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SYNTHESIS OF 11β-(ALKYNYL)SUBSTITUTED 19-NORSTEROIDS

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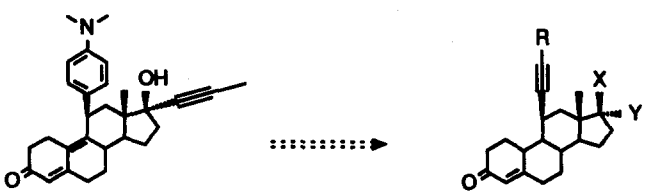
Abstract: A new access to 11β-(alkynyl)estranes **I** is described. The synthesis of key intermediate 11β-ethynylestr-4-ene-3,17-dione **8** can be achieved by stereoselective thermodynamically controlled formation of 11β-aldehyde **1**, its conversion to vinyl bromide **7** by Wittig reaction and subsequent dehydrobromination. Broad variation of the acetylenic 11β-substitution is possible by nucleophilic substitution as well as transition metal mediated coupling reactions.

The interest in stereoselective, synthetically useful routes to steroidal 11β-substitution has dramatically increased since the discovery of mifepristone type competitive progesterone antagonists[1] in the early eighties. A variety of potential pharmacological applications[2] has further stimulated the search for new chemical classes of antigestagens. To get further insight into structure activity relationships, particularly 11β-alkynyl substituted steroids **I** of the 19-nor series are an attractive synthetic goal. In analogy to the 4'-substituted phenyl group in RU 38 486, an 11β-alkynyl linker transfers a pharmacophoric group into a



RU 38 486
(mifepristone)

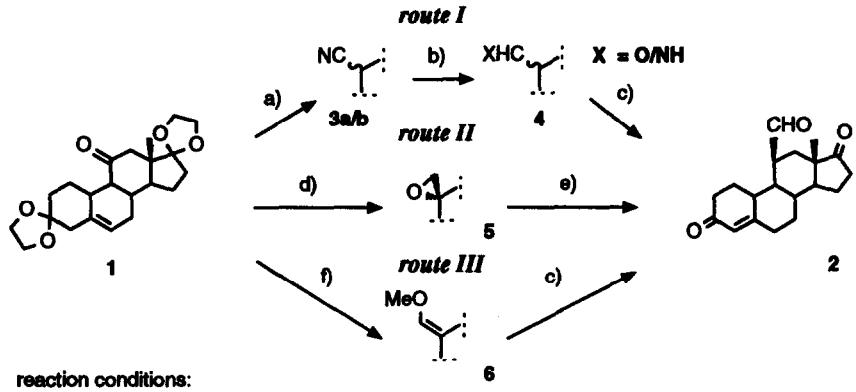
I

figure 1

similar axial position, serving therefore as an ideal isosteric spacer (*figure 1*). In addition, 1,3-diaxial sterical hindrance with a potential 10β-substituent is minimized, an interaction known to cause synthetic problems in the 11β-aryl series.[3] Finally, an acetylenic terminus of a steroidal 11β-ethynyl group offers high synthetic flexibility for further modifications.

The well explored epoxide route for stereospecific introduction of 11β-carbon substituents developed by Teutsch, Nedelec[4] and coworkers is limited to alkyl, vinyl, and aryl residues due to the copper(I) chemistry involved.

Therefore, to achieve the desired acetylenic 11β-substitution we focused on the chemistry of 11β-carbaldehyde **2**. Based on work of Campbell[5] at Upjohn and our own laboratories[6] aldehyde **2** is readily obtained in a stereoselective fashion from estr-5-ene-3,11,17-trione 3,17-bis(cyclic 1,2-ethanediyl acetal) by the synthetic routes depicted in *scheme 1*.



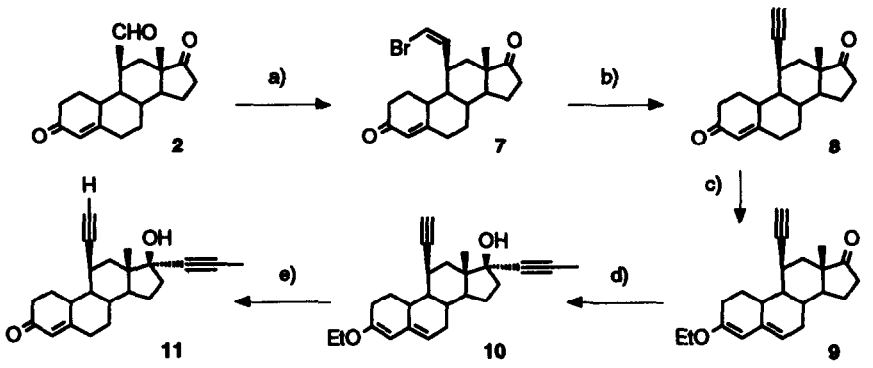
a) TosMIC, KOtBu,HOtBu, DME (60%); b) DIBAH, THF (85%); c) 4n aq. HCl, acetone (78%);
d) $Me_3S^+I^-$, DMF, KOtBu (75%); e) 1. $BF_3{\cdot}Et_2O$, toluene 2. 2n aq. H_2SO_4, MeOH, THF (49%);
f) $MeOCH_2PPh_3^+Cl^-$, KOtBu, toluene (85%); c) 4n aq. HCl, acetone (91%).

scheme 1

Conversion of the ketone[7] **1** via tosylmethyl isocyanide to the mixture of epimeric 11-carbonitriles **3 a/b**,[8] diisobutylaluminum hydride reduction, and acidic work up resulted in the formation of the desired thermodynamically more stable aldehyde **2** (***route I***: 40% overall yield). Attempts to improve the synthetic accessibility of **2** by formation of 11α-spiroepoxide **5** and its subsequent Lewis acid induced rearrangement (***route II***: 37% overall yield[7,13]) did not succeed. Altogether the approach via methoxyvinyl ether[5] **6** proved to be the most efficient route (***route III***). Aldehyde **2** can be prepared via Wittig reaction of **1** with methoxymethyltriphenylphosphonium chloride under oxygen free conditions and subsequent acidic removal of the protecting groups in an excellent 77% overall yield.

To establish the desired 11β-ethynyl group, aldehyde **2** was chemo- and stereoselectively converted to *cis*-vinyl bromide[9] **7** via Wittig reaction with bromomethylenetriphenylphosphorane[10]. Subsequent dehydrohalogenation using excess lithium diisopropylamide in tetrahydrofuran at - 70 °C afforded **8** (68% overall yield[13]). Regioselective protection of the 3-keto function in **8** as 3-ethoxy-3,5-dienol ether followed by nucleophilic addition of propynyl lithium to the unprotected 17-carbonyl group in **9** generated **10** in 87% yield. Mild deprotection of the 3-keto-4-ene system in **10** was achieved with aqueous acetic acid to furnish 11β-ethynyl derivative **11** (*scheme 2*).

The inherent reactivity of the acetylenic terminus in steroids **10** and **11** can be conveniently used for further 11β-side chain variations. First of all, dienol ether **10** is easily deprotonated with butyllithium and reacted with carbonyl compounds. As an example, trapping of the dianion of **10** with acetone is given, furnishing after acidic workup propargylic alcohol derivative **12**. In addition, construction of unsymmetrically substituted diyne residues (see **14** *scheme 3*) in 11β-position can be achieved by Cadiot-Chodkiewicz type

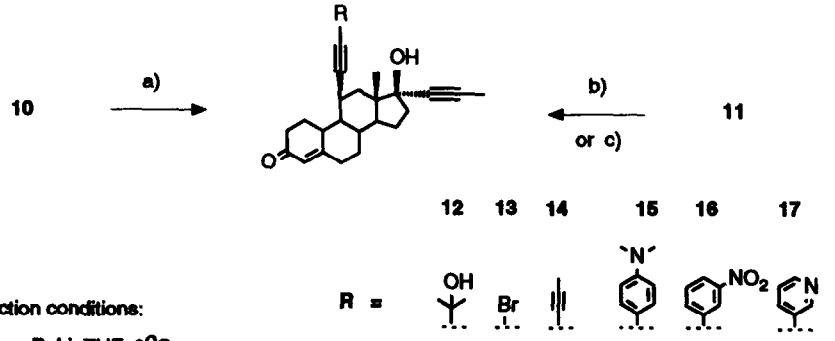


reaction conditions:

a) $BrCH_2PPh_3^+Br^-$, KOtBu, THF,-60°C (72%); b) 10 eq. LDA, THF, -78°C-0°C, (95%); c) PTSA, $HC(OEt)_3$, EtOH, 0°C (92%); d) $MeC{\equiv}C^-Li^+$, THF, 0°C, (95%); e) $AcOH/H_2O$ 7:3, RT (89%).

scheme 2

couplings[11] of bromide **13** generated from **11** by a standard procedure[11]. Thus oxidative C-C- bond formation with propyne resulted in formation of **14**. Finally compounds **10** and **11**, respectively, are well suited for palladium catalyzed coupling reactions[12] with aromatic halides as is demonstrated by the generation of compounds **15**, **16** and **17** (*scheme 3*).



(51%) (94%) (36%) (36%) (78%) (83%)

reaction conditions:

a) 1. n-BuLi, THF, 0°C;
2. acetone, 0°C;
3. 4n aq. HCl,acetone, RT (51% 12).
b) 1. acetone, NBS, $AgNO_3$, RT (94% 13);
2. propyne, DMF, n-$BuNH_2$, CuCl, RT (36% 14).
c) $(PPh_3)_4Pd$, Cu (I), Et_3N, Ar-Br, 60°C (15-17).

scheme 3

In summary, a flexible approach for the synthesis of a broad variety of 11β-ethynyl substituted estranes[13] has been developed. These obtained 11β-(alkynyl) substituted 19-norsteroids show an excellent affinity for the progesterone receptor. Resulting structure activity relationships will be published elsewhere.

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13. Characteristic spectroscopical data of selected compounds: **2**: IR (KBr): 1735, 1715, 1665, 1620; NMR (300 MHz, $CDCl_3$): δ= 9.85 (1H, d, J1Hz), 5.88 (1H, s), 3.21-3.34 (1H, m), 2.85-2.91 (1H, m), 0.8 (3H, s); $[\alpha]_D$+51^0(c=0.5, $CHCl_3$); m. p. 143-145^{0}C(Me_2Cl_2/diisopropylether). **7**: IR (KBr): 1730, 1660, 1615; NMR (300 MHz, $CDCl_3$): δ= 6.24-6.37 (2H, m), 5.87 (1H, s), 3.14-3.25 (1H, m), 0.92 (3H, s); $[\alpha]_D$+95^0(c=0.51, $CHCl_3$); m. p. 183-185^{0}C(Me_2Cl_2/diisopropylether). **11**: IR (KBr): 2240, 2100, 1665, 1615; NMR (300 MHz, $CDCl_3$): δ= 5.87 (1H, s), 3.03-3.1 (1H, m), 2.19 (1H, d, J2Hz), 1.86 (3H, s), 1.18 (3H, s); $[\alpha]_D$+50^0(c=0.5, $CHCl_3$); m. p. 183-184^{0}C(Me_2Cl_2/diisopropylether). **12**: NMR (300 MHz, $CDCl_3$): δ= 5.87 (1H, s), 3.01-3.08 (1H, m), 1.85 (3H, s), 1.5 (6H, s), 1.17 (3H, s); $[\alpha]_D$+50^0(c=0.505,$CHCl_3$). **14**: NMR (300 MHz, $CDCl_3$): δ= 5.87 (1H, s), 3.08-3.15 (1H, m), 1.93 (3H, s), 1.85 (3H, s), 1.15 (3H, s); $[\alpha]_D$+127^0(c=0.5,$CHCl_3$). **15**: NMR (300 MHz, $CDCl_3$): δ= 7.27 (2H, d, J9Hz), 6.62 (2H, d, J9Hz), 5.87 (1H, s), 3.21-3.28 (1H, m), 2.96 (6H, s), 1.88 (3H, s), 1.26 (3H, s); $[\alpha]_D$+147^0(c=0.5,$CHCl_3$).

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