Method for mild trimethylsilylation of the 14α-hydroxy group in ecdysteroids

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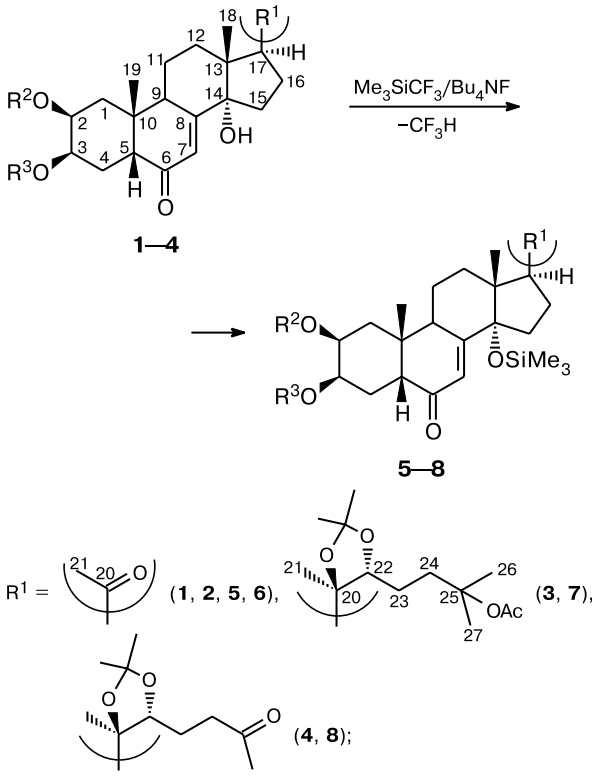
In the reactions of poststerone derivatives and 20-hydroxyecdysone with (trifluoromethyl)trimethylsilane catalyzed by tetrabutylammonium fluoride, the 14α-hydroxy group is readily subjected to trimethylsilylation.

Key words: ecdysteroids, poststerone, 20-hydroxyecdysone, derivatives, trimethylsilylation, (trifluoromethyl)trimethylsilane.

To analyze ecdysteroids by gas-liquid chromatography and to perform their directed transformations, it is necessary to protect the hydroxy groups. Trimethylsilyl ethers of ecdysteroids are most often synthesized with the use of *N*,*O*-bis(trimethylsilyl)acetamide and *N*-(trimethylsilyl)imidazole. However, trimethylsilylation of the 14α-hydroxy group proceeds only under drastic conditions (at a temperature higher than 100 °C) and is complicated by undesirable side processes.[1]

We developed a procedure for trimethylsilylation of the 14α-hydroxy group in ecdysteroids and applied it to derivatives of poststerone (**1**, **2**) and 20-hydroxyecdysone (**3**, **4**) (compounds **1**—**3** were prepared according to procedures described previously,[2—4] compound **4** was prepared by ozonolysis of the dehydration product at the 25-OH group of 20-hydroxyecdysone diacetonide[5]). The reactions of **1**—**4** with (trifluoromethyl)trimethylsilane (Me_3SiCF_3) in the presence of catalytic amounts of tetrabutylammonium fluoride (TBAF) afforded the corresponding 14α-(trimethylsilyloxy) derivatives **5**—**8** in high yields.

The transformation of the 14α-OH group into 14α-$OSiMe_3$ is evidenced from a substantial decrease in polarity of the reaction products ($\Delta R_f = 0.4$—0.5) and also from the presence of signals at δ 0.09—0.12 (^{1}H) and 1.79—1.81 (^{13}C) in the NMR spectra of compounds **5**—**8**. In addition, the signals for the C(14), C(13), and C(9) atoms in the ^{13}C NMR spectra of compounds **5**—**8** are substantially shifted downfield ($\Delta\delta$ = 1.4—3.5) with respect to the corresponding signals in the spectra of the starting compounds **1**—**4**, which is indicative of the replacement of the hydrogen atom of the hydroxy group.[6] The positions of the signals of the O=C(6)—C(7)H=C(8) fragment in the ^{1}H and ^{13}C NMR spectra of the reaction products are virtually identical to those observed in the spectra of the corresponding starting compounds. The UV spectra also provide evidence for the retention of the ring B in compounds **5**—**8**. The IR spectra have a band at 840 cm^{-1} ($SiCH_3$) instead of a broad absorption band at 3450 cm^{-1} (OH).



The Me_3SiCF_3—Bu_4NF system is used for trifluoromethylation of carbonyl compounds.[7,8] It was noted that if protic impurities are present in the reaction mixture, the process is accompanied by evolution of volatile trifluoromethane as a side reaction. Apparently, this is the reason that the reactions with the hydroxy-containing

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compounds proceeded at the OH group to give trimethylsilylated derivatives **5**—**8** in the reactions of compounds **1**—**4**, respectively.

Experimental

The IR spectra were recorded on a Specord 75-IR spectrometer (in KBr pellets). The UV spectra were measured on a Specord M-40 spectrometer in $CHCl_3$. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument (300.13 MHz for ^1H and 75 MHz for ^{13}C) in $CDCl_3$ as the solvent. The chemical shifts are given in the δ scale relative to Me_4Si (internal standard). The melting points were measured on a Boetius stage. The specific rotation was determined on a Perkin—Elmer 141 polarimeter. The TLC was carried out on SiO_2 plates (Silufol); spots were visualized by spraying with a vanilline solution in ethanol acidified with sulfuric acid.

Trimethylsilylation of compounds 1—4 (general procedure). Tetrabutylammonium fluoride (1.6 mg, 0.006 mmol) was added to a stirred mixture of the corresponding substrate **1**—**4** (1 mmol) and Me_3SiCF_3 (0.17 g, 1.2 mmol) in anhydrous THF (3 mL) at 0 °C. The reaction was completed in 2 min (TLC control). The reaction mixture was concentrated and the residue was chromatographed on a column (3 g of SiO_2, elution with $CHCl_3$). The corresponding derivatives **5**—**8** were prepared.

2,3-Di-*O*-acetyl-14-*O*-(trimethylsilyl)poststerone (5). The yield was 83%. R_f 0.73 ($CHCl_3$—MeOH, 10 : 1), m.p. 77—80 °C, $[\alpha]_D^{21}$ +103 (*c* 0.87, $CHCl_3$). IR, ν/cm^{-1}: 840 ($SiCH_3$), 1250 (SiMe, OCOMe), 1665 (C=CC=O), 1700 (C=O), 1740 (COMe). UV, λ_{max}/nm (ε): 241 (15240). ^1H NMR, δ: 0.12 (s, 9 H, $SiMe_3$); 0.56 (s, 3 H, C(18)H_3); 1.01 (s, 3 H, C(19)H_3); 1.5—2.4 (m, 12 H, CH_2); 2.00 (s, 3 H, C(21)H_3); 2.10 (s, 3 H, MeCO); 2.13 (s, 3 H, MeCO); 2.39 (dd, 1 H, H(5), *J* = 13.2 Hz and *J* = 4.6 Hz); 2.99 (m, 1 H, H(9)); 3.12 (t, 1 H, H(17), *J* = 8.5 Hz); 5.02 (br.d, 1 H, H(2), *J* = 12.2 Hz); 5.36 (br.s, 1 H, H(3)); 5.85 (d, 1 H, H(7), *J* = 2.2 Hz). ^{13}C NMR, δ: 1.8 (SiMe), 16.3 (C(18)), 20.4 (C(11)), 21.0 and 21.0 ($\underline{C}H_3CO$), 21.4 (C(16)), 24.1 (C(19)), 29.1 (C(15)), 29.9 (C(12)), 30.3 (C(4)), 31.3 (C(21)), 33.8 (C(9)), 33.9 (C(1)), 38.4 (C(10)), 49.2 (C(13)), 50.8 (C(5)), 58.8 (C(17)), 66.8 (C(3)), 68.5 (C(2)), 87.4 (C(14)), 122.8 (C(7)), 162.6 (C(8)), 170.0 and 170.2 (Me$\underline{C}$O), 201.4 (C(6)), 209.3 (C(20)).

2,3-*O*-Isopropylidene-14-*O*-(trimethylsilyl)poststerone (6). The yield was 84%. R_f 0.75 ($CHCl_3$—MeOH, 20 : 1), m.p. 70—72 °C, $[\alpha]_D^{25}$ +40 (*c* 1.75, $CHCl_3$). IR, ν/cm^{-1}: 840 and 1250 (SiMe), 1664 (C=CC=O), 1700 (C=O). UV, λ_{max}/nm (ε): 242 (13100). ^1H NMR, δ: 0.11 (s, 9 H, $SiMe_3$); 0.75 (s, 3 H, C(18)H_3); 1.03 (s, 3 H, C(19)H_3); 1.37 and 1.50 (both s, 6 H, CMe_2); 2.13 (s, 3 H, C(21)H_3); 1.25—2.40 (m, 13 H, CH, CH_2); 2.67 (m, 1 H, H(9)); 3.13 (t, 1 H, H(17), *J* = 8.5 Hz); 4.19 (m, 1 H, H(2)); 4.26 (m, 1 H, H(3)); 5.81 (d, 1 H, H(7), *J* = 2.1 Hz). ^{13}C NMR ($CDCl_3$), δ: 1.8 (SiMe); 16.3 (C(18)), 21.0 (C(11)), 21.5 (C(16)), 23.9 (C(19)), 26.2 (C(15)), 26.3 and 28.5 ($\underline{C}H_3C\underline{C}H_3$), 29.6 (C(12)), 31.6 (C(4)), 37.2 (C(1)), 37.4 (C(10)), 49.9 (C(13)), 50.2 (C(5)), 58.9 (C(17)), 71.5 (C(3)), 72.4 (C(2)), 87.6 (C(14)), 108.2 (OCO), 122.4 (C(7)), 162.5 (C(8)), 201.9 (C(6)), 209.3 (C(20)).

25-*O*-Acetyl-2,3:20,22-di-*O*-isopropylidene-14-*O*-(trimethylsilyl)-20-hydroxyecdysone (7). The yield was 98%. R_f 0.80 ($CHCl_3$—MeOH, 20 : 1), m.p. 62—64 °C, $[\alpha]_D^{25}$ +88 (*c* 0.39, $CHCl_3$). IR, ν/cm^{-1}: 840 (SiMe), 1250 (SiMe, OCOMe), 1665 (C=CC=O), 1740 (COMe). UV, λ_{max}/nm (ε): 242 (12800). ^1H NMR, δ: 0.10 (s, 9 H, $SiMe_3$); 0.70 (s, 3 H, C(18)H_3); 1.03 (s, 3 H, C(19)H_3); 1.12 (s, 3 H, C(21)H_3); 1.26, 1.28, 1.38, and 1.42 (all s, 12 H, CMe_2); 1.45 (s, 3 H, C(26)H_3); 1.47 (s, 3 H, C(27)H_3); 1.94 (s, 3 H, $\underline{C}H_3CO$); 1.20—2.20 (m, 17 H, CH, CH_2); 2.34 (dd, 1 H, H(17), *J* = 11.0 Hz, *J* = 5.0 Hz); 2.63 (m, 1 H, H(9)); 3.61 (dd, 1 H, H(22), *J* = 8.5 Hz, *J* = 4.0 Hz); 4.18 (m, 1 H, H(2)); 4.25 (m, 1 H, H(3)); 5.77 (d, 1 H, H(7), *J* = 1.7 Hz). ^{13}C NMR, δ: 1.7 (SiMe), 16.2 (C(18)), 21.1 (C(11)), 21.4 (C(16)), 21.8 ($\underline{C}H_3CO$), 22.3 (C(19)), 23.2 (C(23)), 23.9 (C(21)), 26.1 (C(15)), 25.6, 26.0, 26.3, and 26.7 ($\underline{C}H_3C\underline{C}H_3$), 28.4 (C(27)), 28.9 (C(26)), 29.4 (C(12)), 31.3 (C(4)), 36.2 (C(9)), 37.0 (C(1)), 37.2 (C(10)), 38.3 (C(24)), 49.3 (C(17)), 49.6 (C(13)), 50.1 (C(5)), 71.4 (C(3)), 72.4 (C(2)), 81.3 (C(22)), 81.7 (C(25)), 84.0 (C(20)), 87.9 (C(14)), 106.7, 106.2 (OCO), 121.6 (C(7)), 162.9 (C(8)), 170.2 (Me$\underline{C}$O), 202.0 (C(6)).

2,3:20,22-Di-*O*-isopropylidene-25-oxo-27-*nor*-ponasterone (8). The yield was 82%. R_f 0.80 ($CHCl_3$—MeOH, 10 : 1), m.p. 81—84 °C, $[\alpha]_D^{25}$ +53 (*c* 3.52, $CHCl_3$). IR, ν/cm^{-1}: 840 (SiMe), 1250 (SiMe), 1664 (C=CC=O), 1700 (C=O). UV, λ_{max}/nm (ε): 242 (12900). ^1H NMR, δ: 0.09 (s, 9 H, $SiMe_3$); 0.72 (s, 3 H, C(18)H_3); 1.03 (s, 3 H, C(19)H_3); 1.12 (s, 3 H, C(21)H_3); 1.29, 1.33, 1.38, and 1.49 (all s, 12 H, CMe_2); 1.25—2.18 (m, 15 H, CH, CH_2); 2.16 (s, 3 H, C(26)H_3); 2.36 (dd, 1 H, H(17), *J* = 10.7 Hz, *J* = 4.9 Hz); 2.49—2.65 (m, 3 H, H(9), H(24)); 3.62 (dd, 1 H, H(22), *J* = 10.1 Hz, *J* = 2.3 Hz); 4.17 (m, 1 H, H(2)); 4.23 (m, 1 H, H(3)); 5.79 (d, 1 H, H(7), *J* = 1.7 Hz). ^{13}C NMR, δ: 1.8 (SiMe), 16.3 (C(18)), 21.2 (C(11)), 21.4 (C(16)), 21.9 (C(21)), 22.7 (C(23)), 24.0 (C(19)), 26.2 (C(15)), 26.3, 26.8, 28.5 and 28.9 ($\underline{C}H_3C\underline{C}H_3$), 29.5 (C(12)), 30.0 (C(26)), 31.3 (C(4)), 36.4 (C(9)), 37.1 (C(1)), 37.3 (C(10)), 40.9 (C(24)), 49.1 (C(17)), 49.7 (C(13)), 50.1 (C(5)), 71.5 (C(3)), 72.9 (C(2)), 80.3 (C(22)), 84.2 (C(20)), 88.1 (C(14)), 106.9 and 108.2 (OCO), 121.8 (C(7)), 163.0 (C(8)), 202.0 (C(6)), 207.9 (C(25)).

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