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Synthesis of Azasteroids

Synthesis of Steroidal D-Ring-Fused Pyrrolidines of Dehydroepiandrosterone

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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,[6] 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 endogeneous 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.

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

(Scheme 1). 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.

![Scheme 1. Combination of (acetyl-protected) DHEA (2) and (2-arylethyl)amine (3) in a pyrrolidine ring.](image)

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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 azonite. From there, (arylethyl)amines are accessible by reduction of the azonite functionality. A retrosynthesis of the target compounds is presented in Scheme 2. Starting from the anticipated pyrrolidine derivatives 17–24, the pyrrolidine rings could be derived from compounds 6–16 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 17–24.](image)

**Table 1. Synthesis of azonites 6–10.**

| Entry | Dipolarophile (R\textsuperscript{1}) | Products (ratio)\textsuperscript{[a][b]} | Yield [%]\textsuperscript{[b]} |
|-------|--------------------------------------|---------------------------------------|-----------------|
| 1     | 26 (Ph)                              | 6a/6b (17:1)                          | 64              |
| 2     | 27 (CO\textsubscript{2}Me)           | 7a/7b (3:1)                           | 82              |
| 3     | 28 [CH(OCH\textsubscript{2})\textsubscript{2}] | 8a/8b (9:1)                          | 59              |
| 4     | 29 (CN)                              | 9a/9b (4:3)                           | 75              |
| 5     | 30 (OAc)                             | 10a/10b (6:1)                         | 67              |

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

Stereochemical 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{24} These two compounds show the same coupling pattern and the same coupling constant values for 3a-H (q, J = 8.1–8.2 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)

The stereoisomerism of azinate 31 could be explained by a stereoselective hetero-Diels–Alder cycloaddition of nitroalkene 25 and the heterodiene with the methoxy group approaching in an endo fashion (Scheme 4).\textsuperscript{24}
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).[25] Azonite 7a formed a mixture of pyrrolidine 18a and pyrrolizidinone 34a (Table 2, Entry 2)[26] 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.

| Entry | Azonite | R¹ | Product(s) R³ | Yield [%] |
|-------|---------|----|---------------|----------|
| 1     | 6a      | Ph | 17a           | Ph       | 74       |
| 2     | 7a      | CO₂Me | 18a + 34a | CO₂Me | 41 + 53 |
| 3     | 8a      | CH(OCH₂)₂ | 19a | CH(OCH₂)₂ | 66       |
| 4     | 9a      | CN | 20a | CH₂NH₂ | 56[^a]  |
| 5     | 10a     | OAc | – | – | –       |

[^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.

| Entry | Heterodiene (R²) | Dipolarophile (R¹) | Products (ratio)[20][22] | Yield [%][b] |
|-------|------------------|-------------------|------------------------|-------------|
| 1     | 25 (Ph)          | Ph                | 11a/11b (5:1)          | 66          |
| 2     | 25 (Ph)          | CO₂Me             | 12a/12b/12c (7:3:2)    | 68          |
| 3     | 25 (Ph)          | CH(OCH₂)₂         | 13a/13b/13c (7:3:2)    | 41          |
| 4     | 25 (Ph)          | CN                | 14a/14b/14c (11:9:6)   | 79          |
| 5     | 25 (Ph)          | OAc               | 15a/15c (5:1)          | 54          |
| 6     | 35 (PhCH=CH)     | CO₂Me             | 16a/16b/16c (8:2:9)    | 71          |

[a] Calculated from the isolated products after purification. It was not possible to determine the ratio from the crude mixtures. [b] Combined yield.
Stereocchemical elucidation of azonites 11–16 was carried out by comparison of their 1H and 13C NMR spectra with the corresponding spectra of azinates 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 β-methylene group at C-13.[30] The formation of isomers of the steroid derivatives could be due to the presence of the β-methylene 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 azinates 31, placing the R2 group (Ph or PhCH=CH) away from the top face.

Finally, the target steroid-derived pyrrolidines were synthesized 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).[25] The reduction of azonites 14a and 15a did not provide the corresponding pyrrolidines, and gavies 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 CH2Cl2 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 depressurization, the reaction mixture was concentrated in vacuo, and the products were separated by column chromatography on silica gel.

Conclusions

The realm of azasteroids is continuously expanding. New pyrrolidines fused to (acetyl-protected) dehydroepiandrosterone on the α-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 steroidal 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 Rf values obtained using thin-layer chromatography (TLC) on silica-gel-coated plates (Merck 60 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 (0.035–0.070 mm, pore diameter ca. 6 nm). NMR spectra were recorded with a Bruker D80 300 (300 MHz) or a Varian 400 (400 MHz) spectrometer in CDCl3 solutions. Chemical shifts are given in parts per million (ppm), with CHCl3 (δ = 7.26 ppm for 1H) and CDCl3 (δ = 77.16 ppm for 13C) 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.

| Entry | Azonite | R1/R2 | Product(s) | R3 | Yield [%] |
|-------|---------|-------|------------|-----|-----------|
| 1     | 11a     | Ph/Ph | 21a        | Ph  | 54        |
| 2     | 12a     | CO2Me | 22a        | CO2Me | 62     |
| 3     | 13a     | CH(OCH2)2/Ph | 23a | CH(OCH2)2 | 81 |
| 4     | 14a     | Cn/Ph | –          | –   | –         |
| 5     | 15a     | OAc/Ph | –          | –   | –         |
| 6     | 16a     | CO2Me/PhCH=CH | 24a | CO2Me | 49[a] |

[a] R2 is PhCH2CH2 after the reduction.
NMR (300 MHz, CDCl$_3$): $\delta = 7.38-7.21$ (m, 5 H, Ph), 4.89 (d, $J = 3.8$ Hz, 1 H, OCHO), 4.71 (d, $J = 8.9$ Hz, 2 H, 2-H), 3.93–3.78 (m, 2 H), 3.72 (q, $J = 8.2$ Hz, 1 H, 3a-H), 3.42 (s, 3 H, OCH$_3$), 2.52 (d, $J = 12.8$, 7.8 Hz, 1 H, 4-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, 1.2 Hz, 1 H, 3-H), 2.10–2.00 (m, 1 H), 1.81–1.53 (m, 4 H), 1.22–1.07 (m, 1 H) ppm. 13C NMR (75 MHz, CDCl$_3$): $\delta = 141.2$ (Ph$_3$O), 128.9, 128.5, 127.2 (Ph$_2$O), 112.5 (C-7a), 103.2 (OCHO), 83.6 (C-2), 73.8 (C-3a), 65.5 (C-5′, C-4′), 52.0 (CH$_3$O), 49.4, 47.0, 33.7, 31.7, 28.6, 22.2 ppm. HRMS (ESI): calcd. for C$_{23}$H$_{38}$O$_3$ [M + Na]$^+$ 370.16304; found 370.16355.

NMR (300 MHz, CDCl$_3$): $\delta = 7.44-7.18$ (m, 10 H, 2 Ph), 5.61 (dd, $J = 9.0$, 6.6 Hz, 1 H, 5′-H), 5.36 (d, $J = 8.4$, 4.9 Hz, 1 H, 4-H), 4.69–4.54 (m, 1 H, 3-H), 4.09 (td, $J = 8.8$, 4.4 Hz, 1 H, 3′-H), 3.50 (s, 3 H, OCH$_3$), 2.70 (t, $J = 9.3$ Hz, 1 H, 4-H), 2.47 (s, 3 H, CO$_2$), 2.17 (dt, $J = 12.1$, 9.0 Hz, 1 H, 4-H), 2.25–2.17 (m, 1 H, 4-H), 2.04 (s, 3 H, CH$_3$O), 1.99–1.82 (m, 4 H, 1 H + 2 H + 7 H + 12 H), 1.77 (dt, $J = 12.8$, 3.0 Hz, 1 H, 12-H), 1.68–1.42 (m, 7 H, 2-H, 7-H, 8-H, 11-H, 14-H, 15-H), 1.25 (dd, $J = 11.9$, 4.8 Hz, 1 H, 15-H), 1.21–1.13 (m, 1 H, 1-H), 1.11–1.01 (m, 1 H, 9-H), 1.03 (s, 3 H, 19-CH$_3$), 0.98 (s, 3 H, 18-CH$_3$) ppm. 11C NMR (100 MHz, CDCl$_3$): $\delta = 170.7$ (CO$_2$), 143.2 (4′-Ph$_3$O), 140.1 (C-5), 138.2 (5′-Ph$_3$O), 128.9, 128.0, 128.4, 127.1, 126.9 (5′-Ph$_3$O), 122.1 (C-6), 110.9 (C-17), 82.7 (C-5′), 74.0 (C-3), 72.0 (C-5′), 51.4 (CH$_3$O), 51.2 (C-14), 50.2 (C-4′), 49.8 (C-15), 48.7 (C-13), 45.6 (C-16), 41.6 (C-4′), 38.2 (C-4), 37.1 (C-3′), 33.9 (C-12), 31.7 (C-7), 31.4 (C-8), 31.1 (C-15), 27.9 (C-2′), 21.6 (CH$_3$CO), 20.8 (C-20′), 19.1 (C-19), 14.2 (C-18′) ppm. HRMS (ESI): calcd. for C$_{32}$H$_{43}$N$_2$O$_2$ [M + H]$^+$ 598.33523; found 598.33551.

Methyl (35,3′R,4′R,5′R,16,17R)-3-Acetoxy-17-methoxy-4-phenyl-3′,4′,4′,5′,16,17-hexahydro[2,1]oxazolo[5,6′,4′,3′-e][1,2]oxazine (12a) and Methyl (35,3′R,4′R,5′S,16,17R)-3-Acetoxy-17-methoxy-4-phenyl-3′,4′,4′,5′,16,17-hexahydro[2,1]oxazolo[5,6′,4′,3′-e][1,2]oxazino[5,6′,16,17]oxadiazet-5-ene-5-carboxylate (12b): Prepared according to the general procedure from enol ether 5 (500 mg, 1.45 mmol), nitroalkane 25 (205 mg, 1.38 mmol), and dipolarophile 26 (317 μL, 288 mg, 2.77 mmol). This reaction gave pure azonite 11a (167 mg, 20%) as a white solid in one fraction, and a 3:1 mixture of azonites 11a and 11b (380 mg, 46%) in a second fraction (total yield 66%) after column chromatography (PhMe/EtO$_2$, 25:1). 1H NMR (400 MHz, CDCl$_3$): $\delta =$ 7.44–7.18 (m, 10 H, 2 Ph), 5.61 (dd, $J = 9.0$, 6.6 Hz, 1 H, 5′-H), 5.36 (d, $J = 8.4$, 4.9 Hz, 1 H, 4-H), 4.69–4.54 (m, 1 H, 3-H), 4.09 (td, $J = 8.8$, 4.4 Hz, 1 H, 3′-H), 3.50 (s, 3 H, OCH$_3$), 2.70 (t, $J = 9.3$ Hz, 1 H, 4-H), 2.47 (s, 3 H, CO$_2$), 2.17 (dt, $J = 12.1$, 9.0 Hz, 1 H, 4-H), 2.25–2.17 (m, 1 H, 4-H), 2.04 (s, 3 H, CH$_3$O), 1.99–1.82 (m, 4 H, 1 H + 2 H + 7 H + 12 H), 1.77 (dt, $J = 12.8$, 3.0 Hz, 1 H, 12-H), 1.68–1.42 (m, 7 H, 2-H, 7-H, 8-H, 11-H, 14-H, 15-H), 1.25 (dd, $J = 11.9$, 4.8 Hz, 1 H, 15-H), 1.21–1.13 (m, 1 H, 1-H), 1.11–1.01 (m, 1 H, 9-H), 1.03 (s, 3 H, 19-CH$_3$), 0.98 (s, 3 H, 18-CH$_3$) ppm. 11C NMR (100 MHz, CDCl$_3$): $\delta = 170.7$ (CO$_2$), 143.2 (4′-Ph$_3$O), 140.1 (C-5), 138.2 (5′-Ph$_3$O), 128.9, 128.0, 128.4, 127.1, 126.9 (5′-Ph$_3$O), 122.1 (C-6), 110.9 (C-17), 82.7 (C-5′), 74.0 (C-3), 72.0 (C-5′), 51.4 (CH$_3$O), 51.2 (C-14), 50.2 (C-4′), 49.8 (C-15), 48.7 (C-13), 45.6 (C-16), 41.6 (C-4′), 38.2 (C-4), 37.1 (C-3′), 33.8 (C-12), 31.7 (C-7), 31.4 (C-8), 31.1 (C-15), 27.9 (C-2′), 21.6 (CH$_3$CO), 20.8 (C-20′), 19.1 (C-19), 14.2 (C-18′) ppm. HRMS (ESI): calcd. for C$_{32}$H$_{43}$N$_2$O$_2$ [M + H]$^+$ 598.33523; found 598.33551.
Prepared according to the general procedure from enol ether 5 (550 mg, 1.60 mmol), nitroalkene 22 (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 %) 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), 1.49 (d, 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, 1″-H), 3.40 (s, 3 H, OCH3), 3.37 (td, J = 11.7, 9.4 Hz, 1 H, 2″-H) (220 μL, 220 mg, 1.48 mmol) and dipolarophile 22 (280 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 %) 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), 4.96 (d, J = 4.2 Hz, 1 H, OCHO), 4.70–4.53 (m, 2 H, 3″, 5″-H), 4.06–3.94 (m, 2 H), 3.94–3.81 (m, 2 H), 3.79 (td, J = 7.6, 6.8 Hz, 1 H, 3″-H), 3.46 (s, 3 H, OCH3), 2.82 (t, J = 6.4 Hz, 1 H, 4″-H) 2.37–2.09 (m, 5 H), 2.04 (s, 3 H, CH3O), 1.99–1.74 (m, 4 H), 1.48–1.72 (m, 4 H), 1.32–1.72 (m, 12 H), 1.21–1.05 (m, 1 H), 1.03–0.97 (m, 1 H), 1.01 (s, 3 H, 19-CH3), 0.92 (s, 3 H, 18-CH3) ppm. 13C NMR (75 MHz, CDCl3): δ = 170.5 (CO2), 144.3 (Ph), 140.0 (C-5), 128.7, 128.6, 126.8 (Ph), 122.0 (C-6), 111.7 (C-13), 103.2 (OCHO), 81.7 (C-5), 73.9 (C-3), 70.4 (C-3), 65.5 (2 x), 51.0 (2 x), 49.7, 49.5, 48.7, 44.0, 38.1, 37.0, 36.6, 33.3 (2 x), 32.2, 31.5, 31.4, 27.7 (2 C), 21.4 (CH3O), 20.6 (C-11), 19.3 (C-14), 14.0 (18-C) ppm. HRMS (ESI): calcd. for C33H42N2O5 [M + H]+ 549.34308; found 549.34197.

Cycano-17-methoxy-[4]oxazolo[2′,3′:2,3]oxazino[5′,6′:16,17]androst-5-en-3-yl acetate (14c): Prepared according to the general procedure from enol ether 5 (500 g, 1.45 mmol), nitroalkene 25 (200 mg, 1.34 mmol), and dipolarophile 29 (179 μL, 145 mg, 2.73 mmol). This reaction gave azonite 14a (250 mg, 34 %) as a white solid, azonite 14b (190 mg, 26 %) as a white solid, and azonite 14c (137 mg, 19 %) as a white solid (total yield 71 %) after column chromatography (heptane/ EtOAc, 6:1). Data for 14a: 1H NMR (300 MHz, CDCl3): δ = 7.35–7.20 (m, 5 H, Ph), 5.35 (d, J = 4.5 Hz, 1 H, 6-H), 5.15 (dd, J = 8.1, 6.6 Hz, 1 H, 5″-H), 4.68–4.53 (m, 1 H, 3″-H), 3.94 (td, J = 7.6, 6.8 Hz, 1 H, 3″-H), 3.45 (s, 3 H, OCH3), 2.81 (bd, J = 7.2, 6.3 Hz, 1 H, 4″-H), 2.65–2.46 (m, 2 H), 2.37–2.14 (m, 2 H), 2.04 (s, 3 H, CH3O), 1.96–1.42 (m, 12 H), 1.32–1.22 (m, 1 H), 1.05–0.97 (m, 1 H), 1.01 (s, 3 H, 19-CH3), 0.93 (s, 3 H, 18-CH3) ppm. 13C NMR (75 MHz, CDCl3): δ = 170.7 (CO2), 143.2 (Ph), 140.1 (C-5), 129.1, 128.5, 127.4, 121.9 (C-6), 116.7 (CN), 111.9 (C-17), 73.9 (C-5), 70.8, 67.1, 51.3, 51.9, 49.8, 49.0, 48.7, 44.1, 38.2, 37.6, 37.1, 36.7, 33.3, 32.2, 31.6, 31.5, 27.8 (C-2), 21.5 (CH3O), 20.7 (C-11), 19.3 (C-14), 14.1 (18-C) ppm. HRMS (ESI): calcd. for C32H39NO5 [M + Na]+ 602.30979; found 602.30904.

Prepared according to the general procedure from enol ether 5 (500 g, 1.60 mmol), nitroalkene 35 (650 mg, 3.71 mmol), and dipolarophile 27 (400 μL, 382 mg, 4.44 mmol). This reaction gave azonite 16a (281 mg, 29 %) as a white solid, and a 2:7 mixture of azonites 16b and 16c (407 mg, 42 %) after column chromatography (heptane/ EtOAc, 5:1). 1H NMR (300 MHz, CDCl3): δ = 7.40–7.71 (m, 5 H, Ph), 6.42–6.32 (m, 2 H, CH=CH), 5.36 (d, J = 4.7 Hz, 1 H, 6-H), 5.05 (dd, J = 8.4, 6.0 Hz, 1 H, 5″-H), 4.68–4.53 (m, 1 H, 3″-H), 3.78 (s, 3 H, CO2CH3), 3.62 (dd, J = 8.4, 4.8 Hz, 1 H, 3″-H), 3.45 (s, 3 H, OCH3), 2.63–2.39 (m, 3 H), 2.38–2.24 (m, 2 H), 2.04 (s, 3 H, CH3O), 2.03–1.78 (m, 5 H), 1.77–1.34 (m, 9 H), 1.20–1.08 (m, 1 H), 1.02 (s, 3 H, 19-CH3), 1.04–0.95 (m, 1 H), 0.93 (s, 3 H, 18-CH3) ppm. 13C NMR (75 MHz, CDCl3): δ = 170.6 (CO2), 170.5 (CO2), 140.1 (C-5), 137.0 (Ph), 133.1, 130.5, 128.6, 127.5 (Ph), 124.2, 122.0 (C-6), 111.5 (C-17), 79.3 (C-5′), 73.9 (C-3′), 69.3 (C-3′), 52.6, 51.1, 50.9, 49.8, 49.8, 45.4, 41.3, 38.2, 37.0, 36.7, 34.7 (C-12), 32.8, 31.8, 31.6, 27.8 (C-2), 21.5 (CH3O), 20.6 (C-11), 19.3 (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 Et3N (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 CHCl3, and the solution was washed with water (2 × 10 ml). The solution was then dried (Na2SO4), filtered, and concentrated. The residue was purified by column chromatography on silica gel.

(R)-1-Phenyl-2-[(2R,3R,3aS,6aS)-3-phenyl-1,2,3,3a,4,5,6,6a-octahydrocycloptenyl][b]pyrrol-2-yl]ethan-1-ol (17a): According to the general procedure, azinate 7a (300 mg, 0.85 mmol) gave pyrrolidine 17a (195 mg, 74 %) as a white solid after column chromatography (CHCl3/MeOH, 97:3, mixed in a 99:1 ratio with a 7N solution of NH3 in MeOH).1H NMR (300 MHz, CDCl3): δ = 7.37–7.13 (m, 10 H, 2 Ph), 5.15 (dd, J = 10.2, 2.8 Hz, 1 H, 1′-H), 4.24 (br s, 2 H, OH, NH), 3.83 (t, J = 7.0 Hz, 1 H, 6′-H), 3.55–3.35 (m, 1 H, 2′-H), 2.79–2.61 (m, 2 H, 3′-, 3a′-H), 1.91–1.38 (m, 8 H) ppm.13C NMR (75 MHz, CDCl3): δ = 145.2 (PhCO), 141.8 (PhCO), 128.8, 128.2, 121.8, 126.9 (PhCO), 126.8 (PhCO), 125.5, 71.4, 64.9, 61.9, 55.3, 52.1, 38.3, 31.4, 28.3, 23.4 ppm. HRMS (ESI): calcld. for C27H33NO2 [M + H]+ 380.2144; found 380.2141.

Methyl (R)-2-Hydroxy-3-[(2R,3R,3aS,6aS)-3-phenyl-1,2,3,3a,4,5,6,6a-octahydrocycloptenyl][b]pyrrol-2-yl]propanoate (18a) and (3aS,6aR,7aR,8R,8aS)-6-Hydroxy-8-phenyl-2,3,3a,6,7a,8,8a-octahydrocyclopenta[b]pyrrolzin-5(1H)-one (34a): According to the general procedure, azinate 7a (600 mg, 1.80 mmol) gave pyrrolidine 18a (212 mg, 41 %) as a white solid, and pyrrolidizine 34a (244 mg, 53 %) after column chromatography (CHCl3/MeOH, 96:4, mixed in a 99:1 ratio with a 7 N solution of NH3 in MeOH). Data for 18a:1H NMR (300 MHz, CDCl3): δ = 7.37–7.17 (m, 10 H, 2 Ph), 5.43 (dd, J = 9.4, 3.6 Hz, 1 H, 2′-H), 3.82 (dd, J = 8.1, 6.5 Hz, 1 H, 6′-H), 3.70 (s, 3 H, CO2CH3), 3.39 (dd, J = 10.6, 6.2, 3.0 Hz, 1 H, 2′-H), 2.65 (q, J = 7.9 Hz, 1 H, 3a′-H), 2.46 (dd, J = 10.2, 9.1 Hz, 1 H, 3′-H), 1.88–1.39 (m, 8 H) ppm.13C NMR (75 MHz, CDCl3): δ = 174.7 (CO2), 141.6 (PhCO), 128.8, 128.0, 126.8 (PhCO), 69.5, 64.1, 62.3, 57.1, 52.4, 52.1, 34.8, 34.0, 31.7, 23.6 ppm. HRMS (ESI): calcld. for C27H29NO4 [M + H]+ 490.17562; found 490.17606. Data for 34a:1H NMR (300 MHz, CDCl3): δ = 7.40–7.19 (m, 5 H, Ph), 4.54 (dd, J = 9.5, 8.5 Hz, 1 H), 4.23 (br s, 1 H, OH), 4.14–4.06 (m, 1 H), 3.82 (td, J = 9.4, 5.4 Hz, 1 H, 3′-H), 3.15–3.02 (m, 1 H), 2.56 (dd, J = 12.4, 7.4, 5.4 Hz, 1 H), 2.56–2.44 (m, 1 H, 2′-H), 2.44 (t, J = 10.1 Hz, 1 H), 1.90–1.49 (m, 6 H, 3a′-H) ppm.13C NMR (75 MHz, CDCl3): δ = 172.2 (CON), 139.0 (PhCO), 128.9, 127.7, 127.4 (PhCO), 74.4, 65.0, 59.5, 57.1, 55.0, 36.7, 29.9, 29.6, 24.4 ppm. HRMS (ESI): calcld. for C27H29NO4 [M + H]+ 490.17562; found 490.17606.
Methyl (2R)-3-((3S,4′S,5′R,16′S,17′R)-Acetoxy-4′-(2-phenyl-ethyl)-4′,5′,16,17-tetrahydro-1′H-pyrrolo[3′,2′,16′:17Androst-5-en-5-yl)-2-hydroxypropanoate (24a): According to the general procedure, aziridine 16a (350 mg, 0.58 mmol) gave pyrrolidine 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), 4.66–5.41 (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, 1′-H), 3.33–3.23 (m, 1 H, 2′′-H), 2.58–2.38 (m, 2 H, 12′-H, 20′-H), 2.50–2.40 (m, 1 H, 20′′-H), 2.00–1.36 (m, 18 H, 12′′-H, 20′′-H), 1.23–1.00 (m, 2 H, 10′-H, 19′-H), 0.82 (s, 3 H, 18′-H). 13C NMR (75 MHz, CDCl3): δ = 173.6 (CO2), 170.4 (CO2), 141.4 (Ph), 139.4 (C-5′), 128.4, 128.0, 126.0 (Ph), 124.9 (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, 31.4, 27.2 (C-2′), 21.3 (CH3CO2H), 20.2 (C-1′′), 19.2 (C-1′-H), 18.1 (C-1′′-H) ppm. HRMS (ESI): calcd. for C35H49NO5 [M + H]+ 564.36890; found 564.36924.

Keywords: Steroids • Nitrogen heterocycles • Cycloaddition • High-pressure chemistry • Cascade reactions

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