Regio- and Stereoselective Azidation of 19-Norsteroids

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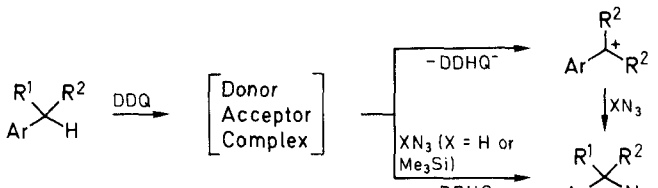
The proton at C-9 of 3-methoxyestra-1,3,5(10)-trienes **1–4** was replaced by an azido group regio- and stereospecifically in one step by reaction with hydrazoic acid in chloroform in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

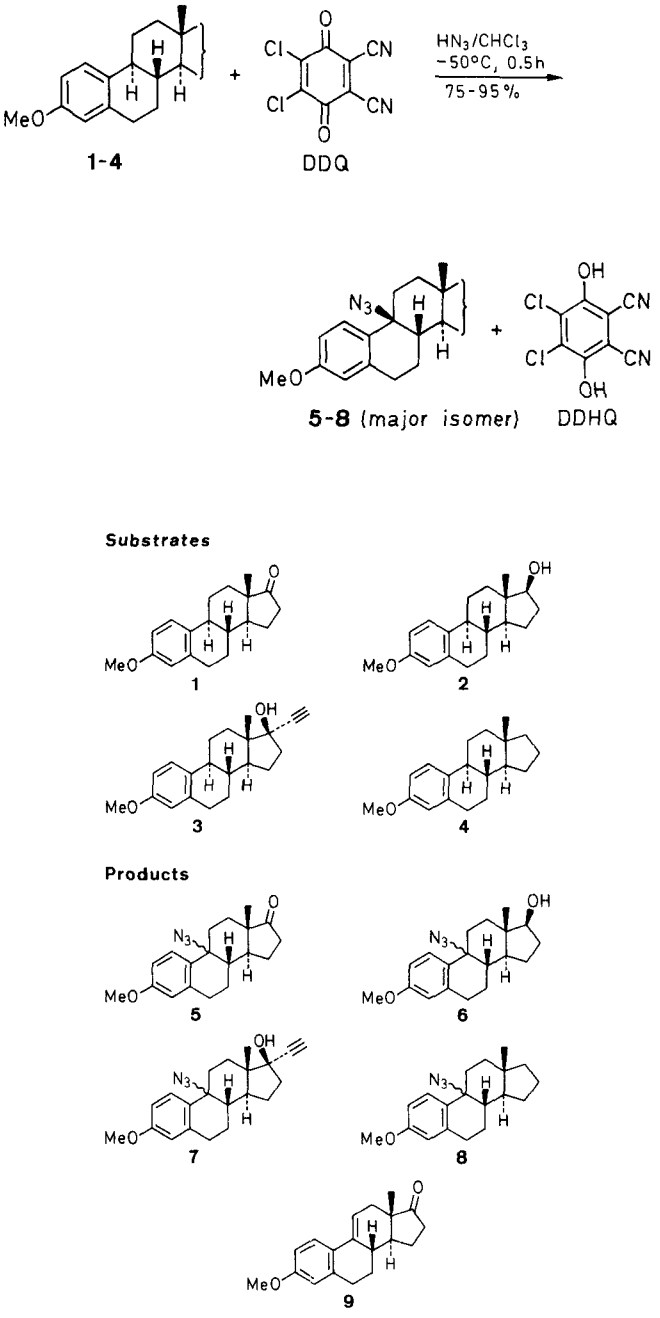
Considering the large spectrum of potential biological activities of estrogen derivatives, the regio- and stereoselective functionalization of 3-oxygenated estra-1,3,5(10)-trienes[1] is an area of considerable importance in steroid chemistry. Remarkable progress has been made in the regioselective introduction of various substituents at positions C-1, C-2 and C-4 of estrogens by rather straightforward procedures.[2] There is also a need for the direct functionalization of ring B/C positions of these steroids. Position C-9 in aromatic steroids is activated by benzylic conjugation and may be converted by oxidative nucleophilic substitution (S_NOx) to a C–N aliphatic bond.[3] (Scheme **1**). This method would lead directly to amino steroids, some of which have been studied as potent inhibitors and probes of the active site of cytochrome P-450$_{scc}$ by binding at the heme iron, e.g. in the biosynthesis of pregnenolone from 22-aminocholesterol.[4]



Scheme **1**

We report here on the regio- and stereoselective introduction of an azido group at the benzylic position of aromatic steroids **1–4** by an S_NOx reaction. Combination of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidant and hydrazoic acid as an azido donor leads to the smooth formation of 9-azido steroids **5–8** in high yield and with high selectivity (Scheme **2**).

The effectiveness of this procedure is clearly shown by the results summarized in Table 1. The reactions were performed at −15 °C in chloroform using equimolar amounts of DDQ (1.05 equiv) so that the formation of Δ^9-steroids, is suppressed; Δ^9-steroids are obtained in 60% yield at 20 °C when DDQ is used in excess (1.2 equiv, Table 1 entries 1, 2). The formation of the major 9β-azido isomer, as well as the effect of temperature on the reaction show that the thermodynamically less stable compound is formed. We presume that the asymmetric center is created in two distinct steps but in a concerted reaction.



Scheme **2**

The first step involves the hydride abstraction of the 9α hydrogen by DDQ from a donor-acceptor complex formed between the aromatic steroid and the electron deficient reagent acting as an acceptor. This interaction shields the α-face and causes the nucleophilic attack of the azide anion to occur at the more hindered β-face in the second step. The effect on decreasing the temperature is consistent with the results observed and leads to an increase in the yield of the 9β-azido derivative formed.

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Table 1. 9-Azido Steroids **5–8** Prepared

Entry	Substrate	Reaction Conditions				Products	HPLC Analysis (Ratio of **5** : **9**)	Yield[a] (%)	de[b] (%)
		DDQ (equiv)	$HN_3/CHCl_3$ (mmol/mL)	Temp. (°C)	Time (min)				
1	**1**	1.20	9.2/2	20	15	**5** + **9**	60 : 40	28	41
2	**1**	1.05	4.6/1	20	15	**5** + **9**	51.5 : 48.5	30	45
3	**1**	1.01	8/2	−12	30	**5** + **9**	45 : 55	37	46
4	**1**	1.01	4.8/1	−15	30	**5**	100	95	72
5	**1**	1.01	4.8/1	−50	30	**5**	100	95	80
6	**2**	1.01	4.8/1	−15	30	**6**	100	80	72
7	**2**	1.01	4.8/1	−50	30	**6**	100	[c]	84
8	**3**	1.01	4.8/1	−15	30	**7**	100	85	63
9	**3**	1.01	4.8/1	−50	30	**7**	100	[c]	74
10	**4**	1.01	4.8/1	−15	30	**8**	100	75	62.5
11	**4**	1.01	4.8/1	−50	30	**8**	100	[c]	82.5

[a] Yield of isolated product.
[b] The de values favoring the 9β isomer are average values from two runs (compounds **2**–**4**).
[c] Not isolated.

Table 2. Analytical and Spectral Data of Compounds **5–8** and **9** Prepared

Product[a]	mp (°C)	Molecular Formula[b] or Lit. mp (°C)	$[\alpha]_D^{20}$ (CH_2Cl_2)	IR (CH_2Cl_2) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
5a	glass	$C_{19}H_{23}N_3O_2$ (325.2)	+174.7° (c = 1.56)	2100, 1725, 1205	0.90 (s, 3H), 1.26–2.84 (m, 14H), 6.72 (d, 1H, J = 2.4), 6.80 (dd, 1H, J = 8), 7.36 (d, 1H, J = 8)
5b	glass		−43° (c = 2)		1.02 (s, 3H), 1.42–2.96 (m, 14H), 3.80 (s, 3H), 6.72 (d, 1H, J = 2.4), 6.80 (dd, 1H, J = 8), 7.36 (d, 1H, J = 8)
6a	76–78	$C_{19}H_{25}N_3O_2$ (327.2)	+94.2° (c = 1.29)	3600, 2100, 1605	0.78 (s, 3H), 1.28–2.92 (m, 15H), 3.80 (s, 3H), 6.70 (d, 1H, J = 6.2), 6.78 (dd, 1H, J = 9), 7.37 (d, 1H, J = 9)
6b					0.91 (s, 3H), 1.62–2.92 (m, 15H), 3.80 (s, 3H), 6.70 (d, 1H, J = 2.6), 6.78 (dd, 1H, J = 9), 7.37 (d, 1H, J = 9)
7a	155–158	$C_{21}H_{25}N_3O_2$ (351.2)	+28.2° (c = 3)	3600, 3300, 2100, 1605	0.89 (s, 3H), 1.27–2.90 (m, 16H), 3.80 (s, 3H), 6.70 (d, 1H, J = 26), 6.79 (dd, 1H, J = 8), 7.38 (d, 1H, J = 8)
7b			−115° (c = 0.5)		1.00 (s, 3H), 1.25–2.76 (m, 16H), 3.80 (s, 3H), 6.70 (d, 1H, J = 2.6), 6.79 (dd, 1H, J = 8), 7.38 (d, 1H, J = 8)
8a	130	$C_{19}H_{25}N_3O$ (311.2)	+94° (c = 1.3)	2100, 1610	0.78 (s, 3H), 1.31–2.95 (m, 16H), 3.80 (s, 3H), 6.74 (d, 1H, J = 2.4), 6.80 (dd, 1H, J = 8), 7.40 (d, 1H, J = 8)
8b					0.90 (s, 3H), 1.31–2.95 (m, 16H), 3.80 (s, 3H), 6.74 (d, 1H, J = 2.4), 6.80 (dd, 1H, J = 8), 7.30 (d, 1H, J = 8)
9	142	139–146	+187° (c = 2.5)	1740[c]	0.94 (s, 3H), 1.65–2.90 (m, 12H), 3.80 (s, 3H), 6.13 (m, 1H), 6.62 (d, 1H, J = 2.8), 6.73 (dd, 1H, J = 8), 7.54 (d, 1H, J = 8)

[a] The mixture of isomeric 9α (**5a**–**8a**) and 9β (**5b**–**8b**) azido steroids were separated by HPLC. Eluents: heptane/EtOAc (70 : 30) for products **5**, **6**, **8** and for the separation of **9** from **5**; heptane/EtOAc (40 : 60) for product **7**.
[b] Satisfactory microanalyses obtained: C ±0.25, H ±0.18, N ±0.26.
[c] KBr pellet.

This two step concerted mechanism competes with a second mechanism involving the dissociation of the donor-acceptor complex and formation of a carbocation (cf. Scheme **1**), which would be attacked principally on the α-face and giving the more thermodynamically stable diastereoisomer. The increase of the olefinic byproduct on increasing the temperature (Table 1, entries 2, 4, 5) and the concentration of HN_3 (Table 1, entries 3, 4) is also indicative of the presence of this carbocation during the course of the reaction. Hence good diastereoselectivity can be obtained by increasing the donor-acceptor interaction between the reagent and the substrate throughout the course of the reaction.

IR spectra were recorded on a Perkin-Elmer 457 spectrophotometer and ^{1}H-NMR spectra on a Bruker AC 200 spectrometer.

Caution! Exposure to vapors of HN_3 causes irritation of eyes and mucous membranes. All the reactions involving HN_3 should therefore be carried out in a well-ventilated hood.

9α- and 9β-Azido-3-methoxyestra-1,3,5(10)-trienes (5a and 5b); Typical Procedure:

DDQ (230 mg, 1.01 mmol) is added in portions in 15 min to a stirred mixture of **1** (284 mg, 1 mmol) and HN_3 solution in $CHCl_3$ (4.8 M, 1 mL, 4.8 mmol) at −50 °C in a dried Ar atmosphere. The deep coloration due to the charge-transfer complex disappears rapidly between each addition of DDQ, and 2,3-dichloro-5,6-dicyano-1,4-benzohydroquinone (DDHQ) precipitates out.

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After stirring at −50 °C for an additional 0.25 h, the pale orange suspension is filtered on Celite and the DDHQ is washed with CH_2Cl_2 (3 × 15 mL). Evaporation of the solvent at temperature below 40 °C gives an oily residue. The 9α,9β azido steroids **5a** and **5b** are separated by preparative HPLC using heptane/EtOAc (70:30) as eluent (Table 1). The spectral data of **5a** and **5b** are given in Table 2.

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(1) For steroid numbering, see:
Pure Appl. Chem. **1989**, *61*, 1783.
(2) Künzer, H.; Thiel, M. *Tetrahedron Lett.* **1988**, *29* 3223.
Bulman Page, P.C.; Hussain, F.; Maggs, J.L.; Morgan, P.; Park, B.K. *Tetrahedron* **1990**, *46*, 2059, and references cited therein.
(3) Guy, A.; Lemor, A.; Doussot, J.; Lemaire, M. *Synthesis* **1988**, 900.
(4) Nagashisa, A.; Foo, T.; Gut, M.; Orme-Johnson, W.H. *J. Biol. Chem.* **1985**, *260*, 846.
Sheets, J.J.; Vickery, L.E. *J. Biol. Chem.* **1983**, *258*, 1720, 11446.
Kellis Jr., J.T.; Sheets, J.J.; Vickery, L.E. *J. Steroid Biochem.* **1984**, *20*, 671.

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