

Electrophile- and Lewis acid-induced nitron formation and 1,3-dipolar cycloaddition reactions in the 13 α - and 13 β -estrone series

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DOI: <http://dx.doi.org/10.3998/ark.5550190.0011.b10>

Abstract

δ -Alkenyl oximes of 13 α -estrone 3-methyl ether undergo intramolecular 1,3-dipolar cycloaddition reactions with BF₃•OEt₂ as catalyst, furnishing isoxazolidines. The reactions of the 13 α - and 13 β -estrone oximes with electrophiles lead to cyclic nitrones in high yields *via* attack of the oxime nitrogen on the intermediate halonium ions. In the intermolecular cycloadditions of 16-halomethyl nitrones to *N*-phenylmaleimide, single condensed aza-D-homo isoxazolidines are formed with high chemo- and stereoselectivity.

Keywords: Steroids, nitrogen heterocycles, cycloaddition, chemoselectivity, stereoselectivity

Introduction

Inter- and intramolecular cycloadditions of nitrones provide the possibility for constructing heterocyclic derivatives of natural products.¹ Nitrones can be generated from oximes, which are ambident nucleophiles, either the N or the O acting as the reactive site, depending on the reaction conditions. It is known that Lewis acids catalyse the cycloadditions of nitrones and olefins.²⁻⁸ Recent *ab initio* calculations demonstrated that the concertedness of nitron cycloadditions to electron-deficient alkenes should depend upon the presence of a Lewis acid catalyst.⁴ The results indicate that the Lewis acid induces the reaction to proceed stepwise. The oxime formed from 16,17-seco-13 β -estrone 17-carboxaldehyde and hydroxylamine hydrochloride undergoes intramolecular 1,3-dipolar cycloaddition with BF₃•OEt₂ as a catalyst to produce a single isoxazolidine.⁹ When *N*-methylhydroxylamine hydrochloride is used for the nitron formation, intramolecular cyclization takes place immediately, furnishing a single stereoisomer in high yield (without a Lewis acid catalyst).

The electrophile-induced cyclization of heteroatom nucleophiles onto an alkene is also a well-known procedure for the synthesis of heterocycles.^{10,11} Grigg *et al.* recently described the halogen- and phenylselenyl halide-induced inter- and intramolecular formation of nitrones from oximes and alkenes.^{12,13} Intermolecular 1,3-dipolar cycloadditions of cyclic nitrones, formed from γ -alkenyl oximes with *N*-methylmaleimide, led to two isoxazolidine stereoisomers and a single oxazine derivative. Nitrones derived from δ -alkenyl oximes reacted in a more selective manner, yielding mixtures of *endo* and *exo* stereoisomers, but reactions with the O atom as the reactive site were not observed. In summary, inter- and intramolecular halogen-induced reactions of oximes with alkenes occurred mainly *via* attack of the oxime nitrogen on the intermediate halonium ions. We recently reported the electrophile-induced cyclization of 13 α - and 13 β -estrone oximes to form cyclic nitrones, and intermolecular 1,3-dipolar cycloadditions of the steroidal nitronium dipoles with *N*-phenylmaleimide (NPM).¹⁴ Additionally, hydride reduction of the initially formed cyclic nitrones, yielded substituted aza-D-homo-estrones and dimeric derivatives.¹⁵

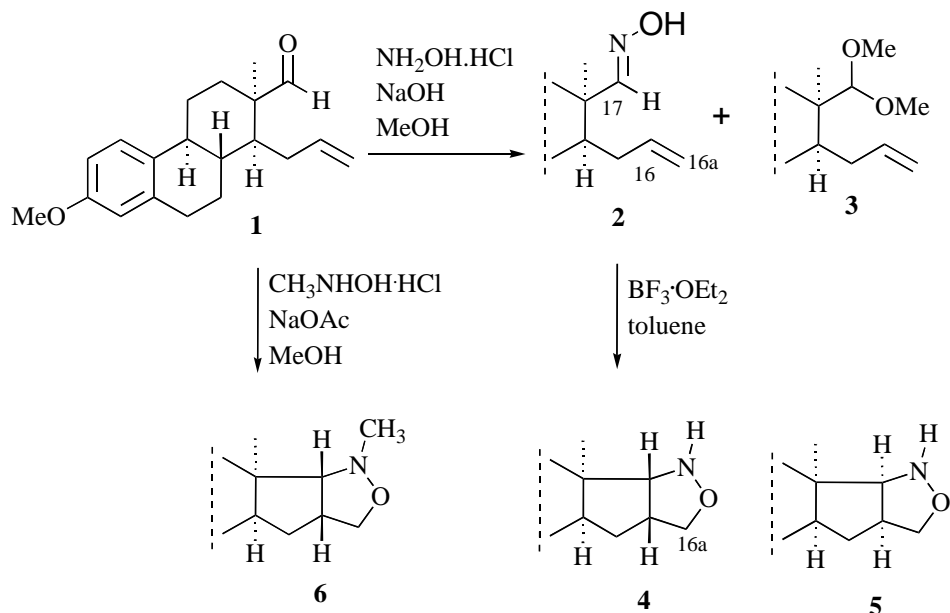
Our first aim was to produce steroidal nitronium dipoles from the oximes derived from 13 α - and 13 β -D-secoestrone derivatives *via* both electrophile- and Lewis-acid induced reactions. Subsequently, intra- and intermolecular (with NPM as the dipolarophile) 1,3-dipolar cycloadditions of the nitrones were carried out. Secondly, we aimed to determine the chemo-, regio- and stereoselectivities of the cycloadditions, i.e. the conformation of the newly formed rings was of particular interest. In contrast to the natural 13 β -estrone derivatives, their 13-epimers possess a quasi-equatorial 13 α -methyl group and a ring D that is directed to the β side and exhibits strongly restricted pseudorotation. The conformations of these derivatives depend upon the substitution pattern of ring D; either the expected conformation or an unusual steroid conformation with a twist-boat ring C is observed.¹⁶⁻²² It would be useful to acquire information on the relationship between the substitution patterns of the condensed aza-D-homo-13 α -estrone derivatives and their resulting conformations. We speculate that through variation of the structure of the dipolarophile, steroids with desired conformations could be synthesized.

Results and Discussion

We recently described the synthesis of the steroidal D-secoaldehyde **1**, which can be obtained by Grob fragmentation.^{23,24} The D-secoaldehyde **1** of 13 α -estrone was transformed into the appropriate oxime **2** in high yield (Scheme 1) using hydroxylamine hydrochloride and sodium hydroxide in methanol. Dimethyl acetal **3** was also formed as a side-product, but this side-reaction could be avoided by using sodium acetate instead of sodium hydroxide.

Firstly we carried out the intramolecular cyclization of oxime **2** with $\text{BF}_3 \cdot \text{OEt}_2$ in toluene. In contrast to the corresponding reaction in the normal estrone series, we obtained two different isoxazolidine stereoisomers, **4** and **5**, with *cis* ring anellations, in similar yields. This can be explained by the flexible molecular framework of the 13 α -estrone derivatives. Under the same

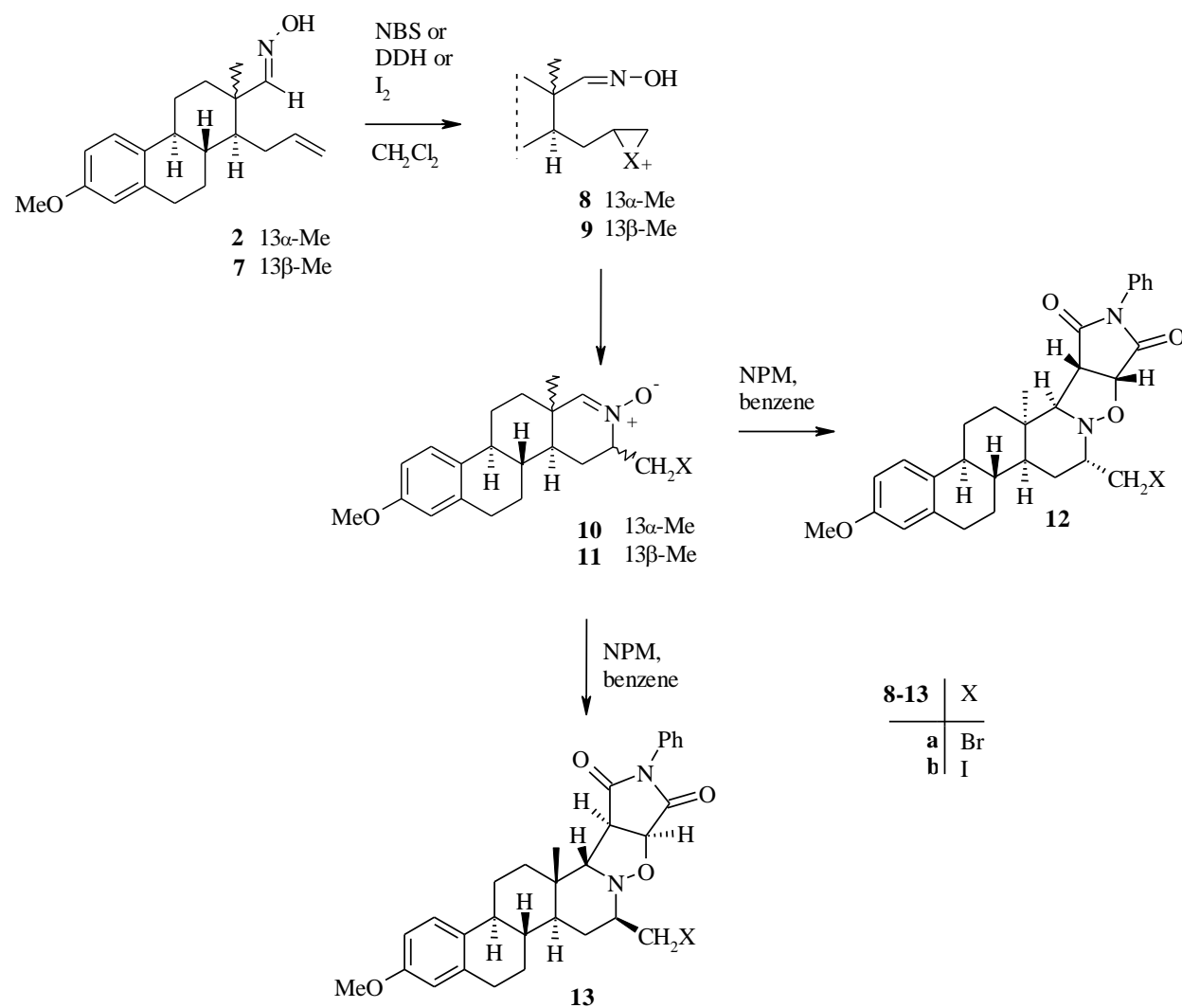
reaction conditions as those used for the oximation, the reaction of **1** with *N*-methylhydroxylamine hydrochloride resulted in one cyclized product **6**. Surprisingly, the formation of other stereoisomers was not observed.



Scheme 1. Lewis acid-induced intramolecular 1,3-dipolar cycloadditions in the 13 α -estrone series.

Electrophile-induced nitrene formation in the 13 α - and 13 β -estrone series was carried out with various halogenating agents: *N*-bromosuccinimide (NBS), 1,3-dibromodimethylhydantoin (DDH) and *N*-iodosuccinimide (NIS) (Scheme 2). After reaction in dichloromethane solution (0.5 h) and evaporation of the solvent, cycloaddition with NPM was carried out in benzene (2 h, 50 °C). Chemoselective nucleophilic attack of the oxime *N* atom on the intermediate halonium ions occurred, and after the dipolar cycloaddition, single D-homo-estrone isomers were isolated with a nitrogen atom in the six-membered ring D of the steroid skeleton. Brominations were performed with NBS or DDH. In both the 13 α - and 13 β -estrone series, the stereoselective addition of the dipolarophile led to a single 16-bromomethyl-aza-D-homo isomer, **12a** or **13a**. Iodination of oximes **2** or **7** with NIS yielded the 16-iodomethyl nitrones **10b** or **11b**, which underwent 1,3-dipolar cycloadditions with NPM to furnish cycloadducts **12b** or **13b** with high stereoselectivity.

Additionally, a 16-bromomethyl nitrene salt **10a** could be isolated in the 13 α -estrone series and was sufficiently stable that it could be purified by column chromatography (on silica gel). The analogous nitrene **11a** in the normal estrone series could not be isolated in pure form. The purified nitrene **10a** reacted with NPM in benzene to give the same cycloadduct **12a** as in reaction without prior isolation of the nitrene.



Scheme 2. Halogen-induced nitron formation and 1,3-dipolar cycloaddition with NPM in both the 13 α - and the 13 β - estrone series.

Stereochemistry

The structure of **2** determined by X-ray diffraction shows it to contain the usual chair-shaped ring C, and that the axial oxime function has E configuration (Figure 1).

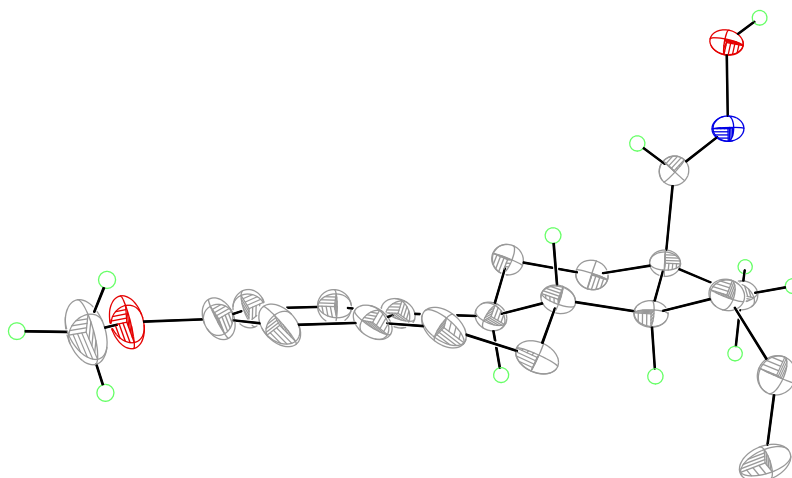


Figure 1. Structure obtained by crystal structure analysis of **2** (thermal ellipsoids are shown at a 50% probability level).

The ^1H NMR spectrum of **4** reveals the doublet of 17-H at 3.5 ppm, the multiplet of 16-H at 3.2 ppm and the multiplets of the 16a-H₂ at 3.7 and 3.8 ppm. In the ^{13}C NMR spectrum, the signals of C-17 and C-16a are observed at around 78 and 80 ppm, which indicates that C-17 has a neighbouring nitrogen, but C-16a has a neighbouring oxygen atom. In the spectra of **5**, the upfield shift of the doublet of 17-H (3.9 ppm) and the downfield shift of the signal of C-17 (70 ppm) demonstrate that two different stereoisomers, **4** and **5**, are formed. The ^1H NMR spectrum of **6** displays the 17-H signal at 3.4 ppm and the 16-H signal at 3.2 ppm, while 16a-H₂ gives a readily distinguishable triplet and a double doublet at 4.1 and 3.6 ppm, respectively. Determination of the stereochemistry of the isoxazolidines **4**, **5** and **6** was based on NOE data. After irradiation of the doublet of 17-H, the multiplet of 16-H and the singlet of *N*-Me appeared in the DNOE spectrum of **6**. The opposite experiment was also positive: after irradiation of the 16-H signal, the doublet of 17-H appeared in the spectrum. The DNOE experiments confirmed, that 16-H and 17-H are both β -oriented.

The configurations of the newly formed stereogenic centres were identified by means of 2D NMR experiments (COSY, NOESY and HSQC) and X-ray diffraction analysis. In the NOESY spectra of **13a** and **13b**, the multiplet of 3'-H shows cross-peaks with the signals of 16-H and 4'-H, and correlations can be seen between the signals of 17a-H and the angular methyl group. This proves the equatorial position of the 16-halomethyl group, the β location of 17a-H, and the α location of 3'-H and 4'-H.

The X-ray diffraction structure of **12a** shows that in this molecule rings C (cyclohexane) and D (piperidine) are in chair conformations. The α -located 16a-bromomethyl substituent assumes an equatorial position, and the annellation of the isoxazolidine ring and the maleimide moiety is *cis* (Figure 2). This is the first condensed aza-D-homo compound in the 13 α -estrone series for which the conformation has been absolutely confirmed.

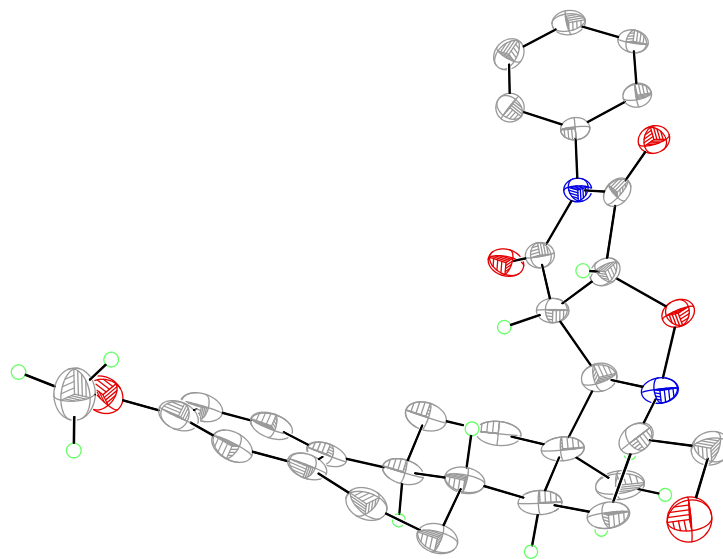


Figure 2. Structure obtained by crystal structure analysis of **12a** (thermal ellipsoids are shown at a 50 % probability level).

Another point of interest concerning the structures of the cycloadducts **12** and **13** is that 16-halomethyl substituents (α), 3'-H (β) and 4'-H (β) in the 13 α -estrone derivatives **12** exhibit opposite orientations compared to the same groups in the 13 β -estrone derivatives **13**.

Conclusions

The Lewis acid-induced intramolecular 1,3-dipolar cycloaddition of the oxime **2** of seco-13 α -estrone 3-methyl ether derivative resulted in two isoxazolidine stereoisomers, **4** and **5**, in nearly the same amounts, in contrast with the observations in the 13 β -estrone series. Reaction of 13 α -D-secoaldehyde **1** with *N*-methylhydroxylamine under the conditions used for oxime formation yielded the single isoxazolidine **6**.

Intramolecular halogen-induced cyclizations of δ -alkenyl oximes **2** or **7** occurred *via* attack of the oxime nitrogen atom on the intermediate halonium ions, yielding cyclic nitrones **10** or **11** with high stereoselectivities in both the 13 α - and the 13 β -estrone series. The subsequent intermolecular 1,3-dipolar cycloadditions of **10** or **11** with NPM furnished single condensed aza-D-homo-estrone isomers **12** or **13**, with *cis* ring anellations of the isoxazolidine and the NPM moieties.

Experimental Section

General. Melting points (mps) were determined with a Kofler hot-stage apparatus and are uncorrected. Specific rotations were measured in chloroform with a POLAMAT-A (Zeiss-Jena) polarimeter and are given in units of 10^{-1} deg $\text{cm}^2 \text{g}^{-1}$. Elemental analyses were performed with a Perkin-Elmer CHN analyzer model 2400. Thin-layer chromatography: silica gel 60 F254; layer thickness 0.2 mm (Merck); solvent: dichloromethane; detection with iodine or UV (365 nm) after spraying with 50% phosphoric acid and heating at 100-120 °C for 10 min. Flash chromatography: silica gel 60, 40-63 μm (Merck). ^1H NMR spectra were recorded in CDCl_3 solution (if not otherwise stated) with a Bruker DRX-500 instrument at 500 MHz, using Me_4Si as internal standard. ^{13}C NMR spectra were recorded with the same instrument at 125 MHz under the same conditions. EI-MS spectra were measured on a Varian MAT 311A.

Syntheses of (2) and (3)

Method A. Compound **1** (0.885 g, 3.00 mmol) and hydroxylamine hydrochloride (0.210 g, 3.00 mmol) were dissolved in methanol (10 mL), and a methanolic solution (10 mL) of sodium hydroxide (500 mg) and 4 drops of water were added. The mixture was heated at reflux for 1 h, poured into water and neutralized with dilute (10%) aqueous hydrochloric acid. After extraction with dichloromethane, the combined dichloromethane solutions were dried over Na_2SO_4 , and then evaporated. Purification by flash chromatography over silica gel with dichloromethane yielded **2** (0.600 g, 65%), mp 90–92 °C, $R_f = 0.19$ (dichloromethane). ^1H NMR (500 MHz, CDCl_3): δ [ppm] = 1.20 (s, 3H, 18- H_3), 2.83 (m, 2H, 6- H_2), 3.77 (s, 3H, 3-OMe), 5.01 (m, 2H, 16a- H_2), 5.83 (m, 1H, 16-H), 6.61 (d, 1H, $J=2.5$ Hz, 4-H), 6.70 (dd, 1H, $J=8.6$ Hz, $J=2.5$ Hz, 2-H), 7.18 (d, 1H, $J=8.6$ Hz, 1-H), 7.57 (s, 1H, 17-H). ^{13}C NMR δ [ppm] = 26.3 (C-18), 27.0, 27.4, 30.3, 33.3, 39.1, 40.9, 42.3, 43.5, 50.8, 55.2 (3-OMe), 111.7 (C-2), 113.4 (C-4), 114.9 (C-16a), 126.4 (C-1), 132.2 (C-10), 137.8 (C-5), 139.4 (C-16), 155.9 (C-17), 157.5 (C-3). MS (70 eV); m/z (%): 313 (100, M^+), 296 (53), 173 (47), 147 (49), 70 (61), 41 (42). Anal. Calcd. for $\text{C}_{20}\text{H}_{27}\text{NO}_2$: C, 76.64; H, 8.68. Found: C, 76.51; H, 8.76. Crystal data: A colourless single-crystal (0.30 x 0.20 x 0.20 mm^3) of $\text{C}_{20}\text{H}_{27}\text{NO}_2$ (313.44) was measured at 100(2) K with a Siemens SMART 6000 area detector system. Unit cell dimensions: $a = 8.8489(3)$, $b = 9.4453(3)$, $c = 23.6805(7)$, $\alpha = 96.806(1)$, $\beta = 90.032(1)$, $\gamma = 116.543(1)$; $V = 1754.9(1)$ \AA^3 ; $\rho = 1.186$ g cm^{-3} . Triclinic space group $P1$ with 4 molecules per asymmetric unit, 23124 reflections collected ($\theta_{\text{max.}} = 58.97^\circ$), 9133 unique ($R_{\text{int}} = 2.37\%$), 8920 observed [$I > 2\sigma(I)$], absorption correction semi-empirical from equivalents (max/min transmission 0.8908/0.8424, absorption coefficient 0.592 mm^{-1}) with SADABS,²⁵ structure solution (direct methods) with SHELXS-97,²⁶ structure refinement (full-matrix least-squares on F^2) with SHELXL-97,²⁶ GOF = 1.038, $R1 = 2.59\%$, $wR2 = 6.30\%$, absolute structure parameter $-0.1(1)$, largest difference peak and hole 0.154 and -0.170 e \AA^{-3} , molecular graphics generated with XP.²⁷ All hydrogen atoms were located by difference Fourier synthesis and were refined using a riding model based on idealized geometries with the 1.2-fold (1.5-fold for methyl and hydroxy groups) isotropic displacement parameters of the

equivalent U_{ij} values of the corresponding carbon atom. CCDC-259980 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223-336-033; or E-mail: deposit@ccdc.cam.ac.uk].

Continued elution yielded **3** (0.120 g, 12%), as an oil, $R_f = 0.48$ (dichloromethane). ^1H NMR (500 MHz, CDCl_3): δ [ppm] = 0.99 (s, 3H, 18- H_3), 2.84 (m, 2H, 6- H_2), 3.43 and 3.48 (2xs, 2x3H, 2xacetal-OMe), 3.76 (s, 3H, 3-OMe), 4.33 (s, 1H, 17-H), 5.00 (m, 2H, 16a- H_2), 5.86 (m, 1H, 16-H), 6.61 (d, 1H, $J=2.5$ Hz, 4-H), 6.70 (dd, 1H, $J=8.6$ Hz, $J=2.5$ Hz, 2-H), 7.19 (d, 1H, $J=8.6$ Hz, 1-H). ^{13}C NMR δ [ppm] = 23.4 (C-18), 27.0, 28.1, 30.5, 32.6, 36.6, 42.1, 42.2 (C-13), 44.1, 52.0, 55.1 (3-OMe), 57.8 and 58.4 (2C, 2xacetal-OMe), 110.7 (C-17), 111.5 (C-2), 113.4 (C-4), 113.5 (C-16a), 126.3 (C-1), 133.1 (C-10), 137.9 (C-5), 141.8 (C-16), 157.5 (C-3). MS (70 eV); m/z (%) 344 (23, M^+), 239 (11), 75 (100). Anal. Calcd. for $\text{C}_{22}\text{H}_{32}\text{O}_3$: C, 76.70; H, 9.36. Found: C, 76.84; H, 9.13.

Method B. Compound **1** (0.300 g, 1 mmol) was dissolved in methanol (10 mL) and hydroxylamine hydrochloride (0.070 g, 1 mmol) and sodium acetate (0.250 g, 3 mmol) were added. The mixture was refluxed for 6 h, cooled to room temperature, poured into water, neutralized with dilute (10%) hydrochloric acid and extracted with dichloromethane. The organic phase was dried over Na_2SO_4 and evaporated. Purification by flash chromatography over silica gel with dichloromethane yielded **2** (0.250 g, 80%).

Syntheses of (4) and (5)

Compound **2** (0.200 g, 0.64 mmol) was dissolved in toluene (5 mL), and a solution of $\text{BF}_3 \cdot \text{OEt}_2$ (0.5 mL) in toluene (5 mL) was added dropwise. After refluxing the mixture for 3 h in a N_2 atmosphere, it was washed with water, dried over Na_2SO_4 and evaporated. Purification by flash chromatography over silica gel with 2:8 *tert*-butyl methyl ether/*n*-hexane first yielded **4** (0.087 g, 44%), mp 100-103 °C, $R_f = 0.47$ (1:1 *tert*-butylmethyl ether/*n*-hexane). ^1H NMR (500 MHz, CDCl_3): δ [ppm] = 1.01 (s, 3H, 18- H_3), 2.83 (m, 2H, 6- H_2), 3.13 (m, 1H, 16-H), 3.45 (d, 1H, $J=7.6$ Hz, 17-H), 3.64 and 3.78 (2xm, 2x1H, 16a- H_2), 3.79 (s, 3H, 3-OMe), 6.62 (d, 1H, $J=2.0$ Hz, 4-H), 6.72 (dd, 1H, $J=8.6$ Hz, $J=2.0$ Hz, 2-H), 7.24 (d, 1H, $J=8.6$ Hz, 1-H). ^{13}C NMR δ [ppm] = 29.2, 29.4, 31.0, 33.2 (C-18), 35.2 (2C), 40.8, 41.9, 44.5 (C-13), 47.6, 52.7, 55.6 (3-OMe), 77.6 (C-17), 79.9 (C-16a), 112.0 (C-2), 113.8 (C-4), 127.7 (C-1), 133.5 (C-10), 138.8 (C-5), 157.6 (C-3). MS (70 eV); m/z (%): 313 (100, M^+), 186 (22), 173 (18), 84 (14). Anal. Calcd. for $\text{C}_{20}\text{H}_{27}\text{NO}_2$: C, 76.64; H, 8.68. Found: C, 76.82; H, 8.51.

Continued elution yielded **5** (0.077 g, 39%), mp 225–228 °C, $R_f = 0.22$ (1:1 *tert*-butyl methyl ether/*n*-hexane). ^1H NMR (500 MHz, CDCl_3): δ [ppm] = 1.07 (s, 3H, 18- H_3), 2.82 (m, 2H, 6- H_2), 3.04 (m, 1H, 16-H), 3.47 (t, 1H, $J=7.6$ Hz) and 3.77 (m, 1H): 16a- H_2 , 3.78 (s, 3H, 3-OMe), 3.84 (d, 1H, $J=8.6$ Hz, 17-H), 6.62 (d, 1H, $J=2.5$ Hz, 4-H), 6.72 (dd, 1H, $J=8.6$ Hz, $J=2.5$ Hz, 2-H), 7.24 (d, 1H, $J=8.6$ Hz, 1-H). ^{13}C NMR δ [ppm] = 24.9 (C-18), 27.6, 28.9, 30.9, 34.1, 36.6, 40.9, 42.4, 43.8 (C-13), 47.6, 54.3, 55.6 (3-OMe), 69.6 (C-17), 77.7 (C-16a), 112.1 (C-2), 114.0 (C-4),

127.3 (C-1), 132.9 (C-10), 138.6 (C-5), 157.9 (C-3). MS (70 eV); m/z (%): 313 (100, M^+), 240 (14), 227 (19), 225 (18), 173 (28), 147 (16), 84 (11). Anal. Calcd. for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68. Found: C, 76.73; H 8.52.

Synthesis of (6)

Compound **1** (0.300 g, 1 mmol) was dissolved in methanol (10 mL), and *N*-methylhydroxylamine hydrochloride (0.150 g, 1.8 mmol) and sodium acetate (0.250 g, 3 mmol) were added. The mixture was heated at reflux for 6 h, cooled to room temperature, poured into water, neutralized with dilute (10%) aqueous HCl and extracted with dichloromethane. The organic phase was dried over Na_2SO_4 and evaporated. Purification by flash chromatography over silica gel with 1:9 ethyl acetate/dichloromethane yielded **6** (0.260 g, 80%), mp 114–116 °C, R_f = 0.62 (dichloromethane). 1H NMR (500 MHz, $CDCl_3$): δ [ppm] = 1.07 (s, 3H, 18- H_3), 2.57 (s, 3H, *N*-Me), 2.82 (m, 2H, 6- H_2), 3.19 (m, 1H, 16-H), 3.36 (d, 1H, $J=9.5$ Hz, 17-H), 3.57 (dd, 1H, $J=8.4$ Hz, $J=2.9$ Hz) and 4.11 (t, 1H, $J=8.4$ Hz): 16a- H_2 , 3.78 (s, 3H, 3-OMe), 6.62 (d, 1H, $J=2.6$ Hz, 4-H), 6.72 (dd, 1H, $J=8.6$ Hz, $J=2.6$ Hz, 2-H), 7.24 (d, 1H, $J=8.6$ Hz, 1-H). ^{13}C NMR δ [ppm] = 25.4 (C-18), 27.0, 28.4, 30.4, 33.6, 35.7, 40.5, 42.0, 43.0 (C-13), 45.6, 45.7, 54.5, 55.2 (3-OMe), 71.3 (C-16a), 76.8 (C-17), 111.7 (C-2), 113.6 (C-4), 126.8 (C-1), 132.5 (C-10), 138.2 (C-5), 157.5 (C-3). MS (70 eV); m/z (%): 327 (100, M^+), 98 (74). Anal. Calcd. for $C_{21}H_{32}N_2O$: C, 77.02; H, 8.93. Found: C, 76.93; H 8.75.

General procedure for the synthesis of brominated cycloadducts (12a, 13a)

Compound **2** or **7** (0.200 g, 0.66 mmol) was dissolved in dichloromethane (10 mL), and 1,3-dibromodimethylhydantoin (0.100 mg, 0.33 mmol) or *N*-bromosuccinimide (0.120 g, 0.66 mmol) was added. The mixture was stirred at room temperature for 0.5 h and then evaporated. The crude product was dissolved in benzene (10 mL) and *N*-phenylmaleimide (0.116 g, 0.66 mmol) was added. The solution was stirred at 50 °C for 2 h and then evaporated.

Cycloadduct (12a). Purification by flash chromatography over silica gel with 3:7 *tert*-butyl methyl ether/*n*-hexane yielded **12a** (0.280 g, 78%), mp 132–137 °C, R_f = 0.33 (dichloromethane). 1H NMR (500 MHz, $CDCl_3$): δ [ppm] = 1.38 (s, 3H, 18- H_3), 2.87 (m, 2H, 6- H_2), 3.42 (dd, 1H, $J=9.9$ Hz, $J=8.0$ Hz) and 3.80 (dd, 1H, $J=9.9$ Hz, $J=2.2$ Hz): 16a- H_2 , 3.44 (d, 1H, $J=8.6$ Hz, 17a-H), 3.78 (s, 3H, 3-OMe), 4.33 (t, 1H, $J=8.0$ Hz, 4'-H), 5.09 (d, 1H, $J=8.0$ Hz, 3'-H), 6.64 (d, 1H, $J=2.4$ Hz, 4-H), 6.73 (dd, 1H, $J=8.6$ Hz, $J=2.4$ Hz, 2-H), 7.23-7.26 and 7.46 (overlapping multiplets, 5H, 1-, 2''-, 3''-, 5''-, 6''-H), 7.40 (t, 1H, $J=7.3$ Hz, 4''-H). ^{13}C NMR δ [ppm] = 26.4, 27.4, 27.7, 29.8, 34.3 (C-18), 34.9, 36.4, 36.6, 38.3, 42.0, 45.0, 50.3, 55.2, 55.6, 74.6 (C-17a), 77.3 (C-3'), 111.9 (C-2), 113.4 (C-4), 126.4 and 129.2 (2x2C, C-2'', -3'', -5'', -6''), 126.7 (C-1), 129.0 (C-4''), 131.1 and 132.3 (2C, C-1'' and C-10), 137.6 (C-5), 157.8 (C-3), 170.8 and 173.6 (2C, C-2' and C-5'). MS (70 eV); m/z (%): 566 (10), 564 (10, M^+), 470 (26), 468 (26), 454 (31), 295 (41), 119 (50), 93 (100). Anal. Calcd. for $C_{30}H_{33}BrN_2O_4$: C, 63.72; H, 5.88. Found: C, 63.91; H, 5.75. **12a**: Crystal data: A colourless single-crystal (0.20 x 0.10 x 0.10 mm³) of

$C_{30}H_{33}BrN_2O_4$ (565.49) was measured at 100(2) K with a Siemens SMART 6000 area detector system. Unit cell dimensions: $a = 13.703(3)$, $b = 27.097(5)$, $c = 29.098(6)$; $V = 10805(4) \text{ \AA}^3$; $\rho = 1.391 \text{ g cm}^{-3}$. Orthorhombic space group $P2_12_12_1$ with 4 molecules per asymmetric unit, 117098 reflections collected ($\theta_{\text{max.}} = 59.14^\circ$), 15559 unique ($R_{\text{int}} = 4.66\%$), 14267 observed [$I > 2\sigma(I)$], absorption correction semi-empirical from equivalents (max/min transmission 0.7967/0.6474, absorption coefficient 2.381 mm^{-1}) with SADABS,²⁵ structure solution (direct methods) with SHELXS-97,²⁶ structure refinement (full-matrix least-squares on F^2) with SHELXL-97,²⁶ GOF = 1.042, $R1 = 2.51\%$, $wR2 = 5.72\%$, absolute structure parameter $-0.031(6)$, largest difference peak and hole 0.464 and $-0.333 \text{ e \AA}^{-3}$, molecular graphics generated with XP.²⁷ All hydrogen atoms were located by difference Fourier synthesis and were refined using a riding model based on idealized geometries with the 1.2-fold (1.5-fold for methyl groups) isotropic displacement parameters of the equivalent U_{ij} values of the corresponding carbon atom. CCDC-260394 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223-336-033; or E-mail: deposit@ccdc.cam.ac.uk].

Cycloadduct (13a). Purification by flash chromatography over silica gel with 3:7 *tert*-butylmethyl ether/*n*-hexane yielded **13a** (0.270 g, 75%), mp 155–158 °C, $R_f = 0.25$ (dichloromethane). $^1\text{H NMR}$ (500 MHz, CDCl_3): δ [ppm] = 1.22 (s, 3H, 18- H_3), 2.78 (m, 1H, 4'-H), 2.88 (m, 2H, 6- H_2), 3.52 (dd, 1H, $J=10.1 \text{ Hz}$, $J=7.3 \text{ Hz}$) and 3.74 (m, 1H): 16a- H_2 , 3.54 (d, 1H, $J=9.2 \text{ Hz}$, 17a-H), 3.77 (s, 3H, 3-OMe), 5.20 (d, 1H, $J=8.0 \text{ Hz}$, 3'-H), 6.64 (d, 1H, $J=2.2 \text{ Hz}$, 4-H), 6.72 (dd, 1H, $J=8.6 \text{ Hz}$, $J=2.2 \text{ Hz}$, 2-H), 7.20 (d, 1H, $J=8.6 \text{ Hz}$, 1-H), 7.29 (d, 2H, $J=7.8 \text{ Hz}$, 2''-, 6''-H), 7.48 (t, 2H, $J=7.8 \text{ Hz}$, 3''-, 5''-H), 7.41 (t, 1H, $J=7.8 \text{ Hz}$, 4''-H), $^{13}\text{C NMR}$ δ [ppm] = 21.3 (C-18), 25.3, 26.5, 28.2, 29.8, 35.4, 37.2, 37.4, 38.4, 41.1, 43.2, 48.5 (C-4'), 55.2 (3-OCH₃), 61.2 (C-16), 77.3 (C-17a), 77.9 (C-3'), 111.7 (C-2), 113.5 (C-4), 126.2 and 128.9 (2x1C, C-1 and C-4''), 126.3 and 129.2 (2x2C, C-2'',3'',5'',6''), 131.1 and 131.9: C-1'' and C-10, 137.5 (C-5), 157.6 (C-3), 170.9 and 173.2 (2C, C-2' and -5'). MS (70 eV); m/z (%): 566 (4), 564 (6, M^+), 468 (38), 449 (30), 293 (100), 278 (62), 173 (37), 95 (47), 93 (47), 81 (38), 79 (38). Anal. Calcd. for $C_{30}H_{33}BrN_2O_4$: C, 63.72; H, 5.88. Found: C, 63.54; H, 5.92.

Synthesis of cyclic nitron (10a)

Compound **2** (0.200 g, 0.66 mmol) was dissolved in dichloromethane (10 mL), and 1,3-dibromodimethylhydantoin (0.100 g, 0.33 mmol) was added. The mixture was stirred at room temperature for 0.5 h and then evaporated. Purification by flash chromatography over silica gel with ethyl acetate yielded **10a** (0.200 g, 80%), $R_f = 0.25$ (ethyl acetate). m.p. 157–160 °C. $^1\text{H NMR}$ (500 MHz, CDCl_3): δ [ppm] = 1.33 (s, 3H, 18- H_3), 2.83 (m, 2H, 6- H_2), 3.60 (dd, 1H, $J=13.0 \text{ Hz}$, $J=1.8 \text{ Hz}$) and 4.44 (dd, 1H, $J=13.0 \text{ Hz}$, $J=5.5 \text{ Hz}$): 16a- H_2 , 3.77 (s, 3H, 3-OMe), 3.86 (m, 1H, 16-H), 6.60 (d, 1H, $J=2.5 \text{ Hz}$, 4-H), 6.70 (dd, 1H, $J=8.5 \text{ Hz}$, $J=2.5 \text{ Hz}$, 2-H), 7.03 (s, 1H, 17a-H), 7.13 (d, 1H, $J=8.5 \text{ Hz}$, 1-H). $^{13}\text{C NMR}$ δ [ppm] = 26.0, 27.3, 28.8, 29.5 (C-18), 30.7, 34.8, 39.4 (C-13), 39.9, 40.0, 42.5, 42.7, 55.8 (3-OMe), 62.6 (C-16), 112.5 (C-2), 114.1 (C-

4), 127.1 (C-1), 131.9 (C-10), 138.0 (C-5), 146.7 (C-17a), 158.3 (C-3). MS (70 eV); m/z (%): 293 (17), 95 (90), 93 (100), 81 (25), 79 (27). Anal. Calcd. for $C_{20}H_{26}BrNO_2$: C, 61.23; H, 6.68. Found: C, 61.15; H, 6.77.

Synthesis of Iodinated Cycloadducts (**12b**) and (**13b**)

Compound **2** or **7** (0.200 g, 0.66 mmol) was dissolved in dichloromethane (10 mL), the mixture was cooled in an ice-water bath, and *N*-iodosuccinimide (0.150 mg, 0.66 mmol) was added in small portions over 1 h. The reaction mixture was stirred at room temperature for 0.5 h and then evaporated. The crude product was dissolved in benzene (10 mL), and *N*-phenyl maleimide (0.110 g, 0.5 mmol) was added. The solution was stirred at 50 °C for 2 h and then evaporated.

Cycloadduct (12b). Purification by flash chromatography over silica gel with 3:7 *tert*-butyl methyl ether/*n*-hexane yielded **12b** (0.330 g, 85%), mp 174–178 °C, R_f = 0.69 (dichloromethane). 1H NMR (500 MHz, $CDCl_3$): δ [ppm] = 1.36 (s, 3H, 18- H_3), 2.54 (m, 1H, 16-H), 2.87 (m, 2H, 6- H_2), 3.26 (t, 1H, $J=8.7$ Hz) and 3.56 (m, 1H): 16a- H_2 , 3.42 (d, 1H, $J=8.5$ Hz, 17a-H), 3.73 (s, 3H, 3-OMe), 4.26 (t, 1H, $J=8.5$ Hz, 4'-H), 4.96 (d, 1H, $J=8.5$ Hz, 3'-H), 6.62 (d, 1H, $J=2.4$ Hz, 4-H), 6.71 (dd, 1H, $J=8.5$ Hz, $J=2.4$ Hz, 2-H), 7.21 (d, 2H, $J=7.3$ Hz, 2''- and 6''-H), 7.26 (d, 1H, $J=8.5$ Hz, 1-H), 7.38 (t, 1H, $J=7.3$ Hz, 4''-H) 7.44 (t, 2H, $J=7.3$ Hz, 3''- and 5''-H). ^{13}C NMR δ [ppm] = 10.4 (C-16a), 27.4, 27.7, 28.2, 29.8, 34.3 (C-18), 36.3 (C-13), 36.7, 38.5, 42.0, 45.2, 50.4 (C-4'), 55.0 (C-16), 55.2 (3-OMe), 74.6 (C-17a), 77.2 (C-3'), 111.9 (C-2), 113.4 (C-4), 126.4 (2C, C-2'' and C-6''), 126.7 (C-1), 129.0 (C-4''), 129.2 (2C, C-3'' and C-5''), 131.1 (C-1''), 132.3 (C-10), 137.7 (C-5), 157.8 (C-3), 170.8 and 173.7 (2C, C-2' and C-5'). MS (70 eV); m/z (%): 612 (M^+ , 14), 471 (21), 253 (52), 173 (100). Anal. Calcd. for $C_{30}H_{33}IN_2O_4$: C, 58.83; H, 5.43. Found: C, 58.96; H, 5.37.

Cycloadduct (13b). Purification by flash chromatography over silica gel with dichloromethane yielded **13b** (0.300 g, 77%), m.p. 160–163 °C, R_f = 0.31 (CH_2Cl_2). 1H NMR (500 MHz, $CDCl_3$): δ [ppm] = 1.23 (s, 3H, 18- H_3), 2.88 (m, 2H, 6- H_2), 3.41 (dd, 1H, $J=10.0$ Hz, $J=6.7$ Hz) and 3.51 (m, 1H): 16a- H_2 , 3.55 (d, 1H, $J=9.0$ Hz, 17a-H), 3.73 (d, 1H, $J=8.5$ Hz, 4'-H), 3.77 (s, 1H, 3-OMe), 5.18 (d, 1H, $J=8.5$ Hz, 3'-H), 6.63 (d, 1H, $J=2.0$ Hz, 4-H), 6.72 (dd, 1H, $J=8.4$ Hz, $J=2.0$ Hz, 2-H), 7.20 (d, 1H, $J=8.6$ Hz, 1-H), 7.29 (d, 2H, $J=7.6$ Hz, 2''- and 6''-H), 7.41 (t, 1H, $J=7.6$ Hz, 4''-H), 7.48 (t, 2H, $J=7.6$ Hz, 3''- and 5''-H). ^{13}C NMR δ [ppm] = 11.0 (C-16a), 21.4 (C-18), 25.3, 26.6, 29.8, 30.1, 37.3, 37.4, 38.4, 41.3, 43.3, 48.7 (C-4'), 55.2 (3-OCH₃), 60.4 (C-16), 77.3 (C-17a), 77.9 (C-3'), 111.8 (C-2), 113.5 (C-4), 126.2 (C-1), 126.3 (2C, C-2'' and C-6''), 128.9 (C-4''), 129.2 (2C, C-3'' and C-5''), 131.2 (C-1''), 131.9 (C-10), 137.5 (C-5), 157.7 (C-3), 170.8 and 173.2 (2C, C-2' and C-5'). MS (70 eV); m/z (%): 612 (10, M^+), 566 (23), 173 (100). Anal. Calcd. for $C_{30}H_{33}IN_2O_4$: C, 58.83; H 5.43. Found: C, 58.91; H 5.51.

Acknowledgements

This work was supported by the New Hungary Development Plan (Project: TÁMOP 4.2.2-08/01-2008-0002) and the Hungarian Scientific Research Fund (OTKA K72309). We also thank Péter

Forgó (University of Szeged, Hungary), Reinhard Machinek (University of Göttingen) for the NMR spectra, and Mrs Györgyi Udvarnoki (University of Göttingen) for the mass spectra.

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