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Stereoselective synthesis of some novel heterocyclic estrone derivatives by intramolecular 1,3-dipolar cycloaddition

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Dedicated to Professor Lutz F. Tietze on the occasion of his 60th birthday

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Abstract—16,17-*seco*-3-Methoxyestra-1,3,5(10),16-tetraen-17-al undergoes intramolecular nitrone 1,3-dipolar cycloaddition with both hydroxylamine and *N*-methylhydroxylamine to produce a single isoxazolidine isomer in each case. The ring-closures of the hydrazones and the aldazine derived from the secoaldehyde lead to fused N-containing heterocycles via Lewis acid-induced cyclization of the intermediate azomethine imines.

1. Introduction

1,3-Dipolar cycloadditions are a generally used and extensively studied method for the synthesis of five-membered heterocycles.[1] The allyl type azomethine imine and nitrone 1,3-dipoles, containing a nitrogen function in the center, can readily react with multiple-bond systems, though mainly thermal reactions have been studied. However catalytic 1,3-dipolar cycloadditions between dipoles and olefinic dipolarophiles activated by Lewis acids are still rare compared with Diels–Alder reactions.[2] A rate acceleration, regioselectivity and diastereoselectivity improvement associated with the internal cycloaddition of olefinic dipoles are mostly observed in the presence of different Lewis acids.[3] However, several examples of 1,3-dipolar cycloadditions catalyzed by metal cations or metal complexes can be found in the literature.[4]

We recently reported that tetrahydroquinoline derivatives can be obtained via the Lewis acid-catalyzed hetero-Diels–Alder cyclization of arylimines derived from the normal secoestrone aldehyde **1** and substituted anilines.[5] The presence of the formyl group and the olefinic moiety in the precursor **1** makes the molecule suitable for condensation and subsequent cyclization reactions to give fused heteroatom-containing frameworks via intramolecular sequences.[6]

In this paper, we report a series of intramolecular 1,3-dipolar cycloaddition reactions of nitrones and azomethine imines derived from **1**.

2. Results and discussion

Oximation[7] of the aldehyde **1** with hydroxylamine hydrochloride in alkaline methanol gave only one of the two possible geometric isomers of the corresponding aldoxime **2**, in 90% yield (Scheme 1). The exact configuration could not be determined from the NMR spectra of the compound, but the formation of the more stable (*E*)-oxime is assumed. The aldoxime **2** was catalytically tautomerized[8] by $BF_3{\cdot}OEt_2$ in boiling toluene into its nitrone form **3**, which then intramolecularly cyclized to produce the condensed isoxazolidine derivative **5**. The cyclization could also be carried out as a one-pot reaction by heating the aldehyde **1** with *N*-methylhydroxylamine hydrochloride. In this case, the *N*-methyl-isoxazolidine **6** was obtained stereoselectively via its nitrone intermediate **4**. In both cases, cycloaddition proceeded to furnish products with the expected *cis* ring junction stereochemistry.

The structures of the products were determined by NMR spectroscopy and X-ray analysis. Thus, X-ray crystal structure analysis of **6** shows the *cis* annelation of rings D

Keywords: nitrones; azomethine imines; 1,3-dipolar cycloaddition; Lewis acid; stereoselective synthesis.

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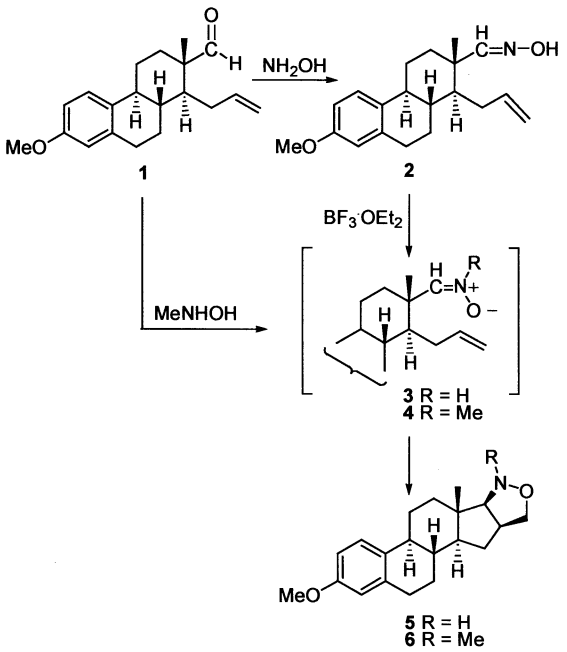


Scheme 1. Synthesis of isoxazolidine derivatives **5** and **6** by internal nitrone 1,3-dipolar cycloaddition.

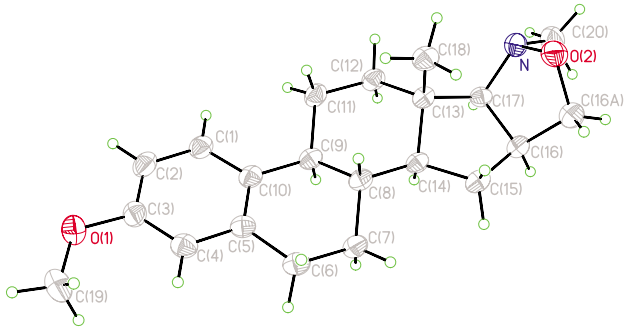


Figure 1. X-Ray crystal structure of **6**.

and E and the α,α orientation of the protons on C-16 and C-17 (Fig. 1).‡

Our attention next focused on an investigation of the Lewis acid-induced isomerization to their 1,3-dipolar tautomers of hydrazones **8a–c** and aldazine **12** derived from the secoaldehyde **1**, since these systems have been shown to act under suitable conditions as quasi-azomethine imines in polar [3+2] cycloadditions (Scheme 2).[9]

The reaction of the aldehyde **1** with phenylhydrazine **7a** in ethanol at room temperature yielded the corresponding phenylhydrazone **8a**, which readily cyclized after purification in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$ to afford a mixture of two kinds of product, **10a** and **11a** (Table 1). The ratio of the pyrazoline (**10a**) and the pyrazole (**11a**) derivatives was mainly determined by the reaction conditions. The pyrazoline **10a** could be obtained as the major product by cyclization of the phenylhydrazone **8a** in ice-cold chloroform, while the corresponding reaction in toluene under reflux gave mainly the pyrazole **11a**, due to the aromatic stabilization (entry 7). The pyrazole **11a** is assumed to be formed by autooxidation of the pyrazoline **10a**. The results of X-ray crystal analysis[§] of the pyrazoline **10a** indicated that the hydrogen on C-16 takes up the β position. The condensation of **1** was also carried out with *p*-methoxyphenylhydrazine hydrochloride **7b** in basic methanol to give a white solid, which proved to be unstable in solution. For this reason, without purification, the thermal and the $BF_3{\cdot}OEt_2$-induced cyclizations of the crude *p*-methoxyphenylhydrazone **8b** were also accomplished (entry 8) to give stereoselectively a single pyrazoline derivative **10b**. The instability of the hydrazone **8b** is not surprising if it is considered, that the electron-donating *p*-methoxy substituent on the phenyl group makes the intermediate azomethine imine **9b** quite reactive for cyclization. This is consistent with the observation that the 2′,4′-dinitrophenylhydrazone **9c** containing two electron-withdrawing nitro groups exhibited great stability against both thermal and Lewis acid-catalyzed cyclizations.

The reaction of the secoestrone aldehyde **1** with half an equivalent of hydrazine hydrate led to an aldazine **12**,[10] which underwent a criss-cross reaction[11] in the presence of $BF_3{\cdot}OEt_2$ to furnish a decacyclic pyrazolidine derivative **13**. In the ^{1}H NMR spectrum of **13**, the double doublet (J=12.0, 7.4 Hz) of the 16aβ and 16′aβ protons appears at 2.73 ppm, and the pentet-like multiplet of the 16aα and 16′aα protons at 3.28 ppm. The NOESY spectrum indicates the β orientation of the protons on C-16, C-16′, C-17 and C-17′.

3. Conclusion

In summary, $BF_3{\cdot}OEt_2$ induced the 1,3-dipolar cyloaddition of nitrones and azomethine imines of a secoestrone aldehyde to produce novel heterocyclic estrone derivatives in high yields. The reactions exhibited high chemo-, regio- and stereoselectivity.

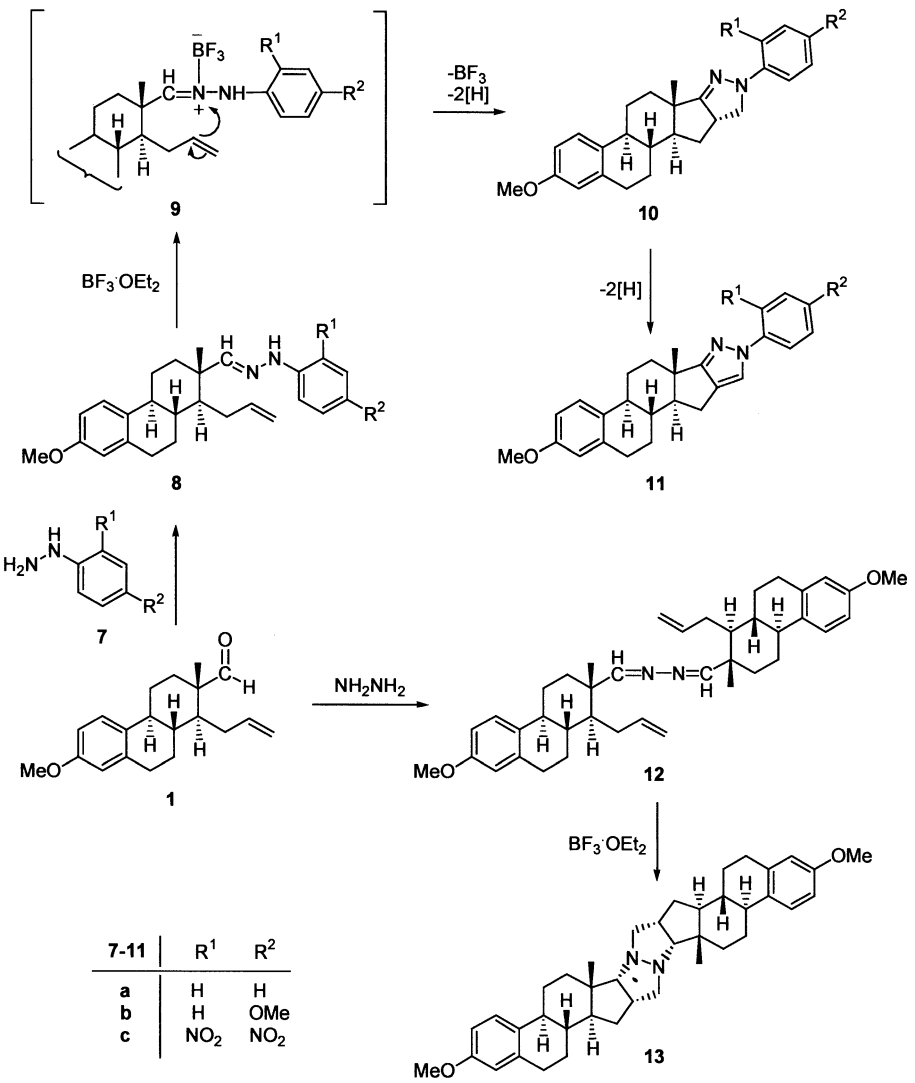
4. Experimental

4.1. General

Melting points were determined on a Kofler block and are uncorrected. Specific rotation was measured in $CHCl_3$ (c=1) at 20°C with Polamat-A and Perkin–Elmer 241 polarimeters. Mass spectra were obtained on a Varian MAT 311A spectrometer. ^{1}H NMR spectra were obtained in $CDCl_3$ solution at 400 MHz (Bruker AM 400), or at 500 MHz (Bruker DRX 500), and the ^{13}C NMR spectra at 100 or 125 MHz on the same instruments. Chemical shifts are reported relative to TMS; J values are given in Hz. ^{13}C NMR spectra are ^{1}H-decoupled. For determination of the multiplicities, the APT pulse sequence was used. Elemental analysis was carried out in the analytical laboratory of the University of Szeged with a Perkin–Elmer CHN analyzer

‡ Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-181111. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CD2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccde.cam.ac.uk.].

§ The X-ray structure of **10a** will be published elsewhere.



Scheme 2. Synthesis of heterocyclic estrone derivatives **10**, **11** and **13**.

Table 1. Reaction conditions and physical data

Entry	Substrate	Reagent	Product(s)	Time (h)	Temperature (°C)	Yield[a] (%)	Mp (°C)
1	**1**	NH_2OH[b]	**2**	6	65	90	131–133
2	**2**	$BF_3{\cdot}OEt_2$[c]	**5**	2	111	85	121–122
3	**1**	MeNHOH[b]	**6**	72	65	75	147–149
4	**1**	**7a**+AcOH[c]	**8a**	2	rt	95	134–136
5	**1**	**7b**[b]	**8b**[d]	2	rt	–	–
6	**1**	**7c**+AcOH[c]	**8c**	2	rt	70	210–212
7	**8a**	$BF_3{\cdot}OEt_2$[c]	**10a**	2	0	79	172–174
				2	111	10	
			11a	2	0	14	178–180
				2	111	68	
8	**8b**	–	**10b**	5	78	85	210–212
	8b	$BF_3{\cdot}OEt_2$[c]	**10b**	1	rt	88	
9	**1**	NH_2NH_2+ACOH[c]	**12**	1	rt	95	181–182
10	**13**	$BF_3{\cdot}OEt_2$[c]	**13**	2	111	74	260–263

[a] After purification by column chromatography.
[b] The hydrochloride salts were used in basic MeOH.
[c] Catalytic amount.
[d] **8b** could not be isolated in pure form due to its instability.

model 2400. All solvents were distilled prior to use. The reactions were monitored by TLC on Kieselgel-G (Merck Si 254 F) layers (0.25 mm thick). The spots were detected by spraying with 5% phosphomolybdic acid in 50% aqueous phosphoric acid. The R_f values were determined for the spots observed by illumination at 254 and 365 nm.

4.1.1. Synthesis of 16,17-*seco*-3-methoxyestra-1,3,5(10)16-tetraen-17-al oxime (2). Secoestrone 3-methyl ether **1** (298 mg, 1.00 mmol) and hydroxylamine hydrochloride (69 mg, 1.00 mmol) were dissolved in MeOH (5 mL) and a solution of NaOH (200 mg, 5 mmol) in MeOH (5 mL) was added. The mixture was refluxed for 6 h until complete conversion (TLC) was achieved. The solution was then poured into water (10 mL), saturated with NH_4Cl and extracted with $CHCl_3$ (3×10 mL). The combined organic layer was dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by column chromatography (silica gel, CH_2Cl_2) and recrystallized from light petroleum to give 282 mg (90%) of pure **2** as colorless crystals. Mp 131–133°C; R_f 0.50 (*tert*-butyl methyl ether/$CHCl_3$=5:95); $[\alpha]_D^{25}$=+90.2 (c=1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 3H, 18-H_3), 1.22–1.75 (overlapping multiplets, 6H), 2.05–2.41 (overlapping multiplets, 5H), 2.85 (m, 2H, 6-H_2), 3.78 (s, 3H, 3-OMe), 4.99 (m, 2H, 16a-H_2), 5.83 (m, 1H, 16-H), 6.63 (d, 1H, J=2.6 Hz, 4-H), 6.72 (dd, 1H, J=8.6, 2.6 Hz, 2-H), 7.19 (d, 1H, J=8.6 Hz, 1-H), 7.29 (s, 1H, 17-H) and 7.92 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6 (C-18), 25.8, 27.4, 30.2, 34.1, 37.7, 40.7 (C-8), 41.5 (C-13), 43.2 (C-9), 47.5 (C-14), 55.2 (3-OMe), 111.7 (C-2), 113.4 (C-4), 114.9 (C-16a), 126.3 (C-1), 132.1 (C-10), 137.8 (C-5), 139.4 (C-16), 157.5 (C-3) and 160.4 (C-17); EI-MS (70 eV) m/z (%): 313 (21) [M^+], 312 (48), 296 (99), 268 (17), 227 (31), 174 (59), 147 (26) and 110 (100); Anal. calcd for $C_{20}H_{27}NO_2$ (313.43): C, 76.64; H, 8.68, N, 4.47; found C, 76.72; H, 8.55; N, 4.70.

4.1.2. Synthesis of 3-methoxy-1′,3′,4′α,5′α-tetrahydro-isoxazolo[4′:5′,16:17]estra-1,3,5(10)-triene (5). To a solution of purified and dried aldoxime **2** (313 mg, 1.00 mmol) in toluene (5 mL), 48% $BF_3{\cdot}OEt_2$ (0.05 mL, 0.17 mmol) was added dropwise and the mixture was heated under a nitrogen atmosphere for 2 h at 111°C. Water (10 mL) was added to the mixture, which was next neutralized with $NaHCO_3$, and the organic phase was separated and dried over Na_2SO_4. After evaporation in vacuo, the crude product was purified by column chromatography (silica gel, *tert*-butyl methyl ether/light petroleum=50:50) to give 266 mg (85%) of pure **5** as a white solid, which was recrystallized from $CHCl_3$/light petroleum. Mp 121–122°C; R_f 0.36 (*tert*-butyl methyl ether/light petroleum=50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 3H, 18-H_3), 1.31–1.90 (overlapping multiplets, 9H), 2.20–2.38 (overlapping multiplets, 2H), 2.86 (m, 2H, 6-H_2), 3.14 (m, 1H, 16-H), 3.46 (d, 1H, J=7.0 Hz, 17-H), 3.73 (m, 1H) and 3.80 (m, 1H): 16a-H_2, 3.77 (s, 3H, 3-OMe), 6.64 (d, 1H, J=2.8 Hz, 4-H), 6.72 (dd, 1H, J=8.6, 2.8 Hz, 2-H) and 7.22 (d, 1H, J=8.6 Hz, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2 (C-18), 26.1, 28.0, 29.8, 32.8, 33.2, 38.8 (C-8), 43.3 (C-9), 44.1 (C-13), 46.2 (C-14), 48.8 (C-16), 55.1 (3-OMe), 74.2 (C-17), 79.1 (C-16a), 111.3 (C-2), 113.7 (C-4), 126.3 (C-1), 132.6 (C-10), 137.8 (C-5) and 157.3 (C-3); EI-MS (70 eV) m/z (%): 313 (21) [M^+], 227 (13), 225 (13), 186 (12), 173 (18), 147 (13), 91 (13) and 84 (18); Anal. calcd for $C_{20}H_{27}NO_2$ (313.43): C, 76.64; H, 8.68, N, 4.47; found C, 76.70; H, 8.75; N, 4.65.

4.1.3. Synthesis of 3-methoxy-1′-methyl-1′,3′,4′α,5′α-tetrahydro-isoxazolo[4′:5′,16:17]estra-1,3,5(10)-triene (6). Secoestrone 3-methyl ether **1** (298 mg, 1.00 mmol) and methyl hydroxylamine hydrochloride (84 mg, 1.00 mmol) were dissolved in a solution of NaOH (200 mg, 5 mmol) in MeOH (5 mL) and the mixture was refluxed for 72 h. The solution was then poured into water (10 mL), saturated with NH_4Cl and extracted with $CHCl_3$ (3×10 mL). The combined organic layer was dried over Na_2SO_4. After evaporation in vacuo, the crude product was purified by column chromatography (silica gel, *tert*-butyl methyl ether/$CHCl_3$=0.5:95.5) and recrystallized from acetone to give 246 mg (75%) of pure **6** as white crystals. Mp 147–149°C; R_f 0.22 (*tert*-butyl methyl ether/$CHCl_3$=5:95); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (s, 3H, 18-H_3), 1.12–2.35 (overlapping multiplets, 11H), 2.61 (s, 3H, N–Me), 2.84 (m, 2H, 6-H_2), 2.98 (d, 1H, J=9.7 Hz, 17-H), 3.14 (m, 1H, 16-H), 3.54 (dd, 1H, J=8.4, 3.9 Hz, 16aβ-H), 3.77 (s, 3H, 3-OMe), 4.08 (dd, 1H, J=8.4, 8.4 Hz, 16aα-H), 6.62 (d, 1H, J=2.8 Hz, 4-H), 6.70 (dd, 1H, J=8.5, 2.8 Hz, 2-H) and 7.19 (d, 1H, J=8.5 Hz, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (C-18), 27.0, 28.2, 30.2, 32.4, 38.4 (N–Me), 39.2, 42.9 (C-13), 44.2, 45.9, 46.9, 54.7 (C-16), 55.6 (3-OMe), 71.2 (C-16a), 84.0 (C-17), 111.9 (C-2), 114.2 (C-4), 126.7 (C-1), 133.0 (C-10), 138.2 (C-5) and 157.8 (C-3); EI-MS (70 eV) m/z (%): 327 (100) [M^+], 312 (3), 282 (3), 240 (7), 173 (3), 98 (22) and 84 (3); Anal. calcd for $C_{21}H_{29}NO_2$ (327.46): C, 77.02; H, 8.93, N, 4.28; found C, 77.15; H, 8.80; N, 4.51; X-ray data: small colorless crystal (0.50×0.40×0.40 mm^3); orthorhombic system, space group $P2_12_12_1$, Z=4, a=9.272(2), b=12.354(2), c=15.574(3) Å, V=1783.9 $Å^3$, d_c=1.219 g cm^{-3}, F(000)=712, λ(Mo Kα)=0.71073 Å, μ=0.077 mm^{-1}; 22486 data measured at 133(2) K (STOE-Siemens-Huber four circle diffractometer equipped with a Siemens CCD area detector), 3042 unique data (R_{int}=0.0539) of which 2514 considered as observed with $I \geq 2.0\ \sigma(I)$; empirical absorption correction. The structure was solved by direct methods using SHELXS-97.[12a] All non-hydrogen atoms were refined anisotropically against F^2 by full-matrix least-squares using SHELXL-97.[12] The hydrogen atoms were included in calculated positions and refined using a riding model. Refinement converged to $R_1(F)[I>2\sigma(I)]$=0.0339 and $wR_2(F^2)$= 0.0755 (for all data with goodness-of-fit S=1.056). In the final difference map, the residual electron density was found between −0.177 and 0.121 e $Å^{-3}$. In the packing of the molecules, only normal van der Waals contacts are observed. Lists of the fractional atomic coordinates, thermal parameters distances, bond and torsion angles have been deposited at the Cambridge Crystallographic Data Centre, UK, as Supplementary Material (CCDC-181111, CIF file).

4.1.4. Synthesis of 16,17-*seco*-3-methoxyestra-1,3,5(10)16-tetraen-17-al phenylhydrazone (8a). To a solution of secoestrone 3-methyl ether **1** (298 mg, 1.00 mmol) in EtOH (10 mL), phenylhydrazine **7a** (0.10 mL, 109 mg, 1.00 mmol) and 2 drops of glacial acetic acid were added. The mixture was stirred for 2 h at room temperature. The solution was then poured into water

(10 mL), the white precipitate was filtered and washed with water and dried. The product was recrystallized from $CHCl_3$/light petroleum to give 369 mg (95%) of pure **8a** as colorless crystals. Mp 134–136°C; R_f 0.57 ($CHCl_3$); $[\alpha]_D^{25}$=+63.8 (c=1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 3H, 18-H_3), 1.26–2.40 (overlapping multiplets, 11H), 2.84 (m, 2H, 6-H_2), 3.78 (s, 3H, 3-OMe), 4.89 (m, 2H, 16a-H_2), 5.84 (m, 1H, 16-H), 6.63 (d, 1H, J=2.5 Hz, 4-H), 6.72 (dd, 1H, J=8.5, 2.5 Hz, 2-H), 6.81 (t, 1H, J=7.3 Hz, 4′-H), 7.01 (d, 2H, J=7.7 Hz, 2′-H and 6′-H), 7.16 (s, 1H, 17-H) and 7.20 (m, 3H, 1-H, 3′-H and 5′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2 (C-18), 26.2, 27.5, 30.4, 34.2, 38.2, 41.2 (C-8), 42.3 (C-13), 43.4 (C-9), 47.8 (C-14), 55.2 (3-OMe), 111.7 (C-2), 112.5 (2C, C-2′ and C-6′), 113.5 (C-4), 114.5 (C-16a), 119.4 (C-4′), 126.4 (C-1), 129.2 (2C, C-3′ and C-5′), 132.4 (C-10), 137.9 (C-5), 140.1 (C-16), 145.6 (C-1′), 149.7 (C-17) and 157.5 (C-3); EI-MS (70 eV) m/z (%): 388 (100) [M^+], 297 (22), 296 (99), 225 (23), 173 (14), 110 (15) and 92 (14); Anal. calcd for $C_{26}H_{32}N_2O$ (388.55): C, 80.37; H, 8.30, N, 7.21; found C, 80.45; H, 8.22; N, 7.50.

4.1.5. Cyclization of 16,17-*seco*-3-methoxyestra-1,3, 5(10)16-tetraen-17-al phenylhydrazone (8a). *Method A*. Phenylhydrazone **8a** (389 mg, 1.00 mmol) was dissolved in ice-cold $CHCl_3$ (5 mL) and 48% $BF_3{\cdot}OEt_2$ (0.08 mL, 0.27 mmol) was added dropwise under a nitrogen atmosphere. The mixture was stirred for 2 h and then poured into water (10 mL), neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (3×10 mL). The organic layer was dried over Na_2SO_4. Evaporation in vacuo and purification by column chromatography (silica gel, $CHCl_3$) afforded 305 mg (79%) of **10a** and 54 mg (14%) of **11a** as white crystals, respectively. **10a** was recrystallized from light petroleum. Mp 172–174°C; R_f 0.33 ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 3H, 18-H_3), 1.20–2.50 (overlapping multiplets, 11H), 2.84 (m, 2H, 6-H_2), 2.96 (dd, 1H, J=13.3, 10.5 Hz, 16aβ-H), 3.63 (m, 1H, 16-H), 3.77 (s, 3H, 3-OMe), 4.20 (dd, 1H, J=10.5, 9.6 Hz, 16aα-H), 6.63 (d, 1H, J=2.4 Hz, 4-H), 6.72 (dd, 1H, J=8.6, 2.4 Hz, 2-H), 6.84 (t, 1H, J=7.4 Hz, 4′-H), 7.07 (d, 2H, J=8.2 Hz, 2′-H and 6′-H) and 7.23 (m, 3H, 1-H, 3′-H and 5′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7 (C-18), 25.9, 26.7, 26.8, 29.6, 32.9, 38.6, 40.8, 44.2, 45.0, 54.8 (C-16), 55.2 (3-OMe), 58.4 (C-16a), 111.5 (C-2), 113.9 (3C, C-4, C-2′ and C-6′), 119.3 (C-4′), 126.3 (C-1), 128.9 (2C, C-3′ and C-5′), 132.1 (C-10), 137.6 (C-5), 148.9 (C-1′), 157.6 (C-3) and 172.1 (C-17); Anal. calcd for $C_{26}H_{30}N_2O$ (386.53): C, 80.79; H, 7.82, N, 7.25; found C, 80.92; H, 7.65; N, 7.05.

Method B. Phenylhydrazone **8a** (389 mg, 1.00 mmol) was dissolved in toluene (10 mL) and 48% $BF_3{\cdot}OEt_2$ (0.08 mL, 0.27 mmol) was added dropwise on refluxing the mixture under a nitrogen atmosphere for 2 h. The solution was then poured into water (10 mL), neutralized with $NaHCO_3$ and extracted with toluene (3×10 mL). The organic layer was dried over Na_2SO_4. Evaporation in vacuo and purification by column chromatography (silica gel, $CHCl_3$) afforded 39 mg (10%) of **10a** and 261 mg (68%) of **11a** as white crystals, respectively. **11a** was recrystallized from $CHCl_3$/acetone. Mp 178–180°C; R_f 0.22 ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 3H, 18-H_3), 1.46–2.76 (overlapping multiplets, 11H), 2.84 (m, 2H, 6-H_2), 3.77 (s, 3H, 3-OMe), 6.66 (d, 1H, J=2.6 Hz, 4-H), 6.74 (dd, 1H, J=8.5, 2.6 Hz, 2-H), 7.21 (t, 1H, J=7.4 Hz, 4′-H), 7.23 (d, 2H, J=8.5 Hz, 1-H), 7.40 (t, 2H, J=7.4 Hz, 3′-H and 5′-H), 7.55 (s, 1H, 16a-H) and 7.63 (d, 1H, J=7.4 Hz, 2′-H and 6′-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.4 (C-18), 24.0, 26.3, 27.5, 29.7, 34.0, 37.7 (C-9), 41.1, 41.4 (C-8), 55.2 (3-OMe), 61.0 (C-14), 111.5 (C-2), 113.9 (C-4), 118.9 (2C, C-2′ and C-6′), 120.9 (C-4′), 124.2 (C-16), 125.3 (C-16a), 126.2 (C-1), 129.3 (2C, C-3′ and C-5′), 132.5 (C-10), 137.7 (C-5), 141.0 (C-1′), 157.3 (C-3) and 171.0 (C-17); Anal. calcd for $C_{26}H_{28}N_2O$ (384.53): C, 81.21; H, 7.34, N, 7.29; found C, 81.32; H, 7.25; N, 7.05.

4.1.6. Synthesis of 3-methoxy-1′-(*p*-methoxyphenyl)-4′β,5-dihydro-1*H*-pyrazolo[4′,3′:16,17]estra-1,3,5(10)-triene (10b). Secoestrone 3-methyl ether **1** (298 mg, 1.00 mmol), *p*-methoxy-phenylhydrazine hydrochloride **7b** (175 mg, 1.00 mmol) and NaOH (50 mg, 1.25 mmol) were dissolved in EtOH (5 mL). The mixture was stirred for 5 h at 78°C (method A) or 48% $BF_3{\cdot}OEt_2$ (0.05 mL, 0.17 mmol) was added under a nitrogen atmosphere and the solution was stirred at room temperature for 1 h (method B). The white precipitate obtained was filtered and dried. Recrystallization from CH_2Cl_2/light petroleum resulted in 354 mg (85%, method A) or 367 mg (88%) of pure **11b** as white crystals. Mp 210–212°C; R_f=0.23 (CH_2Cl_2); $[\alpha]_D^{25}$=+21.3 (c=1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 3H, 18-H_3), 1.28–2.41 (overlapping multiplets, 11H), 2.84 (m, 3H, 6-H_2 and 16aβ-H), 3.61 (m, 1H, 16-H), 3.76 (s, 6H, 3-OMe and 4′-OMe), 4.15 (dd, 1H, J=10.5, 9.6 Hz, 16aα-H), 6.62 (d, 1H, J=2.5 Hz, 4-H), 6.71 (dd, 1H, J=8.6, 2.5 Hz, 2-H), 6.84 (d, 2H, J=7.0 Hz, 2′-H and 6′-H), 7.03 (d, 2H, J=7.0 Hz, 3′-H and 6′-H), 7.20 (d, 1H, J=8.6 Hz, 1-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7 (C-18), 25.8, 26.5, 26.7, 29.6, 32.9, 38.6, 40.7 (C-13), 44.2, 45.2, 54.8 (C-16), 55.2 and 55.7 (2C, 3-OMe and 4′-OMe), 59.8 (C-16a), 111.5 (C-2), 113.9 (C-4), 114.4 (2C, C-2′ and C-6′), 115.5 (2C, C-3′ and C-5′), 126.3 (C-1), 132.2 (C-10), 137.6 (C-5), 143.7 (C-1′), 153.6 (C-4′), 157.6 (C-3), 172.1 (C-17); Anal. calcd for $C_{27}H_{32}N_2O_2$ (416.57): C, 77.85; H, 7.74, N, 6.72; found: C, 77.98; H, 7.54; N, 6.88.

4.1.7. Synthesis of 16,17-*seco*-3-methoxyestra-1,3, 5(10)16-tetraen-17-al 2′,4′-dinitro-phenylhydrazone (8c). To a solution of secoestrone 3-methyl ether **1** (298 mg, 1.00 mmol) and 2,4-dinitrophenylhydrazine **7c** (198 mg, 1.00 mmol) in EtOH (10 mL), 2 drops of glacial acetic acid was added. The mixture was stirred for 2 h at room temperature. The solution was then poured into water (10 mL), the yellow precipitate was filtered and washed with water and dried. The crude product was purified by column chromatography (silica gel, $CHCl_3$) to give 335 mg (70%) of pure **8c** as yellow crystals after recrystallization from $CHCl_3$. Mp 210–212°C; R_f 0.53 ($CHCl_3$); $[\alpha]_D^{25}$=+118.3 (c=1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 3H, 18-H_3), 1.32–2.47 (overlapping multiplets, 11H), 2.87 (m, 2H, 6-H_2), 3.79 (s, 3H, 3-OMe), 4.94 (m, 2H, 16a-H_2), 5.83 (m, 1H, 16-H), 6.64 (d, 1H, J=2.6 Hz, 4-H), 6.74 (dd, 1H, J=8.6, 2.6 Hz, 2-H), 7.21 (d, 1H, J=8.6 Hz, 1-H), 7.36 (s, 1H, 17-H), 7.94 (d, 1H, J=9.6 Hz, 6′-H), 8.30 (dd, 1H, J=9.6, 2.4 Hz, 5′-H), 9.13 (d, 1H, J=2.4 Hz, 3′-H) and 10.99 (s, 1H, N–H, 3′-H and 5′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0 (C-18), 25.8, 27.4,

30.2, 34.3, 37.7, 40.8, 43.2, 43.4 (C-13), 47.4 (C-14), 55.2 (3-OMe), 111.8 (C-2), 113.5 (C-4), 115.2 (C-16a), 116.6 (C-6′), 123.5 (C-3′), 126.3 (C-1), 128.9 (C-2), 129.9 (C-5′), 131.9 (C-10), 137.8 (2C, C-5 and C-4′), 139.3 (C-16), 145.2 (C-1′), 157.7 (C-3) and 160.7 (C-17); EI-MS (70 eV) *m/z* (%): 478 (37) [M^+], 296 (100), 225 (62), 191 (19), 174 (42), 173 (38), 171 (24), 147 (29) and 110 (37); Anal. calcd for $C_{26}H_{30}N_4O_5$ (478.55): C, 65.26; H, 6.32, N, 11.71; found C, 65.38; H, 6.05; N, 11.95.

4.1.8. Synthesis of *N,N′*-bis-[16,17-*seco*-3-methoxyestra-1,3,5(10)16-tetraen-17-al]-hydrazine (12). To a solution of secoestrone 3-methyl ether **1** (596 mg, 2 mmol) in EtOH (10 mL), 98% hydrazine hydrate (0.05 mL, 52 mg, 1.00 mmol) and 2 drops of glacial acetic acid were added. The mixture was stirred for 1 h at room temperature and then was poured into water. The white precipitate obtained was filtered and dried. Purification by column chromatography afforded 563 mg (95%) of pure **12** as white crystals. Mp 181–182°C; R_f=0.24 (*tert*-butyl methyl ether/ light petroleum=10:90); $[\alpha]_D^{25}$=+39.1 (*c*=1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 6H, 18-H_3 and 18′-H_3), 1.38–2.44 (overlapping multiplets, 24H), 2.85 (m, 4H, 6-H_2 and 6′-H_2), 3.78 (s, 6H, 3-OMe and 3′-OMe), 4.96 (m, 4H, 16a-H_2 and 16a′-H_2), 6.63 (d, 2H, *J*=2.7 Hz, 4-H and 4′-H), 6.72 (dd, 2H, *J*=8.7, 2.7 Hz, 2-H and 2′-H), 7.21 (d, 2H, *J*=8.7 Hz, 1-H and 1′-H) and 7.61 (s, 2H, 17-H and 17′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0 (2C, C-18 and C-18′), 26.0 (2C), 27.5 (2C), 30.4 (2C), 34.4 (2C), 37.4 (2C), 41.0 (2C, C-8 and C-8′), 42.6 (2C, C-13 and C-13′), 43.4 (2C, C-9 and C-9′), 47.2 (2C, C-14 and C-14′), 55.3 (3-OMe and 3′-OMe), 111.8 (2C, C-2 and C-2′), 113.6 (2C, C-4 and C-4′), 114.9 (2C, C-16a and C-16a′), 126.5 (2C, C-1 and C-1′), 132.4 (2C, C-10 and C-10′), 138.0 (2C, C-5 and C-5′), 139.8 (2C, C-16 and C-16′), 157.6 (2C, C-3 and C-3′) and 171.2 (2C, C-17 and C-17′); EI-MS (70 eV) *m/z* (%): 592 (100) [M^+], 323 (20), 297 (35), 296 (23), 173 (17) and 110 (12); Anal. calcd for $C_{40}H_{52}N_2O_2$ (592.87): C, 81.04; H, 8.84, N, 4.73; found C, 81.22; H, 8.98; N, 4.50.

4.1.9. Cyclization of *N,N′*-bis-[16,17-*seco*-3-methoxyestra-1,3,5(10)16-tetraen-17-al]-hydrazine (12). Compound **12** (593 mg, 1.00 mmol) was dissolved in toluene (10 mL) and 48% $BF_3{\cdot}OEt_2$ (0.10 mL, 0.23 mmol) was added dropwise under a nitrogen atmosphere. The solution was heated under reflux for 2 h until complete conversion (TLC) was achieved. The mixture was poured into water, neutralized with $NaHCO_3$ and the phases were separated. The organic layer was dried over Na_2SO_4 and was evaporated in vacuo. The crude product was purified by column chromatography (silica gel, *tert*-butyl methyl ether/light petroleum=90:10) and recrystallized from *tert*-butyl methyl ether/light petroleum to give 439 mg (74%) of pure **13** as white crystals. Mp 260–263°C; R_f=0.11 (*tert*-butyl methyl ether/light petroleum=50:50); $[\alpha]_D^{25}$=+90.4 (*c*=1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (s, 6H, 18-H_3 and 18′-H_3), 1.30–2.37 (overlapping multiplets, 22H), 2.73 (dd, 2H, *J*=12.0, 7.4 Hz, 16aβ-H and 16a′β-H), 2.80 (d, 2H, *J*=7.9 Hz, 17β-H and 17′β-H), 2.83 (m, 4H, 6-H_2 and 6′-H_2), 3.09 (m, 2H, 16β-H and 16′β-H), 3.28 (dd, 2H, *J*=12.0, 9.2 Hz, 16aα-H and 16a′α-H), 3.78 (s, 6H, 3-OMe and 3′-OMe), 6.62 (d, 2H, *J*=2.6 Hz, 4-H and 4′-H), 6.71 (dd, 2H, *J*=8.8, 2.6 Hz, 2-H and 2′-H) and 7.21 (d, 2H, *J*=8.8 Hz, 1-H and 1′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8 (2C, C-18 and C-18′), 26.6 (2C, C-11 and C-11′), 28.6 (2C, C-7 and C-7′), 30.3 (2C, C-6 and C-6′), 32.6 (2C, C-15 and C-15′), 33.4 (2C, C-12 and C-12′), 38.9 (2C, C-8 and C-8′), 42.4 (2C, C-16 and C-16′), 43.8 (2C, C-9 and C-9′), 44.0 (2C, C-13 and C-13′), 46.8 (2C, C-14 and C-14′), 55.6 (3-OMe and 3′-OMe), 61.0 (2C, C-16a and C-16a′), 78.4 (2C, C-17 and C-17′), 111.8 (2C, C-2 and C-2′), 114.2 (2C, C-4 and C-4′), 126.8 (2C, C-1 and C-1′), 133.4 (2C, C-10 and C-10′), 138.4 (2C, C-5 and C-5′) and 157.6 (2C, C-3 and C-3′); EI-MS (70 eV) *m/z* (%): 592 (100) [M^+]; Anal. calcd for $C_{40}H_{52}N_2O_2$ (592.87): C, 81.04; H, 8.84, N, 4.73; found C, 81.25; H, 8.90; N, 4.82.

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References

1. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984.
2. (a) Wilson, R. M.; Rekers, J. W.; Packard, A. B.; Elder, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 1633–1641. (b) Hassner, A.; Maurya, R.; Meskó, E. *Tetrahedron Lett.* **1988**, *29*, 5313–5316. (c) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687–5691. (d) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron Lett.* **2001**, *42*, 6715–6717.
3. (a) Kanemasa, S.; Tsuruoka, T.; Yamamoto, H. *Tetrahedron Lett.* **1995**, *36*, 5019–5022. (b) Kanemasa, S.; Tsuruoka, T. *Chem. Lett.* **1995**, 49–50. (c) Kanemasa, S.; Ueno, N.; Shirahase, M. *Tetrahedron Lett.* **2002**, *43*, 657–660.
4. (a) Gardiner, M.; Grigg, R.; Kordes, M.; Sridharan, V.; Vicker, N. *Tetrahedron* **2001**, *57*, 7729–7735. (b) Grigg, R.; Millington, E. L.; Thornton-Pett, M. *Tetrahedron Lett.* **2002**, *43*, 2605–2608. (c) Kitagaki, S.; Yasugahira, M.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2000**, *41*, 5931–5935. (d) Bayón, P.; de March, P.; Espinosa, M.; Figueredo, M.; Font, J. *Tetrahedron: Asymmetry* **2000**, *11*, 1757–1765.
5. (a) Wölfling, J.; Frank, É.; Schneider, Gy.; Bes, M. T.; Tietze, L. F. *Synlett* **1998**, 1205–1206. (b) Wölfling, J.; Frank, É.; Schneider, Gy.; Tietze, L. F. *Eur. J. Org. Chem.* **1999**, 3013–3020. (c) Bes, M. T.; Wölfling, J.; Usón, I.; Pelikán, Sz.; Tietze, L. F.; Frank, É.; Schneider, Gy. *Acta Crystallogr.* **1998**, *C54*, 1341–1343.
6. Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442–6443.
7. (a) Hassner, A.; Maurya, R. R.; Friedman, O.; Gottlieb, H. E. *J. Org. Chem.* **1993**, *58*, 4539–4546. (b) Hassner, A.; Falb, E.; Nudelman, A.; Albeck, A.; Gottlieb, H. E. *Tetrahedron Lett.* **1994**, *35*, 2397–2400.
8. Uddin, M. J.; Kikuchi, M.; Takedatsu, K.; Arai, K.-I.;

Fujimoto, T.; Motoyishiya, J.; Kakehi, A.; Iriye, R.; Shirai, H.; Yamamoto, I. *Synthesis* **2000**, *3*, 365–374.
9. (a) Fouchet, B.; Joucla, M.; Hamelin, J. *Tetrahedron Lett.* **1981**, *22*, 1333–1336. (b) Malomidou-Xenikaki, E.; Nicolaides, D. N. *Tetrahedron* **1986**, *42*, 5081–5088. (c) Sun, B.; Adachi, K.; Noguchi, M. *Tetrahedron* **1996**, *52*, 901–914.
10. Sugihara, Y.; Noda, K.; Nakayama, J. *Bull. Chem. Soc. Jpn* **2000**, *73*, 2351–2356.
11. (a) Burger, K.; Schickaneder, H.; Hein, F.; Gieren, A.; Lamm, V.; Engelhardt, H. *Liebigs Ann. Chem.* **1982**, *5*, 845–852. (b) Potacek, M.; Marek, R.; Zak, Z.; Trottier, J.; Janousek, Z.; Viehe, H. G. *Tetrahedron Lett.* **1993**, *34*, 8341–8344. (c) Abdul-Ghani, M. M.; Tipping, A. E. *J. Fluorine Chem.* **1995**, *73*, 203–212.
12. (a) Sheldrick, G. M. *SHELXL-97: Program for the Refinement of Crystal Structures*; University of Göttingen, Germany, 1997. (b) Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.