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First total synthesis of 3-aza-11-thia-1,3,5(10)-trieno steroids

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Abstract—The first total synthesis of 3-aza-11-thia-1,3,5(10)-trieno steroids was achieved via an intramolecular Diels–Alder cycloaddition of *o*-quinodimethanes as the key step.

Heterosteroids are of substantial current interest because of their biological and medicinal properties.[1] If carefully selected substituents are added to the basic skeleton of steroids, there can be considerable changes in the properties of the new compound.[2] Thus, it has been reported that replacement of the 11-carbon atom of the pregnane skeleton resulted in interesting modifications of the biological activities.[3] For example, anti-bacterial[4] and neuromuscular-blocking activities[5] have been found for some aza steroids.

We recently described, the first total synthesis of *N*-oxido-3-aza-1,3,5(10)-trieno steroids.[6] Our strategy is based on an intramolecular Diels–Alder cycloaddition of orthoquinodimethane[7] which is generated from a 3-azabicyclo[4.2.0]octa-1,3,5-trien-7-one ketal. In connection with our ongoing interest in the total synthesis of steroids, here we wish to report the extension of our method for the preparation of 3-aza-11-hetero-1,3,5-(10)-trieno steroids. To the best of our knowledge, there is no total synthesis of such compounds reported in the literature before. And firstly, we turned our attention to the obtention of 3-aza-1,3,5(10)-trieno steroids with a sulfur atom at the position 11.

The key reactions leading to those new heterosteroids are schematically depicted in Scheme 1. The condensation of BISTRO **1** with chloroacetic anhydride led to (*d*,*l*)-2,5-divinylcyclopentan-1-ol **2** which was treated by *t*-BuOK in ethanol to give epoxide **3** in good yield.[8] Treatment of epoxide **3** with potassium thioacetate led to compound **4**. The thioacetate **4** is converted to the corresponding thiol by treatment with pyrrolidine in acetonitrile.[9] The thiol generated in this manner has been alkylated in situ with 3-aza-7-iodo-bicyclo[4.2.0]octa-1,3,5-triene[10] **5**, providing a convenient way to produce sulfide **6**. Thermolysis[11] of (*d*,*l*)-cyclobutene **6** afforded a mixture of two thia steroids **7a** and **b** in 82% yield and a 5:1 ratio, which were easily separable by flash chromatography on silica gel.

The relative stereochemistry of those steroids was determined by a series of 1D NMR, COSY and NOESY experiments (400 MHz). The steroids **7a** and **b** have, respectively, a trans-anti-trans and a cis-anti-cis ring fusion.[12] Interestingly, the main product **7a** matches the trans-anti-trans ring fusion configuration of natural products. The trans relationship between H-(8) and H-(9) was confirmed by the vicinal coupling constant $J = 10.9$ Hz for **7a** and for **7b** the value is 4.3 Hz corresponding to a cis relationship (δ (H-9) = 3.60 ppm for **7a** and δ (H-9) = 3.76 ppm for **7b**). Moreover, the structure of **7a** was confirmed unambiguously by the NOE effects and by an X-ray structure determination (Fig. 1).

Otherwise, sulfone derivatives are known to have some biological interests.[13] So, we undertook the oxidation of our thia steroids. Thus, the reaction of the major one **7a** with 3 equiv of *m*-chloroperbenzoic acid[14] in dichloromethane led to the corresponding *N*-oxide sulfone **8** in good yield (Scheme 2).

Keywords: Thia steroids; Pyridine; Intramolecular Diels–Alder reaction; Thermolysis.
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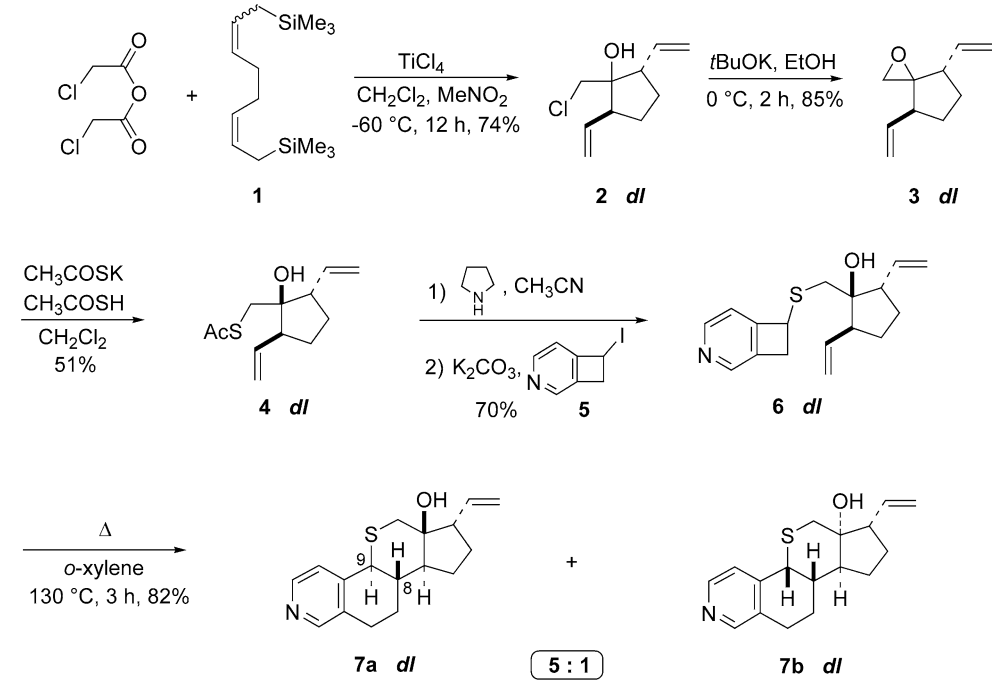


Scheme 1.

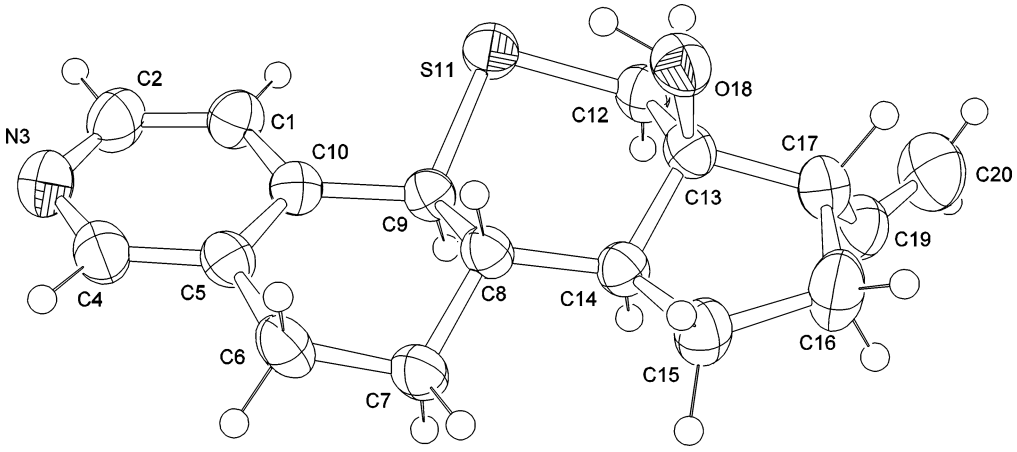
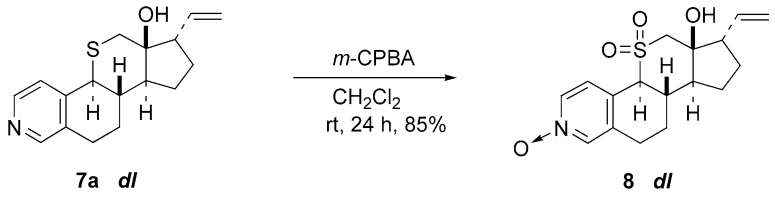


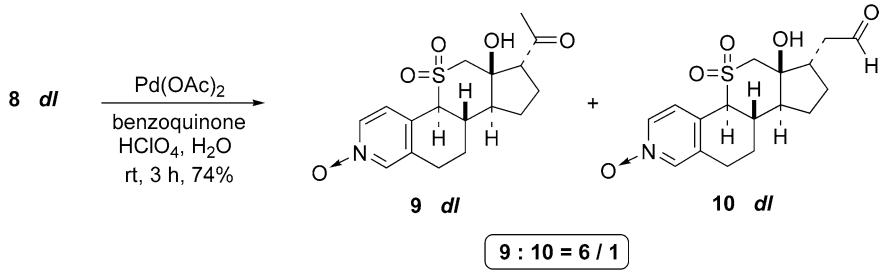
Figure 1. ORTEP drawing of the crystal structure of thia steroid **7a**, *d,l*.



Scheme 2.

Moreover, terminal olefins can be regarded as masked methyl ketones. So, a Wacker-type oxidation of the vinyl group of **8** afforded the corresponding ketone **9** and aldehyde **10** resulting from an anti-Markovnikov hydroxypalladation in a 6:1 ratio and 74% overall yield (Scheme 3).

In conclusion, we have described the first short and efficient synthesis of 11-thia steroids possessing a pyridine as an A ring. Application of our strategy to the obtention of 3-aza-11-oxa-1,3,5(10)-trieno and 3,11-diaza-1,3,5(10)-trieno steroids is in progress.



Scheme 3.

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10. The compound 3-aza-7-iodo-bicyclo[4.2.0]octa-1,3,5-triene **5** is used as a racemate and prepared in 81% yield by treatment of the corresponding mesylate, previously reported,[6] with NaI in acetone at reflux during 24 h. Spectral data of **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (d, $J = 15$ Hz, 1H), 4.01 (dd, $J = 4.7$ Hz, $J = 14.9$ Hz, 1H), 5.46 (d, $J = 4.8$ Hz, 1H), 7.01 (d, $J = 4.8$ Hz, 1H), 8.28 (s, 1H), 8.57 (d, $J = 4.9$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.1, 44.7, 117.4, 138.3, 143.8, 149.1, 156.4.
11. The typical procedure of thermolysis is as follows: a solution of **6** (0.255 g, 0.88 mmol) in 10 mL of *o*-xylene was stirred under argon at 130 °C for 3 h. After cooling, the solvent was removed under pressure (1 mmHg). The resulting oil was purified by flash chromatography on silica gel (petroleum ether–diethyl ether 2:8) to afford compound **7a** (0.175 g, 68%) and compound **7b** (0.036 g, 14%).
12. 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), 2.65 (d, $J = 13.4$ Hz, 1H), 2.80 (m, 1H), 2.95 (d, $J = 13.4$ Hz, 1H), 3.25 (s, 1H), 3.60 (d, $J = 10.9$ Hz, 1H), 5.00 (m, 2H), 5.60 (m, 1H), 7.40 (d, $J = 5.1$ Hz, 1H), 8.29 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3, 26.7, 27.3, 28.1, 40.2, 42.8, 47.8, 51.2, 53.6, 76.8, 116.0, 122.4, 132.5, 139.6, 144.0, 147.6, 150.8. Compound **7b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (m, 1H), 1.34 (m, 1H), 1.57 (m, 1H), 1.87 (m, 1H), 1.92 (m, 1H), 2.03 (m, 1H), 2.12 (m, 1H), 2.32 (d, $J = 13.5$ Hz, 1H), 2.37 (d, $J = 13.5$ Hz, 1H), 2.46 (m, 1H), 2.65 (td, $J = 2.9$, $J = 9.0$ Hz, 1H), 2.76 (m, 2H), 3.76 (d, $J = 4.3$ Hz, 1H), 4.83 (dd, $J = 1.5$, $J = 9.1$ Hz, 1H), 4.92 (m, 1H), 5.29 (dt, $J = 1.5$, $J = 9.8$ Hz, $J = 16.9$ Hz, 1H), 7.85 (d, $J = 5.2$ Hz, 1H), 8.31 (br s, 1H), 8.39 (d, $J = 5.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.6, 26.2, 26.7, 27.3, 35.2, 27.2, 41.8, 42.1, 53.6, 76.7, 115.5, 123.1, 133.1, 139.1, 144.4, 147.5, 150.2.
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