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$Pd(PPh_3)_4$/AgOAc-catalyzed coupling of 17-steroidal triflates and alkynes: Highly efficient synthesis of D-ring unsaturated 17-alkynylsteroids

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ABSTRACT

A novel and practical procedure was developed for the preparation of D-ring unsaturated 17-alkynyl steroids by $Pd(PPh_3)_4$/AgOAc-catalyzed coupling of steroidal 17-triflates and alkynes. Firstly treatment of the steroid-17-ones with $PhN(Tf)_2$ and KHMDS in dried THF at −78 °C for 2 h gives the corresponding steroidal 17-triflates products in high yields (97–98%), following the coupling of steroidal 17-triflates and various 1-alkynes by $Pd(PPh_3)_4$/AgOAc-catalyzed in the presence of DIPEA for 24 h to yield the desired D-ring unsaturated 17-alkynyl steroids (86–97%). Moreover, it was found that the coupling reaction catalyzed by $Pd[(C_6H_5)_3P]_4$/AgOAc system is selective for aryl triflates or vinyl triflates. By optimizing the reaction conditions, the sole C17-coupling products from steroidal bistriflates were obtained in satisfactory yields. Since D-ring unsaturated 17-alkynyl steroids with conjugated double and triplet bond can be subsequently converted into pentacyclic steroids and 17-oxosteroid derivatives at the side chain of D-ring, this general method provides a highly efficient route to these biologically important compounds.

1. Introduction

Steroids are a class of important multi-cyclic compounds because of their special biological activities. Except for the naturally occurring substances, most of steroidal pharmaceuticals were semi-synthetic compounds. The development of new compounds to improve the selectivity and to minimize side effects of steroidal drugs has been a challenge for a long time [1]. For many years, the modification of 3-hydroxysteroids has attracted considerable attention from medicinal and synthetic organic chemists. Various derivatives of steroids by modified at 17-postion side chain with antibacterial, anticancer activity and cytotoxic activity have been reported [2]. Other examples showed that isoxazoline derivatives of 17-oxoandrostane at the side chain of D-ring can inhibit Na/K-ATPase [3]. Moreover, some studies found that pentacyclic steroids obtained by fusion of a carbocyclic ring such as benzene or cyclohexane or cyclopentane to the steroid nucleus or pentacyclic steroids derived by the fusion of a carbocyclic ring to a heterosteroid skeleton exhibit interesting and diverse biological properties [4]. And it is proved that a number of biologically important properties of modified steroids are dependent upon structural features of the steroid D-ring and side chain [5]. Chemical modification of the steroid D-ring and side chain provides a way to alter the functional groups, sizes, and stereochemistry of the D-ring, and numerous structure–activity relationships have been established by such synthetic alterations. As an example on the modification of steroidal 17-postion side chain, 3α,5α-17-phenylandrost-16-en-3-ol is a neurosteroid antagonist [6]. 3α,5α-17-Phenylandrost-16-en-3-ol antagonizes selectively the GABA-modulatory and GABA-mimetic effects of 3α,5α-THPROG and related 5α-pregnane steroids [6,7].

In our recent research, several analogues of steroidal-ynenes (Fig. 1) have been designed as key precursors for the preparation of 23-substituted corticosteroids and for the synthesis of a series of pentacyclic steroids fused with benzene, pyridine, furan and oxirane. In particular, methods for the preparation of the noncommercially available and modified 17-side chain and D-ring steroids have received considerable attention. Among of reported methods, the two main routes were described that steroidal alkenyl iodides (17-iodo-androsta-16-ene and 17-iodo-4-methyl-4-aza-androsta-16-ene-3-one) were reacted with conjugated unsaturated esters in Heck reaction and 17-carbonyl group of steroids was reacted with organolithium, organomagnesium, organotin or 1-alkynes under a strong base condition in nucleophile addition [6,8]. However, a major drawback to this otherwise efficient synthetic approach to modified 17-side chain and D-ring steroids has been the relatively poor yields obtained. Thus, to overcome the low yields associated with Heck reaction and addition reaction of steroid 17-carbonyl we undertook this study. We report here coupling reaction conditions that accomplish this goal.

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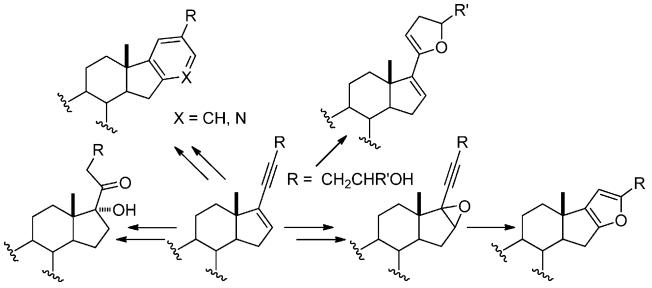


Fig. 1. Structures of 17-alkynylsteroids and their derivatives.

2. Experimental

2.1. General remarks

All melting points were determined on a Yanaco melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet FT-IR 5DX spectrometer as KBr pellets. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker ACF-300 spectrometer with TMS as internal reference. The *J* values are given in hertz. Optical rotations were determined on a Perkin-Elmer 343 polarimeter. The elemental analyses were performed on a Perkin-Elmer 240C instrument.

2.2. Organic synthesis

2.2.1. General procedure for the synthesis of triflates **2a**–**c** from steroid-17-ones **1a**–**c**

To a mixture of steroid-17-ones (**1a**–**c**) (0.5 mmol) and PhN(Tf)$_2$ (268 mg, 0.75 mmol) in dried THF (15 mL) was added KHMDS (0.5 M in toluene, 3 mL, 1.5 mmol) at −78 °C and the resultant mixture was stirred at the same temperature for 2 h. After the reaction was quenched by adding sat. NH_4Cl (aq), the mixture was extracted with DCM (2× 15 mL), the organic phase was washed with water and brine, dried over Na_2SO_4. Removal of solvent, the residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 1/20) to give product **2a**–**c**.

*2.2.1.1. (8R,9S,13S,14S)-3-Methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthren-17-yl trifluoromethanesulfonate (**2a**).* Following the general procedure, the title compound **2a** (98%) was obtained as an oil; $[\alpha]_D^{20}$ = +67.00° (*c* = 0.784, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 7.09 (m, 1H), 6.65 (m, 1H), 6.57 (m, 1H), 5.54 (m, 1H), 3.69 (s, 3H), 2.80 (m, 2H), 2.32 (m, 3H), 2.01 (m, 1H), 0.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.55, 157.88, 137.82, 132.33, 126.11, 118.88 (q, *J* = 319 Hz), 114.65, 114.15, 111.7, 55.33, 53.79, 45.28, 44.40, 36.93, 32.95, 29.61, 28.54, 26.93, 26.02, 15.50; IR (KBr): 3082, 1630, 1601, 1499, 1408, 1143, 1040, 684 cm^{-1}; Anal. Calcd. for $C_{20}H_{23}F_3O_4S$: C, 57.68; H, 5.57; Found C, 57.56; H, 5.27.

*2.2.1.2. (3S,8R,9S,10R,13S,14S)-3-(Methoxymethoxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl trifluoromethanesulfonate (**2b**).* Following the general procedure, the title compound **2b** was obtained as a white solid, mp 70–72 °C (hexanes); 98% in yield; $[\alpha]_D^{20}$ = −43.55° (*c* = 0.671, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 5.58 (m, 1H), 5.36 (d, *J* = 5.1 Hz, 1H), 4.70 (s, 2H), 3.43 (m, 1H), 3.38 (s, 3H), 1.04 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.40, 141.32, 121.02, 118.85(q, *J* = 327 Hz), 114.63, 94.83, 76.98, 55.28, 54.45, 50.66, 44.80, 39.65, 37.22, 37.06, 32.84, 30.70, 30.09, 28.95, 28.72, 20.27, 19.33, 15.21; IR (KBr, cm^{-1}): 3085, 1629, 1599, 1496, 1421, 1143, 1043, 603 cm^{-1}; Anal. Calcd. for $C_{22}H_{31}F_3O_5S$: C, 56.88; H, 6.73; Found C, 57.00; H, 6.64.

*2.2.1.3. (3R,5S,8R,9S,10S,13S,14S)-3-(Methoxymethoxy)-10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl trifluoromethanesulfonate (**2c**).* Following the general procedure, the title compound **2c** was obtained as a white solid; mp 48–50 °C (hexanes); 97% in yield; $[\alpha]_D^{20}$ = +15.82° (*c* = 0.158, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 5.56 (m, 1H), 4.66 (m, 2H), 3.83 (m, 1H), 3.37 (s, 3H), 2.20 (m, 1H), 1.95 (m, 1H), 0.96 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.56, 118.73 (q, *J* = 319 Hz), 114.51, 94.72, 71.65, 55.22, 54.89, 54.50, 45.01, 40.06, 36.22, 33.76, 33.62, 32.88, 32.73, 30.89, 28.62, 28.40, 26.43, 20.22, 15.38, 11.42; IR (KBr): 3081, 1628, 1423, 1142, 1050, 601 cm^{-1}; Anal. Calcd. for $C_{22}H_{33}F_3O_5S$: C, 56.64; H, 7.13; Found C, 56.34; H, 7.00.

2.2.2. General procedure for the coupling reaction from triflates and 1-alkynes

To the mixture of compound **2a**–**c** (0.5 mmol), AgOAc (17 mg, 0.10 mmol), Pd[$(C_6H_5)_3P$]$_4$ (30 mg, 0.026 mmol) and DIPEA (200 mg, 1.55 mmol) in DMF (8 mL) was added 1-alkyne (0.6 mmol) by syringe at room temperature under nitrogen. The resultant mixture was stirred under nitrogen at room temperature for 30 min. After the mixture was diluted with DCM (15 mL) and the solid was removed by filtered, the residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 1/10–1/4) to give product **3aa**–**ce**.

*2.2.2.1. 4-((8S,9S,13S,14S)-3-Methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthren-17-yl)but-3-yn-1-ol (**3aa**).* Following the general procedure, the title compound **3aa** was obtained as a white solid, 97% in yield, mp 56–58 °C (hexanes); $[\alpha]_D^{20}$ = +46.04° (*c* = 0.202, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 7.19 (d, *J* = 8.4 Hz, 1H), 6.72 (m, 1H), 6.64 (m, 1H), 5.97 (m, 1H), 3.77 (s, 3H), 3.75 (t, *J* = 6.3 Hz, 2H), 2.87 (m, 2H), 2.64 (t, *J* = 6.3 Hz, 2H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 157.66, 138.02, 137.61, 134.93, 132.97, 126.17, 114.04, 111.60, 89.74, 78.14, 61.43, 55.57, 55.34, 48.25, 44.49, 37.74, 34.81, 31.83, 29.86, 27.93, 26.66, 24.17, 16.36; IR (film, cm^{-1}): 3391, 3050, 2977, 2246, 1608, 1576, 1499, 1048, 813, 730; Anal. Calcd. for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39; Found C, 82.16; H, 8.27.

*2.2.2.2. 4-((8S,9S,13S,14S)-3-Methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthren-17-yl)but-3-yn-2-ol (**3ab**).* Following the general procedure, the title compound **3ab** was obtained as a white solid, 97% in yield; mp 110–112 °C (hexanes); $[\alpha]_D^{20}$ = +45.41° (*c* = 0.540, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 7.19 (d, *J* = 8.4 Hz, 1H), 6.72 (m, 1H), 6.64 (m, 1H), 6.04 (m, 1H), 4.70 (m, 1H), 3.77 (s, 3H), 2.87 (m, 2H), 1.50 (d, *J* = 6.6 Hz, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 157.67, 138.02, 137.00, 136.09, 132.95, 126.18, 114.07, 111.63, 94.81, 79.67, 59.09, 55.62, 55.36, 48.36, 44.51, 37.74, 34.73, 31.97, 29.86, 27.94, 26.64, 24.80, 16.36; IR (film, cm^{-1}): 3391, 3050, 2977, 2211, 1609, 1576, 1499, 815; Anal. Calcd. for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39; Found C, 82.02; H, 8.18.

*2.2.2.3. 4-((8S,9S,13S,14S)-3-Methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthren-17-yl)-2-methylbut-3-yn-2-ol (**3ac**).* Following the general procedure, the title compound **3ac** was obtained as a white solid, 96% in yield; mp 118–119 °C (hexanes); $[\alpha]_D^{20}$ = +53.55° (*c* = 0.310, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 7.19 (d, *J* = 8.7 Hz, 1H), 6.72 (m, 1H), 6.64 (m, 1H), 6.01 (m, 1H), 3.77 (s, 3H), 2.88 (m, 2H), 1.57 (s, 6H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 157.71, 138.07, 137.13, 135.56, 133.00, 126.21, 114.10, 111.66, 97.78, 77.73, 65.86, 55.63, 55.39, 48.39, 44.55, 37.78, 34.76, 31.98, 31.88(2C), 29.89, 27.99, 26.69, 16.38; IR (film, cm^{-1}): 3233, 3051, 2981, 2214, 1611, 1574, 1495,

1257, 813; Anal. Calcd. for $C_{24}H_{30}O_2$: C, 82.24; H, 8.63; Found C, 82.09; H, 8.48.

*2.2.2.4. (8S,9S,13S,14S)-3-methoxy-13-methyl-17-(4-methylpent-1-ynyl)-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthrene (**3ad**).* Following the general procedure, the title compound **3ad** was obtained as a white solid, 95% in yield, mp 95–96 °C (hexanes); $[\alpha]_D^{20}$ = +49.38° (*c* = 0.282, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 7.19 (d, *J* = 8.4 Hz, 1H), 6.72 (m, 1H), 6.64 (m, 1H), 5.92 (m, 1H), 3.77 (s, 3H), 2.88 (m, 2H), 2.26 (d, *J* = 6.3 Hz, 2H), 1.00 (d, *J* = 6.6 Hz, 6H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 157.69, 138.28, 138.10, 133.51, 133.10, 126.21, 114.07, 111.63, 92.82, 77.05, 55.60, 55. 36, 48.35, 44.58, 37.82, 34.93, 31.80, 29.93, 28.96, 28.45, 27.99, 26.76, 22.16(2C), 16.41; IR (film, cm^{-1}): 3051, 2956, 2215, 1608, 1579, 1500, 1239, 814 cm^{-1}; Anal. Calcd. for $C_{25}H_{32}O$: C, 86.15; H, 9.25; Found C, 86.19; H, 9.16.

*2.2.2.5. (8S,9S,13S,14S)-3-methoxy-17-((4-methoxyphenyl)ethynyl)-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthrene (**3ae**).* Following the general procedure, the title compound **3ae** was obtained as a white solid, 86% in yield, mp 101–103 °C (hexanes); $[\alpha]_D^{20}$ = +24.61° (*c* = 1.633, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 7.39 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.73 (m, 1H), 6.65 (m, 1H), 6.08 (m, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 2.88 (m, 2H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.39, 157.49, 137.85, 137.64, 134.74, 132.96(2C), 132.83, 126.00, 115.84, 113.90(2C), 113.85, 111.41, 92.83, 83.63, 55.46, 55.23, 55.14, 48.40, 44.34, 37.60, 34.68, 31.87, 29.69, 27.78, 26.52, 16.33; IR (film, cm^{-1}): 3047, 2994, 2195, 1608, 1580, 1507, 1287, 1247, 1034, 831; Anal. Calcd. for $C_{28}H_{30}O_2$: C, 84.36; H, 7.59; Found C, 84.20; H, 7.43.

*2.2.2.6. 1-(((8S,9S,13S,14S)-3-Methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthren-17-yl) ethynyl)cyclohexanol (**3af**).* Following the general procedure, the title compound **3af** was obtained as a white solid, 92% in yield; mp 144–146 °C (hexanes); $[\alpha]_D^{20}$ = +36.88° (*c* = 0.892, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 7.20 (d, *J* = 8.7 Hz, 1H), 6.73 (m, 1H), 6.64 (m, 1H), 6.01 (m, 1H), 3.78 (s, 3H), 2.88 (m, 2H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 157.74, 138.11, 137.21, 135.37, 133.03, 126.23, 114.13, 111.69, 97.58, 80.16, 69.52, 55.65, 55.42, 48.51, 44.60, 40.48 (2C), 37.80, 34.90, 32.01, 29.93, 28.00, 26.75, 25.47, 23.82 (2C), 16.49; IR (film, cm^{-1}): 3282, 3050, 2998, 2214, 1611, 1574, 1496, 1257, 1071, 815; Anal. Calcd. for $C_{27}H_{34}O_2$: C, 83.03; H, 8.77; Found C, 82.89; H, 8.58.

*2.2.2.7. 4-((3S,8R,9S,10R,13S,14S)-3-(Methoxymethoxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl)but-3-yn-1-ol (**3ba**).* Following the general procedure, the title compound **3ba** was obtained as needles, 96% in yield, mp 105–107 °C (hexanes); $[\alpha]_D^{20}$ = −48.18° (*c* = 0.343, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 6.95 (s, 1H), 5.36 (d, *J* = 4.8 Hz, 1H), 4.69 (s, 2H), 3.73 (m, 2H), 3.42 (m, 1H), 3.37 (s, 3H), 2.63 (t, *J* = 6.3 Hz, 2H), 1.05 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 141.32, 137.41, 135.03, 121.49, 94.88, 89.65, 78.16, 77.09, 61.41, 56.36, 55.31, 50.86, 47.87, 39.75, 37.34, 37.16, 34.71, 32.13, 31.74, 30.86, 29.08, 24.18, 20.93, 19.44, 16.14; IR (film, cm^{-1}): 3392, 3040, 2245, 1667, 1589, 1461, 1449, 1440, 1147, 1101, 1042, 730; Anal. Calcd. for $C_{25}H_{36}O_3$: C, 78.08; H, 9.44; Found C, 78.22; H, 9.35.

*2.2.2.8. 4-((3S,8R,9S,10R,13S,14S)-3-(Methoxymethoxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl)but-3-yn-2-ol (**3bb**).* Following the general procedure, the title compound **3bb** was obtained as an oil, 94% in yield, $[\alpha]_D^{20}$ = −42.60° (*c* = 1.22, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 6.00 (m, 1H), 5.36 (d, *J* = 5.1 Hz, 1H), 4.70 (m, 3H), 3.39 (m, 1H), 3.37 (s, 3H), 1.49 (d, *J* = 6.6 Hz, 3H), 1.05 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 141.32, 136.82, 136.15, 121.46, 94.85, 79.61, 77.11, 58.97, 56.37, 55.33, 50.83, 47.95, 39.75, 37.34, 37.14, 34.64, 32.26, 31.74, 30.84, 29.07, 24.80, 20.92, 19.44, 16.12; IR (film, cm^{-1}): 3433, 3049, 2246, 1667, 1590, 1452, 1036, 733; Anal. Calcd. for $C_{25}H_{36}O_3$: C, 78.08; H, 9.44; Found C, 78.02; H, 9.18.

*2.2.2.9. 4-((3S,8R,9S,10R,13S,14S)-3-(Methoxymethoxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-methylbut-3-yn-2-ol (**3bc**).* Following the general procedure, the title compound **3bc** was obtained as needles, mp 115–117 °C (hexanes), 97% in yield, $[\alpha]_D^{20}$ = −46.86° (*c* = 0.406, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 5.96 (s, 1H), 5.36 (d, *J* = 5.1 Hz, 1H), 4.69 (s, 2H), 3.42 (m, 1H), 3.37 (s, 3H), 1.55 (s, 6H), 1.05 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 141.32, 136.91, 135.58, 121.46, 97.72, 94.85, 77.66, 77.09, 65.71, 56.37, 55.31, 50.86, 47.95, 39.75, 37.34, 37.14, 34.62, 32.23, 31.85 (2C), 31.74, 30.86, 29.08, 20.92, 19.44, 16.11; IR (film, cm^{-1}): 3434, 3049, 2245, 1667, 1591, 1452, 1437, 1370, 1149, 1105, 1037, 733; Anal. Calcd. for $C_{26}H_{38}O_3$: C, 78.35; H, 9.61; Found C, 78.20; H, 9.41.

*2.2.2.10. (3S,8R,9S,10S,13S,14S)-3-(Methoxymethoxy)-10,13-dimethyl-17-(4-methylpent-1-ynyl)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthrene (**3bd**).* Following the general procedure, the title compound **3bd** was obtained as needles, mp 103–105 °C (hexanes), 96% in yield, $[\alpha]_D^{20}$ = −41.95° (*c* = 0.677, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 5.88 (s, 1H), 5.36 (d, *J* = 4.8 Hz, 1H), 4.69 (s, 2H), 3.42 (m, 1H), 3.37 (s, 3H), 2.24 (d, *J* = 6.6 Hz, 2H), 1.05 (s, 3H), 0.99 (d, *J* = 6.6 Hz, 6H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 141.30, 138.04, 133.59, 121.55, 94.90, 92.65, 77.09 (2C), 56.34, 55.30, 50.91, 47.92, 39.78, 37.37, 37.16, 34.79, 32.07, 31.77, 30.89, 29.11, 28.90, 28.40, 22.12 (2C), 20.99, 19.46, 16.14; IR (film, cm^{-1}): 3046, 2245, 1632, 1589, 1451, 1437, 1368, 1146, 1103, 1041; Anal. Calcd. for $C_{27}H_{40}O_2$: C, 81.77; H, 10.17; Found C, 81.59; H, 10.40.

*2.2.2.11. (3S,8R,9S,10R,13S,14S)-3-(Methoxymethoxy)-17-((4-methoxyphenyl)ethynyl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthrene (**3be**).* Following the general procedure, the title compound **3be** was obtained as needles, 97% in yield, mp 130–132 °C (hexanes); $[\alpha]_D^{20}$ = −17.73° (*c* = 0.615, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 7.37 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 6.05 (s, 1H), 5.37 (d, *J* = 4.5 Hz, 1H), 4.69 (s, 2H), 3.80 (s, 3H), 3.43 (m, 1H), 3.37 (s, 3H), 1.06 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.58, 141.35, 137.63, 135.11, 133.15(2C), 121.54, 116.07, 114.08(2C), 94.91, 92.94, 83.89, 77.11, 56.44, 55.43, 55.34, 50.90, 48.22, 39.80, 37.37, 37.19, 34.81, 32.41, 31.79, 30.94, 29.13, 21.01, 19.48, 16.32; IR (film): 3047, 2192, 1665, 1607, 1508, 1440, 1248, 1038, 830; Anal. Calcd. for $C_{30}H_{38}O_3$: C, 80.68; H, 8.58; Found C, 80.54; H, 8.42.

*2.2.2.12. 1-(((3S,8R,9S,10S,13S,14S)-3-(Methoxymethoxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl)ethynyl)cyclohexanol (**3bf**).* Following the general procedure, the title compound **3bf** was obtained as needles, mp 139–140 °C (hexanes); 96% in yield, $[\alpha]_D^{20}$ = −39.82° (*c* = 0.445, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 5.97 (m, 1H), 5.36 (d, *J* = 5.1 Hz, 1H), 4.69 (s, 2H), 3.43 (m, 1H), 3.37 (s, 3H), 1.05 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 141.35, 137.00, 135.35, 121.51, 96.51, 94.88, 80.11, 77.11, 69.38, 56.39, 55.34, 50.91, 48.09, 40.44 (2C), 39.78, 37.37, 37.17, 34.76, 32.26, 31.75, 30.87, 29.11, 25.44, 23.77 (2C), 20.99, 19.48, 16.20;

IR (film, cm^{-1}): 3434, 3049, 2209, 1666, 1591, 1462, 1445, 1370, 1148, 1105, 1037, 731; Anal. Calcd. for $C_{29}H_{42}O_3$: C, 79.41; H, 9.65; Found C, 79.22; H, 9.44.

*2.2.2.13. 4-((3R,5S,8R,9S,10S,13S,14S)-3-(Methoxymethoxy)-10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)but-3-yn-2-ol (**3cb**).* Following the general procedure, the title compound **3cb** was obtained as an oil; 98% in yield, $[\alpha]_D^{20}$ = +37.10° (*c* = 0.593, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 5.99 (m, 1H), 4.66 (m, 3H), 3.83 (m, 1H), 3.37 (s, 3H), 2.22–2.12 (m, 1H), 2.09 (d, *J* = 5.1 Hz, 1H), 2.00–1.90 (m, 1H), 1.48 (d, *J* = 5.1 Hz, 3H), 0.82 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): 137.00, 136.29, 94.75(2C), 79.83, 71.86, 59.08, 56.45, 55.33, 55.08, 48.21, 40.16, 36.32, 34.78, 34.52, 33.86, 32.91, 32.19, 32.06, 28.72, 26.56, 24.83, 20.84, 16.38, 11.57; IR (film, cm^{-1}): 3429, 3050, 2213, 1590, 1446, 1095, 1040 cm^{-1}; Anal. Calcd. for $C_{25}H_{38}O_3$: C, 77.68; H, 9.91; Found C, 77.54; H, 10.02.

*2.2.2.14. (3R,5S,8R,9S,10S,13S,14S)-3-(Methoxymethoxy)-17-((4-methoxyphenyl)ethynyl) -10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthrene (**3ce**).* Following the general procedure, the title compound **3ce** was obtained as a white solid, mp 118–120 °C (hexanes), 96% in yield, $[\alpha]_D^{20}$ = +77.93° (*c* = 0.415, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 7.36 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 6.02 (t, *J* = 2.4 Hz, 1H), 4.65 (m, 3H), 3.83 (s, 1H), 3.79 (s, 3H), 3.36 (s, 3H), 2.20–2.17 (m, 1H), 0.89 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.51, 137.78, 135.10, 133.10 (2C), 116.12, 114.05 (2C), 94.73, 92.83, 83.97, 71.80, 56.45, 55.39, 55.27, 55.08, 48.41, 40.13, 36.29, 34.88, 34.55, 33.85, 32.88, 32.27, 32.04, 28.72, 26.55, 20.89, 16.52, 11.54; IR (film, cm^{-1}): 3049, 2248, 1608, 1577, 1508, 1447, 1032, 834, 734 cm^{-1}; Anal. Calcd. for $C_{30}H_{40}O_3$: C, 80.31; H, 8.99; Found C, 80.16; H, 9.22.

*2.2.2.15. (8R,9S,13S,14S)-13-Methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthrene-3,17-diyl bis(trifluoromethanesulfonate) (**5**).* To a mixture of 3-hydroxyestrone **4** (1.00 g, 3.7 mmol), triethylamine (1.125 g, 11.1 mmol) and catalyst DMAP (80 mg) in dichloromethylene (15 mL) was added trifluoromethanesulfonic anhydride (3.13 g, 11.1 mmol) dropwise at 0 °C under nitrogen. Then the mixture was stirred for 10 h from 0 °C up to room temperature. After water (10 mL) was added to the reaction mixture, the mixture was extracted with methylene chloride (DCM, 2× 20 mL) and the organic phase was washed with water and brine, dried over Na_2SO_4. Removal of solvent, the residue was purified by flash chromatography (silica gel, DCM/hexanes, 1/1.5) to give product **5** (1.67 g, 86%) as an oil; $[\alpha]_D^{20}$ = +50.00° (*c* = 1.55, $CHCl_3$); ^1H NMR ($CDCl_3$) 7.32 (d, *J* = 8.7 Hz, 1H), 7.04 (m, 2H), 2.94 (dd, *J* = 4.5 Hz, 2H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.04, 147.61, 140.34, 139.20, 126.77, 121.19, 118.74 (q, *J* = 318.75 Hz), 118.59 (q, *J* = 318.75 Hz), 118.23, 114.51, 53.47, 44.93, 44.24, 36.08, 32.62, 29.10, 28.26, 26.21, 25.51, 15.18; IR (film): 1629, 1606, 1490, 1422, 1210, 1142, 921 cm^{-1}; Anal. Calcd. for $C_{20}H_{20}F_6O_6S_2$: C, 44.94; H, 3.77; Found C, 44.68; H, 3.62.

2.2.3. General procedure for the coupling reaction from bistriflates and 1-alkynes

The mixture of compound **5** (267 mg, 0.5 mmol), 1-alkynes (0.55 mmol), AgOAc (20 mg, 0.1 mmol), $Pd[(C_6H_5)_3P]_4$ (30 mg, 0.026 mmol) and DIPEA(129 mg, 1.0 mmol) in DMF (8 mL) was stirred at 80 °C for 15 min. After the reaction was quenched with water (2 mL) and the mixture was extracted with EtOAc (25 mL), the organic phase was washed with 10% HCl and sat. NH_4Cl, dried over Na_2SO_4. After the solvent was removed by vacuum, the residue was purified by flash chromatography (silica gel, CH_2Cl_2/hexanes, 1/5) to give product **6a–e**.

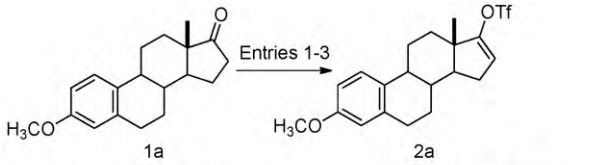
*2.2.3.1. (8S,9S,13S,14S)-17-(3-Hydroxybut-1-yn-1-yl)-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthren-3-yl trifluoromethanesulfonate (**6a**).* Following the general procedure, the title compound **6a** was obtained as an oil; 94% in yield; $[\alpha]_D^{20}$ = +29.29° (*c* = 1.81, $CHCl_3$); ^1H NMR ($CDCl_3$) 7.33 (d, *J* = 8.7 Hz, 1H), 7.03 (m, 2H), 6.04 (s, 1H), 4.71 (m, 1H), 2.91 (m, 2H), 1.50 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 147.46, 140.90, 139.36, 136.58, 135.79, 126.83, 121.08, 118.74 (q, *J* = 318.75 Hz), 118.08, 94.73, 79.23, 58.85, 55.28, 47.98, 44.37, 36.85, 34.38, 31.69, 29.34, 27.23, 26.14, 24.56, 16.06; IR (film): 3367, 3055, 1605, 1490, 1420, 1214, 1142, 917 cm^{-1}; Anal. Calcd. for $C_{23}H_{25}F_3O_4S$: C, 60.78; H, 5.54; Found C, 60.50; H, 5.60.

*2.2.3.2. (8S,9S,13S,14S)-17-(3-Hydroxy-3-methylbut-1-yn-1-yl)-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthren-3-yl trifluoromethanesulfonate (**6b**).* Following the general procedure, the title compound **6b** was obtained as an oil; 96% in yield; $[\alpha]_D^{20}$ = +28.87° (*c* = 1.16, $CHCl_3$); ^1H NMR ($CDCl_3$) 7.33 (d, *J* = 8.7 Hz, 1H), 7.04 (m, 2H), 6.01 (dd, *J* = 3.0, 1.8 Hz, 1H), 2.92 (m, 2H), 2.22 (s, 1H), 1.58 (s, 6H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 147.45, 140.90, 139.36, 136.64, 135.21, 126.82, 121.06, 118.74 (q, *J* = 318.75 Hz), 118.06, 97.64, 77.24, 65.59, 55.25, 47.95, 44.38, 36.85, 34.35, 31.65, 31.57 (2C), 29.32, 27.21, 26.12, 16.03; IR (film): 3368, 3054, 1606, 1490, 1423, 1212, 1142, 918 cm^{-1}; Anal. Calcd. for $C_{24}H_{27}F_3O_4S$: C, 61.52; H, 5.81; Found C, 61.48; H, 5.66.

*2.2.3.3. (8S,9S,13S,14S)-17-((4-Methoxyphenyl)ethynyl)-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthren-3-yl trifluoromethanesulfonate (**6c**).* Following the general procedure, the title compound **6c** was obtained as an oil; 93% in yields; $[\alpha]_D^{20}$ = +2.88° (*c* = 3.06, $CHCl_3$); ^1H NMR ($CDCl_3$) 7.39 (dm, *J* = 9.0 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 1H), 7.04 (m, 2H), 6.84 (dm, *J* = 9.0 Hz, 2H), 6.07 (dd, *J* = 3.0, 1.8 Hz, 1H), 3.80 (s, 3H), 2.92 (m, 2H), 2.41–2.29 (m, 3H), 2.17–1.94 (m, 3H), 1.69–1.63 (m, 4H), 1.62–1.46 (m, 1H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.44, 147.48, 141.02, 139.42, 137.43, 134.65, 132.69 (2C), 126.88, 121.08, 118.74 (q, *J* = 318.75 Hz), 118.07, 115.68, 113.90 (2C), 92.98, 83.44, 55.34, 55.20, 48.22, 44.41, 36.93, 34.55, 31.83, 29.38, 27.26, 26.23, 16.25; IR (film): 1607, 1585, 1568, 1508, 1489, 1422, 1212, 1141, 921 cm^{-1}; Anal. Calcd. for $C_{28}H_{27}F_3O_4S$: C, 65.10; H, 5.27; Found C, 64.88; H, 5.12.

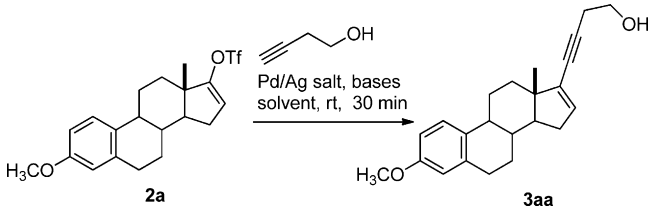
*2.2.3.4. (8S,9S,13S,14S)-17-((1-Hydroxycyclohexyl)ethynyl)-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthren-3-yl trifluoromethanesulfonate (**6d**).* Following the general procedure, the title compound **6d** was obtained as an oil; 96% in yield; $[\alpha]_D^{20}$ = +27.97° (*c* = 0.36, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 7.33 (d, *J* = 8.7 Hz, 1H), 7.04 (m, 2H), 6.01 (dd, *J* = 3.0, 1.8 Hz, 1H), 2.91 (m, 2H), 2.39–2.27 (m, 4H), 2.14–1.39 (m, 16H), 1.28–1.23 (m, 2H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 147.45, 140.92, 139.36, 136.74, 134.92, 126.80, 121.06, 118.74 (q, *J* = 318.75 Hz), 118.06, 96.46, 79.66, 69.21, 55.26, 48.05, 44.40, 40.15 (2C), 36.85, 34.47, 31.66, 29.32, 27.21, 26.18, 25.16, 23.53 (2C), 16.10; IR (film): 3399, 3054, 1606, 1584, 1489, 1423, 1212, 1142, 919 cm^{-1}; Anal. Calcd. for $C_{27}H_{31}F_3O_4S$: C, 63.76; H, 6.14; Found C, 63.57; H, 5.96.

*2.2.3.5. (8S,9S,13S,14S)-13-Methyl-17-(3-methylbut-3-en-1-yn-1-yl)-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthren-3-yl trifluoromethanesulfonate (**6e**).* Following the general procedure, the title compound **6e** was obtained as an oil; 89% in yield; $[\alpha]_D^{20}$ = +32.29° (*c* = 1.98, $CHCl_3$); ^1H NMR ($CDCl_3$) 7.26 (d,



Entry	Reaction Conditions	Yield of **2a** (%)
1	Tf_2O/pyridine/CH_2Cl_2/rt/24h	52
2	Tf_2O/NaH/CH_2Cl_2/0°C to rt/1h	83
3	$PhN(Tf)_2$/KHMDS/THF/-78°C/2h	98

Scheme 1. Preparation of triflate 2a using various reaction conditions.



Scheme 2. Various Pd/Ag or Cu salt system-catalyzed cross-coupling reaction.

J = 8.7 Hz, 2H), 6.91 (m, 2H), 5.97 (m, 1H), 5.20 (d, J = 20.0 Hz, 2H), 2.86–2.83 (m, 2H), 2.28–2.20 (m, 3H), 1.87 (t, J = 1.2 Hz, 3H), 0.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 147.49, 140.99, 139.40, 137.21, 135.34, 127.00, 126.88, 121.43, 121.11, 118.73 (q, J = 318.75 Hz), 118.10, 94.27, 83.76, 55.33, 48.15, 44.43, 36.93, 34.45, 31.83, 29.40, 27.27, 26.21, 23.62, 16.19. IR (film): 3055, 1600, 1490, 1426, 1200, 1150, 917 cm^{-1}; Anal. Calcd. for $C_{24}H_{25}F_3O_3S$: C, 63.98; H, 5.59; Found C, 63.76; H, 5.64.

*2.2.3.6. 4,4′-((8S,9S,13S,14S)-13-Methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthrene-3,17-diyl)bis(2-methylbut-3-yn-2-ol) (**7**).* The mixture of bistriflates **5** (267 mg, 0.5 mmol), 2-methylbut-3-yn-2-ol (92.4 mg, 1.10 mmol), CuI (38 mg, 0.2 mmol), Pd[$(C_6H_5)_3P]_4$ (60 mg, 0.052 mmol) and DIPEA(258 mg, 2.0 mmol) in DMF (8 mL) was stirred at 80 °C for 120 min. After the reaction was quenched with water (5 mL) and the mixture was extracted with EtOAc (2× 15 mL), the organic phase was washed with 10% HCl and sat. NH_4Cl, dried over Na_2SO_4. After the solvent was removed by vacuum, the residue was purified by flash chromatography (silica gel, CH_2Cl_2/hexanes, 1/5) to give the title product **7** (187.2 mg, 93%) as an oil; $[\alpha]_D^{20}$ = +26.88° (c = 2.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 7.20 (s, 1H), 7.17 (d, J = 10.8 Hz, 1H), 7.16 (d, J = 10.8 Hz, 1H), 6.01 (dd, J = 3.0, 2.1 Hz, 1H), 2.85 (m, 2H), 2.34–2.26 (m, 3H), 1.60 (s, 6H), 1.57 (s, 6H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 140.92, 136.76, 136.61, 135.38, 132.04, 128.78, 124.98, 119.80, 97.55, 92.97, 82.25, 65.68, 65.62, 55.45, 48.05, 44.73, 37.11, 34.47, 31.74, 31.63 (2C), 31.52 (2C), 31.02, 29.05, 27.52, 26.08, 16.12; IR (film): 3368, 3051, 2244, 1603, 1496, 1454, 1370, 1164, 958, 910 cm^{-1}; Anal. Calcd. for $C_{28}H_{34}O_2$: C, 83.54; H, 8.51; Found C, 83.44; H, 8.42.

*2.2.3.7. (8S,9S,13S,14S)-3-((4-Methoxyphenyl)ethynyl)-13-methyl-17-(3-methylbut-3-en-1-yn-1-yl)-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthrene (**8**).* The mixture of triflate **6e** (225 mg, 0.5 mmol), 1-ethynyl-4-methoxybenzene (72.7 mg, 0.55 mmol), CuI (19 mg, 0.1 mmol), Pd[$(C_6H_5)_3P]_4$ (30 mg, 0.026 mmol) and DIPEA(129 mg, 1.0 mmol) in DMF (8 mL) was stirred at 80 °C for 120 min. After the reaction was quenched with water (2 mL) and the mixture was extracted with EtOAc (2× 15 mL), the organic phase was washed with 10% HCl and sat. NH_4Cl, dried over Na_2SO_4. After the solvent was removed by vacuum, the residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 1/6) to give the title product **8** (198.7 mg, 92%) as an oil; $[\alpha]_D^{20}$ = +22.29° (c = 1.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 7.45 (d, J = 8.4 Hz, 2H), 7.44 (m, 3H), 6.87 (d, J = 8.7 Hz, 2H), 6.05 (q, J = 3.0, 1.8 Hz, 1H), 5.27 (d, J = 20.1 Hz, 2H), 3.82 (s, 3H), 2.90–2.87 (m, 2H), 2.38–2.29 (m, 3H), 1.95 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.47, 140.70, 137.32, 136.70, 135.47, 132.98 (2C), 131.84, 128.64, 127.06, 125.09, 121.37, 120.67, 115.68, 113.96 (2C), 94.21, 88.54, 88.26, 83.92, 55.51, 55.28, 48.27, 44.82, 37.20, 34.56, 31.89, 29.16, 27.59, 26.15, 23.66, 16.27. IR (film): 1610, 1498, 1420, 1208, 1144, 919 cm^{-1}; Anal. Calcd. for $C_{32}H_{32}O$: C, 88.85; H, 7.46; Found C, 88.66; H, 7.60.

3. Results and discussion

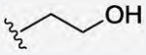
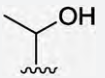
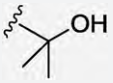
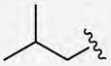
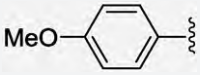
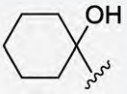
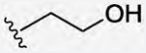
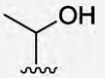
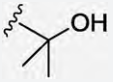
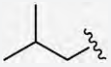
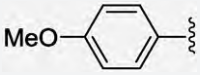
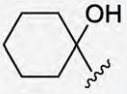
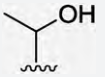
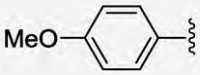
Considering the synthesis of these complex steroids with a modified D-ring and the formation of Csp2–Csp bond, we needed an active intermediate for sp2–sp coupling reactions. However, the

Table 1
Pd/Ag or Cu salt-catalyzed cross-coupling reaction of triflate **2a** with but-3-yn-1-ol to give compound **3aa**.[a]

Entry	[Pd] catalyst	Co-catalyst	Base	Solvent	Yield (%)[b]
1	$PdCl_2(PPh_3)_2$	CuI (20 mol%)	$^iPr_2NEt$	DMF	72
2	$Pd(PPh_3)_4$	CuI (20 mol%)	$^iPr_2NEt$	DMF	82
3	$PdCl_2(PPh_3)_2$	AgI (20 mol%)	$^iPr_2NEt$	DMF	78
4	$PdCl_2$	AgI (20 mol%)	$^iPr_2NEt$	DMF	68
5	$Pd(OAc)_2$	AgI (20 mol%)	$^iPr_2NEt$	DMF	72
6	$Pd(PPh_3)_4$	AgI (20 mol%)	$^iPr_2NEt$	DMF	85
7	$Pd_2(dba)_3$	AgI (20 mol%)	$^iPr_2NEt$	DMF	76
8	$Pd(PPh_3)_4$	AgBr (20 mol%)	$^iPr_2NEt$	DMF	80
9	$Pd(PPh_3)_4$	AgOTf (20 mol%)	$^iPr_2NEt$	DMF	96
10	$Pd(PPh_3)_4$	Ag_2CO_3 (20 mol%)	$^iPr_2NEt$	DMF	72
11	$Pd(PPh_3)_4$	AgOAc (20 mol%)	$^iPr_2NEt$	DMF	97
12	$Pd(PPh_3)_4$	$AgBF_4$ (20 mol%)	$^iPr_2NEt$	DMF	82
13	$Pd(PPh_3)_4$	AgOAc (0 mol%)	$^iPr_2NEt$	DMF	32
14	$Pd(PPh_3)_4$	AgOAc (10 mol%)	$^iPr_2NEt$	DMF	91
15	$Pd(PPh_3)_4$	AgOAc (30 mol%)	$^iPr_2NEt$	DMF	96
16	$Pd(PPh_3)_4$	AgOAc (20 mol%)	$^iPr_2NEt$	THF	85
17	$Pd(PPh_3)_4$	AgOAc (20 mol%)	$^iPr_2NEt$	MeCN	90
18	$Pd(PPh_3)_4$	AgOAc (20 mol%)	Et_3N	DMF	92
19	$Pd(PPh_3)_4$	AgOAc (20 mol%)	Pyridine	DMF	39
20	$Pd(PPh_3)_4$	AgOAc (20 mol%)	K_2CO_3	DMF	43

[a] Reaction conditions: triflate **2a**/3-butyn-1-ol/base = 1/1.2/3.0. Isolated yield based on triflate **2a**.

Table 2
Pd(PPh$_3$)$_4$/AgOAc-catalyzed preparation of D-ring unsaturated 17-alkynylsteroids.[a].

1, **2**	R^1	R^2	R^3	Yield of **2** (%)	**3**	R	Yield of **3** (%)
a	OMe	$\Delta^{1,3,5(10)}$-triene		98	**aa**		97
					ab		97
					ac		95
					ad		95
					ae		86
					af		92
b	β-OMOM	$\Delta^{5(6)}$	Me	98	**ba**		96
					bb		94
					bc		97
					bd		96
					be		97
					bf		92
c	α-OMOM	α-H	Me	97	**cb**		98
					ce		96

[a] Reaction conditions: triflate/1-alkyne (RC≡CH)/base = 1/1.2/3.1, Pd(PPh$_3$)$_4$(5 mol%)/AgOAc (20 mol%); room temperature, reaction time: 30 min, nitrogen. Isolated yield based on triflate.

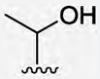
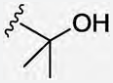
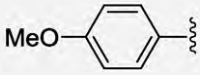
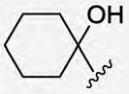
conventional Sonogashira sp2–sp coupling reaction of vinyl iodide with terminal alkynes catalyzed by palladium in the presence of copper salts under an Ar or N_2 atmosphere has some weak points such as the Glaser-type oxidative dimerization of terminal alkynes and low yield. Many studies indicated that the successful implementation of vinyl and aryl triflates as the electrophilic components in these reactions has greatly expanded the utility of these transformations, as the reactive species are readily available from the corresponding carbonyl compounds or phenolic [9].

Fortunately, the use of vinyl triflate in place of vinyl iodide as the electrophilic component dramatically improved the Sonogashira sp2–sp coupling reaction, and avoided Glaser-type oxidative dimerization of terminal alkynes.

Initially, the published methods which were used for the preparation of vinyl triflates from ketones were scanned on the model compound **2a**. Reagents and solvents investigated for the reaction were Tf_2O/NaH/CH_2Cl_2 [10], Tf_2O–pyridine–CH_2Cl_2, PhN(Tf)$_2$–KHMDS–THF. Although the reaction was mild at ambient temperature while using Tf_2O–pyridine–CH_2Cl_2 as reagents and solvent, the yield of compound **2a** was just moderate and the reaction took almost 24 h (52% in yield, Scheme 1, entry 1). Similar result was obtained in 83% (Scheme 1, entry 2) when base reagent NaH was used as a replacement in dichloromethane at 0 °C. Compound **2a** were also prepared from 3-methoxyestr-17-one by the reaction with KHMDS and PhN(Tf)$_2$ in THF at −78 °C (98% in yield, Scheme 1, entry 3). The result showed that PhN(Tf)$_2$–KHMDS–THF reaction system gave the best result.

To achieve this goal for the formation of Csp2–Csp bond, at first the coupling reaction palladium-catalyzed was studied with triflate

Table 3
The selectively coupling reaction of estr-16-en-3,17-diyl bistriflate catalyzed by $Pd(PPh_3)_4$/AgOAc.[a].

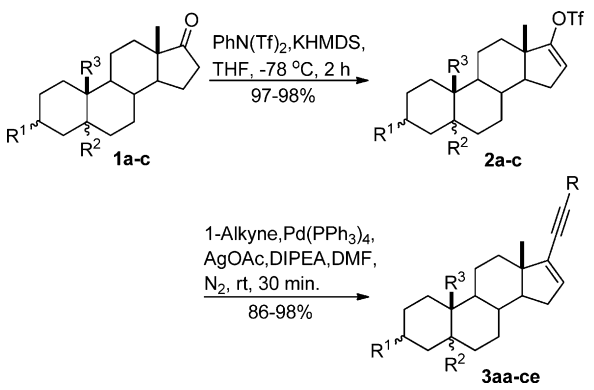
Entry	Product	R	Yield of **6** (%)
1	**6a**		94
2	**6b**		96
3	**6c**		93
4	**6d**		96
5	**6e**		94

[a] Reaction conditions: triflate/1-alkyne (RC≡CH)/base = 1/1.1/3.1, $Pd(PPh_3)_4$ (5 mol%)/AgOAc (20 mol%); 80 °C, reaction time: 15 min, nitrogen. Isolated yield based on triflate.

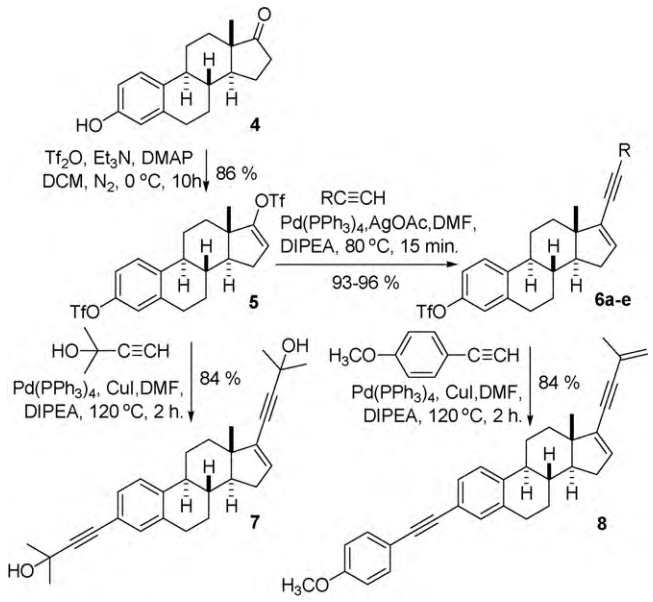
2a and but-3-yn-1-ol, which were selected as suitable substrates for reaction development (Scheme 2, Table 1). At the outset, various palladium catalysts were screened according to reported results [11]. To our delight, we observed the reactions using various palladium catalysts worked well when the reaction was carried out using triflate **2a** and but-3-yn-1-ol (1.1 equiv.), the formation of the desired product **3aa** when the reaction was carried out using the commercially available CuI (20 mol%) as a co-catalyst in the presence of $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ (5 mol%) and $^iPr_2NEt$ (1.5 equiv.) in DMF at room temperature for 30 min (72% yield, Table 1, entry 1 and 82% in yield, Table 1, entry 2, respectively). Considering the replacement of copper iodide by silver halides for the efficiently coupling of sensitive vinyl triflates and 1-alkyne [13], we firstly tested this reaction using the above said triflate **1a** and but-3-yn-1-ol **2a** in DMF under nitrogen in the presence of $Pd(PPh_3)_2Cl_2$ using silver iodide as a co-catalyst. We were delighted to find that $Pd(PPh_3)_2Cl_2$/AgI catalysts in DMF gave product **3aa** in 78% yield (Table 1, entry 3). This result encouraged us to make a detailed investigation. Therefore, we examined the reaction in the presence of various palladium catalysts such as $PdCl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ using silver iodide as a co-catalyst in the same reaction conditions (Table 1, entries 4–7). It was evident that $Pd(PPh_3)_4$ (5 mol%) was the most effective catalyst for this transformation (85% yield, Table 1, entry 6). It is known that in many reactions catalyzed by Pd catalysts, silver salts were the better co-catalysts such as silver triflate AgOTf [11–13], $AgBF_4$, Ag_2CO_3 and AgOAc. Next, we examined this reaction in the presence of $Pd(PPh_3)_4$ and various other silver salts such as AgBr [14], AgOTf, Ag_2CO_3, and AgOAc similar reaction conditions. The results showed that the $Pd(PPh_3)_4$/AgOTf and $Pd(PPh_3)_4$/AgOAc catalyst systems gave product **3aa** in 96% and 97% yields, respectively (Table 1, entries 9 and 11). Owing to AgOAc being inexpensive, the $Pd(PPh_3)_4$/AgOAc catalyst system was chosen perfectly. However $Pd(PPh_3)_4$/AgBr, $Pd(PPh_3)_4/Ag_2CO_3$ and $Pd(PPh_3)_4/AgBF_4$ catalyst systems similar to $Pd(PPh_3)_4$/AgI gave product **3aa** in good yields (Table 1, entries 8, 10 and 12). Subsequently we examined this reaction in the presence of $Pd(PPh_3)_4$ and varied amount of AgOAc. Both decreasing and increasing the amount of AgOAc (Table 1, entries 13–15) somewhat decreased the product yield. The use of a further excess amount of AgOAc (30% equiv.) did not improve the yield (Table 1, entry 15). We also examined various solvents (DMF, THF and MeCN) and bases ($^iPr_2NEt$, Et_3N, pyridine, and K_2CO_3) (Table 1, entries 11, 16–20). Among these tested conditions, $^iPr_2NEt$, Et_3N could promote efficiently this reaction in DMF as solvent in high yield. However, the weak base pyridine and sodium carbonate promoted limitedly this coupling reaction in lower yields (Table 1, entries 19, 20).

These results showed that the experimental procedure for this coupling reaction of 17-steroidal triflates and alkynes was very simple and straightforward. A mixture of triflate compound (1 mmol), 1-alkyne (1.2 mmol) and DIPEA (3.9 mmol) in DMF (20 mL) was stirred at room temperature in the presence of $Pd[(C_6H_5)_3P]_4$ (5 mol%) and AgOAc (20 mol%) for 30 min under nitrogen. The resultant mixture was stirred under nitrogen at room temperature for 30 min. Then after a simple workup the product was directly purified using column chromatography. Following the general reaction conditions, we next examined the scope of this reaction with various 17-steroidal triflates and 1-alkynes, and the results are summarized in Table 2. In general the reaction was proceeded smoothly for various17-steroidal triflates and 1-alkynes to produce the desired D-ring unsaturated 17-alkynylsteroids in excellent yields (86–98%). As illustrated in Scheme 3 and Table 2, the yields of **3aa**–**ce** were not significantly affected by substituents or stereochemistry at C-3, C-5, and C-10 of steroids and by substituents of 1-alkynes.

Encouraged by above investigations, subsequently, we investigated this coupling reaction with estr-16-en-3,17-diyl bistrifluoromethanesulfonate (**5**) and various 1-alkynes in DIPEA and



Scheme 3. $Pd(PPh_3)_4$/AgOAc-catalyzed preparation of 17-alkynylsteroids through corresponding triflates.



Scheme 4. The coupling reaction of estr-16-en-3,17-diyl bistriflate catalyzed by $Pd(PPh_3)_4$/AgOAc or CuI.

DMF in the presence of $Pd[(C_6H_5)_3P]_4$ and AgOAc under nitrogen, the results are presented in Table 3. We were delighted to find that the coupling reaction catalyzed by $Pd[(C_6H_5)_3P]_4$/AgOAc system is selective for aryl triflates or vinyl triflates. By optimizing the reaction conditions, the sole C17-coupling products **6a–e** (Scheme 4, Table 3) were obtained in satisfactory yields. It was observed that the selective coupling reaction of steroidal bistriflates is quite temperature and reaction time dependent, and higher reaction temperature (80 °C) and shorter reaction time (15 min) are recommended so that the coupling reactions occur quickly in a short time. However, the coupling reaction from bistriflate **5** and 2-methylbut-3-yn-2-ol by $Pd[(C_6H_5)_3P]_4$/CuI system gave the desired 3,17-dialkynyl steroid 7 at 120 °C for 2 h (Scheme 3). Next, under the same reaction conditions, 3,17-dialkynyl steroid **8** was yielded in 84% from triflate **6e** and 1-ethynyl-4-methoxybenzene.

4. Conclusion

In summary, we have successfully developed a novel and operationally simple coupling reaction for highly efficient synthesis of D-ring unsaturated 17-alkynylsteroids by employing 17-steroidal triflates and alkynes using a new $Pd[(C_6H_5)_3P]_4$/AgOAc system. Interestingly, we found that the coupling reaction catalyzed by $Pd[(C_6H_5)_3P]_4$/AgOAc system is selective for vinyl triflates over aryl triflates, the sole C17-coupling products were obtained from 3,17-bistriflate of estrogen and 1-alkyne in higher temperature (80 °C) and shorter reaction time (15 min). This general method provides high yield access to D-ring unsaturated 17-alkynylsteroids compounds which are key intermediates for the preparation of some biologically important modified 17-side chain steroids and structurally related fused pentacyclic steroids.

Acknowledgements

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