Construction of the Steroid Framework via a Functionalized Macrocyclic Compound

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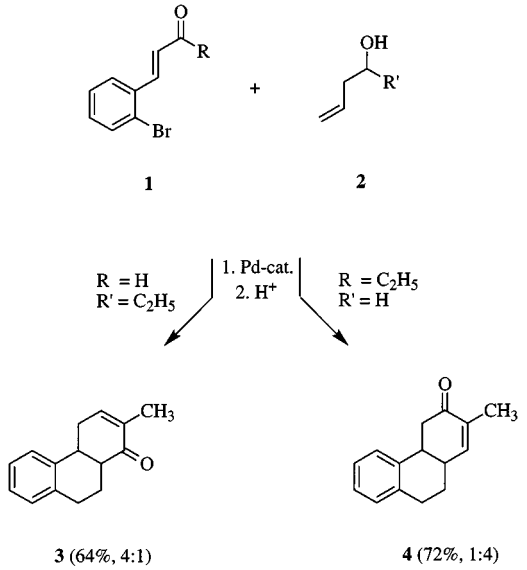
A palladium-catalyzed intramolecular coupling process leads to a functionalized macrocycle suitable for a double transannular cyclization. The resulting steroid framework, and its stereo- and regioisomers, are identified by analysis of the NMR-spectroscopic data.

The efficient and facile synthesis of complex target molecules from simple building blocks is usually based on an elegant combination of powerful transformations. However, in addition to such combinations of classical reactions, transition metal catalyzed processes are of increasing importance. Recently, we have evaluated combinations of the Heck reaction[1] with classical carbonyl reactions: The Heck reaction, with allylic and homoallylic alcohols as the olefinic coupling components, leads to carbonyl compounds.[2] This is the basis for reaction sequences[3] that include the Michael addition, aldol condensation[4] or imine formation,[5] depending on the presence of appropriate functional groups. For instance, the Heck reaction of functionalized aryl bromides **1** with homoallylic alcohols **2** and a subsequent Robinson-type annulation is a new route to the tricyclic ring systems **3** and **4**,[6] whereby the substituents R and R′ control the regiochemistry of the annulation reaction (see Scheme 1).



Scheme 1. Heck reaction of **1** and **2** followed by a Robinson-type annulation

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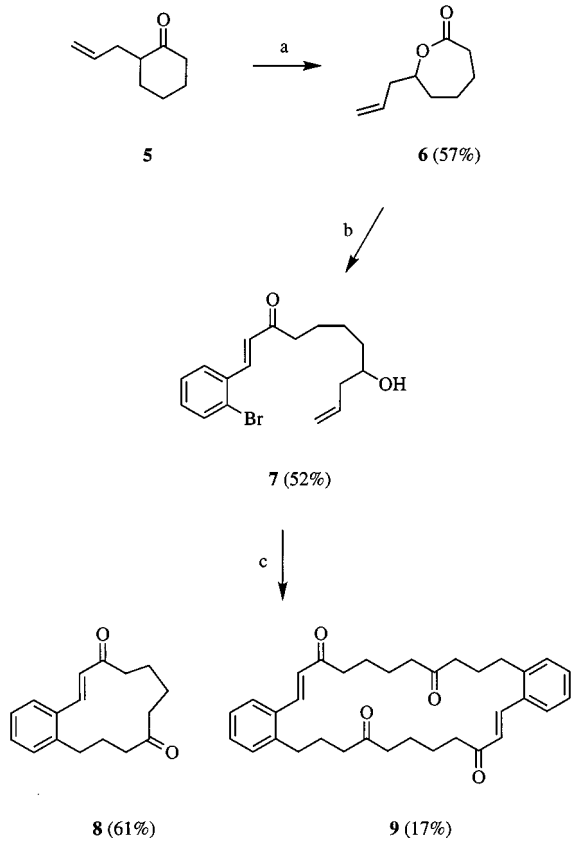
In the model compound **7** the substituents R and R′ are replaced by a butanediyl chain connecting the structural units of the coupling components **1** and **2** (see Scheme 2). It was envisioned that an analogous sequential transformation of **7** should result in the straightforward construction of the steroid framework.[7]



Scheme 2. Reaction conditions: a: *m*-Chloroperbenzoic acid, $NaHCO_3$, dichloromethane, room temp., 16 h. − b: 1. 2 equiv. CH_2PPh_3, THF, from −78°C to room temp., 16 h, 2. aqueous HBr, 3. 2-bromobenzaldehyde, THF, reflux, 2 d. − c: High dilution (see Experimental Section), 5 mol-% $Pd(OAc)_2$, *N*-ethyldiisopropylamine, LiCl, DMF, 80°C, 2 d

Compound **7** is synthesized in a few preparative steps starting from the allyl-substituted cyclohexanone **5**, which is easily transformed into the 7-membered ring lactone **6** by a Bayer-Villiger oxidation.[8] In a one-pot procedure **6** is

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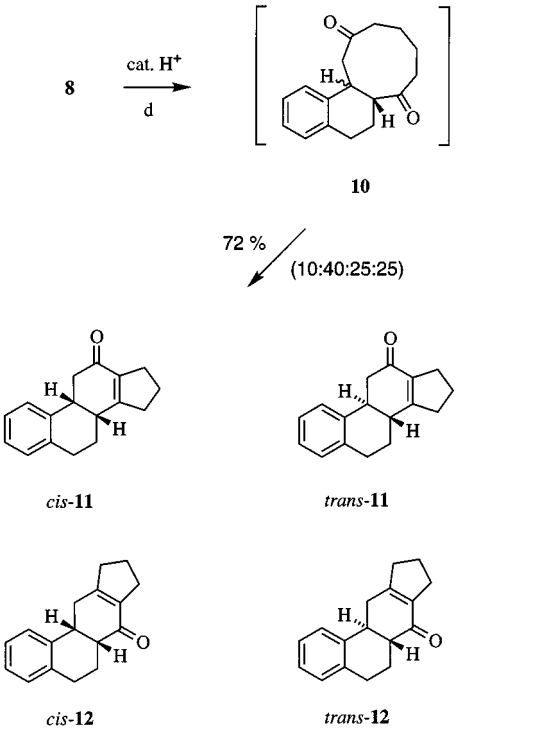
first treated with triphenylphosphonium methylide,[9] giving rise to an intermediary phosphonium alkoxide. This then undergoes a Wittig reaction with 2-bromobenzaldehyde to yield exclusively the *trans* isomer of **7,** in an overall isolated yield of 52%. Compound **7** is identified in the ^{1}H-NMR spectrum by the 16 Hz coupling constant of the vinylic protons at the α,β-unsaturated ketone (δ = 6.64 and 7.91).

The formation of macrocycles by intramolecular[10] Heck reaction is well documented[11] and in the case of **7** an acceptable yield of the 13-membered ring **8** is obtained; a relatively high dilution of the starting material (4 mmol/L) is crucial for this result. Most interestingly, the 26-membered macrocyle **9**, the result of two consecutive Heck reactions (intermolecular followed by intramolecular) is identified as by-product. These two macrocycles are easy to separate: Compound **8** is distilled at 150°C/0.5 mbar in a Kugelrohr apparatus, and the less soluble product **9** is isolated from the residue by crystallization. Due to the symmetry of **9** the NMR spectra of **8** and **9** have the same number of signals, however, their mass spectra are clearly distinguishable.



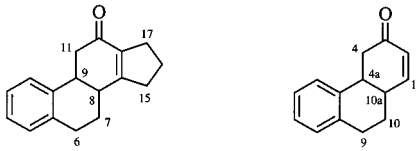
Scheme 3. Reaction conditions: d: 10 mol-% *para*-toluenesulfonic acid, chloroform, reflux, 16 h

The double transannular cyclization[12] of **8** proceeds smoothly under acidic conditions in chloroform at reflux temp. (see Scheme 3). The racemic mixture of the four stereo- and regioisomers (*cis*/*trans*-**11** and *cis*/*trans*-**12**, with *trans*-**11** as the main component) results from a Michael addition via the tricyclic system **10**, followed by an aldol condensation. This last reaction step turned out to be particularly unselective, yielding a 1:1 ratio between the steroid framework **11** and its regioisomer **12**. Compound *trans*-**12** was readily separated by flash chromatography, and a pure sample of *trans*-**11** was isolated by preparative HPLC. The stereoisomer *cis*-**11** proved to be by far the thermodynamically more stable of the two. Isomerization of the product mixture under acidic conditions led to sufficient enrichment of *cis*-**11**, which was then further purified by crystallization. Similarly, a sample of *trans*-**12** was partially isomerized to *cis*-**12,** which could then be isolated by flash chromatography.

All isomeric tetracycles have been fully characterized by spectroscopic means and can be distinguished by analyzing their NMR spectra, including two-dimensional correlation and NOEs. In the case of *trans*-**11** the ^{1}H-^{1}H-NOESY spectrum is especially informative; the positive NOE between the bridgehead proton 8-H and 11-H_{ax} confirms the *trans* annulation, and the correlation between 8-H and one proton at C-17 of the 5-membered ring shows them to obviously be in close proximity. In the case of the ^{1}H-^{1}H-NOESY spectrum of *trans*-**12** the NOEs between the methylene group protons 10-H and 11-H confirm the position of the 5-membered ring.

Comparison with NMR spectra of the tricyclic pendants **13** and **14**[6] confirms the structural assignments (see Tables 1 and 2). For all *trans* isomers well-separated signals in the aliphatic region of the ^{1}H-NMR spectra are typical. Moreover, the similarity of the coupling patterns between the spectra of *trans*-**11** and *trans*-**13** and between *trans*-**12** and *trans*-**14** is evident. In the ^{13}C-NMR spectra of the *trans* isomers the signals of the bridgehead carbon atoms are found at significantly lower field than those of the corresponding *cis* isomers.

Table 1. Comparison of selected ^{13}C-NMR signals of the stereoisomers of **11** and **13**[6]



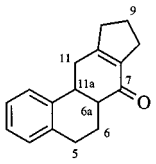
	cis-**11**	*trans*-**11**		*cis*-**13**	*trans*-**13**
C-7	22.42	26.14	C-10	23.43	28.32
C-6	29.72	29.45	C-9	29.58	29.50
C-8	36.62	40.07	C-10a	35.45	39.29
C-9	38.88	42.12	C-4a	37.18	41.28
C-11	43.39	42.82	C-4	43.29	42.52
C-14	168.13	168.35	C-1	153.24	155.23
C-12	196.61	196.87	C-3	199.03	199.49

In summary, we have developed a short route to the steroid framework, including some stereo- and regioisomers, by a reaction sequence consisting of an intramolecular Heck reaction, Michael addition and aldol condensation. The scope and limitations of palladium-catalyzed macrocyclizations, with allylic and homoallylic alcohols as coupling components, are currently under investigation.

Experimental Section

General: M.p. (uncorrected): Reichert Thermovar. − IR: Perkin Elmer 983. − UV: Perkin Elmer 554. − NMR: Bruker DRX 500,

Table 2. Comparison of selected ^{13}C-NMR signals of the stereoisomers of **12** and **14**[6]



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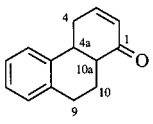

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	cis-**12**	*trans*-**12**		*cis*-**14**	*trans*-**14**
C-6	21.7[a]	21.9[b]	C-10	21.28	21.54
C-5	29.33	29.57	C-9	28.83	29.18
C-11	33.18	32.95	C-4	31.82	32.47
C-11a	38.55	40.96	C-4a	37.45	39.76
C-6a	46.17	48.53	C-10a	46.20	48.91
C-10a	164.02	163.20	C-3	148.94	148.50
C-7	199.96	198.16	C-1	201.96	200.55

[a] δ = 21.62 or 21.78. − [b] δ = 21.92 or 21.93 (distinction between signals of C-6 and C-9 is not unambiguous).

Bruker WM 300; ^{1}H-NMR spectra (500 MHz or 300 MHz) recorded in $CDCl_3$ with TMS as the internal standard; ^{13}C-NMR spectra (125.8 MHz or 75.5 MHz) measured by using $CDCl_3$ as the solvent and the internal standard. − MS: MAT 311A (70 eV). − Analytical TLC: Precoated plastic sheets POLYGRAM SIL G/UV254 from Macherey-Nagel used.

7-Allyloxepan-2-one (6): A suspension of 5.52 g (40.0 mmol) of 2-allylcyclohexanone (**5**),[13] 5.04 g (60.0 mmol) of $NaHCO_3$ and 10.1 g (41.0 mmol) of *m*-chloroperbenzoic acid (75%) in 250 mL of dichloromethane was stirred at room temp. for 26 h. Solid material was filtered off and washed with dichloromethane (2 × 50 mL). After concentration to 100 mL, the filtrate is washed with satd. aqueous $NaHCO_3$ solution (50 mL) and filtered through silica; TLC (silica, petroleum ether/ethyl acetate, 3:1): R_f = 0.79 (**5**), 0.70, 0.50 (**6**), 0.27, 0.00. After evaporation of the solvent, flash chromatography of the residue gave 0.45 g (8%) of the starting material **5** and 3.19 g (52%; 57% based on recovered starting material) of **6** as a colourless oil, whose ^{1}H-NMR spectrum is in accord with the reported data.[14] − ^{1}H NMR (300 MHz): δ = 1.50−1.67 (m, 2 H), 1.89−2.00 (m, 2 H), 2.27−2.38 (m, 2 H), 2.43−2.53 (m, 2 H), 2.55−2.71 (m, 2 H), 4.28 (m, 1 H, 7-H), 5.13 (m, 2 H), 5.84 (m, 1 H). − ^{13}C NMR (75.5 MHz): δ = 22.94 (t), 28.17 (t), 33.82 (t), 34.86 (t), 40.56 (t), 79.80 (d, C-7), 118.13 (t), 133.43 (d), 175.35 (s).

1-(2-Bromophenyl)-8-hydroxyundeca-1,10-dien-3-one (7): 25.0 mL (40.0 mmol) of a 1.6 M solution of *n*-butyllithium in hexane was added dropwise under N_2 and at 0°C to a suspension of 14.3 g (40.0 mmol) of methyltriphenylphosphonium bromide in 75 mL of dry THF. After stirring at room temp. for 4 h, the red solution was cooled to −78°C, 3.08 g (20.0 mmol) of lactone **6** was added and stirring continued for 16 h at room temp. The reaction mixture was washed with 50 mL of aqueous HBr (2 weight-%) followed by 50 mL of aqueous $NaHCO_3$ solution (2 weight-%) and dried with Na_2SO_4. Then 3.70 g (20.0 mmol) of 2-bromobenzaldehyd was added and after 48 h under N_2 at 100°C, the crude product was fractionated by flash chromatography; TLC (silica, petroleum ether/*tert*-butyl methyl ether, 2:1): R_f = 0.77 (2-bromobenzaldehyde), 0.46, 0.23, 0.13 (**7**), 0.09, 0.00.

First Fraction: 476 mg (13%) of recovered 2-bromobenzaldehyde.

Second Fraction: 3.52 g (52%) of **7** as a slightly yellow oil. − IR (film): $\tilde{\nu}$ = 3434 cm^{-1} (m, br., OH), 3434 (m), 3073 (w), 2935 (s), 2864 (m), 1690 (s), 1655 (s), 1609 (s), 1587 (m), 1560 (w), 1463 (s), 1437 (s), 1369 (m), 1317 (m), 1282 (m), 1264 (m), 1202 (m), 1171 (m), 1114 (m), 1077 (m), 1045 (m), 1026 (s), 976 (m), 915 (m), 754 (s). − UV/Vis (acetonitrile): λ_{max} (lg ε) = 212 nm (4.31), 229 (4.25), 280 (4.48). − ^{1}H NMR (500 MHz): δ = 1.42−1.55 (m, 4 H), 1.69−1.77 (m, 3 H), 2.17 (m, 1 H, 9-H_A), 2.31 (m, 1 H, 9-H_B), 2.74 (t, *J* = 7.3 Hz, 2 H, 4-H), 3.68 (m, 1 H, 8-H), 5.12 (m, 1 H, 11-H_A), 5.15 (m, 1 H, 11-H_B), 5.83 (m, 1 H, 10-H), 6.64 (d, *J* = 16.3 Hz, 1 H, 2-H), 7.23 ("dd", "*J*" = 8.1, 6.6 Hz, 1 H), 7.33 ("t", "*J*" = 7.5 Hz, 1 H), 7.62 ("dd", "*J*" = 8.1, 1.1 Hz, 2 H), 7.91 (d, *J* = 16.3 Hz, 1 H, 1-H). − ^{13}C NMR (75.5 MHz): δ = 24.21 (t), 25.39 (t), 36.55 (t), 40.33 (t), 42.02 (t), 70.43 (d, C-8), 118.17 (t, C-11), 125.67 (s, C-2′), 127.75 (d), 127.80 (d), 129.11 (d), 131.36 (d), 133.48 (d), 134.67 (s, C-1′), 134.82 (d), 140.96 (d), 200.29 (s, C-3). − MS (70 eV; 145°C); *m/z* (%): 338/336 (0.39/0.35) [M^+], 320/318 (2/2) [$M^+ - H_2O$], 297/295 (18/18), 251/249 (23/21), 224/222 (32/31), 211/209 (96/99), 183/181 (29/26), 171 (22), 170 (98), 169 (36), 145 (66), 130 (23), 103 (16), 102 (100), 101 (28), 75 (17), 67 (32), 41 (36). − $C_{17}H_{21}BrO_2$ (337.3): calcd. C 60.54, H 6.28; found C 60.30, H 6.25.

Intramolecular Heck Reaction of 7. − (2*E*)-1(1,2)-Benzenacyclododecaphan-2-ene-4,9-dione (8) and 1,13(1,2)-Dibenzenacyclotetracosaphane-2,14-diene-4,9,16,21-tetraone (9): A mixture of 169 mg (0.501 mmol) of **7**, 0.52 g (4.0 mmol) of *N*-ethyldiisopropylamine, 21 mg (0.50 mmol) of LiCl, and 5.6 mg (25 μmol) of $Pd(OAc)_2$ in 125 mL of dry DMF in a sealed tube was stirred under N_2 at 80°C for 2 d. The solvent was evaporated (50°C, 10 mbar) and the residue treated with warm ethyl acetate (100 mL) and water (50 mL). The organic phase was concentrated in vacuo and after 1 h of drying at 50°C/0.5 mbar in a Kugelrohr apparatus, the residue was distilled at 150°C/0.5 mbar to yield 79 mg (61%) of the 13-membered macrocycle **8** as a colourless solid with m.p. 98°C. − IR (film): $\tilde{\nu}$ = 2940 cm^{-1} (m), 2866 (w), 1696 (s), 1658 (s), 1463 (m), 1437 (w), 1404 (m), 1369 (w), 1301 (w), 1261 (w), 1222 (w), 1166 (w), 1135 (w), 1020 (w), 979 (m), 924 (w), 788 (w), 760 (m), 747 (w). − UV/Vis (acetonitrile): λ_{max} (lg ε) = 213 nm (4.03), 225 (4.00), 282 (4.16). − ^{1}H NMR (500 MHz): δ = 1.76−1.85 (m, 4 H), 1.97 (m, 2 H), 2.50 (m, 2 H), 2.65−2.74 (m, 6 H), 6.39 (d, *J* = 16.6 Hz, 1 H, 3-H), 7.21 ("d", "*J*" = 7.6 Hz, 1 H), 7.25 ("t", "*J*" = 7.5 Hz, 1 H), 7.32 ("t", "*J*" = 7.5 Hz, 1 H), 7.50 ("d", "*J*" = 7.3 Hz, 1 H), 7.65 (d, *J* = 16.6 Hz, 1 H, 2-H). − ^{13}C NMR (75.5 MHz): δ = 21.38 (t), 26.47 (t), 26.87 (t), 32.31 (t), 37.97 (t), 39.92 (t), 41.95 (t), 126.42 (d), 127.04 (d), 128.85 (d), 130.42 (d), 130.47 (d), 133.25 (s), 141.09 (s), 142.27 (d, C-2), 202.69 (s, C-4), 210.79 (s, C-9). − MS (70 eV; 115°C); *m/z* (%): 257 (7) [M^+ + 1], 256 (36) [M^+], 238 (16) [$M^+ - H_2O$], 185 (17), 170 (88), 157 (100), 144 (35), 130 (62), 115 (44). − $C_{17}H_{20}O_2$ (256.3): calcd. C 79.65, H 7.86; found C 79.50, H 7.78. − The residue of the distillation was crystallized from 3 mL of chloroform by letting 1 mL of petroleum ether slowly interfuse: 22 mg (17%) of the 26-membered macrocycle **9** as a colourless solid with m.p. 228°C. − IR (KBr): $\tilde{\nu}$ = 3058 cm^{-1} (w), 2961 (m), 2941 (w), 2885 (w), 1710 (s), 1650 (s), 1619 (w), 1601 (w), 1483 (w), 1456 (w), 1443 (w), 1404 (m), 1377 (m), 1337 (w), 1324 (w), 1275 (w), 1248 (m), 1178 (s), 1103 (m), 1092 (w), 991 (m), 905 (w), 881 (w), 760 (m), 751 (m). − UV/Vis (acetonitrile): λ_{max} (lg ε) = 211 nm (4.15), 224 (4.06), 232 (3.95, sh), 282 (4.24). − ^{1}H NMR (500 MHz): δ = 1.68−1.83 (m, 12 H), 2.55 ("t", "*J*" = 7.7 Hz, 4 H), 2.59 ("t", "*J*" = 5.6 Hz, 4 H), 2.71 (m, 4 H), 3.24 ("t", "*J*" = 7.7 Hz, 4 H), 6.62 (d, *J* = 16.5 Hz, 2 H, 3-H, 15-H), 7.19 ("dd", "*J*" = 7.5, 1.3 Hz, 2 H), 7.24 ("td", *J* = 7.6, 1.3 Hz, 2 H), 7.30 ("td", "*J*" = 7.4, 1.4 Hz, 2 H), 7.65 ("d", "*J*" = 7.2 Hz, 2 H), 8.34 (d, *J* = 16.5 Hz, 2 H, 2-H, 14-H). − ^{13}C NMR (75.5 MHz): δ = 23.39 (t), 23.90 (t), 26.21 (t), 33.59 (t), 38.17 (t),

41.60 (t), 43.34 (t), 126.23 (d), 126.82 (d), 129.36 (d), 130.25 (d, signals of four carbon atoms superimposed), 133.27 (s), 141.01 (d, C-2, C-14), 142.37 (s), 202.41 (s, C-4, C-16), 209.85 (s, C-9, C-21). − MS (70 eV; 260°C); *m/z* (%): 513 (3) [M^+ + 1], 512 (9) [M^+], 495 (38), 494 (100) [$M^+ - H_2O$], 476 (22), 293 (34), 222 (26), 209 (24), 197 (22), 196 (26), 195 (25), 117 (29). − $C_{34}H_{40}O_4 \cdot H_2O$ (530.7): calcd. C 76.95, H 7.98; found C 77.05, H 7.80.

Acid-Catalyzed Transannular Cyclization of 8. − (9*R,10*S**)-6,7,8,9,11,15,16,17-Octahydrocyclopenta[*a*]phenanthren-12-one (11) and (6a*R**,11a*S**)-5,6,6a,8,9,10,11,11a-Octahydrocyclopenta[*b*]-phenanthren-7-one (12):** A solution of 256 mg (1.00 mmol) of the 13-membered macrocycle **8** and 19 mg (10 mol-%) of *para*-toluenesulfonic acid in 10 mL of chloroform was stirred under reflux for 16 h. After the addition of 100 mg of $NaHCO_3$ at room temp., the reaction mixture was filtered through silica and the solvent evaporated; TLC (silica, petroleum ether/*tert*-butyl methyl ether, 2:1): R_f = 0.89, 0.68 (*trans*-**12**), 0.59 (*cis*-**12**, *trans*-**11**, cis-**11**), 0.33, 0.22, 0.00. The residue was fractionated by flash chromatography (silica, petroleum ether/methyl *tert*-butyl ether, 5:1).

First Fraction: 43 mg (18%) of *trans*-**12** as a colourless solid with m.p. 131°C. − IR (KBr): $\tilde{\nu}$ = 2961 cm^{-1} (w), 2960 (m), 2925 (m), 2864 (w), 1654 (s), 1634 (m), 1492 (w), 1442 (w), 1431 (w), 1398 (m), 1352 (w), 1177 (w), 1125 (w), 1091 (w), 1034 (w), 889 (w), 745 (m), 712 (w), 543 (w), 435 (w). − UV/Vis (acetonitrile): λ_{max} (lg ε) = 215 nm (3.98), 247 (4.02), 273 (2.96, sh), 287 (2.29, sh), 316 (1.98), 332 (1.98). − ^{1}H NMR (500 MHz): δ = 1.58 (m, 1 H, 6-H_{ax}), 1.96 (m, 2 H, 9-H), 2.29 ("dt", "*J*" = 12.1, 3.0 Hz, 1 H, 6a-H), 2.37 (m, 1 H, 11-H_{ax}), 2.51−2.63 (m, 3 H, 6-H_{eq}, 8-H), 2.65 ("t", "*J*" = 7.3 Hz, 2 H, 10-H), 2.91 (m, 2 H, 5-H), 3.08−3.20 (m, 2 H, 11-H_{eq}, 11a-H), 7.13−7.22 (m, 3 H), 7.29 ("d", "*J*" = 7.5 Hz, 1 H, 1-H). − ^{13}C NMR (125.8 MHz): δ = 21.92 (t), 21.93 (t), 29.22 (t, C-8), 29.57 (t, C-5), 32.95 (t, C-11), 37.72 (t, C-10), 40.96 (d, C-11a), 48.53 (d, C-6a), 125.57 (d, C-1), 126.01 (d), 126.30 (d), 129.29 (d), 136.88 (s), 137.76 (s), 138.40 (s), 163.20 (s, C-10a), 198.16 (s, C-7). − MS (70 eV; 100°C); *m/z* (%): 239 (16) [M^+ + 1], 238 (82) [M^+], 237 (13), 223 (11), 209 (15), 130 (32), 129 (17), 128 (13), 116 (13), 109 (12), 108 (100), 79 (14). − $C_{17}H_{18}O$ (238.3): calcd. C 85.67, H 7.61; found C 85.62, H 7.59.

Second Fraction: 129 mg (54%) of a mixture of *cis*-**12**, *trans*-**11** and *cis*-**11** in the ratio 2:4:1 according to the ^{1}H-NMR spectrum. An analytical sample of *trans*-**11** was obtained by preparative HPLC (acetonitrile/water, 78:22; 8 ml/min, t_R = 29.41 for *cis*-**11** and *cis*-**12**, t_R = 33.29 min for *trans*-**11**). The functionalized steroid framework *trans*-**11** was obtained as a colourless solid with m.p. 151°C. − IR (KBr): $\tilde{\nu}$ = 2958 cm^{-1} (m), 2909 (m), 2828 (m), 1651 (s), 1627 (m), 1486 (m), 1452 (w), 1421 (m), 1389 (s), 1325 (w), 1289 (w), 1258 (w), 1163 (w), 1130 (w), 1097 (w), 1037 (w), 827 (m), 778 (m), 629 (w), 521 (w), 451 (w). − UV/Vis (acetonitrile): λ_{max} (lg ε) = 214 nm (3.98, sh), 250 (4.01). − ^{1}H NMR (500 MHz): δ = 1.66 (m, 1 H, 7-H_{ax}), 1.96 (m, 2 H, 16-H), 2.30 ("dtt", "*J*" = 12.9, 6.3, 2.7 Hz, 1 H, 7-H_{eq}), 2.39 (dd, *J* = 16.4, 13.5 Hz, 1 H, 11-H_{ax}), 2.48 (m, 1 H, 8-H), 2.56−2.64 (m, 3 H, 17-H, 15-H_{eq}), 2.77 (m, 1 H, 15-H_{ax}), 3.01 (m, 2 H, 6-H), 3.12 (m, 1 H, 9-H), 3.23 (dd, *J* = 16.4, 4.0 Hz, 1 H, 11-H_{eq}), 7.13−7.19 (m, 3 H), 7.24 (m, 1 H, 1-H). − ^{13}C NMR (125.8 MHz): δ = 21.79 (t, C-16), 26.14 (t, C-7), 29.33 (t, C-17), 29.45 (t, C-6), 34.76 (t, C-15), 40.07 (d, C-8), 42.12 (d, C-9), 42.82 (t, C-11), 125.02 (d, C-1), 126.11 (d), 126.42 (d), 129.23 (d), 135.85 (s), 137.76 (s), 138.15 (s), 168.35 (s, C-14), 196.87 (s, C-12). − MS (70 eV; 110°C); *m/z* (%): 239 (13) [M^+ + 1], 238 (67) [M^+], 223 (13), 211 (20), 210 (100), 182 (40), 181 (42), 167 (18), 165 (16), 142 (10), 141 (12), 129 (14), 121 (44), 115 (19), 95 (96), 93 (29), 91 (24), 77 (23). − $C_{17}H_{18}O$ (238.3): calcd. C 85.67, H 7.61; found C 85.70, H 7.57. − In order to obtain a pure sample of *cis*-**11** 123 mg (0.516 mmol) a mixture of *cis*-**12**, *trans*-**11** and *cis*-**11** in the ratio 2:4:1 (see above) was treated with 9.9 mg (10 mol-%) of *para*-toluenesulfonic acid in 10 mL of chloroform under reflux for 5 d. The crude product was fractionated by flash chromatography (silica, petroleum ether/*tert*-butyl methyl ether, 5:1).

First Fraction: 11 mg (5%) of *trans*-**12**.

Second Fraction: 86 mg (36%) of a mixture of *cis*-**12**, *trans*-**11** and *cis*-**11** in the ratio 3:1:14. Repeated crystallization from petroleum ether/*tert*-butyl methyl ether (5:1) gave a pure sample of *cis*-**11** as a colourless solid with m.p. 132°C. − IR (KBr): $\tilde{\nu}$ = 2918 cm^{-1} (m), 2892 (m), 2873 (m), 2829 (m), 1652 (s), 1625 (m), 1486 (w), 1452 (w), 1424 (w), 1392 (m), 1356 (w), 1338 (w), 1315 (w), 1289 (w), 1263 (w), 1241 (w), 1203 (w), 1154 (w), 1111 (w), 1087 (w), 1047 (w), 1009 (w), 982 (w), 969 (w), 952 (w), 874 (w), 772 (m), 721 (w), 670 (w), 600 (w), 514 (w), 465 (w), 445 (w), 410 (w). − UV/Vis (acetonitrile): λ_{max} (lg ε) = 212 nm (4.04, sh), 249 (4.02). − ^{1}H NMR (500 MHz): δ = 1.79 (m, 1 H, 7-H_{ax}), 1.96 (m, 2 H, 16-H), 2.01 (m, 1 H, 7-H_{eq}), 2.51−2.61 (m, 5 H, 11-H, 15-H_{ax}, 17-H), 2.65 (m, 1 H, 8-H), 2.78 (m, 1 H, 15-H_{eq}), 2.93 (m, 2 H, 6-H), 3.46 ("quint", "*J*" = 5.9 Hz, 1 H, 9-H), 7.11−7.19 (m, 4 H). − ^{13}C NMR (125.8 MHz): δ = 21.75 (t, C-16), 22.42 (t, C-7), 29.09 (t, C-17), 29.72 (t, C-6), 35.93 (t, C-15), 36.62 (d, C-8), 38.88 (d, C-9), 43.39 (t, C-11), 126.15 (d), 126.33 (d), 128.86 (d), 129.13 (d), 135.50 (s), 137.16 (s), 138.53 (s), 168.13 (s, C-14), 196.61 (s, C-12). − MS (70 eV; 100°C); *m/z* (%): 239 (18) [M^+ + 1], 238 (100) [M^+], 210 (33), 196 (21), 195 (10), 182 (16), 181 (24), 167 (14), 165 (13), 144 (17), 142 (15), 141 (11), 129 (16), 128 (25), 121 (43), 115 (17), 108 (14), 95 (53), 93 (27), 91 (20), 77 (20). − $C_{17}H_{18}O$ (238.3): calcd. C 85.67, H 7.61; found C 85.71, H 7.67. − The isolation of a pure sample of *cis*-**12** was achieved by the acidic isomerization of *trans*-**12**: 130 mg (0.540 mmol) of *trans*-**12** was treated with 10.2 mg (10.0 mol-%) *para*-toluenesulfonic acid in 10 mL of chloroform under reflux for 17 h. The two diastereomers were separated by flash chromatography (silica, petroleum ether/*tert*-butyl methyl ether, 5:1).

First Fraction: 62 mg (48%) of *trans*-**12**.

Second Fraction: 49 mg (38%) of *cis*-**12** as a colourless oil. − IR (KBr): $\tilde{\nu}$ = 2920 cm^{-1} (w), 1654 (s), 1488 (w), 1451 (w), 1430 (m), 1393 (m), 1337 (w), 1273 (w), 1088 (w), 1054 (w), 761 (m), 744 (m), 724 (w), 566 (w), 525 (w), 474 (w). − UV/Vis (acetonitrile): λ_{max} (lg ε) = 211 nm (3.99, sh), 249 (3.79), 273 (3.03). − ^{1}H NMR (500 MHz): δ = 1.84−1.99 (m, 4 H, 6-H, 9-H), 2.43 (m, 1 H, 11-H_{ax}), 2.56−2.64 (m, 6 H, 6a-H, 8-H, 10-H, 11-H_{eq}), 2.94 (m, 2 H, 5-H), 3.42 ("quint", "*J*" = 5.5 Hz, 1 H, 11a-H), 7.10−7.18 (m, 4 H). − ^{13}C NMR (125.8 MHz): δ = 21.62 (t), 21.78 (t), 29.16 (t, C-8), 29.33 (t, C-5), 33.18 (t, C-11), 37.66 (t, C-10), 38.55 (d, C-11a), 46.17 (d, C-6a), 126.02 (d), 126.50 (d), 128.45 (d), 129.35 (d), 135.53 (s), 136.00 (s), 138.90 (s), 164.02 (s, C-10a), 199.96 (s, C-7). − MS (70 eV; 130°C); *m/z* (%): 239 (20) [M^+ + 1], 238 (100) [M^+], 237 (23), 223 (20), 210 (13), 209 (21), 130 (31), 129 (22), 128 (16), 115 (13), 109 (11), 108 (83), 79 (18). − $C_{17}H_{18}O$ (238.3): calcd. C 85.67, H 7.61; found C 85.65, H 7.62.

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[1] J. Tsuji, *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, Chichester, **1995**.
[2] J. B. Melpolder, R. F. Heck, *J. Org Chem*. **1976**, *41*, 265−272. − A. J. Chalk, S. A. Magennis, *J. Org Chem*. **1976**, *41*, 273−278, 1206−1209. − Y. Tamaru, Y. Yamada, Z. Yoshida, *J. Org. Chem*. **1978**, *43*, 3396−3398. − W. Smadja, S. Czernecki, G. Ville, C. Georgoulis, *Organometallics* **1987**, *6*, 166−169. − R. C. Larock, W.-Y. Leung, S. Stolz-Dunn, *Tetrahedron Lett*. **1989**, *30*, 6629−6632. − S.-K. Kang, K.-Y. Jung, C.-H. Park, E.-Y. Namkoong, T.-H. Kim, *Tetrahedron Lett*. **1995**, *36*, 6287−6290.
[3] L. F. Tietze, U. Beifuss, *Angew. Chem*. **1993**, *105*, 137−170; *Angew. Chem. Int. Ed. Engl*. **1993**, *32*, 131−163.
[4] G. Dyker, P. Grundt, *Tetrahedron Lett*. **1996**, *37*, 619−622.
[5] G. Dyker, H. Markwitz, *Synthesis*, in press.
[6] G. Dyker, P. Grundt, H. Markwitz, G. Henkel, *J. Org. Chem*. **1998**, *63*, 6043−6047.
[7] Steroid synthesis with Heck reactions as key steps: L. F. Tietze, T. Nöbel, M. Spescha, *Angew. Chem*. **1996**, *108*, 2385−2386; *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 2259−2261.
[8] G. R. Krow in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), vol. 7, Pergamon, Oxford **1991**, p. 671−688. − H. O. House, *Modern Synthetic Reactions*, 2nd ed., Benjamin, Menlo Park **1972**, p. 321−329.
[9] P. J. Murphy, H. L. Williams, D. E. Hibbs, M. B. Hursthouse, K. M. A. Malik, *Tetrahedron* **1996**, *52*, 8315−8332.
[10] S. E. Gibson, R. J. Middleton, *Contemp. Org. Synth*. **1996**, *3*, 447−471. − E. Negishi, C. Copéret, S. Ma, S.-Y. Liou, F. Liu, *Chem. Rev*. **1996**, *96*, 365−393.
[11] F. E. Ziegler, U. R. Chakraborty, R. B. Weisenfeld, *Tetrahedron* **1981**, *37*, 4035−4040. − S. Ma, E. Negishi, *J. Am. Chem. Soc*. **1995**, *117*, 6345−6357. − M. J. Stocks, R. P. Harrison, S. J. Teague, *Tetrahedron Lett*. **1995**, *36*, 6555−6558. − S. E. Gibson, N. Guillo, R. J. Middleton, A. Thuilliez, M. J. Tozer, *J. Chem. Soc., Perkin Trans. 1* **1997**, 447−455. − K. Akaji, Y. Kiso, *Tetrahedron Lett*. **1997**, *38*, 5185−5188.
[12] Other examples of transannular cyclization to steroids: L. Quellet, P. Langois, P. Deslongchamps, *Synlett* **1997**, 689−690. − P. Langlois, P. Soucy, Y. L. Dory, P. Deslongchamps, *Can. J. Chem*. **1996**, *74*, 129−143.
[13] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, R. Terrell, *J. Am. Chem. Soc*. **1963**, *85*, 207−222.
[14] S. E. Jacobson, F. Mares, P. M. Zambri, *J. Am. Chem. Soc*. **1979**, *101*, 6938−6946.

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