A Simple High-Yielding Synthesis of Spiro[cyclopropane-1,2′-steroids]

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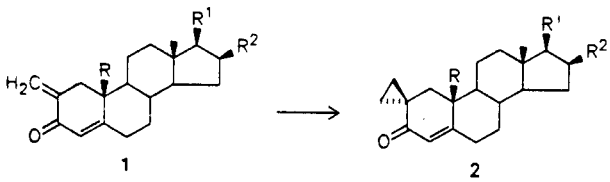
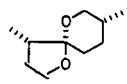
A high-yielding synthesis of biologically active spiro-[cyclopropane-1,2′-steroids] with a $\Delta^{4'}$-3′-one moiety by using the Simmons Smith reaction is described. 2-Methylene-4-en-3-one steroids are treated with methylene iodide (ratio 1:1).

In connection with an ongoing laboratory project aimed at the development of new steroid haptens[1], we required multigram quantities of spirocyclopropanes **2**. Literature reports many ways of preparing these biologically very potent compounds. The Michael addition using sulfur ylides[2,3] did not provide high yields of the title compounds in our hands, confirming to the reported results[4]. The diazo addition–decomposition[5] is not feasible for large-scale preparative purposes while other miscellaneous methods[6,7] are not adaptable for all positions of the steroids. Surprisingly, the Simmons Smith method, although performed on methylene-keto systems[8], has not been reported at all on these substrates.



1 **2**

1, 2	R	R^1	R^2	% Yield Corey's reagent	% Yield Simmons Smith
a[11]	Me	C_8H_{17}	H	59	80
b[11,15]	Me	OH	H	52	76
c[12]	Me	=O	H	–	90
d[13]	Me	$OCOCF_3$	H	–	62
e[14]	H			38	72

On performing the Simmons Smith reaction with the conventionally generated Zn-Cu couple in refluxing ether with a 1:1 ratio of methylene iodide and 2-methylene-4-en-3-one steroids and monitoring the progress of the reaction by using the UV absorbance of the substrate **1** and product **2**, it was observed that the reaction smoothly proceeds within about 4 h[9]. The purification of the products requires short-column chromatography with yields up to 80% in contrast to at best 50% obtainable with Corey's reagent. Workup involving pyridine[10] gave a 5% higher yield in one instance. Scaling up to 10 g was affected by a decrease in yield of about 5%.

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Experimental

All melting points are uncorrected. – Solvents were predried according to literature procedures. – Methylene iodide was purchased from Fluka AG and used as such. – NMR spectra were recorded in $CDCl_3$ with TMS as internal standard with Bruker AM500 or Varian VXR300S spectrometers. – IR spectra were recorded with a Perkin-Elmer 688 spectrometer. – UV spectra were obtained with a UV-VIS Shimadzu spectrophotometer. – Mass spectra were obtained with a Shimadzu QP1000 spectrometer. – Elemental analyses were performed with a CEST MOD.110 analyser.

General Reaction Method: Cupric acetate dihydrate (500 mg) was dissolved in hot boiling anhydrous acetic acid (15 ml, under nitrogen) and Zn dust (2.83 g, 325 mesh) added with stirring. The solution was allowed to cool after stirring for 30 s when all cupric acetate had been adsorbed. Excess acetic acid was syringed off and the reddish couple was freed of acetic acid by means of repeated washings with anhydrous diethyl ether (10 × 25 ml). A few drops of CH_2I_2 were added to the couple and gentle reflux started. A solution of **1** (3.1 mmol) and CH_2I_2 (3.2 mmol) in anhydrous diethyl ether (50 ml) was added dropwise under reflux. After the required time the couple was washed repeatedly with diethyl ether, and the organic layer was washed with acidic water. Evaporation and short column chromatography on SiO_2 with ethyl acetate/petroleum ether (b.p. 60–80°C) eluent yielded the product.

Spiro[4-cholestene-2,1′-cyclopropane]-3-one (**2a**): M.p. 80°C. – UV (MeOH): λ_{max} (lg ε) = 241.8 nm (4.239). – IR (KBr): $\tilde{\nu}$ = 1670 cm^{-1} (C=O), 1620 (C=C). – ^1H NMR ($CDCl_3$): δ = 5.79 (d, *J* = 1.59 Hz, 4-H), 2.27 (d, *J* = 13.92 Hz, 1β-H), 1.22 (s, 19-H_3), 0.91 (d, *J* = 6.4 Hz, 21-H_3), 0.876 (d, *J* = 1.46 Hz, 26-H_3), 0.855 (d, *J* = 1.46 Hz, 27-H_3), 0.79–0.71 (m, 1H, cyclopropyl), 0.70 (s, 18-H_3), 0.50–0.44 (m, 1H, cyclopropyl).

$C_{29}H_{46}O$ (410.7) Calcd. C 84.81 H 11.29
Found C 85.22 H 11.47 [Mol. mass 410 (MS)]

Spiro[cyclopropane-1,2′-testosterone) (**2b**): M.p. 147°C. – UV (MeOH): λ_{max} (lg ε) = 242 nm (4.189). – IR (KBr): $\tilde{\nu}$ = 3440 cm^{-1} (OH), 1650 (C=O), 1615 (C=C). – ^1H NMR ($CDCl_3$): δ = 5.798 (d, *J* = 1.83 Hz, 4-H), 3.657 (t, *J* =

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13.37 Hz, 1β-H), 1.242 (s, 19-H_3), 0.79 (s, 18-H_3), 0.80–0.74 (m, 1H, cyclopropyl), 0.43–0.50 (m, 1H, cyclopropyl).

$C_{21}H_{30}O_2$ (314.5) Calcd. C 80.21 H 9.62
Found C 79.81 H 9.47 [Mol. mass 314 (MS)]

Spiro[4-androstene-2,1'-cyclopropane]-3,17-dione (**2c**): M.p. 144°C. – UV ($CHCl_3$): λ_{max} (lg ε) = 244.8 m (4.225). – IR (KBr): $\tilde{\nu}$ = 1656.4 cm^{-1} (C=O), 1613.7 (C=C). – ^1H NMR ($CDCl_3$): δ = 5.82 (d, *J* = 1.47 Hz, 4-H), 1.258 (s, 19-H_3), 0.92 (s, 18-H_3), 0.745–0.808 (m, 1H, cyclopropyl), 0.45–0.52 (m, 1H, cyclopropyl).

$C_{21}H_{28}O_2$ (312.5) Calcd. C 80.72 H 9.03
Found C 80.60 H 9.24 [Mol. mass 312 (MS)]

Spiro[cyclopropane-1,2'-testosterone]-17β-trifluoroacetate (**2d**): M.p. 157°C. – UV ($CHCl_3$): λ_{max} (lg ε) = 244 nm (4.163). – IR (KBr): $\tilde{\nu}$ = 1779.5 cm^{-1} ($COCF_3$), 1659.6 (C=O), 1611.0 (C=C). – ^1H NMR ($CDCl_3$): δ = 5.81 (d, *J* = 1.65 Hz, 4-H), 4.80 (dd, *J* = 7.69, 9.16 Hz, 17-H), 1.243 (s, 19-H_3), 0.89 (s, 18-H_3), 0.75–0.81 (m, 1H, cyclopropyl), 0.45–0.52 (m, 1H, cyclopropyl).

$C_{23}H_{29}F_3O_3$ (410.5) Calcd. C 67.30 H 7.12
Found C 67.07 H 7.33
[Mol. mass 410 (MS)]

(25R)-Spiro[cyclopropane-1,2'-(19-nor-22xO-spirost-4-en)]-3-one (**2e**): M.p. = 197°C. – UV ($CHCl_3$): λ_{max} (lg ε) = 243.6 nm (4.079). – IR ($CHCl_3$): $\tilde{\nu}$ = 1656.0 cm^{-1} (C=O), 1618.5 (C=C). – ^1H NMR ($CDCl_3$): δ = 5.89 (t, *J* = 1.83 Hz, 4-H), 4.42 (dt, *J* = 7.69, 7.14 Hz, 16-H), 3.51–3.45 (m, 27-H), 0.97 (d, *J* = 6.77 Hz, 21-H_3), 0.84 (s, 18-H_3), 0.79 (d, *J* = 6.41 Hz, 26-H_3), 0.71–0.65 (m, 1H, cyclopropyl), 0.56–0.49 (m, 1H, cyclopropyl).

$C_{28}H_{40}O_3$ (424.6) Calcd. C 79.20 H 9.49
Found C 78.89 H 9.25 [Mol. mass 424 (MS)]

CAS Registry Numbers

1a: 127063-81-4 / **1b**: 2137-38-4 / **1c**: 2137-47-5 / **1d**: 127063-82-5 / **1e**: 127063-83-6 / **2a**: 127063-84-7 / **2b**: 2428-81-1 / **2c**: 17779-82-7 / **2d**: 127063-85-8 / **2e**: 127085-49-8

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[15] Required THF for solubilizing.

[33/90]