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Efficient Synthesis of an Enantiopure Thiasteroid by a Double Heck Reaction*

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The thiaestrane **7** was synthesized by two sequential Heck reactions starting from the thiophene derivatives **8a**–**8c**, which contain a (*Z*)-halogenovinyl group, and the enantiopure hydrindene **2a**. The first intermolecular Pd-catalyzed reaction leads to **11a** and **11b** in a highly regio- and diastereoselective manner. A subsequent intramolecular Heck reaction catalyzed by the palladacycle **4** then gave the thiasteroid **7** with an unusual *cis*-junction of the rings B and C.

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Natural estrogens and their synthetic analogues are of great importance due to their pronounced biological activity,[1] e.g. as oral contraceptives.[2] Recently, it has been shown that estradiol **6** also acts as a ligand at the β-subunit of the Maxi-K^+ channel which is the key modulator of vascular smooth muscle tone.[3] Therefore, at present the preparation of novel estrogens is of great research significance. In recent years emphasis has been put on the synthesis of nor-steroids, homosteroids, and heterocyclic steroids.[4] Along this line several attempts have been made to introduce a thiophene moiety as an A-ring of the estrane skeleton, but only racemic products using non-convergent routes were obtained. There are several known total syntheses of steroids;[5] however, most approaches towards this class of compounds start from naturally occurring precursors.[6] Recently, we have developed a new highly efficient synthesis of estradiol **6** and analogues based on a double Heck reaction between 2-bromo-1-bromovinylbenzene **1** and hydrindene **2a** (Scheme 1).[7] In the first Pd-catalyzed step, the vinyl bromide moiety within **1** reacts in a regio- and stereoselective manner with the olefin in **2a** to give **3**. This transformation is followed by a second Pd-catalyzed reaction using the palladacene **4** to afford **5** containing the complete steroidal skeleton along with an unusual *cis*-junction of the rings B and C. Hydrogenation with accompanying isomerization of the benzylic stereogenic centre and deprotection led to the enantiopure estradiol **6** in high yield and excellent selectivity.

Besides the synthesis of estradiol, we also prepared the novel D-homoestradiol[8] and a novel 19-nor-steroid[9] using this method. In addition, several aza-heterocyclic compounds were also obtained by similar twofold Heck approaches.[10]

In this paper we describe the use of this approach for the synthesis of the novel enantiopure thiaestrane **7**. The retrosynthetic analysis of **7** led to the doubly functionalized (*Z*)-2-(2-halogenoethenyl)-3-halogenothiophenes **8a**–**8c** and the hydrindene **2** (Scheme 2).

The dibromothiophene derivative **8a** was prepared by a Corey–Fuchs reaction of 3-bromothiophene-2-carbaldehyde **9a**.[11] The initially formed tribromide **10** was then treated with Bu^n_3SnH as hydride donor and $Pd(PPh_3)_4$ to allow a selective exchange of the (*E*)-bromo atom for a hydrogen by a Pd-catalyzed cross-coupling reaction (Scheme 3).[12]

The (*Z*)-2-(2-iodoethenyl)thiophenes **8b** and **8c** were prepared by a Wittig reaction of the aldehydes **9a** and **9b** with the phosphonium salt $[ICH_2PPh_3]^+ \cdot I^-$ in the presence of KHMDS as a base. The hydrindene **2** was synthesized from the well-known Hajos–Wiechert ketone[13] in a five step reaction sequence which includes a Pd-catalyzed rearrangement of an allyl formate[14] to obtain the *trans*-annulation of the CD-ring system.[15]

In the Pd-catalyzed reaction between **2** and **8a**–**8c**, it was expected that attack at the double bond within **2** would occur from below due to the β-orientation of the angular methyl group. Alternatively, it was not clear that a selective reaction of the vinyl halide moiety in **8a–8c** would be possible nor could it be predicted that the C—C bond formation would take place at the more hindered C4 position in **2**, as found in the previous reaction of **1** and **2a**.

Results and Discussion

The reactions of **2** and **8a**–**8c** were performed using a mixture of $Pd(OAc)_2$ and PPh_3 as the catalyst in either $DMF/CH_3CN/H_2O$ (5 : 5 : 1) or CH_3CN in the presence of

* Dedicated to Professor Lewis N. Mander on the occasion of his 65th birthday.

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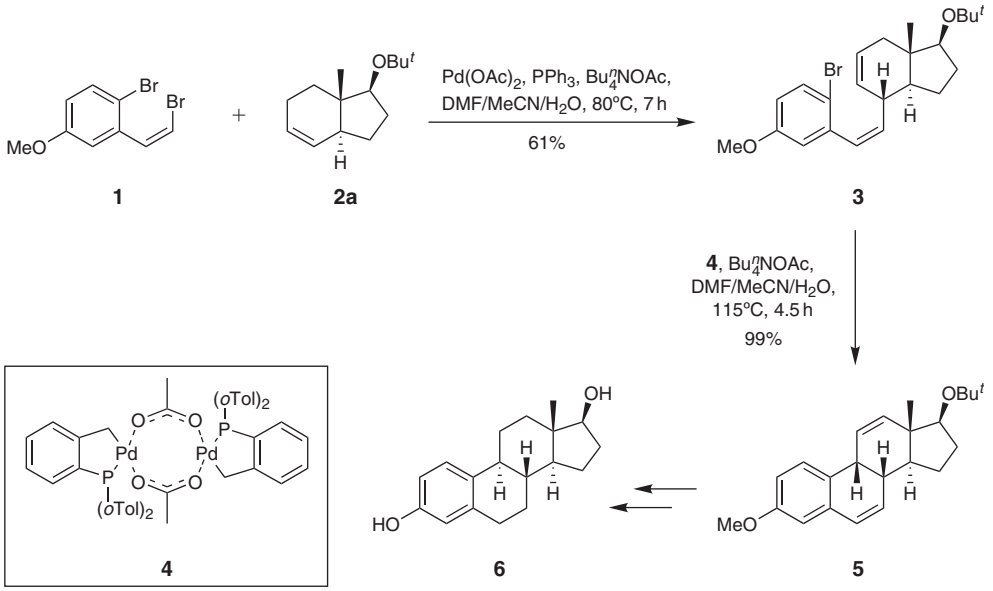
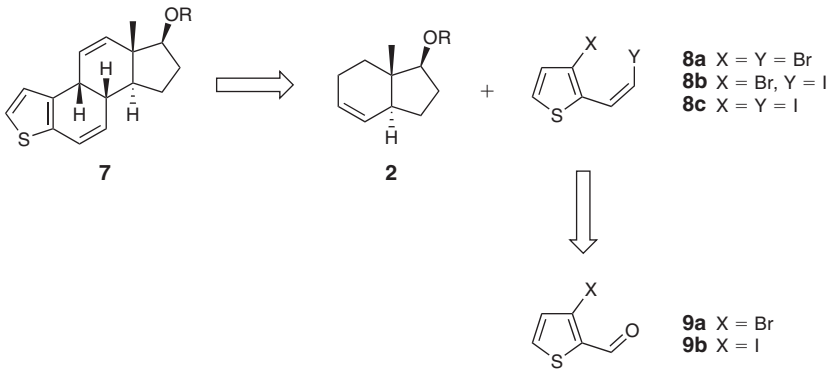
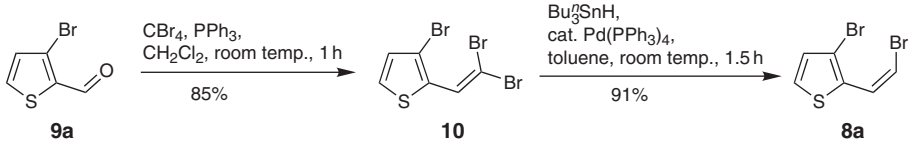


Scheme 1. Synthesis of estradiol **6** by a twofold Heck reaction.[7]



Scheme 2. Retrosynthesis of thiasteroid **7**.

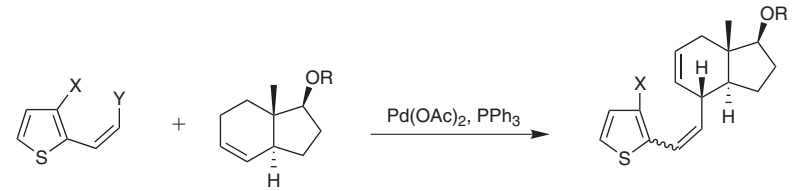


Scheme 3. Synthesis of dibromothiophene derivative **8a**.

tetrabutylammonium acetate or silver phosphate (Scheme 4, Table 1).

The best results were obtained for the reaction of **2a** and **8a** to afford **11a** in 83% yield, while the use of **2a** and **8b** yielded **11a** in 73%, and the use of **2a** and **8c** provided **11b** in 53% yield. We also investigated the transformation of **8a** with the hydrindene **2b**, containing a free hydroxyl group, to provide evidence whether the protecting group is necessary: unfortunately, here only 22% yield of the corresponding product **12** was obtained. However, in the products from all reactions a partial isomerization of the exocyclic double bond was observed (approx. 10% for the first and second reaction and 30% in the third reaction), even under strict exclusion of light. The use of silver salts such as Ag_3PO_4, known for their ability to suppress double-bond isomerization, caused by a readdition of the H–Pd–X species and consecutive β-hydride elimination, did not improve the situation. Furthermore, pure (*Z*)-product could not be obtained by chromatography with silver-impregnated silica gel[16] or by HPLC. Hence, the following step was conducted using the crude mixture of **11**.

In the formation of **11** a migration of the double bond in the hydrindene moiety was not observed. In addition, as required, **8** reacts exclusively at the vinylhalide and not at the halothiophene moiety. Moreover, the C─C bond formation seems to be very selective, since the only product obtained was that of an addition at the 4-position within **2a**. We assume that the insertion of the primarily formed Pd–alkenyl species occurs unselectively at both ends of the double bond in **2a** to give the intermediates **A** and **B** (Scheme 5). However, the formation



8a X = Y = Br
8b X = Br, Y = I
8c X = Y = I

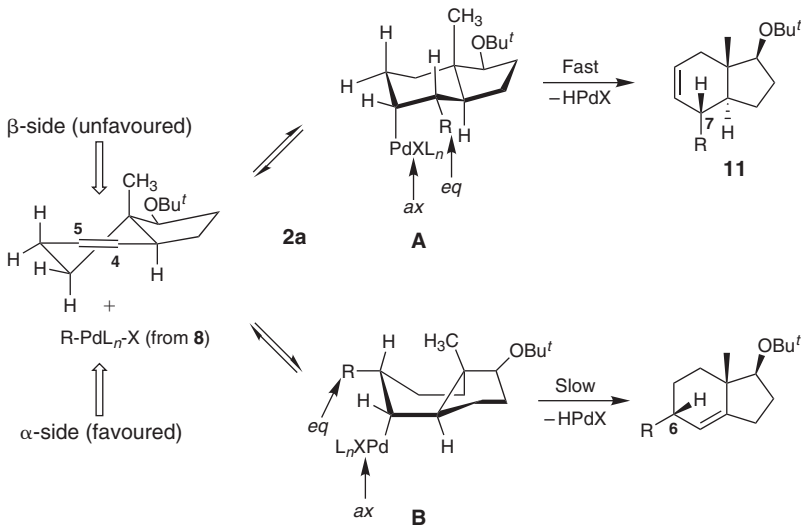
2a R = Bu^t
2b R = H

11a X = Br, R = Bu^t
11b X = I, R = Bu^t
12 X = Br, R = H

Scheme 4. Intermolecular Heck reaction of **8a**–**8c** and **2**.

Table 1. Conditions for Heck reaction of 8a–8c and 2

Entry	Substrates	Catalyst	Solvent	Additive	Product	Yield [%]	(*Z*)/(*E*) Ratio
1	**8a**/**2a**	10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 70°C, 16 h	DMF/MeCN/H_2O	Bu^n_4NOAc (2.5 equiv.)	**11a**	83	10 : 1
2	**8b**/**2a**	10 mol% $Pd(OAc)_2$, 80°C, 20 h	MeCN	Ag_3PO_4 (2.6 equiv.)	**11a**	73	10 : 1
3	**8c**/**2a**	10 mol% $Pd(OAc)_2$, 80°C, 15 h	MeCN	Ag_3PO_4 (1.3 equiv.)	**11b**	53	3 : 1
4	**8a**/**2b**	10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 70°C, 16 h	DMF/MeCN/H_2O	Bu^n_4NOAc (2.5 equiv.)	**12**	22	–

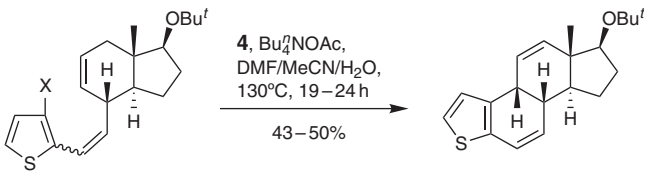


Scheme 5. Diastereo- and regioselectivity of the intermolecular Heck reaction of **2a** and **8a**–**8c**.

of **A** and **B** should be reversible, and since **B** would exist in a boat conformation from which a β-hydride elimination is not favoured, **11** formed via **A** is the only product.

For the cyclization of **11a** and **11b** to provide **7**, several catalytic Pd systems were screened. The palladacycle **4** developed by Herrmann and Beller[17] was the only catalyst to allow the transformation. Treating crude **11a** with 2 mol% of **4** and tetrabutylammonium acetate as base in a mixture of DMF/CH_3CN/H_2O (5 : 5 : 1) at 130°C led to the thiaestrane **7** in 50% yield (Scheme 6). Furthermore, crude **11b** was also transformed to **7** in a slightly lower yield, presumably due to the higher content of (*E*)-**11b** which did not cyclize. Separation of the thiasteroid **7** from the (*E*)-configured substrate was easily performed by standard silica gel chromatography.

The formation of **7** from **2a** and **8a** can also be performed in a domino process.[18] Thus, **2a** and **8a** were heated in the presence of $Pd(OAc)_2$/PPh_3 and palladacycle **4** initially for 16 h at 70°C and afterwards at 130°C for 24 h. However, the yield for this domino process was only 16% which is lower than the overall yield in the stepwise mode.



11a X = Br
11b X = I

7

Scheme 6. Intramolecular Heck reaction of **11a**/**11b**.

The relative configuration of **7** with the unusual *cis*-connection of the BC-ring system was proven by X-ray structural analysis.[19]

To conclude, the novel enantiopure 4-thiaestrane **7** was synthesized stereoselectively in a highly efficient way by forming the B-ring using two successive Heck reactions. The connection between ring B and ring C has an unusual *cis*-configuration and the two double bonds in the C5 and C10 positions provide the opportunity for further derivatization.

Experimental

General

All reactions were performed in oven-dried glassware under an argon atmosphere. Solvents were degassed using the freeze–pump–thaw method or by bubbling argon through the solution for 30 min. TLC was performed on precoated silica gel SIL G/UV$_{254}$ plates (Macherey, Nagel & Co.), and silica gel 32–63 (0.032–0.064 mm; Merck) was used for column chromatography. Melting points were determined on a Mettler FP61. Optical rotations were determined on a Perkin–Elmer 241. IR spectra were determined on a Bruker IFS 25. UV-vis spectra were determined on a Perkin–Elmer Lambda 9. NMR spectra were determined on Varian VXR 200 (200 MHz, ^{1}H), Bruker AM-300 (300 and 75 MHz for ^{1}H and ^{13}C, respectively), Varian VXR-500 (500 and 125 MHz for ^{1}H and ^{13}C, respectively), and VXR-600 (600 and 150 MHz for ^{1}H and ^{13}C, respectively) instruments. For ^{1}H and ^{13}C NMR, $CDCl_3$ and C_6D_6 were used as solvents and TMS as internal standard. Chemical shifts are reported on the δ scale and signals are quoted as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), and br (broad). Mass spectra were determined on a Varian MAT 311A (70 eV, EI, DCI) instrument. HRMS were determined on a Varian MAT 731 instrument. Elemental analyses were determined by the Mikroanalytisches Labor des Instituts für Organische und Biomolekulare Chemie Göttingen.

*Intermolecular Heck Reaction of **8a**/**8b** and **2a***

A solution of hydrindene **2a** (709 mg, 3.40 mmol), dibromothiophene **8a** (1.37 g, 5.12 mmol), and Bu^n_4NOAc (2.56 g, 8.51 mmol) in DMF/CH_3CN/H_2O (5 : 5 : 1, 20 mL) was thoroughly degassed and warmed to 40°C. Subsequently, triphenylphosphane (179 mg, 20 mol%) and $Pd(OAc)_2$ (76.0 mg, 10 mol%) were added under an atmosphere of argon. The reaction mixture was heated at 70°C and stirred for 16 h with the exclusion of light. After cooling the solution to room temperature, diethyl ether (20 mL) and water (10 mL) were added, the layers separated, and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under vacuum. After column chromatography (pentane/*tert*-butyl methyl ether, 100 : 1) on SiO_2, the desired product (1.11 g, 2.81 mmol, 83%) was obtained as an inseparable mixture of (*Z*)-**11a** and (*E*)-**11a** in a 10 : 1 ratio.

$Pd(OAc)_2$ (6.0 mg, 10 mol%) and Ag_3PO_4 (265 mg, 0.64 mmol) were added to a degassed solution of **8b** (79.0 mg, 0.25 mmol) and **2a** (106 mg, 0.58 mmol) in CH_3CN (5 mL) at 40°C under an atmosphere of argon. The reaction mixture was heated at 80°C for 20 h with the exclusion of light. After the usual workup (see above) and column chromatography (pentane/*tert*-butyl methyl ether, 1 : 100) on SiO_2, the desired product **11a** (43.0 mg, 0.11 mmol, 73%) was obtained as an inseparable mixture of (*Z*)-**11a** and (*E*)-**11a** in a 10 : 1 ratio.

*(1*R*,3a*S*,4*S*,7a*S*)-3-Bromo-2-(Z)-[2-[1*-tert-*butoxy-7a-methyl-2,3, 3a,4,7,7a-hexahydro-1*H*-inden-4-yl]ethenyl]thiophene **11a***

R_F 0.32 (pentane/*tert*-butyl methyl ether, 100 : 1). λ_{max}/nm (CH_3CN, log ε) 282.5 (4.13), 371.0 (2.94). ν_{max}/cm^{-1} (KBr) 3017, 2971, 1460, 1361, 1018, 700. δ_H (300 MHz, $CDCl_3$) 0.84 (s, 3 H, 7a′-CH_3), 1.16 (s, 9 H, OBu^t), 1.32–1.66 (m, 3 H, 2 × H2′, H$_a$3′), 1.82–1.96 (m, 2 H, H3b′, H3a′), 2.06 (dddd, *J* 17.0, 5.0, 3.5, 1.5, 1 H, H7′$_a$), 2.31–2.44 (m,1 H, H7′$_b$), 3.39–3.47 (m$_c$, 1 H, H4′), 3.52 (t, *J* 8.5, 1 H, H1′), 5.41 (dddd, *J* 10.0, 6.0, 3.0, 1.5, 1 H, H5′), 5.44 (dd, *J* 11.5, 10.5, 1 H, H2″), 5.73 (dddd, *J* 10.0, 5.0, 2.5, 2.0, 1 H, H6′), 6.59 (d, *J* 11.5, 1 H, H1″), 6.99 (d, *J* 5.5, 1 H, H4), 7.22 (d, *J* 5.5, 1 H, H5). δ_C (50.3 MHz, $CDCl_3$) 11.5 (7a′-CH_3), 24.6 (C3′), 28.8 [OC(CH_3)$_3$], 30.5 (C2′), 38.79 (C7′), 39.8 (C4′), 41.3 (C7a′), 46.8 (C3a′), 72.3 [O*C*(CH_3)$_3$], 80.6 (C1′), 111.8 (C3), 120.5 (C1″), 124.7 (C4), 127.8 (C6′), 128.1 (C5′), 129.9 (C2″), 134.1 (C2), 135.1 (C5). *m*/*z* (EI, 70 eV) 396.2 (28%, [M$^+$]), 339.1 (18, [M$^+$ – C_4H_9]), 321.1 (6, [M$^+$ – C_4H_9O]), 259.2 (12, [M$^+$ – Br – C_4H_9]), 241.2 (23, [M$^+$ – Br – C_4H_9O]), 79.1 (8, [Br$^+$]), 57.1 (100, [$C_4H_9^+$]), 41.1 (22, [$C_3H_5^+$]). Found: 394.0966. Calc. for $C_{20}H_{27}BrOS$: 394.0966.

*Intermolecular Heck Reaction of **8a** and **2b***

A solution of the hydrindene **2b** (6.0 mg, 39 μmol), **8a** (16.0 mg, 59.1 μmol), and Bu^n_4NOAc (30.0 mg, 99.0 μmol) in DMF/CH_3CN/H_2O (5 : 5 : 1, 1 mL) was thoroughly degassed and warmed to 40°C. Subsequently, $Pd(OAc)_2$ (1.0 mg, 10 mol%) and PPh_3 (2.0 mg, 20 mol%) were added under an atmosphere of argon. The reaction mixture was heated at 70°C with stirring for 16 h with exclusion of light. After usual workup (see above) and column chromatography (pentane) on SiO_2, the desired product **12** (3.0 mg, 8.8 μmol, 22%) was obtained as a mixture of (*Z*)-**12** and (*E*)-**12** (colourless oil).

*(1*R*,3a*S*,4*S*,7a*S*)-4-(Z)-[2-(3-Bromothiophen-2-yl)vinyl]-7a-methyl-2, 3,3a,4,7,7a-hexahydro-1*H*-inden-1-ol **12***

R_F 0.59 (pentane/*tert*-butyl methyl ether, 1 : 1). δ_H (300 MHz, $CDCl_3$) 0.83 (s, 3 H, 7a′-CH_3), 1.17–1.70 (m, 5 H, 2 × H2′, H$_2$3′, 1′-OH), 1.91–2.15 (m, 3 H, H3a′, H$_2$7′), 3.43 (m$_c$, 1 H, H4′), 3.78 (t, *J* 8.6, 1 H, H1′), 5.38–5.44 (m, 1 H, H5′), 5.41 (dd, *J* 11.5, 10.4, 1 H, H2″), 5.72 (dddd, *J* 9.8, 5.2, 2.6, 2.0, 1 H, H6′), 6.57 (d, *J* 11.5, 1 H, H1″), 6.97 (d, *J* 5.4, 1 H, H4), 7.21 (d, *J* 5.4, 1 H, H5). δ_C (50.3 MHz, $CDCl_3$) 10.7 (7a′-CH_3), 24.3 (C3′), 30.1 (C2′), 38.2 (C7′), 39.6 (C4′), 42.0 (C7a′), 46.1 (C3a′), 81.8 (C1′), 109.2 (C3), 121.6 (C1″), 123.2 (C4), 127.0 (C6′), 128.5 (C5′), 130.5 (C2′), 135.1 (C5), 137.0 (C2). *m*/*z* (EI, 70 eV) 340.1 (24%, [M$^+$]), 323.1 (0.5, [M$^+$ – OH]), 281.0 (0.5, [M$^+$ – C_4H_9]), 259.1 (3, [M$^+$ – Br]), 241.1 (3, [M$^+$ – Br – H_2O]), 189.9 (8, [M$^+$ – Br – C_4H_9O]), 41.1 (6, [$C_3H_5^+$]).

*Intermolecular Heck Reaction of **8c** and **2a***

A solution of hydrindene **2a** (416 mg, 2.00 mmol) and diiodothiophene **8c** (362 mg, 1.00 mmol) in CH_3CN (20 mL) was thoroughly degassed and warmed to 40°C. Subsequently, $Pd(OAc)_2$ (22.4 mg, 10 mol%) and Ag_3PO_4 (544 mg, 1.30 mmol) were added under an atmosphere of argon. The reaction mixture was heated at 80°C with stirring for 15 h under exclusion of light. After usual workup (see above) and column chromatography (pentane) on SiO_2, the desired product **11b** (43.0 mg, 0.11 mmol, 53%) was obtained as a mixture of (*Z*)-**11b** and (*E*)-**11b** (yellow oil) in a 3 : 1 ratio.

*(1*R*,3a*S*,4*S*,7a*S*)-3-Iodo-2-(Z)-[2-[1*-tert-*butoxy-7a-methyl-2,3, 3a,4,7,7a-hexahydro-1*H*-inden-4-yl]ethenyl]thiophene **11b***

R_F 0.18 (pentane/*tert*-butyl methyl ether, 100 : 1). λ_{max}/nm (CH_3CN, log ε) 197.0 (4.26), 279.0 (4.08), 329.0 (2.84). ν_{max}/cm^{-1} (KBr) 3082, 3016, 1470, 1077, 859, 699. δ_H (500 MHz, $CDCl_3$) 1.05 (s, 3 H, 7a′-CH_3), 1.07 (s, 9 H, OBu^t), 1.14–1.80 (m, 6 H, H2′, H3′, H7′), 1.95–2.09 (m, 2 H, H3a′), 3.26 (t, *J* 8.3, 1 H, H1′), 3.65 (dd, *J* 10.5, 1.5, 1 H, H4′), 5.41 (dd, *J* 11.5, 10.5, 1 H, H2″), 5.54 (dddd, *J* 10.0, 6.0, 3.0, 1.5, 1 H, H5′), 5.69 (dddd, *J* 10.0, 7.5, 3.0, 2.0, 1 H, H6′), 6.53 (dd, *J* 5.3, 0.6, 1 H, H4), 6.71 (d, *J* 11.5, 1 H, H1″), 6.77 (d, *J* 5.3, 1 H, H5). δ_C (50.3 MHz, $CDCl_3$) 11.5 (7a′-CH_3), 24.6 (C2′), 28.7 [OC(CH_3)$_3$], 30.5 (C3′), 38.7 (C7′), 39.6 (C4′), 41.3 (C7a′), 46.7 (C3a′), 72.2 [O*C*(CH_3)$_3$], 80.5 (C1′), 83.4 (C3), 123.4 (C1″), 126.1 (C5), 127.7, 128.0 (C5′, C6′), 134.7 (C2″), 136.0 (C4), 137.5 (C2). *m*/*z* (EI, 70 eV) 442.1 (58%, [M$^+$]), 385.0 (32, [M$^+$ – C_4H_9]), 314.2 (9, [M$^+$ – I]), 258.1 (20, [M$^+$ – I – C_4H_9]), 241.1 (30, [M$^+$ – I – C_4H_9O]), 57.0 (100, [$C_4H_9^+$]), 41.0 (20, [$C_3H_5^+$]). Found: 442.0827. Calc. for $C_{20}H_{27}IOS$: 442.0827.

*Synthesis of 7 by Intramolecular Heck Reaction of **11a** and **11b***

(*a*) Palladacycle **4** (4.0 mg, 2.0 mol%) was added to a degassed solution of **11a** (90 mg, 0.22 mmol) and Bu^n_4NOAc (172 mg, 0.57 mmol) in DMF/CH_3CN/H_2O (5 : 5 : 1, 6 mL) under an atmosphere of argon. The reaction mixture was heated in a sealed vessel to 130°C and stirred for 19 h with exclusion of light. After cooling to room temperature, diethyl ether (20 mL) and water (10 mL) were added, the layers separated, and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under vacuum. After column chromatography (pentane) on SiO_2, the desired product **7** (36 mg, 0.11 mmol, 50%) was obtained as white-yellow crystals.

(*b*) Palladacycle **4** (5.0 mg, 2.0 mol%) was added to a degassed solution of **11b** (112 mg, 0.25 mmol) and Bu^n_4NOAc (153 mg, 0.51 mmol) in DMF/CH_3CN/H_2O (5 : 5 : 1, 5.5 mL) under an atmosphere of argon. The reaction mixture was heated in a sealed vessel to 130°C and stirred for 24 h with exclusion of light. After usual workup and column chromatography (pentane) on SiO_2, the desired product **7** (34.0 mg, 0.11 mmol, 43%) was obtained as white-yellow crystals.

(–)-A-nor-*17*-tert-*Butoxy-4-thia-9β-estra-2,5(10),6,11(12)-pentaene 7*

R_F 0.22 (pentane/*tert*-butyl methyl ether, 100 : 1), mp 112–113°C, $[\alpha]_D^{20}$ −78.4 (*c* 0.25, $CHCl_3$). λ_{max}/nm (CH_3CN, log ε) 234.5 (3.73), 288.0 (3.89), 297.5 (3.92). ν_{max}/cm^{-1} 3095, 2971, 1078, 718. δ_H 0.95 (s, 3 H, H18), 1.02 (s, 9 H, 17-OBu^t), 1.07–1.50 (m, 3 H, 2 × H15, H_a16), 1.54–1.68 (m_c, 1 H, H_b16), 1.82 (dt, *J* 12.9, 6.5, 1 H, H14), 2.54 (ddd, *J* 8.6, 5.8, 2.5, 1 H, H8), 3.16 (dd, *J* 8.6, 7.2, 1 H, H17), 3.68 (dd, *J* 8.6, 4.4, 1 H, H9), 5.56 (dd, *J* 10.0, 5.8, 1 H, H7), 5.89 (dd, *J* 10.0, 4.4, 1 H, H11), 6.13 (dd, *J* 10.0, 1.8, 1 H, H12), 6.29 (d, *J* 10.0, 1 H, H6), 6.75 (d, *J* 5.2, 1 H, H2), 6.80 (d, *J* 5.2, 1 H, H3). δ_C (150 MHz, C_6D_6) 15.1 (C18), 23.2 (C15*), 28.8 (OC(CH_3)$_3$), 32.0 (C16*), 34.4 (C8), 37.6 (C9), 41.3 (C14), 44.3 (C13), 72.2 (O*C*(CH_3)$_3$), 76.4 (C17), 119.5 (C6), 122.4 (C2), 125.8 (C11), 126.9 (C3), 127.4 (C7), 132.7 (C-5), 135.9 (C-12), 136.4 (C-10); resonances marked with an asterisk may be interchanged. *m*/*z* (EI, 70 eV) 314.2 (47%, [M^+]), 257.1 (44, [M^+ – C_4H_9]), 239.1 (100, [M^+ – C_4H_9 – H_2O]), 57.0 (66, [$C_4H_9^+$]). Found: C 76.2, H 8.1. Calc. for $C_{20}H_{26}OS$: C 76.4, H 8.3%.

*Domino Heck Reaction of **8a** and **2a***

A solution of hydrindene **2a** (100 mg, 0.48 mmol), dibromothiophene **8a** (154 mg, 0.58 mmol), and Bu^n_4NOAc (362 mg, 1.20 mmol) in DMF/CH_3CN/H_2O (5 : 5 : 1, 5 mL) was thoroughly degassed and warmed to 40°C in a sealed vessel. PPh_3 (25.0 mg, 20 mol%), $Pd(OAc)_2$ (11.0 mg, 10 mol%), and palladacycle **4** (9.00 mg, 2 mol%) were added subsequent under an atmosphere of argon. The reaction mixture was heated in a sealed vessel at 70°C for 16 h and then at 130°C for 24 h. After usual workup (see above) and column chromatography (pentane) on SiO_2, **7** (24 mg, 7.64 μmol, 16%) was obtained as white-yellow crystals.

Accessory Materials

Experimental procedures with NMR assignments for compounds **8a–8c** and **10** are available from the author or, until July 2009, the *Australian Journal of Chemistry*.

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[19] Crystallographic data (excluding structure factors) for the structure of **7** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-230286. Copies of the data can be obtained free of charge on application to the CCDC (e-mail: deposit@ccdc.cam.ac.uk).