Synthesis of the Anti-Prostate Cancer Drug Abiraterone Acetate

Supporting Information

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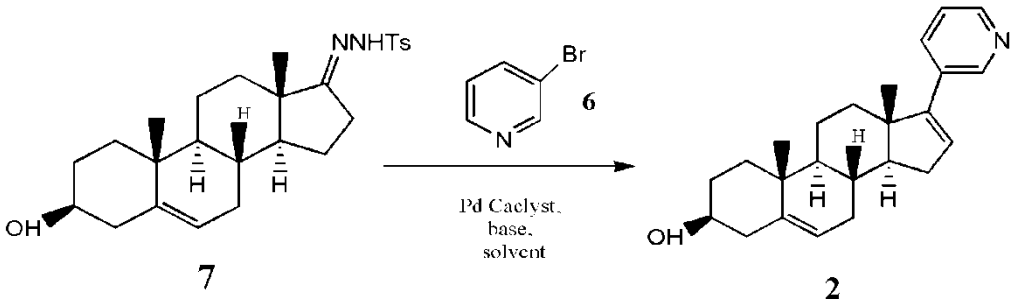
General Experimental Methods

All glassware's were over-dried at 120℃ and all reactions were conducted under a nitrogen atmosphere. Solvents: methanol and CH_3CN, for chromatography were distilled before use. THF, toluene, DME and 1,4-dioxane were pre-dry over Na wire. Reflux the pre-dried solvent over Na(1% w/v) and Benzophenone (0.2% w/v) under a nitrogen atmosphere until the blue colour of the benzophenone ketyl radical anion persists.

Instruments.

Reagents were uesd as such without purification. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) were recorded using a Bruker spectrometer. The chemical shift data are reported as δ (ppm) using tetramethylsilane as internal standard. Mass spectra were recorded using an Agilent 1200-6320 Ion Trap XCT instrument.

Typical Procedure for Pd-Catalyzed Coupling reaction



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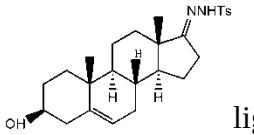
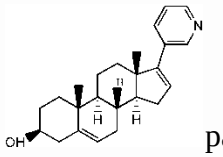
A stirred solution of **7**(4mmol) in 1,4-dioxane(50mL) in a 100 mL round-bottomed flask was purged with nitrogen andPd-Catalyst (0.04mmol) and ligand(0.07mmol) were added. After sitrring for 10 minutes, to the resultant refous solution was added base (3 mmol) base,then sitrring for 5 minutes and **6** (5 mmol) was added. The flask was fitted with a reflux condenser and these were purged with nitrogen. The mixture was heated to the refluxing temperaturein a oil bath pan with stirring for 24 hours. The reaction was completed and the solution turned to orange from dark brown.

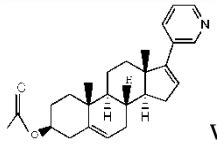


light green solid(91.6%,yield) m.p.: 176-178℃; Rf= 0.47(1/40 CH_2Cl_2/methanol). **^{1}H NMR (600MHz, $CDCl_3$)**: δ 1.05(s, 3H, 19-CH_3), 1.07(s, 3H, 18-CH_3), 2.26-2.30(m, 2H, 16-2H), 2.42(s, 24-CH_3), 3.51-3.58(m, 1H, 3α-H), 5.39(d,1H, J=4.8Hz, 6-H), 7.29(d, 2H, Ts2-H, Ts6-H), 7.82(d, 2H, Ts3-H, Ts4-H).

^{13}C NMR (150MHz, $CDCl_3$): δ 16.56, 19.37, 20.47, 21.58, 23.39, 25.98, 31.22, 31.30, 31.58, 33.69, 36.62, 37.20, 42.21, 44.74, 50.29, 53.60, 71.62, 120.92, 128.01, 128.28, 129.31, 129.94, 135.56, 141.07, 143.75, 171.63.



pale yellow solid(58.9%, yield) m.p.: 213-215℃, **lit.** [1] 212-215℃; Rf= 0.24(1/40 CH_2Cl_2/methanol). **^{1}H-NMR (600MHz,$CDCl_3$)**: δ 0.95(s, 3H, 19-CH_3), 0.97(s, 3H, 18-CH_3), 3.41-3.63(m, 1H, 3α-H), 5.32(d,1H, J=4.8Hz, 6-H), 5.90(s,1H, 16-H), 7.12-7.18(m, 1H, Py5-H), 7.58(d, 1H, J=8.0Hz, Py4-H), 8.37(d,1H,J=4.4Hz, Py6-H), 8.54(s, 1H, Py2-H). **^{13}C NMR (150MHz, $CDCl_3$)**: δ 16.56, 19.33, 19.41, 20.37, 30.47, 31.46, 31.62, 31.80, 35.28, 36.66, 37.22, 42.30, 47.35, 51.80, 57.57, 71.50, 121.24, 123.05, 129.28, 133.05, 133.78, 141.13, 147.67, 151.67.



white solid(44.3%, yield). m.p.: 143-145℃, lit. [2] 144-145℃;Rf= 0.36(1/40 CH_2Cl_2/methanol). ^{1}H-NMR (600MHz,$CDCl_3$): δ1. 05 (s,3H, 19-CH3), 1.08(s,3H, 18-CH_3), 2.04(s, 3H, CH_3CO_2), 4.58-4.66(m, 1H, 3α-H), 5.42(d, 1H, J=4.76Hz, 6-H), 5.99(s, 1H, 16-H), 7.22(dd, 1H, J_1=4.8Hz, J_2=7.8Hz, Py5-H), 7.64(d, 1H, J=7.9Hz, Py4-H), 8.46(d, 1H, J=4.6Hz, Py6-H), 8.63(s, 1H, Py2-H). ^{13}C NMR (150MHz, $CDCl_3$): δ 16.56, 19.29, 20.48, 21.44, 27.72, 30.37, 31.78, 35.27, 36.64, 37.02, 38.17, 47.35, 50.34, 57.46, 73.82, 122.16, 122.89, 132.87, 133.64, 140.62, 147.82,147.96, 151.66, 170.38.

yellow solid(8.4%, yield).m.p.154-156℃; Rf= 0.28(1/40 CH_2Cl_2/ methanol). ^{1}H-NMR (600MHz,$CDCl_3$): δ0.95(s, 3H, 19-CH_3), 0.97(s, 3H, 18-CH_3), , 5.32(d,1H, J=4.8Hz, 6-H), 5.90(s,1H, 16-H), 7.12-7.18(m, 1H, Py5-H), 7.20-7.25(m,1H, Py'5-H), 7.58(d, 1H, J=8.0Hz, Py4-H), 7.69(d,1H,J=6.8Hz, Py'4-H), 8.21(d,1H,J=4.2Hz, Py6-H), 8.31(d,1H,J=3.2Hz, Py'6-H), 8.42(s, 1H, Py'2-H), 8.54(s, 1H, Py2-H). ^{13}C NMR (150MHz, $CDCl_3$): δ 16.56, 19.32, 19.41, 20.37, 30.46, 31.46, 31.61, 31.80, 35.28, 36.70, 37.21, 42.30, 47.53, 51.80, 57.57, 71.50, 120.83, 121.24,

123.05, 127.95, 129.28, 133.05, 133.78, 138.39, 141.13, 141.23, 147.67, 147.77, 151.67

^{1}H, ^{13}C - NMR spectra

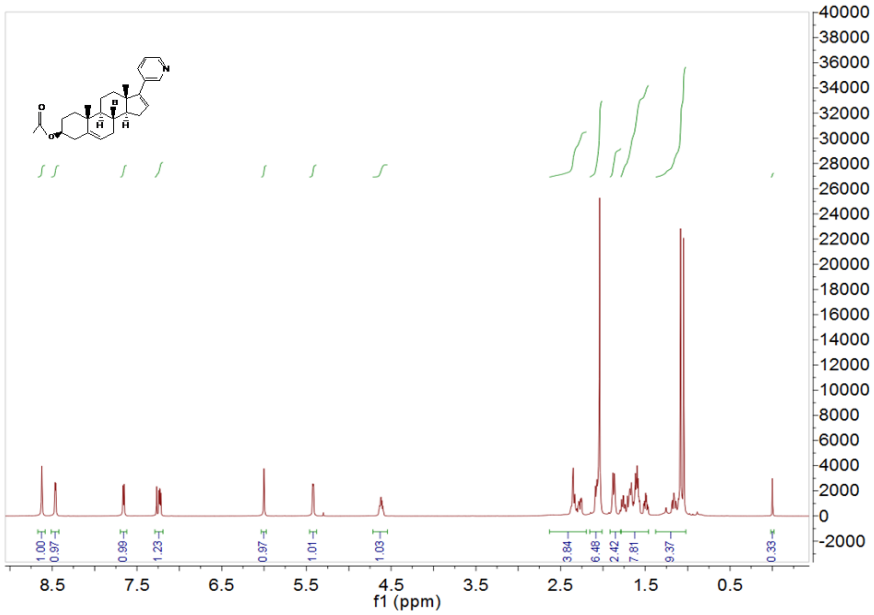


Figure 1S. ^{1}H NMR Spectrum (600 MHz, $CDCl_3$) of abiraterone acetate(compound 1)

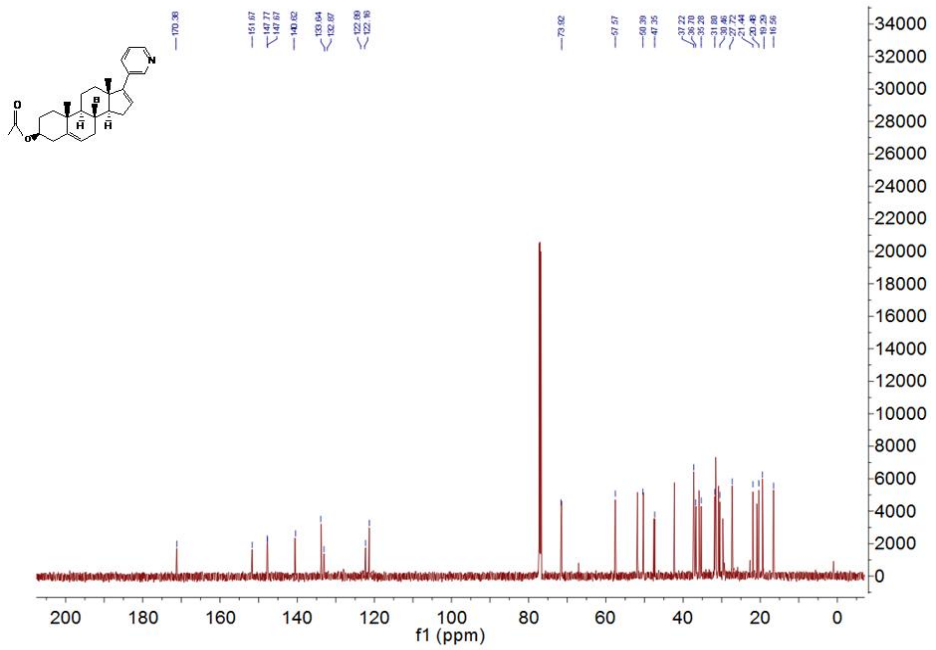


Figure 2S. ^{13}C NMR Spectrum (150 MHz, $CDCl_3$) of abiraterone acetate (compound 1)

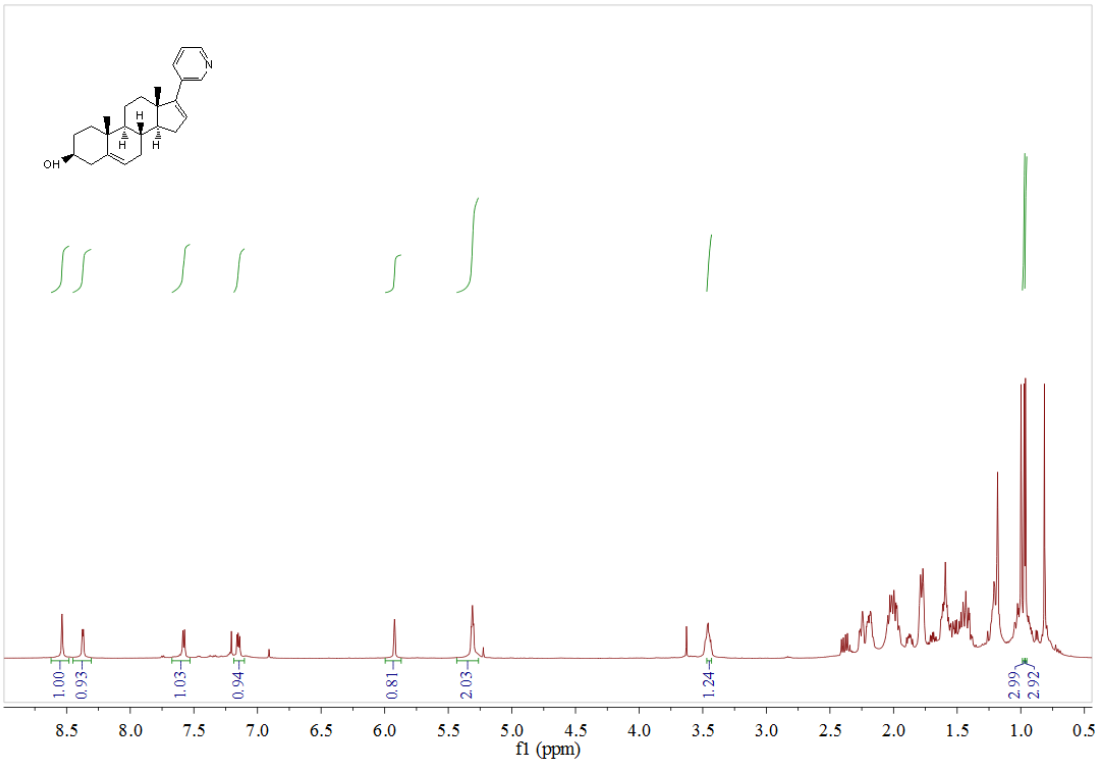


Figure 3S. ^{1}H NMR Spectrum (600 MHz, $CDCl_3$) of abiraterone(compound 2)

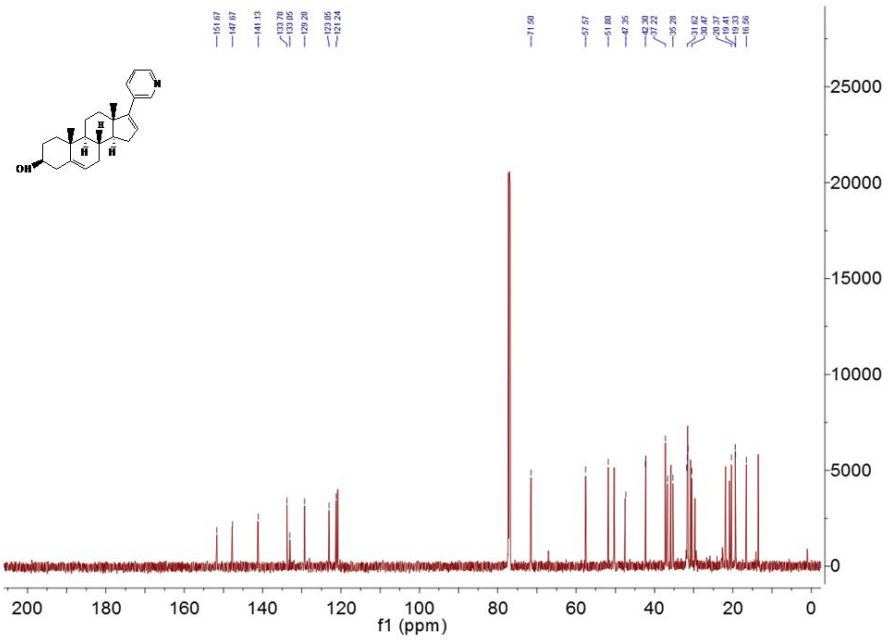


Figure 4S. ^{13}C NMR Spectrum (150 MHz, $CDCl_3$) of abiraterone(compound 2)

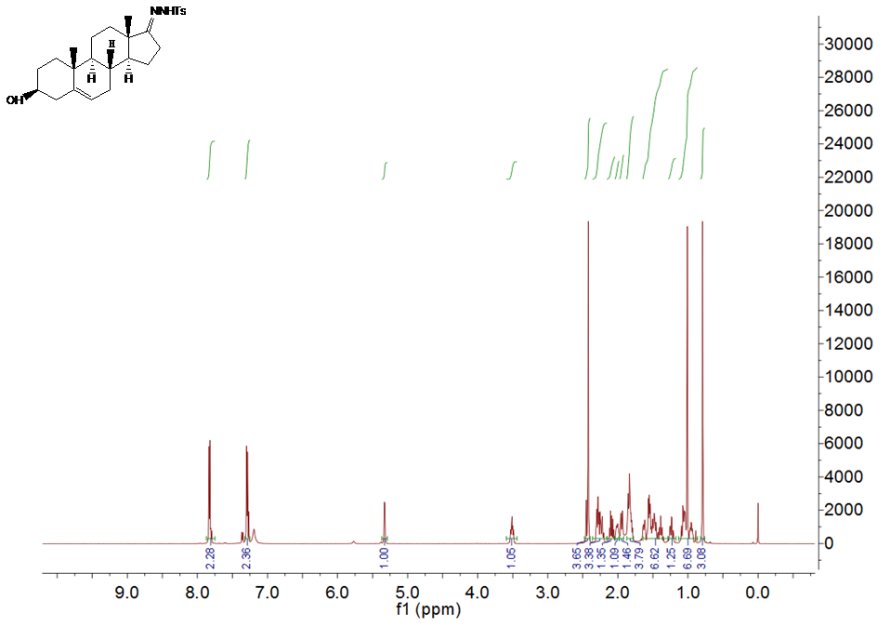


Figure 5S. 1H NMR Spectrum (600 MHz, CDCl3) of Dehydroepiandrosterone-17 N-tosylhydrazones(compound 7)

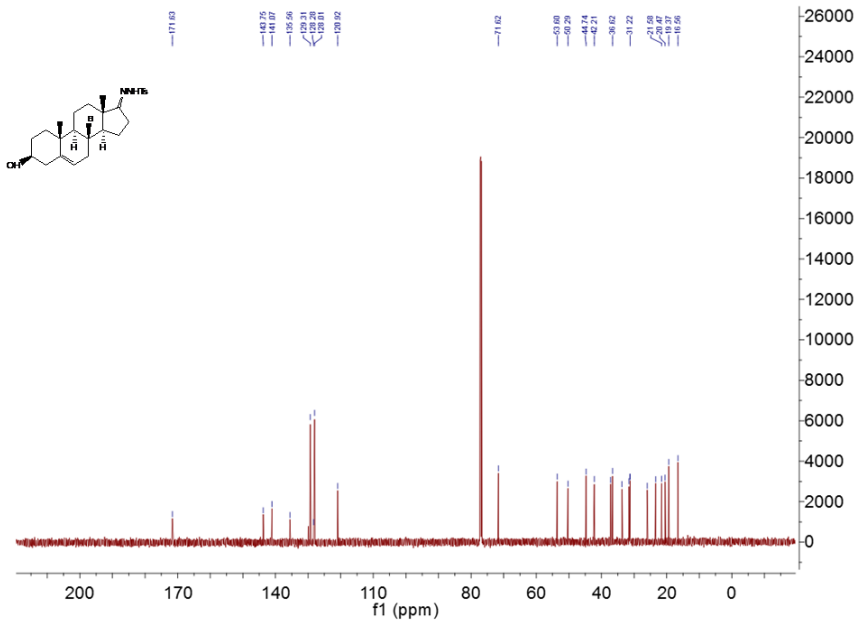


Figure 6S. ^{13}C NMR Spectrum (150 MHz, $CDCl_3$) of Dehydroepiandrosterone-17 N-tosylhydrazones (compound 7)

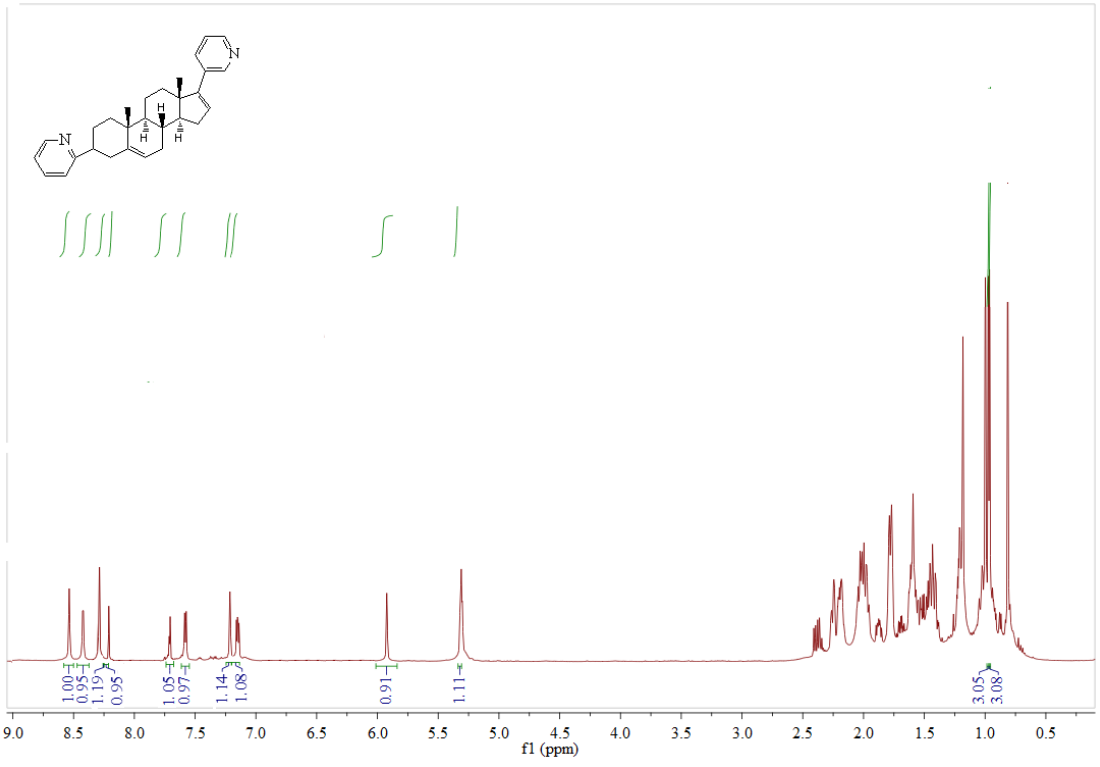


Figure 7S. 1H NMR Spectrum (600 MHz, CDCl3) of compound 9

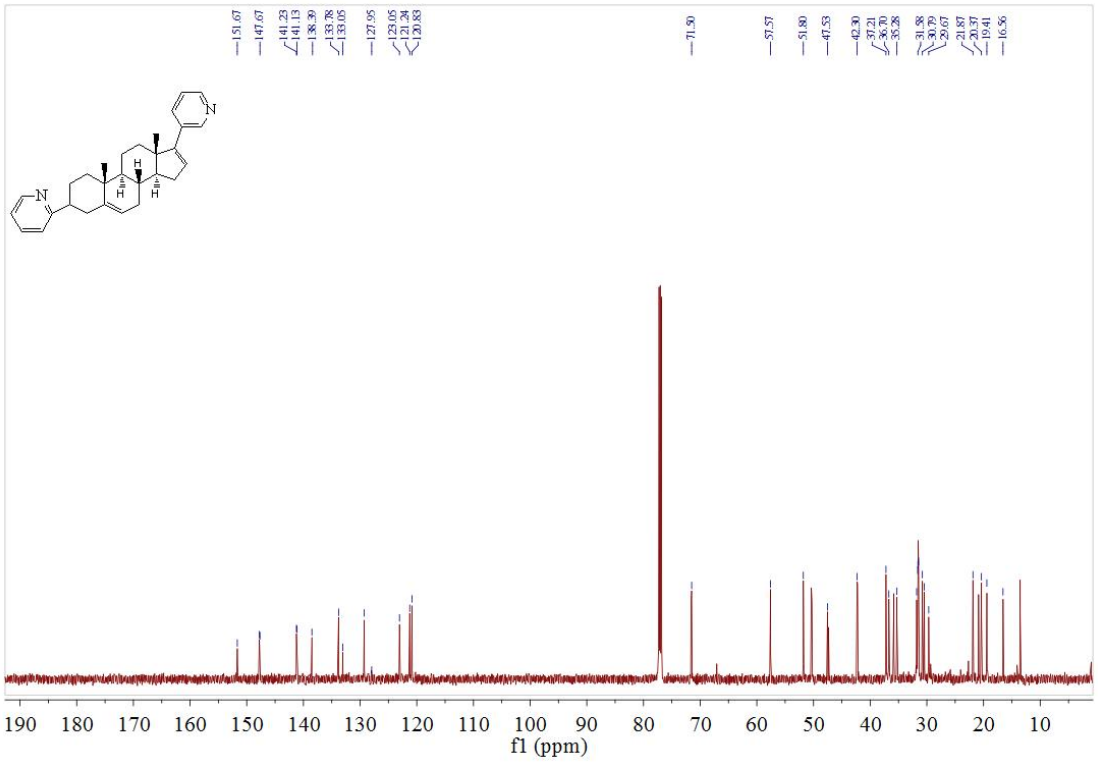


Figure 8S. ^{13}C NMR Spectrum (150 MHz, $CDCl_3$) of compound 9

References

1. Gerard A. Potter, Ian R. Hardcastle, and Michael Jarman. "A CONVENIENT, LARGE-SCALE SYNTHESIS OF ABIRATERONE ACETATE [3β-ACETOXY-17-(3-PYRIDYL)ANDROSTA-5,16-DIENE], A POTENTIAL NEW DRUG FOR THE TREATMENT OF PROSTATE CANCER." Organic Preparations & Procedures International 29.1(1997):123-128.

2. Gerard A. Potter, Ian R. Hardcastle. Synthesis of 17-(3-pyridyl) steroids: GB，2282377[P]. 1995-05-04