Copper-catalyzed cyclization of steroidal acylaminoacetylenes: Syntheses of novel 11β-aryl-17,17-spiro[(4'*H*,5'-methylene)oxazol]-substituted steroids

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Supporting Information Part 1

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General Methods.

Unless otherwise stated, reagent-grade chemicals and compound **5** were obtained from commercial sources and were used without further purification. All moisture- and air-sensitive reactions and reagent transfers were carried out under dry nitrogen or argon. Analytical thin-layer chromatography (TLC) was carried out using EMD silica gel 60 F_{254} TLC plates. Compounds were normally visualized by UV light (254 nm) or *para*-anisaldehyde spray. Preparative column chromatography employed EM Science silica gel, 60Å (230-400 mesh). Solutions were concentrated by use of a rotoevaporator under water aspirator pressure at ambient temperature. NMR (^{1}H, ^{13}C, gCOSY, gHMBC, gHSQC and ROESY) spectra were obtained using a Bruker Avance DPX-300 MHz or a Varian Unity Inova 500 MHz NMR spectrometer. Chemical shifts are reported in parts per million (ppm) with reference to internal solvent. HRMS were recorded on a Waters Autospec Ultima mass spectrometer and were performed at the University of Michigan, Ann Arbor, MI. Elemental analysis was performed by Atlantic Microlab Inc., Atlanta, GA. HPLC analyses were performed on a Varian dual pump system consisting of two HPLC pumps (Ranin HPXL solvent delivering system), a Rheodyne injector and a Varian ProStar 325 UV-Vis detector, and a Varian Star Workstation software for gradient control and data handling. Compounds **14a**, **14b**, **14d**, **14e**, **14g-j** and **15** were above 98% pure as determined by HPLC analyses. The purity of compounds **14c** and **14f** was not determined due to their decompositions under HPLC conditions.

Experimental Procedures.

Procedure for the Synthesis of 11β-(3,4-Difluorophenyl)-17α-ethynyl-17β-[(1-oxopropyl)amino]estra-4,9-dien-3-one (4a).

3,3-[l,2-Ethanediylbis(oxy)]-5α,10α-oxidoestr-9(11)-en-17-one (**6**). To a solution of **5** (32.0 g, 102 mmol) in CH_2C1_2 (192 mL) at 0 °C was added hexafluoroacetone trihydrate (7.04 mL, 50.9 mmol) followed by Na_2HPO_4 (2.46 g, 17.3 mmol), and then a 50% solution of H_2O_2 (8.64 mL, 153 mmol) was added dropwise to the efficiently stirred mixture (overhead mechanical stirring). Efficient stirring was continued for 18 h, during which time the temperature was allowed to gradually rise to room temperature, then saturated $Na_2S_2O_3$ (192 mL) was added. After being stirred for 20 min, the mixture was combined with another (32.0 g) batch which had been prepared identically up to this point in parallel. The aqueous layer was separated and extracted with EtOAc (3 x 80 mL). The combined EtOAc extract was diluted with EtOAc (240 mL) and washed with $NaHCO_3$ (2 x 80 mL), brine (2 x 80 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resultant yellow solid (76.1 g) was triturated with Et_2O (320 mL) with magnetic stirring for 12 h in a closed flask. The resultant white slurry was combined with three other batches (3 x 32.0 g) which had been prepared identically (and proportionally) to this point, in parallel, then suction filtered through a coarse-porosity sintered glass funnel, rinsing with Et_2O (3 x 40 mL), and allowed to suck dry for 1.5 h. The white filter cake was dried *in vacuo* to afford epoxide **6** (89.5 g, 53% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (br s, 1H), 3.98-3.88 (m, 4H), 2.52-2.44 (m, 2H), 1.32-1.12 (m, 1H), 0.88 (s, 3H) (other aliphatic resonances not reported).

11β-(3,4-Difluorophenyl)-3,3-[1,2-ethanediylbis(oxy)]-5α-hydroxyestr-9-en-17-one (7). To a well-stirred slurry of CuI (38.0 g, 200 mmol) and epoxide **6** (33.0 g, 100 mmol) in dry THF (200 mL) at 0 °C under argon was added a 0.5 M solution of 3,4-difluorophenyl magnesium bromide in

THF (800 mL, 400 mmol). After being stirred at 0 °C for 30 min, the reaction mixture was poured into a saturated NH_4Cl solution (500 mL), stirred at room temperature for 30 min and extracted with EtOAc (3 x 300 mL). The combined EtOAc extract was washed with saturated NH_4Cl (3 x 200 mL), brine (3 x 200 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (20 → 60% EtOAc-hexane) to afford adduct **7** (40.8 g, 92% yield). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.10-6.88 (m, 3H, Ar-H), 4.40 (s, 1H, 5-OH), 4.25 (d, *J* = 6.0 Hz, 1H, 11-H), 4.10-3.80 (m, 4H), 2.50-2.20 (m, 4H), 2.16-1.40 (m, 13H), 1.28-1.12 (m, 1H), 0.50 (s, 3H).

11β-(3,4-Difluorophenyl)-3,3-[1,2-ethanediylbis(oxy)]-5α-hydroxy-17-(*N*-hydroxyimino)estr-9-ene (8). To a stirred solution of **7** (11.1 g, 25.0 mmol) in dry pyridine (100 mL) at room temperature under nitrogen was added 4Å molecular sieve (5 g) followed by hydroxylamine hydrochloride (3.15 g, 45.0 mmol). After being stirred at room temperature for 10 h, the reaction mixture was filtered through a short pad of Celite and the pyridine was removed *in vacuo*. The resultant residue was dissolved in EtOAc (500 mL), washed with 1 N HCl (2 x 100 mL), brine (2 x 100 mL), $NaHCO_3$ (2 x 100 mL), brine (100 mL) and dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded crude oxime **8** (11.5 g, 100% yield), which was used in the next step without further purification. ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.13 (br s, 1H), 7.30-6.90 (m, 3H, Ar-H), 4.41 (s, 1H, 5-OH), 4.22 (d, *J* = 6.0 Hz, 1H, 11-H), 4.10-3.80 (m, 4H), 2.70-1.20 (m, 18H), 0.53 (s, 3H).

11β-(3,4-Difluorophenyl)-3,3-[1,2-ethanediylbis(oxy)]-5α-hydroxy-17β-nitroestr-9-ene (9). To a stirred solution of NBS (13.4 g, 75.0 mmol), $KHCO_3$ (15.0 g, 150 mmol) in dioxane (105 mL) and water (60 mL) at room temperature was slowly added a solution of crude **8** (11.5 g, 25.0 mmol) in dioxane (200 mL) and water (100 mL). The reaction mixture was stirred at room

temperature for 16 h. $NaBH_4$ (5.67 g, 150 mmol) was then added. After being stirred for 1 h, the reaction was quenched by addition of an aqueous solution of hydroxylamine hydrochloride (1.5 M, 400 mL) and extracted with EtOAc (3 x 200 mL). The combined EtOAc extract was washed with $NaHCO_3$ (3 x 100 mL), brine (3 x 100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (20 → 50% EtOAc-hexane) to afford **9** (10.3 g, 86% yield). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.10-6.88 (m, 3H, Ar-H), 4.42 (s, 1H, 5-OH), 4.34 (t, *J* = 6.1 Hz, 1H, 17-H), 4.25 (d, *J* = 6.0 Hz, 1H, 11-H), 4.10-3.80 (m, 4H), 2.67 (d, *J* = 12.0 Hz, 1H), 2.60-2.30 (m, 3H), 2.22-1.18 (m, 13H), 1.28-1.12 (m, 1H), 0.35 (s, 3H).

11β-(3,4-Difluorophenyl)-3,3-[1,2-ethanediylbis(oxy)]-17α-ethynyl-5α-hydroxy-17β-nitroestr-9-ene (10). To a stirred solution of **9** (9.50 g, 20.0 mmol) in DMSO (64 mL) at room temperature under argon was added KO*t*Bu (2.60 g, 22.0 mmol) and the reaction mixture was stirred for 1 h. A separate three-neck round-bottom flask was charged with $Pb(OAc)_4$ (19.5 g, 44.0 mmol). This was stirred *in vacuo* at room temperature for 2 h to afford a fine white powder, which after back-filling the flask with argon was dissolved in DMSO (86 mL). A solution of (enthynyl)tributyltin (16.3 mL, 54.0 mmol) in DMSO (30 mL) was then added to the solution. After being stirred for 3 min and 15 seconds, the above nitronate solution was added and stirred for 20 min. The reaction mixture was poured into a 1:1 mixture of saturated NH_4Cl and H_2O (320 mL) followed by the addition of KF (34.9 g, 600 mmol) and EtOAc (200 mL). After being stirred for 20 min, the resultant mixture was filtered through a pad of Celite. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined EtOAc extract was washed with brine (3 x 100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (20 → 33% EtOAc-hexane) to afford **10** (8.07 g, 81% yield). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.11-6.85 (m, 3H, Ar-H), 4.43 (s,

1H, 5-OH), 4.33 (d, J = 6.0 Hz, 1H, 11-H), 4.10-3.86 (m, 4H), 3.09-2.96 (m, 1H), 2.79 (s, 1H, CCH), 2.70-2.28 (m, 4H), 2.20-1.13 (m, 13H), 0.38 (s, 3H).

11β-(3,4-Difluorophenyl)-3,3-[1,2-ethanediylbis(oxy)]-17α-ethynyl-5α-hydroxy-17β-(*N*-hydroxyamino)estr-9-ene (11). To a stirred solution of **10** (9.00 g, 18.0 mmol) in THF (300 mL) and 50% EtOH-H_2O (300 mL) at 0 °C was added NH_4Cl (9.60 g, 180 mmol) followed by zinc dust (5.90 g, 90.0 mmol). After being stirred for 30 min, the reaction mixture was diluted with EtOAc (300 mL) and filtered through a pad of Celite. The filtrate was washed with brine (3 x 100 mL) and dried (Na_2SO_4). Removal of solvent *in vacuo* afforded crude hydroxylamine **11** (8.75 g, 100% yield), which was used in the next step without further purification. ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.10-6.90 (m, 3H, Ar-H), 5.15 (br s, 1H), 4.76 (br s, 1H), 4.40 (s, 1H, 5-OH), 4.31 (d, J = 6.0 Hz, 1H, 11-H), 4.10-3.89 (m, 4H), 2.62-2.54 (m, 1H), 2.53 (s, 1H, CCH), 2.48-2.30 (m, 3H), 2.20-1.48 (m, 12H), 1.40-1.15 (m, 2H), 0.48 (s, 3H).

17β-Amino-11β-(3,4-difluorophenyl)-3,3-[1,2-ethanediylbis(oxy)]-17α-ethynyl-5α-hydroxyestr-9-ene (12). To an aqueous solution of $Na_2B_4O_7$ (0.2 M, 324 mL, 64.8 mmol) at room temperature under nitrogen was added 0.1 N HCl (18.0 mL, 1.80 mmol) followed by 2-mercaptoethyl ether (2.40 mL, 19.8 mmol) and an aqueous solution of $FeSO_4(NH_4)_2SO_4$ (0.01 M, 54.0 mL, 0.54 mmol). A solution of crude **11** (8.75 g, 18.0 mmol) in THF (90 mL) and EtOH (180 mL) was then added. After being refluxed for 5 h, the reaction mixture was concentrated *in vacuo* to remove most of the THF. The resultant aqueous layer was decanted and the residue was dissolved in EtOAc (300 mL), washed with brine (3 x 100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (20 → 66% EtOAc-hexane) to afford **12** (6.90 g, 82% yield). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.10-6.90 (m, 3H, Ar-H), 4.39 (s, 1H, 5-OH), 4.31 (d, J = 6.0 Hz, 1H, 11-H), 4.10-3.89 (m, 4H), 2.50-1.20

(m, 21H), 0.41 (s, 3H).

11β-(3,4-Difluorophenyl)-3,3-[1,2-ethanediylbis(oxy)]-17α-ethynyl-5α-hydroxy-17β-[(1-oxopropyl)amino]estr-9-ene (13). To a stirred solution of **12** (6.80 g, 14.5 mmol) in CH_2Cl_2 (100 mL) at 0 °C under nitrogen was added Et_3N (6.06 mL, 43.5 mmol) followed by propionyl chloride (2.57 mL, 29.0 mmol). After being stirred at 0 °C for 1 h, the reaction mixture was washed with brine (3 x 30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (20 → 33% EtOAc-hexane) to afford **13** (6.82 g, 90% yield). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.10-6.90 (m, 3H, Ar-H), 5.42 (s, 1H), 4.40 (s, 1H, 5-OH), 4.28 (d, J = 6.0 Hz, 1H, 11-H), 4.10-3.90 (m, 4H), 2.70-2.57 (m, 2H), 2.46 (s, 1H, CCH), 2.44-2.30 (m, 3H), 2.23-1.50 (m, 13H), 1.40-1.20 (m, 2H), 1.12 (t, J = 7.5 Hz, 3H), 0.40 (s, 3H).

11β-(3,4-Difluorophenyl)-17α-ethynyl-17β–[(1-oxopropyl)amino]estra-4,9-dien-3-one (4a). To a stirred solution of **13** (2.11 g, 4.02 mmol) in a mixture of CH_2Cl_2 (170 mL) and H_2O (17 mL) at 0 °C was added TFA (4.03 mL, 52.3 mmol). After being stirred at 0 °C for 5 h, the reaction was quenched with excess of $NaHCO_3$. The CH_2Cl_2 layer was separated, washed with brine (3 x 50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (20 → 60% EtOAc-hexane) to afford **4a** (1.80 g, 97% yield). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.14-6.86 (m, 3H, Ar-H), 5.79 (s, 1H, 4-H), 5.43 (s, 1H), 4.38 (d, J = 6.0 Hz, 1H, 11-H), 2.80-2.25 (m, 11H), 2.19 (q, J = 7.5 Hz, 2H), 2.10-1.80 (m, 4H), 1.62-1.19 (m, 2H), 1.14 (t, J = 7.5 Hz, 3H), 0.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 172.9, 155.8, 150.4 (dd, $J_{C\text{-}F}$ = 246, 13 Hz), 148.6 (dd, $J_{C\text{-}F}$ = 246, 13 Hz), 143.9, 141.7 (t, $J_{C\text{-}F}$ = 4.1 Hz), 130.1, 123.6, 122.9 (dd, $J_{C\text{-}F}$ = 5.8, 3.5 Hz), 117.3 (d, $J_{C\text{-}F}$ = 17 Hz), 116.0 (d, $J_{C\text{-}F}$ = 17 Hz), 85.0, 72.9, 62.6, 50.2, 47.8, 40.4, 39.9, 39.2, 38.9, 36.7, 31.0, 29.8, 27.6, 25.8, 23.7, 14.9, 9.6; HRMS (ESI)

Calcd. for $C_{29}H_{31}F_2NO_2$ $[M + H]^+$: 464.2401. Found: 464.2394.

General Procedure for the Copper-catalyzed Cyclization Reaction.

11β-(3,4-Difluorophenyl)-4',5'-dihydro-2'-ethyl-5'-methylenespiro[estra-4,9-dien-17β, 4'-oxazol]-3-one (14a). To a stirred solution of **4a** (92.6 mg, 0.20 mmol) in a mixture of benzene (2 mL) and Et_3N (2 mL) at room temperature under argon was added CuI (3.80 mg, 0.02 mmol). After being stirred at 90 °C for 30 min, the reaction mixture was diluted with EtOAc (50 mL), washed with NH_4Cl (3 x 10 mL), brine (3 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (0 → 30% EtOAc-hexane) to afford **14a** (90.0 mg, 97% yield). ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.06 (dd, J = 18.0, 9.0 Hz, 1H), 6.97-6.90 (m, 1H), 6.88-6.81 (m, 1H), 5.79 (s, 1H, 4-H), 4.80 (d, J = 2.5 Hz, 1H), 4.29 (d, J = 7.3 Hz, 1H, 11-H), 4.20 (d, J = 2.5 Hz, 1H), 2.70 (ddd, J = 15.0, 5.3, 5.3 Hz, 1H), 2.64-2.58 (m, 2H), 2.56-2.49 (m, 1H), 2.49-2.32 (m, 5H), 2.30-2.20 (m, 1H), 2.14-2.06 (m, 1H), 2.01 (dd, J = 13.0, 7.3 Hz, 1H), 1.86-1.70 (m, 4H), 1.58-1.48 (m, 2H), 1.24 (t, J = 7.5 Hz, 3H), 0.61 (s, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 199.0, 166.7, 165.1, 155.9, 150.3 (dd, $J_{C\text{-}F}$ = 232, 13 Hz), 148.3 (dd, $J_{C\text{-}F}$ = 232, 13 Hz), 144.1, 141.6, 130.2, 123.5, 122.6, 117.2 (d, $J_{C\text{-}F}$ = 17 Hz), 115.8 (d, $J_{C\text{-}F}$ = 17 Hz), 86.7, 83.0, 48.5, 48.2, 39.6, 38.5, 37.7, 36.6, 36.5, 31.0, 27.8, 25.8, 24.2, 21.6, 16.5, 10.4; HRMS (ESI) Calcd. for $C_{29}H_{31}F_2NO_2$ $[M + H]^+$: 464.2401. Found: 464.2394; Anal. Calcd. for $C_{29}H_{31}F_2NO_2$: C, 75.14; H, 6.74; N, 3.02. Found: C, 74.98; H, 6.80; N, 3.01.

11β-(3,4-Difluorophenyl)-4',5'-dihydro-2'-methyl-5'-methylenespiro[estra-4,9-dien-17β, 4'-oxazol]-3-one (14b). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.05-6.72 (m, 3H, Ar-H), 5.72 (s, 1H, 4-H), 4.74 (d, J = 3.0 Hz, 1H), 4.22 (d, J = 6.0 Hz, 1H, 11-H), 4.14 (d, J = 3.0 Hz, 1H), 2.70-2.10 (m, 7H), 2.03 (s, 3H), 2.02-1.90 (m, 2H), 1.82-1.60 (m, 4H), 1.58-1.48 (m, 3H), 0.53 (s, 3H); HRMS (ESI) Calcd. for $C_{28}H_{29}F_2NO_2$ $[M + H]^+$: 450.2245. Found: 450.2263.

11β-(3,4-Difluorophenyl)-4',5'-dihydro-2'-trifluoromethyl-5'-methylenespiro[estra-4,9-dien-17β, 4'-oxazol]-3-one (14c). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.16-6.80 (m, 3H, Ar-H), 5.81 (s, 1H, 4-H), 5.07 (d, *J* = 3.0 Hz, 1H), 4.47 (d, *J* = 3.0 Hz, 1H), 4.32 (d, *J* = 6.0 Hz, 1H, 11-H), 2.77-2.19 (m, 8H), 2.18-1.98 (m, 2H), 1.97-1.45 (m, 6H), 0.63 (s, 3H); HRMS (ESI) Calcd. for $C_{28}H_{26}F_5NO_2$ $[M + H]^+$: 504.1962. Found: 504.1956.

4',5'-Dihydro-11β-[4-(*N*,*N*-dimethylamino)phenyl]-2'-ethyl-5'-methylenespiro[estra-4,9-dien-17β, 4'-oxazol]-3-one (14d). ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.96 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.65 (d, *J* = 9.0 Hz, 2H, Ar-H), 5.76 (s, 1H, 4-H), 4.80 (d, *J* = 3.0 Hz, 1H), 4.26 (d, *J* = 6.0 Hz, 1H, 11-H), 4.20 (d, *J* = 3.0 Hz, 1H), 2.91 (s, 6H), 2.80-2.23 (m, 10H), 2.16-1.70 (m, 6H), 1.67-1.46 (m, 2H), 1.24 (t, *J* = 7.5 Hz, 3H), 0.66 (s, 3H); HRMS (ESI) Calcd. for $C_{31}H_{38}N_2O_2$ $[M + H]^+$: 471.3012. Found: 471.3032.

4',5'-Dihydro-11β-[4-(*N*,*N*-dimethylamino)phenyl]-2'-methyl-5'-methylenespiro[estra-4,9-dien-17β, 4'-oxazol]-3-one (14e). ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.97 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.65 (d, *J* = 9.0 Hz, 2H, Ar-H), 5.76 (s, 1H, 4-H), 4.80 (d, *J* = 3.0 Hz, 1H), 4.28 (d, *J* = 6.0 Hz, 1H, 11-H), 4.20 (d, *J* = 3.0 Hz, 1H), 2.91 (s, 6H), 2.78-2.20 (m, 8H), 2.09 (s, 3H), 2.07-2.68 (m, 6H), 1.60-1.42 (m, 2H), 0.65 (s, 3H); HRMS (ESI) Calcd. for $C_{30}H_{36}N_2O_2$ $[M + H]^+$: 457.2855. Found: 457.2837.

4',5'-Dihydro-11β-[4-(*N*,*N*-dimethylamino)phenyl]-2'-trifluoromethyl-5'-methylenespiro[estra-4,9-dien-17β, 4'-oxazol]-3-one (14f). ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.96 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.65 (d, *J* = 9.0 Hz, 2H, Ar-H), 5.77 (s, 1H, 4-H), 5.06 (d, *J* = 3.0 Hz, 1H), 4.47 (d, *J* = 3.0 Hz, 1H), 4.29 (d, *J* = 6.0 Hz, 1H, 11-H), 2.91 (s, 6H), 2.82-2.26 (m, 8H), 2.18-1.45 (m, 8H), 0.67 (s, 3H); HRMS (ESI) Calcd. for $C_{30}H_{33}F_3N_2O_2$ $[M + H]^+$: 511.2572. Found: 511.2589.

4',5'-Dihydro-11β-[4-(*N*,*N*-dimethylamino)phenyl]-5'-methylenespiro[estra-4,9-dien-17β, 4'-oxazol]-3-one (14g). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.04 (s, 1H), 6.96 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.64 (d, *J* = 9.0 Hz, 2H, Ar-H), 5.77 (s, 1H, 4-H), 4.90 (d, *J* = 3.0 Hz, 1H), 4.31 (d, *J* = 3.0 Hz, 1H), 4.28 (br d, 1H, 11-H), 2.91 (s, 6H), 2.80-2.65 (m, 1H), 2.64-2.18 (m, 7H), 2.12-2.01 (m, 1H), 1.92-1.68 (m, 5H), 1.62-1.41 (m, 2H), 0.65 (s, 3H); HRMS (ESI) Calcd. for $C_{29}H_{34}N_2O_2$ $[M + H]^+$: 443.2694. Found: 443.2690.

11β-[4-(Acetyl)phenyl)-4',5'-dihydro-2'-ethyl-5'-methylenespiro[estra-4,9-dien-17β, 4'-oxazole]-3-one (14h). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.88 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.24 (d, *J* = 9.0 Hz, 2H, Ar-H), 5.80 (s, 1H, 4-H), 4.82 (d, *J* = 3.0 Hz, 1H), 4.38 (d, *J* = 6.0 Hz, 1H, 11-H), 4.21 (d, *J* = 3.0 Hz, 1H), 2.77-2.02 (m, 14H), 1.92-1.70 (m, 4H), 1.64-1.45 (m, 3H), 1.24 (t, *J* = 7.5 Hz, 3H), 0.58 (s, 3H); HRMS (ESI) Calcd. for $C_{31}H_{35}NO_3$ $[M + H]^+$: 470.2695. Found: 470.2708.

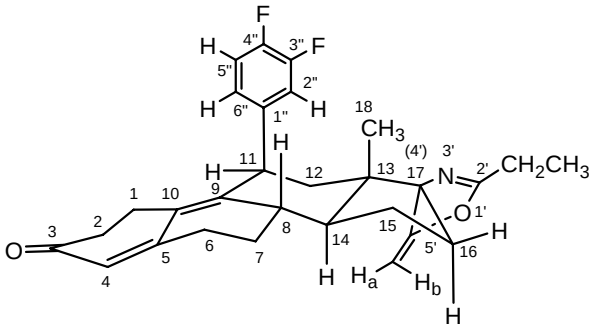
11β-[4-(Acetyl)phenyl)-4',5'-dihydro-2'-methyl-5'-methylenespiro[estra-4,9-dien-17β, 4'-oxazole]-3-one (14i). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.88 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.25 (d, *J* = 8.1 Hz, 2H, Ar-H), 5.80 (s, 1H, 4-H), 4.82 (d, *J* = 3.0 Hz, 1H), 4.38 (d, *J* = 7.2 Hz, 1H, 11-H), 4.22 (d, *J* = 3.0 Hz, 1H), 2.78-2.60 (m, 4H), 2.57 (s, 3H), 2.50-2.05 (m, 9H), 2.00-1.50 (m, 6H), 0.58 (s, 3H); HRMS (ESI) Calcd. for $C_{30}H_{33}NO_3$ $[M + H]^+$: 456.2539. Found: 456.2534.

11β-[4-(Acetyl)phenyl)-4',5'-dihydro-5'-methylenespiro[estra-4,9-dien-17β, 4'-oxazole]-3-one (14j). ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.87 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.24 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.05 (s, 1H), 5.81 (s, 1H, 4-H), 4.93 (d, *J* = 3.0 Hz, 1H), 4.39 (d, *J* = 6.0 Hz, 1H, 11-H), 4.33 (d, *J* = 3.0 Hz, 1H), 3.75 (q, *J* = 7.5 Hz, 1H, $CH_3\underline{CH_2}OH$), 2.80-1.73 (m, 17H), 1.70-1.48 (m, 2H), 1.24 (t, *J* = 7.5 Hz, 1.5H, $\underline{CH_3}CH_2OH$), 0.58 (s, 3H); HRMS (ESI) Calcd. for $C_{29}H_{31}NO_3$ $[M + Na]^+$: 464.2202. Found: 464.2203.

17α-Acetyl-11β-(3,4-difluorophenyl)-17β-[(1-oxopropyl)amino]estra-4,9-dien-3-one (15). A

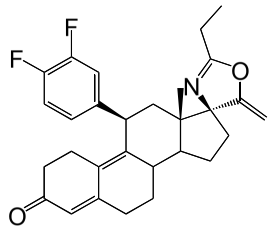
solution of **14a** (26.0 mg) in MeOH (5 mL) was refluxed for 10 h. The solvent was removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (20 → 60% EtOAc-hexane) to afford **15** (26.0 mg, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-6.85 (m, 3H, Ar-H), 6.17 (s, 1H), 5.78 (s, 1H), 4.32 (d, J = 6.0 Hz, 1H), 2.96-2.82 (m, 1H), 2.75-2.16 (m, 13H), 2.12-1.80 (m, 4H), 1.65-1.25 (m, 3H), 1.16 (t, J = 7.5 Hz, 3H), 0.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.3, 199.1, 174.5, 155.8, 150.6 (dd, $J_{C\text{-}F}$ = 247, 13 Hz), 148.8 (dd, $J_{C\text{-}F}$ = 247, 13 Hz), 142.8, 141.4 (t, $J_{C\text{-}F}$ = 4.1 Hz), 130.8, 123.9, 122.8 (dd, $J_{C\text{-}F}$ = 5.7, 3.3 Hz), 117.7 (d, $J_{C\text{-}F}$ = 17 Hz), 116.2 (d, $J_{C\text{-}F}$ = 17 Hz), 75.8, 48.2, 47.1, 40.1, 40.0, 39.0, 36.9, 34.5, 31.2, 29.6, 28.2, 27.8, 26.0, 25.3, 17.4, 9.8; HRMS (ESI) Calcd. for $C_{29}H_{33}F_2NO_3$ $[M + H]^+$: 482.2507. Found: 482.2496.

NMR data and assignments of **14a**



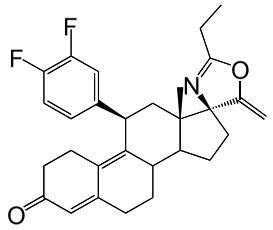
Assignment	Carbon (δ)	DEPT	Proton (δ)	HMBC (C→H)
$CH_2\underline{C}H_3$	10.4	CH_3	1.24	$C\underline{H_2}CH_3$
18-CH_3	16.5	CH_3	0.61	H12, H14
$\underline{C}H_2CH_3$	21.6	CH_2	2.41	$CH_2C\underline{H_3}$
15	24.2	CH_2	1.54 (β-H), 1.82 (α-H)	H14, H16
1	25.8	CH_2	2.26, 2.70	H2
7	27.8	CH_2	1.54, 2.10	H6, H14
6	31.0	CH_2	2.61	H4, H7
16	36.5	CH_2	1.82 (α-H), 2.37 (β-H)	H15
2	36.6	CH_2	2.40	H1, H4
12	37.7	CH_2	1.78, 2.01	H11, H14, 18-CH_3
8	38.5	CH	2.53	H6, H7, H11, H14, H15
11	39.6	CH	4.29	H12, H2", H6"
14	48.2	CH	1.74	H12, H15, H16, 18-CH_3
13	48.5	C	-	H11, H12, H15, H16, 18-CH_3
17 (4')	83.0	C	-	H12, H15, H16, 18-CH_3, vinylic H
vinylic	86.7	CH_2	4.20 (H_a), 4.80 (H_b)	-
2"	115.8	CH	6.93	H11, H6"
5"	117.2	CH	7.06	-
6"	122.6	CH	6.84	H11, H2"
4	123.5	CH	5.79	H2, H6
10	130.2	C	-	H1, H2, H4, H6, H11
1"	141.6	C	-	H11, H12, H5"
9	144.1	C	-	H1, H7, H11, H12, H14
4"	148.3	CF	-	H2", H5", H6"
3"	150.3	CF	-	H2", H5"
5	155.9	C	-	H1, H6, H7
2'	165.1	C	-	$C\underline{H_2}C\underline{H_3}$
5'	166.7	C	-	H16, vinylic H
3	199.0	C	-	H1, H2

14a PROTON

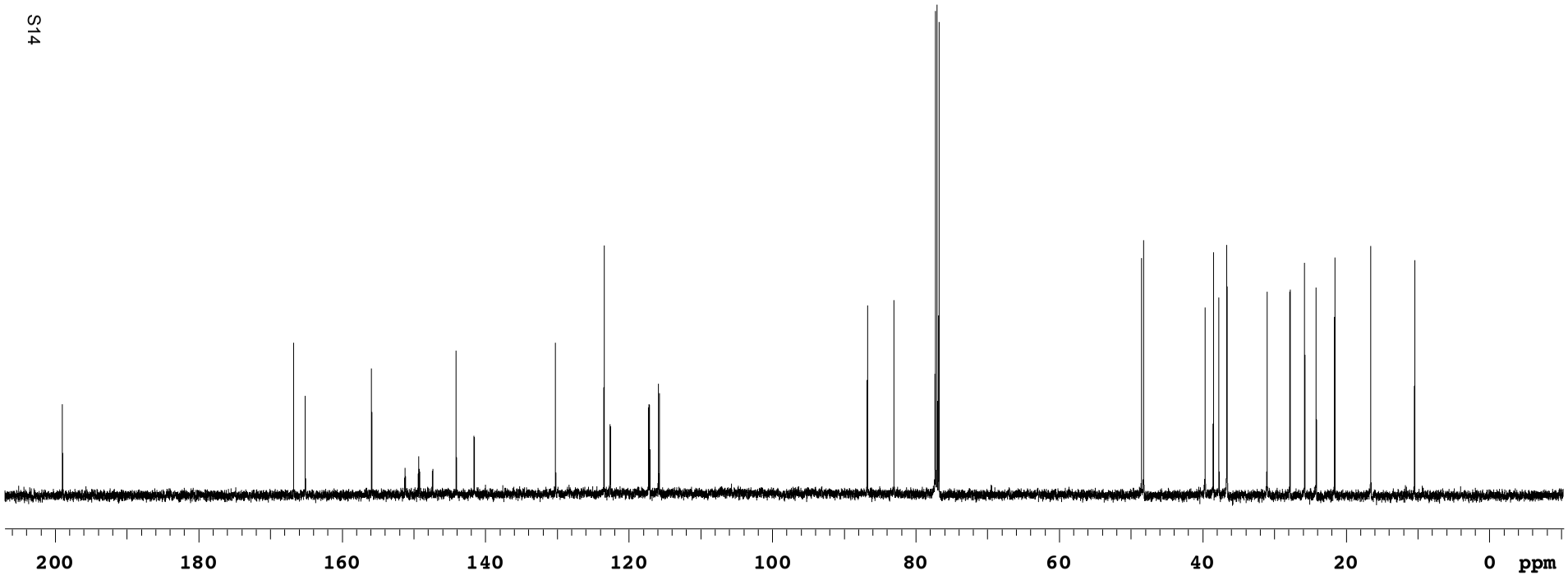


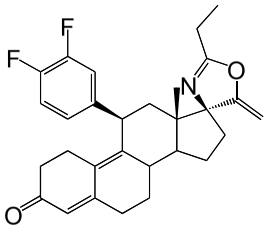
14a

14a CARBON



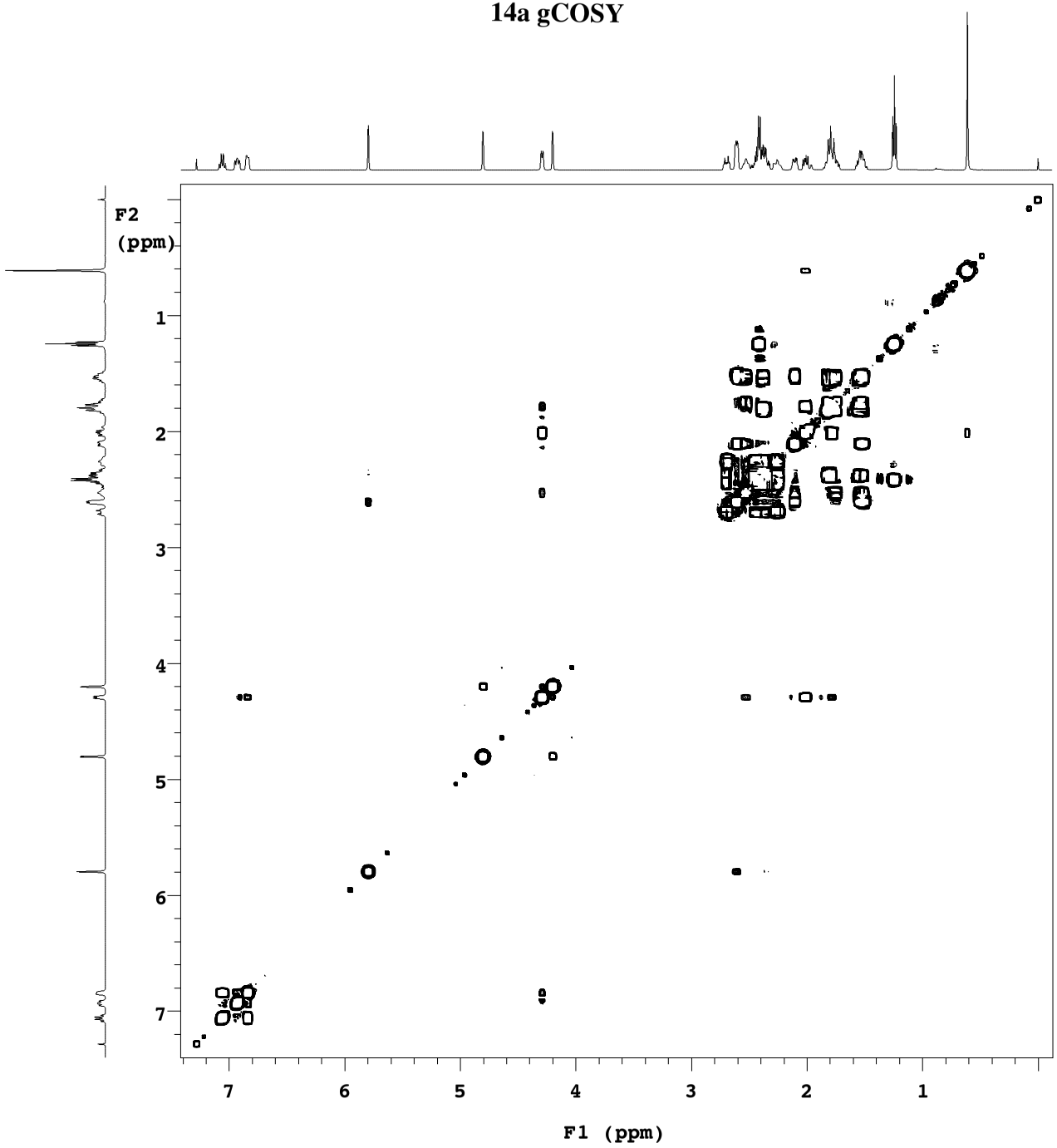
14a

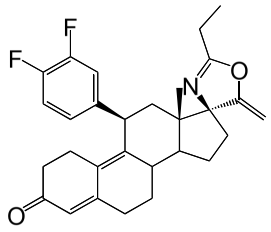




14a

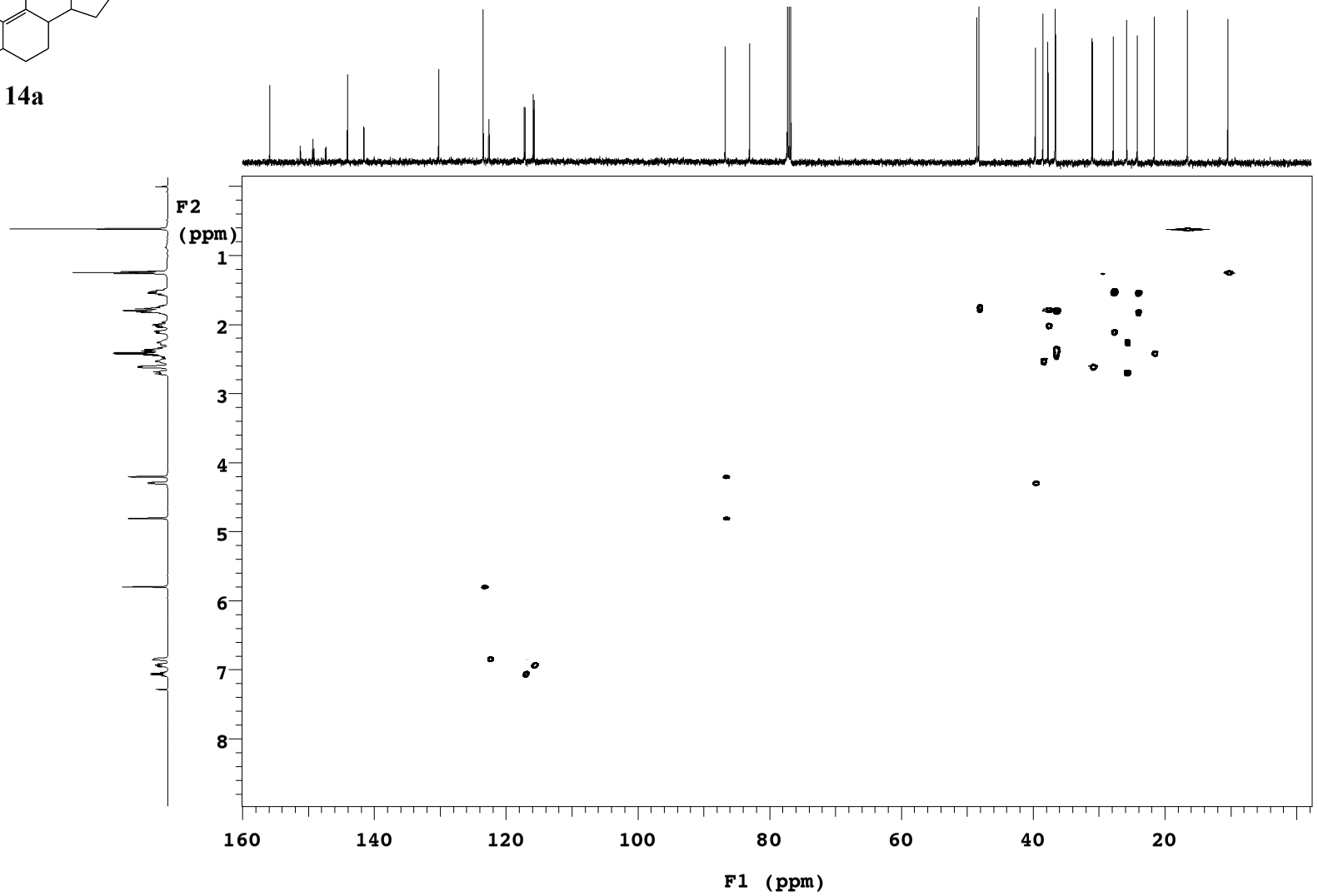
14a gCOSY



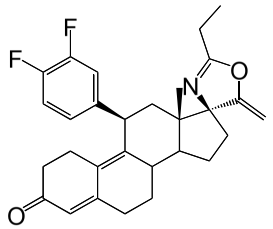


14a

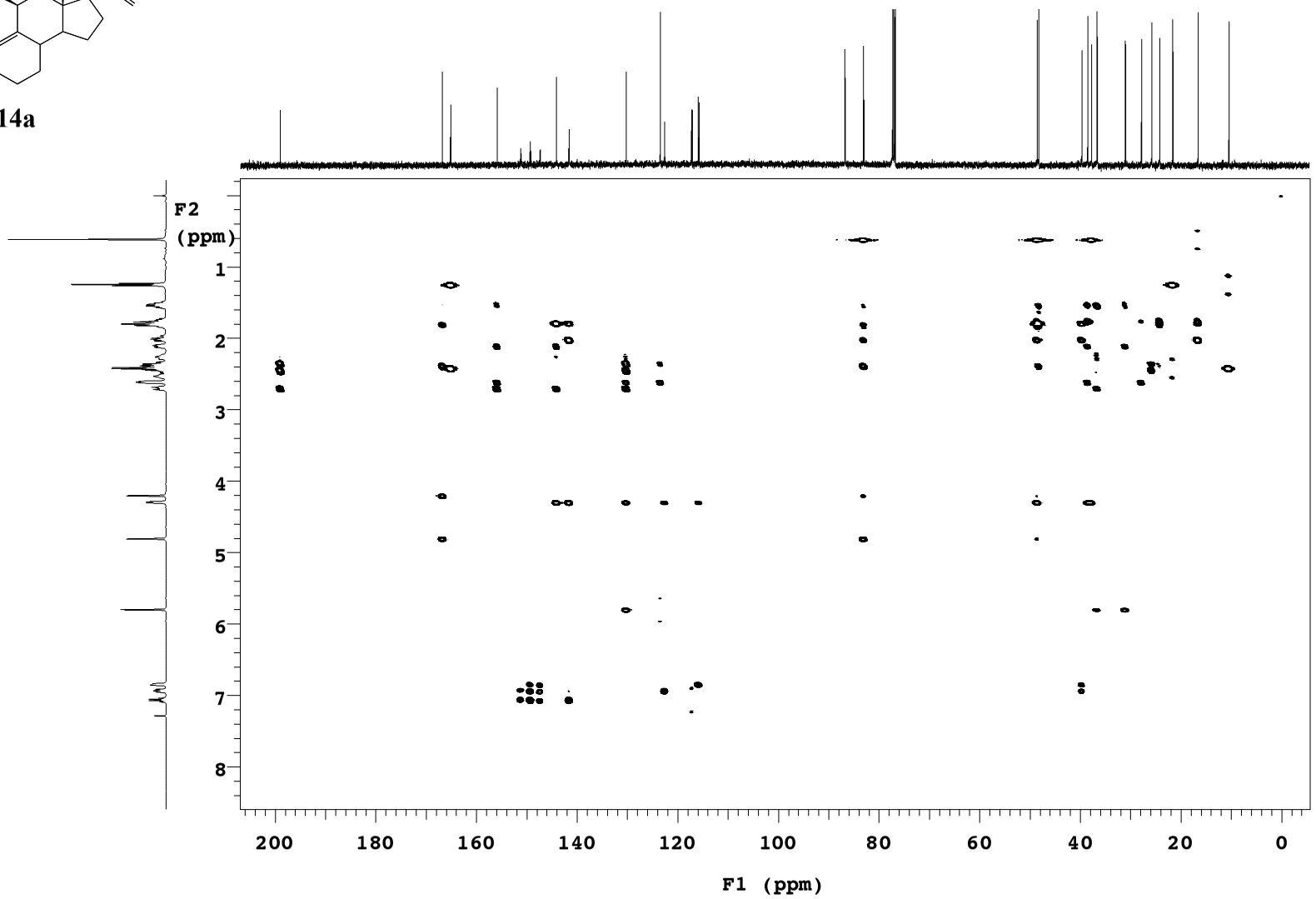
14a gHSQC

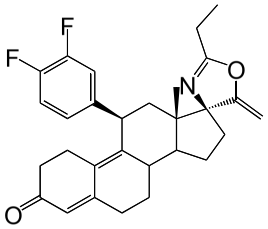


14a gHMBC



14a





14a

14a ROESY