Partial Synthesis of Camptothecin Analogues, 2[+] Oxidation of the CDE Rings of Pentacyclic Quinoline Compounds Derived from Tetrahydroalstonine

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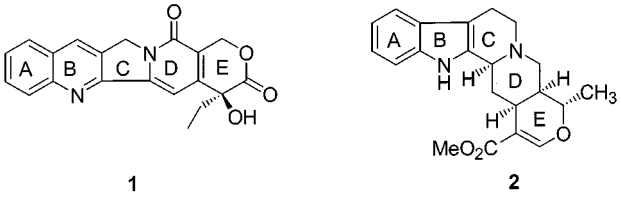
New polycyclic 8,9-dihydro-7*H*-indolizino[1,2-*b*]quinolin-11-ones have been synthesized from tetrahydroalstonine (**2**) through sequential oxidation reactions.

Introduction

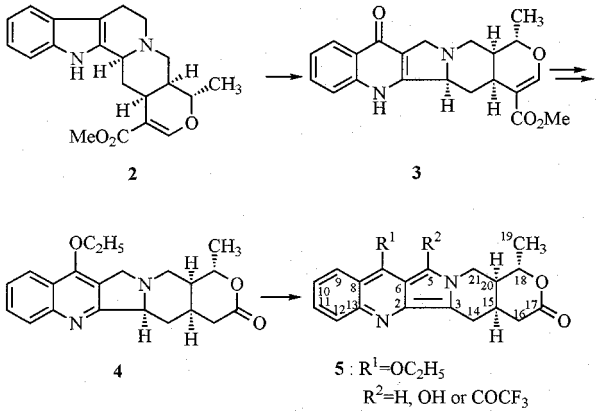
The pentacyclic alkaloid camptothecin (**1**) (Figure 1) exhibits an original cytotoxic activity due to its inhibition of topoisomerase I.[1] This potent activity has been the cause of extensive synthetic work, including total[2] and semisynthetic[3] approaches. The clinical use of **1** as an antitumor agent was limited because of its toxicity and an extremely poor solubility profile. To avoid these problems, numerous analogues were synthesized, providing some information on structure-activity relationships. Studies initiated as early as 1969, as well as recent molecular ones,[4] established that as far as topoisomerase I was concerned, the α-hydroxy lactone of the E ring is essential to the activity. The planarity of the ABCD rings was revealed to be crucial too, as the interaction of camptothecin, DNA and topoisomerase I creates a ternary complex which is stabilized by stacking of the planar moiety of the pentacyclic system.



1 **2**

Figure 1. Camptothecin (**1**) and tetrahydroalstonine (**2**)

In a preliminary communication, we have reported[5] a strategy for the partial synthesis of camptothecin analogues **5** (Scheme 1) from tetrahydroalstonine (**2**) (Figure 1), an easily available heteroyohimbine alkaloid extracted from *Catharanthus* sp. This partial synthesis involved a biomimetic oxidation of the indole nucleus to quinolone **3**, followed by formation of the corresponding quinoline lactone **4** and a Polonovski-Potier oxidation [*m*-CPBA/$(CF_3CO)_2O$] of the tertiary amine to **5**.



Scheme 1

We wish to report in this paper the synthesis of new pentacyclic quinoline compounds derived from tetrahydroalstonine (**2**), possessing enamide CD rings and a C-16-substituted lactone E ring.

Results and Discussion

We first investigated the oxidation of quinoline lactone **4** [obtained from tetrahydroalstonine (**2**) in 5 steps and 36% overall yield].[5]

Oxidation of **4** with metal oxides (MnO_2, CrO_3) led to the formation of the dienamide **6** (Scheme 2). The yields were generally modest because of degradation. Under acidic conditions (H_2SO_4/DMF), **4** was oxidized by CrO_3 to **6** in 15% yield. Use of MnO_2 in chloroform also afforded **6**, in 16% yield, but the best results were obtained by the use of CrO_3 in pyridine at 60 °C (yield 36%).

[+] Part 1: C. Dumas, C. Kan-Fan, J.-F. Carniaux, J. Royer, H.-P. Husson, *Tetrahedron Lett*. **1999**, *40*, 8211.

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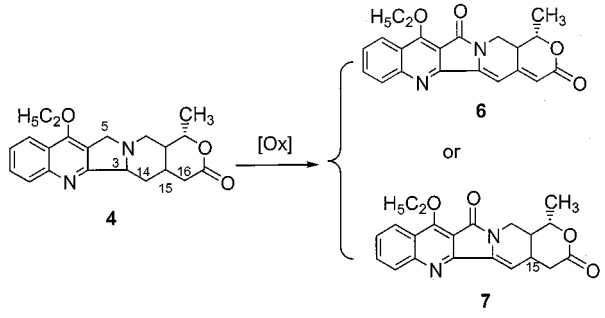
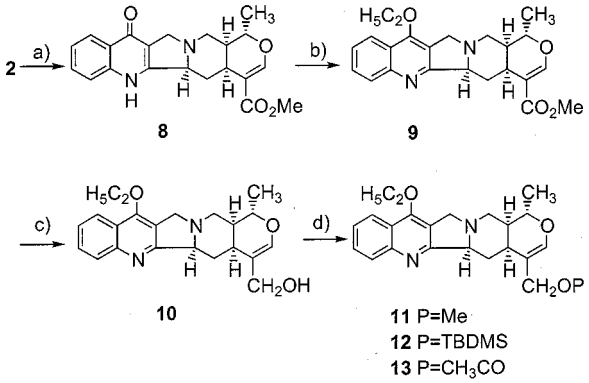
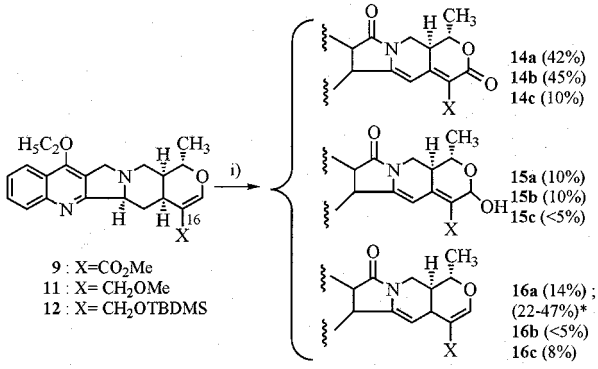


Scheme 2



Scheme 3. Reagents: a) *t*BuOK, O_2, DMF, room temp., 6 h (72%); b) EtI, *t*BuOK, DMF, room temp., 12 h (95%); c) $LiAlH_4$, THF/Et_2O, 0 °C, 3 h (87%); d) NaH, MeI, THF, 0 °C, 6 h (76%) or TBDMSCl/imidazole, DMF, room temp., 12 h (71%) or Ac_2O, CH_2Cl_2, Et_3N, DMAP, room temp., 5 h (47%)



Scheme 4. a: X = CO_2Me; b: X = CH_2OMe; c: X = $CH_2OTBDMS$; reagents: i) MnO_2, $CHCl_3$, room temp., 24 h; * I_2/EtOH/EtONa or DDQ/dioxane was used

Using I_2/AcONa in EtOH, lactone **4** was oxidized only at the CD rings, to give enamide **7**, but in poor yield (19%). Surprisingly, reaction of $Pb(OAc)_4$ in refluxing benzene also led to **7**, in 25% yield from **4**.

Direct transformations of tertiary amines into enamides are rare, but have been mentioned for reactions with I_2[6] and DDQ.[7] In our case, these novel and straightforward oxidations presumably started at the doubly activated C-3 position, giving the more favourable iminium, which further oxidized at C-5 to give enamide **7**. The allylic C-15 position can be oxidized under certain conditions to give dienamide **6**, the overall conjugation of the pentacyclic structure of **6** clearly being the driving force of this reaction.

Attempts to continue the synthesis of camptothecin analogues by functionalization at the C-16 position were not successful. Despite considerable efforts (use of different bases and different solvents), all direct deprotonation-alkylation reactions of compounds **5** or **7** surprisingly remained impossible. It is noteworthy that ethylation at the equivalent position was accomplished in the total synthesis of camptothecin (or analogues), the position being a more favourable benzylic one of the aromatic D ring in those instances.[8] In our case, the lack of reactivity at a nonactivated position could explain why alkylation did not occur. Thus, our plan was modified, using the acrylate function of tetrahydroalstonine (**2**) as a precursor for substitution on the E ring, before oxidation of the CD ring system.

Winterfeldt oxidation[9] of the indole ring of tetrahydroalstonine (**2**) to quinolone **8** was achieved using standard conditions (72% yield). Alkylation of **8** to ethoxyquinoline **9** was easily accomplished in excellent yield (95%) and could be performed on a 20-g scale (Scheme 3). Reduction of the acrylate function of **9** with $LiAlH_4$ in THF/ether mixture provided the allylic alcohol **10** (87% yield), which could be protected as the methyl or TBDMS ethers **11** and **12**.

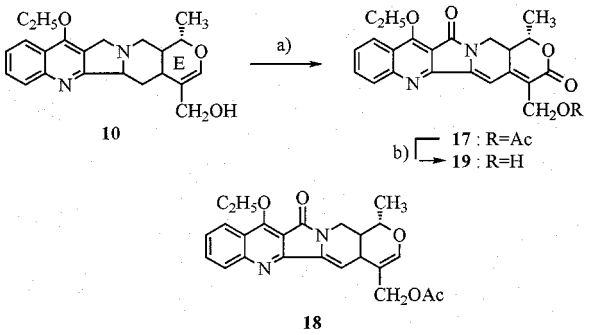
Once again, oxidation of **9**, **11** and **12** proved to be highly dependent on reagents and conditions. Use of MnO_2 provided mixtures of enamides **14**, **15** and **16** (Scheme 4). Although a mixture of compounds was formed in each case, it is interesting to note that this oxidation mainly gave products of type **14**, possessing both a dienamide function and an α-substituted lactone.

Oxidation of **9** with iodine in the presence of EtONa in EtOH led to enamide **16a** in modest yield (22%). DDQ in apolar conditions also gave the enamide **16a** as the sole product in better yield: 31% when using toluene or 47% when using dioxane.

Compounds **16,** which comprise an enamide function, were obviously formed by the same mechanism as enamide **7** (vide supra). The formation of diene function **15** presumably arose from an allylic oxidation at C-15, followed by a rearrangement to lactol **15**.[10] Lactone **14** is the result of lactol **15** oxidation. To check this hypothesis, lactol **15a** was treated with MnO_2 in $CHCl_3$ for 24 h. Lactone **14a** was largely obtained, although surprisingly a small amount of enamide **16a** was also detected.

Similar reactivity was also observed in attempted acetylation of allylic alcohol **10**, which gave unexpected results. When treated with Ac_2O in CH_2Cl_2 solution at 0 °C in the presence of DMAP/Et_3N, allylic alcohol **10** was acetylated to give **13** (Scheme 3), albeit in modest yield (47%). In order to improve the yield, the acetylation was performed in pyridine. Among numerous products formed, the enamide lactone **17** was, to our surprise, isolated as the major product (25%) (Scheme 5).

The mechanism of this unusual formation of lactone **17** could not be clearly established, but a reasonable explanation is the formation of a transient *N*-oxide by the action of dissolved molecular oxygen (bubbling oxygen through



Scheme 5. Reagents: a) Ac_2O, pyridine, O_2, room temp., 12 h; b) K_2CO_3, MeOH/THF, room temp., 12 h (45%)

slightly enhanced the yield to 28%, but also led to degradation products). Then, in the presence of acetic anhydride, a Polonovski reaction would have been initiated, leading to an iminium ion which, upon further oxidation, would have given enamide **17**.

In order to validate this hypothesis, we first treated alcohol **10** with *m*-CPBA [formation of *N*(b)-oxide], followed by Ac_2O/pyridine. Mixtures of enamide **18** (10%) and lactone **17** (15%) were thus obtained. The same conditions, applied to acrylate ester **9**, also gave a mixture of the corresponding enamide **16a** (21%) and lactone **14a** (31%). Under these modified conditions, the overall yield of oxidation had been slightly enhanced.

The oxidation of the dihydropyran E ring to dihydropyranone can be attributed to dissolved molecular oxygen, through an allylic hydroperoxide intermediate.[11] Dehydrogenation of this latter could eventually give the dihydropyranone **17.** The singular conjugated system, which extends over the whole ring system of the compound, is clearly the driving force behind this efficient oxidation.

Allylic alcohol **19** was readily obtained from acetate **17** under mild basic conditions. Compound **19** is therefore the first analogue of camptothecin possessing an original indolizino CD ring substructure with an alcohol group on a lactone E ring.

Conclusion

The biological activity of the new heterocyclic systems **14a−c**, **17** and **19** was evaluated. Unfortunately, none of these gave attractive results in cytotoxicity tests against L1210 cells.

It clearly appears that these derivatives do not satisfy all of the stringent geometric requirements for formation of the ternary complex. The CD rings are not completely planar and there is no tertiary hydroxy lactone as required.

Despite the lack of activity of these products, compound **19** displays an interesting structure from the point of view of structure-activity relationships (S.A.R.). None of the camptothecin analogues so far described bore the lactam group at the C ring instead of the D ring. 5-Hydroxy-, 5-alkoxy- and 5-acetoxycamptothecins did not show antitumor activity,[12] but (20*S*)-5-ethylidenecamptothecin exhibited activity similar to that of (20*S*)-camptothecin in the P388 cell line assay. This result suggests that a certain degree of bulk tolerance is allowed at the C-5 position of camptothecin.[13] Furthermore, camptothecin analogues with a β-hydroxy lactone group at the E ring have been described and were claimed to display very high antitumor activity.[14] Work is in progress to obtain analogues more closely satisfying the S.A.R.; i.e. with planar ABCD ring systems.

Experimental Section

General Remarks: IR spectra [cm^{-1}] were obtained using a Nicolet 205-FT infrared spectrophotometer. Only noteworthy IR absorptions are listed (cm^{-1}). ^1H and ^{13}C NMR spectra (δ [ppm], *J* [Hz]) were recorded with Bruker AC-200 (200 and 50.3 MHz, respectively), Bruker AC-250 (250 and 62.5 MHz) or Bruker AC-300 (300 and 75.5 MHz) instruments using $CDCl_3$ as solvent with tetramethylsilane as internal standard. Chemical shifts for both ^1H-NMR and ^{13}C-NMR spectra are reported in ppm downfield from tetramethylsilane (TMS). Signals of some quaternary carbon atoms could not be observed. Elementary analyses were performed at the Microanalysis Laboratory at ICSN (Gif-sur-Yvette). Mass spectra were recorded with an AEI MS-9 (CI: isobutane) or AEI MS-50 (EI) instrument. Optical rotations were measured at room temp. with a Perkin−Elmer 241 polarimeter.

(1*S*,14a*S*)-11-Ethoxy-1-methyl-3,12-dioxo-3,12,14,14a-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline (6). − Procedure with CrO_3/DMF/H_2SO_4: To a solution of lactone **4** (200 mg, 0.57 mmol) in DMF (10 mL) under argon was added CrO_3 (200 mg) and H_2SO_4 (0.1 mL). After 12 h of stirring at room temp., a second portion of CrO_3 (200 mg) was added. After a further 12 h of stirring at this temperature, the solution was poured into a solution of 15% aqueous ammonia (50 mL), extracted with diethyl ether (3× 70 mL), dried with Na_2SO_4 and filtered. The solvent was removed in vacuo and the residue was purified on a silica gel column (CH_2Cl_2/MeOH, 98:2) to give lactone **6** (31 mg, 15%) as a pale solid.

Procedure with CrO_3/Pyridine: To a solution of lactone **4** (200 mg, 0.57 mmol) in pyridine (15 mL) under argon was added CrO_3 (200 mg). The mixture was stirred at 60 °C for 12 h before adding a second portion of CrO_3 (200 mg). After 12 h at this temperature, the solution was poured into a solution of 15% aqueous ammonia (50 mL), extracted with ether (3 × 70 mL), dried with Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was purified on a silica gel column (CH_2Cl_2/MeOH, 98:2) to give lactone **6** (75 mg, 36%).

Procedure with MnO_2/$CHCl_3$: To a solution of lactone **4** (200 mg, 0.57 mmol) in $CHCl_3$ (10 mL) under argon was added MnO_2 (600 mg). The mixture was stirred at room temp. for 24 h and was filtered through a pad of Celite. The solvent was removed in vacuo and the residue purified on a silica gel column (CH_2Cl_2/MeOH, 98:2) to afford lactone **6** (33 mg, 16%). − IR: $\tilde{\nu}$ = 1719 (C=O), 1698 (C=O), 1643 (C=C), 1599/1377 (quinoline). − MS (CI): *m*/*z* (%) = 363 (100) $[MH]^+$. − ^1H NMR (200 MHz, $CDCl_3$): δ = 8.45 (d, ^3J = 8.3, 1 H), 8.10 (d, ^3J = 8.4,1 H), 7.87 (ddd, $^3J \approx {}^3J'$ = 7.1, 1 H), 7.73 (ddd, $^3J \approx {}^3J'$ = 7.1, 1 H), 6.90 (s,1 H), 6.18 (s, 1 H), 5.21 (qd, ^2J = 10.0; ^3J = 7.8, 1 H), 5.01 (qd, ^2J = 10.0; ^3J = 7.0, 1 H), 4.34 (m, 2 H), 2.94 (m, 2 H), 1.30 (m, 6 H). − ^{13}C NMR (50.5 MHz, $CDCl_3$): δ = 164.5, 163.0, 160.8, 153.9, 147.2, 141.0, 132.5, 129.5, 127.4, 124.8, 114.3, 100.2, 76.5, 72.8, 38.6, 38.0, 19.0,

15.8. − HRMS (CI): calcd. for $C_{21}H_{19}N_2O_4$ $[MH]^+$ 363.13448, found 363.13639.

(1*S*,4a*S*,14a*S*)-11-Ethoxy-3,4,4a,12,14,14a-hexahydro-1-methyl-3,12-dioxo-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline (7). − Procedure with I_2: To a solution of lactone **4** (200 mg, 0.57 mmol) and sodium acetate (220 mg, 4.5 equiv.) in ethanol (10 mL) was slowly added a solution of iodine (420 mg, 3 equiv.) in ethanol (6 mL). The reaction mixture was stirred at 90 °C for 1 h, cooled to room temp. and diluted with CH_2Cl_2 (50 mL). The solution was washed with saturated aqueous $NaHSO_3$ (30 mL), dried with $MgSO_4$ and filtered. The solvent was removed by rotary evaporation and the residue purified on a silica gel column (CH_2Cl_2/MeOH, 98:2) to give enamide **7** as a yellow brown solid (40 mg, 19%).

Procedure with $Pb(OAc)_4$: To a solution of lactone **4** (100 mg, 0.26 mmol) in benzene (10 mL) was added $Pb(OAc)_4$ (500 mg, 4 equiv.). The mixture was refluxed with stirring for 5 h. After cooling, the solution was washed three times with H_2O (8 mL), dried with $MgSO_4$ and filtered. The mixture was concentrated in vacuo and the residue was purified on a short silica gel column (CH_2Cl_2/MeOH, 98:2) to give enamide **7** (25 mg, 25%). − IR: $\tilde{\nu}$ = 1702 (C=O), 1604 (C=C), 1572/1384 (quinoline), 1115 (C−O). − MS (CI): *m*/*z* (%) = 364 (100) $[MH]^+$. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.35 (dd, ^3J = 8.2; ^4J = 1.0, 1 H), 7.99 (d, ^3J = 8.2, 1 H), 7.75 (ddd, $^3J \approx {}^3J'$ = 7.0; ^4J = 1.5, 1 H), 7.52 (ddd, $^3J \approx {}^3J'$ = 7.1; ^4J = 1.0, 1 H), 6.10 (d, ^3J = 3.7, 1 H), 5.04 (q, ^3J = 7.0, 2 H), 4.36 (qd, ^2J = 8.3; ^3J = 6.0, 1 H), 3.90 (dd, ^2J = 13.6; ^3J = 5.8, 1 H), 3.77 (dd, ^2J = 13.6; ^3J = 4.5, 1 H), 3.19 (m, 1 H), 2.91 (dd, ^2J = 17.2; ^3J = 6.7, 1 H), 2.58 (dd, ^2J = 17.2; ^3J = 7.2, 1 H), 2.29 (m, 1 H), 1.50 (m, 6 H). − ^{13}C NMR (50.5 MHz, $CDCl_3$): δ = 170.3, 163.1, 160.8, 154.5, 150.6, 135.2, 132.0, 128.9, 126.4, 124.5, 122.8, 104.1, 75.4, 72.6, 38.4, 36.8, 34.6, 29.6, 20.3, 15.7. − HRMS (CI): calcd. for $C_{21}H_{21}N_2O_4$ $[MH]^+$ 365.15013, found 365.15156.

Methyl (1*S*,4a*S*,5a*S*,14a*S*)-4a,5,5a,6,11,12,14,14a-Octahydro-1-methyl-11-oxo-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-4-carboxylate (8): Dioxygen was bubbled for 6 h through a DMF (50 mL) solution of tetrahydroalstonine (**2**) (6.0 g, 17 mmol) and sublimated potassium *tert*-butoxide (3.6 g, 34 mmol). The solution was poured into saturated aqueous Na_2CO_3 (1 L), then extracted with CH_2Cl_2 (3 × 1 L). The combined extracts were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The mixture was passed through a short silica gel column, first using diethyl ether as eluent, which gave tetrahydroalstonine (**2**) (1.5 g, 25%), and then using a mixture of CH_2Cl_2/MeOH (95:5), which provided quinolone **8** (2.9 g, 62%) as a pale amorphous solid. − IR: $\tilde{\nu}$ = 3530 (N−H), 1695 (C=O), 1625 (C=C−O), 1590 (C=O quinolone), 1525/1470 (quinolone). − MS (EI): *m*/*z* = 366 $[M]^{+\bullet}$. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.19 (d, ^3J = 8.1, 1 H), 7.55 (d, ^3J = 1.1, 1 H), 7.55 (m, 2 H), 7.21 (ddd, ^3J = 8.1; ^3J = 6.0; ^4J = 2.2, 1 H), 4.37 (m, 1 H), 4.01 (d, ^2J = 11.7, 1 H), 3.66 (s, 4 H), 3.40 (dd, ^3J = 11.5; ^3J = 3.7, 1 H), 3.25 (m, 1 H), 2.89 (dd, ^2J = 12.3; ^3J = 3.7, 1 H), 2.68 (m, 2 H), 1.65 (m, 1 H), 1.42 (dd, ^2J = 11.4; ^3J = 11.5, 1 H), 1.33 (d, ^3J = 6.2, 3 H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 173.8, 167.7, 155.7, 154.2, 140.1, 131.0, 126.1, 125.4, 123.6, 118.5, 116.8, 109.1, 72.4, 66.4, 53.8, 51.2, 50.8, 38.2, 31.4, 31.2, 18.5. − $C_{21}H_{22}N_2O_4$ (366.4142): calcd. C 66.32, H 6.58, N 7.03; found C 66.42, H 6.38, N 7.18.

Methyl (1*S*,4a*S*,5a*S*,14a*S*)-11-Ethoxy-4a,5,5a,12,14,14a-hexahydro-1-methyl-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-4-carboxylate (9): To a solution of quinolone **8** (10.0 g, 27.3 mmol) in dry DMF (80 mL) was added sublimated potassium *tert*-butoxide (3.7 g, 32.8 mmol). The reaction mixture was stirred for 10 min, then ethyl iodide (2.4 mL, 30 mmol) was added and the solution was further stirred for 12 h. The solvent was distilled under reduced pressure and the residue partitioned with CH_2Cl_2 (500 mL) and water (300 mL). After separation, the aqueous layer was extracted with CH_2Cl_2 (2 × 500 mL). The combined extracts were dried with $MgSO_4$, filtered and the solvent was removed in vacuo. The mixture was triturated with MeOH (50 mL), filtered and the solid washed with MeOH to give quinoline **9** (10.3 g, 95%) as pale powder. − IR: $\tilde{\nu}$ = 1700 (C=O), 1629 (C=C−O), 1573/1379 (quinoline), 1084 (C−O). − MS (CI): *m*/*z* (%) = 395 (100) $[MH]^+$, 381 (21) $[MH-CH_2]^+$. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.15 (d, ^3J = 8.1, 1 H), 7.95 (d, ^3J = 8.3, 1 H), 7.59 (ddd, $^3J \approx {}^3J'$ = 8.1, ^4J = 0.9, 1 H), 7.54 (s, 1 H), 7.41 (dd, $^3J \approx {}^3J'$ = 7.7, 1 H), 4.38 (m, 4 H), 3.73 (s, 3 H), 3.68 (dd, ^2J = 11.8, ^3J = 1.1, 1 H), 3.36 (d, ^3J = 11.0, 1 H), 3.28 (d, ^2J = 11.7, 1 H), 2.84 (m, 3 H), 1.69 (m, 1 H), 1.58 (m, 1 H), 1.48 (t, ^3J = 6.9, 3 H), 1.41 (d, ^3J = 6.2, 3 H). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 167.8, 166.8, 155.6, 155.0, 148.9, 129.1, 128.4, 125.1, 122.4, 122.0, 113.1, 110.1, 72.2, 67.0, 66.7, 55.6, 52.4, 51.2, 38.6, 32.1, 31.4, 18.7, 15.6. − $C_{23}H_{26}N_2O_4$ (394.4678): calcd. C 70.03, H 6.64, N 7.10; found C 70.14, H 6.83, N 7.16.

(1*S*,4a*S*,5a*S*,14a*S*)-11-Ethoxy-4a,5,5a,12,14,14a-hexahydro-4-hydroxymethyl-1-methyl-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]-quinoline (10): To a cold solution (−78 °C) of quinoline **9** (1.7 g, 4.3 mmol) in dry THF (10 mL) and dry diethyl ether (80 mL) was added $LiAlH_4$ (0.5 g, 12.9 mmol) portionwise. The reaction was monitored by TLC. After 3 h, H_2O (0.5 mL), 15% aqueous NaOH (0.5 mL) and H_2O (0.9 mL) were added successively. A CH_2Cl_2/MeOH (95:5, 500 mL) mixture was added before filtration through a pad of Celite. The resulting solution was dried ($MgSO_4$), filtered and the solvents were removed by rotary evaporation and the crude extract chromatographed (CH_2Cl_2/MeOH, 95:5) to afford **10** as yellow needles (1.27 g, 87%). − IR: $\tilde{\nu}$ = 3330 br. (OH), 1667 (C=C), 1627 (C=C−O), 1574/1378 (quinoline), 1061 (C−O). − MS (CI): *m*/*z* (%) = 367 (100) $[MH]^+$, 349 (43) $[MH - H_2O]^+$. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.17 (dd, ^3J = 8.2; ^4J = 0.8, 1 H), 8.02 (d, ^3J = 8.2, 1 H), 7.65 (ddd, $^3J \approx {}^3J'$ = 7.1; ^4J = 1.4, 1 H), 7.45 (ddd, $^3J \approx {}^3J'$ = 7.2; ^4J = 0.9, 1 H), 6.23 (s, 1 H), 7.45 (m, 2 H), 4.26 (m, 4 H), 3.99 (d, ^2J = 12.0, 1 H), 3.60 (d, ^2J = 11.6, 1 H), 3.29 (m, 2 H), 2.91 (dd, ^3J = 9.0;^3J = 2.6, 1 H), 2.81 (dd, ^2J = 11.7; ^3J = 3.6, 1 H), 2.57 (m, 1 H), 1.81 (m, 1 H), 1.64 (d, ^3J = 11.9, 1 H), 1.47 (t, ^3J = 7.0, 3 H), 1.32 (d, ^3J = 6.1, 3 H). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 167.0, 155.8, 148.5, 141.5, 129.3, 128.1, 125.1, 122.4, 122.0, 116.5, 113.0, 70.4, 67.1, 66.6, 61.1, 55.8, 52.5, 39.5, 32.0, 31.3, 18.8, 15.6. − $C_{22}H_{26}N_2O_3$ (366.4578): calcd. C 72.11, H 7.64, N 7.01; found C 71.78, H 7.64, N 7.21.

(1*S*,4a*S*,5a*S*,14a*S*)-11-Ethoxy-4a,5,5a,12,14,14a-hexahydro-4-methoxymethyl-1-methyl-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]-quinoline (11): A cold (0 °C) solution of allylic alcohol **10** (200 mg, 0.55 mmol) in dry THF (2 mL) was stirred under argon with NaH (130 mg, 5.5 mmol) for 10 min. Methyl iodide (30μL, 1.1 equiv.) was slowly added to the red solution, which was stirred until completion (6 h). H_2O (4 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were dried with $MgSO_4$, filtered and the solvent was removed in vacuo. The crude mixture was then purified on a silica gel column (CH_2Cl_2/MeOH, 99:1), to afford **11** as a dark amorphous solid (158 mg, 76%) which was unstable if stored for several days. − IR $\tilde{\nu}$ = 1697, 1573/1378 (quinoline), 1082 large (C−O−C). − MS (CI): *m*/*z* = 381 $[MH]^+$, 349 $[M - CH_3OH]^+$. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.19 (d, ^3J = 8.3, 1 H), 7.98 (d, ^3J = 8.4, 1 H), 7.66 (dd, ^3J = 8.3; ^3J = 7.0, 1 H), 7.44 (dd, ^3J = 8.0; ^3J =

7.1, 1 H), 6.32 (d, ^3J = 6.0, 1 H), 4.82 (m, 1 H), 4.37 (m, 6 H), 3.75 (m, 1 H), 3.27 (m, 2 H), 2.85 (dd, ^3J = 12.6; ^3J = 3.3, 1 H), 2.65 (m, 1 H), 2.30 (m, 1 H), 1.90 (m, 1 H), 1.73 (m, 1 H), 1.50 (t, ^3J = 6.9, 3 H), 1.35 (d, ^3J = 6.1, 3 H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 166.9, 155.7, 148.9, 142.8, 129.1, 128.1, 125.1, 122.4, 122.0, 113.3, 113.0, 71.2, 70.5, 67.1, 66.7, 57.1, 55.7, 52.5, 39.5, 32.3, 31.2, 18.8, 15.6. − HRMS (CI): calcd. for $C_{23}H_{27}N_2O_3$ $[MH]^+$ 381.21782, found 384.21701.

(1*S*,4a*S*,5a*S*,14a*S*)-4-*tert*-Butyldimethylsilyloxymethyl-11-ethoxy-4a,5,5a,12,14,14a-hexahydro-1-methyl-1*H*-pyrano[3′,4′:6,7]-indolizino[1,2-*b*]quinoline (12): Allylic alcohol **10** (200 mg, 0.55 mmol) and imidazole (370 mg, 0.55 mmol) were dissolved under argon in dry DMF (2 mL). *tert*-Butyldimethylsilyl chloride (495 mg, 3.3 mmol) was added to the solution, which was stirred for 5 h. The reaction mixture was poured into water (4 mL) and the red layer was extracted with ethyl acetate (3× 8 mL). The combined organic layers were dried with $MgSO_4$, filtered and the solvent was removed in vacuo. The residue was purified on a silica gel column (CH_2Cl_2/MeOH, 98:2) to afford **12** as a yellow amorphous compound (185 mg, 71%) which was unstable if stored for several days. − IR ṽ = 1604 (C=C), 1509/1378 (quinoline), 1057 large (O−Si). − MS (CI): *m*/*z* (%) = 481 (100) $[MH]^+$, 349 (32) [MH − *t*BDMsOH]$^+$, 348 (70) [MH − *t*BDMsOH$_2$]$^+$. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.19 (dd, ^3J = 8.1; ^4J = 1.2, 1 H), 7.99 (d, ^3J = 8.1, 1 H), 7.63 (ddd, $^3J \approx {}^3J'$ = 7.0; ^4J = 1.5, 1 H), 7.45 (ddd, $^3J \approx {}^3J'$ = 7.0; ^4J = 1.1, 1 H), 6.37 (s, 1 H), 4.40 (m, 4 H), 4.01 (d, ^2J = 12.2, 1 H), 3.73 (dd, ^3J = 11.7; ^4J = 1.5, 1 H), 3.34 (d, ^2J = 11.5, 1 H), 2.85 (m, 2 H), 2.45 (m, 1 H), 1.82 (m, 1 H), 1.65 (m, 1 H), 1.53 (t, ^3J = 7.0, 3 H), 1.35 (d, ^3J = 6.2, 1 H), 0.93 (s, 9 H), 0.09 (s, 6 H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 167.0, 155.5, 148.8, 140.3, 129.0, 128.3, 125.0, 122.4, 121.9, 116.2, 112.9, 70.3, 67.2, 66.6, 61.8, 55.7, 52.5, 39.5, 31.9, 31.3, 26.0, 18.8, 15.5, −5.0, −5.2. − HRMS (CI); calcd. for $C_{28}H_{41}N_2O_3Si$ $[MH]^+$ 481.28864, found 481.28687.

(1*S*,4a*S*,5a*S*,14a*S*)-4-Acetoxy-11-ethoxy-4a,5,5a,12,14,14a-hexahydro-1-methyl-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline (13): To a solution of alcohol **10** (200 mg, 0.55 mmol) in CH_2Cl_2 (1 mL) under argon was slowly added acetic anhydride (80μL, 1.5 equiv.) and two drops of TMSOTf. The mixture turned red and, after 10 min of stirring, MeOH (40μL) and then saturated aqueous $NaHCO_3$ (5 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduce pressure. The crude product was purified on a silica gel column (CH_2Cl_2/MeOH, 98:2) to afford **13** (105 mg, 47%) as a yellow amorphous solid, which was unstable if stored for several days. − IR: ṽ = 1735 large (C=O), 1574/1378 (quinoline), 1186 (C−O−C). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.19 (d, ^3J = 8.2, 1 H), 7.99 (d, ^3J = 8.2, 1 H), 7.63 (ddd, ^3J = 8.2; ^3J = 7.0; ^3J = 1.1, 1 H), 7.46 (dd, ^3J = 8.2; ^3J = 0.9, 1 H), 6.50 (s, 1 H), 4.45 (m, 4 H), 3.77 (m, 1 H), 3.30 (m, 2 H), 2.86 (dd, ^3J = 12.4; ^3J = 3.5, 1 H), 2.65 (m, 1 H), 2.44 (m, 1 H), 2.10 (s, 3 H), 1.86 (m, 1 H), 1.68 (m, 1 H), 1.51 (t, ^3J = 7.0, 3 H), 1.35 (d, ^3J = 6.2, 3 H). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 170.9, 166.5, 155.2, 148.4, 144.1, 128.9, 127.9, 124.9, 122.2, 121.7, 112.6, 111.3, 70.3, 66.8, 66.4, 63.7, 55.4, 52.1, 39.2, 32.6, 31.2, 21.0, 18.5, 15.3. − HRMS (CI): calcd. for $C_{24}H_{29}N_2O_4$ $[MH]^+$ 409.21273, found 409.21162.

General Procedure for the MnO_2 Oxidation of Quinolines 9, 11 and 12: The appropriate quinoline (200 mg) and MnO_2 (600 mg) were suspended under argon in $CHCl_3$ (10 mL). After 24 h of stirring at room temp., the crude mixture was filtered through a pad of Celite. The solvent was removed in vacuo and the residue purified on a silica gel column (CH_2Cl_2/MeOH, 98:2) to afford a mixture of compounds of type **15**, **16** and **17**.

Methyl (1*S*,14a*S*)-11-Ethoxy-3,12,14,14a-tetrahydro-1-methyl-3,12-dioxo-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-4-carboxylate (14a): Yellow powder. − $[\alpha]_D$ = 685 (*c* = 0.73, $CHCl_3$). − IR: ṽ = 1709 br. (C=O), 1629 (C=C), 1571/1388 (quinoline). − MS (CI): *m*/*z* (%) = 421 (100) $[MH]^+$. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.11 (d, ^3J = 8.2, 1 H), 7.85 (ddd, $^3J \approx {}^3J'$ = 7.2; ^4J = 1.4, 1 H), 7.63 (ddd, $^3J \approx {}^3J'$ = 8.0; ^4J = 0.9, 1 H), 7.18 (s, 1 H), 5.12 (qd, ^3J = 7.0; ^2J = 10.3, 1 H), 4.95 (qd, ^3J = 7.0; ^2J = 10.4, 1 H), 4.51 (m, 2 H), 3.98 (s, 3 H), 3.10 (m, 2 H), 1.54 (t, ^3J = 7.0, 3 H), 1.55 (d, ^3J = 6.3, 3 H). − ^{13}C NMR (62.5 MHz, DMSO): δ = 135.4, 132.0, 130.5, 127.0, 98.1, 78.1, 75.0, 55.2, 40.2, 40.0, 20.9, 18.1. − HRMS (CI): calcd. for $C_{23}H_{21}N_2O_6$ $[MH]^+$ 421.13996, found 421.13970.

(1*S*,14a*S*)-11-Ethoxy-3,12,14,14a-tetrahydro-4-methoxymethyl-1-methyl-3,12-dioxo-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline (14b): Yellow powder. − IR ṽ = 1702 (C=O), 1636 (C=C), 1602 (C=C), 1571/1376 (quinoline), 1087 (C−O−C). − MS (CI): *m*/*z* (%) = 435 (21) $[MH]^+$, 375 (100) [MH − $C_2H_4O_2$]$^+$. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.45 (d, ^3J = 8.3, 1 H), 8.12 (d, ^3J = 8.4, 1 H), 7.85 (ddd, $^3J \approx {}^3J'$ = 7.0; ^4J = 1.1, 1 H), 7.61 (dd, $^3J \approx {}^3J'$ = 8.0, 1 H), 7.08 (s, 1 H), 5.17 (qd, ^2J = 10.3; ^3J = 6.9, 1 H), 4.98 (qd, ^2J = 10.3; ^3J = 6.9, 1 H), 4.49 (m, 4 H), 3.50 (s, 3 H), 3.15 (m, 2 H), 1.58 (m, 6 H). − ^{13}C NMR (62.5 MHz, DMSO): δ = 132.4, 129.5, 127.3, 124.8, 98.0, 75.5, 72.8, 65.6, 58.8, 38.5, 18.9, 15.8. − HRMS (CI): calcd. for $C_{23}H_{22}N_2O_5$ $[MH]^+$ 407.16070, found 407.16127.

(1*S*,14a*S*)-4-*tert*-Butyldimethylsilyloxymethyl-11-ethoxy-3,12,14,14a-tetrahydro-1-methyl-3,12-dioxo-1*H*-pyrano[3′,4′:6,7]-indolizino[1,2-*b*]quinoline (14c): Yellow powder. − $[\alpha]_D$ = 310 (*c* = 1.13, $CHCl_3$). − IR: ṽ = 1702 (C=O), 1637 (C=C), 1600 (C=C−C=O), 1571/1398 (quinoline), 1149 (C−N), 1063 (C−O−C). − MS (FAB): *m*/*z* (%) = 479 (100) [MH−C_2H_4]$^+$, 391 (33) [MH − *t*BDMSH]$^+$, 375 (72) [MH − *t*BDMSOH]$^+$. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.43 (d, ^3J = 8.5, 1 H), 8.09 (d, ^3J = 8.3, 1 H), 7.82 (ddd, $^3J \approx {}^3J'$ = 6.9; ^4J = 1.3, 1 H), 7.60 (ddd, $^3J \approx {}^3J'$ = 7.0; ^4J = 1.0, 1 H), 7.30 (s, 1 H), 5.17 (qd, ^2J = 10.4; ^3J = 7.0, 1 H), 4.99 (qd, ^2J = 10.4; ^3J = 7.0, 1 H), 4.78 (d, ^2J = 15.0, 1 H), 4.71 (d, ^2J = 15.0, 1 H), 4.44 (m, 2 H), 3.13 (dd, $^3J \approx {}^3J'$ = 13.0, 1 H), 3.02 (dd, $^3J \approx {}^3J'$ = 13.0, 1 H), 1.58 (t, ^3J = 7.0, 3 H), 1.57 (d, ^3J = 6.1, 3 H), 0.95 (s, 9 H), 0.18 (s, 3 H), 0.19 (s, 3 H). − ^{13}C NMR (50.3 MHz, DMSO): δ = 132.3, 129.6, 127.1, 124.7, 98.9, 75.5, 72.7, 57.7, 38.6, 26.1, 18.9, 15.8, −5.0. − HRMS (CI): calcd. for $C_{28}H_{34}N_2O_5$ $[MH]^+$ 507.23152, found 507.23305.

Methyl (1*S*,14a*S*)-11-Ethoxy-3,12,14,14a-tetrahydro-3-hydroxy-1-methyl-12-oxo-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-4-carboxylate (15a): Yellow powder. − $[\alpha]_D$ = 328 (*c* = 0.3, $CHCl_3$). − IR: ṽ = 3500−3220 large (OH), 1701 (C=O), 1571/1333 (quinoline), 1149 (C=N), 1121 (C−O−C). − MS (CI): *m*/*z* (%) = 423 (27) $[MH]^+$, 405 (100) [MH − H_2O]$^+$. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.37 (dd, ^3J = 8.3; ^4J = 1.0, 1 H), 8.10 (d, ^3J = 8.2, 1 H), 7.81 (ddd, $^3J \approx {}^3J'$ = 7.0; ^4J = 1.4, 1 H), 7.61 (s, 1 H), 7.56 (ddd, $^3J \approx {}^3J'$ = 7.1; ^4J = 1.0, 1 H), 5.95 (s, 1 H), 5.08 (qd, ^2J = 10.3; ^3J = 7.0, 1 H), 4.97 (qd, ^2J = 10.4; ^3J = 7.0, 1 H), 4.41 (dd, ^2J = 12.8; ^3J = 6.1, 1 H), 4.17 (qd, ^3J = 10.0; ^3J = 6.2, 1 H), 3.39 (s, 3 H), 3.15 (dd, ^{2}J ≈ ^3J = 13.2, 1 H), 2.61 (m, 1 H), 1.54 (t, ^3J = 7.0, 3 H), 1.42 (d, ^3J = 6.2, 3 H). − ^{13}C NMR (62.5 MHz, DMSO): δ = 166.2, 162.8, 160.7, 154.6, 150.5, 141.5, 139.1, 132.1, 129.5, 126.9, 124.6, 123.7, 123.1, 100.6, 89.4, 72.6, 64.8, 52.2, 39.6, 38.7, 19.2, 15.8. − HRMS (CI): calcd. for $C_{23}H_{22}N_2O_6$ $[MH]^+$ 523.15661, found 423.15645.

(1*S*,14a*S*)-4-*tert*-Butyldimethylsilyloxymethyl-11-ethoxy-3,12,14,14a-tetrahydro-3-hydroxy-1-methyl-12-oxo-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline (15c): Yellow powder. − MS (CI): *m*/*z* (%) = 509 (15) $[MH]^+$, 493 (100) $[MH - 16]^+$, 377 (25) $[M - t\text{BDMSiH}]^+$, 361 (60) $[MH - t\text{BDMSiOH}]^+$. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.40 (dd, ^3J = 8.5; ^4J = 1.1, 1 H), 8.07 (d, ^3J = 8.3, 1 H), 7.79 (ddd, $^3J \approx {}^3J'$ = 6.9; ^4J = 1.4, 1 H), 7.54 (ddd, $^3J \approx {}^3J'$ = 6.9; ^4J = 1.1, 1 H), 6.90 (s, 1 H), 5.65 (s, 1 H), 5.16 (qd, ^2J = 10.4; ^3J = 7.1, 1 H), 5.00 (qd, ^2J = 10.4; ^3J = 7.0, 1 H), 4.67 (d, ^3J = 12.5, 1 H), 4.52 (d, ^3J = 12.5, 1 H), 4.40 (dd, ^2J = 12.7; ^3J = 5.8, 1 H), 4.09 (qd, ^3J = 9.9; ^3J = 6.2, 1 H), 3.03 (dd, ^{3}J ≈ ^2J = 12.8, 1 H), 2.52 (m, 1 H), 1.56 (t, ^3J = 7.0, 3 H), 1.42 (d, ^3J = 6.2, 3 H), 0.91 (s, 9 H), 0.18 (s, 6 H).

Methyl (1*S*,4a*S*,14a*S*)-11-Ethoxy-4a,12,14,14a-tetrahydro-1-methyl-12-oxo-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-4-carboxylate (16a): Pale amorphous solid. − $[\alpha]_D$ = 77.5 (*c* = 0.9, $CHCl_3$). − IR: ṽ = 1702 br. (C=O), 1632 (C=C), 1602 (C=C−C=O), 1572/1354 (quinoline), 1085 (C−O−C). − MS (CI): *m*/*z* = 407 $[MH]^+$. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.32 (dd, ^3J = 8.5; ^4J = 1.0, 1 H), 7.96 (d, ^3J = 8.2, 1 H), 7.69 (ddd, $^3J \approx {}^3J'$ = 7.0; ^4J = 1.5, 1 H), 7.58 (s, 1 H), 7.45 (ddd, $^3J \approx {}^3J'$ = 7.0; ^4J = 1.0, 1 H), 6.25 (dd, ^3J = 2.3; ^3J = 0.7, 1 H), 5.03 (qd, ^2J = 10.3; ^3J = 7.0, 1 H), 4.97 (qd, ^2J = 10.3; ^3J = 7.0, 1 H), 4.40 (dd, ^2J = 13.8; ^3J = 2.3, 1 H), 3.86 (qd, ^3J = 9.5; ^3J = 6.3, 1 H), 3.76 (s, 1 H), 3.66 (m, 1 H), 4.54 (dd, ^2J = 13.8; ^3J = 3.5, 1 H), 2.12 (m, 1 H), 1.51 (d, ^3J = 6.3, 3 H), 1.41 (t, ^3J = 7.3, 3 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.3, 162.6, 160.8, 155.8, 155.1, 150.7, 132.4, 131.8, 129.4, 129.0, 126.1, 124.4, 122.7, 107.4, 106.5, 72.6, 71.9, 51.5, 38.5, 35.8, 30.6, 18.5, 15.8. − HRMS (CI): calcd. for $C_{23}H_{22}N_2O_5$ $[MH]^+$ 407.16070, found 407.16009.

(1*S*,14a*S*)-4-Acetoxymethyl-11-ethoxy-3,12,14,14a-tetrahydro-1-methyl-3,12-dioxo-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline (17): To a suspension of allylic alcohol **10** (150 mg, 0.41 mmol) in acetic anhydride (1.90 mL, 20.5 mmol) under argon, was added pyridine (8 mL). The suspension turned first yellow then brown. After 12 h of stirring, MeOH (8 mL) and H_2O (8 mL) were added and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried with $MgSO_4$, filtered and the solvents were removed under reduced pressure. The crude product was then purified on a silica gel column (CH_2Cl_2/MeOH, 99:1) to afford lactone **17** as a yellow powder (44 mg, 25%). − $[\alpha]_D$ = 308 (*c* = 0.7, $CHCl_3$). − IR: ṽ = 1738 (C=O), 1708 (C=O), 1572/1379 (quinoline), 1118 (C−N), 1061 (C−O). − MS (CI) *m*/*z* (%) = 435 (21) $[MH]^+$, 375 (100) $[MH - C_2H_4O_2]^+$. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.39 (ddd, $^3J \approx {}^3J'$ = 8.1; ^4J = 0.8, 1 H), 8.10 (d, ^3J = 8.4, 1 H), 7.83 (ddd, $^3J \approx {}^3J'$ = 8.4; ^4J = 1.3, 1 H), 7.57 (ddd, ^3J = 8.0; $^3J'$ =7.2; ^4J = 0.9, 1 H), 6.90 (s, 1 H), 5.12 (m, 3 H), 4.95 (qd, ^2J = 10.4; ^3J = 7.1, 1 H), 4.46 (m, 2 H), 3.08 (m, 2 H), 2.09 (s, 3 H), 1.55 (m, 6 H). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.0, 164.7, 163.1, 161.2, 154.1, 150.8, 147.1, 141.2, 132.5, 129.6, 127.4, 124.7, 123.1, 118.9, 106.5, 96.9, 75.4, 72.7, 57.9, 38.7, 38.4, 21.1, 18.9, 15.7. − HRMS (CI): calcd. for $C_{24}H_{22}N_2O_6$ $[MH]^+$ 435.15661, found 435.15324.

(1*S*,14a*S*)-11-Ethoxy-3,12,14,14a-tetrahydro-4-hydroxymethyl-1-methyl-3,12-dioxo-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline (19): To a solution of lactone **17** (100 mg, 0.2 mmol), dissolved in a mixture of THF (1 mL) and MeOH (2 mL), was added a saturated aqueous solution of K_2CO_3 (1 mL). After 2 h of stirring, H_2O (4 mL) was added, the solution extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers were dried with $MgSO_4$. The solvents were removed in vacuo and the crude mixture separated by column chromatography (CH_2Cl_2/MeOH, 96:4) to afford alcohol **19** as a yellow powder (41 mg, 45%) and to recover lactone **17** (40 mg, 40%). − MS (FAB): *m*/*z* (%) = 393 (78) $[MH]^+$, 377 (100) $[MH - O]^+$, 375 (86) $[M - H_2O]^+$. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.54 (d, ^3J = 7.3, 1 H), 8.19 (d, ^3J = 8.1, 1 H), 7.99 (ddd, $^3J \approx {}^3J'$ = 7.1; ^4J = 1.3, 1 H), 7.75 (ddd, $^3J \approx {}^3J'$ = 7.6; ^4J = 0.9, 1 H), 7.28 (s, 1 H), 5.28 (qd, ^3J = 7.0, ^2J = 10.4, 1 H), 5.11 (qd, ^3J = 7.0, ^2J = 10.4, 1 H), 4.64 (d, ^2J = 12.5, 1 H), 4.40 (m, 1 H), 3.03 (d, ^2J = 12.0, 1 H), 3.00 (m, 1 H), 1.71 (t + d, ^3J = 7.0; ^3J = 6.2, 6 H). − ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 132.2, 128.3, 126.9, 124.2, 97.4, 75.3, 72.4, 55.4, 37.9, 18.1, 15.0. − HRMS (CI): calcd. for $C_{22}H_{20}N_2O_5$ $[MH]^+$ 393.14505, found 393.14447.

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