Long-Range Through-Bond Photoactivated Sigma Bond Cleavage in Steriods. Intramolecular Sensitized Debromination

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Supporting information

Synthesis. All reactions were conducted in oven-dried glassware, sealed with rubber septa and inerted with argon unless otherwise indicated.

3α-(Triphenylsiloxy)-5α-androstane (1). 3α-Hydroxy-5α-androstane (1.20 g, 4.35 mmol) was silylated with chlorotriphenylsilane (1.41 g, 4.78 mmol) in dry 15 mL of DMF with DIPEA (10.1 g, 78.3 mmol) at 0°C under Ar. The reaction mixture was stirred for 1 hour, then diluted with CH_2Cl_2 and washed quickly with H_2O only. The organic layer was dried over Na_2SO_4 and evaporated to give crude **1**, which was purified by column chromatography (10% EtOAc/hexane) to give white solid. A further recrystallization (EtOAc) was necessary and afforded colorless solid 1.7 g (70%). Mp: 158-159°C. ^{1}H NMR ($CDCl_3$) δ 0.68 (s, 3H), 0.73 (s, 3H), 0.76-1.99 (m, 24H), 4.19 (m, 1H), 7.26-7.47 (m, 9H), 7.60-7.63 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 11.5, 17.6, 20.6, 20.9, 25.6, 28.7, 29.4, 32.6, 32.8, 35.9, 36.2, 36.3, 39.0, 39.3, 40.5, 40.9, 54.6, 54.7, 68.6, 127.8, 129.9, 135.3, 135.5; MS (CI) *m/z* (%) 535 (M + H, 3); HRMS (FAB) : $C_{37}H_{46}SiO$, calculate mass 535.3396, actual mass 535.3392.

17α-Bromo-3α-(triphenylsiloxy)-5α-androstane (2). To a solution of 17β-hydroxy-5α-androstan-3-one (2.32 g, 8.0 mmol) in 30 mL of dry CH_2Cl_2 and 5.2 mL of pyridine was added Tf_2O (2.7 mL, 16.0 mmol) at 0°C. The solution was left standing for 15 min at 0°C and then, while rapid stirring, the excess reagent was quenched by stepwise addition of 20 mL of H_2O. 100 mL of CH_2Cl_2 was added and the organic layer was extracted with H_2O (2 × 30 mL), then dried with Na_2SO_4 and filtered. The solution was concentrated under vacuum to obtain brown solid 3.18 g (7.5 mmol, 94%). This compound was used for next step without further purification to avoid any moisture because it is sensitive and labile.

A solution of the 17β-triflate-5α-androstan-3-one (3.18 g, 7.5 mmol), anhydrous Li_2CO_3 (1.08 g, 14.7 mmol) and anhydrous LiBr (1.9 g, 22.0 mmol) in 10 mL of anhydrous DMF was heated at 70 °C under Ar for 2 hours. After the mixture was cooled, 80 mL of H_2O was added to result in precipitation of crude bromide. It was separated by filtration, washed with excess of H_2O, and dried in a vacuum desicator to obtain a solid 1.7g (4.7 mmol, 62%). Mp: 180-181.5°C (Lit.[1]: 181-183°C). ^{1}H NMR ($CDCl_3$) δ 0.84 (s, 3H), 1.02 (s, 3H), 1.13-2.41 (m, 21H), 2.55-2.73 (m, 1H), 4.24 (dd, 1H, J=1.0, 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 12.0, 18.9, 22.0, 25.2, 29.3, 32.4, 35.4, 36.2, 36.4, 36.5, 38.6, 38.9, 45.1, 46.5, 46.9, 48.9, 53.6, 66.5, 212.3; MS (EI) *m/z* (%) 352 and 354(M, 21, 20), 273(M-Br, 57); HRMS: $C_{19}H_{29}OBr$, calculate mass 353.1480, actual mass 353.1479.

The 17α-bromo-5α-androstan-3-one (1.37 g, 3.88 mmol) in dry 170 mL of tetrahydrofuran under Ar was stirred at -78°C for 10 min. K-Selectride (4.66 mL, 4.66 mmol of the 1 M solution in tetrahydrofuran) was added and solution was left for 45 min

at -78 °C. The mixture was warmed to room temperature, stirred for 20 min, and hydrolyzed by the addition of 22 mL of 50% ethanol in water. Then 150 mL of H_2O was added into the solution and the pH was adjusted to 7 by adding 5% HCl solution. After removal of THF at reduced pressure, the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, washed with saturated KCl solution (50 mL × 2) and dried over anhydrous Na_2SO_4. After removal of the solvent *in vacuo*, the crude product was purified by silica gel chromatography (40% EtOAc/60% hexane) to afford 17α-bromo-3α-hydroxy-5α-androstane 1.07 g (78%) as a white solid. The rest of 22% is the corresponding β-isomer. Mp: 95-96°C. ^{1}H NMR ($CDCl_3$) δ 0.78 (s, 3H), 0.81 (s, 3H), 0.87-1.73 (m, 19H), 1.84-1.88 (m, 1H), 2.14-2.25 (m, 1H), 2.56-2.60 (m, 1H), 4.04 (q, 1H, J = 3 Hz), 4.22 (dd, 1H, J = 0.9, 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 11.3, 17.6, 20.9, 24.8, 28.5, 29.1, 32.2, 35.0, 35.9, 36.0, 36.1, 36.2, 39.1, 46.1, 48.6, 53.7, 66.4, 66.6; MS (EI) *m/z* (%) 356 and 354 (M, 8, 8) 338 (84), 336 (83).

17α-bromo-3α-hydroxy-5α-androstane (0.93 g, 2.62 mmol) was silylated with chlorotriphenylsilane (0.85 g, 2.88 mmol) in dry 10 mL of DMF with DIPEA (8 mL) at room temperature under Ar. The reaction mixture was stirred for 12 hours and precipitate was formed. The precipitate was filtered, washed with plenty of H_2O and dried *in vacuo*. The crude product was purified by silica gel chromatography (5% EtOAc/95% hexane) to afford 1.16 g (72%) of **2** as white solid. These were further recrystallized from acetonitrile/THF (90:10) to afford the analytically pure title compound. Mp: 170-171.5°C. ^{1}H NMR ($CDCl_3$) δ 0.75 (s, 3H), 0.80 (s, 3H), 0.82-1.98 (m, 20H), 2.18-2.30 (m, 1H), 2.52-2.70 (m, 1H), 4.2-4.29 (m, 2H), 7.32-7.48 (m, 9H), 7.62-7.69 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 11.5. 17.7, 20.9, 24.8, 28.5, 29.4, 32.3, 32.7, 35.1, 36.1, 36.2, 36.2, 36.3,

39.2, 46.1, 48.7, 53.8, 66.5, 68.5, 127.8, 129.9, 135.3, 135.5; MS (FAB) *m/e* 615 (M+H), 613(M+H); HRMS : $C_{37}H_{45}SiOBr$, calculate mass 613.2501, actual mass 613.2493.

17α-Bromo-3α-(triphenylsiloxy)-5α-androstan-6-one (3). To a solution of 5.39 g (17.7 mmol) 17β-hydroxy-5α-androstan-3, 6-dione (from testosterone acetate which had been prepared from testosterone) in 60 mL of dry CH_2Cl_2 and 11.5 mL of pyridine was added Tf_2O (6.0 mL, 35.4 mmol) at 0°C. The solution was left standing for 15 min at 0°C and then, while rapid stirring, the excess reagent was quenched by stepwise addition of 400 mL of H_2O. 200 mL of CH_2Cl_2 was added and the organic layer was extracted with H_2O (2 × 60 mL), then dried with Na_2SO_4 and filtered. The solution was concentrated under vacuum to obtain brown solid 7.56 g (17.3 mmol, 98%). This compound was used for next step without further purification to avoid any moisture because it is sensitive and labile.

A solution of the 17β-triflate-5α-androstan-3, 6-dione (7.56 g, 17.3 mmol), anhydrous Li_2CO_3 (2.56 g, 34.6 mmol) and anhydrous LiBr (4.51 g, 52.0 mmol) in 30 mL of anhydrous DMF was heated at 70 °C under Ar for 2 hours. After the mixture was cooled, 150 mL of H_2O was added to result in precipitation of crude bromide. It was separated by filtration, washed with excess of H_2O and hexane, and dried in a vacuum desicator. 17α-bromo-5α-androstan-3, 6-dione was further purified by recrystallization from isopropyl alcohol/EtOAc (95% : 5 %) to obtain a white crystal 4.2 g (11.4 mmol, 66%). Mp: 180-182°C. ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 3H), 0.96 (s, 3H), 0.99-2.70 (m, 2OH), 4.5 (dd, 1H, J = 1.0, 6.6Hz); ^{13}C NMR ($CDCl_3$) δ 13.1, 17.9, 22.2 24.9, 35.3, 36.1, 37.4, 37.8, 38.5, 38.9, 41.6, 46.7, 47.1, 49.3, 53.3, 57.8, 65.5, 209.0, 211.4; MS(EI) *m/z*

(%) 368 (M^+, 29), 366 (M^+, 29), 339 (96), 337 (100); HRMS: $C_{19}H_{27}O_2Br$, calculate mass 367.1273, actual mass 367.1275.

17α-bromo-5α-androstan-3, 6-dione (2.80 g, 7.64 mmol) in 350 mL of dry THF under Ar was stirred at -78°C for 10 minutes. K-Selectride (8.02 mL, 8.02 mmol of the 1M solution in THF) was added and solution was left for 45 minutes at -78°C. The solution was warmed to room temperature, stirred for 20 minutes and hydrolyzed by the addition of 42 mL of 50% ethanol in water and adjusted the pH to 7 by using 5% HCl solution. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with saturated KCl solution, dried with Na_2SO_4 and removed at reduced pressure. The residue was purified by column chromatography(40% EtOAc/60% hexane) to give a pure colorless solid 2.1 g (76%). Mp: 185-186°C. ^{1}H NMR ($CDCl_3$) δ 0.73 (s, 3H), 0.82 (s, 3H), 1.16-2.61 (m, 20 H), 4.13-4.18 (m, 1H), 4.23 (dd, 1H, J = 0.9, 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 12.4, 17.5, 21.2, 24.4, 27.7, 28.2, 31.7, 34.8, 35.8, 38.5, 41.5, 46.3, 47.0, 49.1, 51.6, 53.2, 65.3, 65.4, 212.4; MS(EI) *m/z* (%) 370 (M^+, 31), 368 (M^+, 30).

17α-Bromo-3α-hydroxy-5α-androstan-6-one (1.6 g, 4.3 mmol) was silylated with chlorotriphylsilane (1.3 g, 4.3 mmol) in dry DMF (20 mL) with DIPEA (3.4 g, 26.1 mmol) at 0°C under Ar. The reaction mixture was stirred for 1 hour, then diluted with CH_2Cl_2 and washed quickly with H_2O only. The organic layer was dried over Na_2SO_4 and evaporated to give crude **3,** which was purified by column chromatography (10% EtOAc/90% hexane) to give white solid. A further recrystallization (EtOAc) was necessary and afforded colorless solid 1.9 g (70%). Mp: 182-183°C. ^{1}H NMR ($CDCl_3$) δ 0.67 (s, 3H), 0.87 (s, 3H), 1.21-2.35 (m, 18H), 2.54-2.70 (m, 1H), 2.89 (dd, 1H, J= 2.9, 12.2 Hz, 5α-H), 4.23 (m, 1H, 17β-H), 4.28 (m, 1H, 3β-H), 7.25-7.43 (m, 9H), 7.56-7.59

(m, 6H); ^{13}C NMR ($CDCl_3$) δ 12.6, 17.5, 21.2, 24.5, 28.2, 28.4, 32.2, 34.9, 35.8, 38.5, 41.5, 46.4, 47.0, 49.1, 52.1, 53.4, 65.5, 67,3, 127.9, 130.1, 134.7, 135.4, 212.7; MS (CI) *m/z* (%) 629 (M+H, 25), 627 (M+H, 25), 547 (100); HRMS: $C_{37}H_{43}O_2SiBr$, calculate mass 627.2294, actual mass 627.2287.

Crystals of 17α-Bromo-3α-(triphenylsiloxy)-5α-androstan-6-one (**3**) were prepared by recrystallization from MeOH-THF. A colorless plate having approximate dimensions of 0.3 x 0.25 x 0.15 mm was mounted on a glass fiber in a random orientation. X-ray data were collected with MO Kα radiation (λ= 0.71073Å) on a Nonius Kappa CCD computer-controlled diffractometer equipped with a graphite crystal, incident beam monochromator. Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 14283 reflections in the range $4° < \theta < 30°$. The data were collected at a temperature of 296 ±1. Data were collected to a maximum 2θ of 61.0°. The results are summarized in **Table 1**.

Table 1. Summary of Crystal Data and Data Collection Parameters for **3**.

formula	$BrSiO_2C_{37}H_{43}$
formula weight	627.75
space group	$P2_12_12_1$ (No. 19)
a, Å	10.1931 (4)
b, Å	13.3290 (5)
c, Å	23.5358 (10)
V, $Å^3$	3197.7 (4)
Z	4
d_{calc}, g cm^{-3}	1.304
crystal dimensions, mm	0.30 × 0.25 × 0.15
temperature, K	296
radiation (wavelength)	MO K_α (0.71073Å)
monochromator	graphite
linear abs coef, mm^{-1}	1.338
absorption correction applied	empirical[a]
transmission factors: min, max	0.63, 0.82
diffractometer	Nonius KappaCCD
h, k, l range	-14 to 14 -18 to 18 -30 to 29
2θ range, deg	8.00-61.04
programs used	SHELXL-97
F_{000}	1320.0
weighting	
$w=1/[\sigma^2(Fo^2)+(0.0348P)^2+0.1235P]$ where $P=(Fo^2+2Fc^2)/3$	
data collected	14283
unique data	8086
R_{int}	0.064
data used in refinement	8086
cutoff used in R-factor calculations	$F_o^2 > 2.0\sigma(F_o^2)$
data with $I > 2.0\sigma(I)$	4647
number of variables	372
largest shift/esd in final cycle	0.00
$R(F_o)$	0.055
$R_w(F_o^2)$	0.100
goodness of fit	1.012
absolute structure determination	known fragment

[a]Otwinowski Z. & Minor, W. *Methods Enzymol.*, **1996**, *276*, 307.

Preparative photolysis of 3α-TPSO-5α-androstan-6-one-17α-bromide (3) in THF-H_2O/NH_4OH) at 300 nm. A degassed solution of THF-H_2O (9 mL : 1 mL) containing **3** (188.0 mg, 30 mM) and NH_4OH (80 μ, 60 mM) was irradiated with a Rayonet Reactor (New England Ultraviolet Co.) equipped with a rotary turntable and fitted with 4 254 nm lamps for 4 hours 45 min. HPLC analysis (Microsorb-MV, C18, CH_3CN : THF = 98 : 2) of the photolysate showed 5 peaks at 8.23 (**3**), 9.12, 9.54, 11.33 and 12.42 min in a peak-area ratio of 14.2 : 15.5 : 18.7 : 1.0 : 15.2 (at 70% loss of **3**). Concentration *in vacuo* gave 210 mg of a residue which was chromatographed on silica gel with 10% EtOAc/90% hexane followed by 30% EtOAc/70% hexane to give three components. The first component (a mixture, 6.2 mg) was further chromatographed with silica gel (10 % EtOAc/90% hexane) to give 3α-TPSO-5α-androstan-6-one (**8**, 3.6 mg). The second component (18 mg) was recovered **3** at t_R = 8.23 min. The third component (86 mg) was chromatographed with 30% EtOAc/70% hexane to give the alcohols **4** (12 mg)/**5** (16 mg) and complex **6** (4.1 mg) / **7** (3.7 mg).

3α-TPSO-6α-hydroxy-5α-androstan-17α-bromide (4) : Mp: 178-119.5°C. HPLC t_R = 9.12 min; ^{1}H NMR ($CDCl_3$) δ 0.71 (s, 3H), 0.77 (s, 3H), 0.83-2.03 (m, 18H), 2.10-2.24 (m, 1H), 2.50-2.64 (m, 1H), 3.14-3.28 (m, 1H), 4.19-4.21 (m, 1H), 4.26-4.31 (m, 1H), 7.30-7.41 (m, 9H), 7.58-7.62 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 12.6, 17.6, 20.9, 24.7, 29.1, 30.0, 32.9, 34.9, 35.0, 36.1, 36.9, 42.1, 46.1, 46.5, 48.4, 53.3, 66.1, 67.9, 69.7, 127.9, 129.9, 135.0, 135.5; MS (FAB) *m/z* 631 (M+H), 629 (M+H); HRMS: $C_{37}H_{45}SiO_2Br$, calculate mass 629.2450, actual mass 629.2443.

3α-TPSO-6β-hydroxy-5α-androstan-17α-bromide (5) : Mp: 177-178.5°C. HPLC t_R = 9.54 min; ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3H), 0.94 (s, 3H), 1.10-1.90 (m, 18H), 2.12-

2.25 (m, 1H), 2.51-2.69 (m, 1H), 3.54-3.60 (m, 1H), 4.20-4.24 (m, 1H), 4.30-4.34 (m, 1H), 7.32-7.41 (m, 9H), 7.58-7.61 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 15.1, 17.7, 20.8, 24.8, 29.4, 31.0, 33.4, 34.5, 35.0, 36.1, 36.2, 39.9, 41.9, 46.2, 48.4, 53.7, 66.5, 68.5, 72.3, 127.9, 129.9, 135.0, 135.5; MS (FAB) *m/z* 631 (M+H), 629 (M+H); HRMS: $C_{37}H_{45}SiO_2Br$, calculate mass 629.2450, actual mass 629.2438.

3α-TPSO-5α-androstan-6α-hydroxy-6β-(tetrahydrofur-2′-yl)-17α-bromide (6): $HPLC_{tR}$ = 12.42 min; ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3H), 0.96 (s, 3H), 1.12-2.64 (m, 24H), 3.70-3.76 (t, 2H), 3.96-4.02 (m, 1H), 4.21-4.26 (m, 2H), 7.32-7.44 (m, 9H), 7.61-7.66 (m, 6H); MS (CI) *m/z* 683 (M+H-H_2O), 681 (M+H-H_2O).

3α-TPSO-5α-androstan-6β-hydroxy-6α-(tetrahydrofur-2′-yl)-17α-bromide (7): $HPLC_{tR}$ = 12.42 min; ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 3H), 0.94 (s, 3H), 0.98-2.65 (m, 24 H), 3.62-3.74 (m, 2H), 3.90-3.97 (m, 1H), 4.18-4.26 (m, 2H), 7.34-7.42 (m, 9H), 7.62-7.67 (m, 6H); MS (CI) *m/z* 683 (M+H-H_2O), 681 (M+H-H_2O).

3α-TPSO-5α-androstan-6-one (8): Mp: 169-170.5°C. $HPLC_{tR}$ = 11.33 min; ^{1}H NMR ($CDCl_3$) δ 0.70 (δ, 6H), 1.15-1.80 (m, 19H), 2.00-2.15 (m, 1H), 2.29-2.38 (m, 1H), 2.83-2.95 (m, 1H), 4.28-4.35 (m, 1H), 7.33-7.48 (m, 9H), 7.57-7.65 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 12.5, 17.5, 20.3, 21.1, 25.2, 28.1, 28.4, 32.2, 38.4, 38.4, 40.1, 41.2, 41.6, 47.2, 52.1, 54.2, 54.9, 67.4, 127.8, 129.9, 134.7, 135.3, 213.2,; MS (EI) *m/z* (%) 548 (M^+, 7), 519 (18), 470 (97), 259 (100); HRMS: $C_{37}H_{44}SiO_2$, calculate mass 549.3189, actual mass 549.3186.

3α-hydroxy-5α-androstan-6-one (3αOH/6ketone).

5α-androstan-3,6-dione (2.13 g, 7.39 mmol) in 300 mL of dry THF under Ar was stirred at -78°C for 10 minutes. K-Selectride (7.77 mL, 7.77 mmol of the 1M solution in

THF) was added and solution was left for 45 minutes at -78°C. The solution was warmed to room temperature, stirred for 20 minutes and hydrolyzed by the addition of 36 mL of 50% ethanol in water and adjusted the pH to 7 by using 5% HCl solution. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with saturated KCl solution, dried with Na_2SO_4 and removed at reduced pressure. The residue was purified by column chromatography(40% EtOAc/60% hexane) to give a pure colorless solid 1.5 g (72%). Mp: 149-150°C. ^{1}H NMR ($CDCl_3$) δ 0.67 (s, 3H), 0.70 (s, 3H), 1.13-2.72 (m, 22H), 4.12 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 12.4, 17.5, 20.4, 21.1, 25.3, 27.7, 28.2, 31.8, 38.4, 40.2, 41.2, 41.7, 47.3, 51.7, 54.1, 55.0, 65.4, 213.1; MS (EI) *m/z* 290 (M^+, 76), 275 (38), 257 (32); HRMS (FAB) : $C_{19}H_{30}O_2$, calculate mass 291.2324, actual mass 291.2326.

References.

(1) Place, P. P.; Roumestant M.-L.; Gore *J. Bull. Soc. Chim. Fr.* **1976**, 169.