CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200601076

An Efficient Access to Novel Enantiomerically Pure Steroidal δ-Amino Acids

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Abstract: A highly chemoselective sequence of Stille and Heck couplings on the heterocyclic bromoenol triflates **2a**–**c** with the bicycloalkenylstannanes *cis*-**3** and *trans*-**3** furnished the intermediate bromobutadienes **4a**–**c** in good yields ranging from 73–94%. A modified Heck coupling protocol employing the palladacycle **8** and an additional bidentate ligand such as 1,4-bis(diphenylphosphinyl)butane allowed a significant reduction in catalyst loading while still obtaining the heterocyclic 1,3,5-hexatrienes **5a**–**c** in good yields (71–94%). The unsymmetrically substituted 1,3,5-hexatrienes **5a**–**c** in solution underwent 6π-electrocyclizations following an optimized microwave-heating protocol to yield the steroidal tetracycles *cis*-**7a**–**c** and *trans*-**7b** (59–69%). Tetracycles *cis*-**7a**–**c** are the products of a subsequent 1,5-hydrogen shift to the thermodynamically more stable, more highly substituted diene units. Removal of the *tert*-butyl groups provided the novel steroidal δ-amino acid **9a** and the δ-amino acid derivatives **9b**,**c** in good yields (76–86%).

Keywords: amino acids · catalysis · cross-coupling · electrocyclic reactions · palladium · steroids

Introduction

Bioactive peptides are frequently being considered as candidates for new therapeutic drugs, but often limitations have been encountered due to severe pharmacological problems such as rapid metabolism, poor absorption, and low bioavailability upon oral administration.[1] Thus, considerable attention has been paid to the development of peptidomimetics, which exhibit peptide-like activity and resistance towards proteases.[2] In this context, non-natural amino acids are of great interest as new building blocks, especially if they lead to highly ordered structures[3] and, like amino acid homologues, introduce additional elements of diversity for new generations of drug candidates.[4] Among such homologues, δ-amino acids have attracted considerable interest in the design of peptidomimetics.[5] Furthermore, δ-amino acids have gained importance as building blocks for backbone generation of peptide nucleic acid (PNA) structures as well as for foldamers, since δ-amino acids demonstrated exceptional capabilities in inducing stable secondary structures in oligopeptides.[6] Considering our previously reported selective Stille–Heck cross-coupling sequence to build up differentially substituted 1,3,5-hexatrienes as precursors to cyclohexadienes,[7] we envisaged the possibility of assembling novel conformationally restrained δ-amino acids with a steroidal skeleton and set out to prepare them.

Results and Discussion

Starting with the Stille coupling of the enantiomerically pure hexahydroindenylstannanes *cis*-**3** and *trans*-**3** with the new heterocyclic bromoenol triflates **2a**–**c**, prepared in good yields (56–80%, see Table 1) from the bromopiperidinones **1a**–**c**,[8] the heterocyclic bromobutadienes *cis*-**4a**–**c** and *trans*-**4b** were assembled. Under the optimized conditions the enol triflates **2a**,**b** were formed with high regioselectivities, yet the enol triflate **2c** was accompanied by a minor

Table 1. Synthesis of the heterocyclic bromoenol triflates.

Starting compound	Product	Yield (%)[a]
1a	**2a**	74
1b	**2b**	80
1c	**2c**	56

[a] Yield of isolated product.

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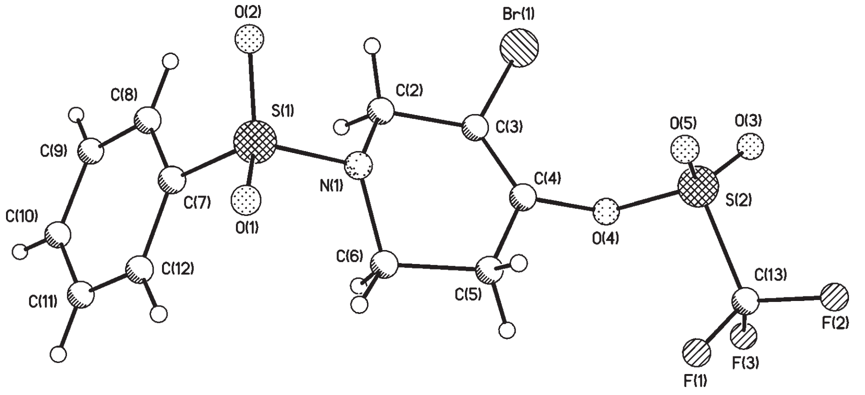
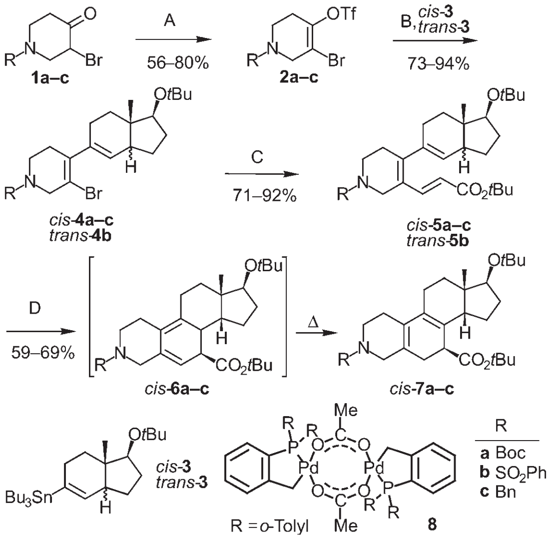


Figure 1. Structure of the bromoenol triflate **2b** in the crystal.[10]

amount of the undesired regioisomer,[9] which had to be removed by column chromatography. The crystal structure of **2b** was proved by X-ray diffraction (Figure 1).[10]

The Stille coupling worked best with a catalyst cocktail consisting of [Pd$_2$(dba)$_3$][11] and a copper(I) cocatalyst using freshly distilled *N*-methylpyrrolidone (NMP) as solvent to provide the products *cis*-**4a–c** and *trans*-**4b** in yields between 73–94% (Scheme 1; Table 2).[12]



Scheme 1. A) Tf$_2$O, NEt$_3$, CH$_2$Cl$_2$, −78→20 °C, 20 h; B) [Pd$_2$(dba)$_3$·CHCl$_3$] (2.5 mol%), CuI (2.5 mol%), LiCl (3.0 equiv), NMP, 65 °C, 10 h; C) **8** (3.0 mol%), dppb (3.0 mol%), *tert*-butyl acrylate (5.0–10.0 equiv), NEt$_3$ (3.0–4.0 equiv), DMF/H$_2$O 10:1, 105 °C, 8 h; D) microwave heating 170 (45 min) → 200 °C (2 min), toluene/DMF 10:1.

The tricyclic bromodienes *cis*-**4a–c** and *trans*-**4b** were immediately subjected to subsequent Heck reactions with *tert*-butyl acrylate to form the unsymmetrically substituted tricyclic 1,3,5-hexatrienes *cis*-**5a–c** and *trans*-**5b**, respectively. The best results for this step were obtained with the palladacycle **8**[13] and dppb[14] as co-ligand in the presence of triethylamine as a base. These conditions were significantly superior to the sole application of palladacycle **8** upon which, for example, the hexatriene *cis*-**5b** was obtained in only 68% yield even with 10 mol% of the precatalyst **8**. The application of **8** with a co-ligand for stabilization to avoid premature decomposition of the catalytically active species has not been reported before and allows for a significant reduction of the amount of precatalyst **8** necessary for complete conversion of the reactants. This protocol can be a convenient alternative to particularly tuned ligands which are either expensive or time consuming when specifically prepared. High yields were achieved (71–92%), by using a solvent mixture consisting of DMF and water.[15]

Table 2. Chemoselective Stille–Heck coupling sequences of the 2-bromo-4-azacyclohexenyl triflates leading to tricyclic 1,3,5-hexatrienes (see Scheme 1).

Starting compound	Alkene	Product	Yield (%)[a]
2a	*cis*-**3**	*cis*-**4a**	85
2b	*cis*-**3**	*cis*-**4b**	94
2c	*cis*-**3**	*cis*-**4c**	73
2b	*trans*-**3**	*trans*-**4b**	90
cis-**4a**	$\diagup\!\!\!\diagup\diagdown$CO$_2t$Bu	*cis*-**5a**	83
cis-**4b**	$\diagup\!\!\!\diagup\diagdown$CO$_2t$Bu	*cis*-**5b**	92
cis-**4b**	$\diagup\!\!\!\diagup\diagdown$CO$_2t$Bu	*cis*-**5b**	68[b]
cis-**4c**	$\diagup\!\!\!\diagup\diagdown$CO$_2t$Bu	*cis*-**5c**	71
trans-**4b**	$\diagup\!\!\!\diagup\diagdown$CO$_2t$Bu	*trans*-**5b**	85

[a] Yields of isolated products. [b] Reaction was performed with 10 mol% of palladacycle **8** without addition of a co-ligand.

The heterocyclic 1,3,4,5,6-pentasubstituted hexatrienes *cis*-**5a–c** and *trans*-**5b** are reasonably well set up for an additional ring closure by a thermally induced 6π-electrocyclization (Scheme 1),[16] and this was achieved best by heating a solution in toluene or in a mixture of toluene and DMF in a microwave oven following a special temperature profile. After 45 min at 170 °C, the hexatrienes *cis*-**5a–c** had been completely converted into a mixture of the expected 6π-electrocyclization product *cis*-**6a–c** and *cis*-**7a–c** (see also Table 3), arising from subsequent 1,5-hydrogen shifts. The

Table 3. Thermal 6π-electrocyclizations of heterocyclic 1,3,4,5,6-pentasubstituted 1,3,5-hexatrienes.

Starting compound	Product	Yield (%)[a]
cis-**5a**	*cis*-**7a**	60
cis-**5b**	*cis*-**7b**	69
cis-**5c**	*cis*-**7c**	59
trans-**5b**	*trans*-**7b**	55

[a] Yield of isolated product.

latter apparently are the thermodynamically more stable isomers, as upon extended heating at 200 °C for 2 min they were the sole products.

The heterotetracyclic compounds *cis*-**7a–c** were obtained as single diastereomers in yields ranging from 59–69 %. However, simply heating solutions of the unsymmetrically substituted hexatrienes *cis*-**5a–c** above 200 °C for 30 min led to increased decomposition and provided the tetracycles *cis*-**7a–c** only in 30–40 % yields. The structure of the steroidal δ-amino acid *cis*-**7b** was rigorously confirmed by X-ray crystallography (Figure 2). Thus, the sequence provides interesting new steroidal δ-amino acids with a *cis* CD-ring junction as it is found in a pharmacologically important class of natural steroids such as cardenolides and bufadienolides.[17]

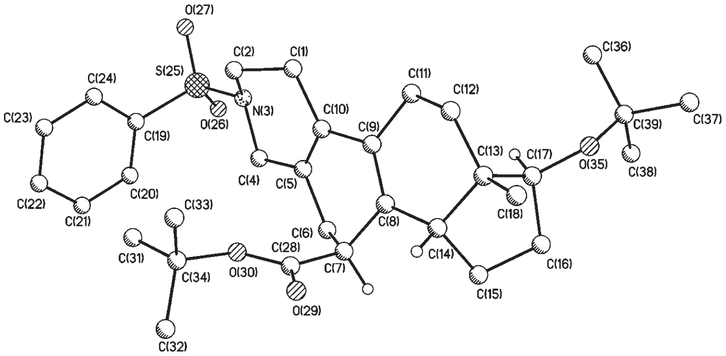
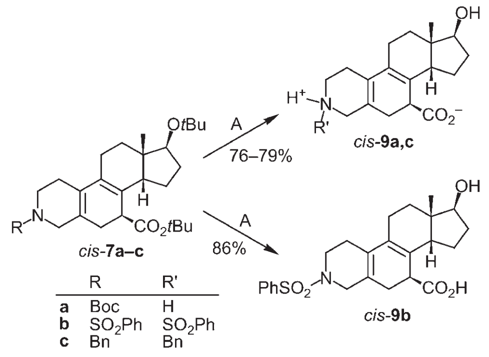


Figure 2. Structure of the steroidal δ-amino acid *cis*-**7b** in the crystal.[20]

Deprotection of the hydroxy, the amino and the carboxyl functionality in *cis*-**7a** could be achieved in one step using boron trifluoride etherate (Scheme 2)[18] to provide, the free steroidal δ-amino acid *cis*-**9a** in good yield (76 %).



Scheme 2. A) BF_3·OEt_2, toluene, 20 °C, 4 h.

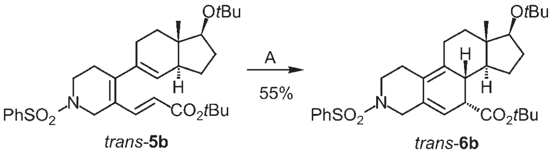
Under the same conditions, only the *tert*-butoxy groups were removed in derivatives *cis*-**7b,c** to furnish the amino acid derivatives *cis*-**9b** and *cis*-**9c** in yields ranging from 79–86 % (Table 4). An attempted removal of the *N*-benzyl group from the tetracycle *cis*-**9c** by catalytic hydrogenation over palladium on charcoal to provide the amino acid *cis*-**9a** was not successful.

Table 4. Deprotection of steroidal amino acids.

Starting compound	Product	Yield (%)[a]	$[\alpha]_D^{20}$[b] [°]
cis-**7a**	*cis*-**9a**	76	−34.3 (0.530)
cis-**7b**	*cis*-**9b**	86	+8.2 (0.45)[c]
cis-**7c**	*cis*-**9c**	79	−3.3 (0.86)

[a] Yield of isolated product. [b] Concentrations c [mg mL^{-1}] in methanol in parentheses. [c] Methyl acetate instead of methanol as a solvent.

Heating the isomer *trans*-**5b** with a *trans*-configured CD-ring junction at 170 °C for 30 min in a microwave oven led to the primary electrocyclization product *trans*-**6b** and traces of a substance which is suggested to be the product *trans*-**7b** of a [1,5]-hydrogen shift (Scheme 3). The steroidal amino acid *trans*-**6b** shows a *trans* relationship of the hydrogens on C8 and C14 and a *trans* CD-ring junction which is typical for the majority of naturally occurring steroids.[19]



Scheme 3. A) Toluene, microwave heating at 170 °C, 30 min.

It is noteworthy that the 6π-electrocyclizations occur with a high degree of disrotational selectivity, as the tetracycles *cis*-**7a–c** and *trans*-**6b** were all isolated as single diastereomers.

Interestingly, the cyclization of the *cis*-configured hexatrienes *cis*-**5a–c** occurred with inward rotational selectivity whereas the *trans*-configured hexatriene *trans*-**5b** cyclized with outward rotational selectivity.[21] These steroidal amino acids ought to be enantiomerically pure as well, since the bicyclic alkenylstannanes *cis*-**3** and *trans*-**3** were enantiomerically pure starting materials, and any racemization along the route would not be probable.

Conclusion

The Stille–Heck sequence of heterocyclic bromoenol triflates with the bicycloalkenylstannanes and *tert*-butyl acrylates as used in this study, provided unsymmetrically substituted (*E*)-1,3,5-hexatrienes, which were converted by highly diastereoselective thermally induced 6π-electrocyclizations to new tetracyclic dienes. Removal of the *tert*-butyl groups provided the new enantiomerically pure steroidal δ-amino acids and amino acid derivatives which are interesting to be tested as novel heterocyclic steroid analogues and as δ-amio acids to be incorporated into peptidomimetics. The described methodology constitutes an efficient sequence by which a remarkable increase of molecular complexicity is achieved. With this process, by variation of the starting materials, a variety of different structurally rigid amino acids with a steroidal skeleton should be accessible.

Experimental Section

General remarks: ^{1}H NMR: Bruker AM 250 (250 MHz). Chemical shifts in CDCl$_3$ are reported as δ values relative to chloroform ($\delta = 7.26$) and benzene ($\delta = 7.20$) as internal reference. ^{13}C NMR: Bruker AW 250 (62.9 MHz). Chemical shifts in CDCl$_3$ are reported as δ values relative to chloroform ($\delta = 77.0$) and benzene ($\delta = 128$); the multiplicity of the signals was determined by the DEPT (62.9 MHz) technique and quoted as (+) for CH$_3$ and CH groups, (−) for CH$_2$ groups and (C$_{\text{quat}}$) for quaternary carbon atoms. IR spectra: Bruker IFS 66. Low-resolution EI mass spectra: Finnigan MAT 95, ionizing voltage 70 eV. High-resolution mass spectra: Finnigan MAT 95; preselected ion peak matching at $R \sim 10000$ to be within ±2 ppm of the exact masses. Elemental analyses: Mikroanalytisches Labor des Instituts für Organische und Biomolekulare Chemie der Universität Göttingen, Germany. Melting points are uncorrected. Solvents for extraction and chromatography were of technical grade and distilled before use. Flash column chromatography (CC) was performed using Merck Kieselgel 60 (200–400 mesh). Aluminum oxide (ICN Alumina N, Super I) was obtained from ICN Biomedicals. Unless otherwise specified, aluminum oxide was deactivated with 5% water. TLC analyses were performed using Machery-Nagel precoated plates, 0.25 mm, Alugram Sil G/UV$_{254}$ (I) and Merck precoated silica gel 60 F$_{254}$ aluminium sheets (II). All reactions were carried out under an atmosphere of dry nitrogen or argon in oven- and/or flame-dried glassware. Unless otherwise specified, solutions of NH$_4$Cl, NaCl, Na$_2$SO$_3$ and NaHCO$_3$ are saturated aqueous solutions. Benzene, decalin, toluene, THF and diethyl ether were distilled from sodium/benzophenone. Dichloromethane was distilled from CaH$_2$.

tert-Butyl 4-trimethylsilanyloxy-3,6-dihydro-2*H*-pyridine-1-carboxylate,[22] 1-benzyl-4-trimethylsilanyloxy-1,2,3,6-tetrahydropyridine,[22] were prepared as described in literature.

1-Benzenesulfonyl-4-trimethylsilanyloxy-1,2,3,6-tetrahydropyridine: Trifluoromethanesulfonic acid trimethylsilyl ester (3.43 g, 15.4 mmol) in dichloromethane (20 mL) was added at −20 °C within 20 min to a solution of 1-benzenesulfonylpiperidine-4-one (5.00 g, 21.0 mmol) and triethylamine (6.60 g, 65.2 mmol) in dichloromethane (100 mL). After stirring for 1.0 h at −20 °C, the reaction mixture was treated with satd. NaHCO$_3$ solution (30 mL) and washed with water (30 mL). The organic phase was dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by CC on silica gel (55 g, pentane/diethyl ether 1:1) to obtain the product as colorless oil (6.41 g, 98 %). $R_f = 0.43$; ^{1}H NMR (250 MHz, CDCl$_3$): $\delta =$ 0.16 [s, 9 H, CH$_3$, Si(CH$_3$)$_3$], 2.19 (m, 2 H, 5-H), 3.06 (t, $^3J = 7.2$ Hz, 2 H, 6-H), 3.40 (m, 2 H, 5-H), 4.71–4.79 (m, 1 H, 2-H), 7.49–7.62 (m, 3 H, Ar-H), 7.77–7.83 (m, 2 H, Ar-H); ^{13}C NMR (62.9 MHz, CDCl$_3$, DEPT): $\delta = 0.17$ [+, 3 C, CH$_3$, Si(CH$_3$)$_3$], 29.85 (−, CH$_2$), 43.18 (−, CH$_2$), 43.74 (−, CH$_2$), 99.17 (+, CH, C-2), 127.55 (+, 2 C, CH, Ar), 129.01 (+, 2 C, CH, Ar), 132.72 (+, CH, Ar), 136.56 (C$_{\text{quat}}$, Ar), 148.68 (C$_{\text{quat}}$, C-4).

General procedure for the synthesis of the α-bromopiperidinones (GP 1): To a solution of *N*-bromosuccinimide (1.30–1.50 equiv) and sodium acetate (0.100 equiv) in THF/water 1:1 at 0 °C was added dropwise the corresponding trimethylsilylenol ether (1.00 equiv). The reaction mixture was warmed to ambient temperature and stirred for the stated time. It was treated with aqueous sodium sulfite solution (10 %) until it decolorized. The reaction mixture was extracted with two portions of diethyl ether. After washing the combined organic phases with satd. sodium hydrogencarbonate, water and brine, it was dried over MgSO$_4$. After concentration in vacuo the crude material was used without further purification. Otherwise it was purified by CC on silica gel.

***tert*-Butyl 3-bromo-4-oxopiperidine-1-carboxylate (1a)**: According to GP 1, *tert*-butyl 4-trimethylsilanyloxy-3,6-dihydro-2*H*-pyridine-1-carboxylate (1.00 g, 4.76 mmol), NBS (1.27 g, 8.25 mmol) and sodium acetate (39.1 mg, 0.476 mmol) in THF/water (45 mL) after 1 h and work-up with diethyl ether (2×50 mL), satd. NaHCO$_3$ solution (20 mL), water (20 mL) and brine (15 mL) yielded the α-bromopiperidinone (**1a**) as a yellow oil (0.948 g, 72 %). $R_f = 0.50$ (pentane/diethyl ether 2:1). The analytical data were consistent with the ones reported previously.[23]

1-Benzenesulfonyl-3-bromopiperidine-4-one (1b): According to GP 1, 1-benzenesulfonyl-4-trimethylsilanyloxy-1,2,3,6-tetrahydropyridine (2.21 g, 7.39 mmol), NBS (1.70 g, 11.1 mmol) and NaOAc (60.6 mg, 0.739 mmol) in THF/water (60 mL) after 1 h and work-up with diethyl ether (2× 70 mL), satd. NaHCO$_3$ solution (35 mL), water (35 mL) and (brine 20 mL) yielded the α-bromopiperidinone (**1b**) as a colorless oil (1.55 g, 68 %). $R_f = 0.45$ (pentane/diethyl ether 2:1); ^{1}H NMR (250 MHz, CDCl$_3$): $\delta = 2.51$–2.68 (m, 1 H, CH$_2$), 2.80–3.07 (m, 1 H, CH$_2$), 3.18–3.47 (m, 2 H, CH$_2$), 3.50–3.63 (m, 1 H, CH$_2$), 3.80–3.99 (m, 1 H, CH$_2$), 4.45 (dd, $^3J = 9.1$, $^3J = 6.1$ Hz, 1 H, 3-H), 7.40–7.64 (m, 3 H, Ar-H), 7.69–7.81 (m, 2 H, Ar-H); ^{13}C NMR (62.9 MHz, CDCl$_3$, DEPT): $\delta = 38.43$ (−, CH$_2$), 45.59 (−, CH$_2$), 49.31 (−, CH$_2$), 52.81 (+, CH$_3$, C-3), 133.25 (+, CH, Ar), 127.09 (+, 2 C, CH, Ar), 129.26 (+, 2 C, CH, Ar), 136.25 (C$_{\text{quat}}$, Ar), 200.51 (C$_{\text{quat}}$, C-4); IR (film): $\tilde{\nu}$ = 3064, 2918 (C-H), 2857, 1734, 1700, 1684, 1653, 1465, 1447, 1358, 1339, 1311, 1288, 1215, 1169, 1095, 1074, 988, 934, 801, 743, 691, 657, 577 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 318/316 (4/4), 276 (1), 238 (3), 196 (6), 177 (2), 169 (3), 140 (22), 132 (8), 97 (5), 77 (100), 55 (9), 51 (22), 42 (24); HRMS: *m*/*z*: calcd for $C_{11}H_{12}O_3NSBr+H^+$ (319.2): 317.97937 (correct HRMS).

1-Benzyl-3-bromopiperidine-4-one (1c): According to GP 1, 1-benzyl-4-trimethylsilanyloxy-1,2,3,6-tetrahydropyridine (2.60 g, 9.92 mmol), NBS (2.27 g, 14.9 mmol) and sodium acetate (81.3 mg, 0.992 mmol) in THF/water (45 mL) after 1 h and work-up with diethyl ether (2×75 mL), sat. NaHCO$_3$ solution (40 mL), water (40 mL) and brine (20 mL) yielded the α-bromopiperidinone (**1c**) as a colorless oil (0.80 g, 31 %). $R_f = 0.25$ (pentane/diethyl ether 2:1). The analytical data were consistent with the ones reported previously.[24]

General procedure for the synthesis of bromoenol triflates (GP 2): To a solution of the α-α-bromopiperidinone (1.00 equiv) and triethylamine (3.00–5.00 equiv) in dichloromethane was added dropwise at −78 °C trifluoromethansulfonic acid anhydride (1.05–1.30 equiv) in dichloromethane. The reaction mixture was slowly warmed to ambient temperature and stirred for a total of 20–24 h. After treatment with satd. NaHCO$_3$ solution, the aqueous phase was extracted with diethyl ether. Then the combined organic layers were washed with water and brine. After concentration in vacuo the residue was purified by CC on silica gel.

***tert*-Butyl 5-bromo-4-trifluoromethanesulfonyl-3,6-dihydro-2*H*-pyridine-1-carboxylate (2a)**: According to GP 2 α-bromopiperidinone (**1a**) (1.20 g, 4.31 mmol) and triethylamine (1.30 g, 12.9 mmol) in dichloromethane (20 mL) were treated with trifluoromethanesulfonic acid anhydride (1.46 g, 5.18 mmol) in dichloromethane (5 mL). Work up with diethyl ether (35 mL) und satd. NaHCO$_3$ solution (15 mL), extraction of the aqueous phases with diethyl ether (2×5 mL) yielded after purification by CC on silica gel (25 g, pentane/diethyl ether 1:1) the bromoenol triflate **1a** as colorless oil (1.31 g, 74 %). $R_f = 0.61$; ^{1}H NMR (250 MHz, CDCl$_3$): $\delta = 1.50$ (s, 9 H, *t*Bu), 2.48–2.61 (m, 2 H, 2-H), 3.69 (t, $^3J = 6.3$ Hz, 2 H, 3-H), 4.25 (br s, 2 H, 6-H); ^{13}C NMR (75.6 MHz, CDCl$_3$, APT): $\delta = 28.2$ [+, 3 C, CH$_3$, C(CH_3)$_3$], 41.5 (−, 2 C, CH$_2$), 48.3 (−, CH$_2$), 81.3 [−, C$_{\text{quat}}$, *C*-(CH$_3$)$_3$], 118.3 (−, q, $^1J = 321$ Hz, C$_{\text{quat}}$, CF$_3$), 119.9 (−, C$_{\text{quat}}$, C-3), 120.0 (−, C$_{\text{quat}}$, C-4), 153.8 (−, C$_{\text{quat}}$, C=O); IR (film): $\tilde{\nu}$ = 2979 (C-H), 2935, 1705, 1653, 1635, 1591, 1457, 1420, 1368, 1337, 1296, 1246, 1215, 1163, 1140, 1116, 1077, 1043, 998, 868, 814, 768, 698, 668, 622 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 355/353 (2/2), 338/336 (3/3), 309/307 (1/1), 273 (1), 221/219 (5/5), 176 (1), 132 (2), 96 (2), 69 (4) [CF$_3^+$], 57 (100).

1-Benzenesulfonyl-5-bromo-4-trifluoromethanesulfonyl-1,2,3,6-tetrahydropyridine (2b): According to GP 2, α-bromopiperidinone **1b** (312 mg, 0.981 mmol) and triethylamine (297 mg, 2.94 mmol) in dichloromethane (10 mL) were treated with trifluoromethanesulfonic acid anhydride (414 mg, 1.47 mmol) in dichloromethane (4 mL). Work up with diethyl ether (20 mL) and sat. NaHCO$_3$ solution (10 mL), extraction of the aqueous phase with diethyl ether (2×20 mL) yielded, after purification on silica gel (15 g, pentane/diethyl ether 1:1), the bromoenol triflate **2b** as a colorless oil (352 mg, 80 %). Good quality crystals for X-ray diffraction were grown from pentane/diethyl ether 1:1 by slow evaporation of solvents at 23 °C. $R_f = 0.43$; ^{1}H NMR (250 MHz, CDCl$_3$): $\delta = 2.44$–2.66 (m, 2H, 2-H), 3.47 (t, ^3J=7.2 Hz, 2H, 3-H), 3.47 (t, ^3J=0.83 Hz, 2H, 6-H), 7.49–7.71 (m, 3H, Ar-H), 7.73–7.84 (m, 2H, Ar-H); ^{13}C NMR (75.5 MHz, CDCl$_3$, APT): δ=29.11 (−, CH$_2$), 42.64 (−, CH$_2$), 50.35 (−, CH$_2$), 110.21 (−, C$_{quat}$, C-3), 118.22 (−, q, ^1J=321 Hz, C$_{quat}$, CF$_3$), 127.33 (+, 2C, CH, Ar), 129.53 (+, 2C, CH, Ar), 133.52 (+, CH, Ar), 136.48 (−, C$_{quat}$, Ar), 143.34 (−, C$_{quat}$, C-4); IR (film): $\tilde{\nu}$ = 3065, 2920, 2863, 1684, 1447, 1422, 1357, 1340, 1250, 1214, 1171, 1138, 1101, 1085, 1024, 999, 967, 951, 915, 866, 815, 748, 739, 715, 690, 677, 624 cm^{-1}; MS (70 eV, EI): *m/z* (%): 450/448 (3/2), 369 (11), 309/307 (17/18), 275 (1), 236 (3), 227 (2), 176/174 (9/9), 140 (40), 96 (1), 77 (100), 51 (22), 42 (6).

1-Benzyl-5-bromo-4-trifluoromethanesulfonyl-1,2,3,6-tetrahydropyridine (2c): According to GP 2, α-bromopiperidinone **1c** (3.80 g, 14.2 mmol) and triethylamine (5.74 g, 56.8 mmol) in dichloromethane (60 mL) were treated with trifluoromethanesulfonic acid anhydride (6.01 g, 21.3 mmol) in dichloromethane (15 mL). Work-up according to GP 2 with diethyl ether (50 mL) and satd. NaHCO$_3$ solution (25 mL), extraction of the aqueous phases with diethyl ether (2×40 mL) yielded after purification on silica gel (35 g, pentane/diethyl ether 3:1) the bromoenoltriflate **2c** as a colorless oil (3.19 g, 56%). R_f=0.53; ^{1}H NMR (250 MHz, CDCl$_3$): δ= 2.50–2.62 (m, 2H, 5-H), 2.86 (t, ^3J=6.1 Hz, 2H, 6-H), 3.39 (t, ^3J= 0.76 Hz, 2H, 2-H), 3.67 (s, 2H, PhC*H*$_2$), 7.28–7.47 (m, 5H, Ar); ^{13}C NMR (75.6 MHz, CDCl$_3$, APT): δ=28.93 (−, CH$_2$), 42.65 (−, CH$_2$), 48.64 (−, CH$_2$), 60.17 (−, CH$_2$, PhCH$_2$), 112.35 (−, C$_{quat}$, C-4), 118.53 (−, q, ^1J= 318 Hz, C$_{quat}$, CF$_3$), 127.61 (+, CH, Ar), 128.52 (+, CH, 2C, Ar), 128.89 (+, CH, 2C, Ar), 137.06 (−, C$_{quat}$, Ar), 143.75 (−, C$_{quat}$, C-3); IR (film): $\tilde{\nu}$ = 3064, 3029, 2976, 2865, 1685, 1495, 1434, 1418, 1383, 1367, 1347, 1250, 1231, 1202, 1146, 1136, 1084, 1075, 1054, 1028, 1012, 997, 976, 919, 880, 858, 820, 768, 739, 698, 630, 604 cm^{-1}; MS (70 eV, EI): *m/z* (%): 401/399 (2/2), 320 (2), 310/308 (1/1), 268 (1), 187 (3), 159 (1), 119 (2), 91 (100), 65 (12); HRMS: *m/z*: calcd for C$_{13}$H$_{13}$O$_3$NBrF$_3$S (400.2): 398.9752 (correct HRMS).

General procedure for Stille couplings of heterocyclic 2-bromocyclohex-1-enyl triflates (GP 3): In a Pyrex bottle containing a magnetic stirring bar were placed NMP (5 mL), the bromoenol triflate (1.00–1.20 equiv) and the stannane (1.00 equiv). The bottle was sealed with a septum and the contained solution was purged with argon in an ultrasonic bath for 5 min. Then [Pd$_2$(dba)$_3$]·CHCl$_3$ (2.5 mol%), LiCl (3.00 equiv), CuI (2.5 mol%) followed, and the suspension was purged with argon for another 5 min. After removal of the septum, the bottle was sealed with a screw cap, and then heated with vigorous stirring at the stated temperature for the stated time. When the reaction had ceased, the mixture was poured into diethyl ether and aqueous NH$_3$ solution (5%). The organic layer was washed with water and the combined aqueous layers were extracted back with diethyl ether (2×30 mL). The combined organic layers were treated with satd. KF solution, dried over MgSO$_4$, concentrated in vacuo, and the residue was purified by column chromatography (CC) on silica gel.

(1′*S*,3a′*S*,7a′*R*)-*tert*-Butyl 5-bromo-4-(1′-*tert*-butoxy-7a′-methyl-2′,3′,3a′,6′,7′,7a′-hexahydro-1′*H*-indene-5′-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate (*cis*-4a): According to GP 3, bromoenol triflate **2a** (615 mg, 1.50 mmol) in NMP (5 mL) and bicycloalkenylstannane *cis*-**3** (845 mg, 1.70 mmol), after treatment with [Pd$_2$(dba)$_3$]·CHCl$_3$ (39 mg, 38 μmol), LiCl (191 mg, 4.50 mmol) CuI (6.8 mg, 36 μmol) at 65 °C for 12 h and work-up with diethyl ether (100 mL), NH$_3$ solution (2×35 mL, 5%), water (35 mL), back extraction of the combined aqueous phases with diethyl ether (2×40 mL) treatment with satd. KF solution (75 mL) and CC on silica gel (35 g, pentane/diethyl ether 5:1) gave the bromobutadiene *cis*-**4a** as a colorless oil which quickly turned yellow at RT (597 mg, 85%). R_f=0.38; ^{1}H NMR (250 MHz, CDCl$_3$): δ=0.91 (s, 3H, CH$_3$), 1.16 [s, 9H, C(CH$_3$)$_3$], 1.31–1.44 (m, 2H), 1.49 [s, 9H, COOC(CH$_3$)$_3$], 1.53–1.62 (m, 3H), 1.93–2.32 (m, 7H), 3.54 (m, 1H), 3.71 (t, ^3J=8.0 Hz, 1H, 4′-H), 4.11 (m, 2H, 6′-H), 5.39 (m, 1H, 1′-H); ^{13}C NMR (62.9 MHz, CDCl$_3$ additional APT): δ=21.1 (+, CH$_3$), 23.4 (−, CH$_2$), 28.3 (−, CH$_2$), 28.4 [+, 3C, C(*C*H$_3$)$_3$], 28.8 [+, 3C, COOC(*C*H$_3$)$_3$], 30.0 (−, CH$_2$), 31.4 (−, CH$_2$), 32.6 (−, CH$_2$), 41.6 (−, CH$_2$), 42.7 (−, CH$_2$), 43.9 (+, CH, C-3′a), 50.2 (−, C$_{quat}$, C-7′a), 72.5 [−, C$_{quat}$, *C*(CH$_3$)$_3$], 76.1 [−, C$_{quat}$, COO*C*-(CH$_3$)$_3$], 80.2 (+, CH, C-1′), 113.1 (−, C$_{quat}$), 130.1 (+, CH, C-4′), 135.9 (−, C$_{quat}$), 138.3 (−, C$_{quat}$), 154.1 (−, C$_{quat}$, C=O); IR (film): $\tilde{\nu}$=2976 (C-H), 2953 (C-H), 2871 (C-H), 2843 (C-H), 1474, 1465, 1457, 1388, 1376, 1361, 1255, 1226, 1199, 1125, 1091, 1071, 1047, 1025, 992, 907, 893, 873, 743 cm^{-1}; MS (70 eV): *m/z* (%): 469/467 (1/1) [M^+], 428/426 (1/1), 412/410 (37/35) [M^+−C$_4$H$_9$], 357/355 (43/56), 339 (23), 312 (8), 276 (32), 258 (28), 232 (79), 231 (25), 220 (6), 174 (4), 131 (5), 91 (8), 57 (100) [C$_4$H$_9^+$], 41 (14); DCI-MS (NH$_3$): *m/z* (%): 487/485 (50/50) [M+NH$_4^+$], 446 (100), 431/429 (52/54), 407 (36), 346 (45), 288 (17), 254 (24), 232 (22), 175 (4), 138 (10).

(1*S*,3a*R*,7a*S*)-1-Benzolsulfonyl-5-bromo-4-(1′-*tert*-butoxy-7a′-methyl-2′,3′,3a′,6′,7′,7a′-hexahydro-1′*H*-indene-5′-yl)-1,2,3,6-tetrahydropyridine (*cis*-4b): According to GP 3, the bromoenol triflate **2b** (1.41 g, 3.13 mmol) in NMP (10.0 mL) and bicycloalkenylstannane *cis*-**3** (1.79 g, 3.61 mmol), after treatment with [Pd$_2$(dba)$_3$] (86.3 mg, 94.2 μmol), LiCl (400 mg, 9.44 mmol), CuI (17.9 mg, 94.0 μmol), work-up with diethyl ether (100 mL), NH$_3$ solution (2×40 mL, 5%), water (40 mL), back extraction with diethyl ether (2×55 mL) treatment with satd. KF solution (75 mL) and CC on silica gel (70 g, pentane/diethyl ether 5:1) gave the bromobutadiene *cis*-**4b** as a colorless oil which quickly turned yellow at RT (1.50 g, 94%). R_f=0.43; ^{1}H NMR (300 MHz, CDCl$_3$): δ=0.85 (s, 3H, CH$_3$), 1.14 [s, 9H, C(CH$_3$)$_3$], 1.27–1.58 (m, 4H), 1.85–2.13 (m, 5H), 2.25 (m, 2H), 3.28 (q, ^3J=6.6 Hz, 2H, 2-H), 3.60 (t, ^3J=7.2 Hz, 1H, 1′-H), 3.87 (m, 2H, 6-H), 5.23 (m, 1H, 4′-H), 7.47–7.63 (m, 3H, Ar*H*), 7.75–7.83 (m, 2H, Ar*H*); ^{13}C NMR (75.5 MHz, CDCl$_3$, APT): δ=20.94 (+, CH$_3$), 23.22 (−, CH$_2$), 28.22 (−, CH$_2$), 28.72 [+, 3C, CH$_3$, C(*C*H$_3$)$_3$], 29.88 (−, CH$_2$), 30.90 (−, CH$_2$), 32.56 (−, CH$_2$), 41.49 (−, CH$_2$), 42.87 (−, C$_{quat}$, C-7a′), 43.75 (+, CH, C-3a′), 51.34 (−, CH$_2$, C-2), 72.47 [−, C$_{quat}$, *C*(CH$_3$)$_3$], 76.10 (+, CH, C-1′), 111.08 (−, C$_{quat}$), 127.52 (+, 2C, CH, Ph), 128.94 (+, 2C, CH, Ph), 130.37 (+, CH, Ph), 132.96 (+, CH, C-4′), 135.30 (−, C$_{quat}$), 136.69 (−, C$_{quat}$), 138.15 (−, C$_{quat}$); IR (film): $\tilde{\nu}$ = 2970 (C-H), 2871 (C-H), 1669 (C=C), 1616, 1587, 1559, 1506, 1458, 1446, 1388, 1356, 1309, 1197, 1170, 1093, 1018, 967, 910, 865, 808 cm^{-1}; EI-MS (70 eV): *m/z* (%): 372 (18), 354 (6), 316 (3), 288 (3), 278 (9), 231/229 (15/13), 212 (4), 169 (8), 140 (13), 91 (11), 83 (18), 77 (48), 57 (100), 40 (31); DCI-MS (NH$_3$): *m/z* (%): 795/793 (5/5), 621 (3), 571 (3), 544/542 (26/24) [M+NH$_3$+NH$_4^+$], 527/525 (38/36) [M+NH$_4^+$], 520 (5), 385 (3), 370 (14), 353 (9), 303 (28), 286 (100), 254 (6), 192 (4), 136 (3).

(3*S*,3a*S*,7a*R*)-1-Benzyl-5-bromo-4-(1-*tert*-butoxy-7a-methyl-2,3,3a,6,7,7a-hexahydro-1*H*-indene-5-yl)-1,2,3,6-tetrahydropyridine (*cis*-4c): According to GP 3, to bromoenol triflate (**2c**) (400 mg, 1.00 mmol) in NMP (4.00 mL) with bicycloalkenylstannane (*cis*-**3**) (522 mg, 1.05 mmol), after treatment with [Pd$_2$(dba)$_3$]·CHCl$_3$ (36.3 mg, 35.1 μmol), LiCl (128 mg, 3.02 mmol) and CuI (6.71 mg, 35.2 μmol), work-up with diethyl ether (80 mL), NH$_3$ solution (2×30 mL, 5%), water (30 mL), extraction with diethyl ether (2×30 mL), treatment with sat. KF solution (60 mL) and CC on silica gel (50 g, pentane/diethyl ether 5:1) gave the bromobutadiene *cis*-**4c** as a colorless oil, which quickly turned yellow at RT (334 mg, 73%). R_f=0.33; ^{1}H NMR (250 MHz, CDCl$_3$): δ=0.95 (s, 3H, CH$_3$), 1.18 [s, 9H, C(CH$_3$)$_3$], 1.31–1.68 (m, 6H), 1.93–2.22 (m, 5H), 2.60-2.73 (m, 2H), 3.29 (m, 2H, 6′-H), 3.62 (m, 2H, PhC*H*$_2$), 3.70 (t, ^3J= 7.5 Hz, 1H, 3-H), 5.42 (brs, 1H, 7a-H), 7.23–7.46 (m, 5H, Ar); ^{13}C NMR (62.9 MHz, CDCl$_3$ additional DEPT): δ=17.76 (+, CH$_3$), 21.09 (−, 2C, CH$_2$), 28.26 (−, CH$_2$), 28.74 [+, 3C, C(*C*H$_3$)$_3$], 30.00 (−, CH$_2$), 31.53 (−, CH$_2$), 32.56 (−, CH$_2$), 41.52 (C$_{quat}$, C-3a), 43.84 (+, CH, C-7a), 49.21 (−, CH$_2$, C-2′), 60.12 (−, CH$_2$, C-3′), 61.45 (−, CH$_2$, Ph*C*H$_2$), 72.41 [C$_{quat}$, *C*-(CH$_3$)$_3$], 75.97 (+, CH, C-3), 114.00 (C$_{quat}$), 127.20 (+, CH, Ar), 128.28 (+, 2C, CH, Ar), 129.07 (+, 2C, CH, Ar), 129.71 (+, CH, C-7), 136.03 (C$_{quat}$), 137.67 (C$_{quat}$); IR (film): $\tilde{\nu}$ = 3063, 2976 (C-H), 2963, 2871 (C-H), 2842, 1692 (C=C), 1424, 1416, 1375, 1341, 1304, 1249, 1197, 1144, 1070, 1041, 1017, 983, 952, 883, 858, 819 cm^{-1}; MS (70 eV): *m/z* (%): 459/457 (10/9) [M^+], 386/384 (3/2), 325 (1), 312 (18), 308 (100), 300 (4), 226 (3), 209 (11), 135 (6).

General procedure for Heck couplings of functionalized bromodienes with acrylates (GP 4): In a Pyrex bottle containing a magnetic stirring bar was charged with DMF/H$_2$O (10:1) and the respective bromodiene (1.00 equiv). The bottle was sealed with a septum, and the contained solution was purged with argon in an ultrasonic bath for 5 min. Then *trans*-di(μ-acetato)bis[*o*-(di-*o*-tolylphosphanyl)benzyl]dipalladium(II) (**8**) (3 mol%), 1,4-bis(diphenylphosphinyl)butane (3 mol%), triethylamine

(3.00–4.00 equiv) and *tert*-butyl acrylate (5.00–10.0 equiv) were added. The reaction mixture was purged with argon for another 2 min. The septum was removed, the Pyrex bottle was sealed with a screw cap and heated with vigorous stirring at the stated temperature for the stated time. After the reaction mixture had cooled down to RT, it was poured into diethyl ether (40 mL) and 5% aqueous NH_3 solution (10 mL). The organic layer was washed with 5% aqueous NH_3 solution (10 mL), and the combined aqueous layers were extracted back with Et_2O (2×25 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo and the residue was purified by column chromatography (CC) on silica gel.

(*E*)-(1″*S*,3a″*R*,7a″*S*)-*tert*-Butyl 5′-(2-*tert*-butoxycarbonylethenyl)-4′-(1″-*tert*-butoxy-7a″-methyl-2″,3″,3a″,6″,7″,7a″-hexahydro-1″*H*-inden-5″-yl)-3′,6′-dihydro-2′*H*-pyridine-1′-carboxylate (*cis*-5a): According to GP 4, to a solution of the bromodiene *cis*-**4a** (1.50 g, 3.21 mmol) in DMF/H_2O 10:1 (11 mL), 1,4-bis(diphenylphosphanyl)butane (41 mg, 96 µmol), palladacycle **8** (90 mg, 96 µmol), triethylamine (1.31 g, 12.9 mmol) and *tert*-butyl acrylate (3.50 g, 27.3 mmol) were added. The resulting mixture was heated at 105°C for 8 h. After CC (30 g silica gel, pentane/diethyl ether 5:1) the hexatriene *cis*-**5a** was obtained as a colorless oil (1.38 g, 83%). $R_f=0.35$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.90$ (s, 3H, CH_3), 1.13 [s, 9H, $C(CH_3)_3$], 1.16–1.39 (m, 4H), 1.45 [$s_{coalesced}$, 18H, $CO_2C(CH_3)_3$], 1.86–2.13 (m, 3H), 2.14–2.24 (m, 2H), 2.29 (m, 2H), 3.38–3.51 (m, 2H), 3.56 (t, $^3J=8.1$ Hz, 1H, 1″-H), 4.01 (m, 2H), 5.37–5.43 (m, 1H, 5″-H), 5.63 (d, $^3J=16.4$ Hz, 1H, 1-H), 7.51 (d, $^3J=16.4$ Hz, 1H, 3-H); ^{13}C NMR (75.5 MHz, $CDCl_3$, additional APT): $\delta=20.9$ (+, CH_3), 24.8 (−, CH_2), 28.2 [+, 3C, $C(CH_3)_3$], 28.5 [+, 3C, $CO_2C(CH_3)_3$], 28.7 [+, 3C, $NCO_2C(CH_3)_3$], 29.2 (−, CH_2), 29.6 (−, CH_2), 30.4 (−, CH_2), 33.0 (−, CH_2), 39.5 (−, CH_2), 43.3 (−, CH_2), 41.5 (−, C_{quat}, C-7a″), 44.4 (+, CH, C-3a″), 72.6 [−, C_{quat}, $C(CH_3)_3$], 77.3 (+, CH, C-1″), 79.9 [−, 2C, C_{quat}, $CO_2C(CH_3)_3$, $NCO_2C(CH_3)_3$], 116.9 (+, CH, C-1), 124.5 (−, C_{quat}), 132.3 (+, CH), 134.4 (−, C_{quat}), 140.5 (+, CH), 148.1 (−, C_{quat}), 154.7 (−, C_{quat}, NC=O), 166.7 (−, C_{quat}, OC=O); IR (film): $\tilde{\nu}$ = 2977, 2958 (C-H), 2933 (C-H)), 1701 (C=O), 1685, 1617 (C=C), 1559, 1507, 1478, 1457, 1393, 1368, 1338, 1319, 1285, 1253, 1197, 1171, 1149, 1043, 1025, 987, 908, 849, 744, 729, 704, 648 cm^{-1}; MS (70 eV): *m*/*z* (%): 515 (2) [M^+], 459 (8) [$M^+-C_4H_8$], 441 (63), 403 (38) [$M^+-2\times C_4H_8$], 402 (30) [$M^+-C_4H_8-C_4H_9$], 385 (64), 346 (62), 328 (52), 302 (76), 284 (72), 258 (73), 240 (38), 57 (100) [$C_4H_9^+$], 41 (29); DCI-MS (NH_3): *m*/*z* (%): 644 (5), 549 (4), 533 (100) [$M+NH_4^+$], 516 (51) [$M+H^+$], 477 (58), 416 (25), 383 (50), 327 (66), 271 (11), 208 (3); HRMS: *m*/*z*: calcd for $C_{31}H_{49}NO_5$: 515.3611 (correct HRMS).

(*E*)-(1″*S*,3a″*R*,7a″*S*)-*tert*-Butyl 3-[1′-benzenesulfonyl-4′-(1″-*tert*-butoxy-7a″-methyl-2″,3″,3a″,6″,7″,7a″-hexahydro-1″*H*-indene-5″-yl)-1′,2′,5′,6′-tetrahydropyridine-3′-yl]-acrylate (*cis*-5b): According to GP 4, to a solution of the bromobutadiene *cis*-**4b** (1.10 g, 2.16 mmol) in DMF/CH_3CN/H_2O 5:5:1 (10 mL), 1,4-bis(diphenylphosphanyl)butane (36.9 mg, 86.5 µmol), palladacycle **8** (81.0 mg, 86.4 µmol), triethylamine (437 mg, 4.32 mmol) and *tert*-butyl acrylate (3.16 mL, 2.77 g, 21.6 mmol) were added. The resulting mixture was heated at 105°C for 8.5 h. Work-up with diethyl ether (120 mL), water (2×35 mL), back extraction with diethyl ether (2×55 mL), brine (35 mL) yielded after CC (50 g silica gel, pentane/diethyl ether 3:1) the hexatriene *cis*-**5b** as a colorless oil (1.10 g, 92%). $R_f=0.50$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=0.88$ (s, 3H, CH_3), 1.12 [s, 9H, $C(CH_3)_3$], 1.15–1.42 (m, 2H), 1.46 [s, 9H, $CO_2C(CH_3)_3$], 1.48–1.58 (m, 3H), 1.77–2.09 (m, 4H), 2.15 (m, 2H), 2.36 (m, 2H), 3.53 (t, $^3J=7.5$ Hz, 1H, 1″-H), 3.72 (m, 2H), 5.30-5.34 (m, 1H, 1″-H), 5.59 (d, $^3J=15.6$ Hz, 1H, 2-H), 7.43 (d, $^3J=15.6$ Hz, 1H, 3-H), 7.49–7.63 (m, 3H, Ph), 7.76–7.82 (m, 2H, Ph); ^{13}C NMR (75.6 MHz, $CDCl_3$, APT): $\delta=20.80$ (+, CH_3), 24.72 (−, CH_2), 28.04 [+, 3C, $C(CH_3)_3$], 28.16 [+, 3C, $CO_2C(CH_3)_3$], 28.65 (−, CH_2), 29.11 (−, CH_2), 29.63 (−, CH_2), 32.94 (−, CH_2), 41.40 (−, CH_2), 42.59 (−, C_{quat}, C-7a″), 44.26 (+, CH, C-3a″), 44.68 (−, CH_2), 72.61 [−, C_{quat}, $C(CH_3)_3$], 77.29 (+, CH, C-1″), 80.19 [−, C_{quat}, $CO_2C(CH_3)_3$], 117.30 (+, CH, C-2), 123.59 (−, C_{quat}), 127.62 (+, 2C, Ph), 129.14 (+, 2C, Ph), 132.74 (+, CH), 132.86 (+, CH), 133.82 (−, C_{quat}), 136.24 (−, C_{quat}), 139.95 (+, CH), 146.82 (−, C_{quat}), 166.31 (−, C_{quat}, C=O); IR (film): $\tilde{\nu}$ = 3063, 2977 (C-H), 2932 (C-H)), 1968, 1902, 1817, 1712 (C=O), 1654, 1615 (C=C), 1446, 1361, 1293, 1233, 1001, 896, 854, 749 cm^{-1}; MS (70 eV): *m*/*z* (%): 555 (5) [M^+], 499 (26) [$M^+-C_4H_8$], 481 (8), 443 (26) [$M^+-2\times C_4H_8$], 442 (34) [$M^+-C_4H_9-C_4H_8$], 398 (24), 358 (22), 314 (5), 302 (64), 284 (33), 256 (26), 209 (10), 184 (6), 141 (10), 83 (7), 77 (20), 57 (100) [$C_4H_9^+$], 41 (24); HRMS: *m*/*z*: calcd for $C_{32}H_{45}O_5SN+H^+$ (556.8): 556.30909 (correct HRMS).

(*E*)-(1″*S*,3a″*R*,7a″*S*)-*tert*-Butyl 3-[1′-benzyl-4′-(1″-*tert*-butoxy-7a″-methyl-2″,3″,3a″,6″,7″,7a″-hexahydro-1″*H*-indene-5″-yl)-1′,2′,5′,6′-tetrahydropyridine-3′-yl]acrylate (*cis*-5c): According to GP 4, to a solution of the bromobutadiene *cis*-**4c** (301 mg, 656 mmol) in DMF/H_2O 10:1 (2.0 mL), 1,4-bis(diphenylphosphinyl)butane (14.0 mg, 32.8 µmol), palladacycle **8** (30.7 mg, 32.7 µmol), triethylamine (199 mg, 1.97 mmol) and *tert*-butyl acrylate (0.400 mL, 0.350 g, 2.73 mmol)were added. The resulting mixture was heated at 105°C for 8 h. Work-up with diethyl ether (60 mL), water (2×15 mL), back extraction with diethyl ether (2×20 mL), brine (15 mL) yielded after CC (30 g silica gel, pentane/diethyl ether 5:1) the hexatriene *cis*-**5c** as a colorless oil (235 mg, 71%). $R_f=0.30$; ^{1}H NMR (250 MHz, C_6D_6): $\delta=1.06$ (s, 3H, CH_3), 1.10 [s, 9H, $C(CH_3)_3$], 1.13–1.41 (m, 3H), 1.46 [s, 9H, $CO_2C(CH_3)_3$], 1.52–1.78 (m, 3H), 1.93–2.10 (m, 3H), 2.13–2.29 (m, 3H), 2.34–2.42 (m, 1H), 3.16 (m, 2H), 3.22 (m, 2H, CH_2Ph), 3.69 (t, $^3J=6.9$ Hz, 1H, 1″-H), 5.42–5.49 (m, 1H, 5″-H), 5.89 (d, $^3J=15.9$ Hz, 1H, 1-H), 7.11–7.23 (m, 3H, Ph), 7.31–7.42 (m, 2H, Ph), 8.04 (d, $^3J=15.9$ Hz, 1H, 3-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): $\delta=21.48$ (+, CH_3), 25.13 (−, CH_2), 28.24 [+, 3C, $C(CH_3)_3$], 28.87 [+, 3C, $CO_2C(CH_3)_3$], 29.07 (−, CH_2), 30.44 (−, CH_2), 31.08 (−, CH_2), 32.84 (−, CH_2), 34.39 (−, CH_2), 42.05 (C_{quat}, C-7a″), 44.45 (+, CH, C-3a″), 49.38 (−, CH_2), 62.78 (−, CH_2, CH_2Ph), 72.50 [C_{quat}, $C(CH_3)_3$], 76.65 (+, CH, C-1″), 79.30 [C_{quat}, $CO_2C(CH_3)_3$], 116.74 (+, CH, C-1), 126.89 (C_{quat}), 127.38 (+, CH, Ar), 128.39 (+, 2C, CH, Ar), 129.13 (+, 2C, CH, Ar), 132.33 (C_{quat}), 134.99 (+, CH), 139.06 (C_{quat}), 141.81 (+, CH), 147.82 (C_{quat}, Ar), 166.74 (C_{quat}, C=O); IR (film): $\tilde{\nu}$ = 3063, 2951 (C-H), 2915 (C-H)), 2843, 2839, 1711 (C=O), 1680, 1658, 1650, 1621 (C=C), 1564, 1503, 1478, 1469, 1450, 1366, 1158, 1144, 1111, 1025, 1018, 850, 767, 731, 672 cm^{-1}; MS (70 eV): *m*/*z* (%): 505 (43) [M^+], 448 (100) [$M^+-C_4H_9$], 432 (8), 404 (34), 392 (30) [$M^+-C_4H_8-C_4H_9$], 355 (4), 298 (12), 257 (4), 242 (8), 208 (2), 171 (1), 131 (3), 120 (8), 91 (85) [Bn^+], 57 (34) [$C_4H_9^+$], 41 (6); HRMS: *m*/*z*: calcd for $C_{33}H_{47}O_3N+H^+$ (506.7): 506.36306 (correct HRMS).

(*E*)-(1″*S*,3a″*S*,7a″S)-*tert*-Butyl 3-[1′-benzenesulfonyl-4′-(1″-*tert*-butoxy-7a″-methyl-2″,3″,3a″,6″,7″,7a″-hexahydro-1″*H*-indene-5″-yl)-1′,2′,5′,6′-tetrahydropyridine-3′-yl]acrylate (*trans*-5b): According to GP 4, to a solution of the bromobutadiene *trans*-**4b** (633 mg, 1.24 mmol) in DMF/CH_3CN/H_2O 5:5:1 (5 mL), 1,4-bis(diphenylphosphanyl)butane (15.9 mg, 37.3 µmol), palladacycle **8** (34.8 mg, 86.5 µmol) triethylamine (314 mg, 3.10 mmol) and *tert*-butyl acrylate (1.59 g, 12.4 mmol) were added. The resulting mixture was heated at 105°C for 8.5 h. Work-up with diethyl ether (55 mL), water (2×20 mL), back extraction with diethyl ether (2×25 mL), brine (30 mL) yielded after CC (40 g silica gel, pentane/diethyl ether 3:1) the hexatriene *trans*-**5b** as a colorless oil (586 g, 85%). $R_f=0.42$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.72$ (s, 3H, CH_3), 1.13 [s, 9H, $C(CH_3)_3$], 1.15–1.44 (m, 2H), 1.47 [s, 9H, $CO_2C(CH_3)_3$], 1.49–1.61 (m, 3H), 1.77–2.16 (m, 5H), 2.38 (m, 2H), 3.20 (t, $^3J=7.3$ Hz, 2H, 4′-H), 3.44 (dd, $^3J=8.8$, $^3J=8.3$ Hz, 1H, 1″-H), 3.73 (m, 2H), 5.32 (m, 1H, 1″-H), 5.58 (d, $^3J=15.7$ Hz, 1H, 2-H), 7.40–7.62 (m, 3H, Ph, 3-H), 7.76–7.82 (m, 2H, Ph); ^{13}C NMR (75.6 MHz, $CDCl_3$, APT): $\delta=11.21$ (+, CH_3), 24.32 (−, CH_2), 26.53 (−, CH_2), 28.13 [+, 3C, $C(CH_3)_3$], 28.63 [+, 3C, $CO_2C(CH_3)_3$], 29.88 (−, CH_2), 31.48 (−, CH_2), 33.62 (−, CH_2), 41.63 (−, C_{quat}, C-7a″), 42.59 (−, CH_2), 43.64 (+, CH, C-3a″), 44.66 (−, CH_2), 72.30 [−, C_{quat}, $C(CH_3)_3$], 79.03 (+, CH, C-1″), 80.29 [−, C_{quat}, $CO_2C(CH_3)_3$], 117.35 (+, CH, C-2), 123.90 (−, C_{quat}), 127.59 (+, 2C, Ph), 129.12 (+, 2C, Ph), 129.58 (+, CH), 132.88 (+, CH), 136.07 (−, C_{quat}), 136.18 (−, C_{quat}), 139.94 (+, CH), 146.64 (−, C_{quat}), 166.45 (−, C_{quat}, C=O); IR (film): $\tilde{\nu}$=3069, 2973 (C-H), 2938 (C-H)), 1960, 1911, 1817, 1716 (C=O), 1652, 1619 (C=C), 1446, 1436, 1360, 1263, 1203, 1035, 891, 850 cm^{-1}; MS (70 eV): *m*/*z* (%): 555 (3) [M^+], 499 (20) [$M^+-C_4H_8$], 454 (7), 442 (17) [$M^+-C_4H_9-C_4H_8$], 380 (9), 358 (21), 314 (9), 302 (25), 284 (18), 256 (17), 209 (11), 170 (5), 141 (8), 117 (2), 77 (29), 57 (100) [$C_4H_9^+$], 41 (29); HRMS: *m*/*z*: calcd for $C_{32}H_{45}O_5SN-H^+$ (556.8): 556.30912 (correct HRMS).

General procedure for the 6π-electrocyclization of the 1,3,5-hexatrienes *cis*-5a–c and *trans*-5b (GP 5): In a thick-walled Pyrex test tube, containing a magnetic stirring bar was charged with the respective hexatriene (1.00 equiv) in toluene/DMF 10:1. The test tube was sealed with a septum, and the solution was purged with argon in an ultrasonic bath for 10 min. The septum was replaced with a screw cap, and the solution was heated in a microwave oven at the stated temperature for the stated time. After the reaction mixture had cooled down to ambient temperature, it was concentrated (25 °C, 5 mbar), and the product purified by column chromatography (CC) on silica gel.

(6a*S*,7*S*,9a*R*,10*S*)-7-*tert*-Butoxy-6a-methyl-1,3,4,5,6,6a,7,8,9,9a,10,11-dodecahydro-1*H*-indeno[5,4-*f*]isoquinoline-2,10-dicarboxylic acid di-*tert*-butyl ester (*cis*-7a): According to GP 5, the hexatriene *cis*-**5a** (1.00 g, 1.94 mmol) was heated in toluene/DMF 10:1 (10 mL) at 170 °C for 45 min and at 200 °C for 2 min. Column chromatography on silica gel (40 g, pentane/Et_2O 5:1) afforded the steroid *cis*-**7a** as a colorless wax (595 mg, 60 %). $R_f=0.37$; ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.95$ (s, 3H, CH_3), 1.13 [s, 9H, $C(CH_3)_3$], 1.29–1.33 (m, 3H), 1.36 [s, 9H, $NCO_2C(CH_3)_3$], 1.42 [s, 9H, $CO_2C(CH_3)_3$], 1.45–1.60 (m, 1H), 1.89–2.32 (m, 6H), 2.72–2.80 (m, 1H), 3.11 (m, 1H), 3.48 (t, $^3J=5.4$ Hz, 1H, 7-H), 3.56–3.78 (m, 2H), 3.80–3.89 (m, 2H), 3.92–4.11 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, additional APT): $\delta=19.6$ (+, CH_3), 22.3 (–, CH_2), 28.0 (–, CH_2), 28.0 [+, 3C, $C(\mathit{C}H_3)_3$], 28.1 (–, CH_2), 28.2 (–, CH_2), 28.5 [+, 3C, $NCO_2C(\mathit{C}H_3)_3$], 28.6 [+, 3C, $CO_2C(\mathit{C}H_3)_3$], 29.0 (–, CH_2), 30.4 (–, CH_2), 30.5 (–, CH_2), 33.6 (–, CH_2), 42.2 (–, C_{quat}, C-6a), 42.9 (+, CH, C-10), 47.4 (+, CH, C-9a), 72.7 [–, C_{quat}, $\mathit{C}(CH_3)_3$], 79.4 [–, C_{quat}, $NCO_2\mathit{C}(CH_3)_3$], 79.8 (+, CH, C-7), 80.2 [–, C_{quat}, $CO_2\mathit{C}(CH_3)_3$], 124.0 (–, C_{quat}), 126.9 (–, 2C, C_{quat}), 130.8 (–, C_{quat}), 154.9 (–, C_{quat}, NC=O), 172.9 (–, C_{quat}, C=O); IR (film): $\tilde{\nu}=2975$ (C-H), 2932 (C-H), 2871 (C-H), 1700 (C=O), 1457, 1392, 1367, 1281, 1249, 1151, 1029, 995, 914, 881, 850, 772 cm^{-1}; MS (70 eV): *m*/*z* (%): 515 (1) [M^+], 459 (1) [$M^+-C_4H_8$], 402 (2) [$M^+-C_4H_8-C_4H_9$], 347 (2), 298 (1), 254 (1), 197 (1), 169 (1), 110 (1), 81 (1), 57 (100) [$C_4H_9^+$], 41 (24); HRMS: *m*/*z*: calcd for $C_{31}H_{49}NO_5$: 515.3611 (correct HRMS).

(6a*S*,7*S*,9a*R*,10*R*)-*tert*-Butyl 2-benzenesulfonyl-7-*tert*-butoxy-6a-methyl-2,3,4,5,6,6a,7,8,9,9a,10,11-dodecahydro-1*H*-indeno[5,4-*f*]isoquinoline-10-carboxylate (*cis*-7b): According to GP 5, the hexatriene *cis*-**5b** (250 mg, 0.450 mmol) was heated in toluene (5.00 mL) at 170 °C for 45 min and at 200 °C for 1.0 min. Column chromatography (20 g silica gel, pentane/diethyl ether 3:1) afforded the steroid *cis*-**7b** as a colorless wax (172 mg, 69 %). $R_f=0.27$; ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.86$ (s, 3H, CH_3), 1.13 [s, 9H, $C(CH_3)_3$], 1.14–1.24 (m, 2H), 1.26 [s, 9H, $CO_2C(CH_3)_3$], 1.30–1.57 (m, 3H), 1.83–2.42 (m, 8H), 2.63–2.76 (m, 2H), 3.24–3.36 (m, 1H), 3.45 (t, $^3J=5.6$ Hz, 1H, 7-H), 3.59–3.67 (m, 1H), 3.69–3.79 (m, 1H), 7.46–7.60 (m, 3H, Ph), 7.74–7.82 (m, 2H, Ph); ^{13}C NMR (75.6 MHz, C_6D_6, additional APT): $\delta=19.55$ (+, CH_3), 22.13 (–, CH_2), 24.48 (–, CH_2), 27.93 [+, 3C, $C(\mathit{C}H_3)_3$], 28.57 [+, 3C, $CO_2C(\mathit{C}H_3)_3$], 28.73 (–, CH_2), 30.19 (–, CH_2), 30.44 (–, CH_2), 33.50 (–, CH_2), 42.20 (–, C_{quat}, C-6a), 42.56 (+, CH, C-10), 43.31 (–, CH_2), 47.20 (+, CH, C-9a), 47.89 (–, CH_2), 72.68 [–, C_{quat}, $\mathit{C}(CH_3)_3$], 79.64 (+, CH, C-17), 80.25 [–, C_{quat}, $CO_2\mathit{C}(CH_3)_3$], 122.33 (–, C_{quat}), 126.34 (–, C_{quat}), 126.43 (–, C_{quat}), 127.62 (+, CH, 2C, Ph), 128.98 (+, CH, 2C, Ph), 131.17 (–, C_{quat}), 132.66 (+, CH, Ph), 136.29 (–, C_{quat}, Ph), 172.55 (–, C_{quat}, C=O); IR (film): $\tilde{\nu}=3078$, 3032, 2956 (C-H), 2909, 2884 (C-H), 1734 (C=O), 1669, 1623, 1576, 1559, 1533, 1465, 1437, 1394, 1339, 1103, 1069, 874, 832, 754 cm^{-1}; MS (70 eV): *m*/*z* (%): 555 (14) [M^+], 499 (62) [$M^+-C_4H_8$], 498 (54) [$M^+-C_4H_9$], 454 (56), 443 (72) [$M^+-2\times C_4H_8$], 442 (72) [$M^+-C_4H_8-C_4H_9$], 424 (28), 398 (18), 358 (61), 349 (9), 302 (79), 256 (24), 209 (26), 169 (11), 141 (9), 77 (21) [Ph^+], 57 (100) [$C_4H_9^+$], 41 (24); HRMS: *m*/*z*: calcd for $C_{32}H_{45}O_5NS+NH_4^+$ (573.7): 573.33572 (correct HRMS).

(6a*S*,7*S*,9a*R*,10*R*)-*tert*-Butyl 2-benzyl-7-*tert*-butoxy-6a-methyl-2,3,4,5,6,6a,7,8,9,9a,10,11-dodecahydro-1*H*-indeno[5,4-*f*]isoquinoline-10-carboxylate (*cis*-7c): According to GP 5, the hexatriene *cis*-**5c** (400 mg, 0.791 mmol) was heated in toluene (10.0 mL) at 170 °C for 45 min and at 200 °C for 1 min. Column chromatography (20 g silica gel, pentane/diethyl ether 3:1) afforded the steroid *cis*-**7c** as colorless wax (237 mg, 59 %). $R_f=0.33$; ^1H NMR (250 MHz, $CDCl_3$): $\delta=0.91$ (s, 3H, CH_3), 1.18 [s, 9H, $C(CH_3)_3$], 1.21–1.37 (m, 3H), 1.41 [s, 9H, $CO_2C(CH_3)_3$], 1.42–1.63 (m, 3H), 1.87–2.38 (m, 8H), 2.72–2.92 (m, 3H), 3.00-3.15 (m, 1H), 3.47 (dd, $^3J_1=5.7$ Hz, $^3J_2=5.3$ Hz, 1H, 7-H), 3.58 (d, $^3J=7.6$ Hz, 2H, $\mathit{C}H_2Ph$), 7.22–7.40 (m, 5H, Ph); ^{13}C NMR (75.6 MHz, $CDCl_3$, additional APT): $\delta=19.74$ (+, CH_3), 22.05 (–, CH_2), 25.50 (–, CH_2), 28.04 [+, 3C, $C(\mathit{C}H_3)_3$], 28.60 [+, 3C, $CO_2C(\mathit{C}H_3)_3$], 29.37 (–, CH_2), 30.42 (–, CH_2), 30.43 (–, CH_2), 33.56 (–, CH_2), 42.19 (–, C_{quat}, C-6a), 43.00 (+, CH, C-10), 47.31 (+, CH, C-9a), 50.31 (–, CH_2), 56.75 (–, CH_2), 62.72 (–, CH_2, $\mathit{C}H_2Ph$), 72.62 [–, C_{quat}, $\mathit{C}(CH_3)_3$], 79.56 (+, CH, C-17), 80.01 [–, C_{quat}, $CO_2\mathit{C}(CH_3)_3$], 124.88 (–, C_{quat}), 126.50 (–, C_{quat}), 126.98 (+, CH, Ph), 127.22 (–, C_{quat}), 128.18 (+, CH, 2C, Ph), 129.17 (+, CH, 2C, Ph), 129.26 (–, C_{quat}), 130.01 (+, CH, Ph), 173.37 (–, C_{quat}, C=O); IR (film): $\tilde{\nu}=3062$ (C-H), 3029, 2972 (C-H), 2928, 2871 (C-H), 1718 (C=O), 1653, 1636, 1617, 1472, 1456, 1389, 1366, 1265, 1251, 1229, 1198, 1152, 1095, 1055, 1027, 944, 911, 850, 735, 699 cm^{-1}; MS (70 eV): *m*/*z* (%): 505 (100) [M^+], 503 (5), 448 (94) [$M^+-C_4H_9$], 402 (19), 392 (38) [$M^+-C_4H_8-C_4H_9$], 346 (3), 334 (12), 288 (2), 248 (2), 229 (1), 169 (2), 134 (4), 120 (9), 91 (55) [Bn^+], 84 (4), 57 (12) [$C_4H_9^+$], 41 (2); HRMS: *m*/*z*: calcd for $C_{33}H_{47}O_3N$: 505.3555 (correct HRMS).

(6a*S*,7*S*,9a*S*,10*S*)-*tert*-Butyl 2-benzenesulfonyl-7-*tert*-butoxy-6a-methyl-2,3,4,5,6,6a,7,8,9,9a,9b,10-dodecahydro-1*H*-indeno[5,4-*f*]isoquinoline-10-carboxylate (*trans*-7b): According to GP 5, the hexatriene *trans*-**5b** (305 mg, 0.549 mmol) was heated in toluene (5.00 mL) at 170 °C for 45 min and at 200 °C for 1.0 min. Column chromatography (30 g silica gel, pentane/diethyl ether 3:1) afforded the steroid *trans*-**7b** as a colorless wax (168 mg, 55 %). $R_f=0.21$; ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.63$ (s, 3H, CH_3), 1.12 [s, 9H, $C(CH_3)_3$], 1.27 [s, 9H, $CO_2C(CH_3)_3$], 1.37–1.72 (m, 4H), 1.75–2.40 (m, 8H), 2.69 (m, 1H), 2.82 (m, 1H), 3.23 (d, $^3J=16.8$ Hz, 1H), 3.47 (t, $^3J=5.9$ Hz, 1H, 7-H), 3.51–3.59 (m, 1H), 3.67 (d, $^3J=16.8$ Hz, 1H), 5.55 (m, 1H, 11-H), 7.45–7.60 (m, 3H, Ph), 7.75–7.80 (m, 2H, Ph); ^{13}C NMR (75.6 MHz, $CDCl_3$, APT): $\delta=11.45$ (+, CH_3), 23.90 (–, CH_2), 24.83 (–, CH_2), 27.98 [+, 3C, $C(\mathit{C}H_3)_3$], 28.68 [+, 3C, $CO_2C(\mathit{C}H_3)_3$], 31.07 (–, CH_2), 31.21 (–, CH_2), 38.99 (–, CH_2), 40.36 (+, CH, C-9a), 40.50 (+, CH, C-9b), 41.54 (–, C_{quat}, C-6a), 43.18 (+, CH, C-10), 43.40 (–, CH_2), 48.54 (–, CH_2), 72.24 [–, C_{quat}, $\mathit{C}(CH_3)_3$], 80.12 (+, CH, C-7), 80.53 [–, C_{quat}, $CO_2\mathit{C}(CH_3)_3$], 120.45 (+, CH, C-10), 124.35 (–, C_{quat}), 125.72 (–, C_{quat}), 127.70 (+, CH, 2C, Ph), 128.94 (+, CH, 2C, Ph), 133.69 (–, C_{quat}), 132.84 (+, CH, Ph), 136.06 (–, C_{quat}, Ph), 172.44 (–, C_{quat}, C=O); IR (film): $\tilde{\nu}=3070$, 3035, 2952 (C-H), 2901, 2883 (C-H), 1729 (C=O), 1672, 1620, 1579, 1564, 1554, 1547, 1461, 1441, 1434, 1394, 1109, 1059, 878, 754 cm^{-1}; ESI-MS (MeOH): *m*/*z* (%): 1128 (100) [$2M+NH_4^+$], 1126 (45), 968 (8), 573 (21), 500 (7); HRMS: *m*/*z*: calcd for $C_{32}H_{45}O_5NS+NH_4^+$: 573.33557 (correct HRMS).

General procedure for the deprotection of steroids *cis*-7a–c (GP 6): In a Schlenk flask sealed with a septum containing a magnetic stirring bar, was placed the respective steroid (1.00 equiv) in toluene. The resulting solution was treated with borontrifluoride etherate (3.00–3.50 equiv) at 0 °C for 1 h and at 22 °C for 3 h. When the reaction had ceased, the mixture was poured into methanol/water 5:1 (2 mL), concentrated in vacuo, and the product purified by column chromatography (CC) on reverse phase silica gel.

(–)-(6a*S*,9b*R*,7*S*,10*S*)-7-Hydroxy-6a-methyl-2,3,4,5,6,6a,7,8,9,9a,10,11-dodecahydro-1*H*-indeno[5,4-*f*]isoquinoline-10-carboxylic acid (*cis*-9a): According to GP 6, the steroid *cis*-**7a** (146 mg, 0.283 mmol) was treated with borontrifluoride etherate (133 mg, 0.936 mmol) in toluene (5 mL). CC on reverse phase silica gel (20 g, methanol/H_2O 1:1) afforded the free steroidal amino acid *cis*-**9a** as a colorless solid (65.3 mg, 76 %). $R_f=0.42$; m.p. 186–188 °C; $[\alpha]_D^{20}=-34.3$ ($c=0.53$, MeOH); ^1H NMR (300 MHz, D_2O): $\delta=0.98$ (s, 3H, CH_3), 1.34–1.50 (m, 3H), 1.56–1.71 (m, 1H), 2.04–2.67 (m, 9H), 3.03–3.11 (m, 1H, 10-H), 3.29–3.51 (m, 2H, 3-H), 3.73 (m, 2H, 1-H), 3.84 (dd, $^3J=5.6$, $^3J=4.4$ Hz, 1H, 7-H); ^1H NMR (600 MHz, D_2O): $\delta=0.97$ (s, 3H, CH_3), 1.36–1.46 (m, 3H), 1.59–1.68 (m, 1H), 2.07–2.16 (m, 1H), 2.19–2.34 (m, 4H), 2.36–2.48 (m, 3H), 2.53–2.63 (m, 1H), 3.02–3.08 (m, 1H, 10-H), 3.30–3.39 (m, 1H, 3-H), 3.42–3.48 (m, 1H, 3-H), 3.72 (q, $^3J=18.7$, 2H, 1-H), 3.84 (dd, $^3J=5.9$, $^3J=4.1$ Hz, 1H, 7-H); ^{13}C NMR (75.5 MHz, D_2O, additional APT): $\delta=18.1$ (+, CH_3), 21.1 (–, CH_2), 21.6 (–, CH_2), 29.2 (–, CH_2), 29.5 (–, CH_2), 29.8 (–, CH_2), 31.5 (–, CH_2), 41.6 (–, CH_2), 42.8 (–, C_{quat}, C-6a), 44.3 (+, CH, C-9a), 44.7 (–, CH_2, C-1), 46.7 (+, CH, C-10), 80.9 (+, CH, C-7), 118.9 (–, C_{quat}), 125.6 (−, C_{quat}), 126.7 (−, C_{quat}), 134.0 (−, C_{quat}), 181.31 (−, C_{quat}, C=O); IR (film): $\tilde{\nu}$ = 3302 (OH), 3041, 2956 (C-H), 2904, 2861 (C-H), 2529, 2337, 1684 (C=O), 1663, 1646, 1569, 1554, 1521, 1472, 1457, 1382, 1362, 1289, 1146, 1027, 901, 832, 807, 721 cm^{-1}; MS (70 eV): *m/z* (%): 303 (3) [M^+], 259 (2), 225 (1), 184 (1), 158 (1), 123 (2), 105 (1), 95 (5), 77 (3), 75 (4), 56 (16), 44 (100), 41 (14); ESI-MS (MeOH): *m/z* (%): 1186 (10), 800 (8), 695 (29), 414 (9), 304 (100) [M+H^+], 243 (20); HRMS: *m/z*: calcd for $C_{18}H_{25}NO_3$ (303.4): 303.1834 (correct HRMS).

(+)-(6a*S*,7*S*,9a*S*,10*S*)-2-Benzenesulfonyl-7-hydroxy-6a-methyl-2,3,4,5,6,6a,7,8,9,9a,10,11-dodecahydro-1*H*-indeno[5,4-*f*]isoquinoline-10-carboxylic acid (*cis*-9b): According to GP 6, the steroid *cis*-**7b** (100 mg, 0.180 mmol) was treated with borontrifluoride etherate (66.4 mg, 75.0 µl, 0.468 mmol) in toluene (4.0 mL). CC (23 g silica gel, $CHCl_3$/EtOAc/MeOH 10:10:2) afforded the steroidal sulfonamide *cis*-**9b** as colorless solid (68.7 mg, 86%). R_f = 0.35; m.p. 197–198 °C; $[\alpha]_D^{20}$ = +8.2 (*c* = 0.45, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (s, 3H, CH_3), 1.07–1.22 (m, 2H), 1.30–1.71 (m, 1H), 1.83–2.52 (m, 9H), 2.77 (m, 1H), 2.82–2.93 (m, 1H), 3.32–3.41 (m, 1H), 3.58 (m, 1H), 3.61–3.80 (m, 3H), 5.23 (brs, 1H, 7-OH), 7.40–7.64 (m, 3H, Ph), 7.69–7.84 (m, 2H, Ph), ^{13}C NMR (75.5 MHz, $CDCl_3$, additional APT): δ = 17.29 (+, CH_3), 22.04 (−, CH_2), 24.66 (−, CH_2), 28.18 (−, CH_2), 28.73 (−, CH_2), 30.44 (−, CH_2), 32.19 (−, CH_2), 41.47 (+, CH, C-9a), 43.13 (−, CH_2), 43.60 (−, C_{quat}, C-6a), 45.93 (+, CH, C-10), 47.69 (−, CH_2, C-1), 81.67 (+, CH, C-7), 122.57 (−, C_{quat}), 126.35 (−, C_{quat}), 126.95 (−, C_{quat}), 127.60 (+, 2C, CH, Ph), 129.04 (+, 2C, CH, Ph), 129.52 (−, C_{quat}), 132.75 (+, CH, Ph), 136.34 (−, C_{quat}, Ph), 177.56 (−, C_{quat}, C=O); IR (film): $\tilde{\nu}$ = 3260 (OH), 3056, 2948 (C-H), 1700 (C=O), 1695, 1646, 1456, 1387, 1362, 1253, 1192, 1034, 993, 911, 882, 848, 773 cm^{-1}; MS (70 eV): *m/z* (%): 441 (2), 413 (1), 396 (6), 364 (2), 347 (6), 334 (8), 299 (18), 272 (12), 255 (100), 253 (38), 222 (12), 209 (17), 194 (42), 180 (30), 168 (20), 143 (14), 91 (10), 77 (48), 44 (17), 42 (10); HRMS: *m/z*: calcd for $C_{24}H_{29}O_5NS$+H^+ (444.1): 444.18424 (correct HRMS).

(−)-(6a*S*,7*S*,9a*S*,10*S*)-2-Benzyl-7-hydroxy-6a-methyl-2,3,4,5,6,6a,7,8,9,9a,10,11-dodecahydro-1*H*-indeno[5,4-*f*]isoquinoline-10-carboxylic acid (*cis*-9c): According to GP 6 the steroid *cis*-**7c** (240 mg, 0.475 mmol) was treated with boron trifluoride etherate (177 mg, 0.200 mL, 1.25 mmol) in toluene (10 mL). CC on reverse phase silica (20 g, methanol/water 1:1) afforded the steroidal amino acid *cis*-**9c** as colorless solid (148 mg, 79%). R_f = 0.35; m.p. 179–181 °C; $[\alpha]_D^{20}$ = −3.3 (*c* = 0.86, MeOH); ^{1}H NMR (300 MHz, d_4-MeOH): δ = 0.97 (s, 3H, CH_3), 1.28–1.45 (m, 2H), 1.52–1.70 (m, 1H), 1.97–2.49 (m, 9H), 2.52–2.71 (m, 3H), 2.98 (m, 1H), 3.58–3.75 (m, 3H), 4.37 (s, 2H, $PhCH_2$), 7.40–7.61 (m, 5H, Ar); ^{13}C NMR (75.6 MHz, d_4-MeOH, additional APT): δ = 18.47 (+, CH_3), 22.94 (−, CH_2), 23.00 (−, CH_2), 29.08 (−, CH_2), 30.55 (−, CH_2), 31.25 (−, CH_2), 33.00 (−, CH_2), 42.74 (+, CH, C-9a), 44.41 (−, C_{quat}, C-6a), 47.75 (+, CH, C-10), 50.31 (−, CH_2), 53.77 (−, CH_2, C-1), 60.48 (−, CH_2, $PhCH_2$), 81.68 (+, CH, C-7), 120.37 (−, C_{quat}), 127.07 (−, C_{quat}), 127.85 (−, C_{quat}), 130.43 (+, 2C, CH, Ph), 130.58 (−, C_{quat}), 131.25 (+, CH, Ph), 132.24 (+, 2C, CH, Ph), 134.35 (−, C_{quat}, Ph), 176.55 (−, C_{quat}, C=O); IR (film): $\tilde{\nu}$ = 3262 (OH), 3091, 3064, 2952 (C-H), 2926, 2873 (C-H), 1739, 1701 (C=O), 1653, 1597, 1572, 1495, 1447, 1388, 1370, 1347, 1248, 1205, 1167, 1082, 1048, 981, 960, 924, 891, 845, 790, 747 cm^{-1}; DCI-MS (NH_3): *m/z* (%): 394 (14) [M+H^+], 348 (100), 289 (3), 272 (9), 256 (20), 254 (10), 198 (1), 134 (2), 106 (4), 91 (1) [Bn^+]; HRMS: *m/z*: calcd for $C_{25}H_{31}O_3N$+H^+ (394.5): 394.23674 (correct HRMS).

Acknowledgements

This work was supported by the State of Niedersachsen as well as the companies BASF AG, Schering AG and Chemetall GmbH (Chemicals). H.W.S. is indebted to the German Merit Foundation (Studienstiftung des Deutschen Volkes) for a graduate student fellowship. The authors are grateful to Dr. Burkhard Knieriem, Göttingen, for his careful proof-reading of the final manuscript.

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[1] E. Danieli, A. Trabocchi, G. Menchi, A. Guarna, *Eur. J. Org. Chem.* **2005**, 4372–4381.

[2] a) J. Gante, *Angew. Chem.* **1994**, *106*, 1780–1802; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699–1720; b) A. Giannis, T. Kolter, *Angew. Chem.* **1993**, *105*, 1303–1326; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244–1267.

[3] a) A. E. Pojitkov, E. N. Efremenko, S. D. Varfolomeev, *J. Mol. Catal. B* **2000**, *10*, 47–55; b) B. Ayers, U. K. Blaschke, J. A. Camarero, G. J. Cotton, M. Holford, T. W. Muir, *Biopolymers* **1999**, *51*, 343–354.

[4] D. Seebach, *Peptides: The Wave of the Future* (Eds.: M. Lebl, R. A. Houghten), American Peptide Society **2001**, pp. 569–571.

[5] a) A. Trabocchi, F. Guarna, A. Guarna, *Curr. Org. Chem.* **2005**, *9*, 1127–1153; b) H.-D. Arndt, A. Knoll, U. Koert, *Angew. Chem.* **2001**, *113*, 2137–2140; *Angew. Chem. Int. Ed.* **2001**, *40*, 2076–2078.

[6] a) L. Szabo, B. L. Smith, K. D. McReynolds, A. L. Parill, E. R. Morris, J. Gervay, *J. Org. Chem.* **1998**, *63*, 1074–1078; b) S. Hannessian, X. Luo, R. Schaum, S. Michnick, *J. Am. Chem. Soc.* **1998**, *120*, 8569–8570; c) T. Hintermann, K. Gademann, B. Jaun, D. Seebach, *Helv. Chim. Acta* **1998**, *81*, 983–1002; d) C. Baldauf, R. Günther, H.-J. Hofmann, *J. Org. Chem.* **2004**, *69*, 6214–6220; e) M. Kuwahara, M. Arimitsu, M. Sisido, *Tetrahedron* **1999**, *55*, 10067–10078.

[7] a) P. v. Zezschwitz, F. Petry, A. de Meijere, *Chem. Eur. J.* **2001**, *7*, 4035–4046; b) H. W. Sünnemann, A. de Meijere, *Angew. Chem.* **2004**, *116*, 913–915; *Angew. Chem. Int. Ed.* **2004**, *43*, 895–897.

[8] The bromoenol triflates were assembled from the *N*-substituted 4-piperidones, to the corresponding trimethylsilyl enol ethers via the α-bromopiperidinones **1a–c** using very economical conditions based on trifluoromethanesulfonic acid anhydride and triethylamine: a) A. Boumendjel, J. C. Roberts, P. E. Hu, *J. Org. Chem.* **1996**, *61*, 4434–4438; b) J. Castro, I. Collins, M. G. N. Russell, A. P. Watt, B. Sohal, *J. Med. Chem.* **1998**, *41*, 2667–2670; c) W. J. Kerr, M. Mc Laughlin, A. J. Morrison, P. L. Pauson, *Org. Lett.* **2001**, *3*, 2945–2948; d) K. A. Parker, H. J. Kim, *J. Org. Chem.* **1992**, *57*, 752–755; e) K. Ritter, *Synthesis* **1993**, 735–762.

[9] The use of different amide bases such as NaHMDS or LiHMDS for an improved regioselectivity during the enolate formation in α-bromopiperidinone **1b**,**c** led to complete decomposition of the substrates.

[10] CCDC-605599 (**2b**) contains the supplementary crystallographic data for compound **2b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif/

[11] The addition of rate enhancing ligands such as $AsPh_3$ and (2-furyl)$_3$P in significant amounts to the catalytic cocktail led to an increased formation of side products.

[12] For reviews on the Stille reaction see: a) T. N. Mitchell, in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, pp. 167–202; b) V. Farina, V. Krishnamurthy, W. J. Scott, *Organic Reactions, Vol. 50* (Ed.: L. A. Paquette), Wiley, New York, **1997**; c) T. N. Mitchell, *Synthesis* **1992**, 803–815; d) M. Kosugi, K. Fugami, in *Handbook of Organopalladium Chemistry for Organic Synthesis* (Eds.: E. Negishi, A. de Meijere), Wiley, New York, **2002**, pp. 263–284.

[13] The palladacycle was prepared from $Pd(OAc)_2$ and (*o*Tol)$_3$P: a) W. A. Herrmann, C. Brossmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem.* **1995**, *107*, 1989–1992; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1844–1848; b) W. A. Herrmann, C. Brossmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, *Chem. Eur. J.* **1997**, *3*, 1357–1364; for reviews on the application of palladacycles in Heck couplings see: c) J. Dupont, C. S. Consorti, J. Spencer, *Chem. Rev.* **2005**, *105*, 2527–2571; d) W. A. Herrmann, V. P. W. Böhm, C.-P. Reisinger, *J. Organomet. Chem.* **1999**, *576*, 23–41; e) V. Farina, *Adv. Synth. Catal.* **2004**, *346*, 1553–1582.

[14] (*o*Tol)$_3$P as co-ligand also allows for a decreased loading of the precatalyst necessary for the full consumption of bromobutadienes *cis*-**4a–c** and *trans*-**4b** in Heck reactions providing higher yields for hexatrienes *cis*-**5a–c** and *trans*-**5b** at the same time.

[15] a) L. Botella, C. Nájera, *Tetrahedron* **2004**, *60*, 5563–5570; b) F. Ozawa, A. Kubo, T. Hayaschi, *Chem. Lett.* **1992**, 2177–2180; c) S. Lemaire-Audoire, M. Savignac, C. Dupuis, J.-P. Genêt, *Tetrahedron Lett.* **1996**, *37*, 2003–2006; d) F. Y. Zhao, M. Shirai, M. Arai, *J. Mol. Catal. A* **2000**, *154*, 39–44; e) L. F. Tietze, T. Nöbel, M. Spescha, *Angew. Chem.* **1996**, *108*, 2385–2386; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2259–2261.

[16] a) T. L. Gilchrist, R. J. Summersell, *J. Chem. Soc. Perkin Trans. 1* **1988**, 2595–2601; b) R. von Essen, D. Frank, H. W. Sünnemann, D. Vidovic, J. Magull, A. de Meijere, *Chem. Eur. J.* **2005**, *11*, 6583–6592.

[17] Another remarkable feature of certain 3-azasteroids is their ability to act as inhibitors of 5α-reductase which converts testosterone to 5α-dihydrotestosterone in androgen sensitive cells: a) A. J. Robinson, I. DeLucca, S. Drummond, G. A. Boswell, *Tetrahedron Lett.* **2003**, *44*, 4801–4804; b) G. H. Rasmusson, G. F. Reynolds, T. Utne, R. B. Jobson, L. Raymond, *J. Med. Chem.* **1984**, *27*, 1690–1701.

[18] a) M. Baumgarth, K. Irmscher, *Tetrahedron* **1975**, *31*, 3109–3118; b) M. D. Ferreira, J. I. Fernando, J. I. Moral, S. Arseniyadis, *Tetrahedron: Asymmetry* **1999**, *10*, 1527–1537.

[19] The structure of the δ-amino acid *trans*-**6b** was confirmed by ^{1}H–^{1}H NOESY NMR experiments in which interactions beween the protons of the methyl group at C13 and the proton at C8 as well as between the proton at C7 and the proton at C8 were observed.

[20] CCDC-605600 (**7b**) contains the supplementary crystallographic data for compound **7b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif/

[21] a) B. M. Trost, P. G. Mc Dougal, *J. Org. Chem.* **1984**, *49*, 458–468; this rotational selectivity has also been termed torquoselectivity. Cf. b) E. A. Kallel, Y. Wang, D. C. Spellmeyer, K. N. Houk, *J. Am. Chem. Soc.* **1990**, *112*, 6759–6763; c) J. D. Evanseck, B. E. Thomas IV, D. C. Spellmeyer, K. N. Houk, *J. Org. Chem.* **1995**, *60*, 7134–7141.

[22] J. Castro, I Collins, M. G. N. Russell, A. P. Watt, B. Sohal, *J. Med. Chem.* **1998**, *41*, 2667–2670.

[23] A. Gangjee, E. Elzein, S. F. Queener, J. J. McGuire, *J. Med. Chem.* **1998**, *41*, 1409–1416.

[24] A. Boumendjel, J. C. Roberts, P. E. Hu, *J. Org. Chem.* **1996**, *61*, 4434–4438.

Received: July 25, 2006