One-step synthesis of shidasterone 22*S*-analogue from ecdysterone

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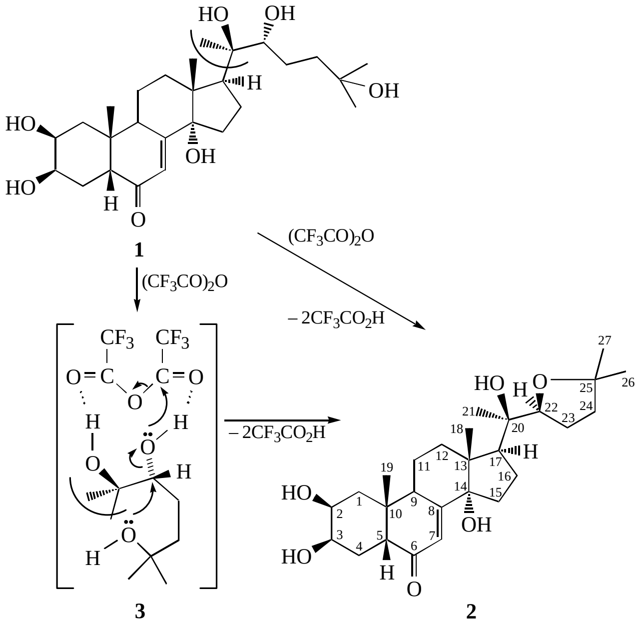
Shidasterone 22*S*-epimer was synthesised by the interaction of ecdysterone and trifluoroacetic anhydride in chloroform.

Ecdysteroids control the moulting and metamorphosis processes in insects and crustaceans.[1] At the same time, ecdysteroids and their analogues are of great interest for medicine. Derivatives of ecdysterone and α-ecdysone with a tetrahydrofurane ring in a side chain were tested for antitumour activity.[2] Shidasterone isolated from the plant *Blechnum niponicum*[3] is known to contain an ether linkage between C-22 and C-25, as was confirmed by mass and ^{13}C NMR spectra.[4] Shidasterone was synthesised by six-step transformation of ecdysterone, and the C-22 chiral centre in natural shidasterone was determined to be of the (*R*)-configuration.[5]

The paper deals with the one-step transformation from ecdysterone **1** to shidasterone 22*S*-analogue **2**, which proceeds under the action of a two-fold molar amount of trifluoroacetic anhydride.†

The dehydration of **1** into **2** was confirmed by the mass spectrum (MS) of the latter. The MS of **2**‡ contained the ions with *m*/*z* of 444, 426 and 408 corresponding to the fragmentation of M$^+$ with the elimination of one, two and three H_2O molecules, respectively, while that of initial compound **1** contained the ions M$^+$ (*m*/*z* 480) and 462, 444, 426 and 408 corresponding to the sequential elimination of four H_2O molecules from M$^+$.[6] Just as in the case of the known shidasterone, a downfield shift of the C-25 signal in the ^{13}C NMR spectrum of epimer **2** (δ 81.3 ppm) respecting the corresponding signal of **1** (δ 71.4 ppm) confirmed the formation of a C-22–C-25 ether linkage. On the other hand, an upfield signal of the chiral C-22 atom of **2** was observed with reference to the corresponding signal of shidasterone ($\Delta\delta$ 7.5 ppm). This fact evidenced the formation of the shidasterone 22*S*-analogue in our case. The ^{1}H NMR spectrum of 22*S*-epimer **2** differed from that of 22*R*-shidasterone by the position of two singlets of the geminal methyl groups of tetrahydrofurane ring, 26-Me and 27-Me (δ 1.56 and 1.58 ppm for epimer **2** and δ 1.24 and 1.25 ppm for shidasterone).[5]



Thus, the reaction changes the configuration of the C-22 atom by intramolecular S_N2 reaction with an attack of the 25-hydroxyl at C-22 in intermediate complex **3**.

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† A mixture of trifluoroacetic anhydride (0.35 g, 166.4 mmol) and ecdysterone **1** (0.4 g, 83.2 mmol) in 5 ml of chloroform was stirred for 15 min at room temperature. After homogenisation of the reaction mixture, TLC analysis (Silufol, $CHCl_3$–MeOH, 5:1) has evidenced the presence of **1** (R_f 0.36) and **2** (R_f 0.48) in a ~1:1 ratio. The product was chromatographed on a silica gel column (eluent $CHCl_3$–MeOH, 5:1) to give 0.16 g of **1** and 0.15 g (37.5%) of **2**, mp 180–182 °C (EtOAc), $[\alpha]_D^{15}$ +34.5° (*c* 0.17, MeOH), $[\alpha]_D^{15}$ +23.5° (*c* 0.08, $CHCl_3$); {for 22*R*-shidasterone $[\alpha]_D^{25}$ +65.0° (*c* 0.18, $CHCl_3$)[5]}, IR (KBr, ν/cm^{-1}): 3400 ($w_{h/2}$ 305), 1635 ($w_{h/2}$ 80). UV (λ_{max}/nm): 242. Found (%): C, 70.10; H, 9.15. Calc. for $C_{27}H_{42}O_6$ (%): C, 69.68; H, 9.07.

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‡ *Spectral data for* **2** [the signals in the ^{13}C NMR spectrum were assigned using a pulse sequence of *J*-modulated spin echo (JMOD)]: ^{1}H NMR (300 MHz, CD_3OD) δ: 5.80 (d, 1H, 7-H, *J* 2.1 Hz), 3.94 (m, 2H, 3-H and 22-H, $w_{h/2}$ 20.0 Hz), 3.85 (dm, 1H, 2-H, *J* 12.0 Hz), 3.15 (ddd, 1H, 9-H, *J* 12.0, 7.5 and 2.1 Hz), 2.36 (m, 2H, 5-H and 17-H, $w_{h/2}$ 25.0 Hz), 2.15 (m, 1H, 12-H_{ax}), 2.0–1.6 (m, 14H, 6CH_2, 1-H_{eq} and 12-H_{eq}), 1.58 (s, 3H, 27-Me), 1.56 (s, 3H, 26-Me), 1.42 (dd, 1H, 1-H_{ax}, *J* 12.0 and 13.0 Hz), 1.21 (s, 3H, 21-Me), 0.99 (s, 3H, 19-Me), 0.90 (s, 3H, 18-Me); ^{13}C NMR (75.5 MHz, CD_3OD) δ: 206.5 (C-6), 168.0 (C-8), 122.2 (C-7), 85.2 (C-14), 81.8 (C-25), 77.9 (C-22), 77.1 (C-20), 68.7 (C-2), 68.5 (C-3), 51.8 (C-5), 50.6 (C-17), 48.6 (C-13), 39.3 (C-10), 37.4 (C-1, C-24), 35.1 (C-9), 32.9 (C-4), 32.3 (C-12), 31.8 (C-15), 26.9 (C-23), 26.0 (C-26), 25.7 (C-27), 24.4 (C-19), 21.8 and 21.5 (C-11 and/or C-16), 20.7 (C-21), 18.1 (C-18). MS, *m*/*z*: 444 (21, $[M-H_2O]^+$), 426 (100, $[M-2H_2O]^+$), 411 (22, $[M-Me-2H_2O]^+$), 408 (28, $[M-3H_2O]^+$), 393 (16, $[M-Me-3H_2O]^+$), 345 (52, $[M-99-H_2O]^+$), 327 (69, $[M-99-2H_2O]^+$), 309 (24, $[M-99-3H_2O]^+$), 300 (64).