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SYNTHESIS OF 17-(3-PYRIDYL) STEROIDS

Background of the invention

1. Field of the invention

This invention relates to the synthesis of steroids which have a 16, 17-double bond and a 17-(3-pyridyl) substituent.

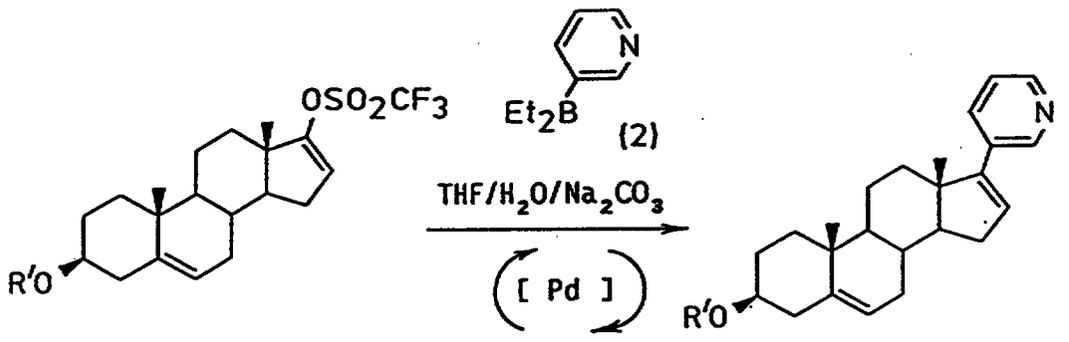
2. Description of the related art

In patent applications GB 2265624A (British Technology Group Limited) and PCT WO 93/20097 (British Technology Group Limited, S.E. Barrie, M. Jarman and G.A. Potter), both filed on 15th March 1993, and published on 6th and 14th October 1993 respectively, we have described 16,17-ene-17-(3-pyridyl) steroids as a class of compounds useful for treatment of androgen- and oestrogen-dependent disorders, especially prostatic and breast cancer respectively. A few of these compounds have previously been mentioned in the literature as intermediates in synthesis, to prepare final products having other uses, but otherwise these compounds were new. Posters have been presented, notably at the SmithKline Beecham Research Symposium, Robinson College Cambridge, England, 25-26 March 1993 and at the British Association for Cancer Research meeting in Sheffield, England, 28-31 March 1993. The Cambridge poster describes the synthesis of an exemplified 16,17-ene-17-(3-pyridyl) steroid as follows:

Synthesis of this molecule was envisaged via a possible palladium catalysed cross-coupling [G.A. Potter and R. McCague, J. Org Chem. 55, 6184-6187 (1990)] of a steroidal enol triflate (trifluoromethylsulfonate) with a suitable 3-pyridyl nucleophilic coupling partner. This was achieved by using diethyl(3-pyridyl)borane in aqueous THF, with sodium carbonate as nucleophilic activator. The reaction proceeded remarkably efficiently, without possible triflate hydrolysis or ethyl coupling, providing the desired compound in 80% isolated yield (Scheme 1):

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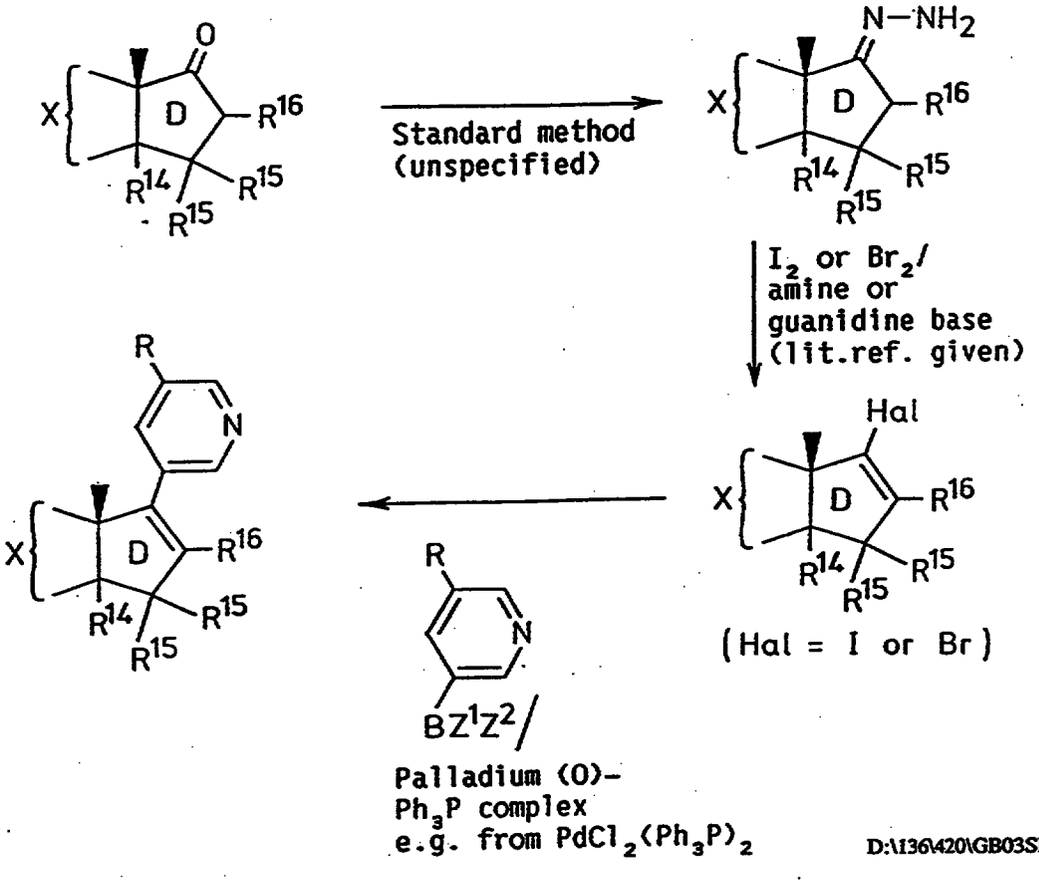
Scheme 1



(wherein in the final compound R' = H)

Triflates are expensive starting materials, so an alternative route is desirable. Further, notwithstanding what might appear from a literal reading of the poster, to obtain the 3-ol the reaction has to be carried out on the 3-acetate as protecting group, not the 3-ol. The 3-acetate is then hydrolysed to the 3-ol subsequently in a separate step. The said patent applications propose in outline an alternative route, as follows (Scheme 2):

Scheme 2

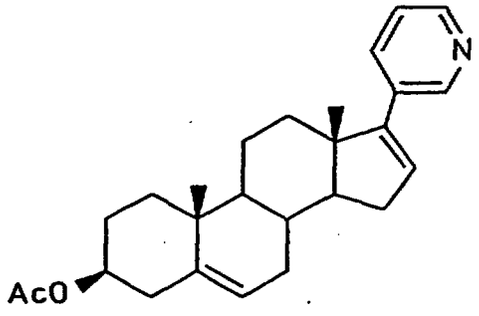


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wherein X represents the residue of the A, B and C rings of a steroid, R represents a hydrogen atom or an alkyl group of 1-4 carbon atoms, R^{14} represents a hydrogen atom, a halogen atom or an alkyl group of 1 to 4 carbon atoms and each of the R^{15} substituents independently represents a hydrogen atom or an alkyl or alkoxy group of 1-4 carbon atoms, a hydroxy group or an alkylcarbonyloxy group of 2 to 5 carbon atoms or together represent an oxo or methylene group or R^{14} and one of the R^{15} groups together represent a double bond and the other R^{15} group represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms, and R^{16} represents a hydrogen atom, halogen atom, or an alkyl group of 1 to 4 carbon atoms, and Z^1 and Z^2 independently represent hydroxy or alkoxy or alkyl of 1-4 carbon atoms each, preferably ethyl or methoxy.

Summary of the invention

It has now surprisingly been found that in the preparation of 3β-acyloxy-16, 17-ene-17-(3-pyridyl) steroids, especially the preferred compound, 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene, of formula (1):



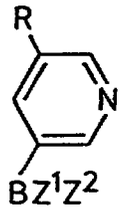
(1)

the reaction can be carried out via the vinyl iodide intermediate, but using the unprotected 3β-hydroxy compound. By-products can be reduced either (a) by keeping the proportion of organoboron compound (borane) used in the cross-coupling reaction to not more than 1.2 equivalents per equivalent of steroid or (b) by crystallising the reaction product of the cross-coupling reaction from a mixture of acetonitrile and

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methanol. This route via the vinyl iodide intermediate is therefore amenable to large scale synthesis.

The principle of the invention may be expressed as a method of preparing a 3β-hydroxy- or 3β-(lower acyloxy)-16,17-ene-17-(3-pyridyl)-substituted steroid, wherein the 3β-(lower acyloxy) group of the steroid has from 2 to 4 carbon atoms, which comprises subjecting a 3β-hydroxy-16,17-ene-17-iodo or -bromo steroid to a palladium complex-catalysed cross-coupling reaction with a (3-pyridyl)-substituted borane, in which the pyridine ring is substituted at the 5-position by an alkyl group of 1 to 4 carbon atoms or is unsubstituted thereat, especially with a said borane of formula (2):



(2)

wherein R is a hydrogen atom or an alkyl group of 1-4 carbon atoms and Z^1 and Z^2 independently represent hydroxy or alkoxy or alkyl or 1-3 carbon atoms each or Z^1 and Z^2 together represent an alkylenedioxy group of 2 or 3 carbon atoms, in a proportion of at least 1.0 equivalent of boron compound per equivalent of steroid, in an organic liquid, which is a solvent for the 3β-hydroxy steroidal reaction product, and optionally esterifying the 3β-hydroxy reaction product to the 3β-acyloxy ester, which method comprises feature (a) or (b) above.

Description of the preferred embodiments

Preferably the 17-iodo ("vinyl iodide") or -bromo starting compound has a D-ring with optional substitution in position 14, 15 and/or 16 as shown in Scheme 2. Most preferably it is prepared from the corresponding 17-ketone, conveniently via the corresponding hydrazone. Preferably the vinyl iodide or bromide is unsubstituted in the 14, 15 and 16-positions, in which case it can be prepared from dehydroepiandrosterone

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(DHEA). In the hydrazination it is preferable to use hydrazine hydrate together with a catalytic amount of a proton provider which is most preferably hydrazine sulfate.

The hydrazone is preferably iodinated with iodine or brominated with bromine in the presence of a strong base such as a tetraalkylguanidine, especially tetramethylguandine which is cheaply and readily available.

In the cross-coupling reaction, the boron compound is preferably a diethylborane or a dimethoxyborane (Z^1=Z^2=Et or OMe). Other boranes include those in which the boron atom is part of a cyclic ether ring e.g. as in Z^1, Z^2 = 1,2-ethylenedioxy or 1,3-propylenedioxy. In embodiment (a) of this invention the proportion of borane added is at least 1.0, but no more than 1.2 equivalents of boron per equivalent of steroid, preferably about 1.1, but in the embodiment (b) a higher proportion is preferred, of at least 1.2 : 1 to 1.5 : 1 equivalents of boron compound to steroid. The higher proportion will give the better yield of product but also more of the contaminating boron, phosphine and/or palladium compounds. According to embodiment (b), however, these are removed with the acetonitrile solvent. In either embodiment, the palladium compound is a palladium (0) phosphine complex such as tetrakis(triphenylphosphine) palladium (0) or a compound reducible to a palladium (0) phosphine species, especially bis(triphenylphosphine) palladium (II) chloride. The reaction vessel is preferably purged with an inert gas, especially argon or nitrogen, to minimise the possibility of oxidation with a corresponding redox reduction of palladium to the metallic state.

The cross-coupling reaction is preferably carried out in two phases, one aqueous, one organic. The organic phase comprises an organic solvent for the 3β-hydroxy steroidal reaction product, especially tetrahydrofuran (THF). Other cyclic ethers such as dioxane could be used in place of THF. Preferably, a nucleophilic activator, such as sodium carbonate, is used, in which case it is normally present in the aqueous phase.

After the reaction, inorganic salts can be removed by first adding another organic solvent, preferably diethyl ether, which is a solvent for the organoboron contaminants produced in the reaction product, and miscible with the first-mentioned organic solvent (e.g. THF), but immiscible with water, whereafter the organic, e.g. THF-diethyl ether,

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phase and water (aqueous phase) can be separated. After this separation, various work-up procedures are operable. In one procedure, particularly suited to embodiment (a), the THF and diethyl ether are removed, e.g. evaporated as a mixture, and the remaining reaction product is washed with a third organic solvent, which can be diethyl ether, preferably cooled to below room temperature, most especially to 10°C or lower. The third organic solvent is one in which the 3β-hydroxy steroid reaction product has a low solubility and which, importantly, removes the organoboron compound/s (and also the contaminating phosphine and palladium compound/s). Diethyl ether is preferred.

A different work-up procedure, used in embodiment (b), comprises crystallisation from acetonitrile/methanol. Acetonitrile is a preferred crystallisation solvent to keep boron compound as well as palladium compound in solution and is therefore used in an excess over methanol e.g. an excess of at least 5 : 1 and preferably about 8 : 1 by volume.

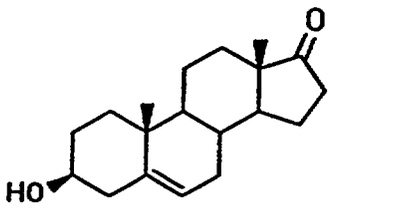
To prepare the 3β-acyloxy (alkylcarbonyloxy) compounds, of which the acetoxy compound is preferred, standard acylating (acyl-esterification) agents such as acetyl, propionyl or butyryl chloride or anhydride can be used in step (d). The final product of step (d) may be crystallised direct from hexane, rather than from ethanol/water followed by hexane. Preferably, the work-up procedure comprises reverse phase chromatography, i.e. using a relatively lipophilic solid phase. In this procedure, the chief by-product, a bis-steroidal compound, is preferentially retained on the solid phase and can be eluted with a good separation from the desired product.

The following Examples illustrate the invention. In Example 1, the 3β-hydroxy product is produced without chromatography, by embodiment (a). In Example 2, the 3β-hydroxy product is not isolated, but in step (d) an impurity has been identified as a 16,17'-bis(steroidal) by-product. This can be removed by reverse phase chromatography, but now that the by-product has been identified, those skilled in the art will be able more easily to identify procedures which will remove it, without the need for chromatography. Further, it is believed that with the higher organoboron : steroid ratios suggested above, the side-reaction leading to this impurity will be reduced.

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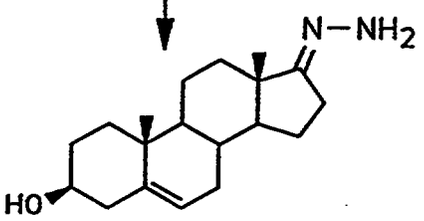
Scheme 3:

illustrative reaction scheme of the present invention



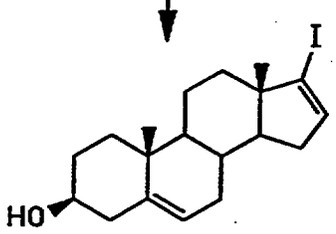
Dehydroepiandrosterone (DHEA)

(a) Modification of lit. method, B. Schweder *et al.* J. Prakt. Chem.. 201-204, 335, (1993).



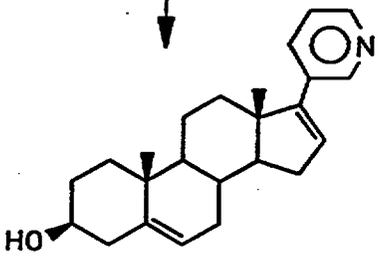
Hydrazone of DHEA

(b) Modification of lit. methods. D.H.R. Barton *et al.*, Tet. Lett.. 1605-1608, 24, (1983). Tetrahedron, 147-162, 44, (1988).



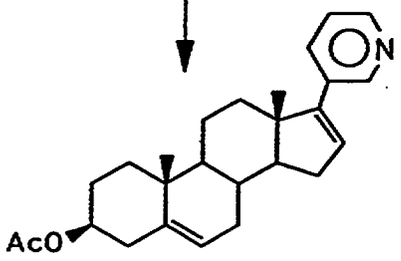
Steroidal vinyl iodide

(c) (Modification of methodology described in the earlier patent applications).



3β-hydroxy steroidal reaction product

(d) Standard acetylation



3β-acetoxy steroidal reaction product

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EXAMPLE 1

This example illustrates embodiment (a).

(a) Dehydroepiandrosterone-17-hydrazone

To a stirred solution of dehydroepiandrosterone (28.8g, 0.1 mol) in ethanol (500ml) was added hydrazine hydrate (19.5ml, 0.4 mol), followed by a solution of hydrazine sulfate (65mg, 0.5 mmol) in water (2ml). After stirring for 3 days the mixture was poured into water (3 litres) to precipitate the product as a white crystalline solid. The product was collected by filtration on a sinter, washed with cold water (2 x 50ml), then with Et_2O (50ml). The product was then dried *in vacuo*, firstly over silica gel, and finally over P_2O_5, to give the title compound as a white cyrstalline solid (29.6g, 98%).

Notes 1) The method of Schweder *et al.*, p.202, compound No. 2 therein (using triethylamine) gave a very fine crystalline product which was difficult to filter.

2) The method of Schweder *et al.* p. 203, compound No. 4 therein (using sodium acetate buffer) gave a slightly lower yield (96%) in trial experiments, whereas the modified procedure used above gave a product amenable for filtration, and in excellent yield (98%).

(b) 17-Iodo-androsta-5,16-dien-3β-ol

To a solution of iodine (53.3g, 0.21 mol) in THF (2L), cooled by an ice/water bath to 0°C, was added 1,1,3,3-tetramethylguanidine (63 ml, 57.6g, 0.50 mol).

A solution of dehydroepiandrosterone-17-hydrazone (30.25g, 0.10 mol) in THF (750ml) was then added slowly to the above iodine solution via a transfer needle over about 2h, whilst maintaining the reaction temperature at 0°C. After all the hydrazone solution was added, the mixture was filtered, and the filtrate concentrated. The remaining oil was then heated on an oil bath for 4h, allowed to cool, and dissolved in Et_2O. The Et_2O solution was washed with 1M HCl until the aqueous phase was acidic, washed with 0.5M NaOH, then 1M $Na_2S_2O_3$, and finally with water. The Et_2O phase was separated, dried ($MgSO_4$), and concentrated to give the crude product. Recrystallisation from Et_2O/hexane (3:2) afforded the title compound as off-white crystals (35.8g, 90%).

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(c) 17-(3-Pyridyl)androsta-5,16-dien-3β-ol

Diethyl(3-pyridyl)borane (3.23g, 22 mmol) from Aldrich Chemical Co. Ltd. was added to a stirred solution of 17-iodo-androsta-5,16-dien-3β-ol (7.96g, 20 mmol) in THF (120ml) containing bis(triphenylphosphine)palladium (II) chloride (140mg, 0.2 mmol). An aqueous solution of sodium carbonate (2M, 50ml) was then added and the mixture heated, with stirring, by an oil bath at 80°C for 48h, and allowed to cool.

The mixture was partitioned between Et_2O and water the organic phase was separated, dried (Na_2CO_3) and twice concentrated from Et_2O by evaporation to remove THF (with Et_2O). The residual solid was then washed with Et_2O (100ml), the Et_2O solution decanted off, and the remaining white solid recrystallised from toluene (3.94g, 56%).

Notes 1) The time required for completion needs to be made longer than when using the vinyl triflate (48h vs 1h) since it has been found that the vinyl iodide reacts much more slowly.

2) It has been found that a smaller excess of borane than described in the earlier applications (for the vinyl triflate) aids in isolation of product.

3) The work-up procedure enables the product to be isolated without chromatography, thereby enabling scaling up.

(d) 3β-Acetoxy-17-(3-pyridyl)androsta-5,16-diene

To a stirred suspension of finely powdered 17-(3-pyridyl)androsta-5,16-dien-3β-ol (3.50g, 10 mmol) in dry diethyl ether (150ml) containing triethylamine (2.3ml, 16 mmol) and dimethylaminopyridine (0.012g, 0.1 mmol) was added acetyl chloride (1.0ml, 14 mmol). The mixture was then stirred at ambient temperature for 12h, over which time a thick white precipitate of triethylammonium chloride had formed. The mixture was then filtered and the filtrate concentrated to afford the crude product which was recrystallised firstly from ethanol/water (1:1), then finally from hexane to afford the title compound (3.30g, 84%).

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EXAMPLE 2

(a) Dehydroepiandrosterone-17-hydrazone

Into a 10L round-bottomed flask, fitted with a magnetic stirrer bar, was placed dehydroepiandrosterone (288g, 1.0 mol) and ethanol (5.0L). To the resultant stirred solution was added hydrazine hydrate (195ml, 4.0 mol), followed by a solution of hydrazine sulfate (0.65g, 0.005 mol) in water (20ml) [note: the hydrazine sulfate dissolved in this volume of water at about 40°C]. After stirring at room temperature for 5 days, water (4.5L) was added, the mixture poured into water (10L), and the white crystalline precipitate allowed to settle. The product was collected by filtration on a sinter, washed with cold water (2 x 500ml), then with Et_2O (2 x 500ml). The product was then dried *in vacuo*, firstly over silica gel, and finally over P_2O_5, to give the title compound as a white crystalline solid, mp 204-206°C (284.8g, 94%).

(b) 17-Iodo-androsta-5,16 dien-3β-ol

A 10L round-bottomed flask, fitted with a magnetic stirrer bar, was charged with iodine (156.1g, 0.615 mol), THF (4.0L; GPR grade), and Et_2O (2.0L; BDH specially dried grade). The resultant stirred solution was cooled by an ice/water bath to 0°C and 1,1,3,3-tetramethylguanidine (188ml, 173g, 1.50 mol) was added. A solution of dehydroepiandrosterone-17-hydrazone from step (a) (90.74g, 0.30 mol) in THF (2.25L) was then added slowly to the above iodine solution via a canula over about 2h, whilst maintaining the reaction temperature at 0°C [note: N_2 is evolved as the hydrazone is added to the iodine solution]. After all the hydrazone solution was added, the mixture was stirred for an additional hour and the precipitate allowed to settle [note: a precipitate of tetramethylguanidium 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 a total of three times, thus using in total 272.2g (0.90 mol) of dehydroepiandrosterone-17-hydrazone from step (a). The concentrated residues from the three separate reactions were combined and heated on an oil bath at 4h, then allowed to cool [note: this converts any 17,17-diiodo by-product in

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vinyl iodide product]. This oil was then dissolved in Et_2O (5L), filtered, and further diluted with additional Et_2O (4L).

The Et_2O solution was washed with aqueous HCl (1M; 3 x 500ml) until the aqueous phase was acidic [note: the ether solution changes colour from brown to yellow when the aqueous phase remains acidified] then finally with water (500ml). The Et_2O phase was separated, dried ($MgSO_4$), and concentrated to a volume of 3L, then left to allow the product to crystallise. The yellow crystals were collected by filtration on a sinter, washed with hexane (3 x 500ml) and dried under vacuum (335.4g, 94%). Recrystallisation from ethanol-water (5:1) afforded the product as white crystals (297.3g, 83%) mp 175-176°C, lit. mp 173-174°C.

(c) 17-(3-Pyridyl)androsta-5,16-dien-3β-ol

In a 2L round-bottomed flask, fitted with a magnetic stirrer bar, was placed the steroidal 17-iodo product from step (b) (98.0g, 0.246 mol) and this was dissolved in THF (1.1L). The flask was purged with argon and bis(triphenylphosphine)palladium (II) chloride catalyst (1.73g, 0.0025 mol) was added, followed by diethyl(3-pyridyl)borane (43.35g, 0.295 mol). To the resultant orange THF solution was added an aqueous solution of sodium carbonate (2M; 500ml). The flask was fitted with a reflux condenser, and the apparatus purged again with argon. The mixture was then heated under reflux (at about 80°C) with stirring on a stirrer/heating mantle (Electrothermal MA) for 4 days [note: upon completion of the reaction the organic phase darkens in colour 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 294.0g (0.74 mol) of the steroidal 17-iodo product from step (b).

The reaction mixtures were combined and Et_2O (5L) added. The organic phase was separated, washed with water (2L), and left to give a first crop of crystals which were 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 (2L) on a steam bath and concentration of the toluene extracts afforded further product. The combined crude

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product from the above procedures was then dissolved in the minimum volume of hot methanol, filtered through a plug of "Celite" (Registered Trade Mark) and an equal volume of acetonitrile added to the methanol solution. The acetonitrile/methanol solution was then concentrated to half its original volume on a rotary evaporator and the solution left to crystallise. The resultant white crystals were collected by filtration on a sinter, washed with acetonitrile and dried *in vacuo* to constant weight (191.1g, 74%), mp 202-212°C. A second recrystallisation from toluene-methanol (50:1) afforded the product as white crystals (146.8g, 57%) mp 214-218°C, lit. mp 228-229°C.

(d) 3β-Acetoxy-17-(3-pyridyl)androsta-5,16-diene

The following reaction was carried out in a 500ml round-bottomed flask, fitted with a magnetic stirrer bar. To a suspension of the steroidal product from step (c) (26.5g, 0.104 mol) in dry pyridine (200ml), was added acetic anydride (75ml) and the mixture stirred at room temperature for 24h. The pyridine and excess acetic anydride were removed on a rotary evaporator, initially with the water bath at 70°C, and finally at 80°C for 30 min. The resulting oil was dissolved in Et_2O (500ml), washed with saturated aqueous $NaHCO_3$ (2 x 200ml), dried (Na_2CO_3), and concentrated to an oil which crystallised on standing. ^{1}H-NMR spectroscopy at this stage showed the product contained about 5% of a 16,17'-bi(steroidal) contaminant, 3β-acetoxy-16-(3'-β-acetoxyandrosta-5',16'-dien-17'-yl)-17-(3-pyridyl)androsta-5,16-diene, which originated as a by-product from the coupling reaction of step (c).

The product was therefore further purified by preparative flash chromatography using a 9cm diameter column, with silica stationary phase (Merck 15111), eluting with dicholoromethane. The by-product eluted first followed by the desired product, although the separation was incomplete. Fractions containing a significant amount of by-product were combined and subjected to further chromatographic purification.

The foregoing reaction and purification procedure was carried out a total of four times, thus using a total of 146g (0.418 mol) of the steroidal product from step (c).

The product-containing dichloromethane fractions from the chromatographic purification were concentrated and recrystallised from hexane to afford

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white crystals which were dried *in vacuo* to constant weight. The total amount of product obtained was 136.0g (83%).

The dichloromethane fractions containing the least by-product were combined, and following recrystallisation from hexane, afforded the title compound as white crystals with mp 142-144°C. Analysis showed this material ("A") contained 6.8% w/w of the bis(steroidal) by-product.

A second crop of white crystals ("B") of the product, containing 21.8% w/w of bis(steroidal) by-product (25g), was obtained.

The two products were purified using reverse phase chromatography. The column was packed with "LiChroprep" (Registered Trade Mark) RP-8 reverse-phase C_8 packing, Art. No. 9324, supplied by E. Merck, Darmstadt, Germany. The course of the chromatography was followed by UV detection at 253 nm, with purity checks by HPLC.

Product "A" (10.17g) was dissolved in 200ml. hot acetonitrile and 40ml. hot methanol, and, after being allowed to cool, the filtrate was applied to a 10cm. diameter column containing about 500g. of the packing. The eluant was 5% 0.05M aqueous ammonium acetate/95% v/v acetonitrile. 7.51g. of product was recovered in fractions 4-10. Fractions (500ml) 4-11 contained the product with some impurities, but not the bis-steroidal by-product. The eluant was changed to 2.5% acetic acid/95.5% v/v acetonitrile and then to 5% acetic acid/95% v/v acetonitrile. A pink colour seen in fractions 16 and 17 evidenced the bis-steroidal by-product. Fraction 18 was colourless. The column can be washed with 100% acetonitrile, for re-use.

Product "B" (1g) was separated by a similar method except that the product was dissolved initially in 100% acetonitrile and the filtrate applied to a 2cm. column packed with 100g. of the solid phase. Excellent separation of the product was achieved with the aqueous ammonium acetate/acetonitrile eluant.

Although, in this Example, the reverse phase column was used in addition to a conventional column, it is clear that the conventional column achieved little separation of the bis-steroidal by-product and it is intended to omit the conventional column in future preparations.

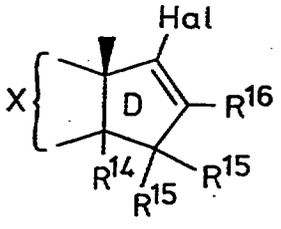
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CLAIMS

1. A method of preparing a 3β-hydroxy- or 3β- (lower acyloxy) 16,17-ene-17-(3-pyridyl)-substituted steroid, wherein the 3β (lower acyloxy) group of the steroid has from 2 to 4 carbon atoms, which comprises subjecting a 3β-hydroxy-16,17-ene-17-iodo or -bromo steroid to a palladium complex-catalysed cross-coupling reaction with a (3-pyridyl)-substituted borane in which the pyridine ring is substituted at the 5-position by an alkyl group of 1 to 4 carbon atoms or is unsubstituted thereat, in a proportion of at least 1.0 equivalent of borane per equivalent of steroid, in an organic liquid which is a solvent for the 3β-hydroxy steroidal reaction product, and, where the 3β-(lower acyloxy) ester is to be prepared, reacting the resulting 3β-hydroxy steroidal reaction product with an esterifying agent effective to replace the hydroxy group by a said lower acyloxy group, which method comprises (a) carrying out the reaction with not more than 1.2 equivalents of borane per equivalent of steroid or (b) crystallising the product of the cross-coupling reaction from a mixture of acetonitrile and methanol.

2. A method according to claim 1, wherein the 3β-hydroxy steroidal reaction product, with or without isolation, is reacted with an acety-esterifying agent to give the corresponding 3β-acetoxy-16,17-ene-17-(3-pyridyl) steroid.

3. A method according to claim 1 or 2, wherein the starting steroid has a D-ring of the following partial formula



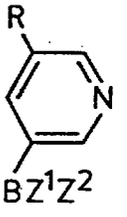
wherein Hal is I or Br, X represents the residue of the A, B and C rings of the steroid. R^{14} represents a hydrogen atom, a halogen atom or an alkyl group of 1 to 4 carbon atoms and each of the R^{15} substituents independently represents a hydrogen atom or an alkyl or alkoxy group of 1-4 carbon atoms, a hydroxy group or an alkylcarbonyloxy

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group of 2 to 5 carbon atoms or together represent an oxo or methylene group or R^{14} and one of the R^{15} groups together represent a double bond and the other R^{15} group represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms, and R^{16} represents a hydrogen atom, halogen atom, or an alkyl group of 1 to 4 carbon atoms.

4. A method according to claim 3, wherein the starting steroid is 3β-hydroxyandrost-5-en-17-one.

5. A method according to any preceding claim, wherein the (3-pyridyl)-substituted borane is of formula:



wherein R represents a hydrogen atom or an alkyl group of 1-4 carbon atoms and Z^1 and Z^2 independently represent hydroxy or alkoxy or alkyl of 1-3 carbon atoms each or Z^1 and Z^2 together represent an alkylenedioxy group of 2 or 3 carbon atoms.

6. A method according to any preceding claim in which the cross-coupling reaction is carried out in two phases, one of which is aqueous and the other of which comprises the said organic liquid.

7. A method according to any preceding claim wherein feature (b) of claim 1 is employed and the volumetric ratio of acetonitrile to methanol is at least 5:1.

8. A method according to any preceding claim wherein feature (b) of claim 1 is employed and the proportion of borane per equivalent of steroid is from 1.2:1 to 1.5:1.

9. A method according to any preceding claim wherein the ester is prepared and after esterification the product is subjected to reverse phase chromatography.