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Stereoselective Synthesis of 22,24-Dihydroxy Steroids

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Abstract—*anti*-22,24-Dihydroxy steroid derivatives were synthesized by successive transformation of 22-hydroxy-24-oxo steroids into β-silyloxy ketones and intramolecular reduction of the latter.

Difunctional organosilicon compounds R_2SiAB in which both A and B are reactive atoms showed good results in stereoselective synthesis of 1,3-diol derivatives due to the possibility for formation of stable complexes between the reagent and substrate [1]. This is especially important from the viewpoint of high level of regio- and stereocontrol in organic reactions.

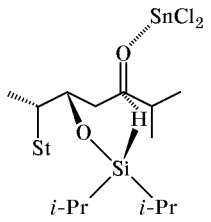
The ability of silanes to add to carbonyl compounds with subsequent intramolecular reduction of the resulting β-siloxy ketone into *trans*-dioxasilinane in the presence of Lewis acids can be utilized in stereoselective reduction of 22-hydroxy-24-oxo steroids. Dioxasilinanes thus formed are resistant toward a number of reagents [2, 3], which makes it possible to effect various transformations of the other moieties in the steroid molecule. We examined intramolecular reduction of β-hydroxy ketone **II** which was obtained in 72% yield by opening of the heteroring in isoxazole derivative **I** [4] over Raney nickel in the presence of aluminum chloride [5]. Compound **II** was treated with chlorodiisopropylsilane and triethylamine in the presence of 4-dimethylaminopyridine [2, 3]. The reaction mixture was heated under reflux and was then separated by flash chromatography to isolate β-siloxy ketone **III** in 91% yield (Scheme 1).

The structure of product **III** was confirmed by spectral data. The most important features of the IR spectrum of **III** are the lack of absorption band due to hydroxy group stretching vibrations and the presence of a band at 2096 cm^{-1} which is typical of Si–H bond. In the ^1H NMR spectrum of **III** we observed a more complicated pattern in the region δ 0.97–1.02 ppm and a broadened one-proton singlet at δ 4.23 ppm from proton on the silicon atom.

Treatment of **III** with tin(IV) chloride in methylene chloride at –78°C gave 58% of (22*S*,24*S*)-dioxasilinane **IV**, i.e., intramolecular reduction of the 24-oxo group was accompanied by cleavage of the 3α,5-cyclopropane ring and chlorine addition at position *3*. Apart from dioxasilinane **IV**, we isolated the product of cyclopropane ring opening, β-siloxy ketone **V**.

Compounds **IV** and **V** showed in the ^1H NMR spectra no signals assignable to cyclopropane ring protons, but a signal from 3-H appeared as a multiplet at δ 3.72 ppm (β-siloxy ketone **V**) and 3.78 ppm (dioxasilinane **IV**); also, a doublet from the vinyl proton on C^6 was observed at δ 5.35 and 5.36 ppm (J = 4.5 and 5 Hz), respectively. The ^1H NMR spectrum of **IV** contained signals from protons at C^{24} and C^{22} as multiplets at δ 3.65 and 4.15 ppm. No Si–H band was found in the IR spectrum of **IV**. The structure of **IV** was also confirmed by the ^{13}C NMR spectrum and fragmentation pattern in the mass spectrum.

According to the ^1H and ^{13}C NMR spectra, dioxasilinane **IV** is formed as a single isomer, in keeping with published data for intramolecular reduction of β-hydroxy ketones of the aliphatic series [2, 3]. The stereoselectivity of this process may be explained by formation of transition state **A**, where attack on the carbonyl group from the opposite side via alternative transition state cannon occur because of unfavorable steric and/or stereoelectronic factors.



A

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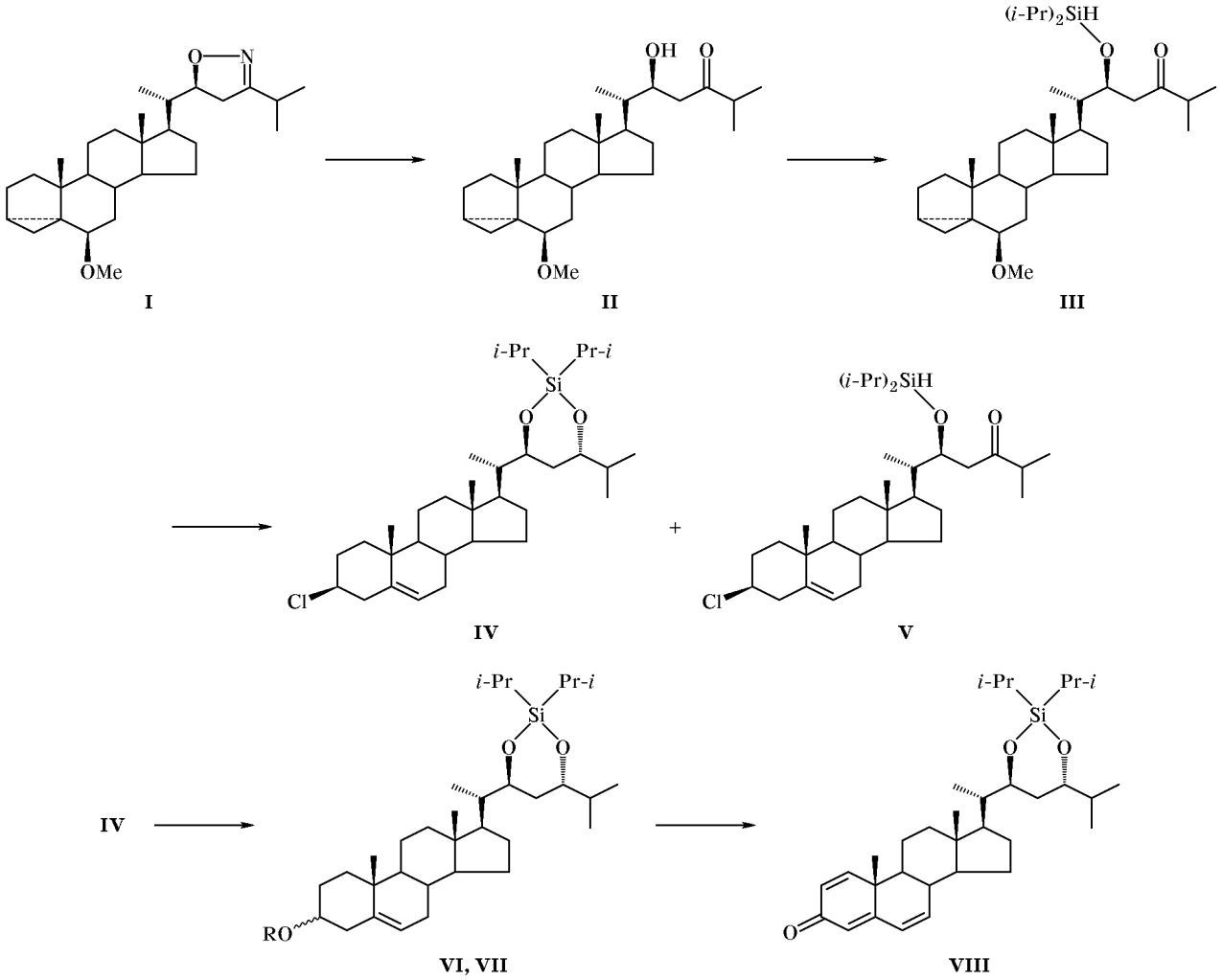
Scheme 1.



VI, R = Ac; **VII**, R = H.

The proposed procedure for stereoselective reduction of β-hydroxy ketones can be used to build up chiral C^{22} and C^{24} centers in the steroid side chain. Obviously, from (22*R*)-22-hydroxy-24-oxo steroid [6] we should obtain 22*R*,24*R*-dioxasilinane derivative which is diastereoisomeric to **IV**.

The stability of *trans*-dioxasilinane **IV** in some reactions was demonstrated by the synthesis of precursors of 1α-hydroxy vitamin D with a 3-oxo-1,4,6-triene moiety. Compound **IV** was converted into the corresponding 3-hydroxy derivative **VII** by heating with potassium acetate in boiling acetic acid (yield 85%) and subsequent hydrolysis of acetate **VI** with potassium hydroxide in ethanol (52%). The formation of alcohol **VII** followed from appearance of OH stretching vibration band (3450 cm^{-1}) in the IR spectrum.

Oxidation of homoallyl alcohol **VII** and dehydration of the carbonyl compound thus formed with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dioxane gave 47% of trienone **VIII** whose spectral parameters were consistent with those reported previously for structurally related compounds [7]. Its ^1H NMR spectrum contained a multiplet in the region δ 5.99–6.31 ppm, which was assigned to protons on C^1, C^2, C^4, and C^6, and a doublet at δ 7.05 ppm (J = 10 Hz) from the 7-H proton.

It is important that, in keeping with published data [2, 3], *trans*-dioxasilinanes can readily be converted into the corresponding *anti*-22,24-diols. Thus, hydroxy-containing chiral C^{22} and C^{24} centers in the side chain of steroid molecule were built up via successive silylation of the corresponding β-hydroxy ketones and intramolecular reduction of β-siloxy

ketones to dioxasilinanes in the presence of tin(IV) chloride. The dioxasilinane moiety is in fact a protected diol, so that further modification of steroid rings **A** and **B** is possible.

EXPERIMENTAL

The NMR spectra were measured on a Bruker AC-E 200 instrument operating at 200 MHz; chloroform-*d* was used as solvent, and tetramethylsilane, as internal reference. The IR spectra were obtained on a Biorad FTS-7UR-20 Fourier transform spectrometer. The mass spectra (electron impact, 70 eV) were recorded on a Shimadzu QP-5000B mass spectrometer with direct sample admission into the ion source (heating rate 20 deg/min from 30 to 350°C). The UV spectra were measured on a Perkin–Elmer UV-Vis spectrophotometer from solutions in methanol. The progress of reactions was monitored by TLC on Silufol UV-254 and Kieselgel 60 F254 (Merck) plates. Kieselgel 60 silica gel (40/60 μm, Merck) was used for preparative chromatographic separations.

(22*S*)-22-Hydroxy-6β-methoxy-3α,5-cyclocholestan-24-one (II). Raney nickel, 0.21 g, and aluminum chloride, 0.54 mmol, were added to a solution of 0.25 g (0.06 mmol) of isoxazole derivative **I** in 6 ml of a 5:1 methanol–water mixture. The mixture was stirred for 3 h, diluted with water, and extracted with diethyl ether. The extract was dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was subjected to column chromatography on silica gel using petroleum ether–ethyl acetate (9:1) as eluent to isolate 0.018 g (72%) of compound **II** as an oily substance. IR spectrum (film), ν, cm^{-1}: 3487, 1705, 1469, 1383, 1099. ^{1}H NMR spectrum, δ, ppm: 0.42 m (1H, 3-H), 0.61 m (1H, 4-H), 0.67 s (3H, 18-Me), 0.90 d (3H, 21-Me, *J* = 6.7 Hz), 0.98 s (3H, 19-Me), 1.07 d (6H, 26-Me, 27-Me, *J* = 6.9 Hz), 2.73 m (1H, 6-H), 3.28 s (3H, OMe), 4.12 m (1H, 22-H). ^{13}C NMR spectrum, δ_C, ppm: 12.1 q, 12.3 q, 13.0 t, 18.0 d.q, 19.3 q, 21.5 d, 22.8 t, 24.1 t, 24.9 t, 27.7 t, 30.5 d, 33.3 t, 34.9 t, 35.2 s, 20.2 t, 40.6 d, 41.5 d, 42.6 s, 43.3 s, 45.2 t, 47.9 d, 52.4 d, 56.2 q, 56.5 d, 68.9 d, 82.4 d, 216.5 s.

(22*S*)-22-Diisopropylsiloxy-6β-methoxy-3α,5-cyclocholestan-24-one (III). To a solution of 0.13 g (0.3 mmol) of β-hydroxy ketone **II** in 4 ml of freshly distilled petroleum ether we added in succession 0.084 ml (0.6 mmol) of triethylamine, 0.024 g (0.2 mmol) of 4-dimethylaminopyridine, and 0.1 ml (0.6 mmol) of chlorodiisopropylsilane. The mixture was heated for 3 h under reflux in a nitrogen atmosphere, cooled to room temperature, and subjected to flash chromatography in a column charged with silica gel (eluent petroleum ether–ethyl acetate, 9:1) to isolate 0.15 g (91%) of β-siloxy ketone **III** as an oily substance. IR spectrum (film), ν, cm^{-1}: 2096 (Si–H), 1714. ^{1}H NMR spectrum, δ, ppm: 0.42 m (1H, 3-H), 0.61 m (1H, 4-H), 0.66 s (3H, 18-Me), 0.91 d (3H, 21-Me, *J* = 7 Hz), 0.97–1.02 m (21H, 19-Me, CH**Me**$_2$), 2.63 d (2H, 23-H, *J* = 6.3 Hz), 2.73 m (1H, 6-H), 3.29 s (3H, OMe), 4.23 br.s (1H, SiH), 4.34 t (1H, 22-H, *J* = 6.3 Hz).

Intramolecular reduction of β-siloxy ketone III. A solution of 0.15 g (0.275 mmol) of ketone **III** in 4 ml of methylene chloride was cooled to –78°C, and 30 μl of tin(IV) chloride was added. The mixture was stirred for 2 h at that temperature under nitrogen, treated with a saturated solution of sodium hydrogen carbonate, and allowed to warm up to room temperature. The product was extracted into methylene chloride, and the extract was washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was subjected to column chromatography on silica gel using petroleum ether–ethyl acetate (100:1) as eluent to isolate 0.09 g of a mixture of β-siloxy ketone **V** and dioxasilinane **IV**. This mixture was dissolved in 2 ml of methylene chloride and treated with 5 μl of tin(IV) chloride according to the above procedure. We thus isolated 0.087 g (58%) of dioxasilinane **IV** and 0.007 g (5%) of β-siloxy ketone **V**.

(20*S*)-3β-Chloro-20-[(4*S*,6*S*)-2,2,6-triisopropyl-1,3,2-dioxasilinan-4-yl]pregn-5-ene (IV). Oily substance. IR spectrum (film), ν, cm^{-1}: 1463, 1382, 1243, 1140, 1094. ^{1}H NMR spectrum, δ, ppm: 0.66 s (3H, 18-Me), 0.80 d (3H, 21-Me, *J* = 6.6 Hz), 0.96 m (21H, 19-Me, CH**Me**$_2$), 3.65 m (1H, 6′-H), 4.15 m (1H, 4′-H), 3.78 m (1H, 3-H), 5.36 d (1H, 6-H, *J* = 5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 11.9 q, 12.4 q, 13.1 d, 13.6 d, 16.8 q, 16.9 q, 17.0 q, 17.1 q, 19.1 q, 19.3 q, 19.7 q, 21.0 t, 24.3 t, 27.7 t, 31.8 d+t, 33.0 d, 33.4 t, 35.5 t, 36.4 s, 39.1 t, 39.7 t, 42.0 s, 42.8 d, 43.4 t, 50.0 d, 52.0 d, 56.4 d, 60.3 d, 69.5 d, 77.6 d, 122.5 d, 140.8 s. Mass spectrum, *m*/*z*: 507, 506, 505 [*M* – *i*-Pr]$^+$, 289.

3β-Chloro-22-diisopropylsiloxypregn-5-en-24-one (V). Oily substance. IR spectrum (film), ν, cm^{-1}: 2097 (Si–H), 1711, 1463, 1383. ^{1}H NMR spectrum, δ, ppm: 0.62 s (3H, 18-Me), 0.87 d (3H, 21-Me, *J* = 7 Hz), 0.99–1.04 m (21H, 19-Me, CH**Me**$_2$), 3.72 m (1H, 3-H), 4.48 d.d (1H, 4′-H, ^1J = 10 Hz, ^2J = 3.3 Hz), 5.35 d (1H, 6-H, *J* = 4.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 11.7 q, 12.1 q, 13.0 q, 13.5 q, 14.0 d, 17.1 q, 17.7 q, 17.8 q, 17.9 q, 18.2 q, 19.3 q, 21.0 t, 24.3 t, 24.9 t, 31.7 d+t, 33.4 t, 36.4 s,

39.1 t, 39.7 t, 40.7 d, 41.5 d, 42.2 s, 43.4 t, 46.1 t, 50.0 d, 52.3 d, 56.9 d, 60.4 d, 70.5 d, 122.5 d, 140.8 s, 212.8 s.

(20*S*)-3ξ-Acetoxy-20-[(4*S*,6*S*)-2,2,6-triisopropyl-1,3,2-dioxasilinan-4-yl]pregn-5-ene (VI). To a solution of 0.04 g (0.073 mmol) of dioxasilinane **IV** in 2 ml of acetic acid we added 0.06 g (0.61 mmol) of potassium acetate, and the mixture was heated for 6 h under reflux, poured into water, and extracted with diethyl ether. The extract was washed with a saturated solution of sodium hydrogen carbonate and with water, dried over anhydrous sodium sulfate, filtered, and evaporated to isolate 0.033 g (85%) of acetate **VI** as an oily substance. IR spectrum (film), ν, cm^{-1}: 1730, 1463, 1382, 1255. ^{1}H NMR spectrum, δ, ppm: 0.65 s (3H, 18-Me), 0.79 d (3H, 21-Me, J = 6.6 Hz), 0.96 m (21H, 19-Me, CH**Me**$_2$), 2.01 s (3H, OAc), 3.64 m (1H, 6′-H), 4.10 m (1H, 4′-H), 4.58 m (1H, 3-H), 5.35 d (1H, 6-H, J = 4.9 Hz).

(20*S*)-20-[(4*S*,6*S*)-2,2,6-Triisopropyl-1,3,2-dioxasilinan-4-yl]pregn-5-en-3ξ-ol (VII). A mixture of 0.033 g (0.062 mmol) of acetate **VI** and 2 ml of a 3% solution of potassium hydroxide in ethanol was heated for 40 min under reflux. It was then poured into water and extracted with diethyl ether. The extract was washed with a saturated solution of ammonium chloride and with water, dried over anhydrous sodium sulfate, filtered, and evaporated to isolate 0.017 g (52%) of 3-hydroxy derivative **VII** as an oily substance. IR spectrum (film), ν, cm^{-1}: 3450, 1462, 1383. ^{1}H NMR spectrum, δ, ppm: 0.67 s (3H, 18-Me), 0.95 m (24H, 19-Me, 21-Me, CH**Me**$_2$), 2.01 s (3H, OAc), 3.53 m (2H, 3-H, 6′-H), 4.21 m (1H, 4′-H), 5.33 d (1H, 6-H, J = 4.3 Hz).

(20*S*)-20-[(4*S*,6*S*)-2,2,6-Triisopropyl-1,3,2-dioxasilinan-4-yl]pregna-1,4,6-trien-3-one (VIII). To a solution of 0.015 g (0.028 mmol) of compound **VII** in 2 ml of freshly distilled dioxane we added 0.21 g (0.0925 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. The mixture was heated for 3 h under reflux in a nitrogen atmosphere (the progress of the reaction was monitored by TLC) and cooled to room temperature, the precipitate was filtered off, and the filtrate was evaporated. The residue was subjected to column chromatography on silica gel using petroleum ether–ethyl acetate (2:1) as eluent to isolate 0.007 g (47%) of trienone **VIII** as an oily substance. IR spectrum (film), ν, cm^{-1}: 1650, 1455, 1383. UV spectrum: λ_{max} 299 nm (log ε 13990). ^{1}H NMR spectrum, δ, ppm: 0.60 s (3H, 18-Me), 0.91 m (24H, 19-Me, 21-Me, CH**Me**$_2$), 3.73 m (1H, 6′-H), 4.04 m (1H, 4′-H), 5.99–6.31 m (4H, 1-H, 2-H, 4-H, 6-H), 7.05 d (1H, 7-H, J = 10 Hz).

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