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Synthesis of enantiopure B-nor-steroids by multiple Pd-catalyzed transformations

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Abstract

The synthesis of the novel enantiopure B-nor-steroid **9** is described employing a combination of a Suzuki- and a Heck-reaction. As substrates the 2-bromobenzylchloride (**11**) and the boronic ester **16** were used; the latter was prepared from the Hajos–Wiechert ketone derivative **17** in five steps. Noteworthy, the Heck-reaction was performed under microwave irradiation, which was much superior compared to the normal thermal reaction. The purpose of the described work is the design of novel estrogens, which bind to the β-unit of the maxi K^+-channel located on the surface of the endothelium without showing the hormonal activity of estradiol **6**.

Keywords: Palladium; Suzuki-reaction; Heck-reaction; Steroids; B-nor-estradiol; Microwave

1. Introduction

Pd-catalyzed transformations as the Heck-reaction and its analogues as well as the Tsuji–Trost-reaction belong to the most powerful synthetic tools in chemistry due to their high tolerance of functional groups and general applicability [1]. Moreover, an enormous increase of efficiency is obtained using multiple Pd-catalyzed transformations, in which the functionalities formed in the first reaction are tied up in the next step [2]. This can be done as a domino process [3] or in a sequential way as shown in the synthesis of cephalotaxin [4] and steroids [5]. Thus, the Pd-catalyzed reaction of a mixture of the bromophenylvinylbromide **1** and the enantiopure indene **2** using $Pd(OAc)_2$ as catalyst led to **3** with excellent regio- and stereo-selectivity. Reaction of **3** employing the Herrmann–Beller palladacene [6] **4** gave **5** which was transformed into the estradiol **6** in a few steps (Scheme 1).

Estrogens like estradiol **6** have a strong effect on serum lipid concentration due to an alteration of gene expression by binding to a steroid hormone receptor which acts as a transcription factor. However, recently it was shown that estrogens also bind extracellulary to the regulatory β-unit of the maxi K^+-channel, which is a key modulator of the vascular muscle tone [7], and only little is known so far about the structure–activity relationship. It can be assumed that the oxygen moieties at C-3 and C-17 in estradiol **6** are essential for binding. However, for the treatment of cardiovascular diseases new types of estrogens are needed which do not show the genomic action, but can selectively activate the β-unit of the maxi K^+-channel.

A possible approach to suppress hormone activity while maintaining a binding to the β-unit is a change of the distance between the two oxygen moieties at C-3 and C-17. PM3 calculations of estradiol **6** and some possible steroid analogues show that the distance of the oxygen atoms at C-3 and C-17 in **6** with $d(O–O) = 1093$ pm can be decreased gradually by changing the size of ring B as in the B-nor-steroid **7** with $d(O–O) = 1077$ pm and the B-homo-steroid **8** with $d(O–O) = 1052$ pm (Fig. 1) [8].

Here we describe the synthesis of the novel B-nor-steroid **9** using two sequential Pd-catalyzed reactions.

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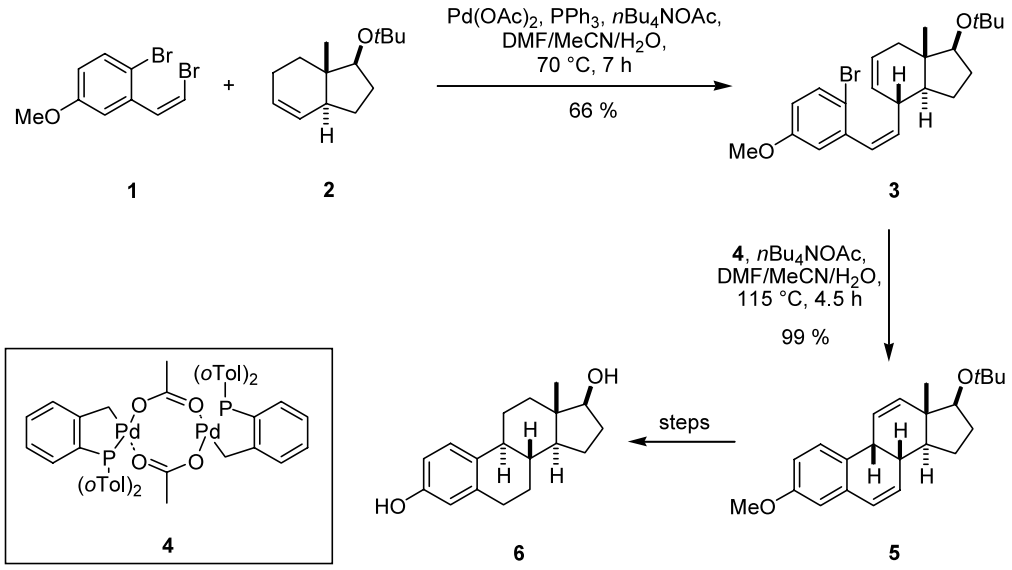


Scheme 1. Synthesis of estradiol **6** by a twofold Heck-reaction.

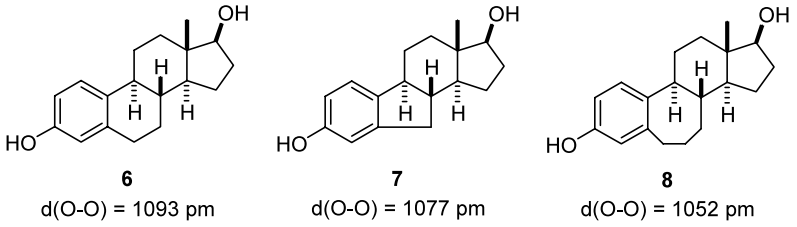


Fig. 1. O–O-distances of possible estradiol analogues.

The synthesis of B-nor-steroids as **9** has so far only little been investigated (Fig. 2) [9].

2. Results and discussion

In our approach to B-nor-steroids like **7** we first investigated a multiple Heck-reaction of the hydrindene **2** with 2-bromo-5-methoxy-benzylchloride (**11**) [10] according to the retrosynthesis as shown in Scheme 2.

However, under Pd-catalysis at a temperature below 80 °C using different solvents and bases reaction of **2** and **11** did not lead to the desired product whereas at higher temperatures only decomposition of the starting material **2** was observed. With more reactive alkenes such as methyl acrylate and cyclopentene a transformation is possible, but only after a long reaction time.

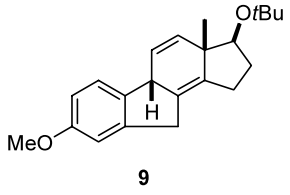


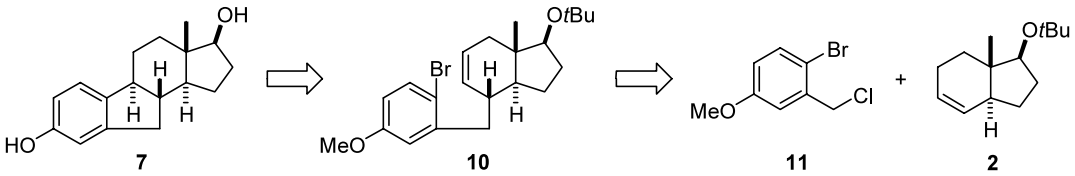
Fig. 2. B-nor-estradiol analogue **9**.

Thus, reaction of **11** and methyl acrylate gave **12** in 37% yield using $Pd(OAc)_2$ as catalyst and NBu_3 as base in a sealed tube for 5 d at 100 °C (Fig. 3); with cyclopentene employing the same conditions for 7 d a 1:1 mixture of **13** and **14** in 30% yield was obtained [11].

We then moved to Pd-catalyzed transformations of benzoylchlorides anticipating that these compounds might be more reactive; however, preliminary investigations of the unsubstituted benzoylchloride and methyl acrylate gave the desired product in less than 20%.

Because of these results we changed our approach and instead of using a double-Heck-reaction we decided to employ a combination of a Suzuki- and a Heck-reaction using the 2-bromobenzylchloride derivative **11** and the boronic ester **16** as starting materials as depicted in the retrosynthetic approach (Scheme 3).

The boronic ester **16** could be obtained easily from the enantiopure Hajos–Wiechert ketone derivative [12] **17** in five steps (Scheme 4). Addition of bromine to **17** in a mixture of diethyl ether and acetic acid in the presence of the base 2,4,6-collidine led to the corresponding α-bromo-enone **18** which was reduced under Luche conditions [13] to give the α-bromo-allylic alcohol **19**. Transformation into the xanthate **20** followed by a thermal *cis*-elimination yielded the vinyl bromide **21**.



Scheme 2. Retrosynthesis of **7**.

Bromine–lithium exchange and quenching with triisopropyl borate gave the corresponding diisopropyl boronic ester, which was directly transesterificated to the more stable cyclic boronic ester **16**.

Suzuki-coupling of **16** and the benzylic chloride **11** with $Pd(PPh_3)_4$ as catalyst and sodium hydroxide as base in THF under reflux gave the *seco*-B-nor-steroid **15** in 72% yield (Scheme 5). The transformation showed a high regioselectivity; thus, the cross-coupling with the boronic ester took place exclusively at the benzyl chloride moiety of **11**, whereas the aryl bromide moiety seemed to be inert under these conditions.

However, ring B could be formed at 140 °C in an intramolecular Heck-reaction using palladacene [6] **4** to give the B-nor-estradiol **9** in 70% yield. As expected, the reaction took place from below *anti* to the angular methyl group to form a single diastereomer. The best results were obtained using microwave irradiation [14] under these conditions the reaction time could be shortened to 5 min and it also allowed us to suppress the aromatization of ring C with opening of ring D as unwanted side reaction, which was observed when the reaction was performed under standard conditions. Thus, heating a mixture of **15** in the presence of **4** in dimethylformamide/acetonitrile/water at 120 °C for 18 h gave only a small amount of **9** but mainly **22** which was isolated in 27% yield. We assume that the formation of **22** proceeds via **9** by a radical cleavage of the bond between C-3 and C-3a. This clearly demonstrates the superiority of the microwave irradiation over the classical heating in this case.

The relative configuration at C-5a in **9** was determined by NOE-experiments which showed a strong correlation between the angular methyl group at C-3a and 5a-H. The two hydrogens at the aliphatic double bond resonate at $\delta = 5.99$ with $J = 9.4$ and 3.2 Hz for 4-H and $\delta = 6.10$ with $J = 9.4$ and 1.8 Hz for 5-H. In the ^{13}C-NMR spectra of **9** ten signals are found in the region for olefinic and aromatic carbons between $\delta =$ 110.3 for C-9 and 158.6 for C-8.

3. Conclusions

An efficient and short synthesis of the novel B-nor-estradiol analogue **9** is described using two subsequent Pd-catalyzed reactions as the key steps, namely a Suzuki-coupling of the benzylchloride **11** and the boronic ester **16** followed by an intramolecular Heck-reaction. Of general interest is the observation that the yields and the selectivity of the final Heck-reaction of the intermediate *seco*-B-nor-steroid **15** could be dramatically improved using microwave irradiation. Further work will focus on the transformation of the B-nor-estradiol **9** and the biological investigations of the obtained derivatives.

4. Experimental

4.1. General

Melting points were measured on a Mettler FP61 melting point apparatus and are uncorrected. UV spectra were taken on a Perkin–Elmer Lambda 2 or Lambda 9, IR spectra on a Bruker IFS 25 and optical rotations on a Perkin–Elmer 241 spectrometer. Mass spectra were measured on a Varian MAT 311A (low resolution) and on a MAT 731 (high resolution) spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Mercury-200, VXR-200, Unity300, Inova-500, Unity Inova-600 (Varian) or a AMX-300 (Bruker) spectrometer. Chemical shifts are reported in δ ppm referenced to TMS (^{1}H-NMR) or to $CDCl_3$ (^{13}C-NMR) as internal standard. Microwave heating was performed in a Personal Chemistry SmithCreator microwave reactor. For TLC chromatography precoated silica gel SIL G/UV_{254} from Macherey–Nagel & Co. and for flash chromatography Kieselgel 60 (0.032–0.063 nm) from Merck was used.

All reactions were performed in oven-dried glassware in an atmosphere of argon. Solvents were dried and

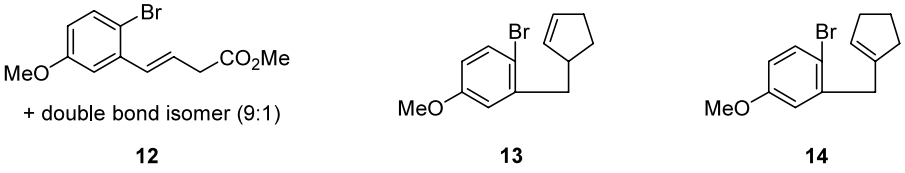
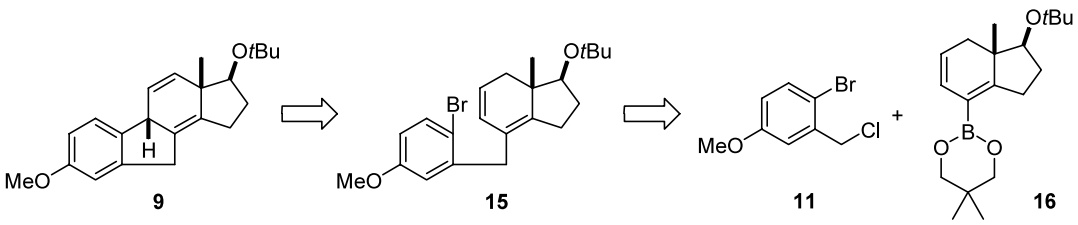


Fig. 3. Products of Heck-reactions between benzylic chlorides and olefins.



Scheme 3. Retrosynthesis of **9**.

distilled prior to use according to usual laboratory methods, commercially available chemicals were used without further purification, (−)-(1*S*,7a*S*)-1-*tert*-butoxy-7a-methyl-1,2,3,6,7,7a-hexahydro-inden-5-one (**17**) [12] and 2-bromo-5-methoxy-benzylchloride (**11**) [10] are known substances and can be prepared according to literature protocols.

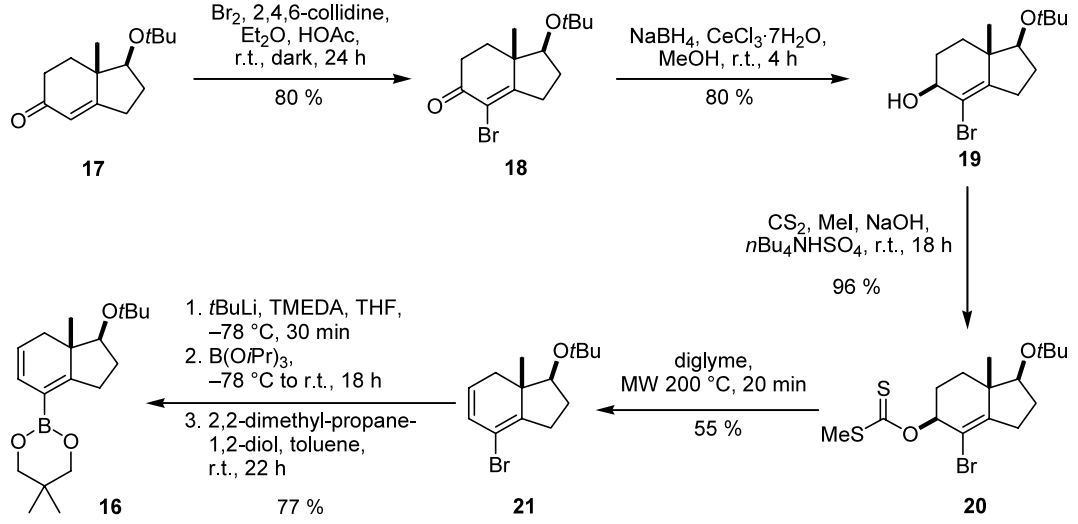
*4.2. Synthesis of (+)-(3S,3aS,5aS)-3-tert-butoxy-8-methoxy-3a-methyl-1,2,3,3a,5a,10-hexahydro-cyclopenta[a]fluorene (**9**)*

*4.2.1. (−)-(1S,7aS)-4-Bromo-1-tert-butoxy-7a-methyl-1,2,3,6,7,7a-hexahydro-inden-5-one (**18**)*

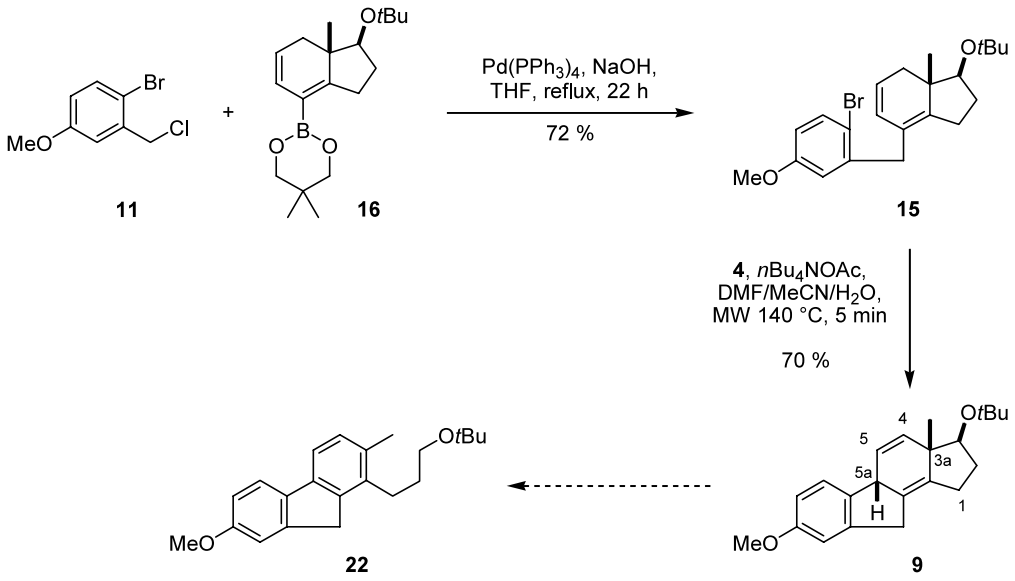
To a solution of **17** (1.0 equivalent, 50.0 mmol, 11.1 g) in Et_2O (500 ml) and 2,4,6-collidine (100 ml) was added a solution of Br_2 (5.0 equivalents, 250 mmol, 12.8 ml) in HOAc (325 ml) at 0 °C, then the mixture was stirred at room temperature (r.t.) for 24 h in the absence of light. Excess of bromine was destroyed by adding a saturated solution of $Na_2S_2O_3$, then the aqueous layer was separated and extracted three times with Et_2O. The combined organic phases were washed with a saturated solution of $NaHCO_3$, then with H_2O, dried over Na_2SO_4 and the solvent was removed in vacuo. Recrystallisation (pentane) of the residue yielded **18** in 80% (12.0 g) as a white solid. $R_f = 0.45$ (pentane/MTBE = 9:1); m.p. 103 °C; UV (CH_3CN): λ_{max} (log ε) = 258 nm (3.924); IR (KBr): $\nu = 2972$ cm^{-1} (CH), 1686 (C=O), 1097 (C–O–C); $[\alpha]_D^{20} = -47.0°$ ($c = 0.5$ in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.16$ (s, 3H, 7a-CH_3), 1.18 (s, 9H, $C(CH_3)_3$), 1.75–2.09 (m, 4H, 2-H_2, 7-H_2), 2.48 (dt, $J = 20.8$, 9.3 Hz, 1H, 3-H_b), 2.58–2.81 (m, 3H, 3-H_a, 6-H_2), 3.66 (dd, $J = 10.2$, 7.3 Hz, 1H, 1-H); ^{13}C-NMR (50.3 MHz, $CDCl_3$): $\delta = 15.67$ (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); MS (DCI, 200 eV): *m*/*z* (%) = 622, 620, 618 (26) $[2M+NH_4]^+$, 320, 318 (100) $[M+NH_4]^+$; Anal. Calc. for $C_{14}H_{21}BrO_2$: C 55.82, H 7.03; Found: C 55.76, H 6.82%.

*4.2.2. (−)-(1S,5S,7aS)-4-Bromo-1-tert-butoxy-7a-methyl-2,3,5,6,7,7a-hexahydro-1H-inden-5-ol (**19**)*

To a solution of **18** (1.0 equivalent, 23.2 mmol, 7.00 g) and $CeCl_3 \cdot 7H_2O$ (1.2 equivalents, 27.9 mmol, 10.4 g) in MeOH (75 ml) was added portionally $NaBH_4$ (1.2 equivalents, 27.9 mmol, 1.06 g) at 0 °C, then the mixture was stirred at r.t. for 4 h. The solvent was removed in vacuo and the resulting residue 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 over Na_2SO_4 and the solvent was removed in vacuo. After purification of the crude product by flash chromatography (200 g SiO_2, pentane/MTBE = 9:1) **19** was obtained in 80% yield



Scheme 4. Synthesis of the boronic ester **16**.



Scheme 5. Synthesis of the B-nor-estradiol analogue **9**.

(5.63 g) as a colourless oil. $R_f = 0.37$ (pentane/MTBE = 9:1); UV (CH_3CN): λ_{max} ($\log \varepsilon$) = 204 nm (3.933); IR (film): $\nu = 3385\ cm^{-1}$ (OH), 2973 (CH), 1099 (C–O–C); $[\alpha]_D^{20} = -17.2^\circ$ ($c = 0.5$ in $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 1.00$ (s, 3H, 7a-CH_3), 1.12 (s, 9H, C(CH_3)$_3$), 1.35 (td, $J = 13.9$, 3.2 Hz, 1H, 7-H_b), 1.65–1.75 (m, 2H, 2-H_b, 7-H_a), 1.82–1.91 (m, 2H, 2-H_a, 6-H_b), 2.13–2.27 (m, 3H, 3-H_b, 6-H_a, OH), 2.29–2.37 (m, 1H, 3-H_a), 3.42 (dd, $J = 10.0$, 7.6 Hz, 1H, 1-H), 4.23 (m_c, 1H, 5-H); ^{13}C-NMR (50.3 MHz, $CDCl_3$): $\delta = 17.18$ (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); 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) $[C_4H_9]^+$; Anal. Calc. for $C_{14}H_{23}BrO_2$: C 55.45, H 7.65; Found: C 55.43, H 7.37%.

4.2.3. (+)-Dithiocarbonic acid O-((1S,5S,7aS)-4-bromo-1-tert-butoxy-7a-methyl-2,3,5,6,7,7a-hexahydro-1H-inden-5-yl) ester S-methyl ester (*20*)

19 (1.0 equivalent, 17.3 mmol, 5.25 g) and MeI (1.1 equivalents, 1.90 mmol, 1.19 ml) were dissolved in a two phase system consisting of CS_2 (20 ml), aqueous NaOH (20 ml, 50% NaOH in H_2O) and n-Bu_4NHSO_4 (0.1 equivalents, 1.73 mmol, 588 mg) and stirred for 18 h at r.t. Then H_2O and Et_2O were added, the aqueous phase was separated and extracted with Et_2O. Drying of the combined organic phases over Na_2SO_4, removal of the solvent and purification of the residue by flash chromatography (200 g SiO_2, pentane/MTBE = 24:1) gave **20** in 96% yield (6.50 g) as a yellow oil. $R_f = 0.67$ (pentane/MTBE = 24:1); UV (CH_3CN): λ_{max} ($\log \varepsilon$) = 209 nm (4.237), 280 (3.925); IR (film): $\nu = 2972\ cm^{-1}$ (CH), 1218 (C=S), 1055 (C–O–C); $[\alpha]_D^{20} = +3.5^\circ$ ($c = 1.0$ in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.07$ (s, 3H, 7a-CH_3), 1.16 (s, 9H, C(CH_3)$_3$), 1.48 (td, $J = 14.0$, 3.3 Hz, 1H, 7-H_b), 1.67–1.99 (m, 4H, 2-H_2, 6-H_b, 7-H_a), 2.24–2.51 (m, 3H, 3-H_2, 6-H_a), 2.59 (s, 3H, SCH_3), 3.58 (dd, $J = 10.1$, 7.5 Hz, 1H, 1-H), 6.26–6.33 (m, 1H, 5-H); ^{13}C-NMR (50.3 MHz, $CDCl_3$): $\delta = 16.99$ (SCH_3), 18.97 (7a-CH_3), 26.46 (C-3), 28.65 (C(CH_3)$_3$), 28.27, 29.41, 33.35 (C-2, C-6, C-7), 47.25 (C-7a), 72.97 (C(CH_3)$_3$), 80.03 (C-1), 82.87 (C-5), 114.0 (C-4), 152.4 (C-3a), 215.7 (CS); MS (DCI, 200 eV): m/z (%) = 412, 410 (90) $[M + NH_4]^+$, 321, 319 (62), 304, 302 (100) $[M - CS_2CH_3]^+$.

4.2.4. (+)-(1S,7aS)-4-Bromo-1-tert-butoxy-7a-methyl-2,3,7,7a-tetrahydro-1H-indene (*21*)

A solution of **20** (16.5 mmol, 6.50 g) in diglyme (30 ml) was heated to 200 °C for 20 min applying microwave irradiation. The reaction was performed six times using the appropriate reaction vessels with a volume of 5 ml. H_2O was added, the aqueous layer was separated and extracted three times with Et_2O, the combined organic layers were washed with H_2O, dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by flash chromatography (250 g SiO_2, pentane/MTBE = 99:1) and **21** was obtained in 55% yield (2.59 g) as a colourless oil. $R_f = 0.80$ (pentane/MTBE = 24:1); UV (CH_3CN): λ_{max} ($\log \varepsilon$) = 267 nm (3.522), 278 (3.509); IR (film): $\nu = 2972\ cm^{-1}$ (CH), 1649 (C=C), 1100 (C–O–C); $[\alpha]_D^{20} = +65.3^\circ$ ($c = 1.0$ in $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 0.93$ (s, 3H, 7a-CH_3), 1.16 (s, 9H, C(CH_3)$_3$), 1.61–1.74 (m, 1H, 2-H_b), 1.89–1.95 (m, 1H, 2-H_a), 2.14–2.23 (m, 3H, 3-H_b, 7-H_2), 2.41 (dd, $J = 20.0$, 10.5 Hz, 1H, 3-H_a), 3.73 (dd, $J = 10.4$, 7.1 Hz, 1H, 1-H), 5.57–5.61 (m, 1H, 5-H), 5.87–5.90 (m, 1H, 6-H); ^{13}C-NMR (50.3 MHz, $CDCl_3$): $\delta = 14.39$ (7a-CH_3), 27.01 (C-3), 28.72 (C(CH_3)$_3$), 29.76 (C-2), 35.35

(C-7), 46.76 (C-7a), 72.79 ($C(CH_3)_3$), 81.57 (C-1), 110.3 (C-4), 125.1 (C-5), 128.0 (C-6), 144.9 (C-3a); MS (EI, 70 eV): m/z (%) = 286, 284 (1) $[M]^+$, 205 (14) $[M-Br]^+$, 185, 183 (98) $[M-C_4H_9-C_2H_2-H_2O]^+$, 57 (100) $[C_4H_9]^+$; HRMS: Anal. Calc. for $C_{14}H_{21}BrO$: 284.0776, Found: 284.0776.

4.2.5. (+)-2-((1S,7aS)-1-tert-Butoxy-7a-methyl-2,3,7,7a-tetrahydro-1H-inden-4-yl)-5,5-dimethyl-[1,3,2]dioxaborinane (16)

To a solution of **21** (1.0 equivalent, 4.91 mmol, 1.40 g) and TMEDA (1.1 equivalents, 5.40 mmol, 810 μl) in THF (50 ml) was added *t*-BuLi (2.05 equivalents, 10.1 mmol, 6.71 ml, 1.5 M in pentane) at −78 °C and the mixture was stirred at this temperature for 30 min. Then B(O*i*-Pr)$_3$ (2.0 equivalents, 9.82 mmol, 2.28 ml) was added, the reaction mixture was slowly warmed to r.t. and stirred for 18 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 over Na_2SO_4 and the solvent was removed in vacuo. The resulting residue was taken up in toluene (50 ml), 3,3-dimethyl-propane-1,2-diol (1.2 equivalents, 5.09 mmol, 613 mg) was added and the mixture was stirred at r.t. for 22 h. H_2O was added, the aqueous layer was separated and extracted three times with CH_2Cl_2, the combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. Purification of the crude product by flash chromatography (75 g SiO_2, pentane/MTBE = 19:1) gave **16** as a slightly yellow solid in 77% yield (12.1 g). $R_f = 0.45–0.79$ (pentane/MTBE = 9:1); m.p. 88 °C; UV (CH_3CN): λ_{max} (log ε) = 282 nm (3.510); IR (KBr): $\nu = 2963$ cm^{-1} (CH), 1638 (C=C), 1097 (C–O–C); $[\alpha]_D^{20} = +71.5°$ ($c = 1.0$ in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (s, 3H, 7a-CH_3), 0.97 (s, 6H, $C(CH_3)_2$), 1.16 (s, 9H, $C(CH_3)_3$), 1.57–1.72 (m, 1H, 2-H_b), 1.81–1.91 (m, 1H, 2-H_a), 2.04 (d_{br}, $J = 16.9$ Hz, 1H, 7-H_b), 2.18 (dd, $J = 16.9$, 6.2 Hz, 1H, 7-H_a), 2.34–2.54 (m, 1H, 3-H_b), 2.73 (dd, $J = 20.4$, 10.5 Hz, 1H, 3-H_a), 3.63–3.69 (m, 5H, 1-H, 2 × OCH_2), 5.50–5.70 (m, 1H, 6-H), 6.13 (dd, $J = 9.4$, 3.0 Hz, 1H, 5-H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 14.31$ (7a-CH_3), 21.92 ($C(CH_3)_2$), 27.42 (C-3), 28.77 ($C(CH_3)_3$), 30.21 (C-2), 31.58 ($C(CH_3)_2$), 35.47 (C-7), 43.69 (C-7a), 71.90 (OCH_2), 72.46 ($C(CH_3)_3$), 81.33 (C-1), 109.2 (C-4), 120.2 (C-5), 126.3 (C-6), 162.9 (C-3a); MS (EI, 70 eV): m/z (%) = 318 (1) $[M]^+$, 131 (100) $[M-C_5H_{10}BO_2-C_4H_8-H_2O]^+$, 57 (87) $[C_4H_9]^+$; HRMS: Anal. Calc. for $C_{19}H_{31}BO_3$: 318.2366; Found: 318.2366.

4.2.6. (+)-(1S,7aS)-4-(2-Bromo-5-methoxy-benzyl)-1-tert-butoxy-7a-methyl-2,3,7,7a-tetrahydro-1H-indene (15)

A solution of **16** (1.2 equivalents, 3.10 mmol, 731 mg), **11** (1.0 equivalent, 3.72 mmol, 1185 mg), $Pd(PPh_3)_4$ (0.05 equivalents, 0.16 mmol, 179 mg) and NaOH (1.5 equivalents, 4.65 mmol, 186 mg) in THF (20 ml) was refluxed for 22 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, dried over Na_2SO_4 and the solvent was removed in vacuo. After flash chromatography (100 g SiO_2, pentane/MTBE = 49:1) of the residue **15** was obtained in 72% yield (910 mg) as a colourless oil. $R_f = 0.52$ (pentane/MTBE = 24:1); UV (CH_3CN): λ_{max} (log ε) = 200 nm (4.627), 228 (4.047), 278 (3.730); IR (film): $\nu = 2971$ cm^{-1} (CH), 1592 (C=C), 1466 (C=C), 1093 (C–O–C); $[\alpha]_D^{20} = +58.3°$ ($c = 1.0$ in $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 0.94$ (s, 3H, 7a-CH_3), 1.16 (s, 9H, $C(CH_3)_3$), 1.61–1.70 (m, 1H, 2-H_b), 1.85–1.92 (m, 1H, 2-H_a), 2.06–2.24 (m, 3H, 3-H_b, 7-H_2), 2.41 (dd, $J = 18.8$, 10.7 Hz, 1H, 3-H_a), 3.34 (d, $J = 16.2$ Hz, 1H, 1″-H_b), 3.39 (d, $J = 16.2$ Hz, 1H, 1″-H_a), 3.67–3.76 (m, 4H, 1-H, OCH_3), 5.57–5.61 (m, 2H, 6-H), 5.64 (dd, $J = 9.4$, 3.0 Hz, 1H, 5-H), 6.60 (dd, $J = 8.7$, 3.1 Hz, 1H, 4′-H), 6.67 (d, $J = 3.1$ Hz, 1H, 6′-H), 7.39 (d, $J = 8.7$ Hz, 1H, 3′-H); ^{13}C-NMR (50.3 MHz, $CDCl_3$): $\delta = 14.68$ (7a-CH_3), 23.79 (C-3), 28.78 ($C(CH_3)_3$), 30.23 (C-2), 36.09 (C-7), 37.16 (C-1″), 43.30 (C-7a), 55.26 (OCH_3), 72.53 ($C(CH_3)_3$), 81.70 (C-1), 113.0 (C-4′), 115.3 (C-6′), 115.6 (C-2′), 123.0 (C-6), 124.0 (C-4), 126.8 (C-5), 132.9 (C-3′), 140.3, 143.2 (C-3a, C-1′), 158.9 (C-5′); MS (DCI, 200 eV): m/z (%) = 830, 828, 826 (3) $[2M+NH_4]^+$, 441, 439 (26) $[M+NH_4+NH_3]^+$, 424, 422 (100) $[M+NH_4]^+$; Anal. Calc. for $C_{22}H_{29}BrO_2$: C 65.18, H 7.21; Found: C 64.96, H 7.05%.

4.2.7. (+)-(3S,3aS,5aS)-3-tert-Butoxy-8-methoxy-3a-methyl-1,2,3,3a,5a,10-hexahydro-cyclopenta[a]fluorene (9)

A solution of **15** (1.0 equivalent, 123 μmol, 50 mg), **4** (0.05 equivalents, 6.2 μmol, 5.8 mg) and *n*-Bu_4NOAc (2.0 equivalents, 247 μmol, 74 mg) in a mixture of DMF/MeCN/H_2O (4 ml, 5:5:1) was heated at 140 °C for 5 min applying microwave irradiation. The reaction mixture was diluted with H_2O and Et_2O, the aqueous layer was separated and extracted three times with Et_2O, the combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by flash chromatography (5 g SiO_2, pentane/MTBE = 49:1) to give **9** as a colourless oil in 70% yield (28 mg). $R_f = 0.54$ (pentane/MTBE = 24:1); UV (CH_3CN): λ_{max} (log ε) = 200 nm (4.453), 276 (3.816), 303 (3.499); IR (KBr): $\nu = 2973$ cm^{-1} (CH), 1609 (C=C), 1098 (C–O–C); $[\alpha]_D^{20} = +12.0°$ ($c = 0.3$ in $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$): $\delta = 1.02$ (s, 3H, 3a-CH_3), 1.15 (s, 9H, $C(CH_3)_3$), 1.74–1.81 (m, 1H, 2-H_β), 1.87–1.93 (m, 1H, 2-H_α), 2.17–2.27 (m, 1H, 1-H_α), 2.36–2.44 (m, 1H, 1-H_β), 3.45 (s, 2H, 10-H_2), 3.48 (dd, $J = 9.8$, 7.5 Hz, 1H, 3-H), 3.77 (s, 3H, OCH_3), 4.06 (m_c, 1H, 5a-H), 5.99 (dd, $J = 9.4$, 3.2 Hz, 1H, 4-H), 6.10 (dd,

$J = 9.4$, 1.8 Hz, 1H, 5-H), 6.75 (dd, $J = 8.3$, 2.4 Hz, 1H, 7-H), 6.81 (s_{br}, 1H, 9-H), 7.21 (d, $J = 8.3$ Hz, 1H, 6-H); ^{13}C-NMR (50.3 MHz, $CDCl_3$): $\delta = 18.03$ (3a-CH_3), 23.48 (C-1), 28.75 (C(CH_3)$_3$), 30.07 (C-2), 34.66 (C-10), 44.51 (C-5a), 46.18 (C-3a), 55.42 (OCH_3), 72.65 ($C(CH_3)_3$), 76.86 (C-3), 110.3 (C-9), 112.3 (C-7), 123.5 (C-6), 125.3 (C-5), 131.7 (C-10a), 134.2 (C-4), 135.7 (C-5b), 136.8 (C-9a), 143.2 (C-10b), 158.6 (C-8); MS (EI, 70 eV): m/z (%) = 324 (2) $[M]^+$, 267 (7) $[M - C_4H_7]^+$, 223 (58), 57 (100) $[C_4H_7]^+$; HRMS: Anal. Calc. for $C_{22}H_{28}O_2$: 324.2089; Found: 324.2089.

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