Stereoselective Synthesis of Novel 19-Nor-Steroids by a Double Heck Reaction

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Dedicated to Professor Frank-Gerrit Klärner on the occasion of his 60th birthday

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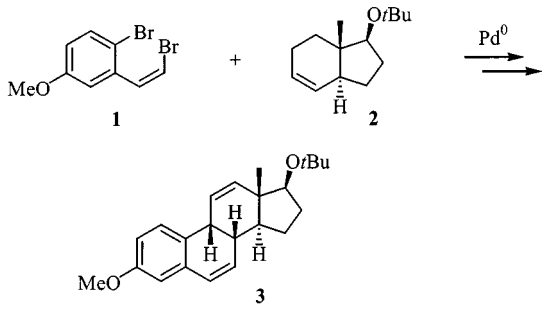
The estrane **4** was synthesized by two successive Heck reactions starting from enantiopure **2** and the cyclohexenone **5**, which contains a (*Z*)-bromovinyl group. The first intermolecular Pd-catalyzed reaction leads to **10** in a highly regio- and diastereoselective manner. Transformation of the enone **10** to give the corresponding enol triflate **14** followed by an intramolecular Heck reaction affords the cyclized product **4** with an unusual *cis*-junction of the rings B and C in high yield.

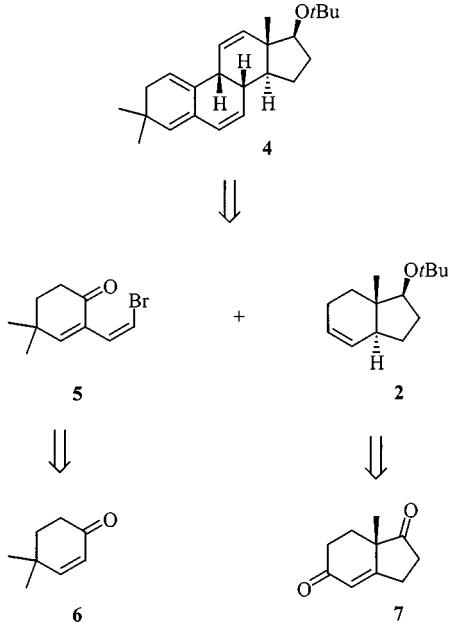
Introduction

Due to their biological activity and broad application in pharmacology, steroids are an attractive synthetic goal in academia as well as in industry. Since the first total synthesis of equilenin in 1939 by Bachmann et al.,[1] numerous synthetic approaches to obtain the tetracyclic structure of steroids have been developed,[2] many of them relying on biomimetic cyclizations of polyolefins,[3] cycloadditions,[4–8] or transition metal-catalyzed cyclizations of alkenes and alkynes.[9,10] But the number of total syntheses of steroids is rather small compared to the countless partial syntheses and derivatizations of naturally occurring steroids.[11] However, a total synthetic approach is indispensable in order to gain access to analogs that cannot be derived from natural steroids. Recently, we have shown that the double Heck reaction[12,13] of **1** and **2** gives access to the estradiol derivative **3** in a very efficient way (Scheme 1).[14,15] A similar approach has also been successfully employed in the synthesis of D-homoestradiols[16] and novel aza-heterocycles.[17]



Scheme 1. Convergent synthesis of the estradiol derivative **3**

Here we describe the stereoselective synthesis of the novel 19-nor-steroid **4** with a nonaromatic ring A in which the ring B of the steroidal skeleton is obtained by two successive Heck reactions. The retrosynthetic analysis of **4** leads to the (*Z*)-(2-bromoethenyl)cyclohexenone **(5)** and the chiral hydrindane **2** (Scheme 2). The latter compound can easily be obtained from the Hajos–Wiechert ketone **7**[18] in a five-step sequence including a stereoselective intramolecular Pd-catalyzed rearrangement of an allyl formate developed by Tsuji et al.,[19,20] which leads to the desired *trans*-annulation of the two rings.[21] The A-ring precursor **5**, bearing an oxygen at C-1 and a bromovinyl moiety at C-2, is accessible in five steps from the commercially available cyclohexenone **6**.



Scheme 2. Retrosynthetic analysis of the estrane **4**

Results and Discussion

For the synthesis of **5**, the known dimethyl cyclohexenone **6**[22,23] was transformed into the aldehyde **8** by hydro-

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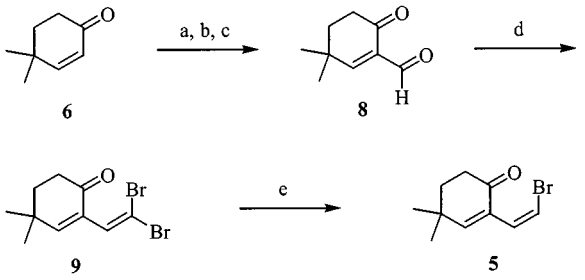
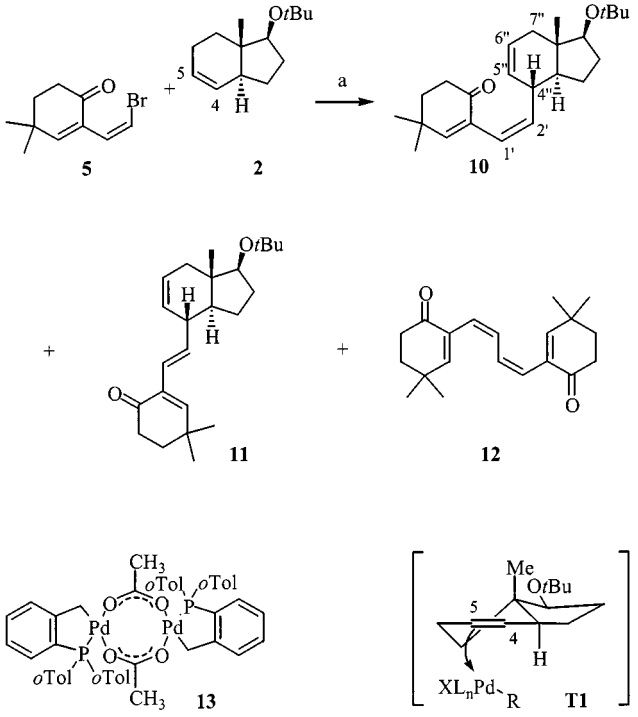
genation of the double bond, Claisen ester condensation with formic acid ethyl ester,[24,25] and subsequent oxidation with DDQ[26] (Scheme 3). A Corey−Fuchs reaction of **8** with tetrabromomethane,[27] followed by the reductive Pd-catalyzed replacement of the (*E*)-bromo atom with a hydride using nBu$_3$SnH[28] afforded the bromoalkene **5** in good overall yield. For the two vinylic hydrogens in **5** a coupling constant of J = 8.0 Hz is observed in the ^{1}H NMR spectrum, which confirms the (*Z*)-configuration of the double bond.



Scheme 3. Synthesis of **5**: a) H_2, Pd/C, pentane, 24 h, 99%; b) NaH, HCO_2Et, CyH, reflux, 4 h; CH_3CO_2H, 94%; c) DDQ, dioxane, room temp., 5 min., 76%; d) CBr_4, PPh_3, CH_2Cl_2, 0 °C → room temp., 2.5 h, 79%; e) nBu$_3$SnH, Pd(PPh$_3$)$_4$, toluene, room temp., 2 h, 71%

For the intermolecular Heck reaction of **5** and **2** several catalysts were investigated (Scheme 4). The usual Pd catalyst derived from Pd(OAc)$_2$ and triphenylphosphane as ligand gave the desired product **10** in 47% yield. In contrast, Pd(PPh$_3$)$_4$ as catalyst and additional silver salt afforded **10** in only 29%. The best result (with 56% yield) was obtained employing the palladacycle **13**, introduced by Herrmann, Beller et al.,[29,30] at 115 °C with tetrabutylammonium acetate as base; it is noteworthy that a small amount of water significantly increased the reaction rate. Traces of the (*E*)-isomer **11** and variable amounts of 5 to 10% of the butadiene **12** were obtained as by-products. The formation of **12**, which results from a Pd-catalyzed homocoupling of the vinyl bromide **5**, could be avoided by employing a twofold excess of **2**. The alkene **2** is stable under these reaction conditions and the unchanged excess can be reisolated quantitatively. The use of the catalyst system consisting of [Pd(CH$_3$CN)$_2$Cl$_2$]·6Ph$_4$PCl and dimethylglycine as additive recently reported by Reetz et al.,[31,32] led to a complete decomposition of the bromoalkene **5**.

The facial selectivity in the formation of **10** is obviously caused by the angular methyl group in **2** directing the attack of **5** to the sterically less-hindered α-side of **2**; on the contrary, the regioselective C−C coupling at C-4 of **2** cannot easily be explained. Since C-5 is clearly sterically less hindered than C-4 one would expect the C−C-coupling to take place at this carbon atom according to the empirical theorem of Heck reactions. We therefore assume that the transformation is governed by a stereoelectronic effect; thus, as the first step an attack of palladium occurs at C-5 from the α-face to allow a chair-like transition state with a subsequent *syn* addition of the vinyl group at C-4 (structure **T1**); an attack of palladium at C-4 in **2** would lead to an energetically less-favored boat-like transition state.[33] However, a high selectivity would also be obtained if one assumes that the first step to give the two possible regioisomeric Pd intermediates is reversible under the reaction conditions, and that the subsequent elimination of a PdH species to provide the undesired regioisomer is slow compared to the formation of **10**.

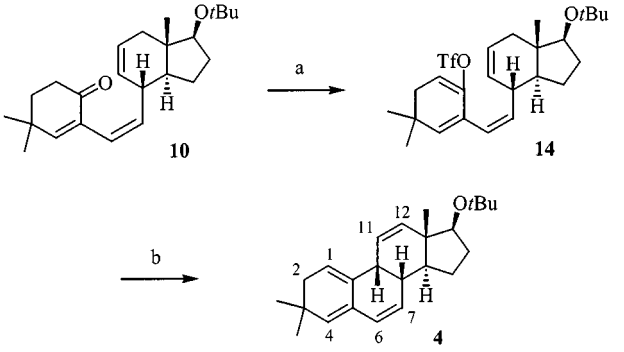


Scheme 4. Intermolecular Heck reaction of **5** and **2**: a) 1.0 mol-% **13**, nBu$_4$NOAc, DMF/CH$_3$CN/H$_2$O, 115 °C, 7 h, 56% (*Z*)-**10**, 10% dimer **12**, traces (*E*)-**11**

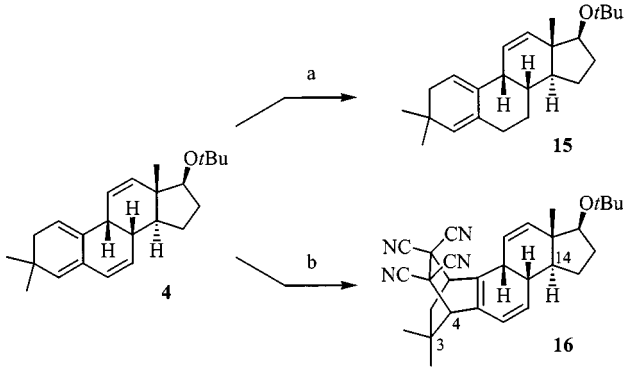
The enone **10** was converted into the enol triflate **14** in 94% yield by treatment with potassium hexamethyldisilazide (KHMDS) and *N*-phenyltriflimide (Tf$_2$NPh) at −78 °C (Scheme 5);[34,35] compound **14** was initially exposed to standard Heck conditions [Pd(OAc)$_2$, PPh$_3$ and NEt$_3$ in MeCN at 70 °C], which provided the desired tetracyclic product **4** in 51% yield. However, when the reaction was performed with Pd(dppb) as catalyst and excess KOAc as base in *N*,*N*-dimethylacetamide at 75 °C, the estrane **4** could be obtained in 85% yield.[36] Compound **4** represents a new type of steroid skeleton with an unnatural *cis*-B/C ring fusion and unsaturations in the positions 1(10), 4, 6, and 11, which allow further derivatizations.

Homogeneous hydrogenation employing Wilkinson's catalyst allowed the selective reduction of the sterically less-hindered $\Delta^{6,7}$ double bond in **4** (Scheme 6). Thus, **4** was transformed into the triene **15** in the presence of 10 mol-% (PPh$_3$)$_3$RhCl in methanol/ethyl acetate at a hydrogen pressure of 3 bar and ambient temperature in 84% yield. The $\Delta^{11,12}$ double bond is much less reactive under these conditions, since attack at the β-face of **4** is hindered by the angular methyl group, while attack at the α-face is hindered by the annulated cyclohexane ring.

The 1,3-butadiene moiety in ring A of **4** can undergo cycloaddition reactions; while *N*-phenylmaleimide proved



Scheme 5. Conversion of enone **10** to enol triflate **14** and subsequent Pd-catalyzed cyclization to estrane **4**: a) KHMDS, Tf_2NPh, THF, −78 °C, 30 min., 94%; b) $Pd(dba)_2$, dppb, KOAc, DMAC, 75 °C, 18 h, 85%



Scheme 6. Derivatization of steroid **4** by hydrogenation and Diels−Alder reaction: a) $(PPh_3)_3RhCl$, 3 bar H_2, EtOAc, MeOH, 12 h, 84%; b) TCNE, toluene, reflux, 2 days, 74%

not to be reactive enough as dienophile, the reaction of **4** and tetracyanoethylene (TCNE) led to the cycloadduct **16** in 74% yield as a single diastereomer. Thus, the attack of the dienophile takes place exclusively from the β-face; this is caused by the hinge-shaped conformation of **4** which prevents an attack from the α-face hence overruling the shielding effect of the angular methyl group. However, as expected, due to the steric hindrance the Diels−Alder reaction is rather slow; thus, to obtain a nearly complete conversion a reaction time of 2 days at 110 °C was necessary.

The structures of the new compounds were confirmed by NMR spectroscopy. In the ^1H NMR spectrum of **10** the signals of 5′′-H and 6′′-H were found at δ = 5.35 and δ = 5.64, respectively, with a coupling constant for these protons of J = 9.8 Hz. The protons at C-2′ and C-1′ resonate at δ = 5.36 and δ = 6.11, respectively, with a coupling constant of J = 11.4 Hz, which is a typical value for a (*Z*) double bond. In the ^1H NMR spectrum of **4**, doublets of doublets at δ = 5.53 and δ = 5.64 are found for the protons at C-7 and C-11, respectively. The doublets at δ = 5.81 and δ = 5.89 were assigned to the protons at C-12 and C-6. The coupling constant between 6-H and 7-H is J = 9.8 Hz; the one between 11-H and 12-H has a comparable value of J = 10.2 Hz. The *cis*-orientation of the rings B and C in **4** was confirmed by ^1H-^1H NOESY experiments in which interactions between the protons of the methyl group at C-13 and the proton at C-8, as well as between the proton at C-8 and the one at C-9, could be detected. The configuration of **16** was also confirmed by NOESY experiments, which show an interaction between one of the methyl groups at C-3 and the proton at C-14.

Conclusion

The novel 19-nor-steroid derivative **4** was synthesized in an efficient approach by forming the ring B of the steroid skeleton using two subsequent stereoselective Heck reactions. Rings B and C of **4** have the unnatural *cis*-configuration and the double bonds in **4** can be used for further interesting functionalizations, as shown by the Diels−Alder cycloaddition of **4** with tetracyanoethylene.

Experimental Section

General: All reactions were performed in oven−dried glassware under an argon atmosphere. Solvents were degassed by the freeze-pump-thaw methodology. TLC chromatography 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: Mettler FP61. Optical rotations: Perkin−Elmer 241. IR: Bruker IFS 25. UV/Vis: Perkin−Elmer Lambda 9. NMR: Varian VXR-200 (200 MHz, ^1H), Bruker AM-300 (300 MHz, 75 MHz, ^1H and ^{13}C, respectively), Varian VXR-500 (500 MHz, 125 MHz, for ^1H and ^{13}C, respectively). For ^1H and ^{13}C NMR, $CDCl_3$ as solvent, TMS as internal standard. Chemical shifts are reported on the δ scale. Signals are quoted as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and br (broad). MS: Varian MAT 311A (70 eV, EI). HRMS: Varian MAT 731. Elemental analysis: Mikroanalytisches Labor des Instituts für Organische Chemie der Universität Göttingen.

2-(2,2-Dibromovinyl)-4,4-dimethylcyclohex-2-enone (9): A solution of PPh_3 (60.1 g, 229 mmol) in CH_2Cl_2 (160 mL) was added slowly to a stirred solution of CBr_4 (38.0 g, 115 mmol) in CH_2Cl_2 (170 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 30 min., and then a solution of the aldehyde **8** (8.72 g, 57.3 mmol) in CH_2Cl_2 (170 mL) was added within 1 h. After continuation of stirring for 1 h at 0 °C and 1.5 h at room temp., the mixture was poured onto petroleum ether (1.5 L), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (petroleum ether/ethyl acetate, 10:1) provided 13.9 g (45.3 mmol, 79%) of the vinyl dibromide **9**. R_f = 0.38 (petroleum ether/ethyl acetate, 10:1). − UV (CH_3CN): λ_{max} (lg ε) = 216 nm (3.64), 266 (3.21). − IR (neat): $\tilde{\nu}$ = 2960, 2928, 2864, 1682, 1602 cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.22 (s, 6 H, 2 × CH_3), 1.89 (t, J = 6.8 Hz, 2 H, 5-H_2), 2.51 (t, J = 6.8 Hz, 2 H, 6-H_2), 7.12 (br. s, 1 H, 3-H), 7.21 (br. s, 1 H, 1′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.5 (2 × CH_3), 33.6 (C-4), 34.3 (C-5), 35.2 (C-6), 91.1 (C-2′), 131.2 (C-3), 132.1 (C-2), 159.1 (C-1′), 196.5 (C-1). − EI-MS (70 eV): *m/z* (%) = 307.9 (4) [M^+], 227.0 (100) [M^+ − Br]. − EI-HRMS ($C_{10}H_{12}Br_2O$): calcd. 305.9255; found 305.9255.

(*Z*)-2-(2-Bromovinyl)-4,4-dimethylcyclohex-2-enone (5): Neat nBu_3SnH (10.6 g, 36.4 mmol) was added with a syringe to a thoroughly degassed solution of the 1,1-dibromoalkene **9** (10.2 g, 33.1 mmol) and $Pd(PPh_3)_4$ (1.53 g, 4.0 mol-%) in anhydrous toluene (200 mL). The reaction mixture was stirred for 2.5 h at room

temp., poured onto petroleum ether (600 mL), washed with water (200 mL) and brine (200 mL), and dried over $MgSO_4$. Concentration in vacuo and purification by column chromatography (petroleum ether/ethyl acetate, 100:1) afforded 5.42 g (23.7 mmol, 71%) of the (*Z*)-bromoalkene **5**. R_f = 0.34 (petroleum ether/ethyl acetate, 10:1). − UV (CH_3CN): λ_{max} (lg ε) = 211 nm (3.79), 262 (3.24). − IR (neat): $\tilde{\nu}$ = 2958, 2928, 2864, 1682, 1608 cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.24 (s, 6 H, 2 × CH_3), 1.90 (t, *J* = 6.8 Hz, 2 H, 5-H_2), 2.53 (t, *J* = 6.8 Hz, 2 H, 6-H_2), 6.41 (d, *J* = 8.0 Hz, 1 H, 2′-H), 6.87 (dd, *J* = 8.0, 1.0 Hz, 1 H, 1′-H), 7.28 (d, *J* = 1.0 Hz, 1 H, 3-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.7 (2 × CH_3), 33.4 (C-4), 34.3 (C-6), 35.3 (C-5), 108.7 (C-2′), 126.4 (C-1′), 130.8 (C-2), 158.7 (C-3), 197.3 (C-1). − EI-MS (70 eV): *m/z* (%) = 228.0 (2) [M^+], 149.1 (100) [M^+ − Br]. EI-HRMS ($C_{10}H_{13}BrO$): calcd. 228.0149; found 228.0149. − $C_{10}H_{13}BrO$ (229.1): calcd. C 52.42, H 5.72, Br 34.87; found C 52.51, H 5.71, Br 34.71.

Intermolecular Heck reaction of 5 and 2: *trans*-Di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphanyl)benzyl]dipalladium(II) (**13**; 9.0 mg, 1.0 mol-%) was added to a thoroughly degassed solution of the hexahydroindene **2** (416 mg, 2.00 mmol), the bromoalkene **5** (229 mg, 1.00 mmol) and nBu_4NOAc (754 mg, 2.50 mmol) in DMF/CH_3CN/H_2O (1:1:0.2, 15 mL) under an argon atmosphere. The reaction mixture was stirred for 6 h at 115 °C and cooled to room temp. Diethyl ether (25 mL) and water (25 mL) were added, and the aqueous phase was extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated in vacuo. Purification of the residue by column chromatography (petroleum ether/ethyl acetate, 20:1) gave 200 mg (0.56 mmol, 56%) of the desired product **10** and 15.0 mg (50.0 μmol, 10%) of the dimer **12**. Furthermore 276 mg (1.32 mmol) of the remaining hydrindane **2** and traces of **11** were isolated.

(*Z*)-2-{2-[(1*R*,3a*S*,4*S*,7a*S*)-1-*tert*-Butoxy-2,3,3a,4,7,7a-hexahydro-7a-methyl-1*H*-indene-4-yl]vinyl}-4,4-dimethylcyclohex-2-enone (10): R_f = 0.12 (petroleum ether/ethyl acetate, 40:1). − $[\alpha]_D^{20}$ = −39.3 (*c* = 0.4, $CHCl_3$). − UV (CH_3CN): λ_{max} (lg ε) = 208 nm (3.68), 260 (3.01). − IR (neat): $\tilde{\nu}$ = 3014, 2964, 2930, 2870, 1680, 1464, 1388, 1360, 692 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.69 (s, 3 H, 7′′a-CH_3), 1.10 (s, 9 H, 1′′-O*t*Bu), 1.16 (s, 6 H, 2 × 4-CH_3), 1.18−1.63 (m, 4 H, 2′′-H_a, 3′′-H_2, 3′′a-H), 1.73−1.83 (m, 2 H, 7′′-H_a, 2′′-H_b), 1.84 (t, *J* = 6.4 Hz, 2 H, 5-H_2), 1.99 (ddt, *J* = 17.2, 5.0, 1.8 Hz, 1 H, 7′′-H_b), 2.46 (t, *J* = 6.4 Hz, 2 H, 6-H_2), 2.94 (m_c, 1 H, 4′′-H), 3.47 (t, *J* = 8.5 Hz, 1 H, 1′′-H), 5.35 (dddd, *J* = 9.8, 2.8, 1.4, 1.4 Hz, 1 H, 5′′-H), 5.36 (dd, *J* = 11.4, 10.5 Hz, 1 H, 2′-H), 5.64 (dddd, *J* = 9.8, 5.0, 2.5, 2.5 Hz, 1 H, 6′′-H), 6.11 (d, *J* = 11.4 Hz, 1 H, 1′-H), 6.49 (s, 1 H, 3-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 11.3 (7′′a-CH_3), 24.9 (C-2′′), 27.7 (4-CH_3), 28.1 (4-CH_3), 28.7 [OC(CH_3)$_3$], 30.5 (C-3′′), 33.2 (C-4), 34.6 (C-6), 35.8 (C-5), 38.4 (C-4′′), 38.8 (C-7′′), 41.3 (C-7′′a), 46.2 (C-3′′a), 72.2 [O*C*(CH_3)$_3$], 80.6 (C-1′′), 124.3 (C-1′), 127.3 (C-6′′), 129.1 (C-5′′), 132.9 (C-2), 136.6 (C-2′), 156.6 (C-3), 198.8 (C-1). − EI-MS (70 eV): *m/z* (%) = 356.2 (9) [M^+], 299.2 (18) [M^+ − C_4H_9], 168.1 (56) [$C_{10}H_{16}O^+$], 124.1 (100) [$C_8H_{12}O^+$], 57.0 (56) [$C_4H_9^+$], 41.0 (19) [$C_3H_5^+$]. − EI-HRMS ($C_{24}H_{36}O_2$): calcd. 356.2715; found 356.2715. − $C_{24}H_{36}O_2$ (356.5): calcd. C 80.85, H 10.18; found C 80.62, H 10.27.

(*E*)-2-{1-[(1*R*,3a*S*,4*S*,7a*S*)-1-*tert*-Butoxy-2,3,3a,7,7,7a-hexahydro-7a-methyl-1*H*-indene-4-yl]vinyl}-4,4-dimethylcyclohex-2-enone (11): R_f = 0.15 (petroleum ether/ethyl acetate, 40:1). − $[\alpha]_D^{20}$ = −77.0 (*c* = 0.5, $CHCl_3$). − UV (CH_3CN): λ_{max} (lg ε) = 211 nm (3.44), 273 (2.97). − IR (neat): $\tilde{\nu}$ = 3016, 2967, 2930, 2871, 1681, 1461, 1389, 1362 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.74 (s, 3 H, 7′′a-CH_3), 1.12 (s, 9 H, 1′′-O*t*Bu), 1.15 (s, 6 H, 2 × 4-CH_3), 1.17−1.70 (m, 4 H, 2′′-H_a, 3′′-H_2, 3′′a-H), 1.76−1.90 (m, 2 H, 7′′-H_a, 2′′-H_b), 1.81 (t, *J* = 6.8 Hz, 2 H, 5-H_2), 1.99 (ddt, *J* = 17.3, 5.2, 1.5 Hz, 1 H, 7′′-H_b), 2.46 (t, *J* = 6.8 Hz, 2 H, 6-H_2), 2.59 (m_c, 1 H, 4′′-H), 3.46 (t, *J* = 8.3 Hz, 1 H, 1′′-H), 5.45 (dddd, *J* = 9.8, 2.2, 1.1, 1.1 Hz, 1 H, 5′′-H), 5.64 (dddd, *J* = 9.8, 4.9. 2.5, 2.5 Hz, 1 H, 6′′-H), 5.95 (dd, *J* = 15.8, 8.3 Hz, 1 H, 2′-H), 6.19 (d, *J* = 15.8 Hz, 1 H, 1′-H), 6.55 (s, 1 H, 3-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 11.3 (7′′a-CH_3), 24.8 (C-2′′), 28.0 (2 × 4-CH_3), 28.7 [OC(CH_3)$_3$], 30.5 (C-3′′), 33.1 (C-4), 35.0 (C-6), 35.8 (C-5), 38.7 (C-7′′), 41.5 (C-7′′a), 43.6 (C-4′′), 46.1 (C-3′′a), 72.2 [O*C*(CH_3)$_3$], 80.6 (C-1′′), 123.7 (C-1′), 126.7 (C-6′′), 129.1 (C-5′′), 133.9 (C-2), 134.8 (C-2′), 153.1 (C-3), 198.1 (C-1). − EI-MS (70 eV): *m/z* (%) = 356.3 (19) [M^+], 299.2 (26) [M^+ − C_4H_9], 57.0 (100) [$C_4H_9^+$], 40.9 (57) [$C_3H_5^+$]. − EI-HRMS ($C_{24}H_{36}O_2$): calcd. 356.2715, found 356.2715.

(*Z*,*Z*)-1,4-Bis(5,5-dimethyl-2-oxocyclohexenyl)-1,3-butadiene (12): R_f = 0.11 (petroleum ether/ethyl acetate, 10:1). − UV (CH_3CN): λ_{max} (lg ε) = 225 nm (3.55), 267 (3.74), 276 (3.71), 289 (3.64), 319 (3.70). − IR (neat): $\tilde{\nu}$ = 3040, 2958, 2864, 1672, 1360 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (s, 12 H, 4 × CH_3), 1.85 (t, *J* = 7.0 Hz, 4 H, 2 × 4′-H_2), 2.51 (t, *J* = 7.0 Hz, 4 H, 2 × 3′-H_2), 6.40 (m_c, 2 H, 2-H, 3-H), 6.68 (s, 2 H, 2 × 6′-H), 6.79 (m_c, 2 H, 1-H, 4-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 28.0 (4 × CH_3), 33.4 (2 × C-5′), 35.1 (2 × C-4′), 35.7 (2 × C-3′), 126.9 (C-2, C-3), 131.3 (C-1, C-4), 133.0 (2 × C-1′), 153.9 (2 × C-6′), 198.1 (2 × C-2′). − EI-MS (70 eV): *m/z* (%) = 298.2 (8) [M^+], 200.1 (100) [M^+ − $C_6H_{10}O$], 91.0 (75) [$C_7H_7^+$]. − $C_{20}H_{26}O_2$ (298.4): calcd. C 80.50, H 8.78; found C 80.30, H 8.88.

(*Z*)-Trifluoromethanesulfonic Acid 6-{2-[(1*R*,3a*S*,4*S*,7a*S*)-1-*tert*-Butoxy-2,3,3a,4,7,7a-hexyhydro-7a-methyl-1*H*-inden-4-yl]vinyl}-4,4-dimethylcyclohexa-1,5-dienyl Ester (14): KHMDS (3.9 mL of a 0.5 M solution in toluene, 1.95 mmol) was added to a solution of enone **10** (458 mg, 1.28 mmol) and *N*-phenyltriflamide (597 mg, 1.67 mmol) in THF (5 mL) at −78 °C. After 30 min., the reaction mixture was allowed to warm to room temp., diluted with ethyl acetate (50 mL) and washed successively with saturated aqueous solutions of NH_4Cl (20 mL), $NaHCO_3$ (20 mL) and brine (20 mL). The organic phase was dried with $MgSO_4$ and concentrated in vacuo. The residual oil was subjected to flash chromatography (petroleum ether/ethyl acetate, 100:1) to afford 590 mg (1.21 mmol, 94%) of the triflate **14**. R_f = 0.47 (petroleum ether/ethyl acetate, 30:1). − $[\alpha]_D^{20}$ = −18.8 (*c* = 1, $CHCl_3$). − UV (CH_3CN): λ_{max} (lg ε) = 222 nm (3.45), 270 (2.74), 313 (2.10), 330 (2.06). − IR (neat): $\tilde{\nu}$ = 3017, 2969, 2932, 2874, 1389, 1362, 1210, 1144 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.80 (s, 3 H, 7′′a-CH_3), 0.84 (s, 3H, 4-CH_3), 1.01 (s, 3 H, 4-CH_3), 1.08 (s, 9 H, 1′′-O*t*Bu), 1.12−1.84 (m, 7 H, 2′′-H_2, 3′′-H_2, 3′′a-H, 7′′-H_a, 3-H_a), 1.74 (dd, *J* = 9.2, 4.7 Hz, 1 H, 3-H_b), 2.04 (m_c, 1 H, 7′′-H_b), 3.22 (m_c, 1 H, 4′′-H), 3.28 (t, *J* = 8.1 Hz, 1 H, 1′′-H), 5.33 (t, *J* = 4.7 Hz, 1 H, 2-H), 5.48 (dd, *J* = 10.9, 10.9 Hz, 1 H, 2′-H), 5.54 (br. s, 1 H, 5-H), 5.60 (dddd, *J* = 9.8, 2.6, 1.5, 1.5 Hz, 1 H, 5′′-H), 5.69 (dddd, *J* = 9.8, 4.9, 2.3, 2.3 Hz, 1 H, 6′′-H), 6.12 (d, *J* = 10.9 Hz, 1 H, 1′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 11.2 (7′′a-CH_3), 24.9 (C-3′′), 26.5 (4-CH_3), 27.1 (4-CH_3), 28.4 [OC(CH_3)$_3$], 30.5 (C-2′′), 31.1 (C-4), 36.0 (C-7′′), 38.7 (C-3), 38.9 (C-4′′), 41.3 (C-7′′a), 45.9 (C-3′′a), 71.7 [O*C*(CH_3)$_3$], 80.4 (C-1′′), 114.5 (C-2), 118.7 (q, *J* = 320 Hz, CF_3), 122.9 (C-1′), 126.7 (C-6), 127.2 (C-6′′), 128.8 (C-5′′), 138.5 (C-2′), 139.9 (C-5), 145.8 (C-1). − EI-MS (70 eV): *m/z* (%) = 488.3 (12) [M^+], 357.0 (58) [M^+ − F_3CSO_2], 119.1 (35) [$C_9H_{11}^+$], 105.0 (44) [$C_8H_9^+$], 91.0 (100) [$C_7H_7^+$], 69.0 (40) [CF_3^+], 57.0 (58) [$C_4H_9^+$], 40.9 (52) [$C_3H_5^+$]. − EI-HRMS ($C_{25}H_{35}F_3O_4S$): calcd. 488.2208; found 488.2208.

Intramolecular Heck reaction of Enol Triflate 14. (−)-17β-*tert*-Butoxy-3,3-dimethyl-9β-estra-1(10),4,6,11-tetraene (4): A 0.07 M solution of Pd(dppb) in *N*,*N*-dimethylacetamide (DMAC) was prepared by stirring $Pd(dba)_2$ (52.8 mg, 92.0 μmol, 13 mol-%) and 1,4-bis(diphenylphosphanyl)butane (dppb) (43.2 mg, 101 μmol, 14 mol-%) in DMAC (1.5 mL) under argon at room temp. until the initial dark red suspension became a green-orange solution (about 15 min.). To this solution was added a solution of the enol triflate **14** (208 mg, 426 μmol) in DMAC (3 mL) and solid anhydrous KOAc (379 mg, 3.86 mmol). The reaction mixture was thoroughly degassed, stirred at 75 °C for 18 h, cooled to room temp., and diluted with diethyl ether (20 mL). After stirring in air for 5 min. the mixture was filtered through a pad of silica gel (8.0 g) wetted with diethyl ether, and the filter pad rinsed with diethyl ether (400 mL). The filtrate was concentrated in vacuo. Purification of the residue by column chromatography on silica gel (petroleum ether/ethyl acetate, 30:1) gave 123 mg (362 μmol, 85%) of **4**. R_f = 0.14 (petroleum ether/ethyl acetate, 100:1). − $[\alpha]_D^{20}$ = −289.0 (c = 1, $CHCl_3$). − UV (CH_3CN): λ_{max} (lg ε) = 220 nm (3.63), 226 (3.68), 269 (3.16). − IR (neat): $\tilde{\nu}$ = 3022, 2970, 2906, 2869, 1388, 1375, 1360, 714 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.83 (s, 3 H, 13-CH_3), 0.93 (s, 3 H, 3-CH_3), 1.03 (s, 3 H, 3-CH_3), 1.12 (s, 9 H, 17-O*t*Bu), 1.18−1.55 (m, 4 H, 14-H, 15-H_2, 16-H_a), 1.87 (m_c, 1 H, 16-H_b), 1.96 (ddd, J = 16.9, 6.4, 1.6 Hz, 1 H, 2-H_a), 2.01 (ddd, J = 16.9, 4.1, 2.6 Hz, 1 H, 2-H_b), 2.41 (ddd, J = 10.9, 5.6, 5.6 Hz, 1 H, 8-H), 2.86 (m_c, 1 H, 9-H), 3.33 (dd, J = 8.6, 6.0 Hz, 1 H, 17-H), 5.17 (s, 1 H, 4-H), 5.39 (ddd, J = 5.6, 2.8, 2.8 Hz, 1 H, 1-H), 5.53 (dd, J = 9.8, 6.0 Hz, 1 H, 7-H), 5.64 (dd, J = 10.2, 4.6 Hz, 1 H, 11-H), 5.81 (d, J = 10.2 Hz, 1 H, 12-H), 5.89 (d, J = 9.8 Hz, 1 H, 6-H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.3 (13-CH_3), 23.1 (C-15), 25.7 (3-CH_3), 28.8 [17-OC(CH_3)$_3$], 30.1 (3-CH_3), 30.6 (C-3), 32.0 (C-16), 35.9 (C-8), 38.9 (C-2), 39.2 (C-9), 45.1 (C-14), 46.0 (C-13), 72.3 [17-OC(CH_3)$_3$], 76.5 (C-17), 120.9 (C-1), 126.2 (C-11), 127.2 (C-6), 129.2 (C-7), 130.4 (C-5), 133.4 (C-4), 134.3 (C-10), 135.6 (C-12). − EI-MS (70 eV): m/z (%) = 338.2 (29) [M^+], 281.2 (42) [$M^+ - C_4H_9$], 263.2 (74) [$M^+ - C_4H_9 - H_2O$], 57.0 (100) [$C_4H_9^+$], 40.9 (37) [$C_3H_5^+$]. − EI-HRMS ($C_{24}H_{34}O$): calcd. 338.2610; found 338.2609.

(−)-17β-*tert*-Butoxy-3,3-dimethyl-9β-estra-1(10),4,11-triene (15): A solution of **4** (87.0 mg, 257 μmol) and $(PPh_3)_3RhCl$ (24.0 mg, 10 mol-%) in methanol/ethyl acetate (1:1, 5 mL) was shaken for 12 h at room temp. under a H_2 atmosphere (3 bar). The reaction mixture was concentrated in vacuo. Purification by column chromatography (petroleum ether/ethyl acetate, 100:1) gave 74.0 mg (216 μmol, 84%) **15** as colorless oil. R_f = 0.18 (petroleum ether). − $[\alpha]_D^{20}$ = −19.0 (c = 0.2, $CHCl_3$). − UV (CH_3CN): λ_{max} (lg ε) = 243 nm (3.40). − IR (neat): $\tilde{\nu}$ = 3014, 2972, 2931, 2869, 1659, 1387, 1362 cm^{-1}. − ^1H NMR (300 MHz, C_6D_6): δ = 0.87 (s, 3 H, 3-CH_3), 0.89 (s, 3 H, 3-CH_3), 1.02 (s, 9 H, 17-O*t*Bu), 1.05 (s, 3 H, 13-CH_3), 1.19−1.64 (m, 4 H, 14-H, 15-H_2, 16-H_a), 1.77−2.08 (m, 6 H, 2-H_a, 16-H_b, 6-H_2, 7-H_2), 2.11−2.37 (m, 2 H, 2-H_b, 8-H), 3.07 (m_c, 1 H, 9-H), 3.52 (dd, J = 8.7, 7.0 Hz, 1 H, 17-H), 5.39 (m_c, 1 H, 1-H), 5.56 (br. s, 1 H, 4-H), 5.97 (dd, J = 9.9, 4.9 Hz, 1 H, 11-H), 6.09 (d, J = 9.9 Hz, 1 H, 12-H). − ^{13}C NMR (75.5 MHz, C_6D_6): δ = 15.5 (13-CH_3), 23.4 (C-15), 25.6 (C-7), 28.2 (3-CH_3), 28.7 (3-CH_3), 28.8 [17-OC(CH_3)$_3$], 30.3 (C-3), 31.7 (C-8), 32.5 (C-16), 39.9 (C-9), 41.0 (C-6), 42.3 (C-14), 45.8 (C-2), 46.5 (C-13), 72.2 [17-OC(CH_3)$_3$], 77.6 (C-17), 121.1 (C-1), 123.7 (C-4), 129.0 (C-11), 133.4 (C-5), 134.8 (C-12), 136.0 (C-10). − EI-MS (70 eV): m/z (%) = 340.3 (6) [M^+], 283.2 (100) [$M^+ - C_4H_9$], 265.2 (52) [$M^+ - C_4H_9 - H_2O$], 105.1 (29) [$C_8H_9^+$], 57.0 (52) [$C_4H_9^+$], 41.0 (20) [$C_3H_5^+$]. − EI-HRMS ($C_{24}H_{36}O$): calcd. 340.2766, found 340.2766.

(−)-17β-*tert*-Butoxy-3,3-dimethyl-1,4-(ethanotetracarbonitrile)-9β-estra-5(10),6,11-triene (16): A solution of tetracyanoethylene (18.0 mg, 140 μmol) in toluene (4 mL) was added to a solution of the steroid **4** (30.0 mg, 87.0 μmol) in anhydrous toluene (3 mL) at room temp. The reaction mixture was refluxed for 2 d, cooled to room temp., diluted with diethyl ether (20 mL) and washed with saturated $NaHSO_3$ solution. The separated organic phase was washed with brine, dried with Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (petroleum ether/ethyl acetate, 10:1) afforded 30.0 mg (64.0 μmol, 74%) of the Diels−Alder product **16** as a white solid. R_f = 0.25 (petroleum ether/ethyl acetate, 10:1). − $[\alpha]_D^{20}$ = −130.3 (c = 0.4, $CHCl_3$). − UV (CH_3CN): λ_{max} (lg ε) = 279 nm (2.93). − IR (KBr): $\tilde{\nu}$ = 3019, 2973, 2941, 2876, 1458, 1363 cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.81 (s, 3 H, 13-CH_3), 1.00 (s, 3 H, 3-CH_3), 1.13 (s, 9 H, 17-O*t*Bu), 1.17−1.60 (m, 3 H, 15-H_2, 16-H_a), 1.36 (dd, J = 14.5, 3.2 Hz, 1 H, 2-H_a), 1.49 (s, 3 H, 3-CH_3), 1.67 (ddd, J = 12.3, 12.3, 6.7 Hz, 1 H, 14-H), 1.88−1.97 (m, 1 H, 16-H_b), 2.08 (dd, J = 14.5, 2.4 Hz, 1 H, 2-H_b), 2.73 (dddd, J = 12.3, 10.1, 3.2, 2.3 Hz, 1 H, 8-H), 2.96 (s, 1 H, 4-H), 3.43 (dd, J = 8.8, 7.0 Hz, 1 H, 17-H), 3.57 (ddd, J = 10.1, 4.4, 2.0 Hz, 1 H, 9-H), 3.64 (dd, J = 3.2, 2.4 Hz, 1 H, 1-H), 5.64 (dd, J = 9.9, 4.4 Hz, 1 H, 11-H), 5.84 (m, 2 H, 6-H, 7-H), 6.12 (dd, J = 9.9, 2.0 Hz, 1 H, 12-H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.3 (13-CH_3), 22.8 (C-15), 28.7 [17-OC(CH_3)$_3$], 29.4 (3-CH_3), 31.6 (C-16), 32.7 (C-3), 32.8 (3-CH_3), 33.7 (C-8), 35.9 (C-2), 37.4 (C-9), 41.4 (C-2′), 42.0 (C-1), 42.1 (2 C, C-14, C-1′), 43.9 (C-13), 53.7 (C-4), 72.5 [17-OC(CH_3)$_3$], 76.1 (C-17), 111.2, 111.9, 112.1, 112.2 (4 × CN), 120.9 (C-11), 122.2 (C-6), 130.9 (C-5), 131.8 (C-7), 134.6 (C-10), 139.1 (C-12). − EI-MS (70 eV): m/z (%) = 446.2 (1) [M^+], 392.3 (12) [$M^+ - C_4H_8 - H_2O$], 350.2 (14) [$M^+ - C_4H_8 - C_4H_9$], 264.2 (22) [$M^+ - C_4H_8 - H_2O$ − TCNE], 222.2 (25) [$C_{15}H_{26}O^+$], 57.0 (100) [$C_4H_9^+$], 41.0 (10) [$C_3H_5^+$]. − EI-HRMS ($C_{30}H_{34}N_4O$): calcd. 466.2733; found 466.2733.

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