H-9) = 5.3 ppm for **9a**). This result was in agreement with those observed by Oppolzer[17] who has described the first total synthesis of (*d*,*l*)-chelidonine.

Terminal olefins can be regarded as masked methyl ketones. So, a Wacker-type oxidation[18] of the vinyl group of the steroids described in this paper is under investigation.

In summary, we reported the synthesis of 11-aza steroids from readily available starting materials by an efficient and simple method. We are now interested in the preparation of further 11-aza derivatives and in the

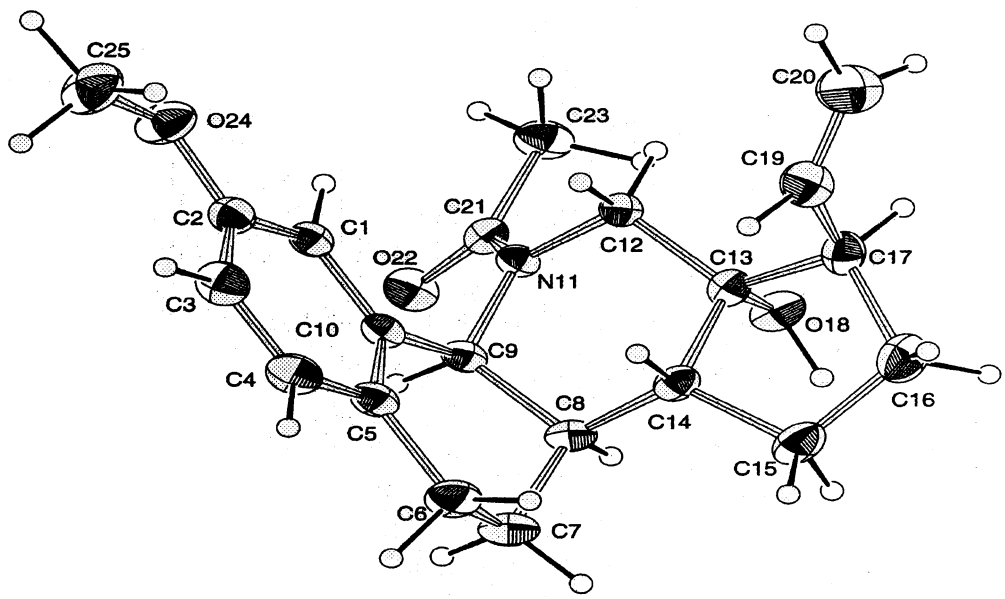

Figure 1. ORTEP drawing of the crystal structure of aza steroid **8a**.

application of our strategy to the obtention of 11-selena or 11-tellura steroids.

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16. The typical procedure of thermolysis is as follows: a solution of **6** (0.3 g, 0.88 mmol) in 20 mL of *o*-xylene was stirred under argon at 130°C for 4 h. After cooling, the solvent was removed under pressure (1 mmHg). The resulting oil was purified by flash chromatography on silica gel (9:1 EP:EE) to afford compound **8a** (0.26 g, 87%) and compound **8b** (0.027 g, 9%).
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