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One-step synthesis of shidasterone from 20-hydroxyecdysone

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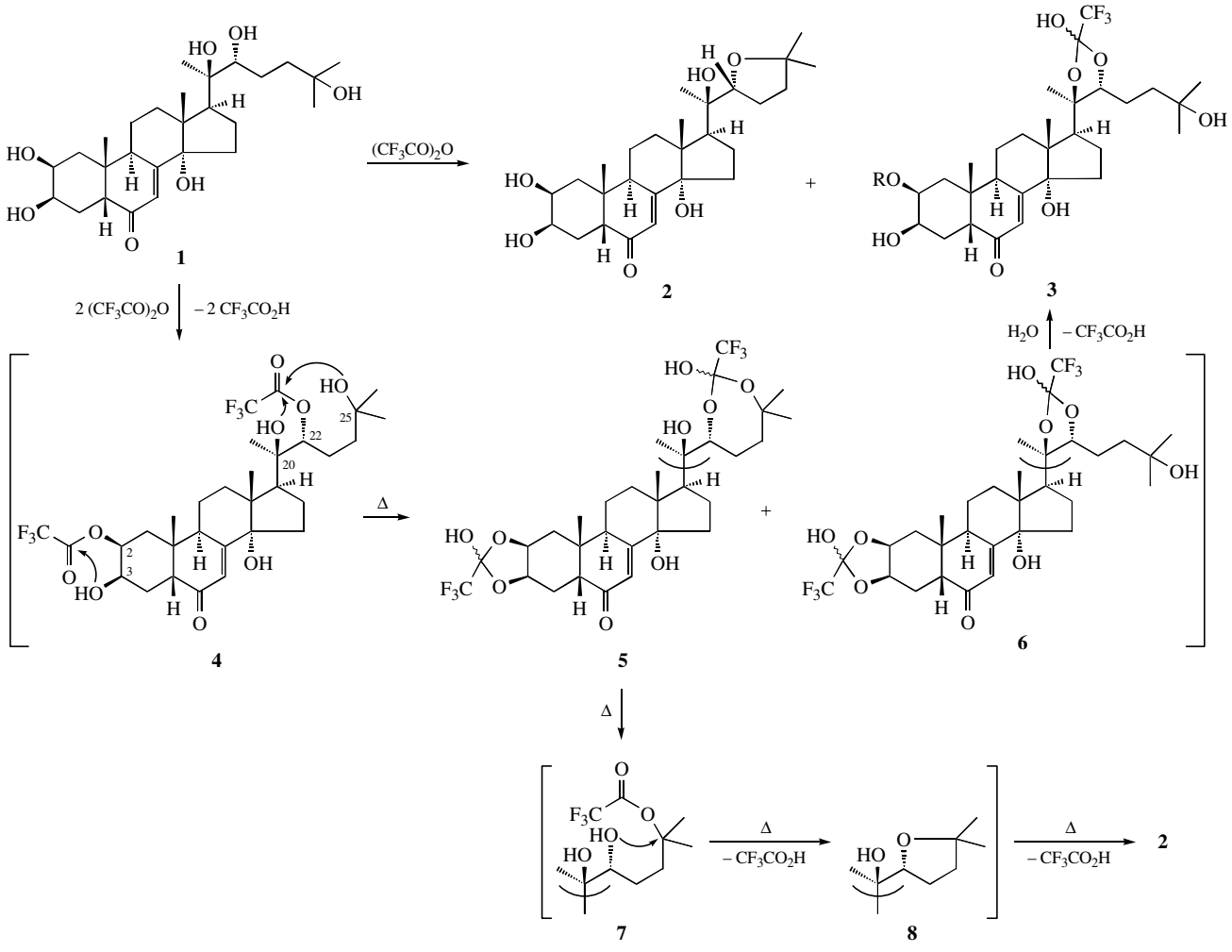
Shidasterone was prepared from 20-hydroxyecdysone by the reaction with an excess of trifluoroacetic anhydride in chloroform.

Ecdysteroids have a widespread occurrence in the animal and plant kingdoms. They control moulting and metamorphosis processes in insects and crustaceans.[1] Because they are pharmacologically active and non-toxic for mammals, these compounds and their analogues are of increasing interest to medicine.[2] Recently, the derivatives of ecdysteroids with heterocycles on their side-chain have attracted interest. Multistep syntheses of 20-hydroxyecdysone and ecdysone derivatives containing tetrahydrofuran rings were published.[3] The first compound, 20,25-anhydro-20-hydroxyecdysone, synthesised in six steps, is identical to the natural shidasterone isolated from the plants *Blechnum niponicum*[4] and *Vitex canescens*.[5]

Here, we describe the one-step synthesis of natural shidasterone **2** from 20-hydroxyecdysone **1**. The reaction proceeds under the action of a three-fold molar amount of trifluoroacetic anhydride (TFAA) on parent **1** in chloroform.† The reaction mixture was homogenised, and it gave a mixture of two compounds, which were chromatographically separated on SiO_2.‡ One of them ($R_f = 0.5$) was found to be identical (IR, UV, ^{1}H and ^{13}C NMR spectra) to shidasterone **2**, which was synthesised previously.[3] The other compound ($R_f = 0.6$) was identified as 20,22-*O*-(1*RS*-hydroxy-2,2,2-trifluoroethylidene)-20-hydroxyecdysone **3** [1′*R*- and 1′*S*-epimer mixture, ~1:1, retention time of 8.0 and 9.8 min (1:13.9 min), according to HPLC analysis (Zorbax Sil, 250×4.6 mm, solvent CH_2Cl_2–Pr^iOH–H_2O, 125:30:1.5, flow-rate of 2 cm^3 min^{-1})].

The structure of **3** was found from its ^{13}C NMR spectrum, which exhibited considerable downfield shifts of C-20 and C-22 signals with respect to the corresponding signals in the spectrum of **1**. These signals were doubled; this fact evidenced for different spatial orientations of OH and CF_3 groups at the C-1′ atom of the dioxolane ring. The signal of the C-1′ atom in the spectrum of **3** was present as two quadruplets (δ 112.8 and 113.1 ppm, $^2J_{CF}$ 47.1 and 47.6 Hz), and the signal of the neigh-

† The use of a two-fold molar amount of trifluoroacetic anhydride transformed 20-hydroxyecdysone into a 22*S*-analogue of shidasterone.[8] Under these conditions the free 25-hydroxyl attacks on C-22 with formation of shidasterone 22*S*-analogue according to an intramolecular S_N2 reaction.



Scheme 1

bouring CF_3 group also formed two quadruplets (δ 121.6 and 122.4 ppm, $^1J_{CF}$ 284.0 and 287.2 Hz). The structure of **3** has been confirmed by high-resolution FAB mass spectrometry (found $[M + H]^+$, *m*/*z* 577.2976; required $[M + H]^+$, *m*/*z* 577.2988).

Dioxolane **3** cannot be an intermediate in the transformation of **1** into **2** in as much as the interaction of **3** with a TFAA–TFA mixture (1:1 or 2:1) or with TFA in $CHCl_3$ did not give **2**.

The cyclic fragment of compound **3** exhibited the structure of 2-hydroxy-2-trifluoromethyl-l,3-dioxolane or 2/3-orthoester of trifluoroacetic acid. The cycles of this type result from the intramolecular interaction of the hydroxyl group with carbonyl of the acetoxy group leading to the migration of acyl groups in polyalcohols.[6] In trifluoroacetate, the interaction is increased due to a rise of a positive charge on carbonyl carbon. Thus, initially generated bis(trifluoroacetate) **4** [by analogy with a reaction of **1** and Ac_2O, in which OH(2) and OH(22) groups are acylated in the first order] is transformed to intermediates **5** or **6** (Scheme 1). In intermediate **5** a migration of the CF_3CO group to OH(25) hydroxyl probably proceeds with the following attack of OH(22) on the C(25) atom induced by the trifluoroacetyl group in intermediate **7** to result in a tetrahydrofurane ring. During the isolation of reaction products, the hydrolysis of 2/3-orthoester groups probably proceeds at secondary OH(2) and OH(3) groups in intermediates **6** and **8**, while 2/3-orthoester, including tertiary OH(20) group, remains in isolated compound **3**.

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‡ A mixture of TFAA (0.53 g, 2.52 mmol) and **1** (0.4 g, 0.83 mmol) in 5 ml of chloroform was stirred at room temperature until the reaction mixture became homogeneous (~15 min); then, it was stirred to the complete transformation of **1** (~20 min, TLC control on Silufol, $CHCl_3$–MeOH, 5:1). The reaction mixture was evaporated, the residue was chromatographed on a column with 20 g of SiO_2 (eluent: $CHCl_3$–MeOH, 6:1) to give 0.17 g (44.2%) of **2** (R_f 0.31, Silufol, $CHCl_3$–MeOH, 6:1), and 0.2 g (42%) of **3** (R_f 0.25, Silufol, $CHCl_3$–MeOH, 6:1).

For **2**: mp 214–215 °C, $[\alpha]_D^{15}$ +66.5 (*c* 2.17, MeOH) {lit.,[3] $[\alpha]_D^{25}$ +65.0 (*c* 0.18, $CHCl_3$); lit.,[2] mp 245–250 °C (decomp.)}. ^{1}H NMR (300 MHz, CD_3OD) δ: 5.81 (d, 1H, 7-H, *J* 2.1 Hz), 3.89–3.98 (m, 2H, 3-H and 22-H), 3.85 (dt, 1H, 2H, *J* 12.1 and *J* 3.7 Hz), 3.13 (m, 1H, 9-H, $w_{1/2}$ 24.0 Hz), 2.31–2.40 (m, 2H, 5-H, 17-H), 2.13 (td, 1H, 12-H_{ax}, *J* 12.7 and 5.0 Hz), 1.00–2.05 (m, 15H, CH_2 and 12-H_{eq}), 1.24 and 1.23 (s, 6H, 27-Me and 26-Me), 1.21 (s, 3H, 21-Me), 0.95 (s, 3H, 19-Me), 0.83 (s, 3H, 18-Me). ^{13}C NMR [75.5 MHz, CD_3OD, the signals were assigned using a pulse sequence of J-modulated spin echo (JMOD)] δ: 206.7 (C-6), 168.2 (C-8), 122.1 (C-7), 85.6 (C-22), 85.3 (C-14), 81.9 (C-25), 77.1 (C-20), 68.7 (C-2), 68.5 (C-3), 51.8 (C-5, C-17), 48.3 (C-13), 39.6 (C-24), 39.3 (C-10), 37.3 (C-1), 35.1 (C-9), 32.8 (C-4), 32.3 (C-12), 31.6 (C-15), 29.0 (C-27), 28.5 (C-23), 28.4 (C-26), 24.4 (C-19), 21.7 and 21.5 (C-11 and/or C-16), 20.7 (C-21), 18.2 (C-18). IR (KBr, ν/cm^{-1}): 1635 ($w_{h/2}$ 74), 3400 ($w_{h/2}$ 301). UV (λ_{max}/nm): 242.

For **3**: mp 138–140 °C (EtOAc), $[\alpha]_D^{15}$ +38.5 (*c* 0.1, MeOH). ^{1}H NMR (300 MHz, CD_3OD) δ: 5.83 (d, 1H, 7-H, *J* 2.1 Hz), 4.10 (dd, 1H, 22-H, *J* 9.8 and 3.2 Hz), 3.96 (m, 1H, 3-H, $w_{1/2}$ 15.0 Hz), 3.84 (dt, 1H, 2-H, *J* 12.4 and 4.2 Hz), 3.15 (m, 1H, 9-H, $w_{1/2}$ 24.0 Hz), 2.33–2.42 (m, 2H, 5-H, 17-H), 1.22–2.21 (m, 16H, CH_2), 1.41, 1.22 (s, 3H, 21-Me), 1.20 (s, 6H, 26-Me and 27-Me), 0.97 (s, 3H, 19-Me), 0.84 and 0.85 (s, 3H, 18-Me). ^{13}C NMR [75.5 MHz, CD_3OD, (JMOD)] δ: 206.6 and 206.5 (C-6), 167.5 and 167.3 (C-8), 122.4 and 121.6 (q, CF_3, $^1J_{CF}$ 287.2 and 284.0 Hz), 122.2 (C-7), 113.1 and 112.8 (q, C-1′, $^2J_{CF}$ 47.6 and 47.1 Hz), 90.3 and 88.0 (C-20), 87.4 and 84.3 (C-22), 85.3 and 85.1 (C-14), 71.0 (C-25), 68.7 (C-3), 68.4 (C-2), 51.7 (C-5), 50.7 and 50.6 (C-17), 48.3 (C-13), 41.6 (C-24), 39.1 (C-10), 37.2 (C-1), 35.0 (C-9), 32.8 (C-4), 32.2 (C-12), 31.7 and 31.5 (C-15), 29.5, 29.0 and 28.9 (C-27 and C-26), 25.0 and 24.3 (C-23), 24.5 (C-19), 22.5 (C-16), 21.1 (C-11), 18.4 and 18.1 (C-21), 17.5 (C-18). IR (KBr, ν/cm^{-1}): 1634, 3400 ($w_{h/2}$ 308). UV (λ_{max}/nm): 242. MS, *m*/*z* (%): 599 $[M + Na]^+$ (51.7), 577 $[M + H]^+$ (54.4), 559 $[M + H - H_2O]^+$ (100). FAB-MS, found: $[M + Na]^+$ 599.2788, calc. for $C_{29}H_{43}O_8F_3Na$: 599.2808; found: $[M + H]^+$ 577.2976, calc. for $C_{29}H_{44}O_8F_3$: 577.2988; found: $[M + H - H_2O]^+$ 559.2870, calc. for $C_{29}H_2O_7F_3$: 559.2883.