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A Facile Method to Append Peptidal Side-Chains onto Steroidal Templates.

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Abstract : Side-chains corresponding to phenylalanine, tyrosine and tryptophan are introduced onto a steroid template in a highly efficient manner via a condensation of the appropriate lithium acetylide with a steroidal ketone. The subsequent acetylene functionality can be selectively reduced in the presence of a modified benzyl ether and steroid ring unsaturation.

INTRODUCTION

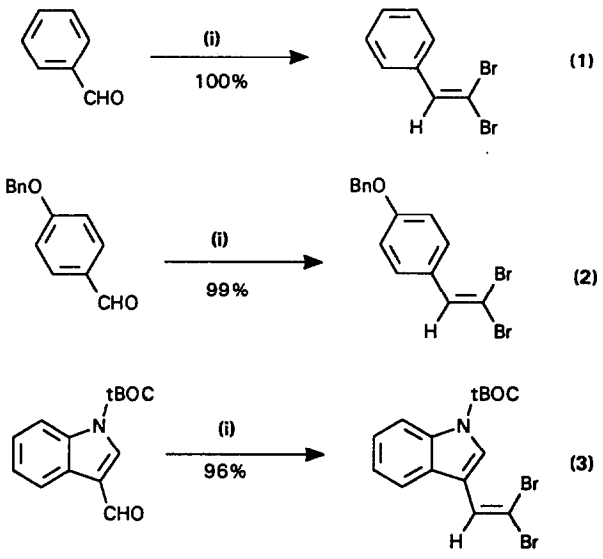
The use of molecular scaffolding to mimic the topographical orientation of α-amino acid side-chains that occur in peptides in particular secondary structural motifs, such as β-turns, γ-turns and α-helices, is of great current interest.[1-4] Recently, the steroid ring system has been chosen to act as a suitable scaffolding to mimic a β-turn conformation.[5] Independently, we have considered the steroid skeleton as an ideal template to mimic the spacial orientation of amino acid side-chains which line up on the same face of an α-helix. As part of this research programme it was necessary to introduce all carbon chains terminating in an aryl group in order to mimic the side-chains of phenylalanine, tyrosine and tryptophan at strategic points along the steroid molecule. Introduction of such groups have previously proved difficult and often ether or amide linkages have been used for synthetic ease.[1-5] In particular, appending indole rings normally involves using gramine or its equivalent with a suitable nucleophile. This has severe limitations on the number of atoms available in the chain. In order to create a more versatile intermediate, the potential use of appropiately functionalised lithium acetylides was investigated. Dibromoolefins have been used to generate lithium acetylides[6], these in turn may be trapped with such electrophiles as methyl chloroformate.[7] It was therefore reasonable to assume that the addition of functionalised lithium acetylides to the keto-groups of steroids may be a convenient and facile method of introducing the required functionality. Such funtionalised lithium acetylides are readily available from the corresponding dibromoolefins which in turn may be generated from the appropriate aldehydes as depicted in scheme 1.

Treatment of (**2**) with 2.2 equivalents of *n*-butyl lithium at -78°C for 1 hour and then at room temperature for 1 hour, gave the lithium acetylide which was added to 3-hydroxy-5-androsten-17-one TBS ether **4** (0.2 equivalents) at -78°C (Scheme **2**). Two products were obtained in good yield. The expected acetylene **5** in 27% yield and the product **6** where alkylation had also occurred at the benzyl position, in 45% yield. This presumably occurs via alpha lithiation and quenching with butyl bromide produced *in situ*. A

similar reaction has been reported on a thiophene derivative.[8]

Hydrogenation of **6** in ethyl acetate with palladium on carbon, for 2 hours at 50 psi gave **8** in quantitative yield after selective reduction of the acetylenic group. The benzyl ether in **5** was cleaved after hydrogenation at 50 psi for 24 hours in 41% yield (56% **7** recovered) to give the diol **9**. In contrast, the substituted benzyl ether in compound **6** was found to be much more stable under these conditions affording less than 5% **9** (82% **8** recovered)and may therefore prove to be useful as a selective protecting group. In order to avoid any undesired compound **7** the dibromoolefin **2** was treated with 4.5 equivalents of butyl lithium at -78°C for 1 hour and room temperature for 16 hours, then quenched with water, gave the acetylene **10** in 68% yield (Scheme **2**). This was then readily converted into the lithium acetylide and used in addition reactions.

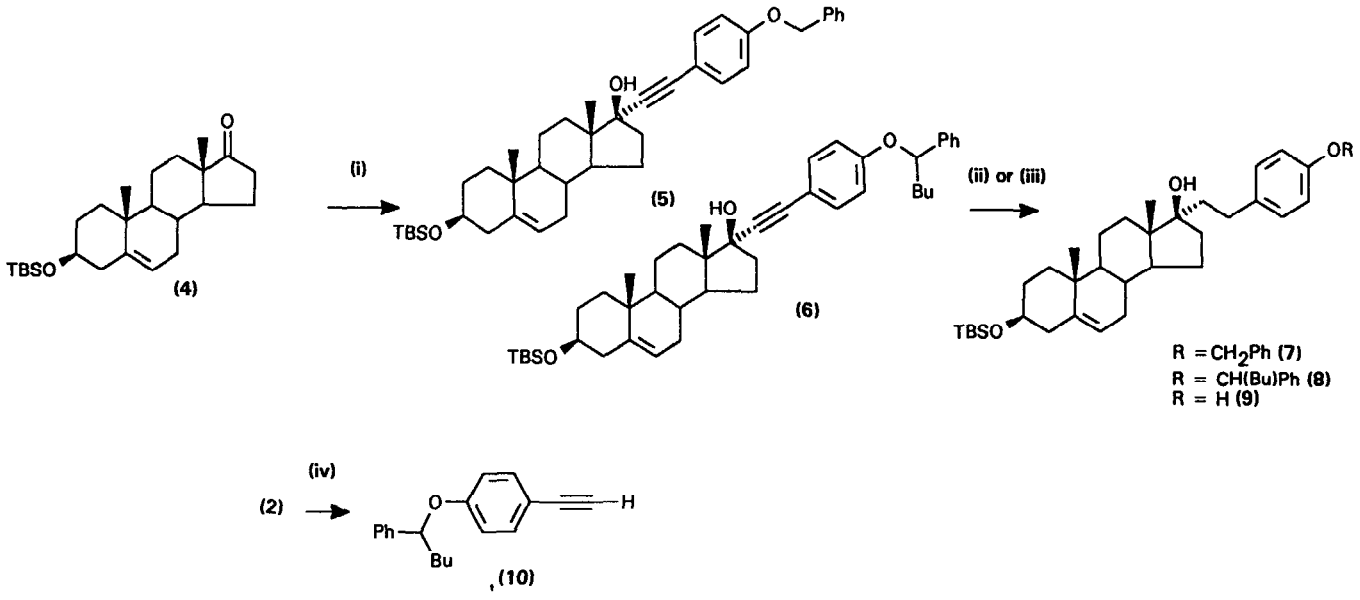
SCHEME 1



Reagents and Conditions: (i) 4eq. Ph_3P, 2eq. CBr_4, CH_2Cl_2, 0°C.

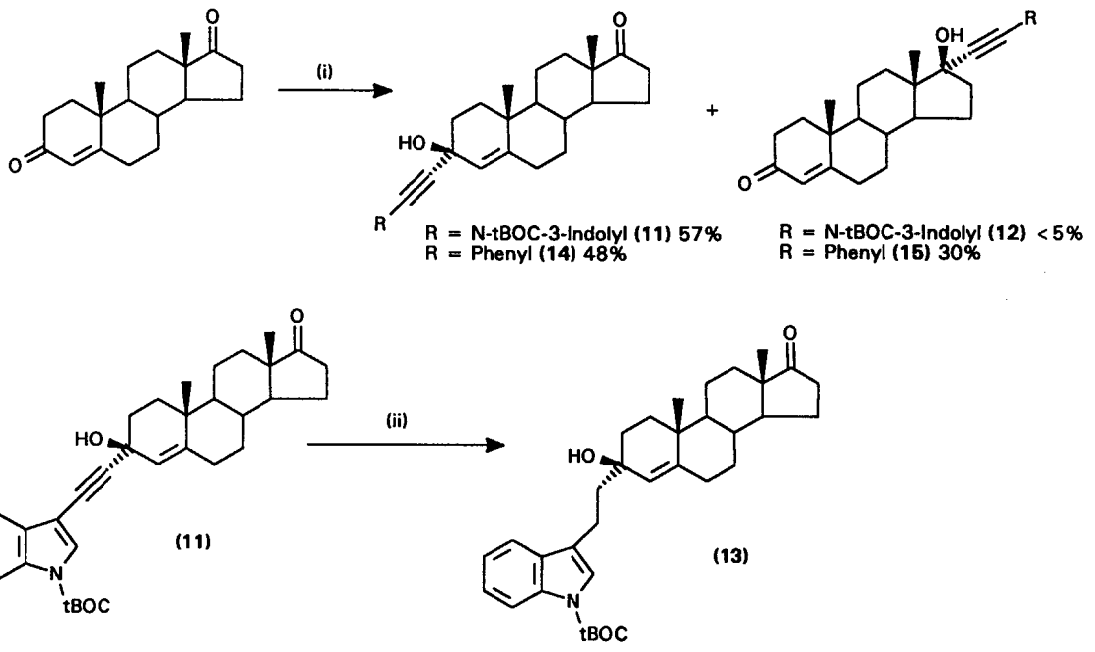
The acetylene generated from the substituted indole **3** could not be isolated due to its instability. Using 2 equivalents of n-butyl lithium to generate the acetylide *in situ* led to unstable products in which the t-butyloxycarbonyl moiety (t-BOC) had been cleaved. This was overcome by treating an excess of the dibromoolefin **3** (3 equivalents) with butyl lithium (3.6 equivalents) at -78°C for 1 hour and room

SCHEME 2



Reagents and Conditions: (i) (2), 2.2eq. nBuLi, 0.2eq. (4), -78°C 1h then RT 1h, 27% (5), 45% (6); (ii) EtOAc, 10% Pd/C, H_2, 50psi, 2h, 100% (8) from (6); (iii) EtOAc, 10% Pd/C, H_2, 50psi, 24h, 41% (9), 56% (7) from (5) and <5% (9), 82% (8) from (6); (iv) 4.5eq. nBuLi, -78°C 1h then RT 16h, 68%.

SCHEME 3



Reagents and Conditions: (i) 1.2eq. (**1**), 2.5eq. nBuLi, THF, -78°C or 3eq. (**3**), 3.6eq. nBuLi, THF, -78°C; (ii) 10% Pd/C, H_2, EtOAc, 50psi, 2h, 66%.

temperature for only 5 minutes, then adding the mixture to 4-androstene-3,17 dione at -78°C. This gave a 57% yield of C-3 addition product, **11** as a single isomer and less than 5% of another product thought to be the C-17 addition product, **12** (Scheme 3). The acetylene containing the Trp- side chain mimetic at steroid position C-3 **11** could be selectively hydrogenated in 66% yield (in ethyl acetate, with palladium on carbon) (Scheme 3). This has provided a compound **13** suitable for further elaboration by introduction of a Tyr- or Phe- side chain mimetic into the C-17 keto group and by further additions to the C4-C5 double bond.

The addition of lithium phenyl acetylide to 4-androstene-3,17 dione was less selective and gave a 1.6:1 mixture of C-3 addition **14** to C-17 addition products **15**. A single isomer was isolated for the C-17 addition product, but an 85:15 mixture of isomers was obtained for the second.

The methods described here allow the addition of functional groups to a template of interest via an acetylide intermediate. The α-substituted aryl ethers generated are removed less easily than their unsubstituted counterparts and therefore may find use as selective blocking agents. This strategy is also applicable to many of the side-chains found in natural and unnatural amino acids and the results of this will be reported in due course.

EXPERIMENTAL

All melting points were determined on a Reichert Thermovar hot stage microscope. I.R spectra were recorded neat using a Perkin Elmer 1750 Fourier transform spectrometer. NMR spectra were recorded on a Bruker AM300 spectrometer. Chemical shifts are reported in parts per million downfield from tetramethylsilane. Mass spectra were determined on a Finnegan 4500 spectrometer or were performed by the SERC mass spectrometry service, Swansea, Wales, U.K. Elemental analyses were determined by Medac Ltd.,Brunel University, Uxbridge, Middlesex, U.K. Preparative chromatography was performed using either a Gilson medium pressure system using Sorbaseal or Lichrosorb RP-18 stationary phase.

(2,2-Dibromoethenyl)-4-(phenylmethoxy)- benzene, (**2**).

Triphenyl phosphine (15g, 57mMol) was added in portions to carbon tetrabromide (9.5g, 28.5mMol) in CH_2Cl_2 (100mL) at 0°C. The solution was stirred at 0°C for 1h then 4-benzyloxybenzaldehyde (3g, 14.3mMol) in CH_2Cl_2 (17mL) was added portionwise. The mixture was stirred at 0°C for 4h then poured onto *n*-hexane (500mL) and stirred for 30 minutes. The precipitated triphenylphosphine oxide was removed by filtration and washed with *n*-hexane (3x200mL). The combined filtrates were evaporated to dryness and chromatography of the residue on silica gel using 5% ethyl acetate in *n*-hexane as eluant yielded the dibromoolefin (**2**) (5.01g, 96%) as a white crystalline solid. mp. 97°C; υ_{max} (film) 3020, 2932, 2876, 1894, 1605, 1510, 1454 cm^{-1}; NMR ($CDCl_3$) δ 5.07 (2H, s), 6.96 (2H, d, J = 8.9Hz), 7.33-7.43 (6H, m), 7.50 (2H,

d, J = 8.7Hz); *m/z* (EI) (Br isotopes) 370 (M^+), 368 (M^+), 366, 298, 278, 91; Anal. $C_{15}H_{12}Br_2O$ Requires: C, 48.95; H, 3.29; Br, 43.42%; Found: C, 49.14; H, 3.32; Br, 43.23%.

3-(2,2-Dibromoethenyl)-1H-indole-1-carboxylic acid, 1,1-dimethylethyl ester, (**3**).

Triphenylphosphine (12.83g,48.9mMol) was added in portions tocarbon tetrabromide (8.10g,24.5mMol) in CH_2Cl_2 (100mL) at 0°C. The solution was stirred at 0°C for 1h then 1-*tert.*-butyloxycarbonyl-3-carboxaldehyde (3.00g,12.2mMol) in CH_2Cl_2 (17mL) was added portionwise. The mixture was stirred at 0°C for 4h then poured onto *n*-hexane (500mL) and stirred for 30 minutes. The precipitated triphenylphosphine oxide was removed by filtration and washed with *n*-hexane (3x200mL). The combined filtrates were evaporated to dryness and chromatography of the residue on silica gel using 5% EtOAc in *n*-hexane as eluant gave the dibromoolefin (**3**)(4.86g, 99%) as a pale yellow crystalline solid. mp. 114°C; υ_{max} (film) 2978, 1738, 1547, 1453 cm^{-1}; NMR ($CDCl_3$) δ 1.69 (9H, s), 7.28 (1H, m), 7.36 (1H, dt, J = 7.3 and 1.3Hz), 7.57 (1H, m), 7.59 (1H, d, J = 0.7Hz), 8.12 (1H, d, J = 8.1Hz), 8.32 (1H, s); *m/z* (EI)(br isotopes) 402 (MH^+), 401 (M^+), 345 (M^+ - tBu), 299 (M^+ - tBOC); Anal. $C_{15}H_{15}Br_2NO_2$ Requires: C, 44.92; H, 3.77; N, 3.49; Br, 39.84%; Found C, 45.00; H, 3.76; N, 3.52; Br, 39.55%.

3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]- (3β)-androst-5-en-17-one, (**4**).

Triethylamine (1.3mL,9.0mMol) was added to a mixture of (+)-dehydro-*iso*-androsterone (2.2g,7.6mMol), *tert.*-butyldimethylsilyl chloride (1.2g,7.6mMol) and DMAP (0.085g,0.7mMol) in CH_2Cl_2 (30mL) at 0°C, under an atmosphere of nitrogen. The solution was stirred at 0°C for 1h and then at room temperature for 16h then poured onto brine (150mL) and extracted into EtOAc (3x40mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was then chromatographed on silica gel using 20-25% EtOAc in *n*-hexane as eluant to yield (**4**)(3.1g, 100%) as a white crystalline solid. mp. 148°C; $[\alpha]_D^{20}$ + 13.8° (c = 1, Me_2CO); υ_{max} (film) 2928, 2890, 2858, 1748, 1463, 1376, 1254 cm^{-1}; NMR ($CDCl_3$) δ 0.00 (6H, s), 0.82 (3H, s), 0.83 (9H, s), 0.97 (3H,s), 0.90-1.04 (3H, m), 1.18-1.26 (3H, m), 1.35-2.25 (13H, m), 2.41 (1H, dd, J = 19.3 and 8.9Hz), 3.44 (1H, *p*, J = 10.8Hz), 5.27 (1H, d, J = 5.1Hz); *m/z* (CI,NH_3) 403 (MH^+), 402 (M^+), 387, 345 (M^+ - tBu), 272, 253; Anal. $C_{25}H_{42}O_2Si$ Requires: C, 74.57; H, 10.51%; Found: C, 74.53; H, 10.68%.

3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-21-[4-phenylmethoxy)phenyl]-pregn-5-en-20-yn-17-ol,(3β,17α)- (**5**) and *3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-21-[4-(1-phenylpentoxy)phenyl]-pregn-5-en-20-yn-17-ol,*

(3β,17α)- (**6**)

n-BuLi (7.9mL, 2.5M in hexanes, 19.7mMol) was added dropwise to a solution of the dibromoolefin (**2**)(3.3g,8.9mMol) in THF (30mL) at -78°C. After 1h the deep red solution was warmed to room temperature and stirred for 1h. This mixture was then added by cannula to a solution of the ketone (**4**)(0.70g,1.74mMol) in THF (20mL) at -78°C. The reaction mixture was stirred at this temperature for 4h then poured onto saturated NH_4Cl solution and extracted with EtOAc (3x30mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was chromatographed on silica gel using 2-10% EtOAc in *n*-hexane as eluant, yielding the least polar starting material (**4**)(0.173g), the more polar acetylene (**6**)(0.558g, 48%) as a colourless foam and the most polar acetylene (**5**)(0.29g, 27%).

Data for (**6**). mp. 56-61°C; $[\alpha]_D^{20}$ -87° (*c* = 1, Me_2CO); υ_{max} (film) 3445, 2932, 2857, 1605, 1506, 1243, 1090 cm^{-1}; NMR ($CDCl_3$) δ 0.00 (6H, s), 0.82 (3H, s), 0.83 (9H, s), 0.96 (3H, s), 1.04 (1H, m), 1.28-1.78 (23H, m), 1.92-1.99 (2H, m), 2.21-2.32 (3H, m), 3.41 (1H, m), 5.01 (1H, dd, *J* = 5.6, 1.0Hz), 5.24 (1H, m), 6.72 (2H, d, *J* = 8.7Hz), 7.16-7.25 (7H, m); *m/z* (CI/NH_3) 667 (MH^+), 666 (M^+), 609 (M^+ -tBu), 520 463; Anal. $C_{44}H_{62}O_3Si$ Requires: C, 79.23; H, 9.37%; Found: C, 79.19; H, 9.32%.

Data for (**5**). mp. 135-137°C; $[\alpha]_D^{20}$ -95.9° (*c* = 1, Me_2CO); υ_{max} (film) 3442, 2931, 2856, 1606, 1508, 1247, 1090 cm^{-1}; NMR ($CDCl_3$) δ 0.00 (6H, s), 0.83 (9H, s), 0.84 (3H, s), 0.97 (3H, s), 0.94-1.05 (2H, m), 1.20-2.36 (18H, m), 3.42 (1H, m), 5.01 (2H, s), 5.25 (1H, d, *J* = 5.0Hz), 6.85 (2H, d, *J* = 8.7Hz), 7.31-7.35 (7H, m); *m/z* (FAB) 610 (M^+), 535 (M^+ -H_2O - tBu), 460, 400, 324, 281; Anal. $C_{40}H_{54}O_3Si$ Requires: C, 79.23; H, 9.37%; Found: C, 79.19; H, 9.32%.

3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-21-[4-phenylmethoxy)phenyl]-pregn-5-en-17-ol,- (3β,17α)- (**7**) and 3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-21-(4-hydroxyphenyl)-pregn-5-en-17-ol,- (3β,17α)- (**9**)

10% Palladium on carbon (20mg) was added to a solution of the acetylene (**5**)(100mg,0.164mMol) in EtOAc (50mL). The mixture was hydrogenated at 50psi for 24h. The catalyst was removed by filtration and washed with EtOAc. The filtrate was evaporated to dryness and the residue chromatographed over silica gel using 15-30% EtOAc in *n*-hexane as eluant to give two products the less polar alcohol (**7**) (56mg, 56%), as a white crystalline solid and the more polar diol (**9**) (35mg, 41%) as a white crystalline solid.

Data for (**7**). mp.160-161°C; $[\alpha]_D^{20}$ -31.6° (*c* = 0.56, Me_2CO); υ_{max} (film) 3410, 2930, 2897, 1601, 1512, 1456 cm^{-1}; NMR ($CDCl_3$) δ 0.05 (6H, s), 0.88 (9H, s), 0.89 (3H, s), 1.01 (3H, s), 1.05 (1H, m), 1.13-1.39 (4H, m), 1.44-1.86 (13H, m), 1.97-2.30 (4H, m), 2.62 (2H, m), 3.41 (1H, septet, *J* = 5.5Hz), 5.04 (2H, s), 5.28

(1H, d, J = 5.1Hz), 6.91 (2H, d J = 8.6Hz), 7.13 (2H, d, J = 8.6Hz), 7.28- 7.43 (5H, m); *m/z* (CI/NH_3) 615 (MH^+), 614 (M^+), 596 (M^+ -H_2O), 557 (M^+ -C_4H_7), 539 (M^+ -H_2O-C_4H_7), 465, 197, 91($C_7H_7^+$); Anal. $C_{40}H_{58}O_3Si$ Requires: C, 78.12; H, 9.51%; Found: C, 78.05; H, 9.52%.

Data for (**9**). mp. mp. 202-204 °C; $[\alpha]_D^{20}$ -37.9° (c = 0.43, Me_2CO); υ_{max} (film) 3495, 3288, 2928, 2854, 1612, 1516, 1444, 1376 cm^{-1}; NMR ($CDCl_3$) δ 0.00 (6H, s), 0.83 (9H, s), 0.84 (3H, s), 0.89 (1H, m), 1.16-1.48 (5H, m), 1.61-1.76 (12H, m), 1.91-2.24 (3H, m), 2.58 (2H, m), 3.39 (1H, p, J = 5.6Hz), 4.72 (1H, br s), 5.24 (1H, d, J = 4.0Hz), 6.68 (2H, d, J = 8.4Hz), 7.04 (2H, d, J = 8.4Hz); *m/z* (CI/NH_3) 525 (MH^+), 524 (M^+), 509, 375, 181, 107; Anal. $C_{33}H_{52}O_3Si$ Requires: C, 75.52; H, 9.99%; Found: C, 75.48; H, 10.00%.

3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-21-[4-(1-phenylpentoxy)phenyl]-pregn-5-en-17-ol, (3β,17α)- (**8**)

10% Palladium on carbon (20mg) was added to a solution of the acetylene (**6**)(100mg,0.15mMol) in EtOAc (50mL). The mixture was hydrogenated at 45psi for 2h. The catalyst was removed by filtration and washed with EtOAc. The filtrate was evaporated to dryness and the residue chromatographed over silica gel using 15% EtOAc in *n*-hexane as eluant to yield the alcohol (**8**)(100mg, 100%) as a colourless foam. mp. 50-64°C; $[\alpha]_D^{20}$ -30.5° (c = 0.57, Me_2CO); υ_{max} (film) 3489, 2931, 2857, 1612, 1509, 1454, 1379 cm^{-1}; NMR ($CDCl_3$) δ 0.00 (6H, s), 0.83 (16H, m), 0.95 (3H, s), 1.13-1.75 (22H, m), 1.91-2.21 (5H, m), 2.59 (2H, m), 3.41 (1H, m), 4.96 (1H, dd, J = 7.8 and 5.1Hz), 5.24 (1H, s), 6.70 (2H, d, J = 8.6Hz), 6.95 (2H, d, J = 8.6Hz) 7.20-7.30 (5H, m); *m/z* (FAB) 671 (M^+), 669, 653, 521, 375, 325; Anal. $C_{44}H_{66}O_3Si$ Requires: C, 78.75; H, 9.91%; Found: C, 78.73; H, 9.96%.

1-(1-Phenylpentoxy)-4-ethynyl benzene, (**10**).

n-BuLi (3.74mL, 2.5M in hexanes, 6.0mMol) was added dropwise to a solution of the dibromoolefin (**2**)(1.0g,2.7mMol) in THF (20mL) at -78°C. After 1h the deep red solution was warmed to room temperature and stirred for 1h. TLC indicated the presence of starting material, therefore the mixture was recooled to -78°C and *n*-BuLi (4mL, 1.6M in hexanes, 6.4mMol) was added. The reaction mixture was allowed to slowly warm to room temperature and was stirred for 16h then poured onto brine and extracted with EtOAc (3x60mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was chromatographed on silica gel using 2% EtOAc in *n*-hexane as eluant to yield the acetylene (**10**)(0.49g, 68%) as a yellow oil. υ_{max} (film) 3288, 3031, 2956, 1605, 1509, 1453 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (3H, t, J = 6.8Hz), 1.33-1.52 (4H, m), 1.77 (1H, m), 2.02 (1H, m), 2.93 (1H, s), 5.06 (1H, dd, J = 7.7 and 5.3Hz), 6.78

(2*H*, d, J = 8.8Hz), 7.21-7.31 (7H, m); *m/z* (CI/NH_3) 265 (M^+), 237, 209, 147, 91; Anal. $C_{19}H_{20}O$; Requires: C,86.32; H, 7.63%; Found: C, 85.97; H, 7.54%.

3-[(3-Hydroxy-17-oxoandrost-4-en-3-yl)ethynyl]-1H-indole-1-carboxylic acid, 1,1-dimethylethyl ester, (3β)-, **(11)**

n-BuLi (3.6mL, 2.5M in hexanes, 8.9mMol) was added dropwise to a solution of the dibromoolefin (**3**)(2.97g,7.4mMol) in THF (20mL) at -78°C. After 1h the deep red solution was warmed to room temperature and stirred for 15 minutes. This mixture was then added by cannula to a solution of 4-androstene-3,17-dione(0.71g,2.50mMol) in THF (10mL) at -78°C. The reaction mixture was stirred at this temperature for 4h then poured onto saturated NH_4Cl solution and extracted with EtOAc (3x30mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was chromatographed on silica gel using 5-40% EtOAc in *n*-hexane as eluant to yield the acetylene (**11**)(0.753g, 57%) as a yellow foam. mp. 109-124°C; $[\alpha]_D^{20}$ +232° (*c* = 1, Me_2CO); υ_{max} (film) 3421, 2939, 1737, 1452, 1372, 1234, 1155 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (3H, s), 1.11(3H, s), 1.30-2.30 (19H, m), 1.66 (9H, s), 2.46 (1H, dd, *J* = 19.0 and 8.9Hz), 5.47 (1H, s), 7.29-7.37 (2H, m), 7.60 (1H, d, *J* = 7.8Hz), 7.73 (1H, s), 8.10 (1H, d, *J* = 8.0Hz); *m/z* (CI/NH_3) 528 (MH^+), 527 (M^+), 472, 287, 186; Anal. $C_{34}H_{41}NO_4$.0.25H2O; Requires: C, 76.73; H, 7.86; N, 2.63%; Found: C, 76.52; H, 7.84; N, 2.60%.

3-[2-(3-Hydroxy-17-oxoandrost-4-en-3-yl)ethyl]-1H-indole-1-carboxylic acid, 1,1-dimethylethyl ester, (3β)-, **(13)**

10% Palladium on carbon (20mg) was added to a solution of the acetylene (**11**)(100mg,0.19mMol) in EtOAc (50mL). The mixture was hydrogenated at 50psi for 2h. The catalyst was removed by filtration and washed with EtOAc. The filtrate was evaporated to dryness and the residue chromatographed over silica gel using 30% EtOAc in *n*-hexane as eluant to yield the alcohol (**13**)(67mg, 66%) as a pale yellow foam. mp. 82-98°C; υ_{max} (film) 3460, 2934, 2881, 1732, 1453, 1372, 1256, 1159 cm^{-1}; NMR ($CDCl_3$) δ 0.75 (1H, m), 0.89 (3H, s), 0.96 (1H, m), 1.09 (3H, s), 1.19-1.42 (3H, m), 1.43-1.72 (4H, m), 1.66 (9H, s), 1.80-1.98 (6H, m), 2.25 (1H, dt, *J* = 13.6 and 4.5Hz), 2.46 (1H, dd, *J* = 19.0 and 8.8Hz), 2.82 (1H, t, *J* = 8.0Hz), 5.34 (1H, s), 7.19-7.30 (2H, m), 7.36 (1H, s), 7.53 (1H, d, *J* = 7.9Hz), 8.09 (1H, d, *J* = 7.9Hz); *m/z* (CI/NH_3) 531 (M^+), 518, 413, 287, 130; Anal. $C_{34}H_{45}NO_4$.0.25H2O; Requires: C, 76.16; H, 8.42; N, 2.61%; Found: C, 76.20; H, 8.52; N, 2.56%.

3-(Phenylethynyl)-androst-4-en-17-one, (3β)- (**14**) and *17-Hydroxy-21-phenyl-pregn-4-en-20-yn-3-one,* (17α)- (**15**).

n-BuLi (1.95mL,1.6M in hexanes,3.1 mMol) was added to a solution of the dibromoolefin **1** (330mg,1.26mMol) in THF (10mL) at -78°C. After 30 minutes the deep red solution was warmed to room temperature and added *via* cannula to a solution of 4-androstene-3,7-dione (300mg, 1.05mMol) in THF (10mL) at -78°C. The reaction mixture was stirred at this temperature for 4h, warmed to room temperature then poured onto brine and extracted with ethyl acetate (3x30mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated to dryness. Chromatography of the residue on silica gel using 20-40% ethyl acetate in n-hexane gradient as eluant, yielded the least polar acetylene (**14**) (110mg, 24%) as a colourless foam, the more polar acetylene (**15**) (70mg, 15%) as a colourless foam and the most polar starting material (130mg). Data for (**14**): mp. 80-92°C; $[\alpha]_D^{20}$ +289 (*c* = 0.5, Me_2CO); υ_{max} (film) 3395, 2941, 2857, 1735, 1442 cm^{-1}; NMR ($CDCl_3$) δ 0.86 (1H, m), 0.89 (3H, s), 1.03 (3H,m), 1.10 (3H, s), 1.23-1.50 (3H, m), 1.53-2.00 (10H, m), 2.06-2.29 (4H, m), 2.43 (1H, dd, J = 19.1 and 8.9Hz), 5.42 (1H, s), 7.27-7.30 (3H, m), 7.40-7.43 (2H, m); *m/z*
(CI, NH_3) 389 (MH^+), 388 (M^+), 371 (MH^+-H_2O), 287; Anal. $C_{27}H_{32}O_2$ Requires: C, 83.46; H,8.30% ; Found: C,83.18; H, 8.18%.

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