Heck Reaction and Robinson-Type Annulation: A Versatile Combination

Gerald Dyker,*,† Peter Grundt, Hardy Markwitz, and Gerald Henkel

Fachbereich 6, Institut für Synthesechemie der Gerhard-Mercator-Universität-GH Duisburg, D-47048 Duisburg, Lotharstrasse 1, Germany

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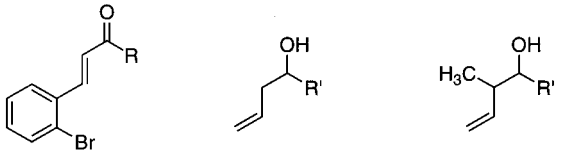
Sequential transformations[1] enable the facile synthesis of complex target molecules from simple building blocks in a single preparative step. Besides combinations of classical reactions, transition metal catalyzed processes are also of increasing importance. Our investigations are based on the Heck reaction[2] with allylic and homoallylic alcohols as olefinic coupling components which are known to give rise to carbonyl compounds.[3] Recently we reported on domino processes that combine this type of Heck reaction with the aldol condensation and with the Michael addition reaction, respectively. Thus, indene derivatives and dihydro- as well as tetrahydronaphthalenes become easily accessible.[4] Now we extend this method to the combination of a Heck reaction and a Robinson-type annulation as a new entry to tricyclic ring systems, which represent a partial structure of the steroid framework.

In a palladium-catalyzed process α,β-unsaturated aldehydes and ketones **1** were coupled with homoallylic alcohols **2** and **3**. The range of products isolated from



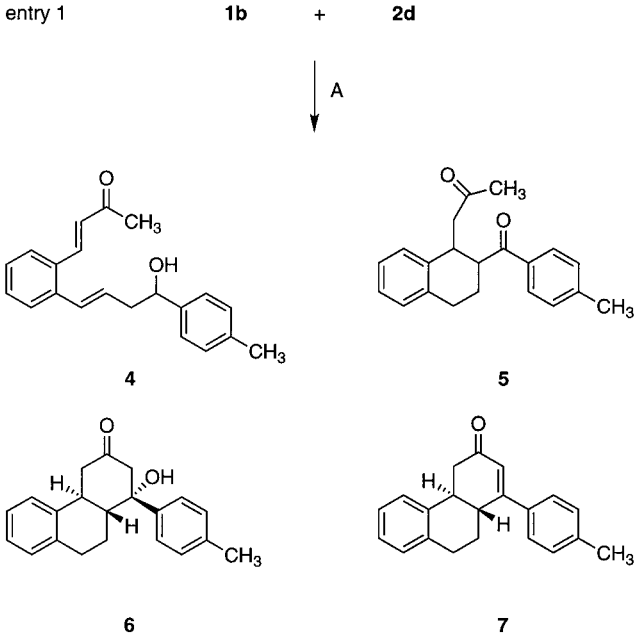
1a: R = H
1b: R = CH_3
1c: R = C_2H_5

2a: R' = H
2b: R' = CH_3
2c: R' = C_2H_5
2d: R' = 4-tolyl

3a: R' = H
3b: R' = CH_3

the reaction of the α,β-unsaturated ketone **1b** with the tolyl-substituted homoallylic alcohol **2d** illustrates the course of the domino process since essential byproducts and intermediates on the way to the final product **7** were identified and spectroscopically characterized (Scheme 1).[5] The CC bond formation via the Heck reaction is of course an early reaction step. The β-hydrogen elimination of an intermediary alkylpalladium bromide toward the benzylic position leads to byproduct **4**. On the other hand the migration of the olefinic double bond until conjugation with the hydroxyl group has to be regarded as the main reaction pathway. This migration takes place via a β-hydrogen elimination/readdition sequence. The resulting enolate that might be in equilibrium with the corresponding ketone undergoes an intramolecular Michael addition reaction. Thus, the resulting tetrahydronaphthalene derivative **5** is isolated as a 1:3-mixture of the *cis*- and the *trans*-isomer. Intramolecular aldol addition of *trans*-**5** leads stereoselectively to the racemic β-hydroxyketone **6**, which upon its low solubility crystallizes out of a solution of the crude product mixture in diethyl ether. The relative configuration of the three stereogenic centers was proven by an X-ray structure analysis:[6] the tolyl group occupies an equatorial and the hydroxyl group an axial position, ideally suited for a dimerization of the two enantiomers via bridging hydrogen bonds between the hydroxyl and the carbonyl groups (Figure 1). By the elimination of water from **6**, the α,β-unsaturated ketone **7** is formed as the final product. The temperature dependence of the product distribution was monitored via analysis of the ^{1}H NMR spectra of the crude products (Table 1). Diastereoisomers of the tricyclic compounds **6** and **7** could not be detected. The formation of the byproduct **4** can be minimized by

Scheme 1. Range of Products of the Annulation Reaction of 1b with 2d[a]



[a] Reaction protocol A: 1 mmol of **1b**, 1 mmol of **2d**, 5 mol % $Pd(OAc)_2$, 3 equiv of LiCl, 8 equiv of Et_3N (or $Et(i\text{-}Pr)_2N$ for reaction temperatures T > 100 °C), 10 mL of DMF, N_2, 2 d at 60−150 °C (see Table 1); isolated yields for T = 150 °C: 6% recovered starting material **2d**, 6% **4**, 48% **6**, 33% **7**.

† Fax: Int.+203/379-4192. e-mail: dyker@uni-duisburg.de.

(1) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem.* **1993**, *105*, 137−170; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131−163; (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136.

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(4) Dyker, G.; Grundt, P. *Tetrahedron Lett.* **1996**, *37*, 619−622.

(5) All isolated diastereoisomers have been fully characterized by spectroscopic means (IR, UV, ^{1}H NMR, ^{13}C NMR, MS, elemental analysis).

(6) Details of the crystal structure investigation may be obtained from the Supporting Information and from the Fachinformationdienst Karlsruhe, D-76344 Eggenstein-Leopoldshafen, on quoting the depository number CSD-59449.

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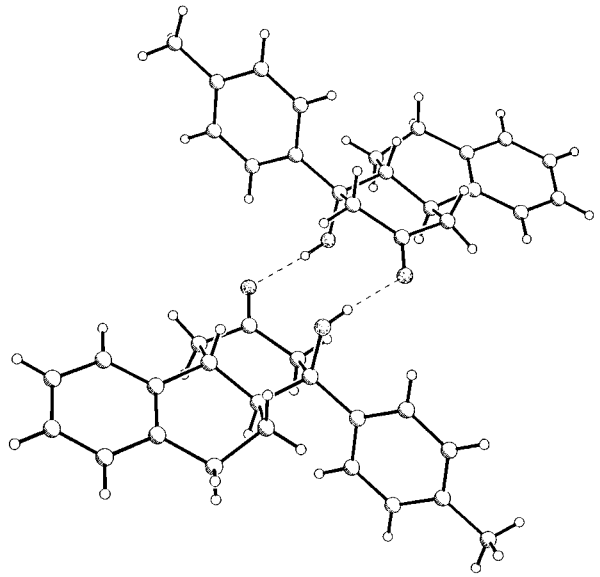


Figure 1. X-ray structure of **6**, atomic radii are arbitrary.[6]

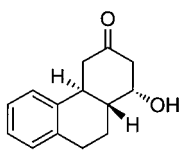
Table 1. Product Distribution for the Reaction of 1b with 2d in Dependence of the Reaction Temperature *T* under Reaction Conditions A (see Scheme 1)[a]

	product distribution				
T, °C	**2d**	**4**	**5**	**6**	**7**
60	17	38	22	23	
80	4	31	31	34	
100	8	12	17	55	8
120	8	5	18	51	18
150	8	3[b]		51	38

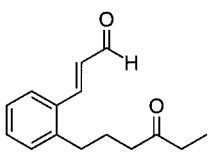
[a] The product ratio was determined from the ^{1}H NMR spectra of the crude product; diagnostic signals of the components: for **2d**, 4.64 ppm (t, 1H); for **4**, 4.77 ppm (t, 1H); for **5**, 3.79−3.89 ppm (m, 2H); for **6**, 3.47−3.57 ppm (m, 1H, 4a−H); for **7**, 6.41 ppm (s, 1H, 2-H). [b] The discrepancy to the 6% yield in Scheme 1 is unimportant, since the results were obtained from two experiments under mutually identical reaction conditions.

increasing the reaction temperature. At 100 °C a maximum yield of **6** is achieved, because the condensation to **7** proceeds rather sluggishly at this temperature.

By the reaction of ketone **1b** with **2a** the parent compound **8**, unsubstituted in the 1-position, is easily accessible (entry 2, Table 2). The β-hydroxyketone **14** can be isolated in up to 35% yield as an intermediary product. The relative configuration at the three stereogenic centers was ascertained by an X-ray analysis.[6] The geometries of **14** and **6** are virtually identical (Figure 2, Supporting Information). Also the enantiomers of **14** are forming dimers in the crystal via bridging hydrogen bonds.



14



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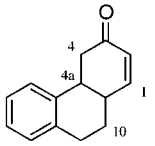
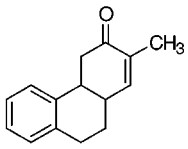
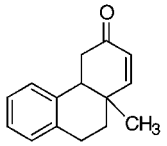
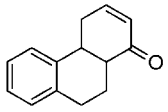
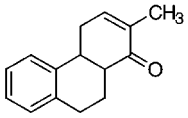
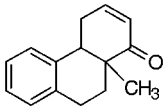
Trace amounts of acid in deuteriochloroform are sufficient to catalyze the dehydration of **14** quantitatively. For the synthesis of the α,β-unsaturated ketones **8** to **10**, a consecutive reaction protocol with an acid-catalyzed aldol condensation has to be favored when compared to an elongated reaction time under the basic conditions of the Heck reaction: for entries 2−7 polycondensation is observed as the competing reaction under basic conditions, a consequence of the reactivity of intermediary aldehydes.

Table 2[a]

entry	substrates	major product	reaction protocol	yield	cis : trans
2	**1b** + **2a**	 **8**	B	56%	1 : 4
3	**1c** + **2a**	 **9**	B	72%	1 : 4
4	**1b** + **3a**	 **10**	B	58%	1 : 8
5	**1a** + **2b**	 **11**	C	67%	1 : 1
6	**1a** + **2c**	 **12**	C	64%	4 : 1
7	**1a** + **3b**	 **13**	C	48%	5 : 1

[a] Reaction protocol B: (1) 1 mmol of **1**, 1 mmol of **2** or **3**, 5 mol % $Pd(OAc)_2$, 1 equiv of LiCl, 8 equiv of $Et(i\text{-}Pr)_2N$, 10 mL of DMF, N_2, 80 °C, 3 d; (2) 100 mg of concd hydrochloric acid, 10 mL of $CHCl_3$, 40 °C, ultrasonic cleaning bath, 4 h. Reaction protocol C: (1) in analogy to B, but 25 mL of DMF; (2) 10 mol % toluene-*p*-sulfonic acid, 10 mL of $CHCl_3$, reflux, 2 d.

By variation of the ketones and the homoallylic alcohols as coupling components, methyl groups can be introduced regioselectively (entries 3 and 4). Also the construction of quaternary centers is within the scope of this reaction sequence, as illustrated by the facile synthesis of compound **10**. The *trans*-annulated isomers of **8**, **9**, and **10** predominate if the reaction time of the acid-catalyzed dehydration is kept short. However, under rough reaction conditions (60 equiv of concentrated HCl in DMF, room temperature, 5 d) the *cis*-annulated isomer

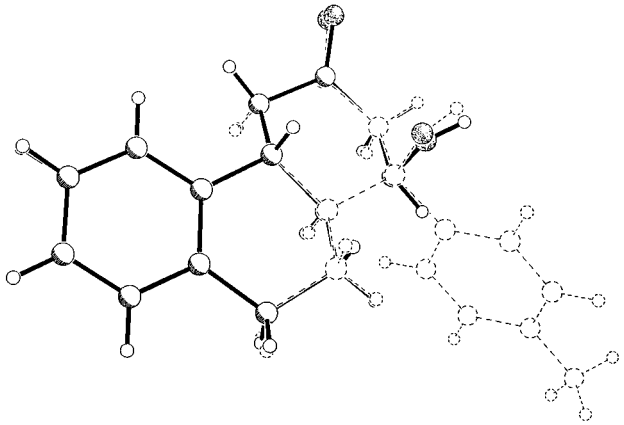


Figure 2. Superposition of the molecular structures of **6** (dashed) and **14** (bold).[6]

of compound **8** proved to be thermodynamically more stable.

Starting from the α,β-unsaturated aldehyde **1a** and the alkyl-substituted homoallylic alcohols **2b**, **2c**, and **3b** an analogous series of regioisomers **11**−**13** with the carbonyl group located in the 1-position instead of the 3-position is obtained. A higher dilution of the reaction mixture and a short reaction time (conditions C) suppress the intermolecular polycondensation, but at the same time the intramolecular Michael addition is inhibited. Thus, the dicarbonyl compound **15** is identified by NMR spectroscopy as the main product of the palladium-catalyzed reaction of aldehyde **1a** with homoallylic alcohol **2c**. The formation of the tricyclic products **11**−**13** proceeds under acidic conditions in a consecutive reaction step. Mainly the *cis*-diastereoisomers are obtained in these cases. The relative configuration at C-4a and C-10a was determined by NOESY experiments: for the *cis*-isomers positive NOE effects between the protons 4_{ax}-H and 10_{ax}-H are typical. In the case of *cis*-**13** the NOESY spectrum proves the close proximity of 4a-H and the methyl group attached at position 10a.

In further studies we are currently trying to extend this type of sequential transformation to the synthesis of analogous tricycles with a methyl group at 4a-position, a structural element which is found in numerous natural products.[7]

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR spectra (300 or 500 MHz) were recorded in $CDCl_3$ with TMS as the internal standard. ^{13}C NMR spectra (75 or 125 MHz) were measured by using $CDCl_3$ as the solvent and as the internal standard ($\delta = 77.05$). The aryl bromides **1** were synthesized by aldol condensation of 2-bromobenzaldehyde with appropriate CH-acidic carbonyl compounds.[8] The homoallylic alcohol **2d** was synthesized by a Barbier reaction.[9]

Palladium-Catalyzed Coupling Reactions of 4-(2-Bromophenyl)-3-buten-2-one (1b) with 1-(4-Tolyl)-3-buten-1-ol (2d): Dependence of Product Distribution from Reaction Temperature (General Procedure A). A mixture of 225 mg (1.00 mmol) of **1b**, 162 mg (1 mmol) of **2d**, 1.0 g (8.0 mmol) of *N*,*N*-diisopropylethylamine, 127 mg (3.00 mmol) of LiCl, 12.0 mg (53 μmol) of $Pd(OAc)_2$, and 10 mL of dry DMF in a sealed tube (for convenience) was stirred for 2 d under N_2 at various temperatures ranging from 60 to 150 °C (see below and Table 1). The reaction mixture was then diluted with 50 mL of water and extracted three times with 25 mL of ethyl acetate. The combined organic extracts were filtered through silica and concentrated. The crude product mixture was separated by flash chromatography (petroleum ether with bp 50−70 °C and ethyl acetate in the ratio 10:1, silica gel) and the isolated products were dried in vacuo.

Coupling Reaction at 80 °C. TLC of the crude reaction mixture (petroleum ether/ethyl acetate in the ratio 4:1, silica gel): $R_f = 0.51$ (**5**), 0.40 (**6**), 0.14 (**4**). A mixture of petroleum ether and ethyl acetate in the ratio 10:1 was applied as eluent for the flash chromatography.

First fraction: 91 mg (30%) of a 3:1 mixture of *trans*-2-(4-methylbenzoyl)-1-(2-oxopropyl)-1,2,3,4-tetrahydronaphthalene (*trans*-**5**) and its *cis*-isomer (*cis*-**5**) as a slightly yellow oil. IR (KBr): 1706 (C=O), 1670 (C=O) cm^{-1}. MS (EI): 306 (7) [M$^+$], 249 (82), 119 (100). Enriched fractions of the isomers were obtained by flash chromatography (petroleum ether/acetone in the ratio 9:1, silica gel), allowing the identification of the ^{1}H NMR and the ^{13}C NMR signals. ***trans*-5**: ^{1}H NMR (300 MHz) $\delta = 1.83-1.96$ (m, 2H), 2.09 (s, 3H), 2.40 (s, 3H), 2.76−3.00 (m, 4H), 3.79−3.99 (m, 2H), 7.06−7.27 (m, 6H), 7.85−7.89 (m, 2H); ^{13}C NMR (75 MHz) $\delta = 21.53$ (q), 25.50 (t), 28.03 (t), 30.41 (q), 35.01 (d), 45.85 (d), 49.80 (t), 125.73 (d), 126.21 (d), 127.55 (d), 128.47 (d), 128.69 (d), 129.33 (d), 133.84 (s), 136.17 (s), 138.65 (s), 143.73 (s), 201.97 (s), 207.71 (s). ***cis*-5:** ^{1}H NMR (300 MHz) $\delta = 1.98$ (s, 3H), 2.11−2.26 (m, 2H), 2.40 (s, 3H), 2.89−2.99 (m, 4H), 3.82 (ddd, $J = 12.1$ Hz, 4.5 Hz, 2.9 Hz, 1H), 3.98 ("q", "J" = 5.2 Hz, 1H), 7.11−7.26 (m, 6H), 7.84−7.86 (m, 2H); ^{13}C NMR (75 MHz) $\delta = 20.64$ (t), 21.64 (q), 28.18 (t), 30.40 (q), 35.57 (d), 44.71 (d), 47.39 (t), 126.56 (d), 128.28 (d), 128.86 (d), 129.14 (d), 129.24 (d), 129.39 (d), 134.11 (s), 135.32 (s), 140.22 (s), 143.93 (s), 202.77 (s), 206.47 (s).

Second fraction: 100 mg (33%) of (1*R**,4a*R**,10a*S**)-1,4,4a,9,10,10a-hexahydro-1-hydroxy-1-(4-methylphenyl)phenanthren-3(2*H*)-one (**6**) as colorless needles with mp 175 °C (crystallized from petrol ether). ^{1}H NMR (300 MHz) $\delta = 1.54$ (m, 2H), 2.17 (s, 1H), 2.20−2.29 (m, 1H), 2.37 (s, 3H), 2.50 (d, $J = 13.0$ Hz, 1H), 2.58 (d, $J = 14.6$ Hz, 1H), 2.79 (t, $J = 6.4$ Hz, 2H), 2.98 (d, $J = 14.6$ Hz, 1H), 3.25 (dq, $J = 13.8$ Hz, 2.2 Hz, 1H), 3.47−3.57 (m, 1H), 7.07−7.25 (m, 6H), 7.32−7.36 (m, 2H); ^{13}C NMR (75 MHz) $\delta = 20.98$ (q), 22.70 (t), 29.89 (t), 38.19 (d), 46.28 (t), 47.37 (d), 56.32 (t), 79.22 (s), 124.45 (d), 125.54 (d), 126.14 (d), 126.20 (d), 128.93 (d), 129.38 (d), 136.57 (s), 136.91 (s), 139.03 (s), 142.37 (s), 208.94 (s).

Third fraction: further purified by distillation at 0.2 Torr/200 °C in a Kugelrohr apparatus for a total of 89 mg (29%) of (*E*)−4-[2-(4-hydroxy-4-*p*-tolyl-1-buten-1-yl)phenyl]-3-buten-2-one (**4**) as a yellow colored oil: ^{1}H NMR (300 MHz) $\delta = 2.13$ (s, 1H), 2.31 (s, 6H), 2.65−2.71 (m, 2H), 4.77 (t, $J = 6.8$ Hz, 1H), 6.05 (dt, $J = 15.7$ Hz, 7.2 Hz, 1H), 6.56 (d, $J = 16.1$ Hz, 1H), 6.71 (d, $J = 15.7$ Hz, 1H), 7.10−7.49 (m, 8H), 7.79 (d, $J = 16.1$ Hz, 1H); ^{13}C NMR (75 MHz) $\delta = 21.01$ (q), 27.55 (q), 42.98 (t), 73.59 (d), 118.41 (d), 125.75 (d), 126.89 (d), 127.33 (d), 127.35 (d), 128.53 (d), 129.04 (d), 129.63 (d), 130.04 (d), 132.08 (s), 137.11 (s), 138.08 (s), 140.98 (s), 141.38 (d), 198.42 (s).

Coupling Reaction at 150 °C. TLC of the crude reaction mixture (petroleum ether/ethyl acetate in the ratio 4:1, silica gel): $R_f = 0.69$ (**7**), 0.54 (weak, **2d**), 0.40 (**6**), 0.17 (**4**). A mixture of petroleum ether and ethyl acetate in a ratio of 10:1 was applied as eluent for the flash chromatography.

First fraction: 95 mg (33%) of 1-(4-methylphenyl)- 4a,9,10,10a-tetrahydrophenanthren-3(4*H*)-one (**7**) as colorless needles with mp 121 °C (crystallized from petroleum ether); ^{1}H NMR (300 MHz) $\delta = 1.78-1.85$ (m, 2H), 2.32 (s, 3H), 2.44−2.65 (m, 2H), 2.79−2.90 (m, 2H), 3.14−3.23 (m, 1H), 3.48 (dt, $J = 13.0$ Hz, 5.3 Hz, 1H), 6.33 (s, 1H), 7.04−7.18 (m, 6H), 7.37−7.41 (m, 2H); ^{13}C NMR (75 MHz) $\delta = 21.32$ (q), 23.40 (t), 29.93 (t), 37.16 (d), 37.99 (d), 42.57 (t), 124.38 (d), 126.29 (d), 126.62 (d), 126.68 (d), 128.88 (d), 129.30 (d), 129.75 (d), 134.83 (s), 135.30 (s), 138.87 (s), 140.63 (s), 163.48 (s), 199.02 (s).

Second fraction: 10 mg (6%) of **2d**.

Third fraction: 146 mg (48%) of **6**.

Fourth fraction: 18 mg (6%) of **4**.

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General Procedures for the Heck Reaction of Aryl Bromides 1 with Homoallylic Alcohols 2 or 3 Followed by a Robinson-Type Annulation Reaction; Procedure B: A mixture of 1.00 mmol of α,β-unsaturated carbonyl compound **1**, 2.50 mmol of homoallylic alkohol **2** or **3**, 1.0 g (8.0 g) of diisopropylethylamine, 42 mg (1.0 mmol) of LiCl, and 11.2 mg (5 mol %) of palladium acetate in 10 mL of dry DMF is heated for 3 d at 80 °C in a sealed tube under a nitrogen atmosphere. The reaction mixture is diluted with 50 mL water and extracted 3 times with 20 mL of methyl *tert*-butyl ether. The combined extracts are washed with 50 mL of water, and the water layer is extracted with 10 mL of ethyl acetate. After filtration of the combined organic extracts over silica gel and concentration under reduced pressure in a Kugelrohr apparatus, the product mixture of the palladium-catalyzed reaction is dissolved in 10 mL of chloroform and treated in the presence of 0.1 g (1 mmol) of hydrochloric acid for 4 h at 40 °C in a ultrasonic cleaning bath. For neutralization 1 g of $NaHCO_3$ is added and after filtration the crude product is purified by flash chromatography.

Procedure C. A mixture of 1.00 mmol of α,β-unsaturated carbonyl compound **1**, 2.50 mmol of homoallylic alkohol **2** or **3**, 1.0 g (8.0 g) of diisopropyl ethylamine, 42 mg (1.0 mmol) of LiCl, and 11.2 mg (5 mol %) of palladium acetate in 25 mL of dry DMF is heated for 3 d at 80 °C in a sealed tube under a nitrogen atmosphere. The solvent is removed under reduced pressure, and the residue is dissolved in 20 mL of methyl *tert*-butyl ether and 50 mL of water. The organic phase is separated, and the aquaous phase is extraced twice with 20 mL of methyl *tert*-butyl ether. The combined extracts are filtered over silica gel and concentrated in a Kugelrohr apparatus under reduced pressure. The crude product of the palladium-catalyzed reaction is dissolved in 10 mL of chloroform and heated in the presence of 19 mg (0.1 mmol) of pTsOH at reflux temperature for 2 d. For neutralization 100 mg of $NaHCO_3$ is added and after filtration the crude product is purified by flash chromatography.

(1*R,4a*R**,10a*S**)-1,4,4a,9,10,10a-Hexahydro-1-hydroxyphenanthren-3(2*H*)-one (14).** A total of 225 mg (1.00 mmol) of ketone **1b** and 180 mg (2.50 mmol) of butenol **2a** were employed in the palladium-catalyzed reaction, according to the general procedure B. The intermediate **14** crystallized by treatment of the crude product of the palladium-catalyzed reaction with 50 mL of methyl *tert*-butyl ether. **14:** yield 77 mg (35%); colorless solid with mp 163 °C; ^{1}H NMR (500 MHz) δ = 1.84−1.98 (m, 3H), 2.01 (s, 1H), 2.31 (dd, J = 14.0, 13.1 Hz, 1H), 2.66 (m, 2H), 2.99 (m, 2H), 3.16 ("dd", "J" = 14.3, 4.3 Hz, 1H), 3.40 (m, 1H), 4.40 ("s", 1H), 7.12−7.21 (m, 4H); ^{13}C NMR (125 MHz) δ = 26.03 (t), 30.03 (t), 35.50 (d), 43.29 (d), 46.39 (t), 49.67 (t), 72.49 (d), 125.79 (d), 126.17 (d), 126.19 (d), 129.13 (d), 136.18 (s), 138.70 (s), 209.58 (s).

(4a*R,10a*R**)-4a,9,10,10a-Tetrahydrophenanthren-3(4*H*)-one (*trans*-8).** A total of 225 mg (1.00 mmol) of ketone **1b** and 180 mg (2.50 mmol) of butenol **2a** were employed in the palladium-catalyzed reaction and treated with hydrochloric acid, according to the general procedure B. Flash chromatography using methyl *tert*-butyl ether/petroleum ether (ratio 1:4) as eluent gave 111 mg (56%) of **8** as a diastereoisomeric oil; *cis*/*trans*-ratio 1:4. Fractional crystallization from methyl *tert*-butyl ether/petroleum ether (ratio 1:10) yields *trans*-8 as a colorless solid with mp 52 °C: ^{1}H NMR (500 MHz) δ = 1.72 (m, 1H), 2.19 (m, 1H), 2.37 (dd, J = 16.5, 13.8 Hz, 1H), 2.46 (m, 1H), 2.99−3.13 (m, 3H), 3.24 (dd, J = 16.4, 3.9 Hz, 1H), 6.10 (d, J = 9.9 Hz, 1H), 6.94 (dd, J = 9.9, 1.9 Hz, 1H), 7.11−7.20 (m, 4H); ^{13}C NMR (75 MHz) δ = 28.32 (t), 29.50 (t), 39.29 (d), 41.28 (d), 42.52 (t), 124.65 (d), 126.15 (d), 126.56 (d), 129.31 (d), 129.65 (d), 135.92(s), 137.45 (s), 155.23 (d), 199.49 (s).

(4a*R,10a*S**)-4a,9,10,10a-Tetrahydrophenanthren-3(4*H*)-one (*cis*-8).** A total of 225 mg (1.00 mmol) of ketone **1b** and 180 mg (2.50 mmol) of butenol **2a** were employed in the palladium-catalyzed reaction, according to the general procedure B. The crude product of the palladium-catalyzed reaction was dissolved in 10 mL of DMF and treated with 6.0 g (60 mmol) of hydrochloric acid for 5 d at room temperature. Flash chromatography using methyl *tert*-butyl ether/petroleum ether (ratio 1:4) as eluent gave 42 mg (21%) of *cis*-**8** as colorless oil: ^{1}H NMR (500 MHz) δ = 1.83 (m, 1H), 1.99 (m, 1H), 2.63 (m, 2H), 2.72 (m, 1H), 2.93 (m, 2H), 3.46 ("dt", "J" = 11.8, 5.7 Hz, 1H), 6.06 ("ddd", "J" = 10.1, 1.3, 0.7 Hz, 1H), 7.02 (dd, J = 10.1, 5.2 Hz, 1H), 7.12−7.20 (m, 4H); ^{13}C NMR (75 MHz) δ = 23.43 (t), 29.58 (t), 35.45 (d), 37.18 (d), 43.29 (t), 126.33 (d), 126.50 (d), 128.64 (d), 128.86 (d), 129.22 (d), 135.33 (s), 138.18 (s), 153.24 (d), 199.03 (s).

(4a*R,10a*R**)-2-Methyl-4a,9,10,10a-tetrahydro-phenanthren-3(4*H*)-one (*trans*-9) and (4a*R**,10a*S**)-2-Methyl-4a,9,10,10a-tetrahydrophenanthren-3(4*H*)-one (*cis*-9).** A total of 239 mg (1.00 mmol) of ketone **1c** and 180 mg (2.50 mmol) of butenol **2a** were employed in the palladium-catalyzed reaction and treated with hydrochloric acid, according to the general procedure B. Flash chromatography using methyl *tert*-butyl ether/petroleum ether (ratio 1:4) as eluent gave 153 mg (72%) of **9** as a diastereoisomeric oil; *cis*/*trans*-ratio 1:4. A pure fraction of *trans*-**9** was obtained by crystallization of the diastereoisomeric mixture from methyl *tert*-butyl ether/petroleum ether (ratio 1:10) as colorless solid with mp 68 °C: ^{1}H NMR (500 MHz) δ = 1.71 (m, 1H), 1.84 (dd, J = 2.5, 1.5 Hz, 3H), 2.15 (m, 1H), 2.37 (dd, J = 16.5, 13.9 Hz, 1H), 2.45 (m, 1H), 2.95−3.09 (m, 3H), 3.37 (dd, J = 16.5, 3.9 Hz, 1H), 6.69 ("quint", "J" = 1.6 Hz, 1H), 7.12−7.22 (m, 4H); ^{13}C NMR (125 MHz) δ = 15.72 (q), 28.61 (t), 29.52 (t), 39.48 (d), 41.63 (d), 42.65 (t), 124.78 (d), 126.11 (d), 126.49 (d), 129.33 (d), 135.76 (s), 136.02 (s), 137.67 (s), 150.51(d), 199.70 (s). ***cis*-9:** ^{1}H NMR (500 MHz): selected signals δ = 1.81 ("t", "J" = 1.4 Hz, 3H), 1.96 (m, 1H), 3.45 ("dt", "J"= 12.2, 5.6 Hz, 1H), 6.75 (dq, J = 5.7, 1.4 Hz, 1H); ^{13}C NMR (75 MHz) δ = 15.82 (q), 23.55 (t), 29.61 (t), 35.69 (d), 37.55 (d), 43.62 (t), 126.25 (d), 126.40 (d), 128.68 (d), 129.19 (d), 134.85 (s), 135.52 (s), 138.43 (s), 148.42 (d), 199.22 (s).

(4a*R,10a*R**)-10a-Methyl-4a,9,10,10a-tetrahydrophenanthren-3(4*H*)-one (*trans*-10) and (4a*R**,10a*S**)-10a-Methyl-4a,9,10,10a-tetrahydrophenanthren-3(4*H*)-one (*cis*-10).** A total of 225 mg (1.00 mmol) of ketone **1b** and 215 mg (2.50 mmol) of butenol **3a** were employed in the palladium-catalyzed reaction and treated with hydrochloric acid, according to the general procedure B. Flash chromatography using methyl *tert*-butyl ether/petroleum ether (ratio 1:4) as eluent gave 123 mg (58%) of **8** as a diastereoisomeric oil; *cis*/*trans*-ratio 1:4. A pure fraction of *trans*-**10** was obtained by crystallization of the diastereoisomeric mixture from methyl *tert*-butyl ether/petroleum ether (ratio 1:10) as colorless solid with mp 60 °C: ^{1}H NMR (500 MHz) δ = 0.96 (s, 3H), 1.89 (m, 2H), 2.52 (dd, J = 17.3, 14.1 Hz, 1H), 3.01 (m, 2H), 3.10 (dd, J = 17.3, 4.5 Hz, 1H), 3.29 (dd, J = 14.0, 4.4 Hz, 1H), 5.99 (dd, J = 9.9, 0.9 Hz, 1H), 6.91 (d, J = 9.9 Hz, 1H), 7.11−7.20 (m, 4H); ^{13}C NMR (75 MHz) δ = 17.12 (q), 25.74 (t), 34.56 (t), 35.27 (s), 37.23 (t), 42.97 (d), 124.51 (d), 126.10 (d), 126.40 (d), 127.24 (d), 128.98 (d), 135.22 (s), 136.76 (s), 160.98 (d), 199.52 (s). ***cis*-10:** ^{1}H NMR (500 MHz): selected Signals δ = 1.16 (s, 3H), 1.67 (ddd, J = 13.5, 3.8, 1.3 Hz, 1H), 2.54 (dd, J = 16.9, 12.7 Hz, 1H), 2.66 (ddd, J = 16.9, 4.8, 0.8 Hz, 1H), 2.90 (m, 2H), 5.96 (dd, J = 10.1, 0.8 Hz, 1H), 6.73 (d, J = 10.1 Hz, 1H); ^{13}C NMR (75 MHz) = 24.37 (q), 25.79 (t), 28.58 (t), 35.04 (s), 43.78 (d), 44.10 (t), 126.10 (d), 126.37 (d), 127.02 (d), 129.15 (d), 129.16 (d), 134.20 (s), 137.85 (s), 159.10 (d), 199.36 (s).

(4a*R,10a*S**)-4a,9,10,10a-Tetrahydrophenanthren-1(4*H*)-one (*trans*-11) and (4a*R**,10a*R**)-4a,9,10,10a-Tetrahydrophenanthren-1(4H)-one (*cis*-11).** A total of 211 mg (1.00 mmol) of aldehyde **1a** and 215 mg (2.50 mmol) of pentenol **2b** were employed in the palladium-catalyzed reaction and treated with *p*-toluenesulfonic acid according to the general procedure C. The residue was chromatographed using methyl *tert*-butyl ether/petroleum ether (ratio 1:6) as eluent. ***trans*-11:** 71 mg (36%), colorless solid; mp 90 °C; ^{1}H NMR (500 MHz) δ = 1.59 (m, 1H), 2.36 (m, 1H), 2.42 ("ddq", "J" = 19.5, 12.0, 2.1 Hz, 1H), 2.54 (m, 1H), 2.90 (m, 2H), 3.09−3.18 (m, 2H), 6.15 (ddd, J = 10.0, 3.0, 0.9 Hz, 1H), 7.08 (ddd, J = 10.0, 5.8, 2.1 Hz, 1H), 7.11−7.22 (m, 3H), 7.27 ("d", "J" = 7.5 Hz, 1H); ^{13}C NMR (75 MHz) δ = 21.54 (t), 29.18 (t), 32.47 (t), 39.76 (d), 48.91 (d), 125.62 (d), 126.09 (d), 126.40 (d), 129.35 (d), 129.76 (d), 136.69 (s), 137.80 (s), 148.50 (d), 200.55 (s). ***cis*-11:** 61 mg (31%), yellow oil; ^{1}H NMR (500 MHz) δ = 1.94 (m, 2H), 2.43 ("ddt", "J" = 19.4, 11.0, 2.6 Hz, 1H), 2.60 ("dtd", "J" = 19.4, 5.7, 1.2 Hz, 1H), 2.70 ("dt", "J" = 12.2, 4.5 Hz, 1H), 2.93 (m, 2H), 3.40 (m, 1H), 6.10 (dddd, J = 10.2, 1.2, 0.7 Hz, 1H), 6.96 (dddd, J = 10.2, 5.7, 2.5, 0.4 Hz, 1H), 7.09−7.18 (m, 4H); ^{13}C NMR (75 MHz) δ = 21.28 (t), 28.83

(t), 31.82 (t), 37.45 (d), 46.20 (d), 126.04 (d), 126.60 (d), 128.38 (d), 129.10 (d), 129.35 (d),135.35 (s), 138.23 (s), 148.94 (d), 202.04 (s).

(4a*R,10a*S**)-2-Methyl-4a,9,10,10a-tetrahydrophenanthren-1(4*H*)-one (*trans*-12) and (4a*R**,10a*R**)-2-Methyl-4a,9,10,10a-tetrahydrophenanthren-1(4*H*)-one (*cis*-12).** A total of 211 mg (1.00 mmol) of aldehyde **1a** and 250 mg (2.50 mmol) of hexenol **2c** were employed in the palladium-catalyzed reaction and treated with *p*-toluenesulfonic acid according to the general procedure C. The crude product was chromatographed using methyl *tert*-butyl ether/petroleum ether (ratio 1:6) as eluent. ***trans*-12:** 27 mg (13%), colorless solid; mp 68 °C; ^{1}H NMR (500 MHz) δ = 1.57 (m, 1H), 1.85 ("q", "*J*" = 1.3 Hz, 3H), 2.31 (m, 1H), 2.45 ("ddt", "*J*" = 19.2, 12.0, 2.5 Hz, 1H), 2.56 ("ddt", "*J*" = 13.5, 5.4, 2.9 Hz, 1H), 2.89 (m, 2H), 3.05−3.13 (m, 2H), 6.83 (m, 1H), 7.01−7.21 (m, 3H), 7.27 ("d", "*J*" = 7.5 Hz, 1H); ^{13}C NMR (75 MHz) δ = 15.97 (q), 21.84 (t), 29.31 (t), 32.40 (t), 40.02 (d), 48.83 (d), 125.56 (d), 126.04 (d), 126.30 (d), 129.28 (d), 135.62 (s), 136.68 (s), 138.16 (s), 143.27 (d), 200.70 (s). ***cis*-12**: 108 mg (51%), colorless solid; mp 82−83 °C; ^{1}H NMR δ = 1.83 ("dt", "*J*" = 2.6, 1.4 Hz, 3H), 1.93 (m, 2H), 2.43 ("ddt", "*J*" = 19.1, 11.2, 2.6 Hz, 1H), 2.54 ("ddt", "*J*" = 19.1, 5.8, 1.3 Hz, 1H), 2.71 (ddd, *J* = 12.4, 5.1, 3.8 Hz, 1H), 2.93 (m, 2H), 3.39 ("dt", *J* = 11.2, 5.4 Hz, 1H), 6.72 (m, 1H), 7.09−7.17 (m, 4H); ^{13}C NMR δ = 16.05 (q), 21.40 (t), 29.02 (t), 32.13 (t), 37.96 (d), 46.27 (d), 126.03 (d), 126.52 (d), 128.38 (d), 129.33 (d), 135.01 (s), 135.47 (s), 138.66 (s), 143.91 (d), 201.96 (s).

10a-Methyl-4a,9,10,10a-tetrahydrophenanthren-1(4*H*)-one (13). A total of 211 mg (1.00 mmol) of aldehyde **1a** and 250 mg (2.50 mmol) of pentenol **3b** were employed in the palladium-catalyzed reaction and treated with *p*-toluenesulfonic acid according to the general procedure C. Flash chromatography using methyl *tert*-butyl ether/petroleum ether (ratio 1:6) as eluent gave 102 mg (48%) of **13** as a yellow diastereoisomeric oil; *cis*/*trans*-ratio 5:1. ^{1}H NMR (500 MHz): signals of ***cis*-13** δ = 1.15 ("s", 3H), 1.56 ("dtd", "*J*" = 13.3, 4.9, 1.4 Hz, 1H), 2.09 (dt, *J* = 13.4, 9.0 Hz, 1H), 2.44 (ddt, *J* = 19.5, 10.2, 2.7 Hz, 1H), 2.62 (dtd, *J* = 19.5, 5.2, 1.2 Hz, 1H), 2.90 (m, 2H), 3.05 (m, 1H), 6.04 (ddd, *J* = 10.1, 2.7, 1.2 Hz, 1H), 6.87 (ddd, *J* = 10.0, 5.5, 2.7 Hz, 1H), 7.08−7.16 (m, 4H). Selected signals of *trans*-**13**: δ = 0.98 (d, *J* = 0.5 Hz, 3H), 1.76 (m, 1H), 2.25 (ddd, *J* = 13.8, 5.3, 3.5 Hz, 1H), 3.21 (dd, *J* = 11.2, 4.8 Hz, 1H), 7.02 ("ddd", "*J*" = 10.1, 5.9, 2.2 Hz, 1H), 7.24 (m, 1H); ^{13}C NMR (125 MHz) signals of *cis*-**13** δ = 20.01 (q), 25.07 (t), 26.50 (t), 33.10 (t), 44.03 (s), 44.12 (d), 126.01 (d), 126.41 (d), 128.59 (d), 128.81 (d), 129.31 (d), 134.51 (s), 138.41 (s), 147.30 (d), 204.41 (s). Signals of *trans*-**13**: δ = 15.00 (q), 25.63 (t), 27.59 (t), 28.62 (t), 41.73 (d), 43.52 (s), 125.53 (d), 126.06 (d), 126.27 (d), 127.99 (d), 129.11 (d), 135.62 (s), 136.65 (s), 147.27 (d), 204.95 (s).

***(E)*-3-[2-(4-Oxo-1-hexyl)phenyl]propenal 15:** yellow oil, rapidly polycondensating at room temperature; ^{1}H NMR (300 MHz) δ = 1.06 (t, *J* = 7.3 Hz, 3H), 1.87 (m, 2H), 2.45 (q, *J* = 7.3 Hz, 2H), 2.49 (t, *J* = 6.8 Hz, 2H), 2.79 (m, 2H), 6.68 (dd, *J* = 15.8, 7.7 Hz, 1H), 7.22−7.30 (m, 2H), 7.36 ("t", "*J*" = 7.4 Hz, 1H), 7.94 (d, *J* = 15.7 Hz, 1 H), 9.80 (d, *J* = 7.7 Hz, 1 H); ^{13}C NMR (75 MHz) δ = 7.84 (q), 25.44 (t), 32.60 (t), 36.08 (t), 41.19 (t), 126.91 (d), 126.95 (d), 129.89 (d), 130.35 (d), 131.06 (d), 132.56 (s), 141.92 (s), 150.07 (d), 194.07 (d), 210.88 (s).

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Supporting Information Available: Additional characterization data for all products including NMR assignments based upon two-dimensional NMR experiments (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS.

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