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Benzothieno and benzofurano annelated estranes

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Abstract

The preparation of estrone derived benzothieno- and benzofurano fused steroids is described. Keystep is an intramolecular thienyl(/furyl)-ene-yne cyclization of 16-ethynyl-17-heterarylestra-1,3,5(10),16-tetraenes. The cyclization was carried out under Pt as well as under Ru catalysis.

Keywords: Synthesis; Estranes; Fused steroids; Heteroaryl-ene-ynes; Diene-ynes; Cyclization

1. Introduction

Recently, a number of ring annelated estranes have been synthesized. They include compounds with a heterocyclic as well as compounds with a carbocyclic E-ring, where the ring annelation has been fused to positions 16,17. Some of these pentacyclic molecules such as cyclopentano- and cyclohexano annelated 3,17β-estradiols, had a good binding affinity to the human estradiol or progesterone receptors and have been advanced as inhibitors of osteoporosis [1]. Ring annelation has been used to link bioactive molecules to estranes such as in the case of the synthesis of estrarubincin, which is a hybrid of estrane and anthraquinone [2]. Moreover, 16,17-ring annelated estranes have been used as key intermediates in the synthesis of natural occurring pentacyclic triterpenoids such as of alnusenone [3]. The routes to these ring annelated steroids have been many-fold and include Robinson annelation [4,5] for cyclohexeno-estranes and the intermolecular Diels Alder reaction with the steroid as diene [2] and, in the case of pyrazolo- and oxazoloestranes, intermolecular 1,3-dipolar cycloaddition reactions of estra-1,3,5(10),16-tetraenes [6] and intramolecular 1,3-dipolar cycloaddition reactions of tricyclic secosteroids [7,8]. Ring annelations at C-16,C-17 in steroids in the non-estrane series, were obtained through intermolecular Diels Alder reactions using the steroid as the ene component [9,10], through a combination of Heck reaction and triene cyclization [11–13]. From our previous experience, however, intermolecular reactions with estra-1,3,5(10),16-tetraenes, in which two bonds are formed, often proceed sluggishly. Thus, the 16,17-olefinic moiety often needs to be activated, especially in cycloaddition reactions. Combinations of Heck reactions with an intramolecular cyclization often suffer from low yields as the temperatures needed for the Heck reaction often induce the cyclization as follow-up reactions, but often without allowing for a completion of the second reaction. Furthermore, partial double bond migration within the newly formed ring system under the reaction conditions often leads to a number of isomeric by-products. In the following, the authors present a novel ring annelation procedure for steroids, which relies on a Suzuki reaction, but potentially can be expanded to other C–C bond forming reactions, in combination with the generally little known heteroaryl-ene-yne cyclization, closely related to the diene-yne cyclization, as the key step of the synthesis. Here, this procedure is used for the preparation of a number of novel 16,17-benzofurano- and benzothieno-annelated estranes.

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2. Experimental

Starting material estrone (**1**) (Wako Pure Chemical Industries Ltd.) was used as purchased. 3-*O*-Methylestrone (**2a**) (KOH, MeI, DMSO [14]), 3-*O*-benzylestrone (**2b**) (BnBr, NaH, dry DMF [15]), 16-hydroxymethylene-3-*O*-methylestrone (**3a**), 16-hydroxymethylene-3-*O*-benzylestrone (**3b**) (HCO_2Et, NaOMe, dry benzene [16]) and 17-bromo-16-formyl-estra-1,3,5(10),16-tetraen-3-ol (**9**) [17] were synthesized by procedures anaologous to ones found in the literature. Bis(η^6-*p*-cymene-dichlororuthenium) was synthesized according to the literature [18]. Ruthenium(III)chloride (Kishida), phellandrene (TCI) and NH_4PF_6 (Aldrich) were used as purchased. Anhydrous THF (stabilizer-free, KANTO) and anhydrous diethyl ether (KANTO) were used as purchased. Benzene, dichloromethane and dimethylformamide were dried over CaH_2. Ethyl formate was distilled over phosphorous pentoxide. Melting points were measured on a Yanaco microscopic hotstage and are uncorrected. IR spectra were measured with JASCO IR-700 and Nippon Denshi JIR-AQ2OM machines. ^1H and ^{13}C NMR spectra were recorded with a JEOL EX-270 (^1H at 270 MHz and ^{13}C at 67.8 MHz) and JEOL Lambda 400 spectrometer (^1H at 395 MHz and ^{13}C at 99.45 MHz). The chemical shifts are relative to TMS (solvent $CDCl_3$, unless otherwise noted). Mass spectra were measured with a JMS-01-SG-2 spectrometer [electron impact mode (EI), 70 eV or fast atom bombardment (FAB)]. Column chromatography was carried out on Wakogel 300.

*2.1. 16-tert-Butoxymethylene-3-methoxyestra-1,3,5(10)-trien-17-one (**4a**)—general procedure A*

Hydroxymethylene ketone **3a** (14.04 g, 45 mmol) was added to a solution of *p*-TsOH–H_2O (425 mg, 2.23 mmol) and *tert*-BuOH (31 mL, 329 mmol) in benzene (200 mL). The solution was heated under reflux with the water formed distilled azeotropically and collected in a Dean–Stark condenser. After the reaction was complete, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with a conc. aqueous $NaHCO_3$ solution (100 mL) and then with water (3 × 200 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography on silica gel (hexane:ether:CH_2Cl_2 = 2:1:1) to give **4a** (11.08 g, 67%) as colorless prisms, mp: 149–151 °C; IR (KBr): 2926, 2853, 1712, 1637, 1574, 1496, 1464, 1425, 1371, 1278, 1256, 1246, 1201, 1154, 1128, 1101, 1052, 989, 965, 900, 872, 813 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ_H 0.92 (s, 3H, CH_3, C-18), 1.32–2.40 (m, 19H), 2.66 (dd, 1H, ^3J 14.7Hz, ^4J 6.1Hz), 2.88–2.93 (m, 2H), 3.78 (s, 3H, OCH_3), 6.64 (d, 1H, ^4J 2.6Hz, C-4), 6.72 (dd, 1H, ^3J 8.6Hz, ^4J 2.6Hz, C-2), 7.21 (d, 1H, ^3J 8.6, C-1), 7.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.7, 24.7, 26.1, 26.8, 28.3, 29.7, 31.6, 37.9, 44.1, 48.7, 48.9, 55.2, 111.5, 113.9, 115.5, 126.3, 132.4, 137.8, 148.4, 157.5, 210.4; MS (70 eV): *m*/*z* (%) 368 (M^+, 70), 312 (100), 227 (86), 160 (55); HRMS found: 368.2347 calcd. for $C_{24}H_{32}O_3$: 368.2347; anal. calcd. for $C_{24}H_{32}O_3$: C 78.22, H 8.75; found: C 78.07 H 8.76.

*2.2. 3-Benzyloxy-16-tert-butoxymethylene-estra-1,3,5(10)-trien-17-one (**4b**)*

Hydroxymethylene ketone **3b** (10.0 g, 25.8 mmol) was reacted with *p*-TsOH–H_2O (245 mg, 1.29 mmol) and *tert*-BuOH (18 mL, 190 mmol) in benzene (100 mL) according to general procedure A. Column chromatography of the crude material on silica gel (hexane:ether:CH_2Cl_2 = 2:1:1) gave **4b** as colorless prisms (9.31 g, 81%); mp: 163–165 °C; IR(KBr): 3062, 3029, 2976, 2936, 2858, 1711, 1636, 1604, 1500, 1454, 1371, 1310, 1285, 1263, 1234, 1161, 1126, 1089, 1055, 1036, 993, 960, 914, 885, 860, 841, 820, 732, 693, 650 cm^{-1}; ^1H NMR (270MHz, $CDCl_3$): δ_H 0.92(s, 3H, CH_3, C-18), 1.27–1.63 (m, 15H), 1.97–2.11 (m, 3H), 2.27–2.39 (m, 2H), 2.66 (dd, 1H, *J* 14.9 Hz, *J* 5.9 Hz), 2.87–2.92 (m, 2H), 5.03 (s, 2H, $PhCH_2O$), 6.73 (d, 1H, ^4J 2.5 Hz, C-4), 6.78 (dd, 1H, ^3J 8.4 Hz, ^4J 2.5 Hz, C-2), 7.20 (d, 1H, ^3J 8.4 Hz, C-1), 7.26–7.53 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.7, 24.7, 26.0, 26.8, 28.3, 29.7, 31.6, 37.9, 44.1, 48.7, 48.9, 70.0, 79.6, 112.3, 114.9, 115.5, 126.3, 127.4, 127.8, 128.5, 132.7, 137.3, 137.9, 148.4, 156.8, 210.4; MS (FAB, 3-nitrobenzyl alcohol): *m*/*z* (%) 445 (MH^+, 27), 444 (M^+, 17), 443 ($M^+ - 1$, 5); HRMS found: 445.2740 calcd. for $C_{30}H_{37}O_3$: 445.2743; anal. calcd. for $C_{30}H_{36}O_3$: C 81.04, H 8.16; found: C 81.10 H 8.12.

*2.3. 16-Formyl-3-methoxy-17-(thien-2′-yl)-estra-1,3,5(10),16-tetraene (**6a**)—general procedure B*

To a solution of 2-bromothiophene (0.77 mL, 8 mmol) in dry ether (20 mL) was added a solution of *n*-butyllithium in pentane (1.6 M, 5 mL) at −78 °C under an argon atmosphere. After 1 h at −78 °C, the solution was stirred for 30 min at 0 °C. Then, the pale yellow solution was cooled to −78 °C, and a solution of **4a** (1.47 g, 4 mmol) in THF (30 mL) was added and the resulting mixture was stirred at −0 °C for 5 h. Then, to the reaction mixture was added water (5 mL) and *p*-toluenesulfonic acid (1.52 g, 8 mmol) and the resulting reaction solution was stirred for 15 h. After the reaction was complete, the solution was poured into aqueous sodium bicarbonate solution (40 mL) and extracted with dichloromethane (3 × 60 mL. The organic phase dried over $MgSO_4$ and concentrated in vacuo. The residue was subjected to column chromatography on silica gel (hexane:ether:dichloromethane = 4:1:1) to give **6a** (1.22 g, 81%) as a greenish yellow powder; IR (KBr): 3074, 3032, 2928, 2901, 2846, 1650, 1617, 1573, 1496, 1457, 1431, 1376, 1319, 1279, 1250, 1227, 1168, 1123, 1091, 1017, 864, 939, 816, 787, 754, 735, 714, 698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ_H 1.09 (s, 3H, CH_3, C-18), 1.20–2.44 (m, 10H), 2.74–2.96 (m, 3H), 3.78 (s, 3H, OCH_3), 6.65 (d, 1H, ^4J 2.5Hz, C-4), 6.71 (d.d., 1H, ^3J 8.4 Hz, ^4J 2.6 Hz, C-2), 7.10–7.20

(m, 3H, ArH), 7.48 (d, 1H, ^3J 4.9 Hz), 9.93 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 16.5, 26.4, 27.5, 29.3, 29.6,34.6, 37.4, 43.9, 51.5, 54.0, 55.2, 111.6, 113.8, 125.9, 127.4, 128.2, 129.9, 132.2, 133.8, 137.9, 140.3, 157.6, 164.5, 190.6; MS (70 eV): *m/z* (%) 378 (M^+, 100); HRMS found: 378.1653, calcd. for $C_{24}H_{26}O_2S$: 378.1654; anal. calcd. for $C_{24}H_{26}O_2S + 0.1H_2O$: C 75.79, H 6.94; found: C 75.72, H 6.98.

2.4. 16-Formyl-17-(2′-furyl)-3-methoxyestra-1,3,5(10), 16-tetraene (**6b**)

Furan (1.5 mL, 20 mmol) in dry THF (20 mL) was reacted with *tert*-butyllithium in pentane (1.47 M, 13 mL) and then with a solution of **4a** (1.47 g, 4 mmol) in dry THF (20 mL) according to general procedure B, using the reaction times given in the preparation of **6a**. Subsequently water (5 mL) and *p*-toluensulfonic acid (1.52 g, 8 mmol) were added, the mixture was stirred for 24 h and then subjected to a work-up according to general procedure B. The crude material was subjected to column chromatography on silica gel (hexane:ether:dichloromethane = 5:1:1) to give **6b** (948 mg, 65%) as colorless prisms; mp: 193–194 °C; IR (KBr): 3115, 2988, 2933, 2853, 1644, 1612, 1586, 1497, 1463, 1327, 1281, 1255, 1233, 1151, 1126, 1038, 883, 871, 779, 761, 746 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ_H 1.11 (s, 3H, CH_3, C-18), 1.42–2.02 (m, 6H), 2.17–2.46 (m, 4H), 2.75–2.95(m, 3H), 3.79 (s, 3H, OCH_3), 6.53 (dd, 1H, ^3J 1.8 Hz, ^3J 3.3 Hz), 6.65 (d, 1H, ^4J 2.6 Hz, C-1), 6.72 (dd, 1H, ^3J 8.6 Hz, ^4J 2.6 Hz, C-2), 7.89 (d, 1H, ^3J 8.7Hz, C-3), 7.59 (d, 1H, ^3J 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 16.8, 26.6, 27.4, 29.4, 29.6, 35.3, 37.2, 43.8, 50.3, 53.8, 55.2, 111.6, 111.8, 113.5, 113.8, 124.7, 125.9, 137.8, 137.9, 144.8, 149.5, 156.1, 157.6, 191.8; MS (70eV): *m/z* (%) 363 (MH^+, 26), 262 (M^+, 100), 347 ($M^+ - 15$, 5); HRMS found: 362.1884 calcd. for $C_{24}H_{26}O_3$: 362.1882; anal. calcd. for $C_{24}H_{26}O_3$: C 79.53, H 7.23; found: C 79.29, H 7.25.

2.5. 3-Benzyloxy-16-formyl-17-(2-thienyl)-estra-1,3,5(10),16-tetraene (**6c**)

2-Bromothiophene (1.6 mL, 16 mmol) in dry THF (20 mL) was reacted with *n*-butyllithium in pentane (1.6 M, 10 mL) and then with a solution of **4b** (3.56 g, 8 mmol) in dry THF (40 mL) according to general procedure B, using the reaction times given for the preparation of **6a**. Then, water (5 mL) and *p*-toluenesulfonic acid (7.61 g, 40 mmol) were added, the resulting mixture was stirred for 25 h and thereafter subjected to a work-up according to general procedure B. Column chromatography of the crude material on silica gel (hexane:ether:dichloromethane = 5:1:1) gave **6c** (2.98 g, 82%) as a yellow powder; mp: 167–168 °C; IR(KBr): 3075, 3032, 2928, 2901, 2846, 1650, 1610, 1573, 1496, 1457, 1431, 1376, 1319, 1279, 1250, 1227, 1168, 1123, 1091, 1017, 864, 839, 816, 787, 754, 735, 714, 698 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ_H 1.12 (s, 3H, C-18, CH_3), 1.47–2.46 (m, 10H), 2.76–2.97 (m, 3H), 5.06 (s, 2H, OCH_2Ph), 6.77 (d, 1H, ^4J 2.5Hz, C-4), 6.80 (dd, 1H, ^3J 8.5Hz, ^4J 2.5Hz, C-2), 7.13–7.51(m, 6H, C-1 and Ph), 9.95 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.5, 26.4, 27.5, 29.3, 29.6, 34.6, 37.4, 43.9, 51.5, 54.0, 70.0, 112.4, 114.9, 126.0, 127.4, 127.4, 127.9, 128.2, 128.6, 129.9, 132.5, 133.8, 137.3, 137.9, 140.4, 156.9, 164.5, 190.7; MS (FAB, 3-nitrobenzyl alcohol): *m/z* (%) 455 (MH^+, 44.1), 454 (M^+, 31.89); HRMS found: 455.2043, calcd. for $C_{30}H_{31}O_2S$: 455.2045; anal. calcd. for $C_{30}H_{31}O_2S$: C 79.26, H 6.65; found: C 79.04, H 6.63.

2.6. 17-(Benzothien-2′-yl)-3-benzyloxy-16-formyl-estra-1,3,5(10),16-tetraene (**6d**)

Benzothiophene (1.9 mL, 16 mmol) in dry Et_2O (40 mL) was reacted with *n*-butyllithium in pentane (1.6 M, 10 mL) and thereafter with a solution of **4b** (3.56 g, 8 mmol) in dry THF (20 mL) according to general procedure B. Thereafter, water (5 mL) and *p*-toluenesulfonic acid (4.57 g, 24 mmol) were added, the mixture was stirred for 25 h and subjected to work-up according to general procedure B. The crude material was separated by column chromatography on silica gel (hexane:ether:dichloromethane = 5:1:1) to give **6d** (3.42 g, 85%) as a yellow powder; mp: 162–168 °C; IR (KBr): 2924, 1656, 1608, 1573, 1497, 1454, 1377, 1281, 1228, 1159, 1024, 860, 837, 781, 748, 696 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ_H 1.15 (s, 3H, CH_3, C-18), 1.26–2.45 (m, 10H), 2.82 (dd, 1H, ^3J 15.6 Hz, ^4J 6.4 Hz), 2.90–2.96 (m, 2H), 5.04 (s, 2H, OCH_2Ph), 6.75 (d, 1H, ^4J 2.6Hz, C-4), 6.79 (dd, 1H, ^3J 8.4 Hz, ^4J 2.8 Hz, C-2), 7.19 (d, 1H, ^3J 8.6 Hz, C-1), 7.29–7.45 (m, 6H), 7.81–7.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 16.5, 26.4, 27.5, 29.4, 29.6, 34.5, 37.4, 44.0, 51.7, 54.1, 70.0, 112.4, 114.9, 120.5, 122.1, 124.0, 124.9, 125.4, 126.0, 126.6, 127.4, 127.9, 128.6, 132.5, 134.1, 137.3, 139.1, 140.8, 141.9, 156.9, 164.8, 190.5; MS (FAB, 3-nitrobenzyl alcohol): *m/z* (%) 505 (MH^+, 6.2), 504 (M^+, 4.8); HRMS found: 505.2198, calcd. for $C_{34}H_{33}O_2S$: 505.2201 (MH^+, FAB); anal. calcd. for $C_{34}H_{32}O_2S$: C 80.91, H 6.39; found: C 80.88, H 6.41.

2.7. 3-Benzoyloxy-16-formyl-17-(thien-2′-yl)-estra-1,3,5(10),16-tetraene (**6e**)—general procedure C

A mixture of bromoaldehyde **9** (183 mg, 0.4 mmol), 2-thienylboronic acid (127 mg, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (15 mg, 0.02 mmol) and PPh_3 (15 mg, 0.06 mmol) in DME (3.5 mL) and 2 M aqueous Na_2CO_3 solution (2.5 mL) was held at 65 °C for 14 h. Thereafter, the cooled solution was poured into water (15 mL) and extracted with chloroform (3 × 15 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was subjected to column chromatography on silica gel (hexane:ether:$CHCl_3$ = 4:1:1) to give **6e** (170 mg, 91%) as pale yellow crystals, mp: 203 °C; IR (KBr): 3078, 2928,

2852, 1734, 1660, 1496, 1452, 1260, 1233, 1219, 1153, 1063, 1024, 709 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ_H 1.11 (s, 3H, CH_3, C-18), 1.56–2.32 (m, 10H), 2.81 (dd, 1H, ^2J 16.5 Hz, ^3J 6.5 Hz), 2.95 (m, 2H), 6.96–7.14 (m, 2H), 7.15–7.19 (m, 2H), 7.33 (d, 1H, ^3J 8.4 Hz), 7.48–7.54 (m, 3H), 7.61 (m, 1H), 8.20 (d, 2H, ^3J 8.1 Hz), 9.94 (s, 1H, CHO); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ_C 16.48, 26.22, 27.28, 29.27, 29.36, 34.52, 36.98, 44.08, 51.45, 53.94, 118.77, 121.74, 126.09, 127.43, 128.27, 128.53, 129.62, 129.93, 130.13, 133.51, 133.75, 137.58, 138.23, 140.26, 148.79, 164.43, 166.01, 190.69; MS (FAB, 3-nitrobenzyl alcohol): *m/z* (%) 469 (4.1, MH^+); HRMS found: 469.1841, calcd. for $C_{30}H_{29}O_3S$: 469.1837 (MH^+, FAB); anal. calcd. for $C_{34}H_{32}O_2S$: C 76.89, H 6.02; found: C 76.55, H 6.02.

*2.8. 3-Benzoyloxy-16-formyl-17-(benzothien-2′-yl)-estra-1,3,5(10),16-tetraene (**6f**)*

A mixture of **9** (189 mg, 0.4 mmol), 2-benzothienylboronic acid (178 mg, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (15 mg, 0.02 mmol) and PPh_3 (15 mg, 0.06 mmol) in DME (3.5 mL) and 2 M aqueous Na_2CO_3 solution (2.5 mL) was held at 65 °C for 14 h. Thereafter, the solution was worked up according to procedure C. Column chromatography of the crude material on silica gel (hexane:ether:$CHCl_3$ = 4:1:1) gave **6f** (155 mg, 75%) as a colorless solid; mp 184 °C; IR (KBr): 2928, 1737, 1662, 1493, 1263, 1216, 1064, 746, 707 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ_H 1.17 (s, 3H, CH_3, C-18), 1.50–2.50 (m, 10H), 2.84 (dd, 1H, ^2J 15.5 Hz, ^3J 6.3 Hz), 2.97 (m, 2H), 6.97–7.88 (m, 10H), 7.33 (d, 1H, ^3J 8.4 Hz), 8.20 (m, 2H), 9.99 (s, 1H, CHO); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ_C 16.42, 26.21, 27.30, 29.37, 34.44, 36.99, 44.10, 51.60, 54.09, 118.79, 121.75, 122.08, 122.17, 123.71, 123.97, 124.86, 124.92, 125.37, 126.11, 126.71, 127.80, 127.96, 129.62, 130.14, 133.51, 137.53, 138.19, 141.79, 148.81, 164.65, 190.55; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 519 (MH^+, 5.6); HRMS found: 519.1993, calcd. for $C_{34}H_{31}O_3S$: 519.1994; anal. calcd. for $C_{34}H_{30}O_3S$: C 78.73, H 5.83; found: C 78.73, H 5.83.

*2.9. 3-Benzoyloxy-16-formyl-17-(fur-2′-yl)-estra-1,3,5(10),16-tetraene (**6g**)*

A mixture of **9** (83 mg, 0.17[6] mmol), 2-furylboronic acid (88 mg, 0.53 mmol), $Pd(PPh_3)_2Cl_2$ (10 mg, 0.013 mmol) and PPh_3 (10 mg, 0.04 mmol) in DME (2.5 mL) and 2 M aqueous Na_2CO_3 solution (2.0 mL) was held at 65 °C for 14 h. Thereafter, the solution was worked up according to procedure C. Column chromatography of the crude material on silica gel (hexane:ether:$CHCl_3$ = 4:1:1) gave **6g** (20 mg, 25%) as a colorless solid; mp 185 °C; IR (KBr) 2920, 2854, 1737, 1652, 1492, 1256, 1233, 1214, 1060, 1023, 756, 713 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ_H 1.12 (s, 3H, CH_3, C-18), 1.50–2.50 (m, 10H), 2.82 (dd, 1H, ^2J 15.5 Hz, ^3J 6.3 Hz), 2.95 (m, 2H), 6.54 (dd, 1H, ^3J 3.8 Hz, ^4J 1.6 Hz), 6.78 (d, 1H, ^3J 3.8 Hz), 6.95–7.01 (m, 2H), 7.32 (d, 1H, ^3J 8.4 Hz), 7.48–7.64 (m, 4H), 8.20 (m, 2H), 10.40 (s, 1H, CHO); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ_C 16.79, 26.41, 27.22, 29.36, 35.23, 36.81, 43.93, 50.20, 53.75, 111.85, 113.51, 118.76, 121.73, 126.08, 128.52, 129.63, 130.13, 133.50, 137.58, 137.70, 138.25, 144.85, 148.79, 149.40, 156.02, 165.50, 191.83; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 453 (MH^+, 23.5); HRMS found: 453.2069, calcd. for $C_{30}H_{29}O_4$: 453.2066; anal. calcd. for $C_{30}H_{28}O_4$: C 79.62, H 6.24; found: C 79.54, H 6.12.

*2.10. 16-Formyl-17-(thien-2′-yl)-estra-1,3,5(10),16-tetraen-3-ol (**10**)*

A solution of **6e** (38 mg, 0.08 mmol) and NaOMe (30 mg, 0.55 mmol) in a mixture of MeOH (5 mL), THF (5 mL) and water (1 mL) was held at reflux for 5 h. Thereafter, the cooled solution was acidified with conc. HCl, diluted with water (10 mL) and extracted with chloroform (3 × 15 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was subjected to column chromatography on silica gel (chloroform:Et_2O = 1:1) to give **10** (21 mg, 71%) as a colorless solid; mp: 207 °C; IR (KBr) 3354 (s, OH), 2924, 2850, 1639, 1581, 1501, 1450, 1231, 1174 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ_H 1.10 (s, 3H, CH_3, C-18), 1.40–2.44 (m, 10H), 2.78 (dd, 1H, ^2J 15.5 Hz, ^3J 6.6 Hz), 2.89 (m, 2H), 4.62 (bs, 1H, OH), 6.60 (dd, 1H, ^3J 8.4 Hz, ^4J 2.7 Hz), 6.65 (d, 1H, ^4J 2.7 Hz), 7.11–7.18 (m, 3H), 7.49 (m, 1H), 9.93 (s, 1H, CHO); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ_C 16.51, 26.38, 27.40, 29.26, 29.41, 34.53, 37.30, 43.86, 51.51, 53.91, 112.76, 115.33, 120.89, 126.17, 127.41, 128.24, 129.91, 132.28, 138.19, 140.29, 153.43, 164.60, 190.72; MS (FAB, 3-nitrobenzyl alcohol): *m/z* (%) 365 (MH^+, 15.4). HRMS found: 365.1572, calcd. for $C_{23}H_{25}O_2S$: 365.1575 (MH^+, FAB).

*2.11. 16-(2′,2′-Dibromoethenyl)-3-methoxy-17-(thien-2″-yl)estra-1,3,5(10),16-tetraene (**7a**)—general procedure D*

A solution of carbontetrabromide (CBr_4) (995 mg, 3 mmol) in dry CH_2Cl_2 (10 mL) was added to **6a** (757 mg, 2 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was stirred at RT for 17 h. Then it was poured into water (40 mL) and extracted with CH_2Cl_2 (100 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography on silica gel (hexane:ether = 4:1) to give **7a** (632 mg, 58%) as colorless prisms; mp: 153–157 °C; $[\alpha]_D$ = +130° (chloroform, *c* = 0.02); IR (KBr): 3104, 3004, 2987, 2926, 2880, 2851, 1606, 1572, 1497, 1459, 1425, 1277, 1256, 1230, 1155, 1123, 1038, 870, 821, 799, 781, 705 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ_H 0.96 (s, 3H, CH_3, C-18), 1.46–1.78 (m, 6H), 1.99–2.11 (m, 2H), 2.30–2.42 (m, 2H), 2.57 (dd, 1H, ^3J 15.6 Hz, ^4J 10.5 Hz), 2.90–3.02 (m, 3H), 3.78 (s, 3H, OCH_3), 6.65 (d, 1H, ^4J 2.6Hz, C-4), 6.72 (dd, 1H, ^3J 8.6 Hz, ^4J 2.8 Hz, C-2), 6.98 (dd, 1H,

^3J 3.6 Hz, ^4J 1.2 Hz), 7.08 (dd, 1H, ^3J 5.1 Hz, ^3J 3.6 Hz), 7.19 (d, 1H, ^3J 8.6 Hz, C-1), 7.35–7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 16.2, 26.5, 27.7, 29.7, 33.6, 35.2, 37.4, 44.0, 49.2, 54.8, 55.2, 88.4, 111.5, 113.8, 126.0, 126.1, 127.0, 127.7, 132.6, 134.6, 135.6, 136.4, 137.8, 150.2, 157.5; MS (FAB, 3-nitrobenzyl alcohol): *m/z* (%) 536 ($^{81}Br_2M^+$, 0.98), 534 (^{79}Br–$^{81}BrM^+$, 1.54); HRMS found: 534.0051 calcd. for $C_{25}H_{26}OS^{79}Br^{81}Br$: 534.0052; anal. calcd. for $C_{25}H_{26}OSBr_2$: C 56.19, H 4.90; found: C 56.38, H 4.99.

*2.12. 16-(2′,2′-Dibromoethenyl)-17—(fur-2″-yl)-3-methoxyestra-1,3,5(10),16-tetraene (**7b**)*

CBr_4 (2.59 g, 7.81 mmol) and PPh_3 (4.09 g, 15.6 mmol) in dry CH_2Cl_2 (15 mL) was allowed to react (17 h, RT) with **6b** (558 mg, 1.56 mmol) in CH_2Cl_2 (10 mL) according to general procedure D. Column chromatography of the crude on silica gel (ether:hexane = 1:4) gave **7b** (227 mg, 28%) as colorless prisms. The product decomposes quickly and must be used for the next step as soon as possible. ^{1}H NMR (270 MHz, $CDCl_3$): δ_H 1.00 (s, 3H, CH_3, C-18), 1.43–2.57 (m, 10H), 2.89–2.99 (m, 3H), 3.78 (s, 3H, OCH_3), 6.35–6.39 (m, 1H), 6.44 (d, 1H, ^4J 1.0 Hz), 6.65 (d, 1H, ^4J 2.6Hz, C-4), 6.72 (dd, 1H, ^3J 8.7Hz, ^4J 2.5Hz, C-2), 7.20 (d, 1H, ^3J 8.6Hz, C-1), 7.49–7.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 16.4, 26.6, 27.7, 29.7, .30.9, 33.8, 35.5, 37.2, 43.9, 48.3, 54.9, 89.2, 110.6, 111.2, 111.5 112.9, 113.8, 126.0, 133.5, 134.6, 135.0, 137.8, 142.5, 152.7, 157.5; MS (FAB, 3-nitrobenzyl alcohol): *m/z* (%) 520 ($^{81}Br_2M^+$, 2), 518 (^{79}Br–$^{81}BrM^+$, 3), ($^{79}Br_2M^+$, 52); HRMS found: 518.0285, calcd. for $C_{25}H_{26}O_2$:$^{79}Br^{81}Br$: 518.0281.

*2.13. 3-Benzyloxy-16-(2′,2′-dibromoethenyl)-17-(thien-2″-yl)estra-1,3,5(10),16-tetraene (**7c**)*

A solution of CBr_4 (9.95 g, 30 mmol) and PPh_3 (15.73 g, 60 mmol) in CH_2Cl_2 was allowed to react (RT, 17 h) with **6c** (757 mg, 2 mmol) in CH_2Cl_2 (150 mL combined volume) and worked up according to general procedure D. The crude material was subjected to column chromatography on silica gel (hexane:ether = 4:1) to give **7c** (2.55 g, 70%) as yellow prisms; mp: 144–152 °C; $[\alpha]_D$ = +135° (chloroform, c = 0.02); IR (KBr): 3102, 3030, 2992, 2929, 2854, 1606, 1573, 1542, 1498, 1453, 1427, 1372, 1280, 1234, 1171, 1122, 1027,820, 797, 732, 711, 692, 669, 652 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ_H 0.99 (s, 3H, CH_3, C-18), 1.48–1.86 (m, 5H), 2.02–2.19 (m, 2H), 2.32–2.43 (m, 2H), 2.58 (dd, 1H, ^2J 15.4 Hz, ^3J 11.4 Hz), 2.91–3.04 (m, 3H), 5.06 (s, H, OCH_2), 6.76 (d, 1H, ^4J 2.6 Hz, C-4), 6.81 (dd, 1H, ^3J 8.5 Hz, ^4J 2.6 Hz, C-2), 7.00 (d, 1H, ^3J 3.5 z), 7.09 (dd, 1H, ^3J 5.1 Hz, ^4J 3.6 Hz), 7.21(d, 1H, ^3J 8.6 Hz, C-1), 7.28–7.46 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 16.2, 26.5, 27.7, 29.7, 33.6, 35.2, 37.4, 44.1, 49.2, 54.8, 70.0, 88.4, 112.3, 114.9, 126.0, 126.1, 127.0, 127.4, 127.7, 127.8, 128.5, 132.9,134.7, 135.6, 136.4, 137.3, 137.9, 150.2, 156.8; MS (FAB, 3-nitrobenzyl alcohol): *m/z* (%) 612 ($^{81}Br_2M^+$, 2), 610 (^{79}Br–^{81}Br M^+, 2), 608 ($^{79}Br_2M^+$, 1). HRMS found: 610.0370; calcd. for $C_{31}H_{30}O^{79}Br^{81}Br$: 608.0366; anal. calcd. for $C_{31}H_{30}OBr_2$: C 60.99, H 4.96; found: C 60.83, H 5.05.

*2.14. 17-(Benzothien-2′-yl)-3-benzyloxy-16-(2″,2″-dibromoethenyl)-estra-1,3,5(10),16-tetraene (**7d**)*

A solution of CBr_4 (2.49 g, 7.5 mmol) in CH_2Cl_2 (30 mL) was (RT, 20 h) was allowed to react with a solution of triphenylphosphine (3.93 g, 15 mmol) and steroid **6d** (2.52 g, 5 mmol) in CH_2Cl_2 (30 mL) and worked-up according to general procedure D (RT, 20 h). The crude material was subjected to column chromatography on silica gel (hexane:ether = 10:1) to give **7d** (2.03 g, 61.5%) as a light brown solid; mp: 86–88 °C; IR (KBr) 3058, 3030, 2924, 2852, 1605, 1574, 1497, 1454, 1432, 1373, 1311, 1281, 1229, 1156, 1135, .1109, 1026, 934, 901, 857, 815, 795, 745, 726, 695, 652 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ_H 1.04 (s, 3H, CH_3, C-18), 1.44–1.84 (m, 5H), 2.01–2.15 (m, 2H), 2.27–2.42 (m, 2H), 2.56–2.66 (m, 1H), 2.91–3.09 (m, 3H), 5.05 (s, 2H, $OC\underline{H}_2Ph$), 6.75 (d, 1H, ^4J 2.6 Hz, C-3), 6.79 (dd, 1H, ^3J 8.6 Hz, ^4J 2.8 Hz, C-2), 7.18–7.21 (m, 2H, C-1 and ArH), 7.29–7.46 (m, 8H), 7.79–7.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 16.2, 26.5, 27.7, 29.6, 33.7, 35.2, 37.3, 44.0, 49.3, 54.9, 70.0, 89.1, 114.8, 115.0, 122.0, 123.5, 124.2, 124.3, 124.4, 126.0, 126.0, 127.4, 127.8, 128.5, 132.8, 134.3, 134.4, 136.9, 137.2, 137.3, 137.9, 139.5, 140.3, 150.4, 156.8; MS (FAB, 3-nitrobenzyl alcohol): *m/z* (%) 661 (MH^+, 7), 660 (M^+, 7).

*2.15. 16-Ethynyl-3-methoxy-17-(thien-2′-yl)-estra-1,3,5(10),16-tetraene (**8a**)*

A solution of *n*-butyllithum in pentane (1.58 M, 2 mL) was added to **7a** (534 mg, 1 mmol) in dry THF (15 mL) at −78 °C under an argon atmosphere and the resulting mixture was stirred for 5 h at −78 °C. To the green solution was added water (5 mL) and it was warmed to RT. After 30 min, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography on silica gel (hexane:ether = 4:1) to give **8a** (322 mg, 86%) as colorless prisms; mp: 152–155 °C (dec); $[\alpha]_D$ = +50° (chloroform, c = 0.02); IR (KBr): 3271, 2933, 2873, 1612, 1574, 1497, 1456, 1376, 1281, 1255, 1152, 1125, 1049, 867, 843, 816, 788, 712, 650, 611 cm^{-1}; ^{1}H NMR (395 MHz, $CDCl_3$) δ_H 1.09 (s, 3H, CH_3, C-18), 1.45–1.96 (m, 7H), 2.29–2.54 (m, 4H), 2.89–2.94 (m, 2H), 3.44 (s, 1H, alkyne), 3.79 (s, 3H, OCH_3), 6.65 (d, 1H, ^4J 2.9Hz, C-4), 6.72 (dd, 1H, ^3J 8.5Hz, ^4J 2.6Hz, C-2), 7.06 (dd, 1H, ^3J 5.1Hz, ^3J 3.9Hz), 7.20 (d, 1H, ^3J 8.8 Hz), 7.30 (dd, 1H, ^3J 4.9 Hz, ^4J 1.0 Hz), 7.59 (dd, 1H, ^3J 3.9Hz, ^4J 1.0Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 16.1, 26.6, 27.5, 29.6, 35.7, 37.0, 37.2, 43.8, 49.6, 54.9, 55.2,

82.9, 85.0, 111.5, 113.8, 116.7, 125.1, 126.0, 126.4, 126.7, 132.4,137.3, 137.9, 153.0, 157.6; MS (FAB, 3-nitrobenzyl alcohol): *m/z* (%) 375 (MH^+, 13), 374 (M^+, 16); HRMS found: 374.1708, calcd. for $C_{25}H_{26}OS$: 374.1704; anal. calcd. for $C_{25}H_{26}OS$; C 80.17, H 7.00; found: C 80.08, H 7.14.

*2.16. 16-Ethynyl-17-(fur-2′-yl)-3-methoxyestra-1,3,5(10),16-tetraene (**8b**)*

n-BuLi (1.58 M in pentane, 1.5 mL) was added to **7b** (196 mg, 0.38 mmol) in dry THF (5 mL) at −78 °C. After 4 h, water (1mL) was added and the temperature was raised to RT. The solution was diluted with CH_2Cl_2 (40 mL) and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and was concentrated in vacuo. The residue was subjected to column chromatography on silica gel (hexane:ether = 4:1) to give **8b** (96 mg, 71%) as a colorless solid; mp: 149–153 °C; $[\alpha]_D$ = +20° (chloroform, *c* = 0.02); IR (KBr): 3257, 2926, 2854, 1606, 1498, 1463, 1371, 1310, 1287, 1236, 1160, 1033, 934, 897, 856, 795, 751, 630, 595 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ_H 1.06 (s, 3H, CH_3, C-18), 1.26–2.55 (m, 11H), 2.88–2.94 (m, 2H), 3.49 (s, 1H, alkyne), 3.78 (s, 3H, OCH_3), 6.46 (dd, 1H, ^3J 3.5Hz, ^4J 1.8 Hz), 6.55 (d, 1H, ^4J 2.6 Hz, C-4), 6.72 (dd, 1H, ^3J 8.5 Hz, ^4J 2.6 Hz, C-2), 7.06 (d, 1H, ^3J 3.3 Hz), 7.20 (d, 1H, ^3J 8.3 Hz, C-1), 7.41(d, 1H, ^3J 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 16.2, 26.6, 27.6, 29.7, 35.6, 36.9, 37.1, 44.0, 48.8, 54.8, 55.2, 82.7, 84.8, 110.1, 111.3, 111.5, 113.8, 114.9, 126.0, 132.6, 137.8, 141.3, 149.2, 151.2, 157.5; MS (FAB, 3-nitrobenzyl alcohol): *m/z* (%) 359 (MH^+, 16), 358 (M^+, 22); HRMS (FAB) found: 358.1932, calcd. for $C_{25}H_{26}O_2$: 358.1933.

*2.17. 3-Benzyloxy-16-ethynyl-17-(thien-2′-yl)estra-1,3,5(10),16-tetraene (**8c**)*

A solution of CH_3Li in dry diethyl ether (1.19 M, 7.35 mL, 8.1 mmol) was added to **7c** (1.23 g, 2.02 mmol) in dry THF (30 mL) at −78 °C under an argon atmosphere. After 5 h, the solution was quenched with water (5 mL). The temperature was raised to RT and the solution was diluted with CH_2Cl_2 (100 mL). The solution was washed with water (2 × 100 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography on silica gel (hexane:ether = 10:1) to give **8c** (790 mg, 87%) as pale yellow needles; mp 101 °C (dec); $[\alpha]_D$ = +25° (chloroform, *c* = 0.02); IR (KBr): 3279, 3032, 2928, 2854, 1606, 1574, 1497, 1454, 1375, 1281, 1233, 1159, 1026, 842, 794, 733, 696, 634 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ_H 1.09 (s, 3H, C-18), 1.48–1.90 (m, 6H), 2.33–2.53 (m, 5H), 2.88–2.94 (m, 2H), 3.43 (s, 1H, alkyne), 5.04 (s, 2H, $PhC\underline{H}_2O$), 6.73 (d, 1H, ^4J 2.8Hz, C-4), 6.79 (dd, 1H, ^3J 8.5 Hz, ^4J 2.8 Hz, C-2), 7.05 (dd, 1H, ^3J 5.1 Hz, ^3J 3.8 Hz), 7.19 (d, 1H, ^3J 8.2Hz, C-1), 7.28–7.45 (m, 5H), 7.58 (dd, 1H, ^3J 3.8 Hz, ^4J 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 16.1, 26.7, 27.5, 29.7, 35.7, 37.0 37.2, 43.9, 49.6, 54.9, 70.0, 82.9, 85.1, 112.7, 114.8, 115.0 116.7, 125.1, 126.0, 126.4, 126.7, 127.5, 128.6, 132.8, 137.4, 137.9, 153.0, 156.9; MS (FAB, 3-nitrobenzylalcohol): *m/z* (%) 451 (MH^+, 2), 450 (M^+, 2); HRMS found: 450.2016, calcd. for $C_{31}H_{30}OS$: 450.2017.

*2.18. 3-Benzyloxy-16-ethynyl-17-(benzothien-2′-yl)-estra-1,3,5(10),16-tetraene (**8d**)*

Dibromide **7d** (119 mg, 0.18 mmol) was added to a solution of tetrabutylammonium fluoride (Bu_4NF) (282 mg, 1.08 mmol) in THF (3.6 mL) and the resulting solution was stirred at RT for 20 h. Thereafter, the reaction mixture was concentrated in vacuo and neutralized with NH_4Cl. Water (10 mL) was added and the mixture was extracted with chloroform (3 × 15 mL), the organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was subjected to column chromatography on silica gel (hexane:ether:$CHCl_3$ = 3:1:1) to give **8d** (57 mg, 63%) with an impurity of the corresponding 16-bromoethynyl derivative (10 mol%); IR (KBr): 3300, 3060, 2930, 2246, 1608, 1500, 1455, 1283, 1250, 1025, 908, 730 cm^{-1}; MS (FAB, 3-nitrobenzyl alcohol): *m/z* (%) 501 (MH^+, 2.9), 500 (M^+, 3.3). HRMS found: 500.2168, calcd. for $C_{35}H_{32}OS$: 500.2174. The material was used immediately for the next step.

*2.19. 3-Methoxyestra-1,3,5(10),16-tetraeno[17,16-g]-1-thianaphthene (**11a**)*

Acetylene **8a** (318 mg, 0.85 mmol) was added to Ru(*p*-cymene)Cl_2PPh_3 (24.2 mg, 42.6 μmol) and NH_4PF_6 (13.9 mg, 85.3 μmol) in dry CH_2Cl_2 (11 mL). The solution was heated at 45 °C for 24 h under an Ar atmosphere. After the reaction, the mixture was subjected to column chromatography on silica gel (hexane:ether = 4:1) to give **11a** (312 mg, 98%) as a pale yellow solid; mp: 179–184 °C; $[\alpha]_D$ = +55° (chloroform, *c* = 0.02); IR (KBr): 3088, 3070, 2979, 2927, 2869, 2833, 1611, 1574, 1498, 1462, 1440, 1373, 1280, 1255, 1177, 1152, 1112, 1099, 1047, 1034, 975, 896, 879, 862, 843, 812, 795, 778, 714, 626 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ_H 1.08 (s, 3H, CH_3, C-18), 1.51–2.09 (m, 7H), 2.35–2.78 (m, 3H), 2.92–3.00 (m, 3H), 3.80 (s, 3H, OCH_3), 6.67 (d, 1H, ^4J 2.8 Hz, C-4), 6.75 (dd, 1H ^3J 8.7Hz, ^4J 2.8 Hz, C-2), 7.24–7.35 (m, 4H), 7.62 (d, 1H, ^3J 7.9Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 16.3, 26.6, 27.9, 32.5, 35.1, 37.6, 44.3, 46.9, 55.2, 56.9, 111.5, 113.9, 121.4, 121.9, 124.1, 125.0, 126.1, 132.7, 133.5, 137.9, 138.3, 139.3, 146.9, 157.5; MS (FAB, 3-nitrobenzyl alcohol): *m/z* (%) 375 (MH^+, 14), 374 (M^+, 20); HRMS (FAB) found: 374.1701, calcd. for $C_{25}H_{26}OS$: 374.1704; anal. calcd. for $C_{25}H_{26}OS$–$0.3H_2O$: C 79.03, H 7.06; found: C 79.13, H 7.17.

*2.20. 3-Methoxyestra-1,3,5(10),16-tetraeno[17,16-g]-1-oxaindene (**11b**)*

To a solution of **8b** (72 mg, 0.2 mmol) in dry CH_2Cl_2 (3 mL) was added Ru(*p*-cymene)Cl_2PPh_3 (5.7 mg, 10 μmol)

and NH_4PF_6 (3.3 mg, 20 μmol) and the resulting mixture was refluxed gently for 15 h under an argon atmosphere. The reaction mixture was subjected directly to column chromatography on silica gel (hexane:ether:dichloromethane = 4:1:1) to give **11b** (55 mg, 77%) as colorless prisms; mp: 179–180 °C; $[\alpha]_D$ = +55 ° (chloroform, c = 0.02); IR (KBr): 2970, 2916, 2854, 1611, 1575, 1495, 1419, 1281, 1254, 1141, 1033, 808, 800, 742 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ_H 1.10(s, 3H, CH_3, C-18), 1.51–2.08 (m, 6H), 2.36–2.51 (m, 2H,), 2.69–2.78 (m, 2H), 2.90–2.98 (m, 3H), 3.79 (s, 3H, OCH_3), 6.67 (d, 1H, ^4J 2.8 Hz, C-4), 6.72–6.76 (m, 2H, C-2 & ArH), 7.15 (d, 1H, ^3J 7.8Hz, ArH), 7.26 (d, 1H, ^3J x.2 Hz, ArH), 7.37 (d, 1H, ^3J 7.7 Hz, ArH), 7.57(d, 1H, ^3J 2.3 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 17.7, 26.6, 27.9, 29.8, 32.7, 35.6, 37.5, 44.3, 45.7, 106.6, 111.5, 113.9, 118.5, 120.0, 126.1, 126.5, 132.8, 136.2, 137.9, 139.5, 144.3, 150.7, 157.5; MS (FAB, 3-nitrobenzyl alcohol): m/z (%) 359 (MH^+, 26), 358 (M^+, 38); HRMS found: 358.1937, calcd. for $C_{25}H_{26}O_2$: 358.1933; anal. calcd. for $C_{25}H_{26}O_2$–0.1H_2O: C 83.34 H 7.33; found: C 83.17; H 7.51.

2.21. 3-Benzyloxy-estra-1,3,5(10)16-tetraeno[17,16-g]-1-thianaphthene (*11c*)

Acetylene **8c** (225 mg, 0.5 mmol) was added to a solution of Ru(*p*-cymene)Cl_2PPh_3 (14.2 mg, 25 μmol) and ammonium hexafluorophosphate (8.15 mg, 50 μmol) in dry CH_2Cl_2 (6.4 mL). The solution was heated at 45 °C for 20 h under an argon atmosphere. The reaction mixture was subjected to column chromatography on silica gel (hexane:ether = 10:1) to give **11c** (198 mg, 88%) as white prisms; mp: 70–72 °C; $[\alpha]_D$ = +50° (chloroform, c = 0.02); IR (KBr): 3033, 2927, 1606, 1574, 1497, 1454, 1382, 1311, 1281, 1235, 1180, 1154, 1110, 1026, 880, 843, 814, 795, 733, 696, 628 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ_H 1.09 (s, 3H, CH_3, C-18), 1.21–2.08 (m, 9H), 2.37–3.00 (m, 4H), 5.06 (s, 2H, $OC\underline{H_2}Ph$), 6.78 (d, 1H, ^4J 2.8 Hz, C-4), 6.82 (dd, 1H, ^3J 8.3 Hz, ^4J 2.8 Hz, C-2), 7.21–7.46 (m, 8H), 7.63 (d, 1H, J 7.9Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 16.3, 26.6, 27.8, 29.7, 32.5, 35.1, 37.5, 44.3, 46.9, 56.8, 69.0, 70.0, 112.4, 114.8, 121.4, 121.9, 124.1, 125.0, 126.1, 127.4, 127.8, 128.5, 133.0, 133.5, 137.3, 138.0, 139.3, 146.9, 156.8; MS (FAB, 3-nitrobenzylalcohol): m/z (%) 451 (MH^+, 3.3), 450 (M^+, 4.7); HRMS found: 450.2016, calcd. for $C_{31}H_{30}OS$: 450.2017; anal. calcd. for $C_{31}H_{30}OS$–0.5H_2O: C 81.01, H 6.80; found: C 81.00, H 6.72.

2.22. 3-Benzyloxyestra-1,3,5(10),16-tetraeno[17,16-a]-9-thiafluorene (*11d*)

Acetylene **8d** (40.8 mg, 81×10^{-3} mmol) was added to the solution of Ru(*p*-cymene)PPh_3Cl_2 (9.3 mg, 16.2×10^{-3} mmol) and NH_4PF_6 (5.3 mg, 32.4×10^{-3} mmol) in dry CH_2Cl_2 (4 mL) under Ar atmosphere. The solution was stirred for 20 h under reflux. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane:ether = 10:1) to give **11d** (19.3 mg, 47%) as a colorless solid; mp. 176 °C; IR (KBr) ν 3057, 2962, 2925, 2851, 1734, 1608, 1570, 1496, 1450, 1435, 1385, 1281, 1261, 1232, 802, 763, 743, 726, 689 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ_H 1.11 (s, 3H, CH_3, C18), 1.52–1.63 (m, 1H), 1.74–1.83 (m, 2H), 1.86–2.08 (m, 3H), 2.38–2.57 (m, 2H), 2.66–2.82 (m, 2H), 2.93–3.03 (m, 3H), 5.06 (s, 2H, OCH_2), 6.77 (d, 1H, 4J 2.6 Hz, C-4), 6.83 (dd., 1H, ^3J 8.6 Hz, ^4J 2.6 Hz, C-2), 7.31 (d, 1H, ^3J 8.5 Hz, C-1), 7.36–7.46 (m, 8H), 7.83–7.87 (m, 1H), 8.00 (d, 1H, ^3J 7.6 Hz), 8.11–8.15 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ_C 16.28, 26.51, 29.74, 32.64, 35.08, 37.52, 44.26, 46.91, 48.12, 56.73, 69.95, 112.29, 114.88, 119.36, 121.28, 121.89, 122.76, 124.22, 126.14, 126.23, 127.45, 127.85, 128.54, 128.66, 132.89, 134.92, 135.62, 137.28, 137.93, 139.31, 141.30, 147.19, 156.79; MS (FAB, 2-nitrobenzyl alcohol) m/z (%) 501 (MH^+, 3.5), 500 (M^+, 4.7); HRMS found: 500.2175; calcd. for $C_{35}H_{32}OS$: 500.2174.

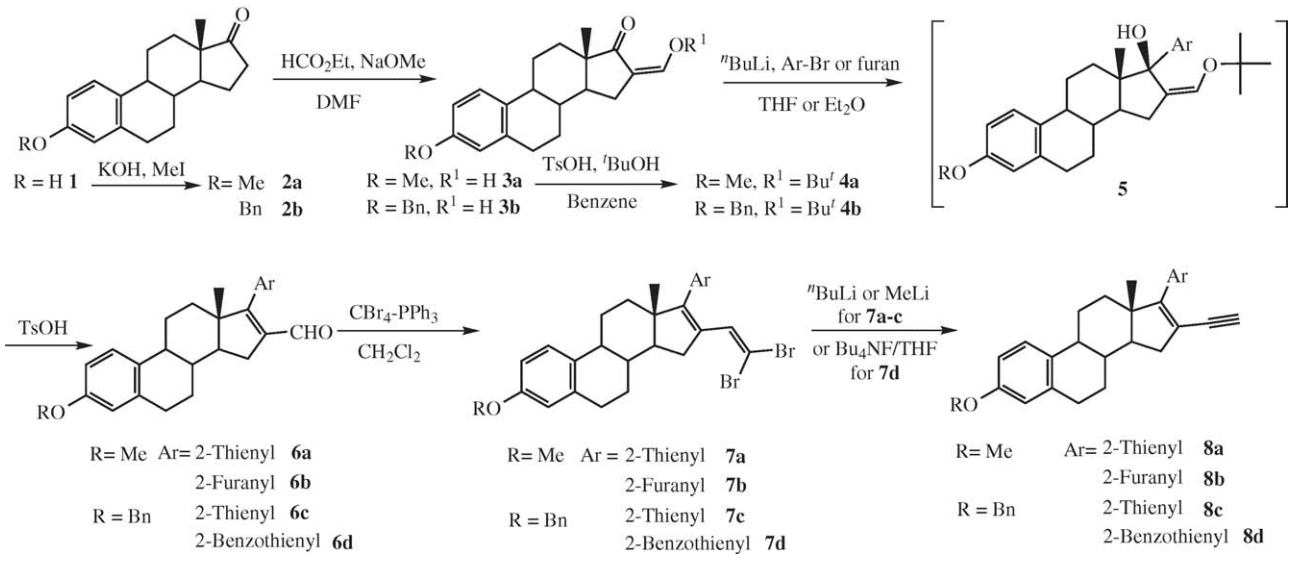
2.23. Cyclization of steroidal heteroaryl-ene-ynes using Pt catalysts

(a) $PtCl_2$ (4.0 mg, 0.015 mmol) was added to a solution of 3-methoxy-16-ethynyl-17-(thien-2′-yl)-estra-1,3,5(10), 16-tetraene (**8a**) (56 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) and the resulting mixture was stirred for 60 h under reflux. The reaction mixture was subjected to column chromatography on SiO_2 (Hexane:ether: CH_2Cl_2 = 6:1:1) to give **11a** (35 mg, 62%).

(b) To a solution of the 3-methoxy-16-ethynyl-17-(thien-2′-yl)-estra-1,3,5(10),16-tetraene (**8a**) (49 mg, 0.13 mmol) in CH_2Cl_2 (2 mL), 10% Pt on carbon nano-fiber (25.5 mg, 0.013 mmol Pt) was added and the resulting mixture was stirred for 60 h under reflux. Then, the catalyst was filtered off and the reaction mixture was subjected to the column chromatography on SiO_2 (hexane:ether = 4:1) to give starting material and product **11a** (4.5 mg, 9%) as determined by ^1H NMR spectroscopy.

(c) To a solution of the 3-benzyloxy-16-ethynyl-17-(thien-2′-yl)estra-1,3,5(10),16-tetraene (**8c**) (135 mg, 0.3 mmol) in CH_2Cl_2 (5 mL), 20% PtRu on carbon nano-fiber (44.5 mg, 0.03 mmol PtRu) was added and the resulting mixture was stirred for 15 h under reflux. The reaction mixture was filtrated over a short column of SiO_2 (CH_2Cl_2). **11c**, as determined by ^1H NMR spectroscopy, was obtained in 21% yield.

(d) To a solution of 3-benzyloxy-16-ethynyl-17-(2-thienyl) estra-1,3,5(10),16-tetraene (**8c**) (135 mg, 0.3 mmol) in CH_2Cl_2 (5 mL), 10% $PtCl_2$ on carbon nano-fiber (80 mg, 0.03 mmol Pt) was added and the resulting mixture was stirred for 15 h under reflux. Then, the reaction mixture was filtered over a short column of SiO_2 (CH_2Cl_2). **11c**, as determined by ^1H NMR spectroscopy, was obtained in 25% yield.

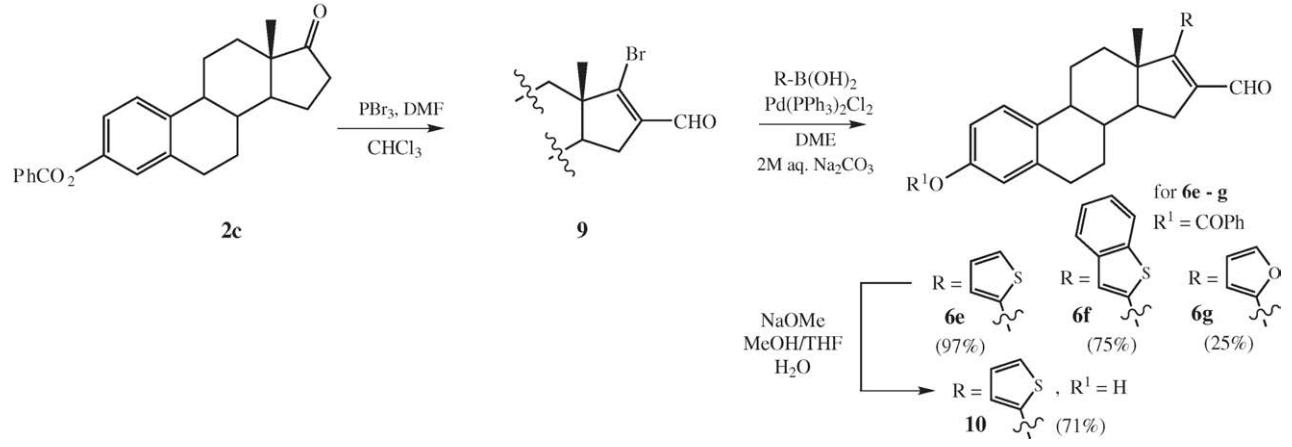


Scheme 1. Preparation of 16-ethynyl-17-hetarylestra-l,3,5(10),16-tetraen-3-ols.

3. Results and discussion

A number of routes to substrates **8** for the final heteroaryl-ene-yne cyclization can be envisaged, including a Sonogashira coupling at C-16 and a Suzuki coupling at C-17. While potentially, these reactions can even be run in the same flask, the preparation of 16,17-dihaloestra-1,3,5(10),16-tetraene is not straightforward. For this reason the synthetic strategy, shown in Scheme 1, was chosen that made use of the 1,2-addition of a lithiated arene or heteroarene to the 17-keto group of an estrane derivative with a protected formyl group at C-16, in form of a *tert*-butyl enol ether. After regeneration of the C-16 formyl group by hydrolysis, reaction of **6** with PPh_3/CBr_4 with subsequent dehydrohalogenation [19] and debromination of the 16-(dibromoethenyl)-substituted intermediates **7** furnished the ene-ynes **8**, substrates for the heteroaryl-ene-yne cyclization. It must be noted that the thienyl and benzothienyl-substituted estra-1,3,5(10),16-tetraen-16-carbaldehydes can also be prepared by Suzuki coupling reaction of thienylboronic acid and benzothienylboronic acid with 3-*O*-protected 17-bromoestra-1,3,5(10),16-tetraen-16-als, which are known direct Arnold–Vilsmeier reaction products of 3-*O*-protected estrones [17,20], the transformation being shown in Scheme 2. In the case of the reaction with furanboronic acid, this transformation gave the desired product only in poor yield, and in this case the first approach to the molecule should be favored.

In this first approach, *O*-methyl and *O*-benzyl protected estrones **2** were transformed to the corresponding 16-hydroxymethylene derivatives in a known reaction of **3a** and **3b**, respectively, with ethyl formate in the presence of sodium methoxide. Subsequent reaction of **3a**/**3b** with *tert*-butyl alcohol under acid catalysis led to the *tert*-butyloxymethyleneketones **4a**/**4b**, which effectively protected the enolized aldehyde function in **3a**/**3b** while leaving a reactive keto group at C-17. After the reaction, sometimes a small amount of starting material remained

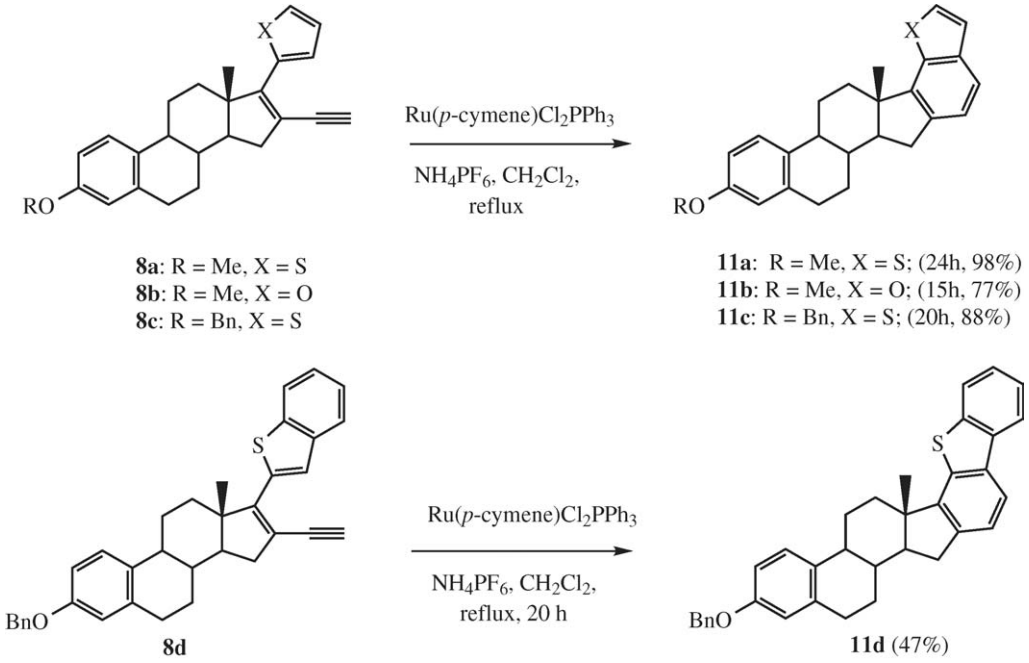


Scheme 2. Preparation of 17-hetarylestra-l,3,5(10),16-tetraen-3-ols by Suzuki-Miyaura reaction.

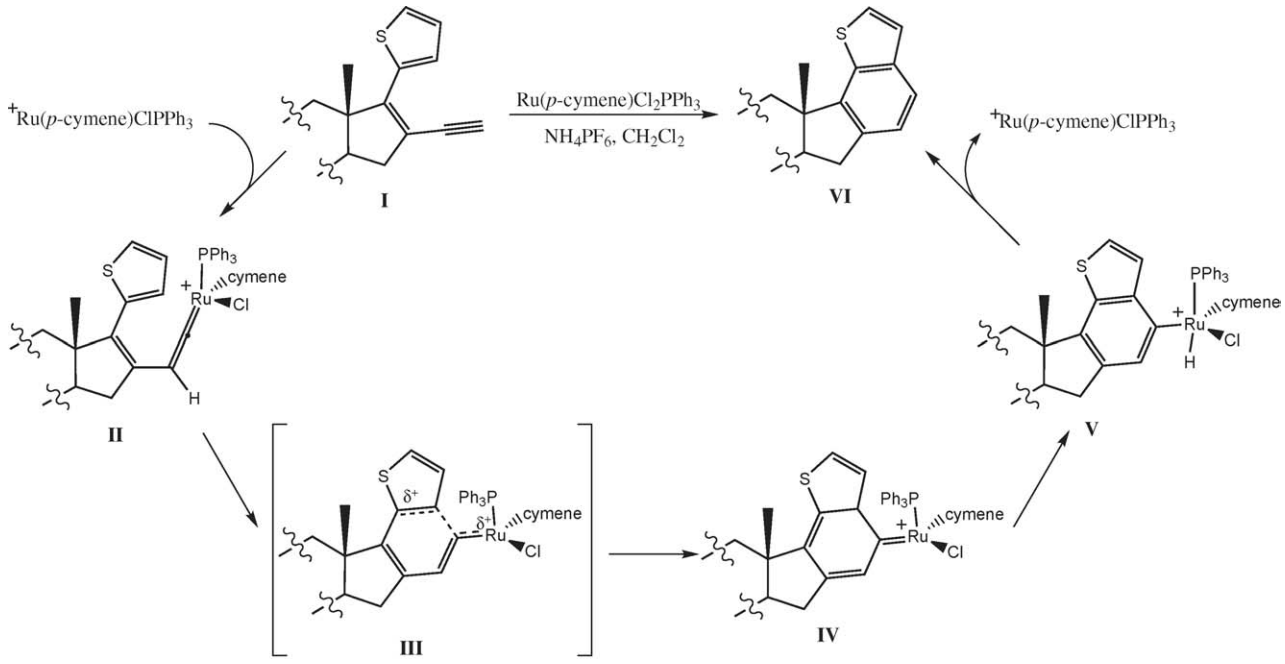
but this could easily be separated from the product by column chromatography. These modified keto aldehydes can be reacted with lithiated heteroaromatics, obtained from 2-thienyl bromide with *n*-BuLi, from furan with *tert*-BuLi and from benzothiophene with *n*-BuLi, to give alcohols **5**. The reaction gave better yields of **5** when using ether as a solvent instead of THF. The alcohols were used in the next step without further purification. For the cleavage of the *tert*-butyl group and elimination of the hydroxyl function, compounds **5** were treated with *p*-TsOH to give the heteroaromatic ring substituted α,β-unsaturated aldehydes **6a**–**6d** in satisfactory yield. The subsequent reaction of **6** with carbontetrabromide/triphenylphosphine formed dibromoethenyl substituted **7** in good yield in the case of the thienyl and benzothienyl substituted substrates; however, the reaction of the furan carrying **6b** proceeded in lower yield. This may be because the vinylidene bromides of the thienyl and benzothienyl substituted compounds **6a**, **6c** and **6d** are stable in air both as solids and in solution, while furan-substituted **6b** is not as stable under these conditions. The yield in the case of **6b** was increased a little with shortening of the reaction time. The compound should be used immediately in the next reaction. In the final step to the ene-yne products **8**, the dibromovinylidenes **7** were treated with alkyllithium, in the case of **7a** and **7b** with *n*-butyllithium or methyllithium. Methyllithium cannot be used in the case of benzothienyl carrying **7d** as MeLi deprotonates benzothienyl at the 6-position. However, **7d** can be transformed to **8d** by reaction with Bu_4NF in THF in a procedure analogous to that reported by Katsumura and co-workers [21].

At first, a combination of Ru(*p*-cymene)PPh_3Cl_2 and ammonium hexafluorophosphate (NH_4PF_6) was used as the catalytic system for the cyclization [22]. Steroids **8** reacted in good yield when the reactions were run in refluxing dichloromethane. Interestingly, this reaction proceeds without decomposition of the starting material. After the reaction, sometimes a small amount of starting material remained as can be identified by TLC analysis, but it can be separated easily from the product by column chromatography. In many cases, though, it was enough to remove the catalyst in the purification of the product. The cyclization most likely proceeds via a metallo-allenylidene species [22], with a strong polarization between the terminal acetylene and the metal with electron density being transferred from the acetylenic unit to the metal. No intermolecular coupling products were observed such as those from a possible intermolecular reaction of the metallocarbene with the electron rich A-ring of the steroidal system (Scheme 3).

Next, platinum salts were used as catalysts in the heteroaryl-ene-yne cyclization (Scheme 4). Here, the initial idea was to induce complexation of a platinum(0) species to the alkyne moiety in η^2-fashion. The subsequent complex would have significant triene character and was expected to undergo cyclization with subsequent cleavage of the metal species. Recently, Fuerstner and Mamane reported on the Pt-catalyzed cyclization of 2-ethynylbiphenyls to phenanthrenes, which incorporates aspects of the diene-yne cyclization [23]. In our case, initial experiments on the cyclization of dihydronaphthalene based diene-ynes with $Pt(PPh_3)_4$ as catalyst failed, however, to give any cyclized product. The reluctance of these substrates to undergo cyclization was thought to be due to the steric demand of $Pt(PPh_3)_4$, where it must be noted that the alkyne moiety of the substrates carried a terminal phenyl substituent. In the present work,

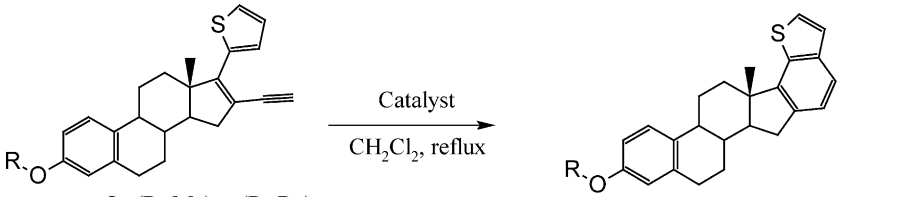


Scheme 3. Cyclization of 16-ethynyl-17-hetarylestra-l,3,5(10),16-tetraen-3-ols using a Ru-catalyst.



Scheme 4. Proposed mechanism for the ruthenium catalyzed hetaryl-ene-yne cyclization according to Merlic and Pauly [22].

Table 1
Cyclization of 16-ethynyl-17-hetarylestra-l,3,5(10),16-tetraen-3-olsusingPt-catalysts under homogeneous and heterogeneous conditions



8a (R=Me), **c** (R=Bn) **11a** (R=Me), **c** (R=Bn)

Catalyst	Ratio of metal (mol%)	Substrate	Time (h)	Yield (%
Ru(*p*-cymene)Cl_2PPh_3	5	**8c**	20	88
$PtCl_2$	10	**8a**	60	62
10 wt%-PtonCNF	10	**8a**	60	9
10 wt%-$PtCl_2$onCNF	10	**8c**	15	25
20 wt%-PtRu on CNF (calcd. on Pt/Rul:l)	10	**8c**	15	21

the much smaller $PtCl_2$ was used as catalyst. Reaction with thienyl-containing **8a** in refluxing dichloromethane again led to the desired cyclization product, however, in lower yield than in the case of using Ru(*p*-cymene)PPh_3Cl_2 as catalyst. It must also be noted that as **8a** carries a non-substituted alkyne unit, and the mechanism of the reaction in this case is not certain, as both a η^2-complexation of the platinum and an end-on complexation are possible. Such end-on complexations have been discussed in the absorption of acetylene itself on Pt-surfaces, where the upright bridge bonded μ-vinylidene of the form $Pt_2{=}C{=}CH_2$ has been characterized by vibrational spectroscopy [24]. Laser ablated Pt atoms have also been found to react with acetylene to form platinum vinylidene ($Pt{=}C{=}CH_2$) [25]. Interestingly, in our case, the reaction still proceeds when run with solid supported platinum species, where the solid support consists of carbon nano-fibers [26,27]. $PtCl_2$ doped, Pt–Ru doped as well as Pt-doped materials could be used. While the yields need to be optimized, cyclization occurred in all three cases. It is not clear whether the reactions themselves take place on the surface of the carbon nano-fiber or whether leached Pt is also acting as catalyst, especially in the case of the $PtCl_2$ doped nano-fibers, as there have been recent studies [28] on the dissolution of metals such as Pd species from carbon supports and their crystallization on the support. Further investigations on the effect of leaching of Pt species on the activity of the catalyst in heteroaryl-ene-yne and diene-yne cyclizations is underway (Table 1).

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[CN28-580 °C, HCl treated], and the catalysts 10 wt% Pt on CNF and 20 wt% PtRu on CNF. Ms. Yasuko Tanaka has carried out MS and HRMS (EI and FAB) measurements. Elemental analyses were performed at the Center for Instrumental Analysis, Hakozaki Campus, Kyushu University. Part of this work has been carried out within the framework of a CREST program. Financial support from the Japan Science and Technology Corporation (JST) is gratefully acknowledged.

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