The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/177970

Please be advised that this information was generated on 2018-11-21 and may be subject to change.
Synthesis of Azasteroids

**Synthesis of Steroidal D-Ring-Fused Pyrrolidines of Dehydroepiandrosterone**


**Abstract:** The commercially available steroid dehydroepiandrosterone 3-acetate (DHEA) was converted into steroidal D-ring-fused pyrrolidines that combine two privileged structures: a steroid and a (2-arylethyl)amine. The three-step transformations proceeded through conversion of the C-17 ketone into an enol ether, followed by high-pressure-mediated cascade [4+2]/[3+2] cycloadditions with two nitroalkenes ([4+2]) and five dipolarophiles ([3+2]) to yield azonite intermediates. Finally, reduction of these azonites formed the new azasteroids, which are suitable for further derivatization.

**Introduction**

Steroids fused through the D-ring to various types of heterocycles, including pyridines,[1] pyrimidines,[2] pyridazines,[3] thiazoles,[4] imidazoles,[5] pyrazoles,[6] indoles,[7] and polyheterocycles,[4,7] have become part of a growing research field. Members of this class of compounds, which are based on the combination of two medicinally relevant privileged core structures into a single molecule, show diverse biological activities. Interestingly, in several cases, these activities are higher than those of the corresponding steroidal reference drugs.[8] The high therapeutic potential of these steroidal alkaloids against cancer and other diseases has recently been reviewed.[9]

The compounds solanidine (1a) and solanine (1b; Figure 1),[10] which contain a pyrrolidine ring fused to the steroid skeleton, are primary examples of this class of compounds. Solanine in particular has attracted much attention because of its antitumor activity.[11]

As part of our research into the preparation of new heterocycle-fused steroids with possible biological activity, in this paper we present new compounds in which the following two privileged structures are combined: (1) (acetyl-protected) dehydroepiandrosterone (DHEA; 2), an endogenous steroid hormone; and (2) a (2-arylethyl)amine moiety (3) contained within a pyrrolidine framework, another common feature in biologically active natural products and pharmaceutical agents (Scheme 1).[12] It is important to emphasize the biological relevance of the (2-arylethyl)amine moiety, which is encountered in numerous compounds that act on the central nervous system.

![Figure 1. Biologically active pyrrolidine-fused steroids.](image-url)

![Scheme 1. Combination of (acetyl-protected) DHEA (2) and (2-arylethyl)amine (3) in a pyrrolidine ring.](image-url)
Furthermore, this privileged structure is present in neurotransmitters such as dopamine, epinephrine, norepinephrine, and serotonin.\textsuperscript{13} We also present model compounds that lack the steroid framework, but helped with the elucidation of the stereochemical outcome of the reactions, and that could shed light on the mechanism of action in a drug-discovery program.

A sequence suitable for this synthesis was recognized in the cascade [4+2]/[3+2] cycloadditions studied by Denmark and others.\textsuperscript{14} In this approach, a nitroalkene (e.g., nitrostyrene) reacts with an enol ether to form a six-membered cyclic azinate (formerly known as nitronate), which then reacts further with a selected alkene in a 1,3-dipolar cycloaddition reaction to produce an azonitride. From there, (arylethyl)amines are accessible by reduction of the azonitride functionality. A retrosynthesis of the target compounds is presented in Scheme 2. Starting from the anticipated pyrrolidine derivatives 17\textendash}24, the pyrrolidine rings could be derived from compounds 6\textendash}16 by reduction of the azonites and subsequent intramolecular reductive amination. A multicomponent cycloaddition should take place to generate these compounds from enol ethers 4 and 5, which in turn could be derived from cyclopentanone and acetyl-protected DHEA (2; Scheme 2). It was discovered by Uitenbogaard et al. that the [4+2]/[3+2] cycloaddition is greatly accelerated by the use of high pressure.\textsuperscript{15} High pressure is also important to overcome the low reactivity of the C-17 position of steroids due to the presence of the C-ring and the methyl group (C-18) at the C–D ring junction.\textsuperscript{16} Thus, we were prompted by the synthetic challenge to synthesize a pyrrolidine E-ring fused to DHEA through a high-pressure-promoted cycloaddition reaction.

![Scheme 2: Retrosynthetic analysis for the synthesis of pyrrolidine derivatives 17\textendash}24.](image)

Results and Discussion

The synthesis of the model compounds began with the known formation of enol ether 4.\textsuperscript{17} The high-pressure-promoted multicomponent cycloadditions were carried out with enol ether 4, nitroalkene 25, and dipolarophiles with different functional groups (26\textendash}30).\textsuperscript{18,19} The [4+2] and [3+2] cycloaddition reactions took place with complete regioselectivity\textsuperscript{20} to give azonites 6\textendash}10 as mixtures of only two diastereoisomers (a and b), via azinate intermediates 31 (Scheme 3, Table 1). In most cases, only the major isomer (a) could be isolated in pure form. The cycloaddition reactions of the electron-deficient dipolarophiles (Table 1, Entries 2 and 4) gave higher product yields than the reactions of electron-rich alkenes (Table 1, Entries 1, 3, and 5). These results were expected, based on the known HOMO\textsubscript{azinate}–LUMO\textsubscript{dipolarophile} interaction.\textsuperscript{21} No product from the competing cycloaddition of azinate 31 with enol ether 4 was observed, probably because of the higher steric hindrance of this substituted alkene compared with the monosubstituted dipolarophiles, and the higher energy of its LUMO.

![Scheme 3: Multicomponent reactions of enol ether 4 to form azonites 6\textendash}10.](image)

Stereocchemical elucidation was carried out based on the single-crystal X-ray diffraction analysis of compound 7a and extensive NMR spectroscopic analysis of 7a and 7b (Figure 2).\textsuperscript{22} These two compounds show the same coupling pattern and the same coupling constant values for 3a-H ($\nu$, $J = 8.1\text{--}8.2$ Hz), indicating a similar dihedral angle and therefore the same configuration at C-3a.

![Figure 2: (a) X-ray crystal structure of compound 7a; and (b) NMR spectroscopic analysis of 7a and 7b.](image)
Scheme 4. Hetero-Diels–Alder cycloaddition for the formation of azinate 31.

Then, a regio- and stereoselective 1,3-dipolar cycloaddition of azinates 31 and dipolarophiles 26–30 yielded azonites 6–10. In all cases, the major products were formed through an exo approach of the dipolarophile exclusively on the Re face of the azinates, probably because of the presence of the phenyl group (Scheme 5).

Scheme 5. Stereoselective formation of azonites 6–10.

The final pyrrolidines were synthesized by reduction of the corresponding azonites. Azonites 6a–10a were hydrogenated with Raney nickel in methanol at room temperature to give pyrrolidines 17a–20a in fair to excellent yields (Scheme 6, Table 2, Entry 2).[25] Pyrrolidine 17a formed a mixture of pyrrolidine 18a and pyrrolizidinone 34a by cyclization of the pyrrolidine with the ester.[27] Pyrrolidines 17a–20a were formed by the stereoselective reduction of imines 33,[28] which in turn were presumably formed by intramolecular condensation of amino hydroxy ketones 32, plausible intermediates after the reduction of azonites 6a–10a. The reduction of azonite 10a did not provide the corresponding pyrrolidine, but gave mixtures of unidentified compounds.

Table 2. Synthesis of pyrrolidines 17a–20a and pyrrolizidinone 34a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Azonite</th>
<th>R 1 Product(s) R 3</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a</td>
<td>Ph</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>7a</td>
<td>CO2Me</td>
<td>41 + 53</td>
</tr>
<tr>
<td>3</td>
<td>8a</td>
<td>CH(OCH2)2</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>9a</td>
<td>CN</td>
<td>56[4]</td>
</tr>
<tr>
<td>5</td>
<td>10a</td>
<td>OAc</td>
<td>–</td>
</tr>
</tbody>
</table>

[a] The product was isolated as the triacetyl derivative.

The synthesis of the corresponding steroid derivatives took place similarly to the synthesis of the model compounds. Treatment of acetyl-protected DHEA (2) with trimethyl orthoformate in methanol with H2SO4 as catalyst gave the corresponding dimethyl acetal, and subsequent demethanolization by distillation gave enol ether 5 in 63 % yield.[29] The high-pressure-promoted multicomponent cycloadditions were carried out with enol ether 5, nitroalkene 25, and the same dipolarophiles 26–30.[18,19] We also included one example using 1-nitro-4-phenylbuta-1,3-diene (35) to achieve a pyrrolidine bearing a (4-phenylbutyl)amine moiety instead of a (2-arylethyl)amine for biological comparison. These cycloaddition reactions took place again with complete regioselectivity and gave azonites 11–16 as mixtures of two or three diastereoisomers (Scheme 7, Table 3). Clearly, the steroid and cyclopentane rings influence the 1,3-cycloaddition reactions differently. Again in most cases, only the major isomer (a) could be isolated in pure form. The cycloadditions of the electron-deficient dipolarophiles (Table 3, Entries 2, 4, and 6) resulted again in higher yields of the products.

Table 3. Synthesis of azonites 11–16.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Heterodiene (R 2)</th>
<th>Dipolarophile (R 3)</th>
<th>Products (ratio)[a][22]</th>
<th>Yield [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25 (Ph)</td>
<td>Ph</td>
<td>11a/11b (5:1)</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>25 (Ph)</td>
<td>CO2Me</td>
<td>12a/12b/12c (13:4:6)</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>25 (Ph)</td>
<td>CH(OCH2)2</td>
<td>13a/13b/13c (7:2:1)</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>25 (Ph)</td>
<td>CN</td>
<td>14a/14b/14c (11:9:6)</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>25 (Ph)</td>
<td>OAc</td>
<td>15a/15b (5:1)</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>35 (PhCH=CH)</td>
<td>CO2Me</td>
<td>16a/16b/16c (8:2:9)</td>
<td>71</td>
</tr>
</tbody>
</table>

[a] Calculated from the isolated products after purification. It was not possible to determine the ratio from the crude mixtures. [b] Combined yield.

Scheme 7. Multicomponent reactions of enol ether 5 to form azonites 11–16.
Stereocchemical elucidation of azonites 11–16 was carried out by comparison of their $^1$H and $^{13}$C NMR spectra with the corresponding spectra of azonites 6–10. The hetero-Diels–Alder cycloaddition of enol ether 5 and heterodienes 25 and 35 took place through reaction on the bottom face of enol ether 5 as a result of the presence of the $\beta$-methyl group at C-13. The formation of isomers c of the steroid derivatives could be due to the presence of the $\beta$-methyl group at C-13. This methyl group might force the methoxy group into a different conformation, and at the same time this may change the conformation of the dihydrooxazine ring of azonites 31, placing the R² group (Ph or PhCH=CH) away from the top face.

Finally, the target steroid-derivised pyrrolidines were synthesised by reduction of azonites 11a–16a under the same conditions as before (Raney-Ni, MeOH, 23 °C) to give pyrrolidines 21a–24a in fair to good yields (Scheme 8, Table 4). The reduction of azonites 14a and 15a did not provide the corresponding pyrrolidines, but gave mixtures of unidentified compounds. The stereochemistry at C-17 was determined by comparison of the coupling constants between 16-H and 17-H of compounds 17a, 18a, and 20a ($J = 7.0$–$8.2$ Hz).[31]

---

**General Procedure for the High-Pressure-Promoted Three-Component Reactions**: A flexible 7.5 mL PTFE tube was loaded with enol ether 4 or 5, nitroalkene 25 or 35, dipolarophile 26–30, and enough CHCl₃ to fill up the 7.5 mL vessel. The reaction mixture put under a pressure of 15 kbar at 23 °C for 18 h. After depressurisation, the reaction mixture was concentrated in vacuo, and the products were separated by column chromatography on silica gel.

**Conclusions**

The realm of azosteroids is continuously expanding. New pyrrolidines fused to (acetyl-protected) dehydroepiandrosterone on the $\alpha$-ring can be synthesized in three steps, of which a high-pressure-promoted multicomponent cycloaddition reaction is the key step. The resulting model and steroidal compounds presented in this publication will be tested and their properties evaluated to demonstrate the influence of the steroid part of the molecules.

**Experimental Section**

**General Methods**: Commercially available chemicals were used without purification. Solvents were distilled from appropriate drying agents before use and stored under nitrogen. Reactions were monitored and $R_f$ values obtained using thin-layer chromatography (TLC) on silica-gel-coated plates (Merck 62 F254). TLC plates were visualized with UV light and by charring at ca. 150 °C after dipping the plate into a basic aqueous solution of KMnO₄. Column or flash chromatography was carried out using Acros silica gel (0.235–0.400 mm, pore diameter ca. 6 nm). NMR spectra were recorded with a Bruker DMX 300 (300 MHz) or a Varian 400 (400 MHz) spectrometer in CDCl₃ solutions. Chemical shifts are given in parts per million (ppm), with CHCl₃ ($\delta$ = 7.26 ppm for $^1$H) and CDCl₃ ($\delta$ = 77.16 ppm for $^{13}$C) used as internal standards. Coupling constants are reported as $J$ values in Hertz (Hz). Melting points were measured with a Reichert Thermopan microscope.

**Table 4. Synthesis of pyrrolidines 21a–24a.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Azonite</th>
<th>R¹/R²</th>
<th>Product(s)</th>
<th>R³</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11a</td>
<td>Ph/Ph</td>
<td>21a</td>
<td>Ph</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>12a</td>
<td>CO₂Me/Ph</td>
<td>22a</td>
<td>CO₂Me</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>13a</td>
<td>CH(OCH₂)₂/Ph</td>
<td>23a</td>
<td>CH(OCH₂)₂</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>14a</td>
<td>CN/Ph</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>15a</td>
<td>OAc/Ph</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>16a</td>
<td>CO₂Me/PhCH=CH</td>
<td>24a</td>
<td>CO₂Me</td>
<td>49[a]</td>
</tr>
</tbody>
</table>

[a] $R^2$ is PhCH₂CH₂ after the reduction.

---

**Scheme 8. Reduction of azonites 11a–16a to form pyrrolidines 21a–24a.**

---

**Table 4. Synthesis of pyrrolidines 21a–24a.**

**Conclusions**

The realm of azosteroids is continuously expanding. New pyrrolidines fused to (acetyl-protected) dehydroepiandrosterone on the $\alpha$-ring can be synthesized in three steps, of which a high-pressure-promoted multicomponent cycloaddition reaction is the key step. The resulting model and steroidal compounds presented in this publication will be tested and their properties evaluated to demonstrate the influence of the steroid part of the molecules.
(2R,3aR,4R,4aS,7aS)-7a-Methoxy-4-phenyl-3,3a,4,4a,5,6,7,7a-octahydro-2H-cyclopenta[e]isoxazolo[2,3-b][1,2]oxazine (8a): Prepared according to the general procedure from enol ether 4 (300 mg, 3.06 mmol), nitroalkene 25 (400 mg, 2.68 mmol), and dipolarophile 28 (400 μL, 400 mg, 4.00 mmol). This reaction gave pure azonite 26 (350 mg, 38%) as a white solid, and a 3:1 mixture of azonites 8a and 8b (200 mg, 21%) in a second fraction (total yield 59%) after column chromatography (heptane/EtOAc, 4:1). 

1H NMR (300 MHz, CDCl₃): δ = 7.38–7.21 (m, 5 H, Ph), 4.89 (d, J = 3.8 Hz, 1 H, OCH), 4.71 (dd, J = 8.9, 5.1 Hz, 2 H, 1a-H), 3.91–3.78 (m, 2 H, 3,7-dq, J = 8.2 Hz, 1 H, 3a-H), 3.42 (s, 3 H, OCH₃), 2.52 (dd, J = 12.8, 7.8 Hz, 1 H, 1a-H), 2.42 (dd, J = 12.8, 7.7, 3.6 Hz, 1 H, 4a-H), 2.29 (dd, J = 12.2, 8.4, 5.1 Hz, 1 H, 3-H), 2.15 (dt, J = 12.2, 8.6, 8.6 Hz, 1 H, 3-H), 2.10–2.00 (m, 1 H), 1.81–1.53 (m, 4 H, 4), 1.22–1.07 (m, 1 H) ppm. 

13C NMR (75 MHz, CDCl₃): δ = 141.2 (Ph), 128.9, 128.5, 127.2 (Ph), 112.5 (C-7a), 103.2 (OCHO), 83.6 (C-3a), 65.5 (C-3a, C-4a), 52.0 (CH₂O), 49.4, 47.0, 33.7, 31.7, 28.6, 22.2 ppm. HRMS (ESI): calcd. for C₂₅H₂₅NO₃ [M + Na]⁺ 370.16304; found 370.16355.

(2R,3aR,4R,4aS,7aS)-7a-Methoxy-4-phenyl-3,3a,4,4a,5,6,7,7a-octahydro-2H-cyclopenta[e]isoxazolo[2,3-b][1,2]oxazine-2-carboline (9a) and (25,25aR,3R,4aS,7aS): 7a-Methoxy-4-phenyl-3,3a,4,4a,5,6,7,7a-octahydro-2H-cyclopenta[e]isoxazolo[2,3-b][1,2]oxazine-2-carboline (9b): Prepared according to the general procedure from enol ether 4 (300 mg, 3.06 mmol), nitroalkene 25 (400 mg, 2.68 mmol), and dipolarophile 29 (352 μL, 285 mg, 5.37 mmol). This reaction gave azonite 29a (336 mg, 42%) as a white solid, and azonite 29b (268 mg, 33%) as a white solid (total yield 75%) after column chromatography (heptane/EtOAc, 4:1). Data for 29a: 1H NMR (300 MHz, CDCl₃): δ = 7.41–7.19 (m, 5 H, Ph), 5.20 (dd, J = 10.0, 5.5 Hz, 1 H, 2-H), 3.89 (q, J = 8.0 Hz, 1 H, 3a-H), 3.41 (s, 3 H, OCH₃), 2.64 (dd, J = 12.4, 8.2, 5.5 Hz, 1 H, 3-H), 2.52 (dd, J = 12.6, 8.2, 5.1 Hz, 2-H), 2.52 (dt, J = 12.5, 8.6, 8 Hz, 1 H, 3-H), 2.42 (dd, J = 12.6, 7.9, 3.6 Hz, 1 H, 4a-H), 2.15–2.20 (m, 1 H), 1.81–1.53 (m, 4 H, 4), 1.22–1.09 (m, 1 H) ppm. 

13C NMR (75 MHz, CDCl₃): δ = 140.0 (Ph), 129.2, 128.4, 128.4, 128.4, 128.4, 116.7 (Ph), 113.1 (C-7a), 74.3 (C-3a), 68.8 (C-2), 51.9 (CH₂O), 47.9, 46.7, 31.0, 28.6, 22.2 ppm. HRMS (ESI): calcd. for C₂₉H₂₅NO₃ [M + H]⁺ 310.15522; found 310.15460. M.p. 138–141°C. 

Data for 29b: 1H NMR (300 MHz, CDCl₃): δ = 7.40–7.21 (m, 5 H, Ph), 4.92 (dd, J = 9.3, 5.2 Hz, 1 H, 2-H), 3.76 (q, J = 8.1 Hz, 1 H, 3a-H), 3.45 (s, 3 H, OCH₃), 2.77 (dd, J = 12.5, 9.5, 8.9 Hz, 1 H, 3-H), 2.70 (dd, J = 12.6, 8.2, 8 Hz, 1 H, 4a-H), 2.51 (dd, J = 12.5, 7.5, 5.3 Hz, 1 H, 3-H), 2.39 (dd, J = 12.6, 7.6, 3.2 Hz, 1 H, 4a-H), 2.18–2.05 (m, 1 H), 1.82–1.53 (m, 4 H, 4), 1.27–1.11 (m, 1 H) ppm. 

13C NMR (75 MHz, CDCl₃): δ = 140.3 (Ph), 129.2, 128.4, 127.7 (Ph), 118.7 (CN), 113.2 (C-7a), 74.5 (C-3a), 68.6 (C-2), 51.3, 49.6, 47.4, 38.5, 31.6, 28.6, 22.2 ppm. HRMS (ESI): calcd. for C₂₉H₂₅NO₃ [M + H]⁺ 310.15522; found 310.15460. M.p. 107–108°C.

© 2017 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim
Prepared according to the general procedure from enol ether 5 (500 mg, 1.60 mmol), nitroalkene 25 (220 mg, 1.48 mmol) and dipolarophile 28 (220 μL, 220 mg, 2.20 mmol). This reaction gave azonite 13a (265 mg, 30%) as a white solid, and a 1:6 mixture of azonites 13a/13b (94 mg, 11%) in a second fraction (total yield 41%) after column chromatography (heptane/EtOAc, 6:1). 

1H NMR (300 MHz, CDCl3): δ = 7.38–7.18 (m, 5 H, Ph), 5.35 (d, J = 4.8 Hz, 1 H, 6-H), 4.95 (dd, J = 9.4, 2.2 Hz, 1 H, 5-H), 4.67–4.53 (m, 1 H, 3-H), 4.14 (dd, J = 11.7, 5.2, 3.9 Hz, 1 H, 3′-H), 3.40 (s, 3 H, OCH3), 3.37 (dt, J = 11.7, 9.4 Hz, 1 H, 2′′-H), 2.94–2.66 (m, 1 H, 2′′-H), 2.13–2.06 (m, 1 H, 2′′-H), 1.26–1.10 (m, 3 H, 2′′-H), 1.07–1.00 (m, 1 H, 1′-H), 0.01 (s, 6 H, 18-C(O)-CH3, 19-C(O)-CH3) ppm. 

13C NMR (75 MHz, CDCl3): δ = 170.6 (CO2), 139.8, 139.2, 129.3, 128.2, 127.9 (PhCH2O), 122.1 (C-17), 118.2 (CN), 112.6 (C-17), 73.9 (C-3), 68.2, 67.6, 51.5, 49.8, 49.5, 43.9, 40.2, 38.1, 37.0, 36.6, 35.3, 32.8, 31.6, 31.5, 27.8 (C-2), 21.5 (CH3CO), 20.7 (C-11), 19.4 (C-19), 13.9 (C-18) ppm. 

19F NMR (300 MHz, CDCl3): δ = 45.8 (F, 5-H, Ph), 29.8 (F, 6-H, Ph). 

Data for 13a: 

HRMS (ESI): calcd. for C34H45NO7 [M + Na]+ 602.30973; found 602.30975.

HRMS (ESI): calcd. for C33H39NO5 [M + Na]+ 547.31720; found 547.32008. Data for 14c: 

1H NMR (300 MHz, CDCl3): δ = 7.42–7.19 (m, 5 H, Ph), 5.31 (d, J = 4.8 Hz, 1 H, 6-H), 4.95 (dd, J = 9.4, 2.2 Hz, 1 H, 5-H), 4.67–4.53 (m, 1 H, 3-H), 4.14 (dd, J = 11.7, 5.2, 3.9 Hz, 1 H, 3′-H), 3.40 (s, 3 H, OCH3), 3.37 (dt, J = 11.7, 9.4 Hz, 1 H, 2′′-H), 2.94–2.66 (m, 1 H, 2′′-H), 2.13–2.06 (m, 1 H, 2′′-H), 1.26–1.10 (m, 3 H, 2′′-H), 1.07–1.00 (m, 1 H, 1′-H), 0.01 (s, 6 H, 18-C(O)-CH3, 19-C(O)-CH3) ppm. 

13C NMR (75 MHz, CDCl3): δ = 170.6 (CO2), 139.8, 139.2, 129.3, 128.2, 127.9 (PhCH2O), 122.1 (C-17), 118.2 (CN), 112.6 (C-17), 73.9 (C-3), 68.2, 67.6, 51.5, 49.8, 49.5, 43.9, 40.2, 38.1, 37.0, 36.6, 35.3, 32.8, 31.6, 31.5, 27.8 (C-2), 21.5 (CH3CO), 20.7 (C-11), 19.4 (C-19), 13.9 (C-18) ppm. 

HRMS (ESI): calcd. for C34H45NO7 [M + Na]+ 602.30973; found 602.30975.

HRMS (ESI): calcd. for C34H45NO7 [M + Na]+ 547.31720; found 547.32008. Data for 14c: 

1H NMR (300 MHz, CDCl3): δ = 7.42–7.19 (m, 5 H, Ph), 5.31 (d, J = 4.8 Hz, 1 H, 6-H), 4.95 (dd, J = 9.4, 2.2 Hz, 1 H, 5-H), 4.67–4.53 (m, 1 H, 3-H), 4.14 (dd, J = 11.7, 5.2, 3.9 Hz, 1 H, 3′-H), 3.40 (s, 3 H, OCH3), 3.37 (dt, J = 11.7, 9.4 Hz, 1 H, 2′′-H), 2.94–2.66 (m, 1 H, 2′′-H), 2.13–2.06 (m, 1 H, 2′′-H), 1.26–1.10 (m, 3 H, 2′′-H), 1.07–1.00 (m, 1 H, 1′-H), 0.01 (s, 6 H, 18-C(O)-CH3, 19-C(O)-CH3) ppm. 

13C NMR (75 MHz, CDCl3): δ = 170.6 (CO2), 139.8, 139.2, 129.3, 128.2, 127.9 (PhCH2O), 122.1 (C-17), 118.2 (CN), 112.6 (C-17), 73.9 (C-3), 68.2, 67.6, 51.5, 49.8, 49.5, 43.9, 40.2, 38.1, 37.0, 36.6, 35.3, 32.8, 31.6, 31.5, 27.8 (C-2), 21.5 (CH3CO), 20.7 (C-11), 19.4 (C-19), 13.9 (C-18) ppm. 

HRMS (ESI): calcd. for C34H45NO7 [M + Na]+ 547.31720; found 547.32008. Data for 14c: 

1H NMR (300 MHz, CDCl3): δ = 7.42–7.19 (m, 5 H, Ph), 5.31 (d, J = 4.8 Hz, 1 H, 6-H), 4.95 (dd, J = 9.4, 2.2 Hz, 1 H, 5-H), 4.67–4.53 (m, 1 H, 3-H), 4.14 (dd, J = 11.7, 5.2, 3.9 Hz, 1 H, 3′-H), 3.40 (s, 3 H, OCH3), 3.37 (dt, J = 11.7, 9.4 Hz, 1 H, 2′′-H), 2.94–2.66 (m, 1 H, 2′′-H), 2.13–2.06 (m, 1 H, 2′′-H), 1.26–1.10 (m, 3 H, 2′′-H), 1.07–1.00 (m, 1 H, 1′-H), 0.01 (s, 6 H, 18-C(O)-CH3, 19-C(O)-CH3) ppm. 

13C NMR (75 MHz, CDCl3): δ = 170.6 (CO2), 139.8, 139.2, 129.3, 128.2, 127.9 (PhCH2O), 122.1 (C-17), 118.2 (CN), 112.6 (C-17), 73.9 (C-3), 68.2, 67.6, 51.5, 49.8, 49.5, 43.9, 40.2, 38.1, 37.0, 36.6, 35.3, 32.8, 31.6, 31.5, 27.8 (C-2), 21.5 (CH3CO), 20.7 (C-11), 19.4 (C-19), 13.9 (C-18) ppm.
General Procedure for the Raney-Nickel-Catalysed Reduction of Compounds 6a–16a: Azonites 6a–16a (ca. 0.5 mmol) were dissolved in MeOH (60 mL) containing Et$_3$N (8 drops). Raney nickel (0.5–1.5 g; wet, washed with MeOH) was added, and the reaction mixture was stirred in a stainless steel autoclave at 50 atm for 4 d. After depressurisation and evaporation of the MeOH, the residue was dissolved in CH$_2$Cl$_2$ and the solution was washed with water (2 × 10 mL). The solution was then dried (Na$_2$SO$_4$) filtered, and concentrated. The residue was purified by column chromatography on silica gel.

(R)-1-Phenyl-2-[(2R,3a,5a,6aS)-3-phenyl-1,2,3,3a,4,5,6,octahydrocyclopenta[b]pyrrol-2-yl]ethan-1-ol (17a): According to the general procedure, azinate 17a (300 mg, 0.85 mmol) gave pyrrolidine 17a (195 mg, 74 %) as a white solid after column chromatography (CHCl$_3$/MeOH, 97:3, mixed in a 99:1 ratio with a 7 n solution of NH$_3$ in MeOH). 1H NMR (300 MHz, CDCl$_3$): δ = 7.37–7.13 (m, 10 H, 2 Ph), 5.99 (m, 1 H, 3-H), 4.53 (m, 1 H, 4-H), 4.06–3.98 (m, 3 H), 3.39 (s, 3 H, CO$_2$CH$_3$), 1.99–1.39 (m, 8 H) ppm. 13C NMR (75 MHz, CDCl$_3$): δ = 174.7 (CO$_2$), 141.2 (Ph), 128.6 (18, 19, 20), 126.7 (Ph), 126.6 (Ph), 125.1, 71.4, 64.9, 61.9, 55.3, 52.1, 38.3, 34.9, 31.8, 23.7 ppm. HRMS (ESI): calcd. for C$_{32}$H$_{45}$NO$_3$ [M + H]$^+$ 536.33760; found 536.33904.

(R)-1-Phenyl-2-[(2R,3a,5a,6aS)-3-phenyl-1,2,3,3a,4,5,6,octahydrocyclopenta[b]pyrrol-2-yl]propanoate (18a): According to the general procedure, azinate 18a (600 mg, 1.80 mmol) gave pyrrolidine 18a (212 mg, 41 %) as a white solid, and pyrrolizidinone 21a (345 mg, 0.56 mmol) as a white solid after column chromatography (CHCl$_3$/MeOH, 98:2 → 97:3) gave pyrrolidine 20a (144 mg, 56 %) as a white solid.

(R′)-1-Acetamido-3-[(2R,3a,5a,6aS)-1-acetyl-3-phenyl-1,2,3,3a,4,5,6,octahydrocyclopenta[b]pyrrol-2-yl]propan-2-yl Acetate (20a): The residue formed after having applied the general procedure with azinate 9a (200 mg, 0.67 mmol) was dissolved in Ac$_2$O (6 mL) and pyridine (2 drops). The resulting mixture was stirred at 23 °C for 3 d. The solvent was then evaporated to dryness under high vacuum. Purification by column chromatography (CHCl$_3$/MeOH, 98:2) gave pyrrolidine 20a (144 mg, 56 %) as a white solid.

Compounds 6a–16a: Azonites 6a–16a (200 mg, 0.67 mmol) were dissolved in MeOH (60 mL) containing Et$_3$N (8 drops). Raney nickel (0.5–1.5 g; wet, washed with MeOH) was added, and the reaction mixture was stirred in a stainless steel autoclave at 50 atm for 4 d. After depressurisation and evaporation of the MeOH, the residue was dissolved in CH$_2$Cl$_2$ and the solution was washed with water (2 × 10 mL). The solution was then dried (Na$_2$SO$_4$) filtered, and concentrated. The residue was purified by column chromatography on silica gel.
3-H), 4.11 (dt, J = 11.5, 3.4 Hz, 1 H, 2′-H), 4.02–3.93 (m, 2 H), 3.90–3.81 (m, 2 H), 3.53 (dt, J = 10.8, 3.6 Hz, 1 H, 5′-H), 3.27 (d, J = 8.1 Hz, 1 H, 17-H), 2.69 (q, J = 8.0 Hz, 1 H, 16-H), 2.57 (dd, J = 10.4, 8.0 Hz, 1 H, 4′-H), 2.37–2.22 (m, 2 H), 2.03 (s, 3 H, CD3CO), 2.00–1.31 (m, 17 H), 1.19–1.01 (m, 2 H), 1.01 (s, 3 H, 19-CMe2), 0.73 (s, 3 H, 18-CH2) ppm. 13C NMR (75 MHz, CDCl3): 6 = 170.5 (CO2), 142.0 (Ph-3), 139.5 (C-5′), 128.7, 128.1, 126.7 (Ph-2,3), 122.5 (C-6), 105.7 (OCHO), 74.1 (C-3), 70.8, 69.6, 63.5, 64.4, 53.5, 49.6, 49.5, 48.0, 43.4, 38.1, 37.0, 36.7, 33.1, 32.7, 32.1, 29.4, 27.8 (C-2), 21.5 (CH3-20), 20.5 (C-11), 19.4 (C-19), 18.8 (C-18) ppm. HRMS (ESI): calcd. for C35H49NO5 [M + H]+: 564.35325; found 564.35325.

Methyl (2R)-3-[[35,4′,5′,6′,16,17-trietatetra-1′H-pyrrolo[3′,2′,16,17]androst-5-en-5-yl]2-hydroxypropanoate (24a): According to the general procedure, azinate 16a (350 mg, 0.58 mmol) gave pyrolloidine 24a (160 mg, 49%) as an off-white solid after column chromatography (CH2Cl2/MeOH, 98:2). 1H NMR (300 MHz, CDCl3): δ = 7.35–7.15 (m, 5 H, Ph), 5.37 (d, J = 4.0 Hz, 1 H, 6′-H), 4.66–4.51 (m, 1 H, 3′-H), 4.52 (dd, J = 10.2, 3.4 Hz, 1 H, 2-H), 3.77 (s, 3 H, CO2CH3), 3.48 (d, J = 8.2 Hz, 1 H, 17′-H), 3.33–3.23 (m, 1 H, 2′-H), 2.83–2.58 (m, 2 H, 2′, 3′-H) ppm. 13C NMR (75 MHz, CDCl3): δ = 173.6 (CO2), 170.4 (CO), 141.4 (Ph-3′), 139.4 (C-5′), 128.4, 128.0, 126.0 (Ph-2,3), 122.1 (C-6), 73.7 (C-3′), 71.2, 68.0, 62.5, 52.4, 49.0, 48.2, 48.0, 45.6, 42.8, 38.1, 36.9, 36.5, 34.1, 33.8, 32.3, 31.9, 31.5, 27.4 (C-7′, 2′-C), 21.3 (CH3CO), 20.2 (C-11′), 19.2 (C-19′), 18.1 (C-18′) ppm. HRMS (ESI): calcd. for C35H49NO5 [M + H]+: 564.36690; found 564.36692.

Keywords: Steroids · Nitrogen heterocycles · Cycloadition · High-pressure chemistry · Cascade reactions

[4] For the synthesis of heterocycles fused to steroids along C-16–C-17, see: I. V. Zavarzin, V. V. Chertkova, I. S. Levina, E. I. Chernoburova, Russ. Chem. Rev. 2011, 80, 661–682.
[7] These products are stable to the isolation and purification procedures used. Thus, the product ratios of the crude mixtures and of the isolated compounds should not differ substantially.
[12] In a separate experiment, pyrrolidine 18a was dissolved in THF, and after 17 h at 15 kbar pyrrolidine 34a was formed in 69 % yield.


[31] For an example whose structure was determined by X-ray crystallography, which has the same cis fusion on the α-ring, and has a similar coupling constant between the bridgehead protons, see ref.[6]

Received: December 31, 2016