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Efficient synthesis of cephalotaxine- and deoxyharringtonine analogues by a trimethylaluminium-mediated domino reaction☆

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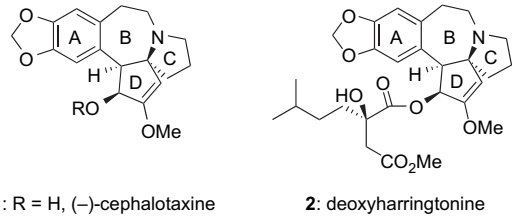
Abstract—The synthesis of cephalotaxine- and cephalotaxine amide analogues **14a–c** and **16a–c** as well as of the deoxyharringtonine analogues **5a**,**b** was performed employing a trimethylaluminium-mediated domino reaction of **9a–c** and **8** to give the spirocyclic compounds **7a–c**, which was followed by a palladium catalyzed α-arylation.

1. Introduction

The development of highly efficient syntheses of natural products and their analogues is one of the major goals in modern preparative organic chemistry. One way to improve the efficiency is the use of domino reactions, which has been very successful so far.[1]

In domino reactions, bonds and new functionalities are formed, which, in turn, react further in subsequent steps under identical conditions. This allows the formation of complex molecules starting from simple substrates. Here we describe the synthesis of cephalotaxine- and harringtonine analogues applying a trimethylaluminium-mediated domino reaction.

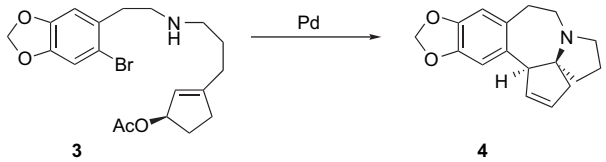
Cephalotaxine (**1**) is the major alkaloid found in the evergreen plum yews *Cephalotaxus*, which are indigenous in South-east Asia. Whereas cephalotaxine (**1**) itself has no pronounced biological activity its 2-alkylhydroxysuccinates have a strong antileukaemic activity with deoxyharringtonine (**2**) possessing the highest IC_{50} value against leukaemic cells[2] (Scheme 1).



1: R = H, (–)-cephalotaxine **2**: deoxyharringtonine

Scheme 1. Cephalotaxine (**1**) and deoxyharringtonine (**2**).

Recently we have described a highly efficient total synthesis of (−)-cephalotaxine (**1**), using two subsequent Pd-catalyzed reactions, namely a Tsuji–Trost- and a Heck-reaction with **3** as a substrate to give the pentacycle **4**[1] (Scheme 2).



3 **4**

Scheme 2. Domino-Tsuji–Trost–Heck-reaction for the synthesis of **3** to give **4**.

Now we wish to report a novel, even shorter approach towards cephalotaxine- and deoxyharringtonine analogues **14a–c**, **5a** and **5b**. Besides the naturally occurring 5,6,7,5,5-skeleton we also were able to synthesize pentacycles with a 5,6,6,5,5- and a 5,6,5,5,5-ring system. The latter type could not be synthesized using the domino-Tsuji–Trost–Heck-approach.

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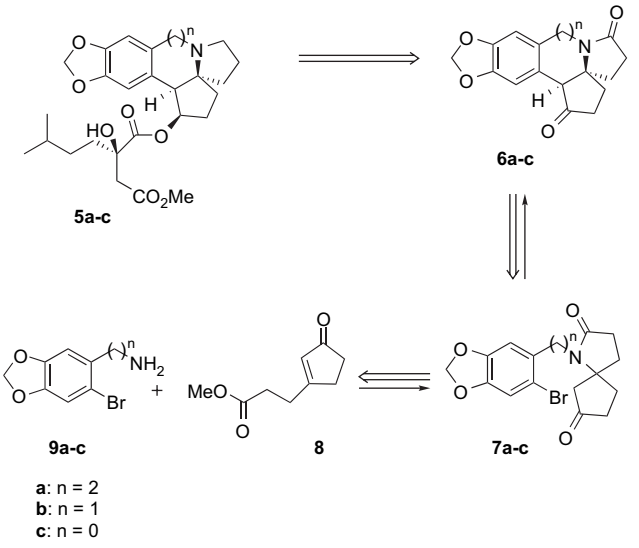
The key reaction of our new synthesis is a trimethylaluminium-mediated domino reaction, which was developed in our group.[3] In this reaction, an amine is transformed into its aluminium amide and further on by an intermolecular reaction with an ester moiety into a metallated carboxylic acid amide, which reacts in an intramolecular mode with an enone moiety present in the molecule. The final product is a spirocyclic lactam. According to Scheme 3, the retrosynthesis of **5a–c** and the cephalotaxine derivatives **6a–c** leads to the ester **8**[4] and the amines **9a–c**[5] via the spirocyclic lactams **7a–c**.



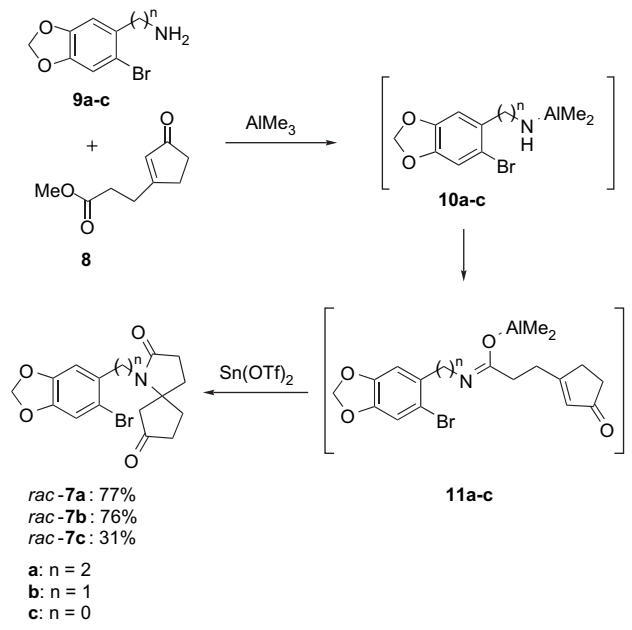
Scheme 3. Retrosynthetic analysis of **5** and **6**.

2. Results and discussion

Reaction of the ester **8** and the amines **9a–c** in the presence of trimethylaluminium afforded the spirononanes **7a–c** in 77%, 76% and 31% yield, respectively. The low yield of **7c** is probably due to the diminished nucleophilicity of the aniline moiety. Several reaction conditions were tested, the best results were obtained using 1.0 equiv of the ester **8** with 2.0 equiv of the amines **9a–c** and 2.08 equiv of trimethylaluminium in acetonitrile as a solvent and tin(II)triflate[6] as a catalyst. In former times we have performed similar reactions without the addition of the Lewis acid. However, this transformation was not reliable leading to the desired products in varying yields. It can be assumed that the Lewis acid interacts with the enone moiety to accelerate the Michael addition. For the domino reaction, we propose the following mechanism. After addition of trimethylaluminium to the amine, a Lewis acid/Lewis base complex is formed, which, after heating to 80 °C, forms the aluminium amides **10a–c**. This has been confirmed by online NMR spectroscopy at different temperatures (Scheme 4).

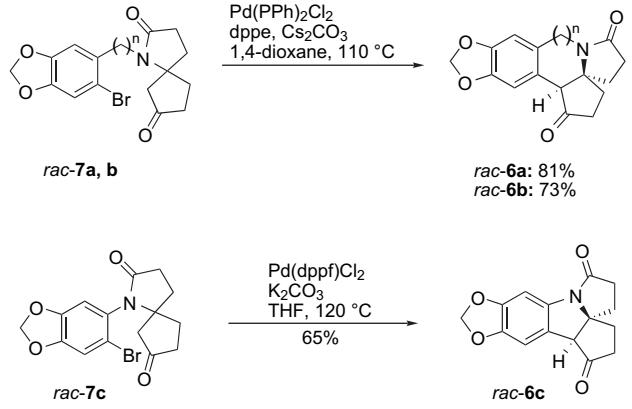
The aluminium amides **10a–c** react with the ester **8** to form the carboxylic acid amide aluminium azaenolates **11a–c**, which undergo an intramolecular Michael reaction with formation of the spiro compounds **7a–c**.

The closure of the C-ring was performed by a palladium catalyzed α-arylation[7] of the keto functionality. Our initial



Scheme 4. Mechanism of the spirocyclization.

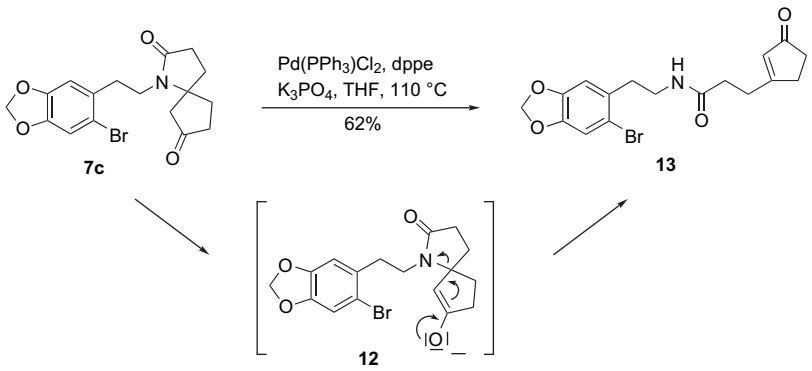
attempts using $Pd(PPh_3)_2Cl_2$ as a catalyst, Cs_2CO_3 as a base and THF as a solvent led to unsatisfactory results. Changing the solvent to 1,4-dioxane and adding dppe as ligand improved the yields for **6a** and **6b** to 81% and 73%, respectively. For **6c**, the catalyst was changed to $Pd(dppf)Cl_2$ and K_2CO_3 was used as a base increasing the yield from initial 22% to 65% (Scheme 5).



Scheme 5. Palladium catalyzed α-arylation of the spirocycles **7a–c**.

Surprisingly, the use of K_3PO_4[7d] as a base, as proposed by Buchwald for this type of reaction, led to a rearrangement of the spirocycle **7a** to give the corresponding carboxylic acid amide **13**. Under these conditions, the formation of the enolate **12** seemed to be faster than the oxidative addition with Pd to allow the elimination of the amide moiety in **12** as the preferred reaction channel (Scheme 6).

For the synthesis of the desired cephalotaxine analogues **14a–c** and **16a–c**, it was necessary to reduce the keto function and to transform the lactam moiety into a tertiary alcohol function. The reagent of choice for these transformations is $LiAlH_4$. Thus, under these conditions, the lactam **6a** led to **14a** as a single diastereomer in 83% yield. Surprisingly, **6b**

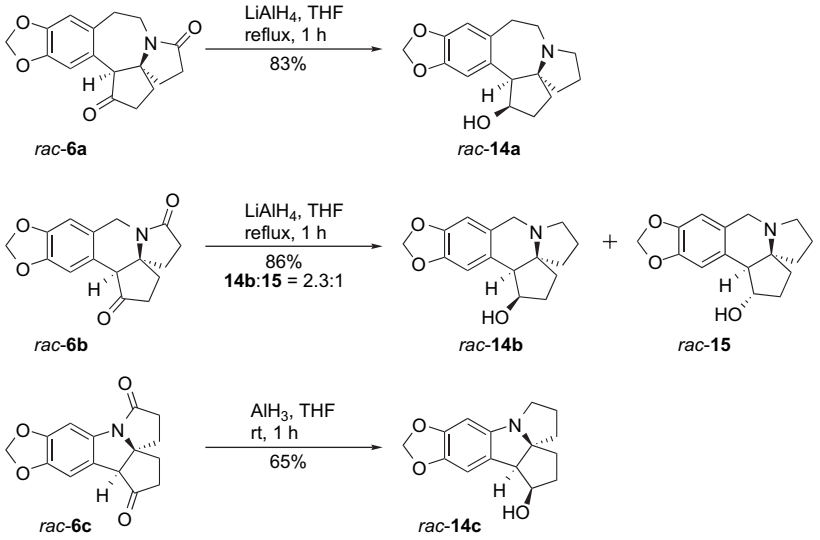


Scheme 6. Rearrangement of spirocycle **7c** into the amide **13**.

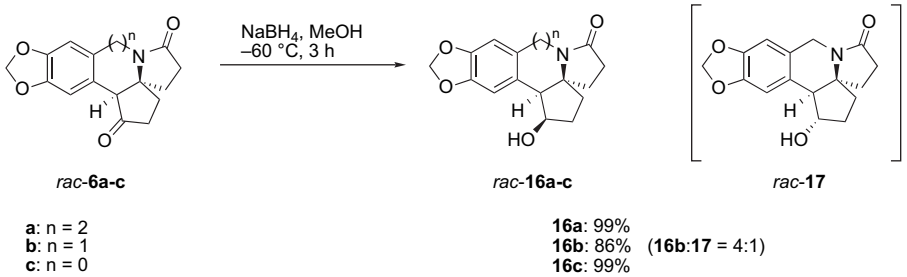
gave a 2.3:1 mixture of the expected isomer **14b** and **15** in 86% yield, whereas **6c** only led to decomposition. However, **6c** could be transformed into **14c** again as a single diastereomer using AlH_3.[8] To explain the different stereoselectivity of the reduction of **6a–c**, we performed Hartree–Fock calculations, applying the HF/3-21G base set, which showed that the *Re*-side of the keto functionality in **6a** and **6c** is strongly shielded, whereas in **6b** both sides of the keto functionality are accessible (Scheme 7).

In addition to the reduction of **6a–c** using $LiAlH_4$ and AlH_3, respectively, we also used sodium borohydride as a reducing agent with similar results. Transformation of **6a** and **6c** led to single diastereomers **16a** and **16c**, respectively, and **6b** led to a 4:1 mixture of **16b** and **17** (Scheme 8).

For the synthesis of the desired harringtonine analogues **5a–c**, it was necessary to transform the alcohols **14a–c** into the esters **20a–c** using the monomethylester of enantiopure malic acid **18**.[9] However, all attempts to transform the alcohols **14a–c** into the corresponding esters failed. Fortunately, the hydroxylactams **16a** and **16b** could be transformed into **20a** and **20b** using the imidazolide **19** in 65% and 53% yield, respectively. In contrast, the alcohol **16c** did not give the

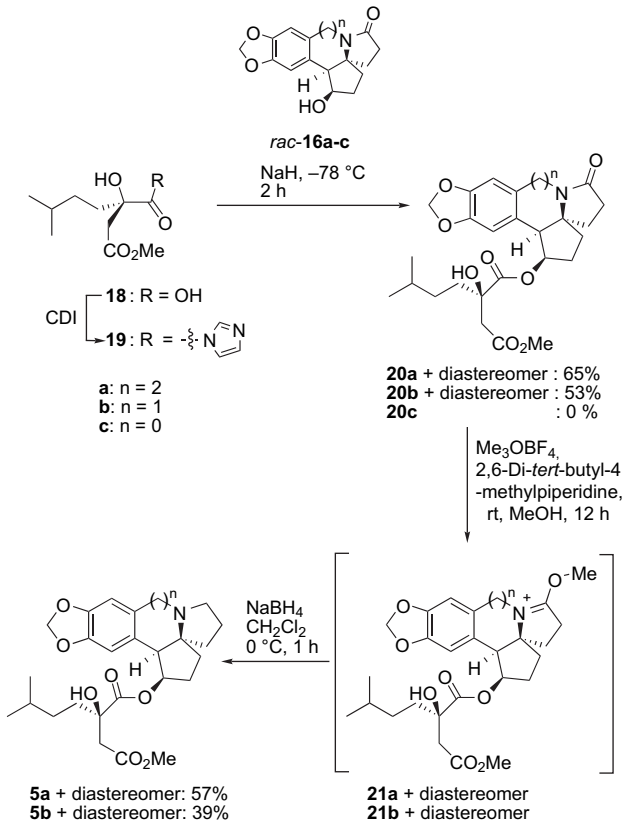


Scheme 7. Reduction of the pentacycles **6a–c** to the cephalotaxine analogues **14a–c** and **15**.



Scheme 8. Reduction of the pentacycles **6a–c** to the cephalotaxine amide analogues **16a–c** and **17**.

corresponding ester using several different methods. Compounds **16a** and **16b** were used as racemic mixtures, whereas **19** was employed as an enantiopure compound. We therefore obtained two diastereomers as an almost 1:1 mixture in each case. The final step in the total synthesis of the harringtonine analogues was the transformation of the lactam moiety into a tertiary amine, which again was not an easy task, since the use of lithium aluminium hydride was not feasible due to the ester moiety in the molecule. However, Boger protocol[10] allowed us the synthesis of **5a** and **5b** in 57% and 39% yield, respectively. For this purpose, the lactam was transformed into the iminomethylethers **21a** and **21b**, which were treated with sodium borohydride. Noteworthy, in all reactions the compounds leading to the natural 5,6,7,5,5-ring system gave the best results (Scheme 9).



Scheme 9. Synthesis of the deoxyharringtonine analogues **5a** and **5b**.

3. Conclusion

We have established a new and highly efficient synthesis for analogues of the pentacyclic core of cephalotaxines **14a–c** and **16a–c** by means of a trimethylaluminium-mediated domino reaction with a successive Pd-catalyzed α-arylation of the keto moiety.

Compounds **16a** and **16b** could further be transformed into the deoxyharringtonine analogues **5a** and **5b** by a coupling with the enantiomerically pure malate **18**. Interestingly, the reaction using the natural 5,6,7,5,5-ring system gave the best yield, whereas the 5,6,5,5,5-system could not be transformed into the deoxyharringtonine analogue.

4. Experimental section

4.1. General

All reactions were performed under an argon atmosphere in flame-dried flasks and the reactants were introduced by syringe. All solvents were dried by standard methods. Solvents used in Pd-catalyzed reactions were degassed by pump and freeze methodology. All reagents obtained from commercial sources were used without further purification. Thin layer chromatography was performed on precoated silica gel plates (SIL G/UV$_{254}$, Macherey-Nagel GmbH & Co. KG). Silica gel 60 (0.032–0.064 mm) (Merck) was used for column chromatography.

UV–vis spectra were recorded in CH_3CN on a Mettler Lambda 2 spectrometer. IR spectra were recorded as KBr pellets of films on a Bruker Vector 22 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL200, VXR200 or a Bruker AM300 spectrometer with tetramethylsilane (TMS) as the internal standard in chloroform-*d* or benzene-d_6. Mass spectra were measured at 70 eV on a Varian MAT311A and high-resolution mass spectra on a Varian MAT731 instrument.

4.2. General procedure I—trimethylaluminium-mediated domino spirocyclisation

A 0.4 M solution of the amines **9a–c** (2.0 equiv) in DMF was cooled to 0 °C, and a solution of $Sn(OTf)_2$ (0.1 equiv) and $AlMe_3$ (2 M in toluene, 2.1 equiv) was added, and the resulting reaction mixture was stirred for 1 h at rt after which a 0.2 M solution of the ester **8** (1.0 equiv) in DMF was added. After stirring for additional 1 h at rt, the reaction mixture was heated at 80 °C in a preheated oil bath for 18 h. The reaction mixture was cooled to 0 °C, quenched with 1 N HCl and extracted with ethyl acetate. The combined organic phases were dried over Mg_2SO_4 and concentrated to dryness in vacuo. The crude product was purified by column chromatography.

4.2.1. 1-[2-(6-Bromobenzo[1,3]dioxol-5-yl)ethyl]1-azaspiro[4.4]nonane-2,7-dione (7a). According to general procedure I, amine **9a** (2.03 g, 8.32 mmol, 2.0 equiv) was reacted with $Sn(OTf)_2$ (168 mg, 0.832 mmol, 0.1 equiv), $AlMe_3$ (4.34 mL, 8.66 mmol, 2.08 equiv) and **8** (700 mg, 4.16 mmol). After purification by column chromatography with ethyl acetate/methanol (10:1) as eluent, **7a** (2.30 g, 6.08 mmol) was obtained in 77% yield.

R_f=0.23 (EE); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.94 (s, 1H, 7″-H), 6.72 (s, 1H, 4″-H), 5.93 (s, 2H, 2″-H$_2$), 3.59–3.20 (m, 2H, 1′-H$_2$), 2.93 (t, J=7.5 Hz, 2H, 2′-H$_2$), 2.49–1.75 (m, 10H, 3-H$_2$, 4-H$_2$, 6-H$_2$, 8-H$_2$, 9-H$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ=213.9 (C-7), 174.9 (C-2), 147.5 (C-7a″), 145.5 (C-3a″), 131.0 (C-5″), 114.4 (C-6″), 112.6 (C-7″), 110.8 (C-4″), 101.7 (C-2″), 66.58 (C-5), 47.95 (C-6), 39.73 (C-1′), 36.66 (C-8), 34.90 (C-2′), 32.52, 32.51, 29.10 (C-3, C-4, C-9); IR (KBr): $\tilde{\nu}$ = 3041 (Ar), 2935 (C–H), 1747 cm^{-1} (C═O), 1684 (NC═O), 1475; UV (CH_3CN): λ_{max} (lg ε)=202.5 (4.596), 238.0 (3.641), 294.5 nm (3.593); MS (70 eV, EI): *m*/*z* (%)=379.0/381.0 (14) [M$^+$], 300.1 (45) [M$^+$−Br], 228.0/226.0 (100) [$C_9H_7BrO_2^+$], 213.0/215.0

(15) [M−$C_8H_6BrO_2^+$], 166.1 (46) [$C_9H_{12}NO_2^+$], elemental analysis calcd (%) for $C_{17}H_{18}BrNO_4$ (379.0): C 53.70, H 4.77; found: C 53.44, H 4.73.

4.2.2. 1-(6-Bromobenzo[1,3]dioxol-5-yl)methyl-1-aza-spiro[4.4]nonane-2,7-dione (7b). According to general procedure I, amine **9b** (4.11 g, 17.9 mmol) was reacted with $Sn(OTf)_2$ (360 mg, 892 μmol), $AlMe_3$ (9.3 mL, 18.6 mmol) and **8** (1.50 g, 8.92 mmol). After purification by column chromatography with ethyl acetate/methanol (10:1) as eluent, **7b** (2.47 g, 6.74 mmol) was obtained in 76% yield.

R_f=0.16 (PN/EE, 1:4); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.97 (s, 1H, 7″-H), 6.75 (s, 1H, 4″-H), 5.97 (s, 2H, 2″-H_2), 4.50 (s, 2H, 1′-H_2), 2.60–2.53 (m, 2H, 3-H_2), 2.46–1.85 (m, 8H, 4-H_2, 6-H_2, 8-H_2, 9-H_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=213.5 (C-7), 174.9 (C-2), 147.9, 147.7 (C-7a″, C-3a″), 129.8 (C-5″), 112.5 (C-6″, C-7″), 108.2 (C-4″), 101.8 (C-2″), 66.67 (C-5), 47.76 (C-6), 42.31 (C-1′), 36.61, 32.77, 32.39, 29.19 (C-3, C-4, C-8, C-9); IR (KBr): $\tilde{\nu}$ = 2961, 2896 (C–H), 1736 (C═O), 1674 cm^{-1} (NC═O); UV (CH_3CN): λ_{max} (lg ε)=229.0 (3.509), 264.0 (2.459), 323.5 nm (2.509); MS (DCI, NH_3): *m/z* (%)=383.2/385.2 (100) [M+NH_4^+], 366.2/368.2 (15) [M+H^+], 305.3 (37) [M−Br+NH_4^+].

4.2.3. 1-(6-Bromobenzo[1,3]dioxol-5-yl)-1-aza-spiro[4.4]-nonane-2,7-dione (7c). According to general procedure I, aniline **9c** (3.86 g, 17.8 mmol) was reacted with $Sn(OTf)_2$ (360 mg, 892 μmol), $AlMe_3$ (9.3 mL, 18.6 mmol) and **8** (1.50 g, 8.92 mmol). After purification by column chromatography with ethyl acetate/methanol (10:1) as eluent, **7c** (973 mg, 2.77 mmol) was obtained in 31% yield.

R_f=0.25 (PN/EE, 1:5); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.08, 7.07 (s, 1H, 7′-H), 6.61, 6.48 (s, 1H, 4′-H), 5.99, 5.95 (AB system, J_{AB}=1.4 Hz, 2H, 2′-H_2), 2.62–2.04 (m, 10H, 3-H_2, 4-H_2, 6-H_2, 8-H_2, 9-H_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=213.7 (C-7), 174.3 (C-2), 148.9, 148.0 (C-3a′, C-7a′), 127.2 (C-5′), 116.7 (C-7′), 113.3 (C-4′), 111.5 (C-6′), 102.6 (C-2′), 68.69 (C-5), 48.17 (C-6), 36.20 (C-8), 33.24, 32.99 (C-3, C-4), 29.46 (C-9); IR (KBr): $\tilde{\nu}$ = 2917, 2886 (C–H), 1745 (C═O), 1700 cm^{-1} (NC═O); UV (CH_3CN): λ_{max} (lg ε)=204.0 (4.497), 241.5 (3.675), 295.0 nm (3.558); MS (DCI, NH_3): *m/z* (%)=369.2/371.2 (100) [M+NH_4^+], 352.1/354.1 (7) [M+H^+], 291.3 (10) [M−Br+NH_4^+], $C_{15}H_{14}BrNO_4$ (352.2); HRMS calcd 351.0106, found 351.0106.

4.3. General procedure II—intramolecular palladium catalyzed arylation of the spirocycles 7a–c

To a degassed 0.02 M solution of the spirocycle **7a–c** catalyst, ligand and base were added. The reaction mixture was heated at 120 °C overnight, poured into saturated NH_4Cl solution and extracted three times with dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated to dryness in vacuo. The crude product was purified by column chromatography.

4.3.1. 2,3,4,5,8,9-Hexahydro-6*H*,14b*H*-cyclopenta-[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-1,6-dion; 1,6-dioxocephalotaxan (6a). According to general procedure II, spirocycle **7a** (40 mg, 0.105 mmol) was reacted in 1,4-dioxane with $Pd(PPh_3)_2Cl_2$ (16 mg, 0.022 mmol, 0.2 equiv) and dppe (18 mg, 0.044 mmol, 0.4 equiv) as a catalyst and Cs_2CO_3 as a base (138 mg, 0.422 mmol, 3.8 equiv). The crude product was purified by column chromatography on silica with ethyl acetate/pentane (4:1) as eluent to give **6a** (24 mg, 0.080 mmol, 81%).

R_f=0.14 (EtOAc/pentane=1:4); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.62 (s, 1H, 10-H), 6.57 (s, 1H, 14-H), 5.89, 5.91 (AB System, J_{AB}=1.4 Hz, 2H, 12-H_2), 4.25 (ddd, *J*= 14.2, 11.2, 8.8 Hz, 1H, 8-H_b), 3.25 (s, 1H, 14b-H), 2.96 (dd, *J*=14.3, 7.9 Hz, 1H, 8-H_a), 2.71–2.06 (m, 10H, 2-H_2, 3-H_2, 4-H_2, 5-H_2, 9-H_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 216.1 (C-1), 174.8 (C-6), 147.6 (C-13a), 146.6 (C-10a), 129.4 (C-14a), 127.0 (C-9a), 111.8 (C-14), 111.0 (C-10), 101.2 (C-12), 67.94 (C-3a), 65.59 (C-14b), 38.00 (C-8), 29.65, 31.06, 32.94, 35.46, 36.73 (C-2, C-3, C-4, C-5, C-9); IR (KBr): $\tilde{\nu}$ = 3027, 2922 (C–H), 1736 (C═O), 1672 cm^{-1} (NC═O); UV (CH_3CN): λ_{max} (lg ε)=201.5 (4.737), 289.0 nm (3.748); MS (70 eV, EI): *m/z* (%)=299.1 (100) [M$^+$], 243.1 (40) [M$^+$−CO–C_2H_4], 161.0 (43) [$C_{10}H_9O_2^+$], 148.1 (76) [$C_9H_8O_2^+$]; elemental analysis calcd (%) for $C_{17}H_{17}NO_4$ (299.3): C 68.21, H 5.72; found: C 68.65, H 5.78.

4.3.2. 2,3,4,5,8,13b-Hexahydro-6*H*-cyclopenta[*a*][1,3]-dioxolo[4,5-*g*]pyrrolo[2,1-*b*]isochinolin-1,6-dione (6b). According to general procedure II, spirocycle **7b** (40 mg, 0.110 mmol) was reacted in 1,4-dioxane with $Pd(PPh_3)_2Cl_2$ (20 mg, 0.028 mmol, 0.25 equiv) as a catalyst and Cs_2CO_3 as a base (174 mmg, 0.533 mmol, 4.8 equiv). The crude product was purified by column chromatography on silica with ethyl acetate/pentane (4:1) as eluent to give **6b** (23 mg, 0.080 mmol, 73%).

R_f=0.18 (EtOAc/pentane=1:4); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.99 (s, 1H, 13-H), 6.60 (s, 1H, 9-H), 5.95, 5.93 (AB System, J_{AB}=1.4 Hz, 2H, 11-H_2), 4.96 (d, *J*=17.2 Hz, 1H, 8-H), 4.09 (d, *J*=17.2 Hz, 1H, 8-H), 3.19 (s, 1H, 13b-H), 2.66–1.93 (m, 8H, 2-H_2, 3-H_2, 4-H_2, 5-H_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ=213.5 (C-1), 173.1 (C-6), 147.2, 147.3 (C-9a, C-12a), 124.2 (C-13a), 120.4 (C-8a), 106.3, 107.9 (C-9, C-13), 101.3 (C-11), 64.09 (C-3a), 55.75 (C-13b), 39.35 (C-8), 29.32, 29.34, 32.43, 35.58 (C-2, C-3, C-4, C-5); IR (KBr): $\tilde{\nu}$ = 2906 (C–H), 1740 (C═O), 1688 cm^{-1} (NC═O); UV (CH_3CN): λ_{max} (lg ε)=198.0 (4.444), 291.5 nm (3.437); MS (70 eV, EI): *m/z* (%)=285.3 (100) [M$^+$], 228.2 (78) [M$^+$−CO–C_2H_4], $C_{16}H_{15}NO_4$ (285.1); HRMS calcd 285.1001, found 285.1001.

4.3.3. 2,3,4,5,6,6a-Hexahydro-1*H*-cyclopenta[*a*][1,3]-dioxolo[4,5-*f*]pyrrolo[1,2-*b*]indol-1,6-dione (6c). According to general procedure II, spirocycle **7c** (564 mg, 1.601 mmol) was reacted in THF with $Pd(dppf)Cl_2$ (261 mg, 0.320 mmol, 0.2 equiv) as a catalyst and K_2CO_3 as a base (885 mmg, 6.404 mmol, 4.0 equiv). The crude product was purified by column chromatography on silica with ethyl acetate as an eluent to give **6c** (278 mg, 1.024 mmol, 65%).

R_f=0.33 (EtOAc/pentane=1:5); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.21 (s, 1H, 11-H), 6.87 (s, 1H, 7-H), 5.96, 5.95 (AB System, J_{AB}=1.4 Hz, 2H, 9-H_2), 3.62 (s, 1H, 6a-H), 3.01 (ddd, *J*=17.2, 7.9, 5.0 Hz, 1H, 2-H_b), 2.61 (ddd,

J=17.1, 7.9, 1.4 Hz, 1H, 2-H_a), 2.47–2.10 (m, 6H, 3-H_2, 4-H_2, 5-H_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=212.6 (C-1), 171.2 (C-6), 145.1, 148.3 (C-7a, C-10a), 132.4 (C-6b), 121.1 (C-11a), 105.4 (C-11), 101.7 (C-9), 98.14 (C-7), 76.28 (C-3a), 59.33 (C-6a), 33.16, 33.57, 34.13, 36.96 (C-2, C-3, C-4, C-5); IR (KBr): $\tilde{\nu}$ = 2926 (C–H), 1741 (C═O), 1686 cm^{-1} (NC═O); UV (CH_3CN): λ_{max} (lg ε)=215.0 (4.192), 266.5 (3.819), 313.0 nm (3.710); MS (70 eV, EI): m/z (%)=271.3 (39) [M^+], 215.2 (100) [M^+–CO–C_2H_4], $C_{15}H_{13}NO_4$ (271.3); HRMS calcd 271.0845, found 271.0845.

4.3.4. 2,3,4,5,8,9-Hexahydro-6*H*,14b*H*-cyclopenta-[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-1-ol (14a). To a solution of **6a** (100 mg, 0.334 mmol) in THF (19 mL) $LiAlH_4$ (2.3 M in THF, 0.36 mL, 0.835 mmol, 2.5 equiv) was added and heated to reflux for 1 h. The reaction mixture was poured into NaCl saturated 10% NH_4Cl solution (80 mL) and extracted with dichloromethane (3×60 mL). The combined organic phases were dried over Mg_2SO_4 and concentrated to dryness in vacuo. The crude product was purified by column chromatography with ethyl acetate/methanol (8:1) and 5% NEt_3 as eluent to give **14a** (80 mg, 0.278 mmol) in 83% yield.

R_f=0.39 (EtOAc/MeOH=8:1, 5% NEt_3); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.69 (C, 1H, 14-H), 6.61 (C, 1H, 10-H), 5.88 (m_c, 2H, 12-H_2), 4.31 (m_c, 1H, 1-H), 3.73 (ddd, J=7.6, 13.2, 14.1 Hz, 1H, 8-H_b), 3.19 (d, J=6.3 Hz, 1H, 1-H), 3.12 (m_c, 1H, 4-H_b), 3.00 (ddd, J=6.5, 11.4, 12.5 Hz, 1H, 9-H_b), 2.62 (m_c, 1H, 9-H_a), 2.49 (m_c, 1H, 4-H_a), 2.37 (m_c, 1H, 8-H_a), 2.16 (ddd, J=6.7, 13.0, 13.0 Hz, 1H, 6-H_b), 1.95 (m_c, 2H, 3-H_b, 2-H_b), 1.85–1.64 (m, 4H, 5-H_2, 2-H_a, 3-H_a), 1.36 (m_c, 1H, 6-H_a).

^{13}C NMR (75 MHz, $CDCl_3$): δ=146.6 (C-10a), 146.1 (C-13a), 133.8 (C-9a), 129.7 (C-14a), 112.2 (C-10), 110.5 (C-14), 100.8 (C-12), 75.87 (C-1), 69.18 (C-3a), 62.27 (C-14b), 54.82 (C-4), 48.84 (C-9), 43.49 (C-2), 31.48 (C-3), 24.55 (C-6), 19.79 (C-5); IR (KBr): $\tilde{\nu}$ = 3418 (–OH), 2945 (C–H), 1479 cm^{-1} (–OH); UV (CH_3CN): λ_{max} (lg ε)= 291.5 (3.627), 232.5 (3.671), 201.5 nm (4.596); MS (70 eV, EI): m/z (%)=287.3 (6) [M^+], 270.2 [$C_{17}H_{20}NO_2^+$], 229.2 (9) [$C_{14}H_{15}NO_2^+$], 217.1 (13) [$C_{12}H_{11}NO_3^+$], $C_{17}H_{21}NO_3$ (287.3); HRMS calcd 287.1521, found 287.1521.

4.3.5. 2,3,4,5,8,13b-Hexahydro-6*H*-cyclopenta[*a*][1,3]-dioxolo[4,5-*g*]pyrrolo[2,1-*b*][3]isochinolin-1-ol (14b). To a solution of **6b** (100 mg, 0.351 mmol) in THF (20 mL) $LiAlH_4$ (2.3 M in THF, 0.38 mL, 0.876 mmol, 2.5 equiv) was added and heated to reflux for 1 h. The reaction mixture was poured into NaCl saturated 10% NH_4Cl solution (80 mL) and extracted with dichloromethane (3×60 mL). The combined organic phases were dried over Mg_2SO_4 and concentrated to dryness in vacuo. The crude product was purified by column chromatography with dichloromethane/methanol (1:1) as eluent to give **14b** (82 mg, 0.278 mmol) in 86% yield as a 2.3:1 (**14b/15**) mixture of isomers of **14b** and **15**.

4.3.6. *trans*-2,3,4,5,8,13b-Hexahydro-6*H*-cyclopenta-[*a*][1,3]dioxolo[4,5-*g*]pyrrolo[2,1-*b*][3]isoquinolin-1-ol (14b). R_f=0.44 (CH_2Cl_2/MeOH, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.52 (s, 1H, 13-H), 6.64 (s, 1H, 6-H), 5.94 (d, J=1.4 Hz, 1H, 11-H_b), 5.91 (d, J=1.4 Hz, 1H, 11-H_a), 4.29 (m_c, 1H, 1-H), 4.00 (d, J=15.7 Hz, 1H, 8-H_b), 3.53 (d, J=15.7 Hz, 1H, 8-H_b), 3.00–2.90 (m, 1H, 6-H_b), 2.79 (d, J=5.2 Hz, 1H, 12b-H), 2.51–2.41 (m, 1H, 6-H_a), 2.35–2.21 (m, 1H, 2-H_b), 2.06–1.92 (m, 1H, 4-H_b), 1.87–1.54 (m, 6H, 2-H_a, 3-H_2, 4-H_b, 5-H_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=146.5 (C-9a), 146.1 (C-12a), 130.0 (C-13a), 126.8 (C-8a), 109.3 (C-13), 108.0 (C-9), 100.7 (C-11), 76.48 (C-1), 69.58 (C-3a), 52.95 (C-13b), 51.28 (C-6), 41.21 (C-4), 41.99 (C-2), 36.15 (C-2), 31.97 (C-3), 22.63 (C-5); IR (KBr): $\tilde{\nu}$ = 3378 (–OH), 2866 (C–H), 1483 cm^{-1} (–OH); UV (CH_3CN): λ_{max} (lg ε)=292.5 (3.538), 231.5 (3.544), 200.0 nm (4.448); MS (70 eV, EI): m/z (%)=287.3 (6) [M^+], 270.2 [$C_{17}H_{20}NO_2^+$], 229.2 (9) [$C_{14}H_{15}NO_2^+$], 217.1 (13) [$C_{12}H_{11}NO_3^+$], $C_{17}H_{21}NO_3$ (287.3); HRMS calcd 287.1521, found 287.1521.

4.3.7. *cis*-2,3,4,5,8,13b-Hexahydro-6*H*-cyclopenta-[*a*][1,3]dioxolo[4,5-*g*]pyrrolo[2,1-*b*][3]isoquinolin-1-ol (15). R_f=0.24 (CH_2Cl_2/MeOH, 1:1); ^{1}H NMR (300 MHz, C_6D_6): δ=6.87 (s, 1H, 13-H), 6.74 (s, 6-H), 5.39 (s, 2H, 11-H), 3.72–3.47 (m, 3H, 8-H_b, 1-H, OH), 3.43–3.34 (d, J=16 Hz, 1H, 8-H_a), 2.78–2.68 (m, 1H, 6-H_b), 2.49–2.36 (m, 2H, 13b-H, 6-H_a), 1.34–1.95 (m, 8H, 5-H_2, 4-H_2, 3-H_2, 2-H_2); ^{13}C NMR (75 MHz, C_6D_6): δ=146.9 (C-5a), 146.3 (C-12a), 131.4 (C-13a), 127.4 (C-8a), 109.6 (C-13), 108.0 (C-9), 100.6 (C-11), 80.26 (C-1), 68.76 (C-3a), 55.19 (C-13b), 51.27 (C-6), 48.50 (C-8), 42.95 (C-4), 34.20 (C-2), 32.83 (C-3), 22.86 (C-5); IR (KBr): $\tilde{\nu}$ = 3341 (–OH), 2954 (C–H), 1484 cm^{-1} (–OH); UV (CH_3CN): λ_{max} (lg ε)=292.5 (3.610), 232.5 (3.671), 200.5 nm (4.513); MS (70 eV, EI): m/z (%)=287.3 (6) [M^+], 270.2 [$C_{17}H_{20}NO_2^+$], 229.2 (9) [$C_{14}H_{15}NO_2^+$], 217.1 (13) [$C_{12}H_{11}NO_3^+$], $C_{17}H_{21}NO_3$ (287.3); HRMS calcd 287.1521, found 287.1521.

4.3.8. 2,3,4,5-Tetrahydro-1*H*-cyclopenta[*b*][1,3]di-oxolo[4,5-*f*]pyrrolo[1,2-*a*]indol-6-(12*bH*)-ol (14c). About 0.41 mL (0.940 mmol, 3.0 equiv) of $LiAlH_4$ solution (2.3 M in THF) was dissolved in THF (10 mL). Sulfuric acid (96%, 25 μL, 0.470 mmol, 1.5 equiv) was carefully added at 0 °C and the resulting suspension stirred for further 2 h at rt. A solution of **6c** (85 mg, 0.313 mmol) in THF (10 mL) was added and the reaction mixture was stirred for 1 h at rt. The suspension was poured into NaCl saturated 10% NH_4Cl solution (80 mL) and extracted with dichloromethane (3×60 mL). The combined organic phases were dried over Mg_2SO_4 and concentrated to dryness in vacuo. The crude product was purified by preparative thin layer chromatography with ethyl acetate as an eluent to give **14c** (53 mg, 0.204 mmol) in 65% yield.

R_f=0.27 (EE); ^{1}H NMR (300 MHz, C_6D_6): δ=6.74 (s, 1H, 12-H), 6.19 (s, 1H, 8-H), 5.42 (s, 2H, 10-H_2), 4.17 (br s, 1H, 1-H), 3.16 (d, J=8.0 Hz, 1H, 12b-H), 3.09–2.99 (m, 1H, 6-H_b), 2.70–2.59 (m, 1H, 6 H_b), 1.85–1.65 (m, 3H, 3-H_b, 4-H_b), 1.59–1.37 (m, 4H, 5-H, 3-H_a, OH), 1.36–1.27 (m, 2H, 2-H_2), 1.20–1.07 (ddd, J=5.8, 11.8, 18.0 Hz, 1H, 4-H_a); ^{13}C NMR (75 MHz, C_6D_6): δ=152.1 (C-8a), 148.6 (C-11a), 141.4 (C-7a), 112.3 (C-12a), 107.4 (C-12, 100.8 (C-10), 94.22 (C-8), 83.17 (C-3a), 75.47 (C-1), 56.18 (C-12b), 52.64 (C-6), 37.36 (C-4), 36.84 (C-2), 34.17 (C-3),

25.77 (C-5); IR (KBr): $\tilde{\nu}$ = 3385 (–OH), 2924 (C–H), 1476 cm^{-1} (–OH); UV (CH_3CN): λ_{max} (lg ε)=328.5 (3.730), 255.0 (3.736), 204.5 nm (4.394); MS (70 eV, EI): *m/z* (%)=259.2 (100) [M^+], 242 (2) [$C_{15}H_{16}NO_2^+$], 230.1 (86) [$C_{14}H_{16}NO_2^+$], $C_{15}H_{17}NO_3$ (259.2); HRMS calcd 259.1208, found 259.1208.

4.4. General procedure III—reduction of the pentacycles 6a–c with $NaBH_4$

To a 0.01 M solution of **6a–c** in MeOH 5.0 equiv $NaBH_4$ was added at −60 °C. The reaction mixture was stirred at −60 °C for 3 h, poured into pH7 buffer solution and extracted three times with dichloromethane. The combined organic phases were dried over $MgSO_4$ and concentrated to dryness in vacuo.

4.4.1. 1-Hydroxy-2,3,4,5,8,9-hexahydro-6*H*,14b*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-6-on (16a). According to general procedure III, pentacycle **6a** (200 mg, 0.668 mmol) was reduced with $NaBH_4$ (128 mg, 3.46 mmol, 5.0 equiv) to give **16a** in 99% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ=6.62 (s, 1H, 10-H), 6.58 (s, 1H, 14-H), 5.89 (s, 2H, 12-H_2), 4.36 (m_c, 1H, 1-H), 3.96 (dt, *J*=5.7, 13.1 Hz, 1H, 8-H_b), 3.79 (dt, *J*=5.4, 13.8 Hz, 1H, 9-H_b), 3.17 (m_c, 2H, 8-H_a, 14b-H), 2.68–2.54 (m, 1H, 5-H_b), 2.47 (m_c, 1H, 9-H_a), 2.29–2.18 (m, 2H, 3-H_2), 2.10–1.94 (m, 3H, 4-H_b, 2-H_2), 1.93–1.77 (m, 1H, 4-H_a), 1.75–1.63 (m, 1H, 5-H_a).

^{13}C NMR (75 MHz, $CDCl_3$): δ=175.1 (C-1), 146.9 (C-13a), 146.3 (C-10a), 132.61 (C-9a), 128.3 (C-14a), 111.9 (C-14), 110.6 (C-10), 100.9 (C-12), 75.87 (C-1), 69.21 (C-3a), 63.14 (C-14b), 39.22 (C-2), 38.99 (C-8), 33.34 (C-5), 31.57 (C-4), 30.46 (C-9), 29.43 (C-3); IR (KBr): $\tilde{\nu}$ = 3396 (–OH), 2921 (C–H), 1662 (NC═O), 1487 cm^{-1} (–OH); UV (CH_3CN): λ_{max} (lg ε)=290.0 (3.568), 236.5 (3.586), 201.5 nm (4.602); MS (70 eV, EI): *m/z* (%)=301.3 (100) [M^+], 272.2 (12) [$C_{16}H_{18}NO_3^+$], 258.2 (6) [$C_{12}H_{11}NO_3^+$], $C_{17}H_{19}NO_4$ (301.3); HRMS calcd 301.1314, found 301.1314.

4.4.2. 1-Hydroxy-2,3,4,5,8,13b-hexahydro-6*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*g*]pyrrolo[2,1-*b*][3]isochinolin-6-on (16b). According to general procedure III, pentacycle **6b** (100 mg, 0.351 mmol) was reduced with $NaBH_4$ (66 mg, 1.74 mmol, 5.0 equiv). The crude product was purified by preparative thin layer chromatography with ethyl acetate as an eluent to give **16b** (85 mg, 0.296 mmol) in 86% yield as a 4:1 (**16b/17**) mixture of isomers.

R_f=0.21 (EE); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.73 (s, 1H, 9-H_1), 6.62 (s, 1H, 13-H_1), 5.91 (s, 2H, 11-H_2), 4.81 (d, *J*=16.2 Hz, 0.8H, *trans*-8-H_1), 4.73 (d, *J*=16.2, 0.2 Hz, *cis*-8-H_1), 4.30 (m_c, 0.2H, *cis*-1-H_1), 3.94 (m_c, 0.7H, *trans*-1-H_1), 3.84 (d, *J*=16.2 Hz, *cis*-8-H_1), 3.78 (d, *J*=16.2 Hz, 0.8H, *trans*-8-H_1), 3.05 (d, *J*=6 Hz, 0.8H, *cis*-13b-H_1), 2.75 (d, *J*=6 Hz, 0.8H, *trans*-13b-H_1), 2.59–2.45 (m, 1H, 5-H_1), 2.59–1.43 (m, 7H, 2-H_2, 3-H_2, 4-H_2, 5-H_1).

^{13}C NMR (75 MHz, $CDCl_3$): δ=172.7 (C-6), 146.8 (C-9a), 146.1 (C-12a), 129.0 (C-13a), 125.9 (C-8a), 108.8 (C-13), 106.5 (C-9), 100.9 (C-11), 80.10 (C-1), 66.20 (C-3a), 56.66 (C-13b), 38.62 (C-8), 36.30 (C-3), 32.40 (C-4), 31.78 (C-2), 30.58 (C-5); IR (KBr): $\tilde{\nu}$ = 3398 (–OH), 2957 (C–H), 1664 (NC═O), 1485 cm^{-1} (–OH); UV (CH_3CN): λ_{max} (lg ε)=291.5 (3.625), 202.0 nm (4.588); MS (70 eV, EI): *m/z* (%)=287.1 (167) [M^+], 285.1 (33) [$C_{15}H_{16}NO_3^+$], 228.1 (100) [$C_{12}H_{14}NO_2^+$]; HRMS calcd 287.1158, found 287.1158.

4.4.3. 1-Hydroxy-2,3,4,5-tetrahydro-1*H*-cyclopenta-[*b*][1,3]dioxolo[4,5-*f*]pyrrolo[1,2-*a*]indol-6-(12b*H*)-on (16c). According to general procedure III, pentacycle **6c** (200 mg, 0.737 mmol) was reduced with $NaBH_4$ (140 mg, 3.69 mmol, 5.0 equiv) to give **16c** in 99% yield.

R_f=0.39 (EE); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.23 (s, 1H, 8-H), 6.78 (s, 1H, 12-H), 5.91 (s, 2H, 10-H_2), 4.50 (m_c, 1H, 1-H), 3.58 (d, *J*=6.9 Hz, 2H, 2-H), 2.84 (ddd, *J*=8.0, 12.3, 20.0 Hz, 1H, 5-H_b), 2.49–2.34 (m, 1H, 5-H_a), 2.29–2.05 (m, 3H, 4-H_b, 3-H_2), 1.97–1.80 (m, 2H, 4-H_a, 2-H_b), 1.56–1.44 (m, 1H, 2-H_a).

^{13}C NMR (75 MHz, $CDCl_3$): δ=173.5 (C-6), 147.5 (C-11a), 144.3 (C-8a), 135.5 (C-7a), 122.3 (C-12a), 107.1 (C-12), 101.4 (C-10), 97.42 (C-8), 78.31 (C-12b), 73.99 (C-1), 55.80 (C-2), 36.75 (C-4), 36.41 (C-3), 24.09 (C-5), 32.94 (C-2); IR (KBr): $\tilde{\nu}$ = 3393 (–OH), 2901 (C–H), 1671 (NC═O), 1479 cm^{-1} (–OH); UV (CH_3CN): λ_{max} (lg ε)= 310.5 (3.817), 264.5 (3.956), 206 nm (4.327); MS (70 eV, EI): *m/z* (%)=273.2 (12) [M^+], 244.2 (5) [$C_{14}H_{14}NO_3^+$], 217.1 (13) [$C_{12}H_{11}NO_3^+$], $C_{15}H_{15}NO_4$ (273.1); HRMS calcd 273.1001, found 273.1001.

4.4.4. 4-Methyl-6-oxo-2,3,4,5,8,9-hexahydro-6*H*,14b*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-1-yl-2-hydroxy(3-methylbutyl)malic acid-ester (20a). To a solution of **18** (75.0 mg, 342 μmol, 2.0 equiv) in THF (2 mL) was added at 0 °C carbonyldiimidazole (59.0 mg, 359 μmol, 2.1 equiv). The reaction mixture was warmed to rt and stirred for 12 h. A solution of **16a** (52.0 mg, 171 μmol) in THF (1 mL) was added and the resulting mixture cooled to −78 °C. NaH (14 mg, 598 μmol, 3.5 equiv) was added, the reaction mixture warmed to rt within 12 h and poured into brine (4 mL). The resulting suspension was extracted with ethyl acetate (4×10 mL), the combined organic phases were dried over Mg_2SO_4 and concentrated to dryness in vacuo. The crude product was purified by preparative thin layer chromatography with ethyl acetate as an eluent to give **20a** (56 mg, 112 μmol) in 65% yield.

R_f=0.38 (EE); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.62 (s, 1H, 10-H_1), 6.57 (s, 0.5H, 14-H_1^*), 6.55 (s, 0.5H, 14-H_1), 5.88 (s, 2H, 12-H_2), 5.51–5.39 (m, 1H, 1-H_1), 4.16–3.99 (m, 1H, 8-H_1), 3.67 (s, 1.5H, OMe), 3.53 (s, 1.5H, OMe), 3.44 (m_c, 2H, 9-H_1, 14b-H_1), 3.18 (m_c, 1H, 8-H_1), 2.71–1.96 (m, 10H, 2-H_2, 3-H_2, 4-H_2, 5-H_1, 9-H_1, 3′-H_2), 1.87–0.91 (m, 6H, 1″-H_2, 2″-H_2, 5-H_1, 3″-H_1), 0.87–0.78 (m, 3H, 3″-CH_3), 0.75–0.63 (m, 3H, 3″-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ=175.0 (C-1′*), 174.9 (C-1′), 174.4 (C-4′*), 174.2 (C-4′), 171.0 (C-6*), 170.8 (C-6), 147.1 (C-10a*), 147.0 (C-10a), 146.4 (C-13a*), 146.3 (C-13a), 131.5 (C-14a*), 131.4 (C-14a), 128.2 (C-9a*), 128.1 (C-9a), 111.8 (C-10*), 111.7 (C-10), 110.4 (C-14*), 110.4 (C-14), 101.1 (C-12*), 101.0

(C-12), 79.43 (C-1*), 79.11 (C-1), 74.83 (C-2′*), 74.77 (C-2′), 69.19 (C-3a), 60.21 (C-14b*), 60.18 (C-14b), 51.80 (OMe*), 51.58 (OMe), 43.22 (C-3′*), 42.90 (C-3′), 39.39 (C-2*), 39.36 (C-2), 38.96 (C-8*), 38.91 (C-8), 36.64, 33.63, 31.62, 30.81, 30.74, 29.97, 29.30, 27.84 (C-3, C-4, C-5, C-9, C-1″, C-2″, C-3″), 22.51 (Me*), 22.46 (Me), 22.17 (Me*), 21.93 (Me); IR (KBr): $\tilde{\nu}=3435$ (–OH), 2955 (C–H), 1741 (N–(C=O)), 1682 cm^{-1} (N–(C=O)); UV (MeCN): λ_{max} (lg ε)=290.0 (5.023), 237.5 (4.936), 202.5 nm (4.867); MS (70 eV, EI): *m/z* (%)=501 (8) [M^+], 300 (8) [$C_{17}H_{18}NO_4^+$], 283 (100) [$C_{17}H_{17}NO_3^+$], $C_{27}H_{35}NO_8$ (501.6); HRMS calcd 501.2363, found 501.2363.

4.4.5. 4-Methyl-6-oxo-1,2,3,4,5,6,8,13b-octahydrocyclopenta[*c*][1,3]dioxolo[4,5-*g*]pyrrolo[1,2-*b*]isoquinolin-1-yl-2-(3-methylbutyl)malic acid-ester (20b). To a solution of **18** (75.0 mg, 342 μmol, 2.0 equiv) in THF (2 mL) was added at 0 °C carbonyldiimidazole (59.0 mg, 359 μmol, 2.1 equiv). The reaction mixture was warmed to rt and stirred for 12 h. A solution of **16b** (52.0 mg, 171 μmol) in THF (1 mL) was added and the resulting mixture cooled to −78 °C. NaH (14 mg, 598 μmol, 3.5 equiv) was added, the reaction mixture warmed to rt within 12 h and poured into brine (4 mL). The resulting suspension was extracted with ethyl acetate (4×10 mL), the combined organic phases were dried over Mg_2SO_4 and concentrated to dryness in vacuo. The crude product was purified by preparative thin layer chromatography with ethyl acetate as an eluent to give **20b** (56 mg, 112 μmol) in 53% yield.

R_f=0.42 (EE); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.96 (s, 0.5 Hz, 12-H_I^*), 6.89 (s, 0.5 Hz, 12-H_1), 6.58 (s, 0.5 Hz, 9-H_I^*), 6.56 (s, 0.5H, 9-H_1), 5.90 (m_c, 2H, 11-H_2), 5.11–5.23 (m, 1H, 1-H_1), 4.84 (d, *J*=16.5 Hz, 1H, 8-H_1), 3.90 (d, *J*=16.5 Hz, 1H, 8-H_1), 3.67 (s, 1.5H, OMe), 3.65 (s, 1.5H, OMe), 3.18 (m_c, 0.5H, 13b-H_I^*), 3.08 (m_c, 0.5H, 13b-H_1), 2.97 (d, *J*=5.3 Hz, 0.5H, 3′-H_1), 2.91 (d, *J*=5.3 Hz, 0.5H, 3′-H_1), 2.76 (d, *J*=5.3 Hz, 0.5H, 3′-H_1), 2.70 (d, *J*=5.3 Hz, 0.5H, 3′-H_1), 2.01–0.92 (m, 13H, 2-H_2, 3-H_2, 4-H_2, 5-H_2, 1″-H_2, 2″-H_2, 3″-H_1), 0.89–0.82 (m, 6H, 2×Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ=174.9 (C-1′), 22.35 (Me), 22.39 (Me*), 22.51 (Me), 22.54 (Me*), 172.9 (C-4′*), 172.8 (C-4′), 171.4 (C-6*), 171.2 (C-6), 147.3 (C-9a), 146.7 (C-12a), 126.7 (C-13a), 125.7 (C-8a*), 125.5 (C-8a), 108.9 (C-9*), 108.7 (C-9), 106.4 (C-13*), 106.2 (C-13), 101.1 (C-11), 83.80 (C-1*), 83.63 (C-1), 75.20 (C-2′*), 75.12 (C-2′), 66.35 (C-3a*), 66.25 (C-3a), 53.62 (C-13b*), 53.38 (C-13b), 51.95 (OMe*), 51.91 (OMe), 43.51 (C-3′*), 43.48 (C-3′), 38.90 (C-8), 38.96 (C-8*), 37.20, 35.37, 34.98, 33.06, 32.83, 32.00, 31.96, 30.22, 30.15, 29.03, 28.75, 28.10, 28.01, 17.24 (C-2, C-2*, C-3, C-3*, C-4, C4*, C-5, C-5*, C-1″, C-1″*, C-2″, C-2″*, C-3″, C-3″*); IR (KBr): $\tilde{\nu}=3467$ (–OH), 2956 (C–H), 1742 (N–(C=O)), 1688 cm^{-1} (N–(C=O)); UV (MeCN): λ_{max} (lg ε)=291.5 (2.073), 202.5 nm (1.915); MS (70 eV, EI): *m/z* (%)=510 (100) [M+Na^+], 998 (8) [2 M+Na^+], $C_{26}H_{33}NO_8$ (487.5); HRMS calcd 487.2206, found 488.2279 $[M+H]^+$ (ESI-HRMS).

4.4.6. 4-Methyl-2,3,4,5,8,9-hexahydro-6*H*,14b*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-1-yl-2-hydroxy-(3-methylbutyl)malic acid-ester (5a). To solution of **20a** (20.0 mg, 40 μmol) in dichloromethane (1 mL) were added di-*tert*-butyl-4-methylpiperidine (29.0 mg, 140 μmol, 3.5 equiv) and trimethyloxoniumtetrafluoroborate (15.8 mg, 100 μmol, 2.5 equiv) at rt and stirred for 12 h. The yellow solution was diluted with MeOH (2 mL), cooled to 0 °C and sodium borohydride (9.0 mg, 240 μmol, 6.0 equiv) was added. After 1 h at 0 °C the reaction mixture was poured into a pH7 buffer solution (10 mL), extracted with dichloromethane (4×15 mL), dried over Mg_2SO_4 and concentrated to dryness in vacuo. The crude product was purified by preparative thin layer chromatography with ethyl acetate/methanol (1:1) as eluent to give **5a** (11 mg, 23 μmol) in 57% yield.

R_f=0.24 (EE/MeOH, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.64 (s, 0.5H, 10-H_I^*), 6.63 (s, 0.5H, 10-H_1), 6.60 (s, 0.5H, 14-H_I^*), 6.59 (s, 0.5H, 14-H_1), 5.87 (m_c, 2H, 12-H_2), 5.45 (m_c, 0.5H, 1-H_I^*), 5.39 (m_c, 0.5H, 1-H_1), 3.65 (s, 1.5H, OMe*), 3.55 (s, 1.5H, OMe), 3.49–3.37 (m, 1H, 14b-H_1), 3.37–0.85 (m, 21H, 2-H_2, 3-H_2, 4-H_2, 5-H_2, 6-H_2, 8-H_2, 9-H_2, 3′-H_2, 1″-H_2, 2″-H_2, 3′-H_1), 0.84–0.75 (m, 3H, 3″-CH_3), 0.74–0.63 (m, 3H, 3″-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ=174.5 (C-1′*), 174.4 (C-1′), 170.8 (C-4′*), 146.8 (C-10a), 146.3 (C-13a*), 146.2 (C-13a), 132.2 (C-14a*), 131.8 (C-14a), 128.7 (C-9a*), 128.2 (C-9a), 112.1 (C-10*), 111.9 (C-10), 110.3 (C-14*), 110.0 (C-14), 101.0 (C-12*), 100.9 (C-12), 79.60 (C-1), 74.93 (C-2′*), 74.80 (C-2′), 71.24 (C-3a*), 70.53 (C-3a), 58.99 (C-14b*), 58.46 (C-14b), 51.73 (OMe*), 51.58 (OMe), 49.16 (C-6*), 48.60 (C-6), 43.50 (C-3′*), 43.22 (C-3′), 37.13, 36.88, 31.65, 31.39, 31.18, 31.11, 30.09, 29.62, 27.86, 27.83, 29.82 (C-2, C-3, C-4, C-8, C-9, C-1″, C-2″, C-3″), 21.92 (Me), 22.19 (Me*), 22.54 (Me); IR (KBr): $\tilde{\nu}=2956$ (C–H), 1741 (N–(C=O)), 1506 cm^{-1} (NH); UV (MeCN): λ_{max} (lg ε)=290.5 (2.071), 201.5 nm (1.912); MS (70 eV, EI): *m/z* (%)=487 (23) [M^+], 286 (5) [$C_{17}H_{21}NO_3^+$], 270 (100) [$C_{17}H_{20}NO_2^+$], $C_{27}H_{37}NO_7$ (487.6); HRMS calcd 487.2570, found 488.26238 $[M+H]^+$ (ESI-HRMS).

4.4.7. 4-Methyl-1,2,3,4,5,6,8,13b-octahydrocyclopenta[*c*][1,3]dioxolo[4,5-*g*]pyrrolo[1,2-*b*]isoquinolin-1-yl-2-(3-methylbutyl)malic acid-ester (5b). To solution of **20b** (29.0 mg, 60 μmol) in dichloromethane (1.5 mL) were added di-*tert*-butyl-4-methylpiperidine (43.0 mg, 209 μmol, 3.5 equiv) and trimethyloxoniumtetrafluoroborate (22.0 mg, 149 μmol, 2.5 equiv) at rt and stirred for 12 h. The yellow solution was diluted with MeOH (3 mL), cooled to 0 °C and sodium borohydride (13.0 mg, 358 μmol, 6.0 equiv) was added. After 1 h at 0 °C the reaction mixture was poured into a pH7 buffer solution (15 mL), extracted with dichloromethane (4×20 mL), dried over Mg_2SO_4 and concentrated to dryness in vacuo. The crude product was purified by preparative thin layer chromatography with ethyl acetate/methanol (1:1) as eluent to give **5b** (11 mg, 23 μmol) in 39% yield.

R_f=0.32 (EE/MeOH, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.88 (s, 0.5H, 12-H_1), 6.83 (s, 0.5H, 12-H_1), 6.57 (s, 0.5H, 9-H_I^*), 6.55 (s, 0.5H, 9-H_1), 5.90 (m_c, 2H, 11-H_2), 5.06 (m_c, 1H, 1-H_1), 3.86 (d, *J*=15.7 Hz, 1H, 8-H_1), 3.68 (s, 1.5H, OMe), 3.66 (s, 1.5H, OMe), 2.94 (m_c, 2H, 13b-H_1), 2.74 (m, 3H, 8-H_1, 3′-H_2), 2.07–1.21 (m, 14H, 2-H_2, 3-H_2, 4-H_2, 5-H_2, 6-H_2, 1″-H_2, 2″-H_2), 0.98 (m_c, 1H,

3″-H), 0.87 (m, 6H, 2×3″-Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ=174.8 (C-1*), 174.7 (C-1′), 171.1 (C-4′*), 171.0 (C-4′), 146.6 (C-9a*), 146.5 (C-9a), 146.2 (C-12a*), 146.1 (C-12a), 128.2 (C-13a), 127.0 (C-8a*), 126.8 (C-8a), 109.0 (C-9*), 108.9 (C-9), 107.2 (C-13*), 107.0 (C-13), 100.1 (C-11), 84.49 (C-1*), 84.31 (C-1), 75.00 (C-2′*), 74.98 (C-2′), 68.55 (C-3a*), 68.42 (C-3a), 51.82 (OMe), 50.93 (C-8*), 50.84 (C-8), 51.04 (C-13b*), 50.51 (C-13b), 48.21 (C-3′*), 48.17 (C-3′), 43.60 (C-6*), 43.50 (C-6), 41.39, 40.91, 37.33, 37.23, 31.94, 31.83, 31.28, 31.11, 29.40, 29.12, 28.07, 27.00 (C-2, C-2*, C-3, C-3*, C-4, C4*, C-1″, C-1″*, C-2″, C-2″*, C-3″, C-3″*), 22.54 (Me*), 22.47 (Me), 22.36 (Me*), 22.30 (Me), 21.64 (C-5*), 21.41 (C-5); IR (KBr): $\tilde{\nu}$ = 2955 (C–H), 1739 (N–(C═O)), 1487 cm^{-1} (NH); UV (MeCN): λ_{max} (lg ε)=369.5 (2.163), 294.0 (2.064), 201.5 nm (1.900); MS (70 eV, EI): *m/z* (%)=487 (23) [M$^+$], 286 (5) [$C_{17}H_{21}NO_3^+$], 270 (100) [$C_{17}H_{20}NO_2^+$], $C_{26}H_{35}NO_7$ (473.6); HRMS calcd 473.2413, found 474.2485 [M+H]$^+$ (ESI-HRMS).

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