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TETRAHEDRON

An Efficient Synthesis of 17-*epi*-Ethynylestradiol

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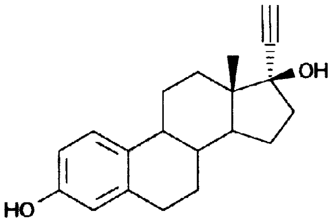
Summary. An efficient synthesis has been developed yielding 17-*epi*-ethynylestradiol **2** in an overall yield of 17 %. The key derivatives **7a-c** were prepared from estrone in four steps. Subsequently epoxides **7a,c** were efficiently transformed into **2** via Takano's method.

17-Ethynylestradiol **1** is the estrogenic component in many oral contraceptives. The established preparation of this drug substance by nucleophilic addition of an acetylenic anion to the 17 carbonyl functionality is accompanied by the formation of small amounts of 17-epi-ethynylestradiol **2** as a side product (up to 0,5%).



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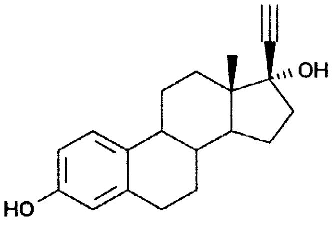

2

As the preparation of a larger amount of this substance was requested and the reported syntheses afforded **2** only in low overall yields[1,2], we set out to develop a new synthesis of target compound **2**.

Our approach was based on the epoxides **7a**, **c** as key intermediates as they possessed the required 17 α-hydroxy stereochemistry and were expected to be convertable into 17-epi-ethynylestradiol **2** according to Takano's method for the construction of propargylic alcohols[4]. The epoxides **7a**, **c** in turn should be accessible via a diastereoselective epoxidation of an allylic alcohol of type **6**. As the diastereoselectivity of *m*-chloroperbenzoic acid (MCPBA) mediated epoxidations of 17-exo alkenes had proven to be unpredictable in the past[3], we decided to investigate the Sharpless epoxidation of allylic alcohols **6** as a method to introduce the 17-α-hydroxy group (Scheme 1). To our knowledge this is the first example of a Sharpless epoxidation of a 17-exo-steroidal allylic alcohol.

In the androstane series the 17 exo-olefination reaction according to Wicha and Bal[5] is completely *E*-selective. Yamamoto *et al.*[6] used the same conditions and also obtained only the *E*-isomer in 97 % yield. The stereoselectivity of the 17 exo-olefin construction in the estrone series through the Emmons-Horner reaction was unknown prior to our investigation.

The *tert*-butyldimethylsilyl (TBDMS) group was chosen as a protecting group for the 3-hydroxy functionality of estrone **3** which was introduced according to the standard procedure. The conditions reported by Bal and Wicha[5] for the olefination of androstane derivatives could not be successfully applied to the synthesis of **5** as they caused an immediate cleavage of the silyl group with subsequent O-ethylation of estrone **3**.

The Horner-Emmons olefination of **4** in toluene with triethylphosphonoacetate proceeded only sluggishly yielding **5a** in low yield as an 8:2 mixture of *E*-*Z* isomers accompanied by several other side products according to HPLC analysis.

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Yet, substituting toluene by tetrahydrofuran improved the conversion as well as the isomer distribution yielding **5a** as a 9:1 mixture of *E-Z* isomers in 90% yield. Dimethylphosphono-*tert*.-butyl-acetate could neither improve the selectivity nor the yield of the olefination reaction and afforded **5b** as a 6:4 mixture of *E-Z* isomers with the only advantage compared to compounds **5a** that they could be separated by preparative HPLC. Subsequent diisobutylaluminium hydride (DIBALH) reduction[7] of **5b** yielded the allylic alcohols **6a,b**.

We decided to investigate the epoxidation of the separated allylic alcohols **6a,b** with the monoperoxyphthalic acid magnesium salt, MCPBA and the Sharpless epoxidation catalyst. Our results show that the configuration of the double bond has a strong influence on the diastereoselectivity of the epoxidation (Scheme 1, Table 1).

Scheme 1

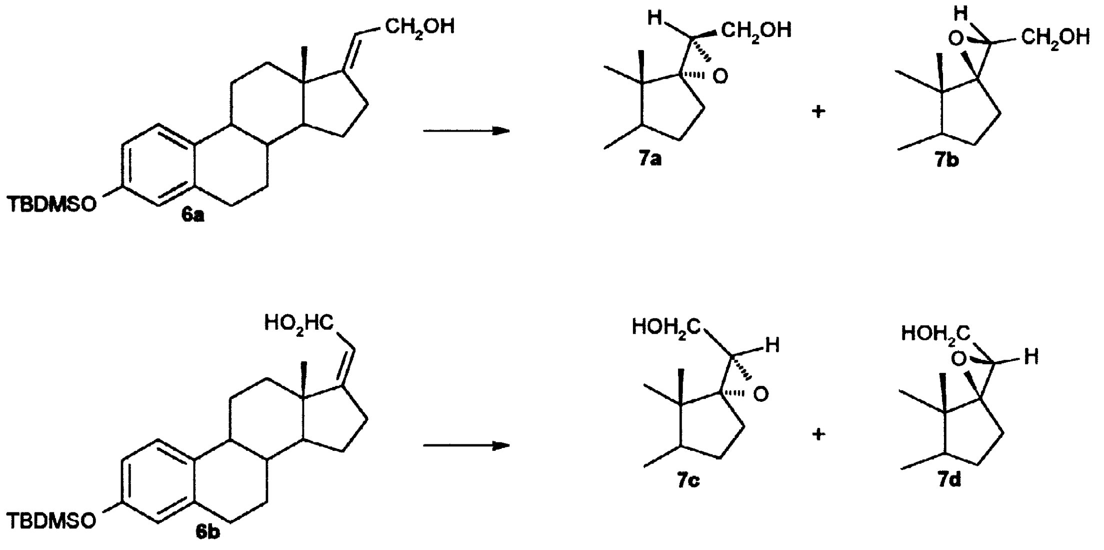


Table 1: Diastereoselectivity of the epoxidation of **6a** and **6b**[a]

entry	allylic alcohol	reagent	7 α:ß
1	**6a**	monoperoxyphthalic acid magnesium salt	1 : 1
2	**6a**	MCPBA	1 : 1
3	**6b**	monoperoxyphthalic acid magnesium salt	>98 : 2
4	**6a**	Ti(OiPr)$_4$, ^{t}BuOOH, (-)-DIPT	>98 : 2
5	**6b**	Ti(OiPr)$_4$, ^{t}BuOOH, (-)-DIPT	>98 : 2

[a]see experimental part for the description of the reaction conditions.

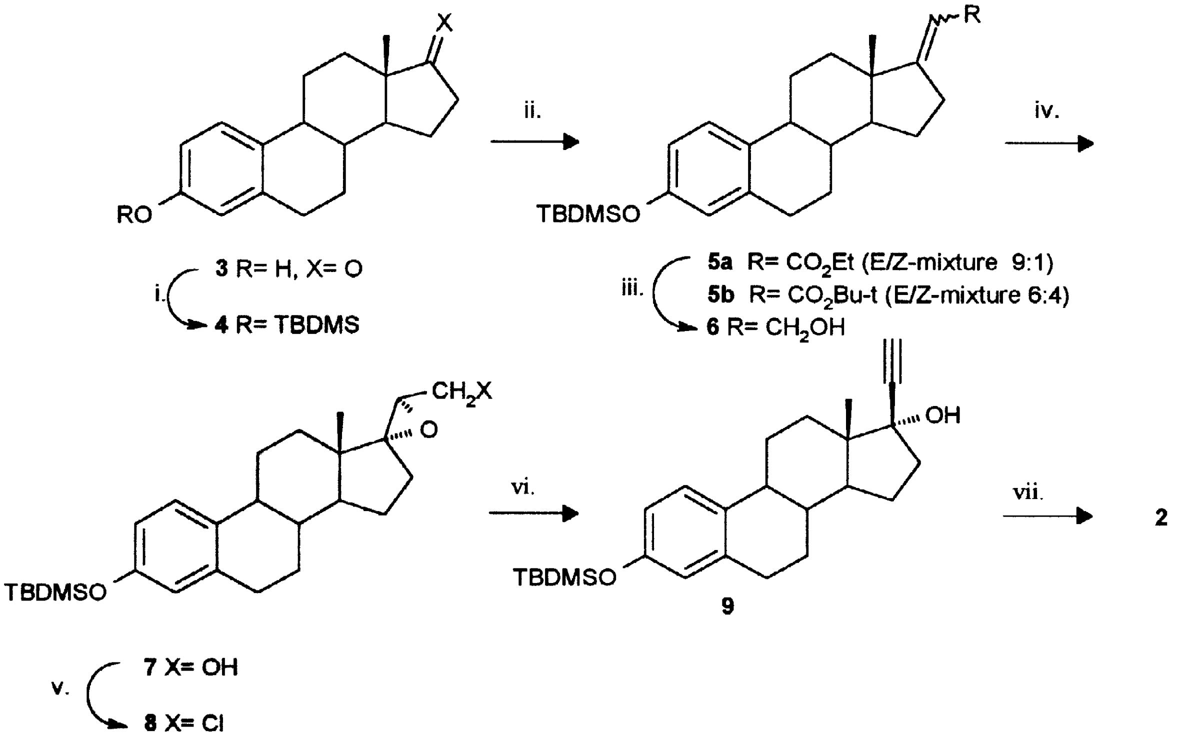
While monoperoxyphthalic acid magnesium salt and MCPBA epoxidized allylic alcohol **6a** without any selectivity affording a 1:1 mixture of diastereomers **7a,b**, the epoxidation of **6b** proceeded under strong substrate control of the steroid backbone. In this configuration the angular methyl group effectively shields the β face of the alkene and directs the attack of the electrophile to the α face thus affording **7c** with >98 : 2 selectivity.

According to the Sharpless rule[8] the use of (-)-DIPT should control the epoxidation of substrate **6a** in favour of the desired α-epoxide, which was found to be the case as its epoxidation afforded **7a** with a selectivity >98 : 2. In light of these results it was an interesting question to us, whether the catalyst control exerted by the chiral titanium catalyst would be strong enough to override the substrate control of allylic alcohol **6b** (mismatch case). The epoxidation of **6b** according to the reaction conditions established for **6a** turned out to be a very slow reaction. While the epoxidation of **6a** was virtually complete after 1h at - 20° to - 15° C, the conversion of **6b** was in the range of 45% after 11h at -10°C. Yet, the reaction proceeded with the same high selectivity observed with monoperoxy phthalic acid magnesium salt affording α-epoxide **7c** as the only observed isomer. Thus the intrinsic selectivity of the catalyst was completely overridden by the substrate control of the steroid backbone.

As it was described in the literature that the Wittig reaction should give mainly the *Z*-isomer of **5a**[9] and the epoxidation of the *Z*-isomer **6b** afforded exclusively the α-epoxide **7c**, we wanted to apply this reaction sequence to the synthesis of target compound **2**. Although we screened different bases (LDA, NaH and KO^tBu) with carboethoxymethylene-triphenylphosphonium bromide as reagent we failed to convert estrone derivative **4** into ester **5**. In each case **4** was recovered quantitatively from the reaction mixture.

At this point we realized that we could effectively combine the large reaction rate differences for the epoxidation of the isomeric allylic alcohols **6a,b** with the Sharpless catalyst with the substrate controlled epoxidation of **6b** for a synthesis of **2**. The Sharpless epoxidation of a mixture of the olefins **6** was expected to yield a mixture of α-epoxides consisting mainly of **7a** and only a small amount of **7c**, while the isomer **6b** should remain mostly unreacted. Both epoxides **7a,c** could then be converted into target compound **2**. Following the DIBALH[6] reduction of the 9:1 mixture of **5a** the subsequent Sharpless epoxidation under the previously established conditions afforded a mixture consisting approximately of 97% α-epoxide **7a**, 2 % of the β-epoxide **7b** and <1% α-epoxide **7c** in 74% isolated yield. As expected, the reaction did not proceed to full conversion what is in accord with the previously observed rate differences for the epoxidation of **6a,b**.

Scheme 2



i. TBDMSCl, DMF, imidazole, 95%; ii. **5a**: triethylphosphonoacetate, NaH, THF, 90%; **5b**: dimethylphosphono-tert. butyl-acetate, NaH, THF, 86%; iii. Dibal, toluene, -20°C, 74%; iv. $Ti(OiPr)_4$, tBuOOH, (-)-DIPT, 74%; v. PPh_3, CCl_4, 96%; vi. 3.0 equiv. BuLi, THF, -35°C, 60%; vii. TBAF, THF, 76%.

The primary hydroxyl function in **7a,c** was then first transformed into the primary chloride **8**[4] which was subsequently treated with BuLi (3 equiv. BuLi, THF, -35°C, 2 h) yielding the silylated 17-epi-ethynylestradiol **9** by double elimination in 60% combined yield. The synthesis was completed by desilylation under standard conditions affording **2** in 17 % overall yield, containing less than 2% of isomer **1** resulting from **7b**.

In conclusion, a new straightforward synthesis of 17-epi ethynylestradiol has been developed based on the kinetic resolution of allylic alcohols **6** by Sharpless epoxidation as the key step. It has been shown that the Horner-Emmons olefination of the 17-keto group in the estrone series is not as selective as reported for the androstane series. It was also found that the epoxidation of *Z*-allylic alcohol **6b** with a conventional epoxidation reagent is under complete substrate control of the steroid backbone affording exclusively the α-epoxide. This substrate control even overrides the catalyst control exerted by the Sharpless epoxidation catalyst.

ACKNOWLEDGMENT. We gratefully thank the Spectroscopical Department of Schering AG for the measurement of the physical data.

EXPERIMENTAL SECTION

All reactions were carried out in an argon atmosphere with standard techniques for the exclusion of air and moisture. Glassware used for moisture-sensitive reactions was oven-dried (200°C). Flash column chromatography was performed on Merck silica gel (grade 60, 230-400 mesh); TLC was performed on Merck Aluminium foils 60 F 254. Infrared (IR) spectra were recorded on a Nicolet 20 SBX spectrophotometer. The melting points are uncorrected. Mass spectral analyses were recorded on a Micromass AutoSpec EQ Massspectrometer. ^{1}H- (300 MHz) NMR spectra were recorded using TMS or the solvent as internal standard.

3-*tert*-Butyl-dimethylsilyloxy-20-carbethoxy-1,3,5(10),17(20)estratetraene (5a): To a solution of triethylphosphonoacetate (14.8 ml, 72 mmol) in dry THF (120 ml) was added sodium hydride (2.4 g, 79 mmol, 80 % mineral oil dispersion) in such a rate that the internal temperature did not exceed 30 °C. **4** (9.3 g, 24 mmol) was added and the reaction mixture was heated at reflux for 6.5 h until the starting material was not detected by TLC monitoring. The reaction mixture was diluted with water and extracted with methyl-*tert*-butyl ether. The etheral layer was washed twice with water and brine, dried, and evaporated affording a crude product, which was purified by column chromatography (ethyl acetate-hexane 1:9) to give **5a** as a *E*-*Z* mixture (9:1) (9.9 g, 90%)

(*E*)-**5a:** MS, *m/z*: 262 (M^+), ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.17 (6H, s, 3-$OSiMe_2$), 0.80 (3H, s, 18-CH_3), 0.97 (9H, s, 3-OSi^tBu), 1.31 (3H, t, J=9 Hz), 1.40-2.94 (15H, m), 4.17 (2H, q, J=9 Hz), 5.58 (1H, t, *J*=2.5 Hz, 20-H), 6.55 (1H, d, *J*=2.5 Hz, 4-H), 6.61 (1H, dd, *J*=2.5 Hz, *J*=9 Hz, 2-H), 7.13 (d, *J*=2.5 Hz, 1-H).

3-*tert*-Butyl-dimethylsilyloxy-20-carboxy-1,3,5(10),17(20)estratetraene-*tert*-butylester (5b): To a solution of dimethylphosphono-*tert*-butyl acetate (15.2 ml, 78 mmol) in dry THF (120 ml) was added sodium hydride (2.6 g, 85 mmol, 80% mineral oil dispersion) in such a rate that the internal temperature did not exceed 30 °C. **4** (10.0 g, 26 mmol) was added of and the reaction mixture was heated at reflux for 6.5 h until the starting material was not detected by TLC monitoring. The reaction mixture was diluted with water and extracted with methyl-*tert*-butyl ether. The etheral layer was washed twice with water and brine, dried, and evaporated affording a crude product, which was purified by HPLC (ethyl acetate-hexane 1:9) to give (*Z*)-**5b** (4.3 g, 34.5%) and (*E*)-**5b** (6.5 g, 51.5%).

(*E*)-5b: mp 142-143 °C, MS, *m/z*: 482 (M^+), ^1H NMR (300 MHz, $CDCl_3$) δ 0.17 (6H, s, 3-OSiMe$_2$), 0.80 (3H, s, 18-CH_3), 0.97 (9H, s, 3-OSi^{t}Bu), 1.49 (9H, s, O^{t}Bu), 1.15-2.84 (15H, m), 5.48 (1H, t, *J*=2.5 Hz, 20-H), 6.55 (1H, d, *J*=2.5 Hz, 4-H), 6.61 (1H, dd, *J*=2.5 Hz, *J*=9 Hz, 2-H), 7.13 (d, *J*=2.5 Hz, 1-H).

(*Z*)-5b: mp 168-169 °C, MS, *m/z*: 482 (M^+), ^1H NMR (300 MHz, $CDCl_3$) δ 0.17 (6H, s, 3-OSiMe$_2$), 0.97 (9H, s, 3-OSi^{t}Bu), 1.05 (3H, s, 18-CH_3), 1.49 (9H, s, O^{t}Bu), 1.15-2.84 (15H, m), 5.62 (1H, t, *J*=2.5 Hz, 20-H), 6.55 (1H, d, *J*=2.5 Hz, 4-H), 6.61 (1H, dd, *J*=2.5 Hz, *J*=9 Hz, 2-H), 7.13 (d, *J*=2.5 Hz, 1-H).

3-*tert*-Butyl-dimethylsilyloxy-20-hydroxymethyl-1,3,5(10),17(20)estratetraene (6): To a solution of **5a** (2.00 g, 4.4 mmol) in dry toluene, was added DIBALH solution in toluene (7.3 ml, 8.8 mmol, 1.2 M) at -20°C. After stirring 3 h at -20°C, water and methyl-*tert*-butyl ether were successively added. The reaction mixture was allowed to warm to room temperature. The organic layer was washed twice with water and dried over anhydrous Na_2SO_4. Solvent was removed and the crude compound was column chromatographed (silica gel, 15 % ethyl acetate in hexane) to afford the alcohols **6a** and **6b** as a *E-Z* mixture (9:1) (1.35 g, 74%).

6a: mp 121.5-122.5 °C (CH_3OH), MS, *m/z*: 412 (M^+), ^1H NMR (300 MHz, $CDCl_3$) δ 0.17 (6H, s, 3-OSiMe$_2$), 0.80 (3H, s, 18-CH_3), 0.97 (9H, s, 3-OSi^{t}Bu), 1.15-2.84 (15H, m), 4.05-4.21 (2H, m, 21-CH_2-O), 5.24 -5.33 (1H, m, 20-H), 6.55 (1H, d, *J*=2.5 Hz, 4-H), 6.61 (1H, dd, *J*=2.5 Hz, *J*=9 Hz, 2-H), 7.13 (d, *J*=2.5 Hz, 1-H); Anal. calcd. for $C_{26}H_{40}O_2Si$: C, 75.67, H, 9.77. Found: C, 75.45%, H, 9.68%.

6b: mp 128-130 °C (CH_3OH), MS, *m/z*: 412 (M^+), ^1H NMR (300 MHz, C_5D_5N) δ 0.17 (6H, s, 3-OSiMe$_2$), 0.80 (3H, s, 18-CH_3), 0.97 (9H, s, 3-OSi^{t}Bu), 1.15-2.84 (15H, m), 4.30-4.47 (2H, m, 21-CH_2-O), 5.40 -5.46 (1H, m, 20-H), 6.55 (1H, d, *J*=2.5 Hz, 4-H), 6.61 (1H, dd, *J*=2.5 Hz, *J*=9 Hz, 2-H), 7.13 (d, *J*=2.5 Hz, 1-H).

3-*tert*-Butyl-dimethylsilyloxy-17α,20*R*-epoxy-20-hydroxymethyl-1,3,5(10),17(20)estratetraene (7a): A dried three-necked round-bottomed flask was charged with dichloromethane and cooled to -20°C. D-(-)-diisopropyl tartrate (2.37 g, 10.1 mmol) and Ti(O-*i*-Pr)$_4$ (via syringe 2.60 ml, 8.58 mmol) were added sequentially with stirring. The reaction mixture was stirred at -20°C as the 9:1-mixture of **6a,b** (2.90 g, 7.0 mmol), dissolved in dichloromethane was added. After stirring 0.5h at -20°C, the *tert*-butylhydroperoxide (7.9 mL in isooctane, 23.6 mmol) was then added dropwise, being careful to maintain the reaction temperature between -20°C and -15°C. After 1 h stirring, tartaric acid, KF and Celite were successively added. The reaction mixture was allowed to warm to room temperature. The mixture was filtered over Celite. Solvent was removed and the crude compound was column chromatographed (silica gel, ethyl acetate / hexane 1:9) to afford the epoxides **7a** (97%),**7b** (2%) and **7c** (1%) (2.23 g, 74%).

7a: MS, *m/z*: 428 (M^+),^1H NMR (300 MHz, C_5D_5N) δ 0.27 (6H, s, 3-OSiMe$_2$), 0.78 (3H, s, 18-CH_3), 1.03 (9H, s, 3-OSi^{t}Bu), 1.10-2.95 (15H, m), 3.32 (1H, dd, *J*=5 Hz, *J*= 7.5 Hz, 20-H), 3.96 (1H, dAB, *J*=7.5 Hz, J_{AB}=12.5 Hz, 21-CH_AH_B-O), 4.09 (1H, dAB, *J*=5 Hz, J_{AB}=12.5 Hz, 21-CH_AH_B-O), 6.84 (1H, d, *J*=2.5 Hz, 4-H), 6.90 (1H, dd, *J*=2.5 Hz, *J*=9 Hz, 2-H), 7.28 (1H, d, *J*=9 Hz, 1-H).

7b: MS, *m/z*: 428 (M^+), ^1H NMR (300 MHz, C_5D_5N) δ 0.27 (6H, s, 3-OSiMe$_2$), 0.91 (3H, s, 18-CH_3), 1.03 (9H, s, 3-OSi^{t}Bu), 1.10-2.95 (15H, m), 3.52 (1H, t, *J*= 7.5 Hz, 20-H), 3.96 (1H, dAB, *J*=7.5 Hz, J_{AB}=12.5 Hz, 21-CH_AH_B-O), 4.09 (1H, dAB, *J*=5 Hz, J_{AB}=12.5 Hz, 21-CH_AH_B-O), 6.84 (1H, d, *J*=2.5 Hz, 4-H), 6.90 (1H, dd, *J*=2.5 Hz, *J*=9 Hz, 2-H), 7.28 (1H, d, *J*=9 Hz, 1-H).

7c: mp. 106-107 °C, MS, *m/z*: 428 (M^+), ^1H NMR (300 MHz, C_5D_5N) δ 0.27 (6H, s, 3-OSiMe$_2$), 0.82 (3H, s, 18-CH_3), 1.03 (9H, s, 3-OSi^{t}Bu), 1.10-2.95 (15H, m), 3.45 (1H, dd, *J*=5 Hz, *J*= 7.5 Hz, 20-H), 4.11 (1H, dAB, *J*=7.5 Hz,

J_{AB}=12.5 Hz, 21-$\mathrm{C}H_A\mathrm{H}_B$-O), 4.21 (1H, dAB, *J*=5 Hz, J_{AB}=12.5 Hz, 21-$\mathrm{CH}_A H_B$-O), 6.84 (1H, d, *J*=2.5 Hz, 4-H), 6.90 (1H, dd, *J*=2.5 Hz, *J*=9 Hz, 2-H), 7.28 (1H, d, *J*=9 Hz, 1-H).

3-*tert*-Butyl-dimethylsilyloxy-17α,20*R*-epoxy-20-chloromethyl-1,3,5(10),17(20)estratetraene (8): To triphenylphosphine (250 mg, 0.58 mmol) in dry carbon tetrachloride was added **7a** (250 mg, 0,59 mmol) at room temperature. After addition was complete the reaction mixture was refluxed for 3 h. Solvent was removed under reduced pressure. The residue obtained was purified by column chromatography (silica gel, hexane) to provide **8** (250 mg, 96%).

8: MS, *m/z*: 428 (M^+), ^{1}H NMR (300 MHz, C_5D_5N) δ 0.23 (6H, s, 3-$OSiMe_2$), 0.73 (3H, s, 18-CH_3), 1.1 (9H, s, 3-OSi^tBu), 1.15-2.89 (15H, m), 3.24 (1H, t, *J*=7.5 Hz, 20-H), 3.61-3.79 (2H, m, CH_2Cl), 6.82 (1H, d, *J*=2.5 Hz, 4-H), 6.88 (1H, dd, *J*=2.5 Hz, *J*=9 Hz, 2-H), 7.24 (1H, d, *J*=9 Hz, 1-H); Anal. calcd. for $C_{26}H_{39}O_2ClSi$: C, 69.84%, H, 8.81%, Cl, 7.93%. Found: C, 69.52%, H, 8.82%, Cl, 7.67.

3-*tert*-Butyl-dimethylsilyloxy-17ß-ethynyl-1,3,5(10)-estratrien-17α-ol (9): To **8** (1.2 g, 2.68 mmol), dissolved in THF, was added *n*-butyl-lithium in hexane (5.0 ml, 8.1 mmol, 1.6 M) at -35°C. After stirring 2 h at -35°C, ammonium chloride was added. The reaction mixture was allowed to warm to room temperature. The suspension was filtered and washed twice with THF. Solvent was removed and the crude compound was column chromatographed (silica gel, 15 % ethyl acetate in hexane) to afford **9** (658 mg, 60%).

9: ^{1}H NMR (C_5D_5N) δ 0.26 (6H, s, 3-$OSiMe_2$), 1,01 (3H, s, 18-CH_3), 1.03 (9H, s, 3-OSi^tBu), 1.21-2.98 (15H, m), 3.29 (1H, s, 21-H), 4.95 (1H, br. s, OH), 6,85 (1H, d, *J*= 2.5 Hz, 4-H), 6,90 (1H, dd, *J*=2.5, *J*=9 Hz, 2-H), 7.30 (1H, d, *J*=9 Hz, 1-H).

17ß-Ethynyl-1,3,5(10)-estratrien-17α-diol (2): To **9** (0.60 g, 1.47 mmol), dissolved in THF, was added *tert*-butylammonium fluoride (1.40 g, 4.4 mmol) at room temperature. After stirring 1.5 h, the mixture was filtered over silica gel (ethyl acetate). Solvent was removed and the crude compound was recrystallized from hexane affording **2** (330 mg, 76%).

2: mp. 207-208 °C (Lit.[2] 210-212°C), $[\alpha]_D^{20}$ = +76.7 (c = 0.0021, THF); MS, *m/z*: 296 (M^+); IR (KBr) $\nu^{cm^{-1}}$: 3280, 2110, 1630, 1580; ^{1}H-NMR (C_5D_5N) δ 1.12 (3H, s, 18-CH_3), 1.24-2.90 (15H, m), 3.40 (1H, s, 21-H), 4.95 (1H, br. s, OH), 7.00 (1H, d, *J*= 2.5 Hz, 4-H), 7.09 (1H, dd, *J*=2.5, *J*=9 Hz, 2-H), 7.33 (1H, d, *J*=9 Hz, 1-H), 11.14 (1H, br. s, OH); Anal. calcd. for $C_{20}H_{24}O_2$: C, 81.03%, H, 8.18. Found: C, 79.98%, H, 8.48%.

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