First Example of Trifluoromethylation in the Ecdysteroid Series. Synthesis of (20RS)-20-O-Hydro-20-trifluoromethylpoststerone

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Abstract—The title compound was synthesized by trifluoromethylation of poststerone derivatives with trimethyl(trifluoromethyl)silane in the presence of tetrabutylammonium fluoride.

Replacement of a methyl group by trifluoromethyl, which has a comparable size but is strongly electron-acceptor and lipophilic, endows an organic molecule with new physical, chemical, and biological properties [1, 2]. Many procedures for introduction of trifluoromethyl group into organic compounds are known [3], but the most promising is the use of trimethyl(trifluoromethyl)silane as nucleophilic trifluoromethylating agent [2, 4]. This reagent is applicable to various organic compounds, including keto steroids [4]; however, no examples of trifluoromethylation in the series of ecdysteroids have so far been reported.

We previously found [5, 6] that polyhydroxysterols do not undergo trifluoromethylation if at least one hydroxy group is not protected [6]. In this case, trifluoromethylation of the hydroxy rather than keto group occurs [5, 6]. We have succeeded in effecting trifluoromethylation of 14α-O-trimethylsilylpoststerone diacetate V and acetonide VI. Compounds V and VI were synthesized by oxidative cleavage at the C20–C22 bond [7] of 20-hydroxyecdysone (I) isolated from Serratula coronata [8]. The resulting poststerone II was converted into diacetate III and acetonide IV which were treated with Me3SiCF3 [5] to obtain ketones V and VI. Subsequent reactions of the latter with Me3SiCF3 in the presence of tetrabutylammonium fluoride gave the corresponding products of nucleophilic addition of CF3 group at the C20=O carbonyl group, (20RS)-14α,20-di-O-trimethylsilyl-20-(trifluoromethyl)poststerone diacetate VII and acetonide VIII. Here, the C8=O group remains intact, as follows from the IR, UV, and 1H and 13C NMR spectra. The fact that the addition of Me3SiCF3 occurred just at the C20=O group in V and VI is confirmed by the following data. The 13C NMR spectra of the products lack signal at about δC 209 ppm, but two quartets appear at δC 78 ppm* (J = 26 Hz) and δ 126 ppm (J = 288 Hz), which belong to the CCF3 fragment. In the 1H NMR spectra of compounds VII and VIII we observed two singlets (1:1) in the δ range from 1.2 to 1.7 ppm with an overall intensity corresponding to three protons (C21H3) instead of the singlet at δ 2.0 ppm from the acetyl group in the spectra of initial ketones V and VI), indicating that a new chiral (RS) center appeared at C20.

Hydrolysis of diacetate VII with sodium hydroxide in aqueous methanol and of acetonide VIII with 70% acetic acid afforded diol IX which was treated with 5% hydrochloric acid in tetrahydrofuran in the presence of tetrabutylammonium fluoride to obtain the target trifluoromethyl-substituted poststerone analog, compound X (Scheme 1).

EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR spectrometer in mineral oil. The UV spectra were measured on a Specord M-40 spectrophotometer from solutions in methanol and chloroform. The 1H and 13C NMR spectra. The fact that the addition of Me3SiCF3 occurred just at the C20=O group in V and VI is confirmed by the following data. The 13C NMR spectra of the products lack signal at about δC 209 ppm, but two quartets appear at δC 78 ppm* (J = 26 Hz) and δ 126 ppm (J = 288 Hz), which belong to the CCF3 fragment. In the 1H NMR spectra of compounds VII and VIII we observed two singlets (1:1) in the δ range from 1.2 to 1.7 ppm with an overall intensity corresponding to three protons (C21H3) instead of the singlet at δ 2.0 ppm from the acetyl group in the spectra of initial ketones V and VI), indicating that a new chiral (RS) center appeared at C20.

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Scheme 1.

\[ \text{I} \xrightarrow{\text{CrO}_3, \text{H}_2\text{SO}_4, \text{Me}_2\text{CO}} \text{II} \]

(1) \( \text{Ac}_2\text{O}, \text{pyridine, DMAP} \)
(2) \( \text{Me}_2\text{CO}, \text{H}_2\text{IP(}\text{Mo}_2\text{O}_{10}\text{)}\text{_4}\)

\[ \text{III, IV} \xrightarrow{\text{Me}_3\text{SiCF}_3, \text{Bu}_4\text{NF, THF}} \text{V, VI} \]

\[ \text{VII, VIII} \xrightarrow{\text{(1) 20\% NaOH/McOH}} \text{IX} \]

\[ \text{IX} \xrightarrow{5\% \text{HCl, Bu}_4\text{NF, THF}} \text{X} \]

\[ \text{III, V, VII, } R = R' = \text{Ac}; \text{ IV, VI, VIII, } RR' = \text{Me}_2\text{C}; \text{ IX, R = SiMe}_3. \]

\(^{14}C\) NMR spectra were obtained on a Bruker AM-300 instrument at 300.13 and 75 MHz, respectively, using chloroform-\(d\), methanol-\(d_4\), or benzene-\(d_6\) as solvent; the chemical shifts were measured relative to tetramethylsilane as internal reference. The melting points were determined on a Boetius microdevice. The optical rotations were measured with the aid of a Perkin-Elmer 141 polarimeter. TLC analysis was performed on Silufol plates; spots were visualized by treatment with a solution of 4-hydroxy-3-methoxy-benzaldehyde in ethanol, acidified with sulfuric acid.

2,3-Di-O-acetylpostosterone (or 2\(\beta\),3\(\beta\)-diacetoxy-14\(\alpha\)-hydroxy-5\(\beta\)-pregn-7-ene-6,20-dione) (III). Post-sterone (II) was prepared according to the procedure described in [7] from 20-hydroxyecdysone (I) isolated from \textit{Serratula coronata} [8]; mp 233–235\(^\circ\)C (cf. [7]), \([\alpha]_D^{18} = +137.2^\circ\) (c = 1.13, MeOH); the IR and \(^1H\) and \(^{13}C\) NMR spectra of II were identical to those reported in [9]. Compound II, 0.2 g (0.55 mmol), was dissolved in 2 ml of pyridine, 0.34 g (3.31 mmol) of acetic anhydride was added to the solution, and \(~0.1\) mg of 4-dimethylaminopyridine was then added.