First Total Synthesis of *N*-Oxido-3-aza-1,3,5(10)-trieno Steroids

Khalid Oumzil, Malika Ibrahim-Ouali,* Maurice Santelli*

UMR 6180 CNRS and Université d'Aix Marseille III, 'Chirotechnologies: catalyse et biocatalyse' Laboratoire de Synthèse Organique associé au CNRS, Faculté des Sciences de Saint Jérôme, 13397 Marseille Cedex 20, France
E-mail: m.santelli@univ.u-3mrs.fr; E-mail: m.ibrahim@univ.u-3mrs.fr

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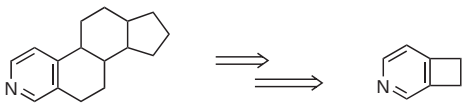
Abstract: An efficient synthesis of 3-aza-steroids bearing a pyridine as an A ring was achieved via intramolecular cycloaddition of orthoquinodimethanes, which were generated from a 3-azabicyclo[4.2.0]octa-1,3,5-trien-7-one ketal.

Key words: aza-steroid, pyridine, intramolecular Diels–Alder reaction, Wacker oxidation

The steroid literature is vast,[1] and recently heterosteroids have received much attention due to their pharmacological interest[2] and their structure has been widely studied.[3,4] This is particularly the case for aza-steroids due to the presence of a nitrogen atom, which is known to result in biologically interesting properties.[5] For example, some aza-steroids have been found to exhibit anti-bacterial[6] and neuromuscular-blocking activities.[7] Though many aza-steroids have been reported, curiously and much to our surprise, 3-aza-1,3,5(10)-trieno steroids have been reported only once and this was not a total synthesis.[8] Nevertheless, a steroidal pyridine-*N*-oxide proved to be a potent inhibitor of the enzyme 5α-reductase (5AR), which catalyzes the conversion of testosterone to the more potent androgen dihydrotestosterone.[9]

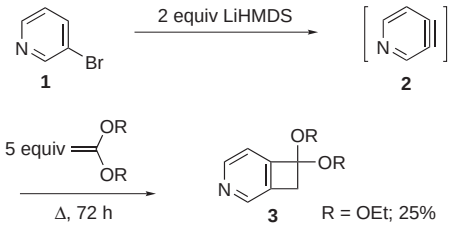
We described previously the total synthesis of 11-thia-,[10] 11-oxa-,[11] and 11-aza-steroids[12] based on our general strategy for elaborating the steroid skeleton.[13] This strategy involved the intramolecular cycloaddition of *o*-xylylenes to generate the BC-ring system, which was developed by Oppolzer[14] and Kametani.[15]

We are now interested in applying our method to the preparation of new aza-steroids bearing this time a pyridine as the A ring. In this communication, we wish to report an efficient method for the preparation of *N*-oxido-3-aza-1,3,5(10)-trieno steroids, using the thermolysis of 4-azabenzocyclobutenes as the key step.



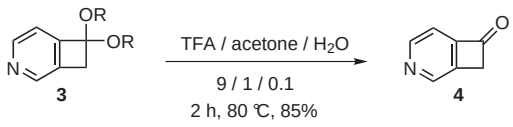
Scheme 1

We have recently reported the first [2 + 2]-cycloaddition of a 3,4-didehydropyridine and a ketene dialkylacetal leading to 3-azabicyclo[4.2.0]octa-1,3,5-trien-7-one ketal (**3**; Scheme 2).[16] The intermediate 3,4-pyridyne **2** was obtained by treatment of 3-bromopyridine **1** with a base. Of note was the remarkable regioselectivity of the elimination reaction where the 3,4-pyridyne was formed exclusively. Moreover, the cycloaddition reaction was also found to be fully regioselective.



Scheme 2

The next step of the synthesis was the deprotection of the ketal (Scheme 3). In this paper, we wish to make a correction and to give a new result concerning this reaction. The hydrolysis of the ketal compound **3** to the ketone **4**, had appeared before to be problematic.[16] Several known acid-promoted cleavage conditions[17] employed gave no product. We attributed this lack of reactivity to the presence of the nitrogen atom of the pyridine ring. Eventually, we found that the amount of acetone and acid was critical for this reaction. Thus, in a solution of trifluoroacetic acid–acetone–water (9:1:0.1),[18] ketal **3** hydrolyzed cleanly to provide 4-azabenzocyclobutenone **4** in 85% yield, within two hours at 80 °C.



Scheme 3

Satisfied with this result which constitutes a novel route to compound **4**, we continued our synthesis using our general scheme. Reduction of **4** with sodium borohydride in ethanol at –20 °C afforded alcohol **5** in 90% yield. 4-Azabenzocyclobutenol **5** was found to be readily converted to the corresponding mesylate **6** in good yield.

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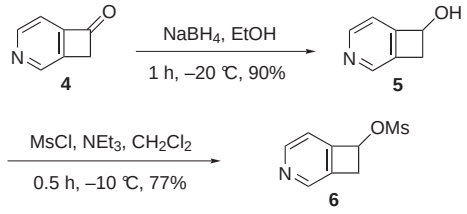
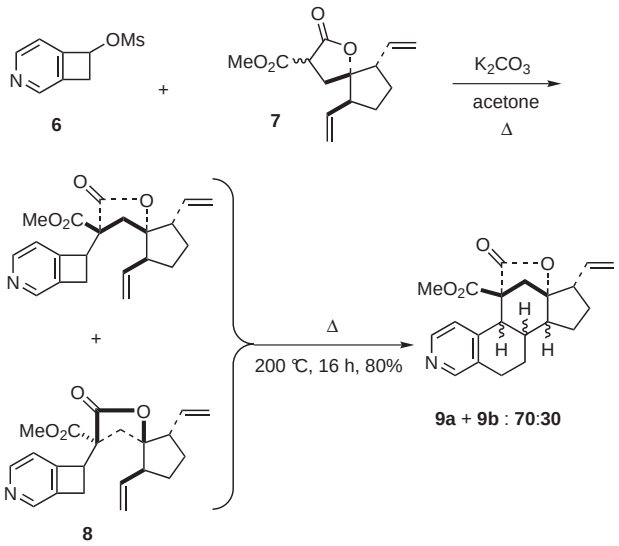


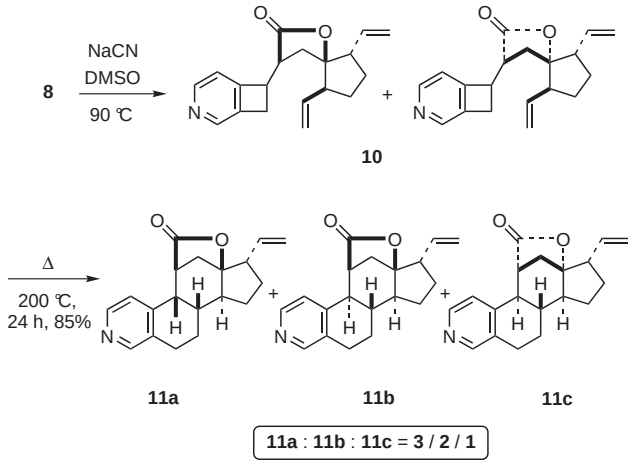
Scheme 4

Having achieved the formation of **6** in only four steps, we turned our attention to the steroid precursor **8** (Scheme 5). Thus, the alkylation of the activated spirolactone **7**[19] was carried out in refluxing acetone in the presence of anhydrous potassium carbonate and our 4-azabenzocyclobutenic derivative **6**.[20] A mixture of two cyclobutene diastereoisomers **8** (2.5:1) was isolated in 82% yield. Upon thermolysis of **8**, an inseparable mixture of two cycloadducts **9a** and **9b** was obtained in a 70:30 ratio and 80% overall yield. Unfortunately, at this step of the synthesis, it was not possible to determine the relative stereochemistry of the 8-, 9-, and 14-positions of these steroids.



Scheme 5

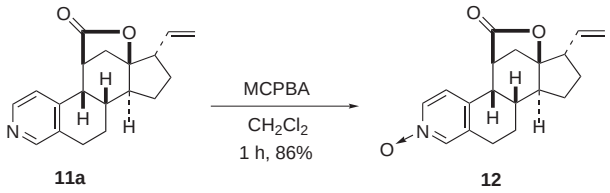
With the aim to access pure steroids with natural stereochemistry, we performed a demethoxycarbonylation of **8** according to the Krapcho procedure (NaCN/DMSO[21]) (Scheme 6). Epimerization occurred and an inseparable mixture of 4-azabenzocyclobutene diastereoisomers **10** was isolated in 91% yield. Heating **10** at 200 °C in 1,2,4-trichlorobenzene for 24 hours yielded three isomeric steroids **11a**, **11b**, and **11c**. Fortunately, these aza-steroids were easily separated by flash chromatography on silica gel. Steroid **11a** exhibits a *cis-anti-trans* structure, while the isomer **11b** matches the *trans-anti-trans* ring-fusion configuration found in the natural products. Isomer **11c** possesses a *trans-anti-cis* structure.



Scheme 6

Structures were characterized on the basis of spectroscopic properties, including a series of NMR experiments (COSY and phase NOESY, 400 MHz). The structure of **11a** was confirmed unequivocally by both spectroscopic methods and X-ray crystallography.[22]

It has been reported that a steroidal *N*-oxido-3-aza-1,3,5(10)-triene proved to be a good inhibitor of the enzyme 5α-reductase.[9] Oxidation of our major steroid was considered (Scheme 7). The pyridine nitrogen of aza-steroid **11a** was oxidized with MCPBA[23] in dichloromethane to produce the target *N*-oxide **12**, in good yield.



Scheme 7

Furthermore, we proceeded to functionalize the terminal chain of the *N*-oxide steroid **12** by a Wacker-type oxidation (Scheme 8).[24] The introduction of an acetyl group at the C-17 position was then effected using palladium acetate/benzoquinone in the presence of perchloric acid.[25] The expected corresponding ketone **13** was isolated in 65% yield accompanied with a minor amount of terminal aldehyde **14** resulting from an *anti*-Markovnikov hydroxypalladation.[26]

In conclusion, we have developed the first short and efficient synthesis of aza-steroids bearing a pyridine as the A ring.[27] Application of this strategy is in progress to prepare variously substituted 3-aza-1,3,5(10)-trieno steroids.

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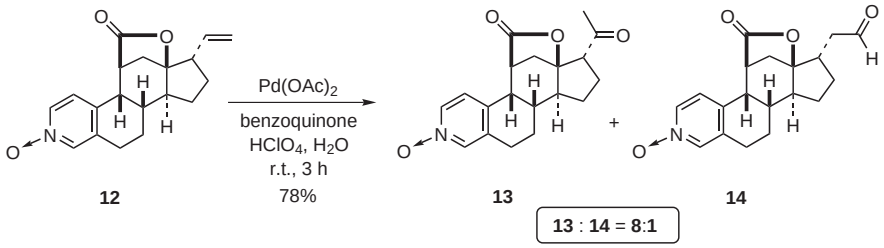

Scheme 8

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(27) All compounds showed satisfactory spectroscopic data as well as microanalytical data. Diastereomeric ratios were established from the ^{1}H NMR spectrum of the crude product. **Experimental procedure for the preparation of 11:** A solution of **10** (0.75 g, 2.53 mmol) in 1,2,4-trichlorobenzene (50 mL) was stirred under argon at 200 °C for 24 h. After cooling, the solvent was removed under reduced pressure (0.2 Torr). The resulting oil was purified by flash chromatography on silica gel (EtOAc–Et_2O, 2:8 to 5:5) to afford compounds **11a** (0.336 g; 41%), **11b** (0.232 g; 29%), and **11c** (0.12 g; 15%) in 85% overall yield. **11a**: White solid; mp 146–147 °C. IR (film): 3083, 2932, 1773, 1610 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 11.9 Hz, 1 H), 1.52 (m, 3 H), 1.92 (m, 3 H), 2.14 (m, 3 H), 2.73 (d, *J* = 3.8 Hz, 1 H), 2.76 (m, 1 H), 2.84 (dt, *J* = 8.5 Hz, *J* = 12.4 Hz, 1 H), 3.23 (m, 1 H), 3.34 (m, 1 H), 4.98 (m, 2 H), 5.42 (m, 1 H), 7.06 (d, *J* = 5.3 Hz, 1 H), 8.35 (m, 2 H). ^{13}C NMR (250 MHz, $CDCl_3$): δ = 21.6, 23.8, 27.5; 28.9, 34.2, 35.1, 37.0, 43.2, 44.8, 49.1, 96.7, 116.6, 121.3, 132.7, 137.2, 144.1, 147.5, 151.0, 177.2. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17. Found: C, 77.48; H, 7.26. **11b**: Oil. IR (film): 2930, 2880, 1762, 1550 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) : δ = 1.49 (m, 1 H), 1.62 (m, 1 H), 1.64

(m, 1 H), 1.69 (m, 1 H), 1.71 (m, 1 H), 1.80 (d, *J* = 11.8 Hz, 1 H), 2.03 (m, 1 H), 2.12 (m, 1 H), 2.26 (m, 1 H), 2.52 (dd, *J* = 5.4, 11.8 Hz, 1 H), 2.65 (d, *J* = 10.5 Hz, 1 H), 2.89 (m, 1 H), 3.44 (d, *J* = 5.4 Hz, 1 H), 5.11 (d, *J* = 9.5 Hz, 1 H), 5.14 (d, *J* = 17.0 Hz, 1 H), 5.64 (dt, *J* = 9.9, 17.2 Hz, 1 H), 7.32 (d, *J* = 5.0 Hz, 1 H), 8.34 (s, 1 H), 8.39 (d, *J* = 5.0 Hz, 1 H). ^{13}C NMR (250 MHz, $CDCl_3$): δ = 25.8, 27.0, 27.1, 29.5, 38.9, 40.4, 41.7, 43.8, 49.1, 49.4, 96.3, 116.7, 119.8, 132.0, 137.2, 144.4, 147.1, 150.4, 175.5. HRMS (EI): *m*/*z* calcd for $C_{19}H_{21}NO_2$ [M^+]: 295.1572; found: 295.1571.

11c: Oil. IR (film): 2928, 1771, 1609 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.09 (qd, *J* = 5.7, 12.2 Hz, 1 H), 1.49 (qd, *J* = 2.7, 11.1 Hz, 1 H), 1.59 (m, 1 H), 1.91 (m, 2 H), 2.01 (d, *J* = 12.2 Hz, 1 H), 2.07 (dd, *J* = 4.2, 12.2 Hz, 1 H), 2.08 (m, 1 H), 2.12 (qd, *J* = 5.4, 11.9 Hz, 1 H), 2.12 (m, 1 H), 2.45 (td, *J* = 7.6, 11.3 Hz, 1 H), 2.90 (m, 1 H), 5.09 (m, 1 H), 5.88 (m, 1 H), 7.18 (d, *J* = 5.1 Hz, 1 H), 8.32 (s, 1 H), 8.37 (d, *J* = 5.1 Hz, 1 H). ^{13}C NMR (250 MHz, $CDCl_3$): δ = 25.7, 26.7, 29.8, 31.6, 32.9, 39.5, 39.8, 41.0, 51.4, 51.9, 94.3, 116.7, 119.0, 132.4, 135.4, 147.2, 147.5, 150.3, 179.7. HRMS (EI): *m*/*z* calcd for $C_{19}H_{21}NO_2$ [M^+]: 295.1572; found: 295.1569.