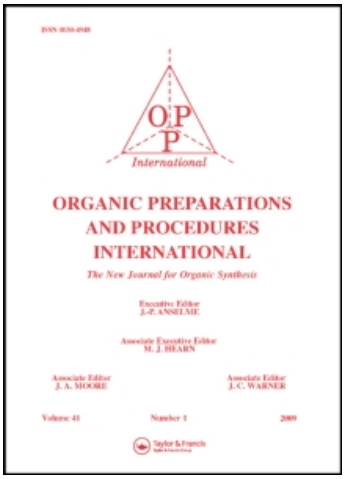

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A CONVENIENT, LARGE-SCALE SYNTHESIS OF ABIRATERONE ACETATE [3β-ACETOXY-17-(3-PYRIDYL)ANDROSTA-5,16-DIENE], A POTENTIAL NEW DRUG FOR THE TREATMENT OF PROSTATE CANCER

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OPPI BRIEFS

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

Submitted by (03/25/96)

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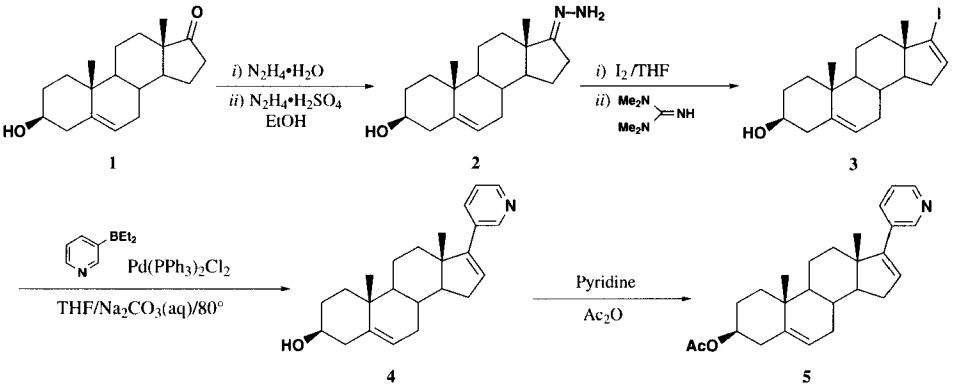
3β-Acetoxy-17-(3-pyridyl)androsta-5,16-diene (abiraterone acetate, **5**) is a pro-drug for 17-(3-pyridyl)androsta-5,16-dien-3β-ol (abiraterone, **4**), a potent inhibitor of human cytochrome $P450_{17\alpha}$ (steroidal 17α-hydroxylase-$C_{17,20}$-lyase).[1] This enzyme is a potential target for a drug designed to treat hormone-dependent prostatic carcinoma, and **5** has been approved for clinical trial in patients with this cancer. In connection with this trial, a method amenable to the synthesis of **5** on a large scale (*ca.* 100 g or more) was required. The present paper reports such a synthesis.

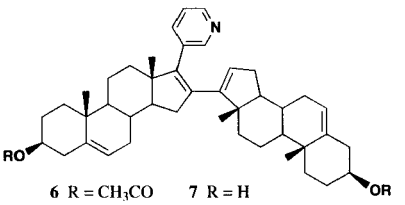


1 2 3 4 5

The key step in the previously reported[1] synthesis of **5** was the palladium-catalysed cross-coupling reaction between diethyl(3-pyridyl)borane and the 17-enol triflate derived from the 3-acetate of dehydroepiandrosterone **1**. The procedure has potential drawbacks as a method for large-scale synthesis. Aside from the use of the expensive and noxious triflic anhydride, the formation of the enol

triflate requires the expensive hindered base 2,6-di-*tert*-butyl-4-methylpyridine.[2] Further, it was accompanied by some elimination of acetic acid to give androsta-3,5,16-trien-17-yl triflate which required chromatographic separation from the desired product, and contributed to reducing its isolated yield from the acetate of **1** to a moderate 58%. These problems prompted consideration of an alternative steroidal precursor suitable for the cross-coupling reaction. It occurred to us that the vinyl iodide **3** might provide a viable alternative to an enol triflate in the palladium catalyzed cross-coupling step. Such steroidal vinyl iodides are easily and cheaply obtained via the corresponding 17-hydrazones.[3-6] The synthesis of **3** iself from the hydrazone[3] **2** by oxidation with iodine in the presence of a hindered guanidine base has been optimised[4,5] to obtain the product on a small scale (0.13 g) in 95% yield. We were able to repeat this reaction on a large scale and obtain a similar yield of **3**. The palladium catalysed cross-coupling reaction of **3** with diethyl(3-pyridyl)borane proceeded without the need to protect the 3-hydroxyl function to give **4**, whereas the use of an enol triflate in the coupling reaction does not conveniently allow this option. However, coupling with the iodide was much slower, requiring 4 days at 80° as compared with the 1 hr required when an enol triflate precursor was used.[1]

Recrystallization of the crude **4** obtained by the foregoing procedure gave a product with melting point lower than that previously reported,[1] and TLC revealed a less mobile contaminant that was not removed by further recrystallization. The crude product was therefore acetylated to give the crude target compound **5** contaminated with a by-product. This by-product was **6**, formed from a precursor **7** present as a contaminant in crude **4**. The prolonged reaction time required for the cross-coupling reaction using the vinyl iodide **3** had enabled a Heck-type reaction[7] to occur between the initial product **4** and the *bis*(triphenylphosphine)-palladium derivative of **3** to form **7**. The very recently reported[8] palladium-catalysed dimerisation of 17-iodo-Δ^{16}-steroids to give 16,17'-coupled products provides a precedent for this side-reaction.



6 R = CH_3CO **7** R = H

Whereas column chromatography on silica-gel of crude **5** afforded pure **6**, which was eluted first, compound **6** contaminated later fractions and could not be completely removed from **5** by recrystallization. However subsequent reverse phase chromatography allowed the complete separation of the now faster eluting **5** from **6**, and recovery of >100 g of pure **5** by batchwise chromatography of the crude product.

The by-product **6** was deacetylated to give **7**, the contaminant present in **4** prepared by the present route. Neither of the new compounds **6** and **7** was appreciably inhibitory towards the human cytochrome $P450_{17\alpha}$ (S. E. Barrie, personal communication). The availability of pure **7** affords the option of exploring the purification of **4** prior to acetylation. However, for chromatographic purification, the greater solubilities of **5** and **6** in suitable organic solvents compared with their non-acetylated counterparts favor the present choice of purification after acetylation.

EXPERIMENTAL SECTION

Diethyl(3-pyridyl)borane was obtained from Aldrich Chemical Co. Ltd, Gillingham, Dorset, UK. ^{1}H-NMR spectra (250 MHz) were determined with a Bruker AC 250 spectrometer. Mass spectra (electron impact, 70 eV) were obtained by direct insertion with a VG 7070H spectrometer and VG 2235 data system. Normal-phase chromatography was conducted on silica gel (Merck Art 15111) and reverse-phase preparative chromatography using a Jobin-Yvon Chromatospac Prep 10 on a 10 cm diam column (500 g) of C8 LiChrosorb packing (Art. No. 9324; E. Merck, Darmstadt, Germany). The analytical HPLC system comprised a Waters 680 gradient controller and two model 510 pumps (Millipore UK Ltd., Watford, Herts, UK) fitted with a Spherisorb S3PC18 cartridge column (15 cm x 4.6 mm: Phase Separations Ltd., Deeside, Clwyd, UK). Compounds were detected with a Perkin-Elmer LC-240 fluorescence detector or with a Waters model 440 absorbance detector. Elemental analyses were determined by CHN Analysis Ltd., South Wigston, Leicester, England.

Dehydroepiandrosterone-17 Hydrazone (2).- Into a 10 L round-bottomed flask, fitted with a magnetic stirrer bar, was placed dehydroepiandrosterone **1** (288 g, 1.0 mol) and ethanol (5.0 L). To the resultant stirred solution was added hydrazine hydrate (195 mL, 4.0 mol) (CAUTION: mutagen, carcinogen), followed by a solution of hydrazine sulfate (0.65 g, 0.005 mol) in water (20 mL). After stirring at room temperature for 5 days, water (4.5 L) was added, the mixture poured into water (10 L), and the precipitate was collected, washed with cold water (2 x 500 mL), then with Et_2O (2 x 500 mL). The product was dried *in vacuo*, over silica gel, then over P_2O_5, to give 284.8 g (94%) of **2** as white crystals, mp. 204-206°, lit.[3] mp. 287° after sintering at 210°.

17-Iodoandrosta-5,16-dien-3β-ol (3).- A stirred solution of iodine (156.1 g, 0.615 mol) inTHF (4.0 L; GPR grade) and Et_2O (2.0 L; BDH specially dried grade)in a 10 L round-bottomed flask was cooled by an ice/water bath to 0° and 1,1,3,3-tetramethylguanidine (188 mL, 173 g, 1.50 mol) was added. A solution of **2** (90.74 g, 0.30 mol) in THF (2.25 L) was then added slowly to the above iodine solution *via* a canula (36", 12 gauge bore) during 2 hrs, whilst maintaining the reaction temperature at 0° (IMPORTANT CAUTION: to avoid risk of explosion while N_2 was evolved as **2** was added to the iodine solution). The mixture was then stirred for a further hr and the precipitate allowed to settle (a precipitate of tetramethylguanidinium iodide forms during the reaction). The mixture was then filtered, and the filtrate concentrated to an oil on a rotary evaporator. This reaction was carried out three times, thus using in total 272.22 g (0.90 mol) of **2**. The concentrated residues from the three separate reactions were combined and heated on an oil bath at 80° for 4 hrs, to convert any 17,17-diiodo by-product into the 17-vinyl iodide product[4,5] then allowed to cool. The resulting oil was then dissolved in Et_2O (5 L), filtered, and further diluted with additional Et_2O (4 L). The Et_2O solution was washed with aqueous HCl (1M; 3 x 500 mL) until the aqueous phase was acidic, whereupon the ether solution changes colour from brown to yellow, then finally with water (500 mL). The Et_2O phase was separated, dried ($MgSO_4$), and concentrated to 3 L. The yellow crystals which separated were collected by filtration on a sinter, washed with hexane (3 x 500 mL) and dried under vacuum to give crude **3** (335.4 g, 94%). Recrystallisation from ethanol-water (5:1) afforded pure **3** as white crystals (297.3 g, 83%) mp. 175-176°, lit.[3] 172-174°, lit.[5] 173-174°.

17-(3-Pyridyl)androsta-5,16-dien-3β-ol (4).- A stirred solution of **3** (98.0 g, 0.246 mol) in THF (1.1 L) in a 2 L round-bottomed flask was purged with argon and *bis*(triphenylphosphine)palladium (II) chloride catalyst (1.73 g, 0.0025 mol) was added, followed by diethyl(3-pyridyl)borane (43.35 g, 0.295 mol). To the resultant orange solution was added an aqueous solution of sodium carbonate (2M; 500 mL). The flask was fitted with a reflux condenser, and the apparatus purged again with argon. The mixture was then heated under reflux (~ 80°) with stirring on a stirrer/heating mantle (Electrothermal MA) for 4 days (upon completion of the reaction the organic phase darkened from orange to dark orange/brown) then allowed to cool. This reaction was carried out a total of three times, thus using a total of 294.0 g (0.74 mol) of **3**. The reaction mixtures were combined and Et_2O (5 L) added. The organic phase was separated, washed with water (2 L), and a first crop of crystals which separated was collected by filtration on a sinter. The filtrate was concentrated and the residue redissolved in Et_2O to afford a second crop of crystals. The aqueous phase and washings from the above work-up were extracted with hot toluene (2 L) on a steam bath and concentration of the toluene extracts afforded further product. The combined crude product from the above procedures was then dissolved in the minimum volume of hot methanol, filtered through celite, and an equal volume of acetonitrile added. The solution was then concentrated to half its original volume on a rotary evaporator and the white crystals which separated were collected on a sinter, washed with acetonitrile and dried *in vacuo* to give crude **4** (191.1 g) of mp. 208-212°, lit.[1] 228-229°. A second recrystallisation from toluene-methanol (50:1) afforded product (146.8 g) of mp. 214-218° which was still impure (see below) but which was used for the next step.

3β-Acetoxy-17-(3-pyridyl)androsta-5,16-diene (5) and 3β-acetoxy-16-(3β-acetoxyandrosta-5,16-dien-17-yl)-17-(3-pyridyl)androsta-5,16-diene (6).- To a stirred suspension of the product from the foregoing reaction (36.5 g, 0.104 mol) in dry pyridine (200 mL) in a 500 mL round-bottomed flask was added acetic anhydride (75 mL) and the mixture stirred at room temperature for 24 hrs. The pyridine and excess acetic anhydride was removed on a rotary evaporator, initially at water pump pressure with the water bath at 70 °, and finally under high vacuum at 80° for 30 min. The resulting oil was dissolved in Et_2O (500 mL), washed with saturated aqueous $NaHCO_3$ (2 x 200 mL), dried (Na_2CO_3), and concentrated to an oil which crystallised on standing. The crude **5** was partly purified by preparative flash chromatography on silica gel using a 9 cm diameter column, eluting with dichloromethane. A by-product (**6**) eluted first and was followed by fractions variously enriched in **5**. The foregoing reaction and purification procedure was carried out a total of four times, thus using a total of 146 g (0.418 mol) of crude **4**. The dichloromethane fractions containing the least by-product were combined and concentrated. Recrystallisation from hexane afforded product (108 g) consisting of **5** containing 6.8% w/wof **6** as impurity as determined by analytical HPLC. The more contaminated fractions similarly afforded product (25 g) containing 21.8% w/w of **6** (we thank Dr C. P. Quarterman, Aston Molecules Ltd, Birmingham U.K. for these analyses). A pure sample of **6** (4 g) was isolated from the combined initial fractions as pale yellow crystals, mp. 269-270° (from hexane); IR 1732 cm^{-1} (C=O str); ^{1}H-NMR: δ 0.85 (s, 3, H-18'), 1.02, 1.04 (2s, 6, H-19,19'), 1.06 (s, 3, H-18), 2.034, 2.039 (2s, 6,

CH_3CO), 4.59 (2m, 2, H-3,3'), 5.13 (s, 1, H-16'), 5.39 (dd, 2, H-6,6'), 7.62 (dd, 1, $J_{5,4}$ = 8.0 Hz, $J_{5,6}$ = 5.4 Hz, pyridyl H-5), 7.94 (d, 1, pyridyl H-4), 8.42 (s, 1, pyridyl H-2), 8.51 (d, 1, pyridyl H-6).

Anal. Calcd for $C_{47}H_{61}NO_4$: C, 80.18; H, 8.73; N, 1.99. Found: C, 80.19; H, 8.78; N, 1.95

The crude **5** was purified by reverse-phase column chromatography. A solution of material from the 108 g batch (10 g) in a hot mixture of acetonitrile (200 mL) and methanol (40 mL) was allowed to cool and filtered. The filtrate was applied to a 10 cm diameter column (500 g) of LiChroprep® RP-8 reverse-phase C_8 packing Art. No. 9324. The column was eluted with acetonitrile-0.05 M ammonium acetate (20:1) with a flow rate of 25 mL/min and 500 mL fractions were collected and analysed by analytical HPLC (see below). Fractions 4-10 contained pure **5**. After a further two fractions, the eluant was changed to acetonitrile-acetic acid (20:1) and pure **6** was completely eluted in fractions 16-19. In 3 subsequent runs using the same column, 25 g portions of the same batch of crude **5** were each dissolved in a mixture of hot acetonitrile (350 mL) and methanol (100 mL) and processed as before. Fractions 2-7 contained pure **5** and, following the change of solvent, fractions 8-12 contained **6**. The four eluates containing **5** were combined and recrystallised from acetonitrile (1200 mL) to give pure **5** (57.5 g), mp. 146-148°, lit.[1] mp. 144-145°, in which **6** was not detected by analytical HPLC (for procedure, see below) at the limit of detection (<0,05% w/w **6**).

Anal. Calcd for $C_{26}H_{33}NO_2$: C, 79.75; H, 8.50; N, 3.58. Found: C, 79.73; H, 8.48; N, 3.62

Further material (14 g) from the 108 g batch was combined with a portion (22 g) of the more impure 25 g batch and the total of 36 g was chromatographed in one batch as above, again giving complete separation of **5** from **6**. Recrystallisation from acetonitrile (600 mL) gave a further 28.5 g of **5** of purity equal to the foregoing crop of 57.5 g **5**. Concentration of the combined mother liquors from these crops followed by addition of water (MeCN:H_2O, 12:1 v/v) gave further pure **5** (17.5 g). The total recovery of pure **5** was therefore 103.5 g (36% based on **3**). The spectroscopic data (NMR, IR, and MS) of the final products from this procedure were identical with those reported for the product obtained by the route previously described.[1]

Procedure for Analysis of Purity of Batches of 5 Using Analytical HPLC.- The eluant was acetonitrile-0.05M ammonium acetate and the flow rate 1.5 mL/min. Components were monitored either by fluorescence detection (excitation wavelength λ_{ex} 262 nm, emission wavelength λ_{em} 353 nm) or by UV detection (254 nm). Typical retention times were: for **5**, 225 sec; for **6**, 1162 sec. For analysis of crystalline products, a solution (5 mg/mL) in acetonitrile was diluted 50 fold to 100 µg/mL and 100 µl of this solution was injected onto the column.

3β-Hydroxy-16-(3β-hydroxyandrosta-5,16-dien-17-yl)-17-(3-pyridyl)androsta-5,16-diene (7).- To a solution of **6** (1.406 g, 2 mmol) in THF (50 mL) was added 10M NaOH (1 mL, 4 mmol) and the mixture was stirred for 6 days at room temperature, then neutralized with M HCl (10 mL). The product was extracted into dichloromethane, the extracts dried ($MgSO_4$) and concentrated. Recrystallization from methanol gave **7** (0.88 g, 71%) as white crystals, mp. 227-230°.

Anal. Calcd for $C_{43}H_{57}NO_2.CH_3OH$: C, 81.06; H, 9.43; N, 2.15. Found: C, 80.85; H, 9.08; N, 2.17

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A CONCISE PREPARATION OF 2,6-DIMETHYL-4-NITROCHLOROBENZENE

Submitted by Stephen W. Wright*
(06/14/96)

Pfizer Central Research
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2,6-Dimethyl-4-nitrochlorobenzene (**1**) is an intermediate of potential use for the preparation of a variety of biologically active molecules.[1] Despite the utility of this compound, it remains poorly known in the literature, with details of its preparation confined to three patents and one journal article.[2] Each of these syntheses proceeds in the same manner, starting with 2,6-dimethylaniline (**2**) and carrying out four steps: (1) N-protection; (2) nitration; (3) N-deprotection; and (4) Sandmeyer reaction. In as much as the overall yields for these four step processes averaged only about 15% to