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High-Pressure-Mediated Extension of the Privileged Steroid Scaffold

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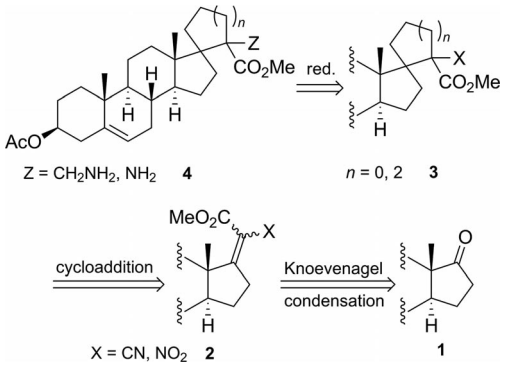
The commercially available steroid dehydroepiandrosterone 3-acetate (DHEA) was converted into new, highly functionalized spiro derivatives by modification of the D-ring. The transformation proceeded through conversion of the C-17 carbonyl group into an electron-deficient alkene, followed by either [2+2] or [4+2] cycloaddition. The cycloaddition reactions were successful for alkylidene malononitriles and 2-cyano acrylates. Application of high pressure (15 kbar) was essential for good conversions due to the high steric hindrance on position C-17. The cycloadducts formed from the reaction of 2-cyano acrylates and Danishefsky's diene have high potential for further functionalization.

Introduction

The modification of natural products to discover new drugs remains an important area of research.[1] In this approach, the natural product (or part of it) is used as a privileged template for recognition by receptor molecules, while the modification can lead to improved or entirely new bioactivity.[2] Among the surfeit of bioactive natural products, steroids are an attractive starting point. Numerous existing drugs are steroidal derivatives that exert a wide variety of biological activities, such as agonistic or antagonistic effects on estrogen, androgen, progestin and corticoid receptors, and inhibition of steroidogenic enzymes.[3] A plethora of interesting examples of steroid modification have been reported,[1c,4] such as the conversion of cholic acid into an orthogonally protected triamino steroid,[5] and the copper-catalyzed cyclization of steroidal acylaminoacetylenes.[6] The latter spiro products showed an improved ratio of antiprogestational over antiglucocorticoid activity as compared to its acyclic counterpart mifepristone.[7]

In previous research, we developed a straightforward approach to the synthesis of compound libraries containing conformationally restrained arylethylamine moieties,[8] which are privileged elements in drugs acting on the central nervous system. In this work, we aimed to apply this newly developed methodology to steroids. Acetyl-protected dehydroepiandrosterone (**1**, DHEA), a biologically active,[9] commercially available steroid containing a C-17 ketone functionality, was chosen as the starting material. The steroid structure acts as a biological directing group for protein-binding ligands, while derivatization of the ketone at C-17 may act as a trigger for new activity. Retrosynthetically, starting from the anticipated steroid derivatives **4**, the amino group could be derived from compounds **3**, possessing a masked amino function such as nitro and cyano, by reduction. Cycloaddition should take place to generate these compounds from the corresponding electron-deficient alkenes **2**, which, in turn, could be derived from DHEA (**1**) through Knoevenagel condensation with active methylene compounds (Scheme 1).



Scheme 1. Sequence of reactions for derivatizing bioactive compounds.

At the outset of our synthetic attempts it was recognized that steric hindrance from the C-ring and the methyl group (C-18) at the C–D ring junction impose a reduction of reactivity of electron-deficient alkenes derived from DHEA. However, knowing that high pressure can overcome steric hindrance,[10] we were prompted by the synthetic challenge to functionalize the D-ring of DHEA through a high-pressure-promoted cycloaddition reaction.

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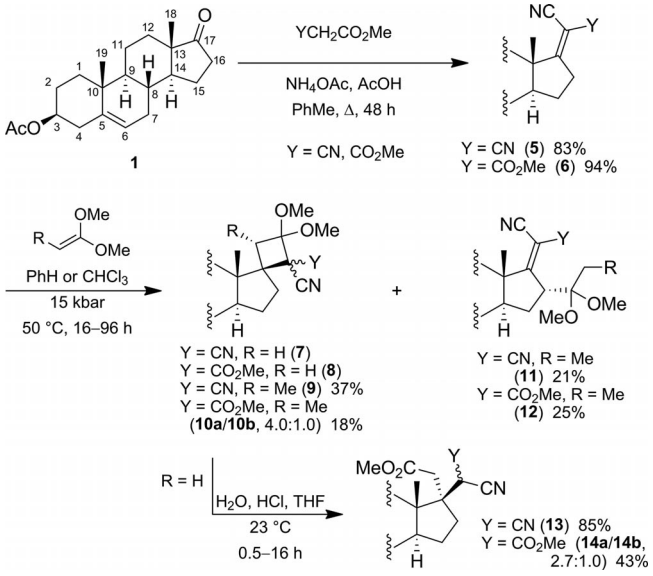
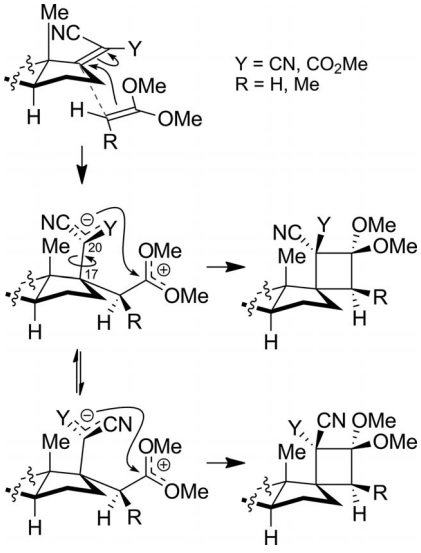
Results and Discussion

Synthesis of the DHEA derivatives commenced with Knoevenagel condensation[11] of an active methylene compound and DHEA (**1**). Treatment of compound **1** with malononitrile or methyl 2-cyanoacetate with ammonium acetate as catalyst in a mixture of acetic acid/toluene gave tetrasubstituted alkenes **5** and **6**, respectively, in high yields (Scheme 2). The Knoevenagel reaction of methyl 2-cyanoacetate is known to selectively form the major products having the nitrile *cis* with respect to the bulkier group of the original ketone.[12] In this case, only the isomers depicted in Scheme 2 were formed. The reaction was also performed with methyl 2-nitroacetate, but once the corresponding product was formed, the alkene isomerized to the β,γ-position, probably due to steric congestion of the tetrasubstituted alkene.[13] The unsuitability of the latter product for the intended cycloaddition reactions led us to abandon the use of nitroacetates.



Scheme 2. Knoevenagel condensation of DHEA (**1**) and subsequent [2+2] cycloaddition.

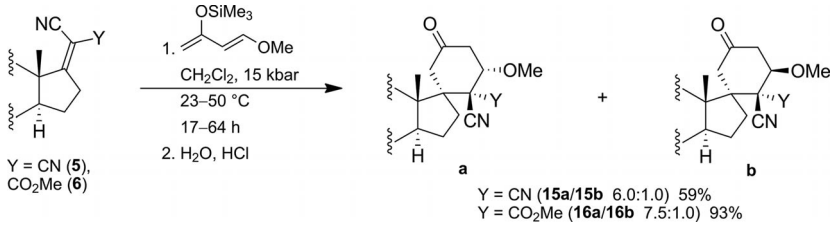
Cyano acrylic derivatives **5** and **6** were used to explore [2+2] and [4+2] cycloaddition reactions towards new steroid derivatives with a more complex hydrocarbon framework. Initial studies on cycloaddition reactions of electron-deficient alkenes **5** and **6** showed that only doubly activated alkenes and dienes under high-pressure conditions yielded cycloadducts. The reactions of compounds **5** and **6** with ethoxyethene and *tert*-butoxyethene were unsuccessful. However, when **5** and **6** were treated with more electron-rich olefins 1,1-dimethoxyethene (in benzene) and 1,1-dimethoxyprop-1-ene (in chloroform) under 15 kbar pressure, products **7**–**12** were formed (Scheme 2). Most likely, the formation of these cyclobutanes proceeds in a stepwise manner via a zwitterionic intermediate.[14] The formation of cyclobutanes **7**–**10** can be explained by reaction of the electron-rich alkene from the bottom face of electron-deficient alkenes **5** and **6** (because of the β-methyl group on C-13),[15] with the R group approaching away from the steroid (Scheme 3). That is, the formation of the first C–C bond is completely diastereoselective and takes place from the *Re* face of C-2 in the case of 1,1-dimethoxyprop-1-ene. The zwitterionic intermediate can rotate through C-17–C-20 and then cyclize on either face of the anion, forming products **7**–**10**. This reaction sequence would explain the formation of a single product and two products in the case of Y = CN and CO_2Me, respectively, when 1,1-dimethoxyprop-1-ene was used.[16] The cycloadducts **7** and **8** partially hydrolyzed to the open products **13** and **14a**,**b** during purification by silica gel column chromatography. In this manner, the crude cycloaddition mixtures were treated directly with 1 N HCl to give full conversion of the hydrolyzed products **13** and an inseparable mixture of compounds **14a** and **14b** (2.7:1.0).[17] Compounds **9** and **10a**,**b** were purified by column chromatography without partial hydrolysis. Interestingly, these compounds were also unreactive to concentrated HCl.[18]



Scheme 3. Reaction sequence for the formation of products **7**–**10**.

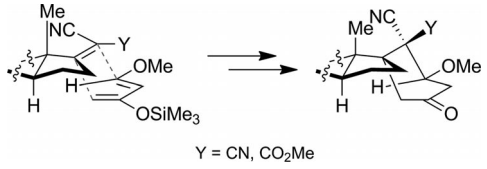
On the other hand, the formation of products **11** and **12** could be explained by an ene reaction of 1,1-dimethoxyprop-1-ene and the β,γ-unsaturated isomers of **5** and **6**. Traces of HCl present in chloroform could probably aid in the isomerization of **5** and **6**. The stereochemistry at C-16 of products **11** and **12** was confirmed by NOESY experiments.

To successfully perform the [4+2] cycloaddition reactions, doubly activated dienes were required. The reactions of compounds **5** and **6** with 2,3-dimethylbuta-1,3-diene and 2-methoxybuta-1,3-diene resulted in no observable cycloadducts. Nevertheless, the Diels–Alder reaction of 1-methoxy-3-[(trimethylsilyl)oxy]buta-1,3-diene (Danishefsky's diene) and electron-deficient alkenes **5** and **6** in dichloromethane under a 15 kbar pressure yielded cycloadducts **15a**,**b** and **16a**,**b**, respectively, after aqueous hydrolysis (Scheme 4). In both cases, a mixture of two isomers was obtained (out of the four possible stereoisomers: *endo*/*exo* and top/bottom approaches). The major isomer was formed by reaction of



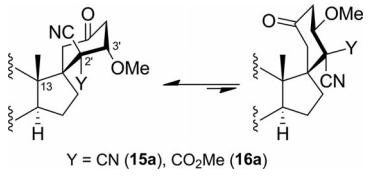
Scheme 4. High-pressure Diels–Alder reaction of cyano acrylic derivatives **5** and **6** with Danishesfky's diene.

the diene from the bottom face of compounds **5** and **6** (this statement was confirmed by a NOESY NMR experiment performed with the final product **20**; see the Supporting Information) approaching away from the steroid (*endo* approach of Y) as depicted in Scheme 5. Thus, the major isomer presents the methoxy group *cis* with respect to the Y group (CN or CO_2Me).



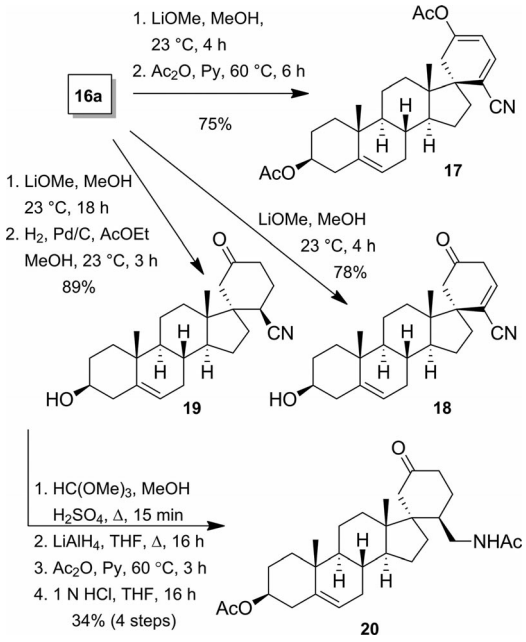
Scheme 5. Major approach for the [4+2] cycloaddition of compounds **5** and **6** and the Danishesfky's diene.

The stereochemistry of the products was confirmed by NMR spectroscopy. The major products of both reactions, compounds **15a** and **16a**, presented a triplet (J = 4.1 Hz and J = 6.4 Hz, respectively) in the ^1H NMR spectra, assigned to the signals of the protons on C-3′. The minor products, compounds **15b** and **16b** on the other hand, presented a doublet of doublets (J = 11.9, 5.0 Hz in both cases) for the same protons. This can be explained by the preferential conformation that compounds **15a** and **16a** adopt (Scheme 6).[19]



Scheme 6. Conformational analysis of cycloadducts **15a** and **16a**.

Due to the higher chemical versatility of esters compared to nitriles, it was decided to proceed with compound **16** for further functional group modification in the quest for new, highly functionalized steroids. In this way, the sacrificial methyl ester required for the cycloadditions to take place was eliminated by reaction with lithium methoxide in methanol. Thus, compound **16a** gave rise to dienecarbonitrile **17** and keto nitrile **18** in good yields (Scheme 7) depending on the procedure used for quenching the reaction mixture (acetic anhydride in pyridine or aqueous work-up, respectively). The elimination reaction of CO_2Me and OMe may follow an E1cB mechanism with CO_2Me as the electrofuge (this could be considered a retro-Claisen condensation) and OMe as the nucleofuge.[20]



Scheme 7. Derivatization of compound **16a**.

Keto nitrile **18** was further derivatized to the protected amino ketone **20** (Scheme 7). Reduction of the less hindered alkene (without purification of compound **18** from **16a**) with a palladium catalyst under a hydrogen atmosphere afforded keto nitrile **19** stereospecifically. Reduction of the nitrile to the primary amine was accomplished with $LiAlH_4$ in tetrahydrofuran (THF) with previous protection of the ketone under standard conditions. Thus, keto nitrile **19** reacted with trimethyl orthoformate in methanol with catalytic sulfuric acid to yield the protected ketone as a dimethyl acetal. Subsequent reduction of the nitrile, followed by acetylation (Ac_2O, pyridine) and deprotection of the ketone afforded the protected amino ketone **20**. The latter is a steroid derivative with potential activity in any of the roles of dehydroepiandrosterone. Furthermore, compound **20** presents four important functional groups that could be used for further derivatization and are hence amenable to combinatorial functionalization.

Conclusions

In summary, the synthesis of new steroid derivatives with complex hydrocarbon frameworks is presented. We have developed an efficient method for the derivatization of C-17 of dehydroepiandrosterone 3-acetate by a Knoevenagel condensation followed by [2+2] or [4+2] cycloaddition. This derivatization includes the formation of a new cycle in a spiro fashion and, in the case of the [4+2] cycloaddition, eventually yields a highly functionalized steroid derivative that could be further derivatized.

Experimental Section

General Methods: Commercially available chemicals were used without purification. Solvents were distilled from appropriate drying agents prior to use and stored under nitrogen. Reactions were followed, and R_F values were obtained, by using thin-layer chromatography (TLC) on silica gel-coated plates (Merck 60 F254). Detection was performed with UV light and by charring at ca. 150 °C after dipping the TLC plate into a basic aqueous solution of $KMnO_4$. 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 DMX 300 (300 MHz) or a Varian 400 (400 MHz) spectrometer in $CDCl_3$ solutions. Chemical shifts are given in parts per million (ppm) with respect to tetramethylsilane (TMS) as internal standard. Coupling constants are reported as *J* values in Hertz (Hz). Elemental analyses were carried out with a Carlo Erba Instruments CHNS-O EA 1108 element analyzer. Low-resolution mass spectra were recorded with a MAT900 (EI and FAB). Melting points were measured with a Reichert Thermopan microscope. IR spectra were recorded with a Bruker Tensor 27 FTIR spectrometer.

(3*S*)-17-(Dicyanomethylidene)androst-5-en-3-yl Acetate (5): A round-bottomed flask fitted with a Dean–Stark apparatus, a reflux condenser, and a drying tube containing calcium chloride was charged with a solution of DHEA (**1**; 4.00 g, 12.12 mmol), $CH_2(CN)_2$ (1.60 g, 24.24 mmol), and NH_4OAc (1.87 g, 24.24 mmol) in AcOH (16 mL) and toluene (60 mL). The resulting mixture was stirred and heated to reflux for 48 h, then concentrated in vacuo. The residue of the reaction was dissolved in CH_2Cl_2 and washed sequentially with 0.5 N $KHSO_4$ and a saturated solution of $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (heptane/EtOAc, 7:3) gave **5** (3.81 g, 10.06 mmol, 83%), m.p. 190–191 °C (*i*Pr_2O). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.38 (d, *J* = 5.1 Hz, 1 H, 6-H), 4.66–4.54 (m, 1 H, 3-H), 3.00–2.87 (m, 1 H, 16-H), 2.80–2.64 (m, 1 H, 16-H), 2.55–2.41 (m, 1 H), 2.41–2.24 (m, 2 H), 2.15–2.00 (m, 1 H), 2.04 (s, 3 H, CH_3CO), 1.97–0.97 (m, 16 H), 1.05 (s, 6 H, 18-CH_3 and 19-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.6 (17-C), 170.0 (CO_2), 139.6 (5-C), 121.3 (6-C), 112.0 (CN), 111.0 (CN), 79.6 [=C(CN)$_2$], 73.5 (3-C), 55.2 (14-C), 49.4, 48.9, 38.1, 36.9, 36.6, 34.8, 37.0, 31.49, 31.46, 27.7, 23.7, 21.5, 20.9, 19.4 (19-C), 16.4 (18-C) ppm. $C_{24}H_{30}N_2O_2$ (378.51): calcd. C 76.16, H 7.99, N 7.40; found C 76.34, H 7.88, N 7.26. MS (FAB+): *m*/*z* (%) = 379 (2) [M + 1]$^+$, 319 (79) [M – AcO]$^+$.

Methyl (*E*)-2-[(3*S*)-3-Acetoxyandrost-5-en-17-ylidene]-2-cyanoacetate (6): A round-bottomed flask fitted with a Dean–Stark apparatus, a reflux condenser, and a drying tube containing calcium chloride, was charged with a solution of DHEA (**1**; 2.42 g, 7.33 mmol), $NCCH_2CO_2Me$ (1.46 g, 11.50 mmol), and NH_4OAc (1.14 g, 14.79 mmol) in AcOH (10 mL) and toluene (40 mL). The resulting reaction mixture was stirred and heated to reflux for 48 h, then concentrated in vacuo. The residue of the reaction was dissolved in CH_2Cl_2 and washed sequentially with 0.5 N $KHSO_4$ and a saturated solution of $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (heptane/EtOAc, 2:1) gave **6** (2.83 g, 6.87 mmol, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.39 (d, *J* = 4.8 Hz, 1 H, 6-H), 4.67–4.54 (m, 1 H, 3-H), 3.81 (s, 3 H, OCH_3), 3.24–3.10 (m, 1 H), 3.01–2.76 (m, 2 H), 2.41–2.24 (m, 2 H), 2.15–1.99 (m, 1 H), 2.04 (s, 3 H, CH_3CO), 1.94–1.81 (m, 3 H), 1.80–1.44 (m, 6 H), 1.42–0.97 (m, 4 H), 1.05 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.2 (17-C), 170.5 (CO_2), 163.1 (CO_2), 139.9 (5-C), 121.8 (6 C), 115.0 (CN), 98.3 (=CCN), 73.7 (3-C), 54.8, 52.4, 49.5, 48.8, 38.0, 36.8, 36.5, 34.8, 34.0, 31.6, 31.3, 27.6, 23.9, 21.4, 21.0, 19.2 (19-C), 15.8 (18-C) ppm. $C_{25}H_{33}NO_4$ (411.54): calcd. C 72.96, H 8.08, N 3.40; found C 72.98, H 8.21, N 3.54.

(3*S*,4′*S*,17*R*)-2′,2′-Dicyano-3′,3′-dimethoxy-4′-methylspiro[androstane-17,1′-cyclobutan]-5-en-3-yl Acetate (9) and (3*S*,16*R*)-17-(Dicyanomethylidene)-16-(1,1-dimethoxypropyl)androst-5-en-3-yl Acetate (11): A flexible 7.5 mL PTFE tube was charged with **5** (900 mg, 2.38 mmol), 1,1-dimethoxyprop-1-ene (720 mg, 7.06 mmol), and enough $CHCl_3$ to fill the tube up. The reaction mixture was set at 15 kbar and 50 °C for 72 h. After this time, the reaction mixture was concentrated in vacuo and heptane was added to the residue. After vigorous stirring, crystals were formed, which were collected by filtration. Further purification of the crystals by column chromatography on silica gel (heptane/EtOAc, 9:1) gave **9** (425 mg, 0.88 mmol, 37%) and **11** (235 mg, 0.49 mmol, 21%).

Compound 9: M.p. 177–178 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.35 (d, *J* = 4.3 Hz, 1 H, 6-H), 4.65–4.52 (m, 1 H, 3-H), 3.49 (s, 3 H, OCH_3), 3.36 (s, 3 H, OCH_3), 2.98 (q, *J* = 7.0 Hz, 1 H, 4′-H), 2.36–2.06 (m, 5 H), 2.03 (s, 3 H, CH_3CO), 2.04–1.92 (m, 1 H), 1.92–1.80 (m, 2 H), 1.72–1.44 (m, 6 H), 1.40–1.23 (m, 2 H), 1.10 (d, *J* = 7.0 Hz, 3 H, 4′-CH_3), 1.19–0.87 (m, 3 H), 1.03 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2 (CO_2), 139.6 (5-C), 121.7 (6-C), 113.6 (CN), 112.6 (CN), 100.5 (OCO), 73.8 (3-C), 54.7, 54.0, 51.4, 51.2, 49.7, 46.1, 43.4, 42.6, 38.2, 37.1, 36.7, 32.9, 32.7, 31.9, 28.3, 27.8, 23.9, 21.6, 20.7, 19.5 (19-C), 14.1 (18-C), 11.7 (4′-CH_3) ppm. $C_{29}H_{40}N_2O_4$ (480.65): calcd. C 72.47, H 8.39, N 5.83; found C 72.36, H 8.44, N 5.65. MS (FAB+): *m*/*z* (%) = 481 (8) [M + 1]$^+$, 449 (14) [M – MeO]$^+$, 421 (9) [M – AcO]$^+$, 389 (6) [M – MeOH – AcO]$^+$.

Compound 11: M.p. 173–174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.38 (d, *J* = 5.4 Hz, 1 H, 6-H), 4.65–4.52 (m, 1 H, 3-H), 3.42 (d, *J* = 8.1 Hz, 1 H, 16-H), 3.21 (s, 3 H, OCH_3), 3.16 (s, 3 H, OCH_3), 2.79–2.74 (m, 1 H), 2.40–2.24 (m, 2 H), 2.11–2.03 (m, 1 H), 2.03 (s, 3 H, CH_3CO), 1.94–1.79 (m, 3 H), 1.79–1.38 (m, 10 H), 1.20–1.02 (m, 2 H), 1.11 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 0.81 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.4 (17-C), 170.5 (CO_2), 140.0 (5-C), 121.6 (6-C), 113.6 (CN), 112.9 (CN), 106.1 (OCO), 83.5 [=C(CN)$_2$], 73.6 (3-C), 53.0, 50.7, 50.6, 49.5, 48.3, 48.5, 38.0, 36.8, 36.6, 34.1, 31.6, 31.1, 27.6, 27.5, 21.4, 20.9, 19.2, 19.0, 9.0 (CH_2CH_3) ppm.

Methyl (2′*S*,3*S*,4′*S*,17*R*)-3-Acetoxy-2′-cyano-3′,3′-dimethoxy-4′-methylspiro[androstane-17,1′-cyclobutan]-5-ene-2′-carboxylate (10a), Methyl (2′*R*,3*S*,4′*S*,17*R*)-3-Acetoxy-2′-cyano-3′,3′-dimethoxy-4′-methylspiro[androstane-17,1′-cyclobutan]-5-ene-2′-carboxylate (10b) and Methyl (*E*)-2-[(3*S*,16*R*)-3-Acetoxy-16-(1,1-dimethoxypropyl)androst-5-en-17-ylidene]-2-cyanoacetate (12): A flexible 7.5 mL PTFE tube was charged with compound **6** (750 mg,

1.82 mmol), 1,1-dimethoxyprop-1-ene (400 mg, 3.92 mmol), and enough $CHCl_3$ to fill the tube up. The reaction mixture was set at 15 kbar and 50 °C for 96 h. After this time, the reaction mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel (heptane/EtOAc, 5:1) to give a 4.0:1.0 mixture of compounds **10a** and **10b** (173 mg, 0.34 mmol, 18%), and compound **12** (236 mg, 0.46 mmol, 25%).

Compounds 10a and 10b: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.36–5.31 (m, 1 H, 6-H), 4.64–4.51 (m, 1 H, 3-H), 3.79 and 3.77 (2 × s, 3 H, OCH_3), 3.46 and 3.32 (2 × s, 3 H, OCH_3), 3.40 and 2.82 (2 × q, J = 6.9 and 7.2 Hz, 1 H, 4′-H), 3.20 and 3.18 (2 × s, 3 H, OCH_3), 2.33–2.20 (m, 4 H), 2.10–1.92 (m, 2 H), 2.01 (s, 3 H, CH_3CO), 1.92–1.80 (m, 2 H), 1.68–0.80 (m, 14 H), 0.98 (s, 3 H, 19-CH_3), 0.99 and 0.69 (2 × s, 3 H, 18-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5 (CO_2), 165.8 (CO_2), 165.2 (CO_2), 139.8 (5-C), 139.7 (5-C), 122.2 (6-C), 122.1 (6-C), 117.4 (CN), 116.6 (CN), 101.2 (OCO), 100.4 (OCO), 73.8 (3-C), 59.2, 56.0, 55.0, 53.0, 52.8, 52.3, 50.9, 50.6, 49.6, 45.8, 41.6, 38.0, 36.9, 36.53, 36.46, 33.9, 32.6, 32.5, 31.8, 30.0, 27.7, 23.9, 23.7, 21.4, 20.9, 20.7, 19.2 (19-C), 14.4 (18-C), 11.5 (4′-CH_3), 11.4 (4′-CH_3) ppm.

Compound 12: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.40–5.36 (m, 1 H, 6-H), 4.64–4.53 (m, 1 H, 3-H), 3.92 (d, J = 8.3 Hz, 1 H, 16-H), 3.79 (s, 3 H, OCH_3), 3.12 (s, 3 H, OCH_3), 3.08 (s, 3 H, OCH_3), 2.82–2.78 (m, 1 H), 2.40–2.25 (m, 2 H), 2.11–2.03 (m, 1 H), 2.04 (s, 3 H, CH_3CO), 1.94–1.79 (m, 3 H), 1.79–1.38 (m, 10 H), 1.20–1.02 (m, 2 H), 1.09 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 0.80 (t, J = 7.6 Hz, 3 H, CH_2CH_3) ppm.

Methyl 2-[(3*S*,17*S*)-3-Acetoxy-17-(dicyanomethyl)androst-5-en-17-yl]acetate (13): A flexible 7.5 mL PTFE tube was charged with **5** (500 mg, 1.32 mmol), 1,1-dimethoxyethene (300 mg, 3.40 mmol), and enough benzene to fill the tube up. The reaction mixture was set at 15 kbar and 50 °C for 16 h. After this time, the reaction mixture was concentrated in vacuo and the residue was dissolved in THF (20 mL) and 10% HCl (6 mL) was added. The reaction mixture was stirred at room temperature for 30 min and then THF was removed under reduced pressure. The resulting aqueous solution was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (heptane/EtOAc, 5:1) gave **13** (510 mg, 1.13 mmol, 85%), m.p. 201–204 °C (heptane/EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.37 (d, J = 5.1 Hz, 1 H, 6-H), 4.87 [s, 1 H, $CH(CN_2)$], 4.66–4.53 (m, 1 H, 3-H), 3.74 (s, 3 H, OCH_3), 2.65 (ABq, $\Delta\delta_{AB}$ = 0.03 ppm, J_{AB} = 15.3 Hz, 2 H, CH_2CO_2), 2.39–2.24 (m, 2 H), 2.03 (s, 3 H, CH_3CO), 2.07–1.72 (m, 7 H), 1.69–1.25 (m, 8 H), 1.21–0.84 (m, 2 H), 1.08 (s, 3 H, CH_3), 1.04 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0 (CO_2), 170.5 (CO_2), 139.8 (5-C), 121.8 (6-C), 112.9 (CN), 112.6 (CN), 73.6 (3-C), 52.1, 51.5, 51.0, 49.4, 47.4, 37.9, 36.9, 36.6, 32.4, 31.9, 31.7, 27.6, 24.3, 21.4, 20.5, 19.2 (19-C), 15.6 (18-C) ppm. $C_{27}H_{36}N_2O_4$ (452.59): calcd. C 71.65, H 8.02, N 6.19; found C 71.56, H 7.97, N 6.06.

Dimethyl (2*R*)-2-Cyano-2,2′-[(3*S*,17*S*)-3-acetoxyandrost-5-ene-17-diyl]diacetate (14a) and Dimethyl (2*S*)-2-Cyano-2,2′-[(3*S*,17*S*)-3-acetoxyandrost-5-ene-17-diyl]diacetate (14b): A flexible 15 mL PTFE tube was charged with **6** (750 mg, 1.82 mmol), 1,1-dimethoxyethene (413 mg, 4.69 mmol), and enough benzene to fill the tube up. The reaction mixture was set at 15 kbar and 50 °C for 64 h, then concentrated in vacuo. The residue was dissolved in THF (20 mL) and 1 N HCl (6 mL) was added. The reaction mixture was stirred at room temperature for 16 h and then THF was removed under reduced pressure. The resulting aqueous solution was extracted with CH_2Cl_2 and the combined organic layers were washed with a solution of $NaHCO_3$, then dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (heptane/EtOAc, 7:1) gave **6** (200 mg, 0.48 mmol) and a 2.7:1.0 mixture of compounds **14a** and **14b** (377 mg, 0.78 mmol; 43%, 58% based on recovered starting material). The assignment of the structure to the numbers **14a** and **14b** was done arbitrarily. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.36 (d, J = 5.1 Hz, 1 H, 6-H), 4.66–4.52 (m, 1 H, 3-H), 4.13 and 4.08 (2 × s, 1 H, CHCN), 3.81 and 3.78 (2 × s, 3 H, OCH_3), 3.70 and 3.65 (2 × s, 3 H, OCH_3), 2.71 and 2.69 (2 × ABq, $\Delta\delta_{AB}$ = 0.24 and 0.23 ppm, J_{AB} = 15.3 and 14.1 Hz, 2 H, CH_2CO_2), 2.36–2.12 (m, 3 H), 2.03 (s, 3 H, CH_3CO), 2.08–1.92 (m, 2 H), 1.91–0.90 (m, 14 H), 1.03 and 1.02 (2 × s, 3 H, CH_3), 0.98 and 0.93 (2 × s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5 (CO_2), 170.5 (CO_2), 166.5 (CO_2), 165.9 (CO_2), 139.7 (5-C), 122.0 (6-C), 116.5 (CN), 73.7 (3-C), 53.2, 52.0, 51.9, 51.8, 51.6, 51.1, 50.9, 49.6, 49.5, 47.8, 47.1, 43.2, 43.0, 38.0, 36.92, 36.86, 36.6, 32.7, 32.6, 32.0, 31.9, 31.7, 31.5, 27.6, 24.3, 21.4, 20.7, 20.6, 19.2, 15.2 ppm. $C_{28}H_{39}NO_6$ (485.62): calcd. C 69.25, H 8.09, N 2.88; found C 69.37, H 8.12, N 2.89.

(3*S*,3′*S*,17*R*)-2′,2′-Dicyano-3′-methoxy-5′-oxospiro[androstane-17,1′-cyclohexan]-5-en-3-yl Acetate (15a) and (3*S*,3′*R*,17*R*)-2′,2′-Dicyano-3′-methoxy-5′-oxospiro[androstane-17,1′-cyclohexan]-5-en-3-yl Acetate (15b): A flexible 7.5 mL PTFE tube was charged with **5** (500 mg, 1.32 mmol), 1-methoxy-3-[(trimethylsilyl)oxy]buta-1,3-diene (455 mg, 2.64 mmol), and enough CH_2Cl_2 to fill the tube up. The reaction mixture was set at 15 kbar and 23 °C for 17 h, then concentrated in vacuo. The residue was dissolved in THF (16 mL) and 1 N HCl (4 mL) was added. The reaction mixture was stirred at room temperature for 1 h and then THF was removed under reduced pressure. The resulting aqueous solution was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (heptane/EtOAc, 4:1) yielded a 6.0:1.0 mixture of compounds **15a** and **15b** (370 mg, 0.77 mmol, 59%).

Compound 15a: After recrystallization: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.34 (d, J = 4.9 Hz, 1 H, 6-H), 4.65–4.49 (m, 1 H, 3-H), 4.23 (t, J = 4.1 Hz, 1 H, 3′-H), 3.50 (s, 3 H, OCH_3), 2.95 (dd, J = 15.0, 3.9 Hz, 1 H, 4′-H), 2.78 (d, J = 14.4 Hz, 1 H, 6′-H), 2.69 (ddd, J = 15.0, 4.2, 1.6 Hz, 1 H, 4′-H), 2.45 (dd, J = 14.4, 1.6 Hz, 1 H, 6′-H), 2.37–2.22 (m, 3 H), 2.03 (s, 3 H, CH_3CO), 2.03–1.92 (m, 2 H), 1.91–1.47 (m, 9 H), 1.44–1.27 (m, 3 H), 1.23 (s, 3 H, 18-CH_3), 1.19–1.05 (m, 1 H), 1.04 (s, 3 H, 19-CH_3), 1.00–0.88 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.5 (5′-C), 170.1 (CO_2), 139.5 (5-C), 121.7 (6-C), 114.8 (CN), 114.1 (CN), 83.2 (3′-C), 73.6 (3-C), 59.4, 56.1, 50.6, 49.4, 48.8, 46.3, 44.0, 41.7, 38.1, 37.0, 36.7, 32.7, 32.6, 32.3, 32.0, 27.8, 24.5, 21.6, 20.8, 19.4 (19-C), 15.9 (18-C) ppm. $C_{29}H_{38}N_2O_4$ (478.63): calcd. C 72.77, H 8.00, N 5.85; found C 72.55, H 7.90, N 5.67. MS (EI+): m/z (%) = 418 (100) [M – AcOH]$^+$, 386 (13) [M – MeOH – AcOH]$^+$.

Methyl (2′*S*,3*S*,3′*S*,17*R*)-3-Acetoxy-2′-cyano-3′-methoxy-5′-oxospiro[androstane-17,1′-cyclohexan]-5-ene-2′-carboxylate (16a) and Methyl (2′*S*,3*S*,3′*R*,17*R*)-3-Acetoxy-2′-cyano-3′-methoxy-5′-oxospiro[androstane-17,1′-cyclohexan]-5-ene-2′-carboxylate (16b): A flexible 15 mL PTFE tube was charged with **6** (2.00 g, 4.86 mmol), 1-methoxy-3-[(trimethylsilyl)oxy]buta-1,3-diene (1.80 g, 10.46 mmol), and enough CH_2Cl_2 to fill the tube up. The reaction mixture was set at 15 kbar and 50 °C for 64 h, then concentrated in vacuo. The residue was dissolved in THF (30 mL) and 1 N HCl (7 mL) was added. The reaction mixture was stirred at room temperature for 1.5 h and then THF was removed under reduced pressure. The resulting aqueous solution was extracted with CH_2Cl_2,

then the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (heptane/EtOAc, 4:1→0:1) gave **16a** (2.03 g, 3.96 mmol, 82%) and **16b** (282 mg, 0.55 mmol, 11%).

Compound 16a: M.p. 243–248 °C (iPr_2O/MeOH, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.36 (d, J = 5.1 Hz, 1 H, 6-H), 4.66–4.53 (m, 1 H, 3-H), 4.12 (t, J = 6.4 Hz, 1 H, 3′-H), 3.84 (s, 3 H, OCH_3), 3.42 (s, 3 H, OCH_3), 3.03–2.73 (m, 4 H), 2.39–2.23 (m, 3 H), 2.03 (s, 3 H, CH_3CO), 2.03–1.91 (m, 1 H), 1.91–1.46 (m, 9 H), 1.43–1.24 (m, 4 H), 1.14 (s, 3 H, CH_3), 1.18–1.05 (m, 1 H), 1.03 (s, 3 H, CH_3), 0.99–0.88 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.9 (5′-C), 170.4 (CO_2), 166.7 (CO_2), 139.6 (5-C), 122.0 (6-C), 119.1 (CN), 80.2 (3′-C), 73.7 (3-C), 58.6, 55.1, 53.9, 53.6, 51.2, 49.3, 48.6, 48.0, 42.3, 38.0, 36.9, 36.6, 33.8, 32.8, 32.04, 31.95, 27.6, 24.4, 21.4, 20.7, 19.2 (19-C), 15.7 (18-C) ppm. $C_{30}H_{41}NO_6$ (511.66): calcd. C 70.42, H 8.08, N 2.74; found C 70.24, H 7.89, N 2.87.

Compound 16b: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.36 (d, J = 5.1 Hz, 1 H, 6-H), 4.65–4.53 (m, 1 H, 3-H), 3.87 (dd, J = 11.9, 5.0 Hz, 1 H, 3′-H), 3.84 (s, 3 H, OCH_3), 3.31 (s, 3 H, OCH_3), 2.98–2.76 (m, 3 H), 2.72 (dd, J = 13.9, 12.2 Hz, 1 H, 4′-H), 2.45–2.10 (m, 4 H), 2.04 (s, 3 H, CH_3CO), 2.03–1.77 (m, 3 H), 1.75–1.07 (m, 11 H), 1.02 (s, 3 H, CH_3), 0.91–0.87 (m, 1 H), 0.90 (s, 3 H, CH_3) ppm.

(3*S*,17*R*)-6′-Cyanospiro[androstane-17,1′-cyclohexane]-3′,5,5′-triene-3,3′-diyl Diacetate (17): Compound **16a** (500 mg, 0.98 mmol) was added to a methanolic LiOMe solution [Li (41 mg, 5.90 mmol) in MeOH (50 mL)]. The resulting reaction mixture was stirred at room temperature for 4 h, then 1 N HCl (12 mL) was added and the volume of the mixture was reduced to one-sixth of its initial value. The resulting aqueous solution was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting residue was dissolved in Ac_2O (30 mL) and pyridine (8 drops) was added. The reaction mixture was stirred at 60 °C for 6 h, then the solvent was evaporated to dryness under high vacuum. Purification by column chromatography on silica gel (heptane/EtOAc, 8:1) gave **17** (340 mg, 0.73 mmol, 75%), m.p. 175–177 °C (from heptane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.80 (d, J = 6.0 Hz, 1 H, 5′-H), 5.80 (dd, J = 6.0, 2.8 Hz, 1 H, 4′-H), 5.38–5.35 (m, 1 H, 6-H), 4.65–4.52 (m, 1 H, 3-H), 2.65 (dd, J = 17.9, 2.8 Hz, 1 H, 2′-H), 2.63–2.54 (m, 1 H), 2.52 (d, J = 17.9 Hz, 1 H, 2′-H), 2.36–2.25 (m, 2 H), 2.20 (s, 3 H, CH_3CO), 2.03 (s, 3 H, CH_3CO), 2.09–1.97 (m, 1 H), 1.91–1.80 (m, 2 H), 1.78–1.06 (m, 12 H), 1.01 (s, 3 H, 19-CH_3), 1.02–0.92 (m, 1 H), 0.86 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6 (CO_2), 167.8 (CO_2), 154.6 (3′-C), 139.7 (5-C and 5′-C), 122.1 (6-C), 120.3 (CN), 113.0 (6′-C), 109.0 (4′-C), 73.8 (3-C), 49.7, 49.6, 48.9, 38.1, 38.0, 37.7, 37.0, 36.6, 34.0, 32.1, 32.0, 27.7, 24.4, 21.4, 21.3, 20.7, 19.2 (19-C), 14.7 (18-C) ppm. $C_{29}H_{37}NO_4$ (463.62): calcd. C 75.13, H 8.04, N 3.02; found C 74.96, H 8.00, N 3.06.

(3*S*,17*R*)-3-Hydroxy-5′-oxospiro[androstane-17,1′-cyclohexane]-2′,5-diene-2′-carbonitrile (18): Compound **16a** (300 mg, 0.59 mmol) was added to a methanolic LiOMe solution [Li (27 mg, 3.89 mmol) in MeOH (35 mL)]. The resulting reaction mixture was stirred at room temperature for 4 h, then 1 N HCl (7 mL) was added and the volume of the mixture was reduced to one-sixth of its initial value. The resulting aqueous solution was extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (heptane/EtOAc, 3:2) gave **18** (175 mg, 0.46 mmol, 78%), m.p. 265–268 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.85 (t, J = 4.0 Hz, 1 H, 3′-H), 5.35–5.31 (m, 1 H, 6-H), 3.57–3.45 (m, 1 H, 3-H), 3.02 (d, J = 4.0 Hz, 2 H, 4′-CH_2), 2.94 (d, J = 16.3 Hz, 1 H, 6′-H), 2.65–2.54 (m, 1 H), 2.35–2.19 (m, 2 H), 2.13 (d, J = 16.3 Hz, 1 H, 6′-H), 2.08–1.96 (m, 1 H), 1.88–1.75 (m, 3 H), 1.69–1.35 (m, 9 H), 1.29–1.20 (m, 2 H), 1.11–1.02 (m, 1 H), 0.99 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 0.99–0.86 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.7 (5′-C), 142.0 (3′-C), 140.7 (5-C), 121.8, 121.1 (6-C), 119.0, 71.6 (3-C), 51.8, 50.5, 50.1, 49.4, 42.1, 37.2, 36.6, 32.7, 32.3, 32.0, 31.5, 24.8, 20.5, 19.3 (19-C), 16.1 (18-C) ppm. $C_{25}H_{33}NO_2$ (379.54): calcd. C 79.11, H 8.76, N 3.69; found C 79.00, H 8.93, N 3.74.

(2′*R*,3*S*,17*S*)-3-Hydroxy-5′-oxospiro[androstane-17,1′-cyclohexan]-5-ene-2′-carbonitrile (19): Compound **16a** (300 mg, 0.59 mmol) was added to a methanolic LiOMe solution [Li (25 mg, 3.60 mmol) in MeOH (30 mL)]. The resulting reaction mixture was stirred at room temperature for 18 h, then 1 N HCl (6 mL) was added and the volume of the mixture was reduced to one-sixth of its initial value. The resulting aqueous solution was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was dissolved in EtOAc/MeOH (1:1, 80 mL) and the tip of a spatula of Pd/C (10 wt.-%) was added. The mixture was stirred at room temperature for 3 h under a hydrogen atmosphere (1 atm). The reaction was filtered and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel (heptane/EtOAc, 3:2) gave **19** (199 mg, 0.52 mmol, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.35–5.31 (m, 1 H, 6-H), 3.58–3.45 (m, 1 H, 3-H), 2.91 (br. s, 1 H, OH), 2.74–2.59 (m, 2 H), 2.43–2.15 (m, 5 H), 2.09 (dt, J = 12.2, 3.3 Hz, 1 H), 2.04–1.78 (m, 4 H), 1.77–1.00 (m, 13 H), 1.02 (s, 3 H, CH_3), 0.98–0.86 (m, 1 H), 0.94 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.7 (5′-C), 140.9 (5-C), 121.0, 120.5, 71.5 (3-C), 52.6, 51.2, 49.6, 45.8, 45.7, 42.1, 37.5, 37.1, 36.4, 32.9, 32.4, 31.9, 31.5, 26.6, 24.1, 20.6, 19.33, 19.28, 14.81, 14.76 ppm. $C_{25}H_{35}NO_2$ (381.56): calcd. C 78.70, H 9.25, N 3.67; found C 78.65, H 9.38, N 3.65, m.p. 245–249 °C. FTIR (neat): $\tilde{\nu}$ = 3460, 2946, 2229, 1709, 1437.

(2′*R*,3*S*,17*S*)-2′-(Acetamidomethyl)-5′-oxospiro[androstane-17,1′-cyclohexan]-5-en-3-yl Acetate (20): A solution of H_2SO_4/MeOH (1:20, 300 μL) was added to a solution of **19** (124 mg, 0.32 mmol) and $HC(OMe)_3$ (2 mL) in MeOH (18 mL). The reaction mixture was stirred and heated to reflux for 15 min, then the solution was neutralized with 1 M NaOH and the volume of the mixture was reduced to one-third of its initial value. The resulting aqueous solution was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was dissolved in anhydrous THF (20 mL) and $LiAlH_4$ (67 mg, 1.76 mmol) was added portionwise. The resulting reaction mixture was stirred and heated to reflux for 16 h, then 0.5 N NaOH (to pH > 10) was added and THF was removed under reduced pressure. The resulting aqueous solution was extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting residue was dissolved in Ac_2O (6 mL) and pyridine (2 drops) was added. The new mixture was stirred at 60 °C for 16 h, then cooled to room temperature and the solvent was evaporated to dryness under high vacuum. The residue was dissolved in THF (5 mL) and 1 N HCl (4 mL) was added. The solvent was removed after stirring the solution at room temperature for 16 h and the resulting residue was dissolved in CH_2Cl_2 and the solution was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (EtOAc) gave **20** (51 mg, 0.11 mmol, 34%), m.p. 284–289 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.66 (br. s, 1 H, NH), 5.35 (d, J = 4.7 Hz, 1 H, 6-H), 4.64–4.52 (m, 1 H, 3-H), 3.66–3.53 (m, 2 H, CH_2N), 2.54 (dt, J = 6.7, 14.6 Hz, 1 H, 4′-H), 2.39 (d, J = 13.8 Hz, 1 H, 6′-H), 2.35–2.24 (m, 2 H, 4-H_2), 2.24–2.13 (m, 2 H), 2.03 (s, 3 H, CH_3CO_2), 2.02 (s, 3 H, CH_3CON), 1.98–1.88 (m, 3 H), 1.88–1.78

(m, 2 H), 1.78–1.60 (m, 3 H), 1.60–1.42 (m, 7 H), 1.40–1.26 (m, 2 H), 1.25–1.05 (m, 2 H), 1.01 (s, 3 H, CH_3, 19-H_3), 0.94 (s, 3 H, CH_3, 18-H_3), 0.95–0.84 (m, 1 H, 9-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.0 (5′-C), 170.6 (CO_2), 170.4 (CON), 139.7 (5-C), 122.5 (6-C), 74.0 (3-C), 53.4 (17-C), 51.7 (14-C), 49.7 (9-C), 45.6 (13-C), 44.9 (6′-C), 41.6 (2′-C), 38.1 (4-C), 37.4 (CH_2N), 37.0 (1-C), 36.8 (4′-C), 36.7 (10-C), 35.5 (16-C), 34.0 (12-C), 32.5 (8-C), 32.1 (7-C), 27.8 (2-C), 24.6 (15-C), 24.1 (3′-C), 23.4 (CH_3CON), 21.6 (CH_3CO_2), 20.9 (11-C), 19.4 (19-C), 13.9 (18-C) ppm. $C_{29}H_{43}NO_4$ (469.66): calcd. C 74.16, H 9.23, N 2.98; found C 74.00, H 9.38, N 3.01.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra for compounds **5**, **6**, **9**, **10a**,**b**, **11**, **13**, **14a**,**b**, **15a**,**b**, **16a**, **17**–**20** are available. Copies of the ^{1}H NMR spectra for compounds **12** and **16b** are also provided.

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