A Partial Synthesis of the Skeleton of Deoxypumiloside, a Putative Intermediate in Camptothecin Biosynthesis

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Ajmalicine (**3**) was used as the starting material for the synthesis of a camptothecin-like skeleton. After C-21 activation through allylic conjugation, regiospecific tertiary amine oxidation was achieved with mercury salts. Subsequent biomimetic oxidation of the indole nucleus then gave quinolone lactam **14**. A two-step process finally afforded **4**, a close analogue of deoxypumiloside (**5**), one of the putative intermediates in the biosynthesis of camptothecin.

Introduction

In continuation of our work on the partial synthesis of analogues of the anticancer alkaloid camptothecin (**1**)[1,2] we wish to report the preparation of a key intermediate **4** from the heteroyohimbane alkaloid ajmalicine (**3**) (Figure 1).

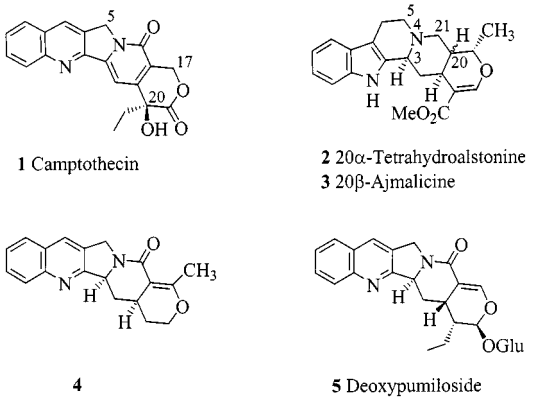

Figure 1

Starting with the epimeric tetrahydroalstonine (**2**), we encountered major difficulties due to the systematic formation of C-5 lactams.[3] In the ajmalicine series, an interesting breakthrough was the formation of the enol ether **7** (Scheme 1), allowing possible oxidation of the activated C-21 position to provide the required lactam.[4] For this purpose the Polonovski−Potier reaction should have been an efficient approach.[5] Indeed, we have shown that *N*-oxides of piperidines bearing a double bond in β-position to the nitrogen atom afforded easily conjugated iminium salts, which afforded α-amino nitriles through potassium cyanide trapping.[6] The anion of the latter was subsequently oxidized with O_2 to produce a lactam.[7]

Unfortunately, a rearrangement of the intermediate *N*-trifluoroacetoxyammonium ion occurred instead of the standard Polonovski−Potier reaction.[4] It was thus necessary to explore other oxidation reactions.

Results and Discussion

When placed in aqueous acidic media under reflux conditions, ajmalicine (**3**) undergoes an unusual rearrangement. Formation of the thermodynamically more stable lactol **6** was first observed by Le Men's group after saponification of ajmalicine and heating of the resultant acid in 2 N HCl solution for 12 h (15% for the two steps).[8] Performing of the reaction in one step in refluxing 2 N HCl for 24 h allowed us to improve the yield greatly. Dehydration of **6** with *para*-toluenesulfonic acid (PTSA) under anhydrous conditions cleanly gave the enol ether **7**, in 82% yield from ajmalicine (**3**) (Scheme 1). The enol ether **7** was assumed to be the required substrate to direct tertiary amine oxidation towards the C-21 position, due to its allylic character (biogenetic numbering for camptothecin and heteroyohimbane derivatives).[9]

Allylic tertiary amines have been oxidized to amides by a few methods including electrochemical anodic oxidation[10] and the use of chromium trioxide−pyridine complex,[11] manganese dioxide,[12] ozone,[13] and potassium permanganate.[14] Furthermore, two sets of oxidation conditions − $Hg(OAc)_2$/EDTA·4Na (pH = 8)[15] and I_2/$NaHCO_3$ [16] − are known to be compatible with an unprotected indole group. However, attempts to oxidize the tertiary amine of **7** to a lactam under the latter conditions failed, and produced the vinylogous amide **8** as the only isolable product in 35% yield. Subjection of **8** to an aqueous acidic medium resulted

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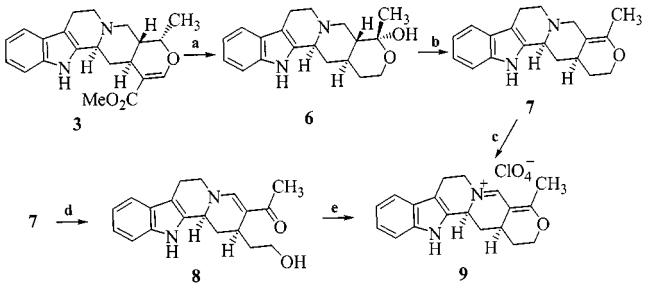
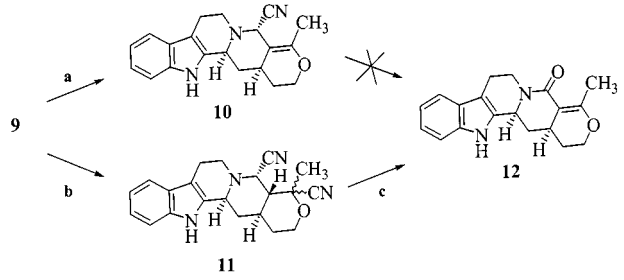
in cyclisation of the E-ring to give a quantitative yield of the desired iminium ion **9**, isolated as its stable perchlorate salt (Scheme 1). The E-ring-opened compound **8** resulted from a Michael-type addition of a water molecule to the intermediate $\Delta^{4(21)}$-iminium ion **9** and opening of the produced lactol to give the stable vinylogous amide. Basic conditions were therefore incompatible with lactam formation, since attack of water would be localized at the 1,4-position of the iminium ion.



Scheme 1. Reagents and conditions: **a**: HCl 2 N, reflux, 24 h; **b**: PTSA 1.1 equiv., 3-Å molecular sieves, dioxane, reflux, 1 h (82% from **3**); **c**: $Hg(OAc)_2$, EDTA·2Na, 60 °C, 3 h, then $HClO_4$ (75%); **d**: I_2, $NaHCO_3$, THF/H_2O, 60 °C, 3 h or $Hg(OAc)_2$, EDTA·4Na, 60 °C, 3 h (35%); **e**: 10% citric acid aqueous solution, reflux, 1 h, then $HClO_4$ (quant.)

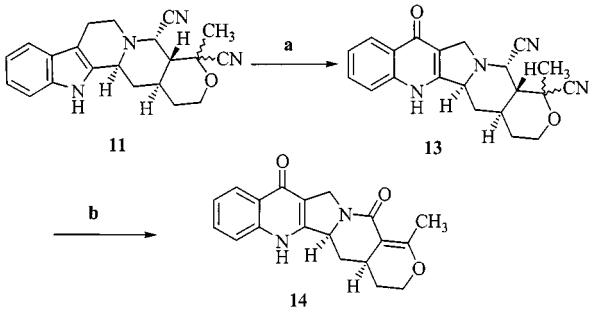
We therefore decided to run the oxidation under slightly acidic conditions in order to obtain the iminium salt in one step. Enol ether **7** was stirred in an aqueous solution of mercuric acetate in the presence of EDTA·2Na (pH = 6) at 60 °C for 3 h, allowing us to isolate the $\Delta^{4(21)}$-iminium salt **9** as the sole regioisomer in 75% yield. Oxidation of the N_b tertiary amine may produce three iminium ions, although with $\Delta^{4(5)}$ strongly disfavored. Competition between $\Delta^{4(3)}$ and $\Delta^{4(21)}$ was expected to occur, because of conjugation with the indole and with the enol ether, respectively; Wenkert et al. obtained the 3-dehydro compound when performing the oxidation on ajmalicine (**3**).[17] In our case, however, we were very pleased to observe total regioselectivity in favor of the desired $\Delta^{4(21)}$-iminium ion. We assumed a crucial influence of the oxygen lone pair, inducing additional electronic delocalisation.[4,18]

Trapping of iminium ion **9** with cyanide anion gave the desired α-amino nitrile **10** in 72% yield and with total stereoselectivity (Scheme 2).[19] Oxidation of an α-amino nitrile anion into a lactam can be achieved by bubbling oxygen through the solution.[7,20] Unfortunately, **10** proved to be very sensitive to decomposition and basic oxidation attempts failed. Conjugation through the C-19/C-20 double bond was assumed to make the cyano group more labile and the compound unstable. To impede electronic delocalization we performed iminium trapping with a large excess of KCN for 48 h. We were thus able to isolate the much more stable dicyano compounds **11** in 68% yield (two diastereoisomers 5:1 in favor of the 19α-cyano as confirmed by NMR spectroscopic analyses including NOESY experiments; Scheme 2).



Scheme 2. Reagents and conditions: **a**: KCN/citric acid, pH = 4, CH_2Cl_2, room temp., 3 h (72%); **b**: KCN excess/citric acid, pH = 4, CH_2Cl_2, room temp., 48 h (68%); **c**: *t*BuOK, O_2, DMF, −20 °C, 4 h (71%)

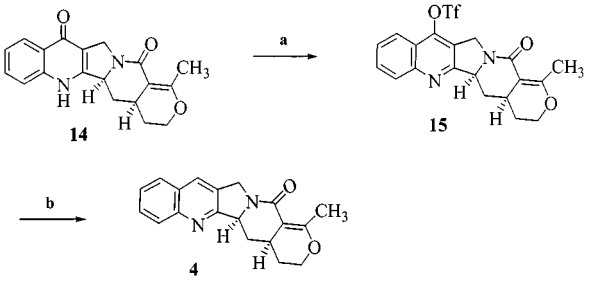
As hoped, treatment of the α-amino nitrile **11** with 6 equiv. of *t*BuOK in DMF at −20 °C with O_2 bubbling cleanly afforded the indole lactam **12** in 71% yield. Conversion of the α-amino nitrile into a lactam was accompanied by an E2 elimination of the second cyanide group to give the α,β-unsaturated lactam (Scheme 2). A change in the reaction temperature dramatically modified the course of the reaction; we observed that indole oxidation began at temperatures above −20 °C. Thus, if performed at room temperature, the reaction would produce a mixture of compounds in which the quinolone lactam **14** (Scheme 3), the result of a double oxidation, could be isolated in 38% yield. In order to improve this yield, we turned to a two-step process; indole oxidation to quinolone was first accomplished quantitatively with O_2 and *t*BuOK/*t*BuOH in THF at room temperature. Interestingly, no trace of α-amino nitrile transformation was detected in these solvents even with an excess of base after 24 h. It is assumed that a medium as protic as *t*BuOH/THF hinders dianion formation. The required quinolone lactam **14** was then obtained by aerobic (O_2) oxidation in DMF with 3 equiv. of *t*BuOK at room temperature. The overall yield for this two-step process reached 55% (Scheme 3).



Scheme 3. Reagents and conditions: **a**: *t*BuOK/*t*BuOH, O_2, 18-crown-6, THF, room temp., 2 h (93%); **b**: *t*BuOK, O_2, DMF, room temp., 4 h (62%)

Transformation of the quinolone into a quinoline was first attempted by quantitative conversion of the quinolone moiety into a chloroquinoline with $SOCl_2$ in DMF at room temperature with subsequent reduction of the chloro substituent. However, because of the instability of the chloroquinoline intermediate, we were not able to isolate the desired quinoline under heterogeneous palladium-catalyzed hydrogenolysis conditions.

Conversion of the quinolone lactam **14** into the corresponding stable triflate **15** was achieved in 82% yield by treatment with *N*-phenylbis(trifluoromethane)sulfonimide and 4-(dimethylamino)pyridine (DMAP) as a catalyst in CH_2Cl_2 at 0 °C. With triflate **15** in hand, we were finally able to proceed with the palladium-catalyzed ammonium formate reduction[21] to obtain the desired quinoline lactam **4** in quantitative yield (Scheme 4).



Scheme 4. Reagents and conditions: **a**: Tf_2NPh, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C, 4 h (80%); **b**: $Pd(OAc)_2$, DPPF, Et_3N, HCO_2H, dioxane, 80 °C, 1 h (86%)

Conclusion

The close analogue **4** of deoxypumiloside (**5**), a biogenetic intermediate of camptothecin (**1**),[22] has been synthesized in seven steps starting from ajmalicine (**3**) (Figure 1). The critical step of this synthesis consisted of the regioselective tertiary amine oxidation through allylic activation. Work to obtain 17-substituted analogues of camptothecin (**1**) is in progress.

Experimental Section

General Remarks: All solvents were dried by standard methods. Melting points were determined with a Leica melting point microscope and are uncorrected. IR spectra were obtained using a Nicolet 205-FT infrared spectrophotometer. Only noteworthy IR absorptions are listed (cm^{-1}). ^1H and ^{13}C NMR spectra (δ values, *J* [Hz]) were recorded with a Bruker AC 300 (300 and 75.5 MHz) instrument. Elemental analyses were performed at the Microanalysis Laboratory of the Pierre et Marie Curie University, Paris. Mass spectra were recorded with an AEI MS-50 instrument. Optical rotations were measured with a Perkin−Elmer 241 polarimeter. IUPAC recommendations were used for the names of all compounds. For numbering different from the biogenetic one in the case of camptothecin derivatives, see Figure 2.

19α-Hydroxy-19β-methyl-18-oxayohimbane (6): Ajmalicine (**3**; 5.00 g, 14.2 mmol) was vigorously stirred under reflux in 250 mL of an aqueous 2 N HCl solution for 24 h. After complete dissolution, the solution was cooled and poured into 100 mL of an ice-cooled saturated Na_2CO_3 aqueous solution. The aqueous layer was extracted with 3 × 250 mL of CH_2Cl_2 and the organic layer was dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude lactol **6** (4.12 g, 92% yield) as a pale yellow solid. R_f = 0.20 (CH_2Cl_2/MeOH, 95:5). M.p. 188 °C. $[\alpha]_D^{22} = -69.5$ (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3591, 3475, 1466, 1447 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (q, *J* = 10.5 Hz, 1 H), 1.42 (s, 3 H), 1.46 (td, *J* = 11.1, 3.8 Hz, 1 H), 1.58 (br. d, *J* = 11.1 Hz, 1 H), 1.72 (td, *J* = 10.8, 2.5 Hz, 1 H), 1.90 (tt, *J* = 10.6, 1.8 Hz, 1 H), 2.07 (dt, *J* = 10.5, 1.0 Hz, 1 H), 2.41 (t, *J* = 10.2 Hz, 1 H), 2.67 (td, *J* = 10.2, 3.1 Hz, 1 H), 2.72 (dd, *J* = 11.1, 2.0 Hz, 1 H), 3.01 (br. d, *J* = 11.1 Hz, 1 H), 3.06−3.09 (m, 2 H), 3.32 (br. d, *J* = 10.5 Hz, 1 H), 3.69 (dd, *J* = 10.2, 2.0 Hz, 1 H), 4.04 (td, *J* = 10.2, 1.2 Hz, 1 H), 7.06 (td, *J* = 7.1, 1.2 Hz, 1 H), 7.12 (td, *J* = 7.1, 1.2 Hz, 1 H), 7.32 (d, *J* = 7.1 Hz, 1 H), 7.47 (d, *J* = 7.1 Hz, 1 H), 7.72 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 27.9, 32.3, 33.4, 36.6, 48.2, 53.4, 56.3, 59.7, 60.8, 96.0, 108.2, 110.8, 118.2, 119.5, 121.4, 127.5, 134.7, 136.1. MS (CI: NH_3): *m*/*z* (%) = 313 (100) [MH^+], 295. $C_{19}H_{24}N_2O_2$ (312.2): C 73.05, H 7.74, N 8.97; found C 72.66, H 7.95, N 8.60.

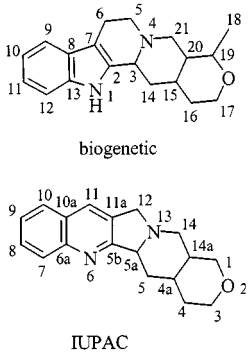


Figure 2. Biogenetic numbering and numbering according to IUPAC in the case of camptothecin derivatives

19,20-Didehydro-19-methyl-18-oxayohimbane (7): *p*-Toluenesulfonic acid (2.75 g, 1.10 equiv.) and 3-Å molecular sieves (10 spatulas, 15 g) were added to a solution of lactol **6** (4.12 g, 13.1 mmol) in dioxane (150 mL). The mixture was stirred under reflux for 1 h, allowed to cool to room temperature, and quenched by addition of 25 mL of a saturated Na_2CO_3 aqueous solution. Extraction with 2 × 50 mL of CH_2Cl_2 afforded an organic phase, which was washed with 100 mL of brine and dried with $MgSO_4$. The solvents were evaporated to give the crude enol ether **7**. Purification by flash chromatography on silica gel with CH_2Cl_2/MeOH/NH_4OH (98:2:1) as eluent afforded pure **7** (3.55 g, 92%) as a white powder. R_f = 0.34 (CH_2Cl_2/MeOH, 95:5). M.p. 208 °C. $[\alpha]_D^{22} = -47$ (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3474, 1682 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (q, *J* = 12.0 Hz, 1 H), 1.62 (qd, *J* = 11.0, 4.2 Hz, 1 H), 1.80 (s, 3 H), 2.02 (m, 1 H), 2.19 (ddd, *J* = 12.0, 4.6, 2.7 Hz, 1 H), 2.32 (m, 1 H), 2.66 (td, *J* = 11.0, 4.4 Hz, 1 H), 2.77 (dd, *J* = 12.1, 2.0 Hz, 1 H), 2.92 (d, *J* = 12.4 Hz, 1 H), 3.03 (m, 1 H), 3.11 (dd, *J* = 11.0, 5.8 Hz, 1 H), 3.38 (br. d, *J* = 11.4 Hz, 1 H), 3.64 (d, *J* = 12.4 Hz, 1 H), 3.84 (td, *J* = 10.5, 2.4 Hz, 1 H), 4.02 (dt, *J* = 10.5, 6.6 Hz, 1 H), 7.06 (td, *J* = 7.2, 1.4 Hz, 1 H), 7.12 (td, *J* = 7.2, 1.4 Hz, 1 H), 7.28 (d, *J* = 7.2 Hz, 1 H), 7.48 (d, *J* = 7.2 Hz, 1 H), 7.78 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3, 21.6, 30.5, 32.0, 37.3, 52.6, 56.5, 59.5, 64.5, 105.7, 108.1, 110.8, 118.1, 119.4, 121.3, 127.4, 134.5, 136.0, 145.8. MS (CI: NH_3): *m*/*z* = 295 [MH^+]. $C_{19}H_{22}N_2O$ (294.2): C 77.52, H 7.53, N 9.52; found C 76.92, H 7.60, N 9.22.

1-[2-(2-Hydroxyethyl)-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]-quinolizin-3-yl]ethanone (8). − Method A: An aqueous $NaHCO_3$ solution (10%, 10 mL) and sublimed iodine (863 mg, 2 equiv.) were added to enol ether **7** (500 mg, 1.71 mmol), dissolved in THF (10 mL). The mixture was stirred at 60 °C for 3 h, concentrated

under reduced pressure, and diluted with 25 mL of a saturated aqueous $Na_2S_2O_3$ solution. The aqueous layer was extracted with 2 × 25 mL of CH_2Cl_2 and the extracts were washed with brine and dried with $MgSO_4$. The solvents were evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel with CH_2Cl_2/MeOH (95:5) as eluent to give the vinylogous amide **8** (182 mg, 35%) as a red solid. − **Method B:** A solution of $Hg(OAc)_2$/EDTA·4Na (1:1, 0.1 M, 16.3 mL, 3 equiv., pH = 10) was added to a stirred solution of enol ether **7** (500 mg, 1.71 mmol) in 2 mL of CH_2Cl_2. The mixture was heated to 60 °C for 3 h, filtered warm through a thick pad of Celite® to remove mercury metal, and then partitioned between CH_2Cl_2 (25 mL) and a saturated solution of $NaHCO_3$ (25 mL). The organic layer was washed with brine and dried with $MgSO_4$, and the solvents were evaporated under reduced pressure. The same purification as mentioned above gave 183 mg of pure **8** in 35% yield. R_f = 0.32 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D^{24}$ = −45 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$ film): $\tilde{\nu}$ = 3469, 3263, 1612, 1572 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.03 (m, 1 H), 1.51 (m, 1 H), 2.26 (s, 3 H), 2.42 (m, 2 H), 2.86 (dd, *J* = 14.1, 4.4 Hz, 1 H), 2.98 (m, 1 H), 3.19 (dd, *J* = 9.5, 4.9 Hz, 1 H), 3.30 (td, *J* = 11.0, 3.0 Hz, 1 H), 3.44 (dt, *J* = 12.0, 2.2 Hz, 1 H), 3.67 (td, *J* = 11.6, 4.5 Hz, 1 H), 3.82 (dd, *J* = 12.9, 5.3 Hz, 1 H), 4.75 (br. s, 1 H), 7.07 (td, *J* = 7.0, 1.0 Hz, 1 H), 7.13 (td, *J* = 7.0, 1.2 Hz, 1 H), 7.34 (d, *J* = 7.2 Hz, 1 H), 7.43 (d, *J* = 7.2 Hz, 1 H), 7.51 (s, 1 H), 10.0 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0, 23.7, 24.7, 30.9, 38.3, 51.3, 52.4, 59.8, 106.8, 111.6, 112.9, 117.6, 119.3, 121.6, 126.9, 133.8, 136.3, 149.7, 194.6. MS (CI:NH_3): *m*/*z* = 311 [MH^+].

19-Methyl-19,20,21-tridehydro-18-oxayohimbanium Perchlorate (9). − Method A: A suspension of the vinylogous amide **8** (100 mg, 0.32 mmol) in 5 mL of a 10% aqueous citric acid solution was heated under reflux for 1 h and then allowed to cool to room temperature. Addition of 2 drops of a concentrated $HClO_4$ solution and extraction with CH_2Cl_2 (2 × 10 mL) afforded 125 mg (quantitative) of the pure iminium perchlorate **9** as a yellow powder. − **Method B:** An aqueous solution of $Hg(OAc)_2$/EDTA·2Na (1:1, 0.1 M, 2 equiv., pH 6, 177 mL) was added to the enol ether **7** (2.60 g, 8.84 mmol). The mixture was heated to 60 °C for 3 h and then filtered warm through a thick pad of Celite® to remove mercury metal. The pad was washed twice with 50 mL of EtOH and the filtrate was then concentrated under reduced pressure (50 mL). Addition of a few drops of concentrated $HClO_4$ after cooling to 0 °C gave a yellow precipitate, which was filtered and washed twice with water. Recrystallisation from EtOH gave 2.60 g (75%) of the pure iminium perchlorate **9** as a yellow powder. R_f = 0.25 (CH_2Cl_2/MeOH, 95:5). UV: λ_{max} (log ε) = 228 (5.25), 306 (4.65), 354 nm (3.12) − ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.33 (q, *J* = 12.2 Hz, 1 H), 1.52 (qd, *J* = 12.3, 3.6 Hz, 1 H), 2.17 (br. d, *J* = 12.3 Hz, 1 H), 2.35 (s, 3 H), 2.76 (m, 1 H), 2.90 (dt, *J* = 12.8, 4.1 Hz, 1 H), 2.98 (m, 2 H), 4.02 (dt, *J* = 11.4, 4.1 Hz, 1 H), 4.34 (t, *J* = 10.8 Hz, 1 H), 4.51 (dd, *J* = 11.8, 3.4 Hz, 1 H), 4.65 (dd, *J* = 11.2, 3.1 Hz, 1 H), 5.32 (br. d, *J* = 9.0 Hz, 1 H), 7.02 (t, *J* = 7.5 Hz, 1 H), 7.12 (t, *J* = 7.3 Hz, 1 H), 7.38 (d, *J* = 7.9 Hz, 1 H), 7.49 (d, *J* = 7.7 Hz, 1 H), 11.02 (s, 1 H). ^{13}C NMR (75 MHz, [D6]DMSO): δ = 18.9, 21.9, 26.8, 27.2, 34.2, 55.3, 56.1, 70.4, 106.9, 106.9, 112.4, 119.2, 120.1, 122.8, 126.7, 131.5, 137.5, 163.3, 177.9. MS: *m*/*z* = 293 [M^+].

21α-Cyano-19-methyl-19,20-didehydro-18-oxayohimbane (10): A buffered aqueous solution of KCN/citric acid (0.2 M, 8.4 mL, 2 equiv.) was added to a suspension of the iminium perchlorate **9** (420 mg, 1.06 mmol) in 10 mL of CH_2Cl_2. The mixture was vigorously stirred for 3 h at room temperature. The aqueous layer was basified by addition of 25 mL of a saturated Na_2CO_3 aqueous solution and extracted with 25 mL of CH_2Cl_2. The organic layer was washed with 25 mL of brine and dried with $MgSO_4$, and the solvents were evaporated under reduced pressure to give 243 mg (72%) of the crude α-amino nitrile **10** as a yellow powder. Unstable on TLC. IR ($CHCl_3$, film): $\tilde{\nu}$ = 2305, 1654 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (q, *J* = 12.2 Hz, 1 H), 1.59 (qd, *J* = 10.4, 3.5 Hz, 1 H), 1.87 (d, *J* = 1.7 Hz, 3 H), 2.02 (m, 1 H), 2.19 (ddd, *J* = 12.2, 4.4, 2.7 Hz, 1 H), 2.58 (m, 1 H), 2.78 (br. d, *J* = 10.8 Hz, 1 H), 2.96 (m, 1 H), 3.00 (m, 1 H), 3.02 (m, 1 H), 3.84 (br. d, *J* = 11.3 Hz, 1 H), 3.86 (td, *J* = 10.5, 2.6 Hz, 1 H), 4.01 (dt, *J* = 10.5, 2.8 Hz, 1 H), 4.63 (s, 1 H), 7.08 (td, *J* = 7.1, 1.1 Hz, 1 H), 7.13 (td, *J* = 7.4, 1.4 Hz, 1 H), 7.29 (d, *J* = 7.4 Hz, 1 H), 7.47 (d, *J* = 7.1 Hz, 1 H), 7.98 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.6, 21.6, 29.2, 30.0, 37.4, 51.2, 54.5, 64.7, 103.1, 107.8, 110.9, 113.2, 116.1, 118.3, 119.7, 121.8, 127.1, 133.4, 136.3, 149.6. MS (CI: NH_3): *m*/*z* = 320 [MH^+], 293 (100).

19α,21α-Dicyano-19β-methyl-18-oxayohimbane (11): A buffered aqueous solution of KCN/citric acid (1.0 M, 23 mL, 10 equiv.) was added to a suspension of the iminium perchlorate **9** (880 mg, 2.24 mmol) in CH_2Cl_2 (10 mL). The mixture was vigorously stirred at room temperature for 36 h. The aqueous layer was basified by addition of 25 mL of a saturated Na_2CO_3 aqueous solution and extracted twice with 25 mL of CH_2Cl_2. The organic layer was washed with 25 mL of brine and dried with $MgSO_4$, and the solvents were evaporated under reduced pressure to give the crude dicyano compound **11**. Purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 80:20) afforded 527 mg (68%) of pure **11** as a white powder. R_f = 0.65 (CH_2Cl_2/MeOH, 95:5). − M.p. 162 °C (dec). $[\alpha]_D^{22}$ = −136 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3334, 2358, 2239, 1452 cm^{-1}. UV (CH_3CN): λ (log ε) = 228 (5.31), 278 nm (3.88) − Major diastereoisomer: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.13 (q, *J* = 12.2 Hz, 1 H), 1.31 (qd, *J* = 11.2, 2.7 Hz, 1 H), 1.41 (m, 1 H), 1.42 (s, 3 H), 1.66 (dd, *J* = 11.9, 7.4 Hz, 1 H), 2.08 (m, 2 H), 2.77 (br. d, *J* = 8.8 Hz, 1 H), 2.98 (m, 3 H), 3.94 (br. d, *J* = 11.8 Hz, 2 H), 3.97 (d, *J* = 7.4 Hz, 1 H), 4.82 (br. d, *J* = 11.0 Hz, 1 H), 7.12 (td, *J* = 7.8, 1.1 Hz, 1 H), 7.18 (td, *J* = 7.4, 1.2 Hz, 1 H), 7.35 (d, *J* = 7.8 Hz, 1 H), 7.47 (d, *J* = 7.6 Hz, 1 H), 8.01 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9, 25.4, 31.8, 32.1, 36.9, 49.7, 51.5, 54.3, 55.2, 65.3, 72.4, 108.1, 111.6, 114.0, 117.8, 118.6, 120.1, 122.3, 127.2, 133.4, 136.7. MS (CI: NH_3): *m*/*z* = 347 [MH^+], 320, 293 (100). $C_{21}H_{22}N_4O$ (346.2): C 72.81, H 6.40, N 16.17; found C 73.17, H 6.68, N 15.84.

19-Methyl-19,20-didehydro-18-oxayohimban-21-one (12): Dioxygen was bubbled for 10 min through a solution of the dicyano compound **11** (200 mg 0.58 mmol) in 10 mL of DMF, cooled to −20 °C. A solution of *t*BuOK (390 mg, 6 equiv.) in 5 mL of DMF was then slowly added. The mixture was stirred under dioxygen bubbling conditions for 4 h at −20 °C and poured into 10 mL of an ice-cooled saturated NH_4Cl aqueous solution. It was extracted twice with 15 mL of CH_2Cl_2 and the organic layer was washed with 20 mL of brine and dried with $MgSO_4$. The solvents were evaporated under reduced pressure. Purification by flash chromatography on silica gel with CH_2Cl_2/MeOH (98:2) as eluent gave 127 mg (71%) of the pure indole lactam **12** as a red powder. R_f = 0.47 (CH_2Cl_2/EtOAc, 80:20). $[\alpha]_D^{22}$ = −112 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3473, 1643, 1582 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.50 (q, *J* = 12.2 Hz, 1 H), 1.55 (qd, *J* = 12.0, 3.8 Hz, 1 H), 2.02 (ddt, *J* = 12.0, 6.9, 2.2 Hz, 1 H), 2.32 (s, 3 H), 2.55 (ddd, *J* = 12.2, 4.5, 3.2 Hz, 1 H), 2.62 (m, 1 H), 2.75 (td, *J* = 9.0, 1.6 Hz, 1 H), 2.86 (d, *J* = 8.1 Hz, 1 H), 2.87 (br. d, *J* = 9.1 Hz, 1 H), 3.91 (td, *J* = 10.6, 2.0 Hz, 1 H), 4.23 (ddd, *J* = 10.7, 3.8, 2.2 Hz, 1 H),

4.76 (dd, J = 11.7, 4.5 Hz, 1 H), 5.19 (d, J = 8.1 Hz, 1 H), 7.10 (t, J = 7.1 Hz, 1 H), 7.16 (t, J = 7.1 Hz, 1 H), 7.31 (d, J = 7.1 Hz, 1 H), 7.49 (d, J = 7.0 Hz, 1 H), 8.28 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5, 21.4, 29.1, 29.7, 35.5, 40.3, 53.6, 65.6, 103.8, 109.7, 111.0, 118.4, 119.7, 122.0, 127.0, 133.8, 136.3, 162.3, 165.0. MS (CI: NH_3): m/z = 309 [MH^+].

(4a*R*,5a*S*)-1-Methyl-4,4a,5,5a,12-hexahydro-14*H*-pyrano-[3′,4′:6,7]indolizino[1,2-*b*]quinoline-11(3*H*),14-dione (14): Dioxygen was bubbled for 15 min through a solution of the dicyano compound **12** (0.87 g, 2.51 mmol) in 25 mL of DMF. A solution of *t*BuOK (1.69 g, 6 equiv.) in 15 mL of dry DMF was then slowly added. The mixture was stirred under oxygen bubbling conditions for 4 h and then poured into 5 mL of an ice-cooled saturated NH_4Cl solution. Extraction with 3 × 50 mL of CH_2Cl_2 and evaporation of the solvents under reduced pressure after drying with $MgSO_4$ gave crude **14**. Purification by flash chromatography on silica gel with CH_2Cl_2/MeOH (90:10) as eluent gave 307 mg (38%) of the pure quinolone lactam **13** as a yellow powder. R_f = 0.35 (CH_2Cl_2/MeOH, 90:10). M.p. 280 °C (dec). IR (KBr): ṽ = 3220, 3096, 1644, 1580, 1520 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$ + 1 drop of CD_3OD): δ = 1.18 (q, J = 12.0 Hz, 1 H), 1.41 (qd, J = 12.3, 3.8 Hz, 1 H), 1.85 (br. d, J = 12.8 Hz, 1 H), 2.10 (s, 3 H), 2.40 (dt, J = 12.1, 3.1 Hz, 1 H), 2.51 (m, 1 H), 3.82 (td, J = 10.4, 2.2 Hz, 1 H), 4.12 (br. d, J = 10.6 Hz, 1 H), 4.18 (dd, J = 15.0, 1.8 Hz, 1 H), 4.72 (br. d, J = 10.2 Hz, 1 H), 4.82 (dd, J = 15.0, 1.8 Hz, 1 H), 7.13 (t, J = 7.9 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 7.39 (t, J = 7.9 Hz, 1 H), 8.04 (d, J = 8.1 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$ + 1 drop of CD_3OD): δ = 20.1, 28.3, 32.0, 32.2, 48.5, 60.9, 66.1, 101.5, 114.0, 117.8, 123.6, 124.8, 125.1, 131.5, 140.2, 150.2, 163.3, 164.7, 174.6. MS (CI: NH_3): m/z = 323 [MH^+]. CI HRMS ($C_{19}H_{19}N_2O_3$): 323.139; found 323.139.

(1*R*,4a*R*,5a*S*,14*S*,14a*R*)-1,14-Dicyano-1-methyl-4,4a,5,5a,6,12,14,14a-octahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-11(3*H*)-one (13): Dioxygen was bubbled for 15 min through a solution of the dicyano compound **11** (1.00 g, 2.89 mmol) and 18-crown-6 (0.1 equiv.) in 25 mL of THF. A solution of *t*BuOK/*t*BuOH (8.67 mL, 1 M, 3 equiv.) was then added dropwise. The reaction mixture was stirred under oxygen bubbling conditions for 2 h and then poured into 5 mL of an ice-cooled saturated aqueous NH_4Cl solution. Extraction with 2 × 50 mL of CH_2Cl_2 and evaporation of the solvents under reduced pressure after drying with $MgSO_4$ gave 967 mg (93%) of crude **13** as a yellow powder. No purification was necessary for the next step. R_f = 0.18 (CH_2Cl_2/MeOH, 95:5). M.p. 195 °C. IR ($CHCl_3$ film): ṽ = 2358, 2239, 1629, 1585, 1508, 1472 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32−1.48 (m, 3 H), 1.59 (s, 3 H), 1.84 (m, 2 H), 2.45 (br. d, J = 9.2 Hz, 1 H), 3.75−3.92 (m, 3 H), 3.94−4.18 (m, 3 H), 7.38 (t, J = 7.6 Hz, 1 H), 7.62 (t, J = 7.8 Hz, 1 H), 7.78 (d, J = 7.9 Hz, 1 H), 8.36 (d, J = 8.1 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8, 31.9, 32.0, 33.5, 32.2, 49.0, 50.5, 51.5, 61.1, 64.9, 72.4, 113.8, 115.4, 117.3, 119.2, 124.4, 125.2, 125.9, 132.1, 140.4, 152.5, 173.9. MS (CI: NH_3): m/z = 361 [MH^+], 334, 307 (100). − CI HRMS ($C_{21}H_{21}N_4O_2$): 361.167; found 361.167.

14: O_2 was bubbled for 15 min through a solution of crude **13** (967 mg, 2.68 mmol) in 20 mL of dry DMF. A solution of *t*BuOK (902 mg, 3 equiv.) in 5 mL of dry DMF was then slowly added. The red mixture was stirred at room temperature under O_2 bubbling conditions for 2 h and then poured into 5 mL of an ice-cooled NH_4Cl aqueous solution. Extraction with 3 × 25 mL of CH_2Cl_2 and evaporation of the solvents after drying with $MgSO_4$ gave 825 mg of crude quinolone lactam **14**. Purification by flash chromatography on silica gel with CH_2Cl_2/MeOH (90:10) as eluent gave 535 mg (62%) of pure **14**.

(4a*R*,5a*S*)-1-Methyl-11-trifluoromethanesulfonyl-3,4,4a,5,5a,12-hexahydro-14*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-14-one (15): *N*-Phenylbis(trifluoromethane)sulfonimide (Tf_2NPh; 266 mg, 1.2 equiv.), Et_3N (0.2 mL), and 4-(dimethylamino)pyridine (DMAP; 15 mg, 0.2 equiv.) were added to a suspension of the quinolone **14** (200 mg, 0.62 mmol) in 10 mL of CH_2Cl_2. The reaction mixture was stirred at 0 °C for 4 h, washed with 10 mL of brine, and dried with $MgSO_4$. The solvents were evaporated under reduced pressure. Purification of the resulting oil by flash chromatography on silica gel with CH_2Cl_2/EtOAc (80:20) as eluent gave 225 mg (80%) of the pure quinoline triflate **15** as an oil. R_f = 0.71 (CH_2Cl_2/EtOAc, 70:30). $[\alpha]_D^{24}$ = −49 (c = 1.0, $CHCl_3$). IR ($CHCl_3$, film): ṽ = 1680, 1580, 1501 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (q, J = 13.2 Hz, 1 H), 1.68 (qd, J = 12.4, 4.0 Hz, 1 H), 2.09 (br. d, J = 12.3 Hz, 1 H), 2.39 (s, 3 H), 2.81 (m, 1 H), 2.85 (dt, J = 13.4, 3.4 Hz, 1 H), 4.03 (td, J = 11.8, 2.3 Hz, 1 H), 4.32 (ddd, J = 11.8, 4.0, 1.7 Hz, 1 H), 4.72 (d, J = 17.4 Hz, 1 H), 4.98 (dd, J = 11.7, 3.2 Hz, 1 H), 5.57 (d, J = 17.4 Hz, 1 H), 7.68 (t, J = 8.1 Hz, 1 H), 7.80 (t, J = 8.1 Hz, 1 H), 8.07 (d, J = 8.3 Hz, 1 H), 8.11 (d, J = 8.4 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5, 28.7, 32.0, 33.3, 46.9, 61.7, 66.2, 102.1, 118.3, 120.9, 121.0, 121.2, 128.1, 129.1, 130.7, 146.5, 150.4, 163.3, 164.4, 164.6. MS (CI: NH_3): m/z = 455 [MH^+], 323 (100). CI HRMS ($C_{20}H_{18}F_3N_2O_5S$): 455.089; found 455.088.

(4a*R*,5a*S*)-1-Methyl-3,4,4a,5,5a,12-hexahydro-14*H*-pyrano-[3′,4′:6,7]indolizino[1,2-*b*]quinolin-14-one (4): $Pd(OAc)_2$ (2.0 mg, 0.02 equiv.), DPPF (11 mg, 0.02 equiv.), Et_3N (183 μL, 3 equiv.), and HCO_2H (34 μL, 2 equiv.) were added to a solution of quinoline triflate **15** (200 mg, 0.44 mmol) in 10 mL of dry dioxane. The mixture was heated to 80 °C for 1 h, cooled to room temperature, diluted with 10 mL of brine, and extracted with 20 mL of CH_2Cl_2. The organic layer was washed with 20 mL of brine and dried with $MgSO_4$, and the solvents were evaporated under reduced pressure. Purification by flash chromatography on silica gel with CH_2Cl_2/MeOH (97:3) gave 130 mg (86%) of the pure quinoline **4** as a pale yellow powder. R_f = 0.31 (CH_2Cl_2/EtOAc, 70:30). M.p. 184 °C. $[\alpha]_D^{22}$ = −108.5 (c = 1.0, $CHCl_3$). IR ($CHCl_3$ film): ṽ = 1637, 1580, 1501 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (q, J = 11.8 Hz, 1 H), 1.67 (qd, J = 13.1, 3.8 Hz, 1 H), 2.08 (br. d, J = 13.2 Hz, 1 H), 2.41 (s, 3 H), 2.83 (m, 1 H), 2.85 (dt, J = 12.2, 3.4 Hz, 1 H), 4.03 (td, J = 10.4, 2.2 Hz, 1 H), 4.32 (ddd, J = 10.8, 4.0, 1.7 Hz, 1 H), 4.64 (d, J = 16.7 Hz, 1 H), 4.92 (dd, J = 11.8, 3.2 Hz, 1 H), 5.36 (d, J = 16.7 Hz, 1 H), 7.53 (t, J = 8.0 Hz, 1 H), 7.69 (t, J = 7.8 Hz, 1 H), 7.80 (d, J = 8.1 Hz, 1 H), 7.99 (s, 1 H), 8.05 (d, J = 7.5 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4, 28.8, 32.3, 33.5, 48.5, 61.5, 66.3, 102.6, 127.6, 127.8, 128.1, 128.8, 129.2, 129.7, 131.2, 147.8, 162.4, 162.7, 164.7. MS (CI: NH_3): m/z = 307 [MH^+]. CI HRMS ($C_{19}H_{19}N_2O_2$): 307.145; found 307.145.

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