Novel Medium Ring Sized Estradiol Derivatives by Intramolecular Heck Reactions

Lutz F. Tietze,*[a] Konrad M. Sommer,[a] Gyula Schneider,*[b] Pál Tapolcsányi,[b] János Wölfling,[b] Peter Müller,[c] Mathias Noltemeyer,[c] Heinrich Terlau[d]

[a] Institut für Organische Chemie, Universität Göttingen, Tammannstr. 2, 37077 Göttingen, Germany
Fax +49(551)399476; E-mail: ltietze@gwdg.de

[b] Department of Organic Chemistry, University of Szeged, Dóm tér 8, 6720 Szeged, Hungary
Fax +36(62)544200; E-mail: schneider@chem.u-szeged.hu

[c] Institut für Anorganische Chemie, Universität Göttingen, Tammannstr. 4, 37077 Göttingen, Germany
Fax +49(551)393373; E-mail: m.noltemeyer@gmx.de; E-mail: peterm@shelx.uni-ac.gwdg.de

[d] Max-Planck-Institut für Experimentelle Medizin, Hermann-Rein-Straße 3, 37075 Göttingen, Germany
Fax +49(551)3899475; E-mail: hterlau@gwdg.de

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Abstract: New steroids with a seven-, eight- or nine-membered D-ring have been synthesized from a D-*seco*-estrone derivative by a Grignard and an intramolecular Heck reaction.

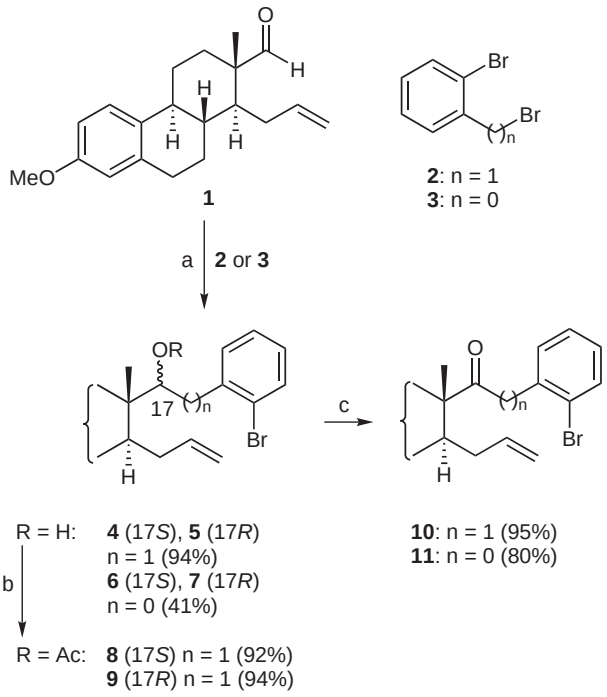
Key words: carbocycles, steroids, Grignard reactions, Heck reaction, estradiol derivatives

The Heck reaction is a powerful synthetic tool for the construction of carbo- and heterocyclic compounds.[1] Recently, we have shown, how this transformation can be successfully used in the synthesis of estradiols, D-*homo*-estradiols, *aza*-heterocycles and 19-*nor*-steroids.[2]

Here, we describe novel estrone derivatives, which are obtained from the D-*seco*-estrone derivative **1**[3] by a Grignard and an intramolecular Heck reaction. The new compounds contain seven-, eight- and nine-membered D-ring systems. There are only very few examples where seven-,[4–8] eight,[8,9] and nine-membered[8,10] carbocycles were prepared by a Heck reaction.

Grignard reaction of **1** with the Mg-compound derived from **2**[11–14] gave the secondary alcohols **4** and **5** as a 1.9:1 mixture of the two diastereomers in 94% yield, which were separated by column chromatography (Scheme 1).

In a similar way, the alcohols **6** and **7** were obtained from **1** in 41% yield and a 1.8:1 ratio with the Grignard reagent derived from **3**.[15] Oxidation of **4** and **5** led to the ketone **10** and that of **6** and **7** to the ketone **11** in 95% and 80% yield, respectively. In addition, we also prepared the acetates **8** and **9** in 92% and 94% yield from **4** and **5** using acetic anhydride/pyridine. To our surprise, the Heck reaction of the free alcohol **4** employing the palladacycle *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II)[16] as a catalyst led to the nine-membered estrone derivative **12** with an *E*-double bond as the main product, which was formed by an *endo* attack; in addition, the two eight-membered ring systems **13** and **15** were obtained (Scheme 2).[17]



Scheme 1 Synthesis of **4**–**11**
Reaction conditions: a) Mg/Et_2O; b) Ac_2O/pyridine; c) Dess–Martin reagent/CH_2Cl_2.

The total yield of the reaction was 45% due to the formation of some side products, which were not characterized. We then performed the Heck reaction of the acetates **8** and **9**, which provided higher yields and showed an interesting selectivity. Thus, the acetate **8** only led to the eight-membered derivatives **14** and **16** in 65% total yield, whereas the diastereomeric acetate **9** gave the eight-membered derivative **17** in 39% and the nine-membered compound **18** in 13% yield. The best results were obtained using the ketone **10**, which led to 60% of the octacycle **19** together with 14% of nonacycle **20** containing a *Z*-double bond.[18]

The Heck reaction of **11** using the palladacycle as the catalyst gave the heptacycles **21** and **22** as a 4:1 mixture of the double bond isomers in 80% yield, which could not be separated by chromatography.

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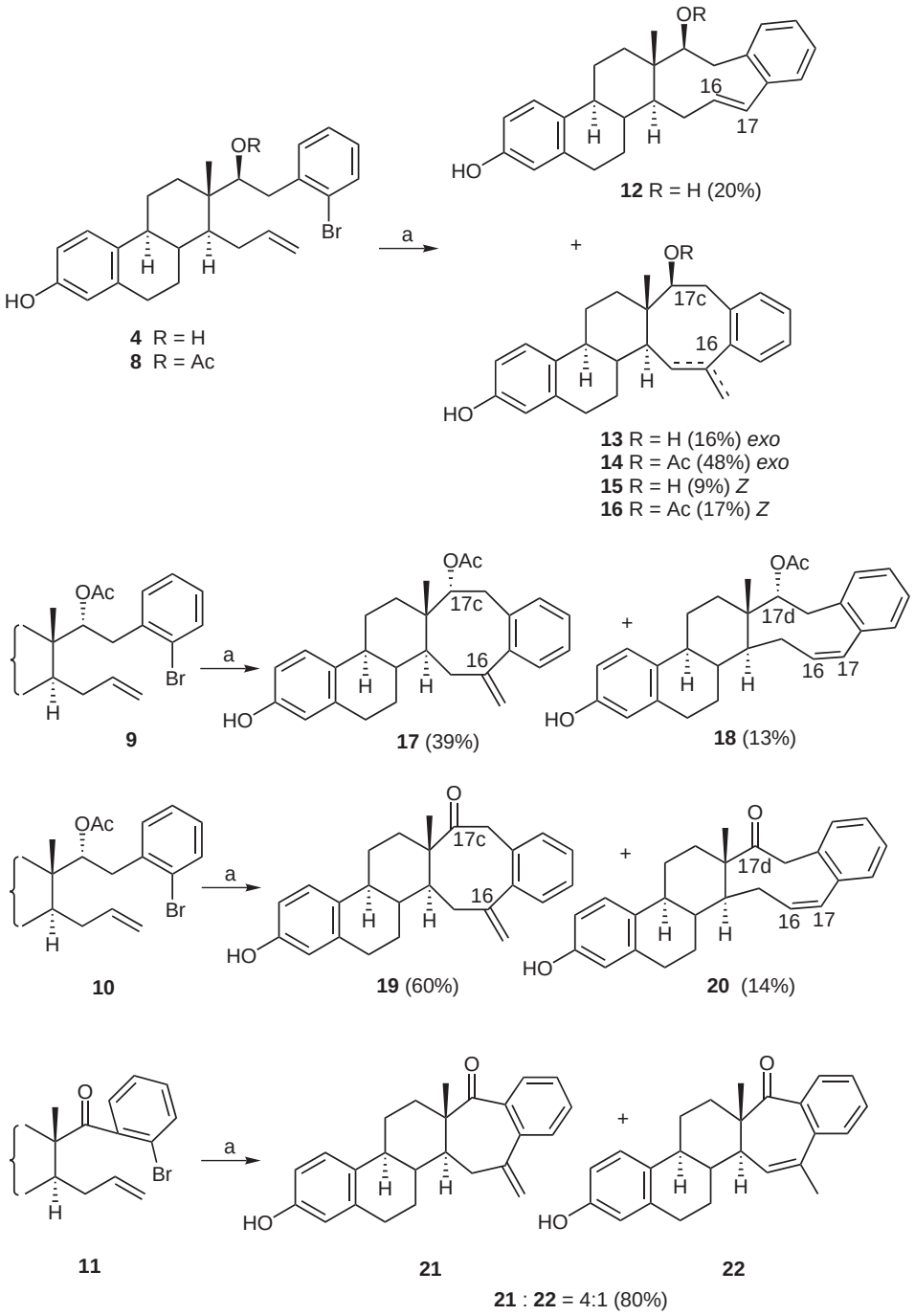

Scheme 2 Heck reaction of **4**, **8** and **9**–**11**
Reaction conditions: a) 2 mol% palladacycle, *n*-Bu_4NOAc, $DMF/CH_3CN/H_2O$ (5:5:1), 120 °C, 4 h.

The structures of **4** and **20** were determined by X-ray analysis.[19] In accordance with the data of these compounds, the structure determination of the other compounds was performed by NMR spectroscopy employing two-dimensional techniques. The configuration of the endocyclic double bond in **12** was determined by ^1H NMR spectroscopy. The large coupling constant of $J = 15.5$ Hz of the signals for the hydrogens at C-16 and C-17 confirm the *E*-configuration, which is unusual in nonacycles.[20] Furthermore, reduction of the keto function in **20** led to two diastereomeric alcohols, none of which is identical with **12**.

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(18) **Experimental Procedure for the Synthesis of 19 and 20:** To a degassed solution of **10** (300 mg, 0.64 mmol) and *n*-Bu_4NOAc (484 mg, 1.60 mmol) in DMF/CH_3CN/H_2O (5:5:1) (10 mL) was added under a nitrogen atmosphere *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)-benzyl]dipalladium(II) (12 mg, 2 mol%) and the mixture was stirred at 120 °C under reflux for 4 h. After cooling, H_2O (40 mL) was added; the resulting mixture was extracted with Et_2O (3 × 25 mL), washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (silica gel, CH_2Cl_2/petrol ether = 6/4) and repeated chromatography using $AgNO_3$-coated silica gel (CH_2Cl_2) afforded 149 mg (60%) of **19** as a colorless oil and 35 mg (14%) of **20** as white crystals.
Selected data for **19**: $[\alpha]_D^{20}$ +22.7 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, TMS): δ = 1.23 (s, 3 H, 18-H), 1.10–2.40 (m, 10 H), 2.76 (d, 1 H), 2.80 (m, 2 H, 6-H), 3.58 (d, 1 H, *J* = 15.2 Hz, 17b-H), 3.76 (s, 3 H, 3-OMe), 4.57 (d, 1 H, *J* = 15.2 Hz, 17b-H), 4.92 (s, 1 H, 16a-H), 5.28 (s, 1 H, 16a-H), 6.62 (d, 1 H, *J* = 2.6 Hz, 4-H), 6.73 (dd, 1 H, *J* = 8.6 Hz, 2.6 Hz, 2-H), 7.02–7.24 (m, 5 H, 1-H, 3′-H, 4′-H, 5′-H and 6′-H). ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 14.2 (C-18), 26.2 and 26.4 (2 C, C-11 and C-12), 29.9 (C-6), 37.3, 40.3, 41.2, 41.9, 42.9, 44.1 (C-17b), 53.0 (C-13), 55.2 (3-OCH_3), 111.7 (C-2), 113.4 (C-4), 120.7 (C-16a), 126.2, 126.5, 127.1, 129.0, 130.2, 132.0 (C-10), 134.0, 137.7 (C-5), 141.1, 147.4 (C-16), 157.7 (C-3), 215.3 (C-17c).

(19) Crystallographic data for **4** and **20** can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Deposition numbers: CCDC 168413 for **4** and CCDC 168412 for **20**.

(20) Selected data for **12**: $[\alpha]_D^{20}$ –28 (*c* 1.0, $CHCl_3$). Mp 173–175 °C. ^1H NMR (500 MHz, $CDCl_3$, TMS): δ = 1.01 (s, 3 H, 18-H), 1.10–2.50 (m, 13 H), 2.88 (m, 2 H, 6-H), 3.12 (d, 1 H, *J* = 11.9 Hz, 17c-H), 3.79 (s, 3 H, CH_3O), 4.00 (d, 1 H, *J* = 10.0 Hz, 17d-H), 5.99 (dt, 1 H, *J* = 15.5, *J* = 6.2 Hz, 16-H), 6.62 (d, 1 H, *J* = 15.5 Hz, 17-H), 6.65 (d, 1 H, *J* = 2.7 Hz, 4-H), 6.74 (dd, 1 H, *J* = 8.6 Hz, 2.7 Hz, 2-H), 7.08–7.37 (m, 5 H, 1-H, 3′-H, 4′-H, 5′-H, 6′-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.8 (C-18), 25.7 (C-11), 28.1 (C-7), 30.4, 30.5, 32.4, 35.8, 41.1, 42.2 (C-8), 43.1 (C-9), 44.8 (C-14), 55.2 (CH_3O), 73.6 (C-17d), 111.6 (C-2), 113.5 (C-4), 126.3, 126.6, 126.9 (2C), 127.1, 131.4, 133.0 (C-10), 135.7, 136.2, 137.3, 138.1 (C-5), 157.5 (C-3).