Synthesis of a Novel Enantiopure Spiro-B-norestradiol Analogue by Multiple Pd-Catalyzed Transformations

Lutz F. Tietze,*[a] J. Matthias Wiegand,[a] and Carsten A. Vock[a]

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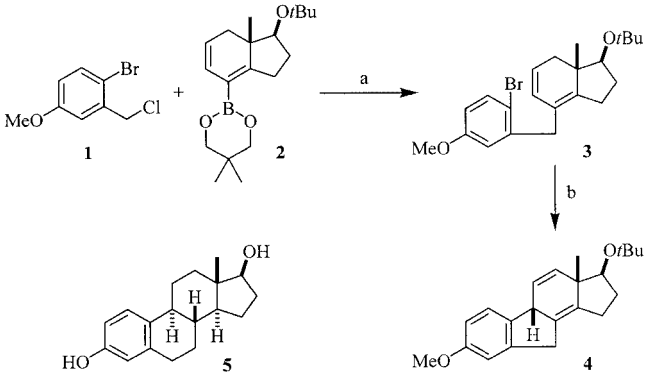
The novel tetracyclic spiro compound **13** was synthesized by the use of two subsequent Pd-catalyzed reactions. Firstly, the *ortho*-bromobenzyl chloride **1** was coupled with the enantiopure boronic ester **8**, obtained from the Hajos–Wiechert ketone in a chemoselective Suzuki-type reaction to give **12** in 77% yield. Unexpectedly, the intramolecular Heck reaction then did not provide the annulated compound **6**, but the spirocyclic compound **13**, containing a quaternary carbon center, in 73% yield. The Heck reaction was also performed under microwave irradiation conditions, allowing a considerably shorter reaction time.

Introduction

Pd-catalyzed reactions such as the Heck reaction or cross-coupling reactions such as the Suzuki and the Stille reactions have become very popular for the formation of C−C-bonds, thanks to their high tolerance of functional groups and their general applicability.[1] The efficiency can often be further improved by use of multiple Pd-catalyzed transformations, either in a domino process[2,3] or in a sequential fashion.[4] Nowadays, it is also possible to couple compounds of lower reactivity, such as organic chlorides, by employment of highly active catalysts[5] such as the Herrmann−Beller palladacene **14**, or by application of new laboratory techniques such as microwave irradiation.[6]

We recently used a multiple Pd-catalyzed process for the synthesis of the B-norestradiol derivative **4** as a possible ligand for the maxi-K^+-channel (Scheme 1).[4a] Compounds of this type might show a protective effect on the cardiovascular system and could therefore be usable in the treatment of cardiovascular diseases. It has been shown that estradiol **5** binds extracellulary to the regulatory β-unit of the maxi-K^+-channel, a key modulator of vascular muscle tone located on the endothelium.[7] Unfortunately, **5** cannot be applied directly as a drug because of its hormonal activity, so derivatives that still activate the maxi-K^+-channel but lack the hormonal properties are required. One possibility is the synthesis of B-norsteroids with a 6,5,6,5 ring system, which have been shown to have reduced hormonal activity in relation to compounds with the natural steroidal 6,6,6,5 scaffold.[8] In this synthesis the benzylic chloride **1** and the boronic ester **2** were coupled in a Suzuki reaction to give the secosteroid **3**. The reaction showed high chemoselectivity, and the coupling took place exclusively at the benzylic chloride moiety of **1**, whereas the aryl bromide moiety seemed to be inert. In a subsequent intramolecular Heck reaction the steroidal compound **4** was formed through the use of **14** as catalyst under microwave irradiation conditions.



Scheme 1. (a) 5 mol % $[Pd(PPh_3)_4]$, NaOH, THF, reflux, 22 h, 72%; (b) 5 mol % **14**, nBu_4NOAc, DMF/MeCN/H_2O, 140 °C (microwave), 5 min, 70%

Our interest now focussed on the synthesis of other estradiol analogues, especially in the B-norestradiol series, in which the positions of the olefinic double bonds differ from those in **4** as in **6** to allow further functionalizations such as epoxidation, bis(hydroxylation), and cyclopropanation. We anticipated that **6** should be available from **1** and **8** via **7** through two Pd-catalyzed transformations as described for **4** (Scheme 2).

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

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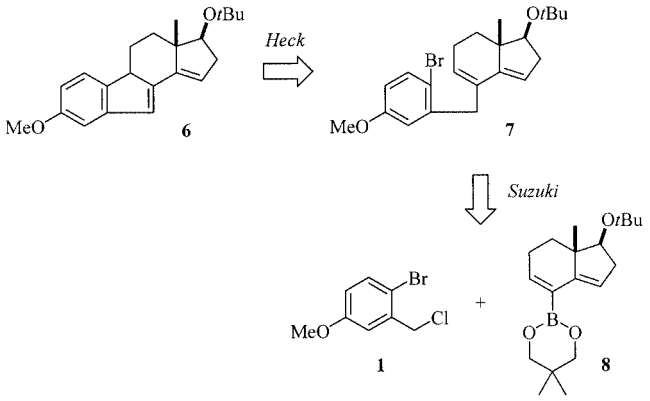
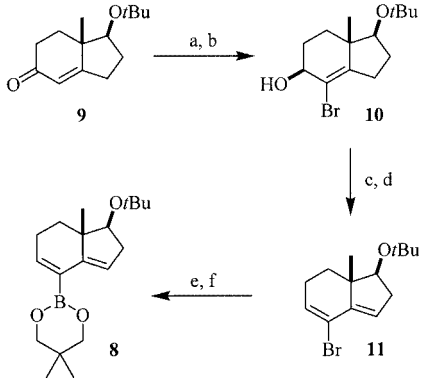


Scheme 2. Retrosynthesis of **6**

Surprisingly, when **7** was subjected to the final intramolecular Heck reaction, the ring closure did not take place as expected to form a steroidal compound of type **6**, but a spirocyclic compound with a quaternary carbon center was created.

Results and Discussion

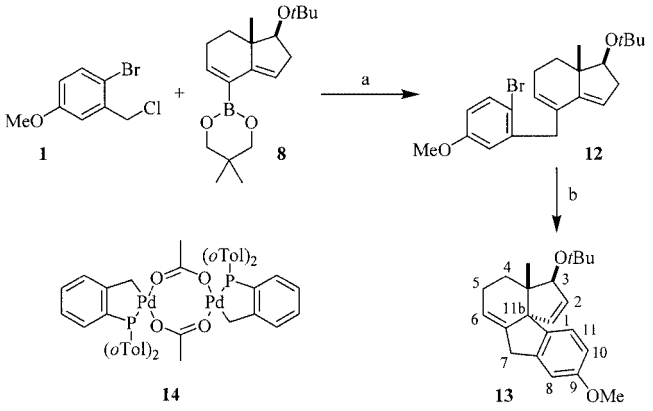
The boronic ester **8** was prepared in four steps starting from the enantiopure Hajos−Wiechert ketone derivative **9** (Scheme 3).[9] Bromination of **9** in a mixture of diethyl ether and acetic acid in the presence of the base 2,4,6-collidine provided the corresponding α-bromo enone **20**, which was then reduced under Luche[10] conditions to give the α-bromo allylic alcohol **10**. Treatment of **10** with mesyl chloride and NEt_3 as base yielded the mesylate, which was directly heated in DBU to give the vinyl bromide **11**. The attack of the base did not take place at the methylene moiety adjacent to the OH group, presumably because of the high steric demand of DBU, but at the vinylogous position. Bromine/lithium exchange and quenching with $B(OiPr)_3$ yielded the corresponding diisopropyl boronic ester, which



Scheme 3. (a) Br_2, 2,4,6-collidine, Et_2O, HOAc, room temp., dark, 24 h, 80%; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, room temp., 4 h, 80%; (c) MsCl, NEt_3, CH_2Cl_2, room temp., 6 h; (d) DBU, 100 °C, 69% (over two steps); (e) *t*BuLi, TMEDA, $B(OiPr)_3$, THF, −78 °C to room temp., 1 h; (f) 2,2-dimethylpropane-1,3-diol, toluene, room temp., 16 h, 68% (over two steps)

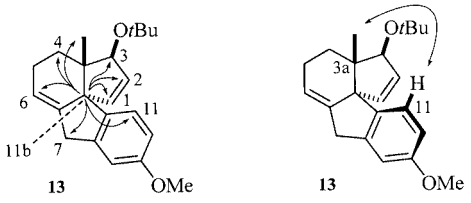
was directly transesterified to give the more stable cyclic boronic ester **8**.

Analogously to the synthesis of **3**, the benzylic chloride **1** and the boronic ester **8** were coupled in a Suzuki reaction with 5 mol % of $[Pd(PPh_3)_4]$ as catalyst and NaOH as base to give the seco-B-norsteroid **12** in 77% yield (Scheme 4). Again, solely the benzylic chloride moiety of **1** reacted and no cross-coupling involving the aryl bromide moiety was observed.



Scheme 4. (a) 5 mol % $[Pd(PPh_3)_4]$, NaOH, THF, reflux, 16 h, 77%; (b) 5 mol % **14**, nBu_4NOAc, DMF/MeCN/H_2O, 180 °C (microwave), 30 min, 73%

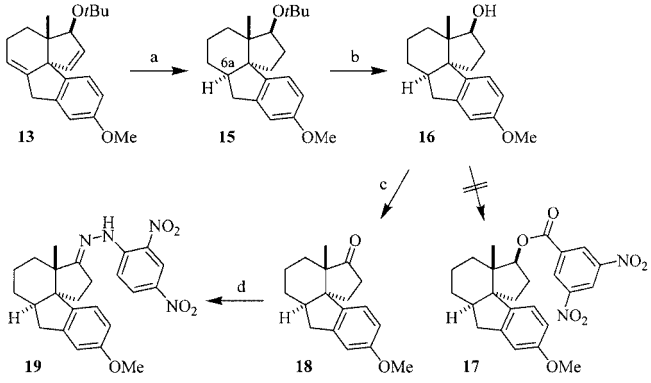
When **12** was heated in a mixture of DMF, MeCN, and H_2O with 5 mol % **14** as catalyst and nBu_4NOAc as base, either under microwave irradiation conditions at 180 °C for 30 min or at 120 °C for 18 h, the novel spirocyclic system **13** was obtained as a single diastereomer in 73% yield under both sets of conditions. The structure of **13** was determined by NMR experiments: the HMBC spectrum, for example, showed correlations between C-11b and 1-H, 2-H, 3-H, 4-H_2, 6-H, 7-H_2, 11-H and 3a-CH_3 (Scheme 5).[11] The configuration of the new stereogenic center C-11b was determined by NOE experiments, with selective irradiation at frequencies assigned to the angular methyl group at C-3a and to the aromatic proton 11-H revealing a strong correlation and thus a *cis* orientation of the angular methyl group and the aromatic ring. On the other hand, there was no correlation of the methyl group and 1-H, clearly indicating that C-11b had to have the proposed (*R*) configuration. Thus, in the Heck reaction of **12** the olefinic double bond in the five-membered ring was, surprisingly, attacked by the Pd−aryl species from the β-face despite the high steric de-



Scheme 5. Structure determination of **13** by HMBC and NOE experiments

mand of the angular methyl group. The selective formation of the spiro compound could be explained by the fact that *exo*-trig additions are favored over *endo*-trig additions. On the other hand, it could also be possible that the carbopalladation is reversible and that only in the intermediate leading to the spiro compound can a conformation appropriate to allow a fast β-hydride elimination be adopted.[4f,12]

It should be noted that **13** is not very stable and decomposes in chloroform solution at 20 °C within 48 h. It was therefore subjected to further transformations (Scheme 6). Hydrogenation of the two olefinic double bonds with 20 mol % $PtO_2 \cdot H_2O$ as catalyst afforded the stable compound **15**, which bears another stereogenic center, in a highly stereoselective manner. Its configuration was again determined by NOE experiments. As would be expected, the attack of hydrogen took place from the less crowded α-face of the molecule to give **15** with an (*R*) configuration at C-6a.[11] The *t*Bu protection group was then removed in 97% yield with TMSI as weak Lewis acid. Interestingly, it was not possible to acylate the resulting alcohol **16**, probably because of the strong shielding of the hydroxy group by the angular methyl group and the aromatic ring. Oxidation of **16** with Dess−Martin periodinane was possible, however, providing the ketone **18** in 76% yield, and this was then transformed into the corresponding 2,4-dinitrophenyl hydrazone **19**.



Scheme 6. (a) 20 mol % $PtO_2 \cdot H_2O$, H_2, MeOH, room temp. 18 h, 96%; (b) TMSI, CH_2Cl_2, room temp., dark, 16 h, 97%; (c) DMP, CH_2Cl_2, room temp., 6 h, 76%; (d) 2,4-dinitrophenylhydrazine, H_2SO_4, EtOH, room temp., 1 h, 77%

Conclusion

The novel unusual spirocyclic compound **13** was synthesized by a sequence of two Pd-catalyzed reactions as the key steps, starting from the benzylic chloride **1** and the boronic ester **8**. In the first Suzuki reaction the benzylic chloride moiety showed a much higher reactivity than the aryl bromide moiety, allowing a chemoselective transformation. In the subsequent intramolecular Heck reaction of **12** only the spiro compound **13** was formed, and none of the expected annulated compounds such as **6**. Here the attack of the Pd−aryl species takes places *syn* to the angular methyl group.

Experimental Section

General Remarks: Melting points were measured with a Mettler FP61 melting point apparatus and are uncorrected. Optical rotations were taken with a Perkin−Elmer 241 spectrometer. ^1H and ^{13}C NMR spectra were recorded with Mercury-200, VXR-200, Unity 300, Inova-500, Unity Inova-600 (Varian) or AMX 300 (Bruker) spectrometers. Chemical shifts are reported in δ ppm referenced to TMS (^1H NMR) or to $CDCl_3$ (^{13}C NMR) as internal standard. IR spectra were taken with a Bruker IFS 25 and UV spectra with a Perkin−Elmer Lambda 2 spectrometer. Mass spectra were measured with a Varian MAT 311A (low resolution) and with a MAT 731 (high resolution). Microwave heating was performed in a Personal Chemistry SmithCreator microwave reactor. Precoated silica gel SIL G/UV_{254} (Macherey−Nagel & Co) was used for TLC, and Kieselgel 60 (0.032−0.063 nm, Merck) for flash chromatography. All reactions were performed under argon in oven-dried glassware. Solvents were dried and distilled prior to use by the usual laboratory methods, commercially available chemicals were used without further purification, 2-bromo-5-methoxybenzyl chloride (**1**) and (−)-(1*S*,7a*S*)-1-*tert*-butoxy-7a-methyl-1,2,3,6,7,7a-hexahydroinden-5-one (**9**) are known substances and can be prepared by literature methods.[9,13]

(−)-(1*S*,7a*S*)-4-Bromo-1-*tert*-butoxy-7a-methyl-1,2,3,6,7,7a-hexahydroinden-5-one (20): A solution of Br_2 (5.00 equiv., 250 mmol, 12.8 mL) in HOAc (325 mL) was added at 0 °C to a solution of enone **9** (1.00 equiv., 50.0 mmol, 11.1 g) in Et_2O (500 mL) and 2,4,6-collidine (100 mL), and the mixture was then stirred in the absence of light at room temperature for 24 h. Excess bromine was destroyed by addition of a saturated solution of $Na_2S_2O_3$, and the aqueous layer was then separated and extracted three times with Et_2O. The combined organic phases were washed with a saturated solution of $NaHCO_3$ and dried with Na_2SO_4, and the solvent was removed in vacuo. Recrystallisation (pentane) of the residue yielded **20** (12.0 g, 39.8 mmol, 80%) as a white solid. R_f = 0.45 (pentane/*t*BuOMe, 9:1). M.p. 103 °C. $[\alpha]_D^{20}$ = −47.0 (*c* = 0.5 in $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 1.13 (s, 3 H, 7a-CH_3), 1.16 [s, 9 H, $C(CH_3)_3$], 1.79 (dt, *J* = 13.7, 5.2 Hz, 1 H, 7-H_b), 1.83 (ddt, *J* = 22.9, 20.8, 10.2 Hz, 1 H, 2-H_b), 1.98−2.04 (m, 2 H, 2-H_a, 7-H_a), 2.45 (dt, *J* = 20.8, 9.3 Hz, 1 H, 3-H_b), 2.58−2.66 (m, 2 H, 3-H_a, 6-H_b), 2.71 (ddd, *J* = 17.9, 14.4, 5.2 Hz, 1 H, 6-H_a), 3.63 (dd, *J* = 10.2, 7.3 Hz, 1 H, 1-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 15.67 (7a-CH_3), 28.57 [$C(CH_3)_3$], 29.60, 30.17 (C-3, C-7), 33.68, 34.13 (C-2, C-6), 48.64 (C-7a), 73.28 [$C(CH_3)_3$], 79.75 (C-1), 118.4 (C-4), 173.5 (C-3a), 190.7 (C-5) ppm. IR (KBr): $\tilde{\nu}$ = 2972 cm^{-1} (CH), 1686 (C=O), 1097 (C−O−C). UV (MeCN): $\lambda_{max.}$ (lg ε) = 258 nm (3.924). MS (DCI, 200 eV): *m*/*z* (%) = 622, 620, 618 (26) [2 M + NH_4^+], 320, 318 (100) [M + NH_4^+]. $C_{14}H_{21}BrO_2$ (301.22): calcd. C 55.82, H 7.03; found C 55.76, H 6.82.

(−)-(1*S*,5*S*,7a*S*)-4-Bromo-1-*tert*-butoxy-7a-methyl-2,3,5,6,7,7a-hexahydro-1*H*-inden-5-ol (10): $NaBH_4$ (1.20 equiv., 27.9 mmol, 1.06 g) was added portionwise at 0 °C to a solution of α-bromoenone **20** (1.00 equiv., 23.2 mmol, 7.00 g) and $CeCl_3 \cdot 7H_2O$ (1.20 equiv., 27.9 mmol, 10.4 g) in MeOH (75 mL), and the mixture was then stirred at room temperature for 4 h. The solvent was removed in vacuo, and the resulting residue was taken up in Et_2O and a saturated solution of NH_4Cl. The aqueous layer was separated and extracted three times with Et_2O, the combined organic phases were dried with Na_2SO_4, and the solvent was removed in vacuo. After purification of the crude product by flash chromatography (200 g SiO_2; pentane/*t*BuOMe, 9:1), **10** was obtained (5.63 g, 18.6 mmol, 80%) as a colorless oil that slowly crystallized. R_f = 0.37 (pentane/

*t*BuOMe, 9:1). M.p. 60 °C. $[\alpha]_D^{20} = -17.2$ ($c = 0.5$ in $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.00 (s, 3 H, 7a-CH_3), 1.12 [s, 9 H, $C(CH_3)_3$], 1.35 (td, J = 13.9, 3.2 Hz, 1 H, 7-H_α), 1.65−1.75 (m, 2 H, 2-H_β, 7-H_β), 1.82−1.91 (m, 2 H, 2-H_α, 6-H_β), 2.13−2.27 (m, 3 H, 3-H_α, 6-H_α, OH), 2.29−2.37 (m, 1 H, 3-H_β), 3.42 (dd, J = 10.0, 7.6 Hz, 1 H, 1-H), 4.23 (m_c, 1 H, 5-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 17.18 (7a-CH_3), 28.01 (C-3), 28.66 [$C(CH_3)_3$], 29.54, 29.63 (C-2, C-6), 33.34 (C-7), 47.52 (C-7a), 71.72 (C-5), 72.85 [$C(CH_3)_3$], 80.10 (C-1), 121.5 (C-4), 148.2 (C-3a) ppm. IR (film): $\tilde{\nu}$ = 3385 cm^{-1} (OH), 2973 (CH), 1099 (C−O−C). UV (MeCN): $\lambda_{max.}$ (lg ε) = 204 nm (3.933). MS (EI, 70 eV): *m*/*z* (%) = 230, 228 (24) [$M^+ - C_4H_8 - H_2O$], 167 (37) [$M^+ - Br - C_4H_8$], 149 (39) [$M^+ - Br - C_4H_8 - H_2O$], 57 (100) [$C_4H_9^+$]. $C_{14}H_{23}BrO_2$ (303.24): calcd. C 55.45, H 7.65; found C 55.43, H 7.37.

(−)-(1*S*,7a*S*)-4-Bromo-1-*tert*-butoxy-7a-methyl-2,6,7,7a-tetrahydro-1*H*-indene (11): Mesyl chloride (1.20 equiv., 36.4 mmol, 2.82 mL) and NEt_3 (1.50 equiv., 45.5 mmol, 6.40 mL) were added to a solution of alcohol **10** (1.00 equiv., 30.3 mmol, 9.20 g) in CH_2Cl_2 (150 mL), and the reaction mixture was stirred at room temperature for 6 h. Et_2O and brine were then added, the aqueous layer was separated and extracted three times with Et_2O, the combined organic phases were dried with Na_2SO_4, and the solvent was removed in vacuo. Without further purification, the obtained mesylate was dissolved in DBU (1.20 equiv., 36.4 mmol, 5.50 mL), and the solution was stirred at 100 °C for 90 min. The reaction mixture was diluted with Et_2O and a saturated solution of NH_4Cl, the aqueous layer was separated and extracted three times with Et_2O, the combined organic phases were washed with brine and dried with Na_2SO_4, and the solvent was removed in vacuo. Purification by flash chromatography (300 g SiO_2; pentane/*t*BuOMe, 24:1) gave **11** as a colorless solid (5.96 g, 20.9 mmol, 69% over two steps). R_f = 0.83 (pentane/*t*BuOMe, 24:1). M.p. 62 °C. $[\alpha]_D^{20} = -26.0$ (c = 0.5 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.95 (s, 3 H, 7a-CH_3), 1.17 [s, 9 H, $C(CH_3)_3$], 1.36 (td, J = 12.2, 5.9 Hz, 1 H, 7-H_b), 1.78−1.86 (m, 1 H, 7-H_a), 2.16−2.28 (m, 1 H, 6-H_b), 2.30−2.50 (m, 3 H, 2-H_2, 6-H_a), 3.83 (t, J = 8.0 Hz, 1 H, 1-H), 5.64 (m_c, 1 H, 3-H), 6.05−6.10 (m_c, 1 H, 5-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 15.42 (7a-CH_3), 26.07 (C-6), 28.64 [$C(CH_3)_3$], 33.11 (C-7), 37.61 (C-2), 47.59 (C-7a), 72.74 [$C(CH_3)_3$], 81.41 (C-1), 117.3 (C-4), 123.8 (C-3), 130.7 (C-5), 144.2 (C-3a) ppm. IR (KBr): $\tilde{\nu}$ = 2972 cm^{-1} (CH), 1587 (C=C), 1088 (C−O−C). UV (MeCN): $\lambda_{max.}$ (lg ε) = 244 nm (3.900). MS (EI, 70 eV): *m*/*z* (%) = 286, 284 (11) [M^+], 230, 228 (14) [$M^+ - C_4H_8$], 201, 199 (10) [$M^+ - C_4H_9 - C_2H_4$], 149 (14) [$M^+ - Br - C_4H_8$], 57 (100) [$C_4H_9^+$]. $C_{14}H_{21}BrO$ (285.22): calcd. 284.0776; found 284.0776.

(−)-2-((1*S*,7a*S*)-1-*tert*-Butoxy-7a-methyl-2,6,7,7a-tetrahydro-1*H*-inden-4-yl)-5,5-dimethyl-[1,3,2]dioxaborinane (8): *t*BuLi (2.05 equiv., 10.3 mmol, 6.83 mL, 1.5 M in pentane) was added at −78 °C to a solution of vinyl bromide **11** (1.00 equiv., 5.00 mmol, 1.43 g) and TMEDA (1.10 equiv., 5.50 mmol, 830 μL) in THF (50 mL), and the mixture was stirred at this temperature for 20 min. $B(OiPr)_3$ (2.00 equiv., 10.0 mmol, 2.32 mL) was then added, and the reaction mixture was stirred at −78 °C for 2 h, at 0 °C for 1 h, and at room temperature for 1 h. Brine and Et_2O were added, the aqueous layer was separated and extracted three times with Et_2O, the combined organic phases were dried with Na_2SO_4, and the solvent was removed in vacuo. The resulting residue was taken up in toluene (50 mL), 2,2-dimethylpropane-1,3-diol (1.20 equiv., 6.00 mmol, 620 mg) was added, and the mixture was stirred at room temperature for 16 h. H_2O was added, the aqueous layer was separated and extracted three times with CH_2Cl_2, the combined organic phases were dried with Na_2SO_4, and the solvent was removed in vacuo. Purification of the crude product by flash chromatography (100 g SiO_2; pentane/*t*BuOMe, 19:1) gave **8** as a slightly yellow solid (1.08 g, 3.39 mmol, 68%). R_f = 0.27−0.66 (pentane/*t*BuOMe, 9:1). M.p. 100 °C. $[\alpha]_D^{20} = -58.8$ (c = 1.0 in $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.86 (s, 3 H, 7a-CH_3), 0.96 [s, 6 H, $C(CH_3)_2$], 1.14 [s, 9 H, $C(CH_3)_3$], 1.26 (td, J = 12.1, 5.9 Hz, 1 H, 7-H_b), 1.78 (dd, J = 12.4, 5.5 Hz, 1 H, 7-H_a), 2.13−2.21 (m, 1 H, 6-H_b), 2.23−2.36 (m, 3 H, 2-H_2, 6-H_a), 3.64 (s, 4 H, 2 × OCH_2), 3.71 (t, J = 8.2 Hz, 1 H, 1-H), 5.82 (m_c, 1 H, 3-H), 6.43−6.49 (m, 1 H, 5-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 15.52 (7a-CH_3), 21.88 [$C(CH_3)_2$], 24.60 (C-6), 28.75 [$C(CH_3)_3$], 31.62 [$C(CH_3)_2$], 33.59 (C-7), 38.22 (C-2), 44.64 (C-7a), 72.06 (2 × OCH_2), 72.40 [$C(CH_3)_3$], 81.29 (C-1), 106.9 (C-4), 120.9 (C-3), 141.5 (C-5), 145.9 (C-3a) ppm. IR (KBr): $\tilde{\nu}$ = 2969 cm^{-1} (CH), 1579 (C=C), 1095 (C−O−C). UV (MeCN): $\lambda_{max.}$ (lg ε) = 195 nm (3.867), 251 (3.876). MS (EI, 70 eV): *m*/*z* (%) = 318 (32) [M^+], 262 (34) [$M^+ - C_4H_8$], 233 (64) [$M^+ - C_4H_9 - C_2H_4$], 131 (64) [$M^+ - C_5H_{10}BO_2 - C_4H_8 - H_2O$], 57 (100) [$C_4H_9^+$]. $C_{19}H_{31}BO_3$ (318.26): calcd. 318.2366; found 318.2366.

(−)-(1*S*,7a*S*)-4-(2-Bromo-5-methoxybenzyl)-1-*tert*-butoxy-7a-methyl-2,6,7,7a-tetrahydro-1*H*-indene (12): A solution of boronic ester **8** (1.20 equiv., 3.00 mmol, 955 mg), benzylic chloride **1** (1.00 equiv., 2.50 mmol, 589 mg), $Pd(PPh_3)_4$ (5.00 mol %, 0.13 mmol, 144 mg), and NaOH (1.50 equiv., 3.75 mmol, 150 mg) in THF (12.5 mL) was heated at reflux for 16 h. H_2O and Et_2O were added to the reaction mixture, the aqueous layer was separated and extracted three times with Et_2O, the combined organic phases were washed with H_2O and dried with Na_2SO_4, and the solvent was removed in vacuo. After flash chromatography (100 g SiO_2; pentane/*t*BuOMe, 99:1), **12** was obtained (784 mg, 1.93 mmol, 77%) as a colorless oil. R_f = 0.60 (pentane/*t*BuOMe, 24:1). $[\alpha]_D^{20} = -63.7$ (c = 1.0 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 0.95 (s, 3 H, 7a-CH_3), 1.17 [s, 9 H, $C(CH_3)_3$], 1.34 (td, J = 12.1, 6.1 Hz, 1 H, 7-H_b), 1.77−1.88 (m, 1 H, 7-H_a), 2.06−2.47 (m, 4 H, 2-H_2, 6-H_2), 3.48 (d, J = 16.4 Hz, 1 H, 1′-H_b), 3.58 (d, J = 16.4 Hz, 1 H, 1′-H_a), 3.74 (s, 3 H, OCH_3), 3.78 (t, J = 8.4 Hz, 1 H, 1-H), 5.32 (m_c, 1 H, 3-H), 5.36−5.43 (m, 1 H, 5-H), 6.62 (dd, J = 8.7, 3.1 Hz, 1 H, 4′′-H), 6.73 (d, J = 3.1 Hz, 1 H, 6′′-H), 7.40 (d, J = 8.7 Hz, 1 H, 3′′-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 15.54 (7a-CH_3), 23.72 (C-6), 28.72 [$C(CH_3)_3$], 33.88 (C-7), 38.14 (C-2), 38.75 (C-1′), 45.29 (C-7a), 55.32 (OCH_3), 72.52 [$C(CH_3)_3$], 81.36 (C-1), 113.4 (C-4′′), 115.4 (C-2′′), 115.7 (C-6′′), 118.1 (C-3), 127.6 (C-5), 130.9 (C-4), 132.9 (C-3′′), 140.7, 145.5 (C-3a, C-1′′), 158.8 (C-5′′) ppm. IR (film): $\tilde{\nu}$ = 2972 cm^{-1} (CH), 1593 (C=C), 1469 (C=C), 1094 (C−O−C). UV (MeCN): $\lambda_{max.}$ (lg ε) = 200 nm (4.618), 231 (4.245), 281 (3.299). MS (EI, 70 eV): *m*/*z* (%) = 406, 404 (1) [M^+], 325 (42) [M^+ − Br], 296 (38) [$M^+ - Br - C_4H_8$], 251 (43) [$M^+ - Br - C_4H_8 - H_2O$], 225 (100) [$M^+ - Br - C_4H_8 - C_2H_2 - H_2O$], 201, 199 (34) [$C_8H_8BrO^+$], 57 (62) [$C_4H_9^+$]. $C_{22}H_{29}BrO_2$ (405.38): calcd. C 65.18, H 7.21; found C 65.50, H 6.89.

(−)-(3*S*,3a*S*,11b*R*)-3-*tert*-Butoxy-9-methoxy-3a-methyl-3,3a,4,5,7,11b-hexahydro-cyclopenta[*d*]fluorene (13): A solution of seco compound **12** (1.00 equiv., 250 μmol, 101 mg), catalyst **14** (5.00 mol %, 12.5 μmol, 11.7 mg), and nBu_4NOAc (2.00 equiv., 500 μmol, 151 mg) in a mixture of DMF/MeCN/H_2O (5 mL, 5:5:1) was heated at 180 °C for 30 min with application of microwave irradiation. (Alternatively, the reaction mixture can be heated under standard conditions at 120 °C for 18 h.) H_2O and Et_2O were then added, the aqueous layer was separated and extracted three times with Et_2O, the combined organic phases were dried with Na_2SO_4, and the solvent was removed in vacuo. The crude product was puri-

fied by flash chromatography (50 g SiO_2; pentane/*t*BuOMe, 200:1) to give **13** as a colorless oil (59.3 mg, 183 μmol, 73%). R_f = 0.68 (pentane/*t*BuOMe, 24:1). $[\alpha]_D^{20}$ = −117.3 (*c* = 1.0 in $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 0.88 (s, 3 H, 3a-CH_3), 1.27 [s, 9 H, $C(CH_3)_3$], 1.45 (dd, *J* = 12.6, 5.3 Hz, 1 H, 4-H_β), 1.74 (td, *J* = 12.6, 5.9 Hz, 1 H, 4-H_α), 1.98−2.04 (m, 1 H, 5-H_α), 2.12−2.20 (m, 1 H, 5-H_β), 3.32 (d, *J* = 17.6 Hz, 1 H, 7-H_b), 3.64−3.69 (m, 1 H, 7-H_a), 3.75 (s, 3 H, OCH_3), 3.96 (d, *J* = 2.5 Hz, 1 H, 3-H), 5.55 (dd, *J* = 5.6, 2.5 Hz, 1 H, 2-H), 5.62 (m_c, 1 H, 6-H), 5.85 (d, *J* = 5.6 Hz, 1 H, 1-H), 6.68−6.71 (m, 2 H, 8-H, 10-H), 7.70−7.72 (m, 1 H, 11-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.83 (3a-CH_3), 22.86 (C-5), 28.58 [C(*C*H_3)$_3$], 34.81 (C-4), 38.35 (C-7), 42.85 (C-3a), 55.24 (OCH_3), 64.41 (C-11b), 73.24 [*C*$(CH_3)_3$], 83.29 (C-3), 108.8 (C-8), 112.2 (C-10), 120.0 (C-6), 128.0 (C-11), 128.1 (C-2), 138.6 (C-11a), 140.9 (C-6a), 141.3 (C-1), 142.5 (C-7a), 158.4 (C-9) ppm. IR (KBr): $\tilde{\nu}$ = 2971 cm^{-1} (CH), 1607 (C=C), 1079 (C−O−C). UV (MeCN): $\lambda_{max.}$ (lg ε) = 200 nm (4.540), 236 (4.287), 281 (3.501), 288 (3.453), 325 (2.554), 339 (2.557). MS (EI, 70 eV): *m*/*z* (%) = 324 (74) [M^+], 286 (100) [$M^+ - C_4H_8$], 250 (36) [$M^+ - C_4H_8 - H_2O$], 57 (42) [$C_4H_9^+$]. $C_{22}H_{28}O_2$ (324.46).

(−)-(3*S*,3a*S*,6a*R*,11b*R*)-3-*tert*-Butoxy-9-methoxy-3a-methyl-1,2,3,3a,4,5,6,6a,7,11b-decahydrocyclopenta[*d*]fluorene (15): $PtO_2 \cdot H_2O$ (20.0 mol %, 45.6 μmol, 11.2 mg) was added to a solution of diene **13** (1.00 equiv., 228 μmol, 74.0 mg) in MeOH (5 mL), and the reaction mixture was stirred at room temperature under hydrogen for 18 h. After filtration and removal of the solvent, the residue was purified by flash chromatography (25 g SiO_2; pentane/*t*BuOMe, 200:1) to give **15** as a colorless oil (72.0 mg, 219 μmol, 96%). R_f = 0.70 (pentane/*t*BuOMe, 24:1). $[\alpha]_D^{20}$ = −9.4 (*c* = 1.0 in $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 0.88 (s, 3 H, 3a-CH_3), 1.14 [s, 9 H, $C(CH_3)_3$], 1.20−1.26 (m, 1 H, 4-H_b), 1.36−1.43 (m, 2 H, 4-H_a, 6-H_b), 1.48−1.53 (m, 2 H, 5-H_2), 1.58−1.63 (m, 1 H, 6-H_a), 1.68−1.74 (m, 1 H, 2-H_b), 1.89 (t, *J* = 8.3 Hz, 2 H, 1-H_2), 2.12−2.20 (m, 2 H, 2-H_a, 6a-H), 2.54 (dd, *J* = 15.4, 6.7 Hz, 1 H, 7-H_β), 2.79 (dd, *J* = 15.4, 7.2 Hz, 1 H, 7-H_α), 3.76−3.80 (m, 4 H, 3-H, OCH_3), 6.66 (dd, *J* = 8.5, 2.5 Hz, 1 H, 10-H), 6.70 (d, *J* = 2.5 Hz, 1 H, 8-H), 7.47 (d, *J* = 8.5 Hz, 1 H, 11-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 18.80 (C-5), 19.25 (3a-CH_3), 27.37 (C-6), 28.71 [C(*C*H_3)$_3$], 32.30 (C-2), 33.66 (C-4), 35.79 (C-1), 37.07 (C-7), 44.41 (C-6a), 47.18 (C-3a), 55.17 (OCH_3), 57.18 (C-11b), 72.61 [*C*$(CH_3)_3$], 79.08 (C-3), 109.6 (C-8), 111.3 (C-10), 126.8 (C-11), 142.9 (C-11a), 144.8 (C-7a), 157.9 (C-9) ppm. IR (KBr): $\tilde{\nu}$ = 2928 cm^{-1} (CH), 1489, 1086 (C−O−C). UV (MeCN): $\lambda_{max.}$ (lg ε) = 200 nm (4.619), 228 (3.966), 281 (3.427), 287 (3.376). MS (EI, 70 eV): *m*/*z* (%) = 328 (48) [M^+], 271 (23) [$M^+ - C_4H_9$], 253 (30) [$M^+ - C_4H_9 - H_2O$], 215 (100), 165 (34). $C_{22}H_{32}O_2$ (328.49): calcd. 328.2402; found 328.2402.

(−)-(3*S*,3a*S*,6a*R*,11b*R*)-9-Methoxy-3a-methyl-1,2,3,3a,4,5,6,6a,7,11b-decahydro-cyclopenta[*d*]fluoren-3-ol (16): A solution of **15** (1.00 equiv., 36.5 μmol, 12.0 mg) and iodotrimethylsilane (1.00 equiv., 36.5 μmol, 5.2 μL) in CH_2Cl_2 (3.5 mL) was stirred in the absence of light at room temperature for 16 h. MeOH (0.1 mL) was added, and the solution was stirred for another 15 min. H_2O was then added, the aqueous layer was separated and extracted three times with CH_2Cl_2, the combined organic fractions were dried with Na_2SO_4, and the solvent was removed in vacuo. Purification by flash chromatography (2 g SiO_2; pentane/*t*BuOMe, 4:1) gave **16** (9.9 mg, 36 μmol, 97%) as a colorless oil. R_f = 0.34 (pentane/*t*BuOMe, 4:1). $[\alpha]_D^{20}$ = −59.8 (*c* = 1.0 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.80 (s, 3 H, 3a-CH_3), 1.25−1.31 (m, 2 H, 4-H_2), 1.45−1.72 (m, 5 H, 5-H_2, 6-H_2, OH), 1.79−1.91 (m, 1 H, 2-H_b), 1.95−2.09 (m, 2 H, 1-H_2), 2.20−2.41 (m, 2 H, 2-H_a, 6a-H), 2.66 (dd, *J* = 15.5, 8.5 Hz, 1 H, 7-H_b), 2.72 (dd, *J* = 15.5, 8.0 Hz, 1 H, 7-H_a), 3.78 (s, 3 H, OCH_3), 3.96 (dd, *J* = 7.4, 3.5 Hz, 1 H, 3-H), 6.67−6.74 (m, 2 H, 8-H, 10-H), 7.40 (d, *J* = 8.3 Hz, 1 H, 11-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 17.82 (C-5, 3a-CH_3), 25.98 (C-6), 31.65 (C-2), 33.97 (C-4), 35.44 (C-1), 36.56 (C-7), 44.85 (C-6a), 47.63 (C-3a), 55.19 (OCH_3), 56.93 (C-11b), 82.43 (C-3), 109.7 (C-8), 111.4 (C-10), 125.6 (C-11), 143.4 (C-11a), 144.7 (C-7a), 158.1 (C-9) ppm. IR (film): $\tilde{\nu}$ = 3441 cm^{-1} (OH), 2925 (CH), 1489, 1246 (C−OH). UV (MeCN): $\lambda_{max.}$ (lg ε) = 200 nm (4.606), 221 (3.886), 228 (3.895), 281 (3.380), 288 (3.328). MS (EI, 70 eV): *m*/*z* (%) = 272 (100) [M^+], 213 (36) [$M^+ - C_3H_7O$], 173 (50), 160 (51). $C_{18}H_{24}O_2$ (272.39): calcd. 272.1776; found 272.1776.

(−)-(3a*S*,6a*R*,11b*R*)-9-Methoxy-3a-methyl-1,2,4,5,6,6a,7,11b-octahydro-3a*H*-cyclopenta[*d*]fluoren-3-one (18): DMP (1.50 equiv., 248 μmol, 105 mg) was added at 0 °C to a solution of alcohol **16** (1.00 equiv., 165 μmol, 45.0 mg) in CH_2Cl_2 (2.5 mL), and the reaction mixture was stirred at room temperature for 6 h. A saturated solution of $NaHCO_3$ (1.5 mL) and a solution of $Na_2S_2O_3$ (1 M, 1.5 mL) were added simultaneously, and the reaction mixture was stirred until it became clear again. H_2O and CH_2Cl_2 were added, the aqueous layer was separated and extracted three times with CH_2Cl_2, the combined organic phases were dried with Na_2SO_4, and the solvent was removed in vacuo. Purification by flash chromatography (5 g SiO_2; pentane/*t*BuOMe, 9:1) gave **18** (34.0 mg, 126 μmol, 76%) as a colorless oil. R_f = 0.34 (pentane/*t*BuOMe, 9:1). $[\alpha]_D^{20}$ = −21.5 (*c* = 0.2 in $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 0.74 (s, 3 H, 3a-CH_3), 1.22−1.30 (m, 1 H, 4-H_b), 1.40−1.56 (m, 3 H, 4-H_a, 5-H_2), 1.60−1.65 (m, 1 H, 6-H_b), 1.66−1.73 (m, 1 H, 6-H_a), 2.03 (ddd, *J* = 13.6, 9.2, 5.2 Hz, 1 H, 1-H_b), 2.22−2.28 (m, 2 H, 1-H_a, 6a-H), 2.51−2.62 (m, 2 H, 2-H_2), 2.69 (dd, *J* = 15.6, 9.4 Hz, 1 H, 7-H_b), 2.80 (dd, *J* = 15.6, 7.9 Hz, 1 H, 7-H_a), 3.75 (s, 3 H, OCH_3), 6.66 (dd, *J* = 8.4, 2.5 Hz, 1 H, 10-H), 6.75 (d, *J* = 2.5 Hz, 1 H, 8-H), 6.95 (d, *J* = 8.4 Hz, 1 H, 11-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 17.46 (C-5), 18.75 (3a-CH_3), 25.46 (C-6), 29.78 (C-1), 31.43 (C-4), 35.28 (C-2), 36.61 (C-7), 43.77 (C-6a), 52.74 (C-3a), 55.17 (C-11b), 55.25 (OCH_3), 110.4 (C-8), 112.3 (C-10), 123.4 (C-11), 141.5 (C-11a), 144.5 (C-7a), 158.7 (C-9), 223.0 (C-3) ppm. IR (film): $\tilde{\nu}$ = 2934 cm^{-1} (CH), 1733 (C=O), 1489, 1248. UV (MeCN): $\lambda_{max.}$ (lg ε) = 199 nm (4.589), 220 (3.897), 282 (3.397). MS (EI, 70 eV): *m*/*z* (%) = 270 (100) [M^+], 213 (35) [$M^+ - C_3H_5O$], 185 (28) [$M^+ - C_3H_5O - C_2H_4$]. $C_{18}H_{22}O_2$ (270.37): calcd. 270.1620; found 270.1620.

(+)-(3a*S*,6a*R*,11b*R*)-9-Methoxy-3a-methyl-1,2,4,5,6,6a,7,11b-octahydro-3a*H*-cyclopenta[*d*]fluoren-3-one (2,4-Dinitro-phenylhydrazone) (19): A solution of ketone **18** (1.00 equiv., 92.5 μmol, 25.0 mg) in EtOH (0.25 mL) was added to a solution of 2,4-dinitrophenylhydrazine (5.46 equiv., 505 μmol, 100 mg) in a mixture of EtOH (2.5 mL), H_2O (0.75 mL) and concentrated H_2SO_4 (0.5 mL), and the reaction mixture was kept at 0 °C for 15 h. After filtration and purification by flash chromatography (10 g SiO_2; pentane/*t*BuOMe, 9:1), **19** was obtained (32.0 mg, 71.0 μmol, 77%) as an orange solid. R_f = 0.42 (pentane/*t*BuOMe, 9:1). $[\alpha]_D^{20}$ = +177.0 (*c* = 0.2 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3 H, 3a-CH_3), 1.41−1.77 (m, 6 H, 4-H_2, 5-H_2, 6-H_2), 2.13 (ddd, *J* = 13.6, 9.1, 4.3 Hz, 1 H, 1-H_b), 2.31−2.44 (m, 2 H, 1-H_a, 6a-H), 2.72−2.94 (m, 4 H, 2-H_2, 7-H_2), 3.78 (s, 3 H, OCH_3), 6.67 (dd, *J* = 8.4, 2.5 Hz, 1 H, 10-H), 6.79 (d, *J* = 2.5 Hz, 1 H, 8-H), 6.88 (d, *J* = 8.4 Hz, 1 H, 11-H), 7.93 (d, *J* = 9.6 Hz, 1 H, 6′-H), 8.28 (dd, *J* = 9.6, 2.6 Hz, 1 H, 5′-H), 9.14 (d, *J* = 2.6 Hz, 1 H, 3′-H), 10.91 (s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 17.80 (C-5), 20.95 (3a-CH_3), 25.17, 26.13 (C-2, C-6), 32.19, 34.72 (C-1, C-4), 36.73 (C-7), 43.19 (C-6a), 49.47 (C-3a), 55.30 (OCH_3), 56.92 (C-11b),

110.4 (C-8), 112.3 (C-10), 116.5 (C-6′), 123.3, 123.5 (C-11, C-3′), 128.9 (C-2′), 129.9 (C-5′), 137.5 (C-4′), 141.3 (C-11a), 144.6 (C-7a), 145.2 (C-1′), 158.8 (C-9), 173.0 (C-3) ppm. IR (KBr): $\tilde{\nu}$ = 3314 cm^{-1} (NH), 2932 (CH), 1618 (C=N), 1335 ($C-NO_2$). UV (MeCN): $\lambda_{max.}$ (lg ε) = 198 nm (4.666), 229 (4.309), 269 (3.997), 368 (4.308). MS (EI, 70 eV): *m/z* (%) = 450 (100) [M^+], 415 (29), 253 (58) [$M^+ - C_6H_5N_4O_4$]. $C_{24}H_{26}N_4O_5$ (450.49): calcd. 450.1903; found 450.1903.

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