Germylated steroids
3*. Synthesis of trialkylgermylated steroids

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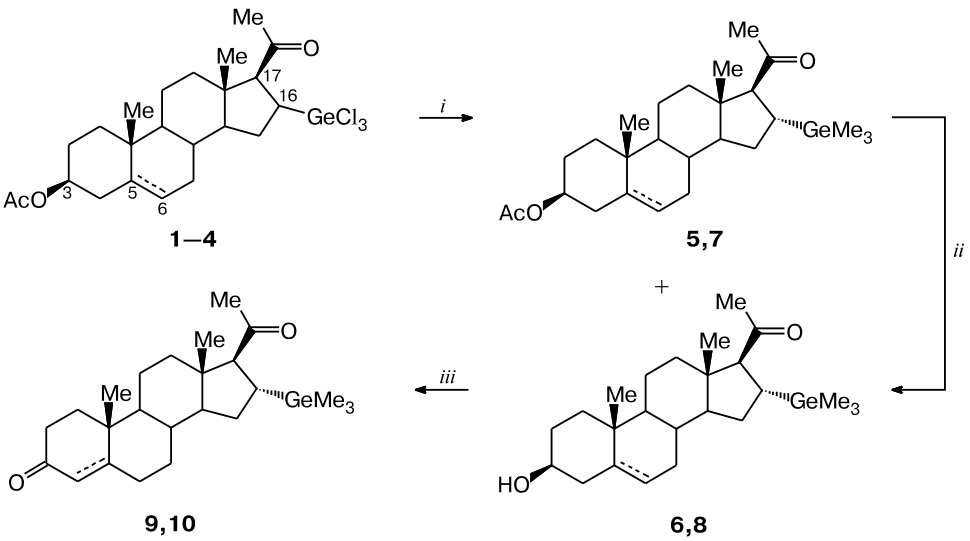
16α-Trichlorogermyl-3β-acetoxypregnan-20-ones react with MeMgBr to form the corresponding stable 16α-trimethylgermyl derivatives, which were further converted to 16α-trimethylgermylprogesterones. Analogous 16β-trichlorogermyl isomers do not react with the Grignard reagents.

Key words: organogermanium compounds, steroids, progesterones, methylmagnesium bromide.

Trichlorogermylated steroids (TCGS) **1**—**4** obtained earlier[2] from the steroid 16-en-20-ones can serve as starting compounds in the synthesis of series of steroids modified with germanium. According to the literature data,[3,4] organogermanium compounds possess a wide range of biological activity and, in contrast to organosilicon and organotin compounds, virtually are not toxic. However, for the conversion of TCGS to the target germylated steroids, it is necessary to transform the moisture-sensitive $GeCl_3$ group to more stable one, best of all to the trialkylgermyl group. In principle, this can be easily accomplished using the Grignard reaction.

We used MeMgBr under conditions which exclude reaction of this reagent with the 20-keto group present in the steroid molecules **1** and **2**.[5] Since the Grignard reagent partially removed the 3-*O*-acetyl group during the reaction, a five-fold excess of MeMgBr was required for the complete transformation of the $GeCl_3$ fragment (Scheme 1).

Scheme 1



1: 5αH, 16βH; **2**: Δ^5, 16βH; **3**: 5αH, 16αH; **4**: Δ^5, 16αH; **5**: 5αH; **6** and **9**: 5αH; **7** and **8**: Δ^5; **10**: Δ^4.

Reagents and conditions: *i*. MeMgBr, CuCl, Et_2O, THF; *ii*. K_2CO_3, MeOH; *iii*. $H_2Cr_2O_7$, acetone (for **6**) or $Al(OPr^i)_3$, cyclohexanone, toluene, reflux, 8 h (for **8**).

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Under these conditions, TCGS **1** led to a mixture of 16α-trimethylgermylated steroids **5** and **6**, which were separated by column chromatography on SiO_2. Similarly, TCGS **2** furnished acetate **7** and the corresponding alcohol **8**. Further alkaline hydrolysis of acetates **5** and **7** gave alcohols **6** and **8**, respectively. Trichlorogermylated steroids TCGS **3** and **4**, whose $GeCl_3$ groups are in the β-configuration, do not react with the Grignard reagent under the same conditions, which is apparently due to the steric hindrance for the reacting species to approach this group. Earlier,[1] TCGS **3** and **4** have not been converted to 16β-germatranes because of the same reasons. Direct trialkylgermylation of the preceding enones upon the action of triethylgermane, methyldiphenylgermane, and dimethylphenylgermane also failed even in the presence of catalytic amounts of 0.1 *M* H_2PtCl_6 in propan-2-ol.

Further oxidation of alcohol **6** with the Jones reagent gave ketone **9**, whereas the Oppenauer oxidation of unsaturated alcohol **7** led to enone **10**, which is a 16α-trimethylgermylated analog of progesterone (see Scheme 1).

The ^{1}H NMR spectra of all the trimethylgermylated steroids exhibit singlets for the protons of the Me_3Ge group in the high-field region δ 0.01—0.07.

The structures of the steroids obtained were confirmed by NMR spectroscopy. Assignment of the signals in the ^{1}H and ^{13}C NMR spectra of compounds **9** and **10** (Tables 1 and 2) were performed using the two-dimensional correlation procedures {^{1}H—^{13}C}HSQC, {^{1}H—^{13}C}HMBC, {^{1}H—^{1}H}COSY, {^{1}H—^{1}H}ROESY, {^{1}H—^{1}H}TOSCY. The results obtained do not contradict to the known data for the alkyl-substituted steroids.[6]

Experimental

All the solvents used were purified by standard procedures. Preparation of the starting TCGS was described earlier.[2] NMR spectra were recorded on Bruker WM (250 MHz), Bruker AC 200, and Bruker AV 600 spectrometers in $CDCl_3$. High resolution mass spectra were recorded on a Thermoscientific DSQ II Ultra GC-MS spectrometer with a TS-5MS capillary column and 5% phenylpolysilphenylene stationary phase.

The reaction progress was monitored by TLC in the hexane—acetone (4 : 1) solvent system. Substances were separated by column chromatography on Kieselgel 60 (0.063—0.2 mm silica gel, Merck).

Table 1. The ^{13}C NMR spectra of compounds **9** and **10***

C	δ		C	δ	
	9	**10**		**9**	**10**
1	38.54	35.72	12	39.08	38.84
2	38.09	33.91	13	45.16	44.91
3	211.66	199.28	14	57.04	56.63
4	44.61	123.93	15	27.67	27.62
5	45.16	170.74	16	22.59	22.56
6	28.79	32.70	17	67.18	66.97
7	21.57	31.91	18	13.71	13.61
8	35.46	35.62	19	11.42	17.35
9	53.65	53.61	20	208.95	208.75
10	35.67	38.55	21	31.61	31.60
11	31.67	21.18	22	−3.94	−3.96

* The spectra were recorded on a Bruker Avance 600 spectrometer (150.92 MHz).

Table 2. The ^{1}H NMR spectra of compounds **9** and **10***

H	δ, *J*/Hz		H	δ, *J*/Hz	
	9	**10**		**9**	**10**
1	2.04 (m)	2.065 (m)	8	1.44 (m)	1.56 (m)
	1.37 (m)	1.73 (td, *J* = 13.9, *J* = 4.6)	9	0.81 (m)	1.01 (m)
			11	1.73 (m)	1.67 (m)
2	2.41 (td, *J* = 14.2, 6.5)	2.45 (m)		0.96 (ddd, *J* = 12.5, *J* = 4.9)	1.48 (m)
	2.33 (m)	2.37 (m)	12	1.99 (m)	2.04 (m)
4	2.28 (t, *J* = 14.5)	5.65 (s)		1.46 (m)	1.48 (m)
	2.11 (m)		14	1.08 (dm, *J* = 11.3, *J* = 7.6)	1.08 (m)
5	1.55 (m)	—	15	1.56 (m)	1.57 (m)
6	1.35 (m)	2.43 (dd, *J* = 14.5, *J* = 4.9)	16	2.05 (m)	2.05 (m)
			17	2.47 (d, *J* = 10)	2.47 (d, *J* = 10)
		2.30 (dm, *J* = 14.5, *J* = 2.4)	18	0.66 (s)	0.7 (s)
7	1.67 (m)	1.89 (dm, *J* = 12.9)	19	1.03 (s)	1.20 (s)
			21	2.13 (s)	2.13 (s)
	1.42 (m)	1.08 (m)	22	0.05 (s)	0.01 (s)

* The spectra were recorded on a Bruker Avance 600 spectrometer (600.13 MHz).

Synthesis of trimethylgermylated steroids (TMGS) (general procedure). Tetrahydrofuran (2 mL) was added to a solution of MeMgBr (1.7 mL, 5 mmol) in diethyl ether and the mixture was concentrated to one-half of the volume. To the thus formed suspension, CuCl (40 mg, 0.4 mmol) and a solution of TCGS (540 mg, 1 mmol) in THF (2 mL) were added with stirring. After 1 h, the reaction mixture was treated with saturated aqueous NH_4Cl, extracted with benzene, the solvent was evaporated. The residue was purified by chromatography on SiO_2 using benzene as an eluent to isolate 3-acetoxy- and 3-hydroxy-substituted TMGS.

3β-Acetoxy-16α-trimethylgermyl-5α-pregnan-20-one (5). The yield was 42%, m.p. 137—140 °C (diethyl ether—hexane). ^{1}H NMR (250 MHz, $CDCl_3$), δ: 0.07 (s, 9 H, $GeMe_3$); 0.62 (s, 3 H, C(18), Me); 0.83 (s, 3 H, C(19), Me); 2.06 (s, 3 H, C(3), OAc); 2.13 (s, 3 H, C(21), Me); 2.46 (d, 1 H, H(17), *J* = 10 Hz); 4.70 (m, 1 H, H(3)). MS (ESI), *m/z*: 496.2838, 501.2392; calculated for $C_{26}H_{42}{}^{74}GeO_3$: *m/z* 496.2846 $[M + NH_4]^+$, 501.2400 $[M + Na]^+$.

3β-Acetoxy-16α-trimethylgermylpregn-5-en-20-one (7). The yield was 36%, m.p. 122—126 °C (MeOH). ^{1}H NMR (200 MHz,

$CDCl_3$), δ: 0.05 (s, 9 H, $GeMe_3$): 0.64 (s, 3 H, C(18), Me); 1.03 (s, 3 H, C(19), Me); 2.06 (s, 3 H, C(3), OAc); 2.14 (s, 3 H, C(21), Me); 2.46 (d, 1 H, H(17), J = 10 Hz); 4.60 (d, 1 H, H(3)); 5.37 (d, 1 H, H(16)). MS (ESI), *m/z*: 459.2286; calculated for $C_{26}H_{42}{}^{74}GeO_3$: *m/z* 459.2294 $[M + Na]^+$.

Alkaline hydrolysis of acetates 5 and 7 (general procedure). A solution of K_2CO_3 (100 mg, 0.72 mmol) in water (1 mL) was added to a solution of acetate **5** (or **7**) (100 mg, 0.21 mmol) in methanol (8 mL), the mixture was stirred for 24 h at room temperature and treated with water (10 mL). A precipitate that formed was filtered and dried *in vacuo* to obtain alcohol **6** (or **8**).

3β-Hydroxy-16α-trimethylgermyl-5α-pregnan-20-one (6). The yield was 45%, m.p. 176—180 °C (hexane). ^{1}H NMR (250 MHz, $CDCl_3$), δ: 0.07 (s, 9 H, $GeMe_3$); 0.61 (s, 3 H, C(18), Me); 0.79 (s, 3 H, C(19), Me); 2.13 (s, 3 H, C(21), Me); 2.44 (d, 1 H, H(17), J = 10 Hz); 3.60 (m, 1 H, H(3)). MS (ESI), *m/z*: 454.2715, 499.2239; calculated for $C_{24}H_{40}{}^{74}GeO_2$: *m/z* 454.2740 $[M + NH_4]^+$, 499.2243 $[M + Na]^+$.

3β-Hydroxy-16α-trimethylgermylpregn-5-en-20-one (8). The yield was 47%, m.p. 158—162 °C (MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ: 0.07 (s, 9 H, $GeMe_3$); 0.66 (s, 3 H, C(18), Me); 1.05 (s, 3 H, C(19), Me); 1.53 (s, 3 H, C(21), Me); 2.45 (d, 1 H, H(17), J = 10 Hz); 3.53 (d, 1 H, H(3)); 5.37 (s, 1 H, H(16)).

16α-Trimethylgermyl-5α-pregnane-3,20-dione (9). The Jones reagent (0.3 g, prepared from CrO_3 (72 g), H_2SO_4 (23 mL), and water (to 100 mL)) was added to a solution of alcohol **6** (140 mg, 0.32 mmol) in acetone (8 mL). The reaction mixture was stirred for 30 min and treated with water. A precipitate that formed was filtered and dried to obtained ketone **9** (110 mg, 78%), m.p. 220—223 °C (benzene—hexane). MS (ESI), *m/z*: 431.2344, 435.2295, 457.2112; calculated for $C_{24}H_{40}GeO_2$: *m/z* 431.2344 $[M + H]^+$ (for ^{70}Ge), 435.2318 $[M + H]^+$ (for ^{74}Ge), 457.2137 $[M + Na]^+$ (for ^{74}Ge).

16α-Trimethylgermylpregn-4-ene-3,20-dione (10). A solution of compound **8** (140 mg, 0.32 mmol), $Al(OPr^i)_3$ (180 mg, 0.88 mmol), and cyclohexanone (1.3 mL) in freshly distilled toluene (12 mL) was refluxed for 8 h with partial removal of the solvent. After cooling, the reaction mixture was treated with dilute AcOH, extracted with benzene. The extract was passed through a layer of SiO_2 to isolate dione **10** (112 mg, 80%), m.p. 139—142 °C (hexane). MS (ESI): 429.2171, 433.2165, 451.1993, 455.1963; calculated for $C_{24}H_{40}GeO_2$: *m/z* 429.2187 $[M + H]^+$ (for ^{70}Ge), 433.2161 $[M + H]^+$ (for ^{74}Ge), 451.2007 $[M + Na]^+$ (for ^{70}Ge), 455.1981 $[M + Na]^+$ (for ^{74}Ge).

The ^{1}H and ^{13}C NMR spectral data for compounds **9** and **10** are given in Tables 1 and 2.

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