Synthesis of (±)-17-Methylcamptothecins[‡]

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(±)-17-Methylcamptothecins (**29**) were synthesized from the heteroyohimbane ajmalicine (**5**) through sequential oxidation steps and E-ring functionalization.

Introduction

With their unique topoisomerase I inhibitory activity,[1] camptothecin (**1**) and its analogues have become one of the most actively studied anticancer agents. The semi-synthetic, water-soluble topotecan (Hycamtin™)[2] and irinotecan (Camptosar™)[3] are used in clinical practice. Clinical studies of other camptothecin analogues − oral 9-nitrocamptothecin (Rubitecan™),[4] intravenous 9-aminocamptothecin,[5] DX-8951f (Exatecan mesylate™),[6] GI147211 (Lurtotecan™),[7] and the homocamptothecins BN 80915 (Diflomotecan™)[8] (**2**) and BN 80927[9] (**3**) − are also under investigation (Figure 1).

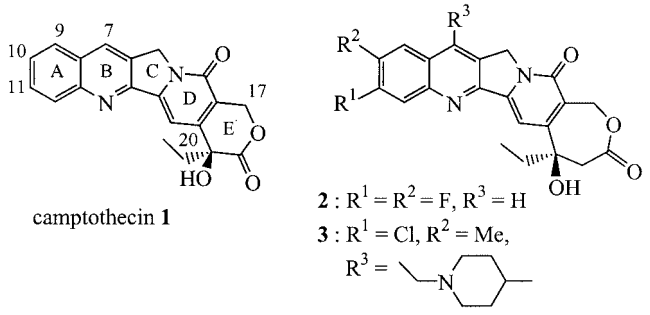

Figure 1. Camptothecin and homocamptothecins

Most of the substitution patterns concerned rings A and B, in which wide possibilities for variation exist, especially on positions C-7, C-9, C-10, and C-11.[10] Substitutions on rings C and D resulted in significant losses of activity; the pyridone D ring seems to be necessary for activity.[11] For a long time, it was considered that the unmodified lactone E ring was also necessary for cytotoxic activity: modifications of the E ring focused on the hydroxylactone function,[12] the chiral center,[13] or substitution on position C-20;[14] except for the insertion of a methylene spacer between the alcohol and carboxyl functions (homocamptothecins),[15] none of these changes resulted in increased activity (Figure 1). To complete structure-activity relationships, we thought it would be of interest to have access to C-17-substituted analogues.[16]

In preceding papers, we reported on our first results concerning the partial synthesis of C-17-methyl camptothecin analogues, starting from tetrahydroalstonine (THA; **4**)[17] and ajmalicine (**5**),[18] easily available heteroyohimbane alkaloids extracted from *Catharanthus* sp. The first strategy from THA (**4**) began with biomimetic oxidation of the indole nucleus to quinolone, followed by its conversion into quinoline lactone **6**. However, the pyridone D ring could not be attained from **6**, and compounds **7** with C ring lactam and overoxidation in rings D and E were obtained. In **6**, the C-5 position appeared to be more activated towards oxidation than the desired C-21 position,[19] so it was necessary to reconsider our strategy, with a regioselective oxidation on the C-21 position of heteroyohimbanes **4** or **5** in a first step, and then biomimetic oxidation of the indole nucleus (Scheme 1).

It appeared that enol ether **8** was a convenient derivative for such a selective activation of C-21. This compound could be obtained only from ajmalicine (**5**) and not from THA (**4**).[18]

[‡] Partial Synthesis of Camptothecin Analogs, 4. Part 3: Ref.[16]

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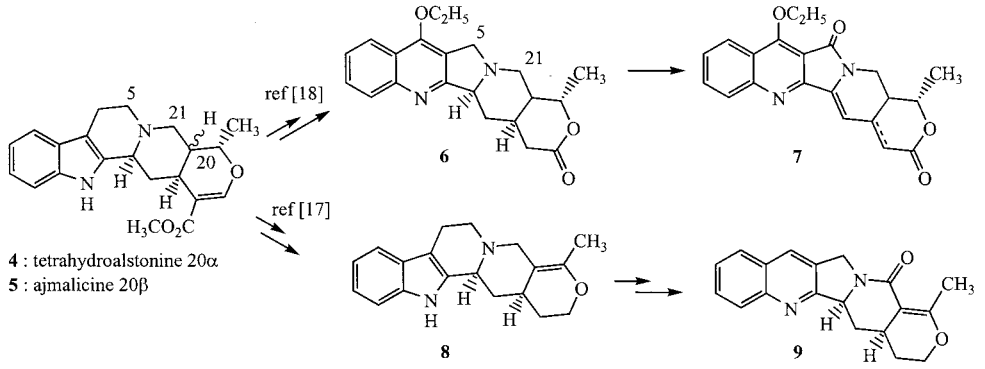
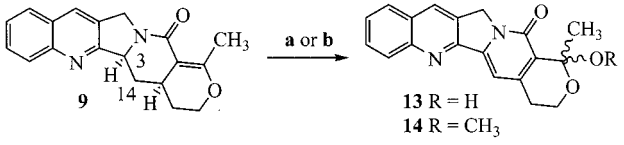


Scheme 1

In this paper we wish to report the completion of the partial synthesis of the two diastereomeric (±)-17-methylcamptothecins.

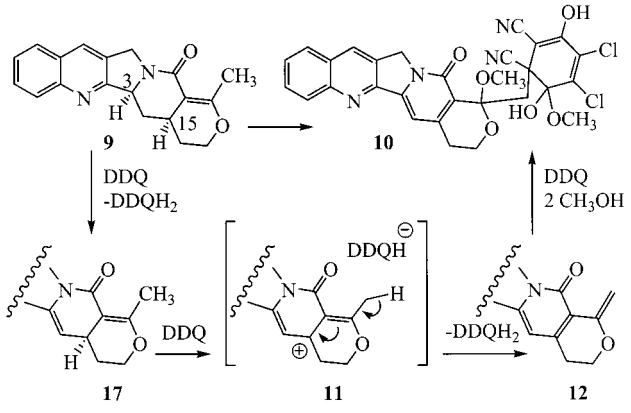
Results and Discussions

The synthetic scheme to obtain 17-methylcamptothecins from lactam **9**[17] required aromatization of the lactam D ring into a pyridone moiety, followed by functionalization of the E ring. A few methods for such an oxidation exist: autooxidation in acidic medium or the use of dehydrogenating agents such as palladium on charcoal (Pd/C) or dichlorodicyanobenzoquinone (DDQ). We first examined autooxidation conditions. Pleasingly, when placed in a mixture of aqueous HCl and acetone at room temperature,[20] compound **9** underwent a rapid autooxidation to give lactol **13** in 51% yield (Scheme 2). This moderate yield could be explained by the difficulties involved in the purification, since the lactol function easily gave rise to the conjugated oxonium cation on silica gel or alumina. We next turned to dehydrogenating agents: our original belief was that compound **9** should be transformable into the same lactol **13** or ketal **14** (Scheme 2) with palladium or DDQ, by dehydrogenation of the C-3/C-14 positions and subsequent aromatization by allylic rearrangement of the enol ether double bond.[21,22] The generated oxonium cation could be trapped by the solvent when the reaction was run in methanol or water, or by the water contained in Pd/C. Treatment of **9** with Pd/C in ethyl acetate at room temperature afforded the expected lactol **13** in only 24% yield (Scheme 2). All attempts to increase the yield [solvents, use of $Pd(OH)_2$, addition of water, number of catalyst equivalents] failed. We assume that a major quantity of lactol **13** remains adsorbed on charcoal.



Scheme 2. Reagents and conditions: a) HCl 1 N, acetone, room temp., 1 h (51%); b) Pd/C, EtOAc, room temp., 48 h (24%)

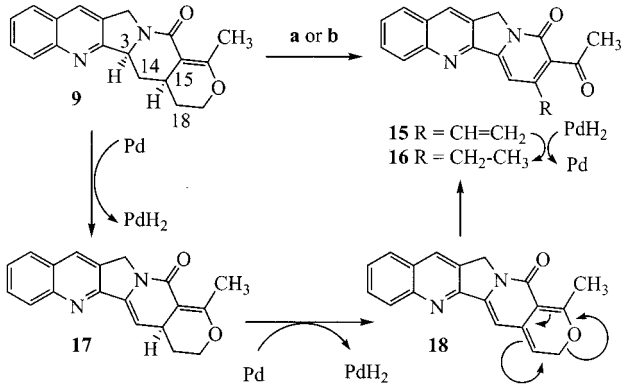
To circumvent the instability of lactol **13**, we planned a synthesis of the more stable ketal **14**. Compound **9** was allowed to react with DDQ in a 1:1 toluene/methanol mixture at 70 °C. The only identifiable product obtained from the complex mixture was the unexpected DDQ-substrate adduct **10**, with a dehydrogenated pyridone D ring and carbon−carbon bond formation between the methyl on C-17 and the reagent (Scheme 3). Such DDQ-substrate adducts had previously been observed in DDQ dehydrogenation of 4-aza-3-keto steroids.[23] Formation of compound **10** presumably proceeds through formation of the charge-transfer complex (CTC) between **9** and DDQ, abstraction of the more labile 3-H, and then departure of the proton on the C-14 position. Formation of a new CTC and subsequent hydride abstraction on C-15 affords the cationic intermediate **11**, which then gives the exo methylene compound **12** through the loss of a proton on C-17. Subsequent reaction of **12** with DDQ and methanol trapping of the intermediate provides adduct **10**.



Scheme 3. Reagent and conditions: DDQ, toluene/methanol, 1:1, 70 °C, 1 h (38%)

Having employed protic conditions in order to obtain a ketal or hemiketal E ring, we next investigated these dehydrogenating agents under aprotic conditions and at higher temperatures. We then observed dramatic changes in reactivity. Heating of enol ether **9** in *p*-cymene at reflux with a

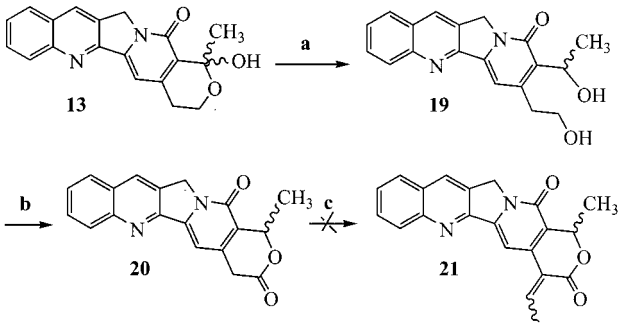
catalytic amount of Pd/C gave a 94% yield of opened E ring compounds **15** and **16** (Scheme 4) in a 1:3 ratio. Changing *p*-cymene for ethyl acetate or tetrahydrofuran resulted exclusively in compound **16**, in 90% yield. Aromatization of the D ring to a pyridone presumably proceeds first by palladium abstraction of 3-H and 14-H to give enamide **17**. The higher temperatures induce a second palladium abstraction, which cannot occur at ambient temperature, of 15-H and 18-H. The unstable intermediate **18** undergoes a pericyclic reaction, which provides the opened E ring compound **15**. Subsequent reduction of the exo double bond by hydrogen adsorbed on Pd/C affords the major compound **16**.[24] In the case of *p*-cymene, we assumed participation of dehydrocymene as a hydrogen scavenger to explain the persistence of vinyl compound **15**.



Scheme 4. Reagents and conditions: a) Pd/C, solvent, reflux, 1 h (*p*-cymene **15/16**, 1:3, 94%, EtOAc **16** 94%, THF **16** 90%); b) DDQ, dioxane, reflux, 1 h, **15** (73%)

This unexpected result prompted us to investigate the action of DDQ on compound **9** under aprotic conditions. When **9** was treated with DDQ in refluxing dioxane, vinyl compound **15** was obtained exclusively in 73% yield. In this case no hydrogen transfer could occur from $DDQH_2$ to **15**. We reasoned that the protic medium (toluene/CH_3OH) allowed stabilization of the ion pair [$DDQH^-$-**19**$^+$], giving the DDQ-substrate adduct **10**, while an aprotic medium (dioxane) and higher temperature (100 °C versus 70 °C) resulted in dehydrogenation of the C-15/C-18 positions.

With lactol **13** and opened E ring compound **15** to hand, we could consider two pathways to 17-methylcamptothecins. Ideally, the shortest route would be to reduce lactol **13** to the diol **19** (Scheme 5), chemoselective oxidation would give the lactone **20**, and ethylation and hydroxylation on C-21 position would then afford 17-methylcamptothecins. As alkylation on compound **20** would give non-regioselective reaction and polyalkylation,[24] we planned to proceed through a silylenol ether or by an aldolisation-crotonisation reaction, followed by reduction of the double bond. To examine this approach, we used isochroman-3-one as a model system. Despite all our efforts, no alkylation of the silylenol ether derived from the model compound could be achieved. In contrast, monoethylation of isochroman-3-one

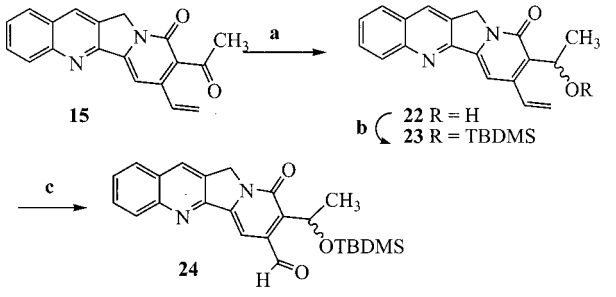


Scheme 5. Reagents and conditions: a) $NaBH_4$, CH_3OH, room temp., 30 min (75%); b) [$RuCl_2(PPh_3)_3$], toluene, room temp., 3 h (45%); c) acetaldehyde, DBU, THF, 0 °C, 18 h

was achieved by condensation with acetaldehyde in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), with subsequent catalytic hydrogenation of the exo double bond. Lactone **20** was obtained as expected from lactol **10** by sodium borohydride reduction followed by chemoselective oxidation of diol **19** by ruthenium complex. Unfortunately, all attempts to reproduce the condensation reaction with lactone **20** to give **21** failed.

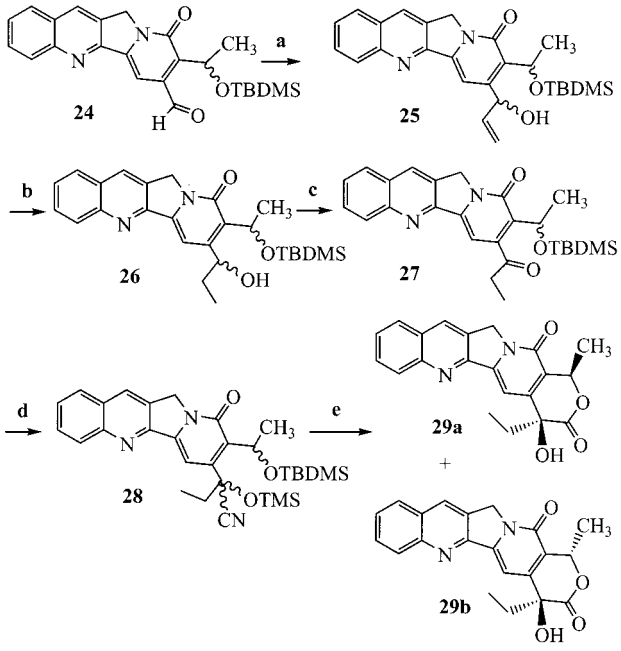
We next turned to the alternative pathway. From opened E ring compound **15**, the remaining tasks were: (a) reduction of the ketone, (b) oxidative cleavage of the exo double bond, (c) Grignard addition of a vinyl group to the aldehyde, (d) isomerization of allylic alcohol into ethyl ketone, (e) cyanosilylation, and then (f) Pinner-type cyclisation to afford 17-methylcamptothecins. Reduction of **15** was achieved under Luche conditions ($NaBH_4$, $CeCl_3$) to yield alcohol **22** (Scheme 6). It is noteworthy that running the reduction without $CeCl_3$ produced a mixture of **22** and reduced double bond compound (90%, 65:35). Protection of the alcohol with a *tert*-butyldimethylsilyl (TBDMS) group and subsequent osmylation and oxidative cleavage gave aldehyde **24** in 64% yield over both steps.

As expected, Grignard addition of vinylmagnesium bromide onto compound **24** in THF at −78 °C (Scheme 7) gave the allylic alcohols **25** in 55% yield. Metal-catalyzed isomerization into ethyl ketone **27** was attempted both with [$RuCl_2(PPh_3)_3$][26] and with $(C_3H_7)_4NRuO_4$ (TPAP).[27] In both cases, starting material was totally recovered. We assume that the quinoline basic nitrogen may inhibit the cata-



Scheme 6. Reagents and conditions: a) $NaBH_4$, $CeCl_3$, CH_3OH, room temp., 30 min (95%); b) TBDMSCl, imidazole, DMF, room temp., 16 h (100%); c) OsO_4, $NaIO_4$, *t*BuOH/THF/H_2O, room temp., 6 h (64%)

lyst. A Grignard reaction with ethylmagnesium bromide did not give the expected alcohols **26** but only reduction of the ketone, probably because of steric hindrance. Ethyl ketones **27** were finally obtained from **25** in two steps, through double bond reduction by catalytic hydrogenation in the presence of platinum(IV) oxide, followed by Swern oxidation of the alcohols **26**, in 72% overall yield. Cyanosilylation of **27** was achieved by addition of cyanotrimethylsilane (TMSCN) catalyzed by KCN/crown-ether 18-C-6.[28] Protected cyanohydrins **28** were obtained as a mixture of diastereomers (*de*, 33%) in 42% yield. Finally, subjection of compounds **28** to an intramolecular Pinner reaction gave a diastereomeric mixture of 17-methylcamptothecins (**29**) in 92% yield (*de*, 33%).



Scheme 7. Reagents and conditions: a) CH_2=CHMgBr, THF, −78 °C, 2 h (55%); b) H_2, PtO_2, EtOAc, room temp., 2 h; c) $(COCl)_2$, DMSO, CH_2Cl_2, then NEt_3, −60 °C, 1 h (72% for both steps); d) TMSCN, KCN, 18-C-6, CH_2Cl_2, room temp., 2 h (42%); e) HCl, EtOH, 90 °C, 30 min (92%)

Attempts to assign the relative configuration were based on Pommier's model and careful analysis of the NMR spectra.[29] From ^{1}H NMR analysis of the mixture of stereomers **29** we evaluate a diastereomeric excess of 33%. We observed clear differences between the ^{1}H NMR spectra of these two diastereomers, the major diastereomer showing a methyl group more deshielded than in the minor one and a more shielded 17-H. From the conformation of the molecule in solution (boat conformation of the E ring) the methyl group in the major diastereomer is thought to be in an equatorial position, closer to the carbonyl group of the pyridone. We thus postulate a *cis* relationship between the hydroxy and the methyl groups for the major **29a**. (Figure 2).

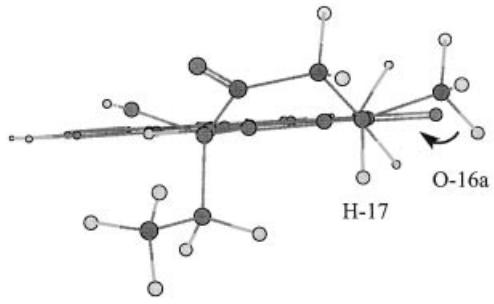


Figure 2. Chem3D model of methylcamptothecin **29a**

The four stereomers were cleanly separated by chiral HPLC (OD, 10 × 250 mm, hexane/2-propanol, 80:20).

Conclusion

New C-17-substituted camptothecins were obtained from ajmalicine (**5**) by partial synthesis. Intense studies of the D-ring aromatization step revealed unusual reactivities for this class of molecules.

The biological activity of the separated optically active compounds will be tested and the results will be published in due course.

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 on a Nicolet 205-FT infrared spectrophotometer. Only noteworthy IR absorptions are listed (cm^{-1}). ^{1}H 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 Université, Paris. Mass spectra were recorded with an AEI MS-50 instrument. IUPAC recommendations were used for the nomenclature of all compounds. For numbering different from the biogenetic one in the case of semisynthetic intermediates, see Figure 3.

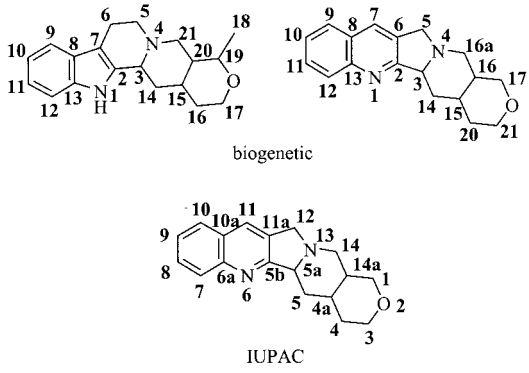


Figure 3. Biogenetic numbering and IUPAC numbering in the case of camptothecin derivatives

1-(3,4-Dichloro-1,6-dicyano-2,5-dihydroxy-2-methoxycyclohexa-3,5-dienyl)methyl-1-methoxy-1,3,4,12-tetrahydro-14*H*-pyrano[3′,4′:6,7]-indolizino[1,2-*b*]quinolin-14-one (10): Dichlorodicyanoquinone (109 mg, 0.48 mmol, 1.5 equivalent) was added to a solution of enol ether **9** (100 mg, 0.32 mmol) in anhydrous toluene/methanol (1:1, 10 mL) at room temp. The reaction mixture was stirred at 70 °C for 1 h, and the hydroquinone was then removed by filtration. The filtrate was evaporated under reduced pressure and the crude mixture was purified by flash chromatography (SiO_2, CH_2Cl_2/CH_3OH, 99:1) to afford adduct **10** as an amorphous solid (72 mg, 38%). IR: $\tilde{\nu}$ = 1716, 1653, 1588, 1586 cm^{-1}. MS (CI): *m*/*z* = 593 $[MH]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.43 (d, ^2J = 15.1, 1 H, *H*-CH-), 2.7 (br. d, ^2J = 14.4, 1 H, H-20), 3.18 (d, ^2J = 15.1, 1 H, *H*-CH-), 3.21 (s, 3 H, OCH_3), 3.30 (s, 3 H, OCH_3), 4.22 (br. d, ^3J = 7.4, 2 H, 21-H), 4.64 (dt, ^2J = 14.5; ^3J = 8.4, 1 H, 20-H), 5.05 (d, ^2J = 17.5, 1 H, 5-H), 5.13 (d, ^2J = 17.5, 1 H, 5-H), 7.28 (s, 1 H, 14-H), 7.67 (td, ^3J = 8.0; ^4J = 4.4, 1 H, 10-H), 7.86 (t, ^3J = 8.3; ^4J = 1.3, 1 H, 11-H), 7.93 (br. d, ^2J = 7.8, 1 H, 9-H), 8.21 (br. d, ^3J = 8.3, 1 H, 12-H), 8.36 (s, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.8, 37.5, 48.3, 50.5, 50.6, 53.3, 63.1, 105.8, 111.6, 114.6, 116.3, 122.6, 125.1, 128.1, 128.4, 128.8, 129.5, 130.9, 131.2, 146.2, 148.8, 151.0, 151.7, 156.8, 159.7, 176.1, 178.6 ppm.

1-Hydroxy-1-methyl-1,3,4,12-tetrahydro-14*H*-pyrano[3′,4′:6,7]-indolizino[1,2-*b*]quinolin-14-one (13). Autooxidation in Acidic Media: Aqueous HCl (1 N, 5 mL) was added to a solution of enol ether **9**[17] (100 mg, 0.32 mmol) in acetone (5 mL). The reaction mixture was stirred for 1 h at room temp. and then treated with aqueous $NaHCO_3$ (10%, 10 mL). The aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic layers were then washed with brine and filtered, and the solvent was evaporated under reduced pressure to give pure **13** (53 mg, 51%) as a yellow powder. **Dehydrogenation:** Pd/C (400 mg, 1.2 equivalent) was added to a solution of enol ether **9** (100 mg, 0.32 mmol) in ethyl acetate (10 mL). After stirring for two days at room temp., the suspension was filtered through a pad of Celite™. The Celite™ was rinsed twice with CH_2Cl_2/CH_3OH (95:5, 15 mL) and the filtrate was evaporated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2/CH_3OH, 96:4) afforded recovered starting material (65 mg) and compound **13** (25 mg, 24%). IR: $\tilde{\nu}$ = 3425, 1658, 1597, 1502 cm^{-1}. MS (CI): *m*/*z* = 321 $[MH]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.92 (s, 3 H, -CH_3), 2.53 (dt, ^2J = 12.5; ^3J = 2.1, 1 H, 20β−H), 3.01 (ddd, ^2J = 12.5; ^3J = 8.2; ^3J = 4.4, 1 H, 20α−H), 4.02−4.16 (m, 2 H, 21-H), 5.28 (s, 2 H, 5-H), 7.19 (s, 1 H, 14-H), 7.63 (t, ^3J = 8.2, 1 H, 10-H), 7.81 (t, ^3J = 8.4, 1 H, 11-H), 7.90 (d, ^3J = 8.4, 1 H, 9-H), 8.21 (d, ^3J = 8.5, 1 H, 12-H), 8.37 (s, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3, 29.5, 49.8, 58.8, 94.6, 102.2, 127.6, 127.8, 128.5, 129.5, 130.2, 131.1, 134.8, 143.8, 147.4, 148.7, 152.5, 159.7 ppm.

8-Acetyl-7-ethenylindolizino[1,2-*b*]quinolin-9(11*H*)-one (15). Palladium Procedure: Pd/C (65 mg, 10% mass, 0.2 equivalent) was added to a solution of **9** (100 mg, 0.32 mmol) in *p*-cymene (10 mL) at room temp. The solution was stirred under reflux for 1 h and then allowed to cool to room temp. and filtered through a pad of Celite™. The Celite™ was rinsed with CH_2Cl_2/CH_3OH, 90:10 and the filtrate was evaporated under reduced pressure. The crude mixture was purified by flash chromatography (SiO_2, CH_2Cl_2/EtOAc, 70:30) to afford 91 mg (94%) of **15** and **16** in a 1:3 ratio. **DDQ Procedure:** Dichlorodicyanoquinone (82 mg, 0.36 mmol, 1.1 equivalent) was added to a solution of **9** (100 mg, 0.32 mmol) in anhydrous dioxane (10 mL) under nitrogen at room temp. The mixture was stirred at 70 °C for 1 h and allowed to cool to room temp., and the hydroquinone was then removed by filtration. The filtrate was evaporated under reduced pressure and the crude mixture was purified by flash chromatography (SiO_2, CH_2Cl_2/CH_3OH, 96:4) to afford compound **15** (71 mg, 73.5%) as a yellow powder. M.p. > 250 °C (EtOAc). IR: $\tilde{\nu}$ = 1687, 1612, 1505 cm^{-1}. HRMS (CI) calculated for $C_{19}H_{15}N_2O_2$ $[MH^+]$: *m*/*z* = 303.1134, found 303.1136. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.68 (s, 3 H, -CH_3), 5.29 (s, 2 H, 5-H), 5.66 (d, ^3J = 11.0, 1 H, 21-H), 6.66 (d, ^3J = 17.3, 1 H, 21-H), 6.98 (dd, ^3J = 17.1; ^3J = 11.0, 1 H, 20-H), 7.53 (s, 1 H, 14-H), 7.63 (td, ^3J = 8.4; ^4J = 1.2, 1 H, 10-H), 7.82 (td, ^3J = 8.3; ^4J = 1.2, 1 H, 11-H), 8.01 (d, ^3J = 8.1, 1 H, 9-H), 8.22 (d, ^3J = 8.6, 1 H, 12-H), 8.39 (s, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.6, 49.9, 98.9, 122.0, 127.9, 128.0, 128.7, 128.9, 129.6, 130.5, 130.9, 132.6, 146.0, 148.0, 152.3, 159.5, 202.1 ppm.

8-Acetyl-7-ethylindolizino[1,2-*b*]quinolin-9(11*H*)-one (16): Yellow powder, m.p. > 250 °C (EtOAc). IR: $\tilde{\nu}$ = 1713, 1651, 1602, 1505 cm^{-1}. MS (CI): *m*/*z* = 305 $[MH^+]$. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, ^3J = 8.5, 3 H, 21-H), 2.68 (s, 3 H, -CH_3), 2.73 (d, ^3J = 8.5, 2 H, 20-H), 5.25 (s, 2 H, 5-H), 7.24 (s, 1 H, 14-H), 7.64 (t, ^3J = 8.3, 1 H, 10-H), 7.81 (t, ^3J = 8.3, 1 H, 11-H), 7.92 (d, ^3J = 8.2, 1 H, 9-H), 8.22 (d, ^3J = 8.6, 1 H, 12-H), 8.39 (s, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7, 26.9, 31.5, 49.8, 102.6, 127.8, 128.0, 128.9, 129.5, 130.4, 130.9, 145.9, 148.7, 152.3, 157.1, 159.3, 202.4 ppm.

8-(1-Hydroxyethyl)-7-(2-hydroxyethyl)indolizino[1,2-*b*]quinolin-9-one (19): Sodium borohydride (38 mg, 1 mmol, 5 equivalents) was added to a solution of lactol **10** (60 mg, 0.19 mmol) in methanol (5 mL). After stirring for 30 min at room temp. the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and the aqueous layer was extracted twice with dichloromethane (15 mL). The combined organic layers were dried with $MgSO_4$ and the solvents were evaporated under reduced pressure. Diol **19** was purified by flash chromatography (SiO_2, CH_2Cl_2/CH_3OH, 90:10), yield 46 mg (75%), yellow powder. IR: $\tilde{\nu}$ = 1637, 1580 cm^{-1}. MS (CI): *m*/*z* = 323 $[MH^+]$. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.59 (d, ^3J = 6.6, 3 H, -CH_3), 2.94 (td, ^3J = 6.4; ^4J = 2.3, 2 H, 20-H), 4.0 (t, ^3J = 6.5, 2 H, 21-H), 5.12 (q, ^3J = 6.5, 1 H, 17-H), 5.14 (s, 1 H, 5-H), 7.25 (s, 1 H, 14-H), 7.57 (td, ^3J = 8.0; ^4J = 1.1, 1 H, 10-H), 7.76 (td, ^3J = 8.2; ^4J = 1.4, 1 H, 11-H), 7.80 (d, ^3J = 8.1, 1 H, 9-H), 8.12 (d, ^3J = 8.3, 1 H, 12-H), 8.23 (s, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0, 35.6, 49.6, 61.7, 66.6, 104.2, 127.5, 127.7, 127.8, 129.3, 130.3, 132.1, 142.8, 147.4, 148.5, 152.4, 161.0 ppm.

1-Methyl-1,12-dihydro-14*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-3(4*H*),14-dione (20): Dichlorotris(triphenylphosphane)ruthenium(II) (150 mg, 0.156 mmol, 2 equivalents) was added under nitrogen to a solution of diol **19** (25 mg, 0.078 mmol) in anhydrous toluene (5 mL). After stirring for 12 h at room temp., the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted twice with dichloromethane (10 mL) and the combined organic layers were dried with $MgSO_4$. The solvents were evaporated under reduced pressure and the crude mixture was purified by flash chromatography (SiO_2, CH_2Cl_2/CH_3OH, 95:5) to afford lactone **26** (10.5 mg, 42%) as a yellow powder. IR: $\tilde{\nu}$ = 1701, 1671, 1609 cm^{-1}. MS (CI): *m*/*z* = 319 $[MH^+]$. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.59, (d, ^3J = 6.6, 3 H, -CH_3), 2.94 (td, ^3J = 6.4; ^4J = 2.3, 2 H, 20-H), 4.0 (t, ^3J = 6.5, 2 H, 21-H), 5.12 (q, ^3J = 6.5, 1 H, 17-H), 5.14 (s, 1 H, 5-H), 7.25 (s, 1 H, 14-H), 7.57 (td, ^3J = 8.0; ^4J = 1.1, 1 H, 10-H), 7.76 (td, ^3J = 8.2, ^4J = 1.4, 1 H, 11-H), 7.80 (d, ^3J = 8.1, 1 H, 9-H), 8.12 (d, ^3J = 8.3, 1 H, 12-H), 8.23 (s, 1 H, 7-H) ppm.

8-(1-Hydroxyethyl)-7-ethenylindolizino[1,2-*b*]quinolin-9(11*H*)-one (22): Cerium(III) chloride heptahydrate (300 mg, 0.805 mmol, 1.5

equivalent) was added to a solution of compound **15** (160 mg, 0.53 mmol) in methanol (10 mL), followed by sodium borohydride (30 mg, 0.8 mmol, 1.5 equivalent). The reaction mixture was stirred at room temp. for 30 min and then quenched with a saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted twice with dichloromethane (10 mL) and the combined organic layers were then washed with brine (10 mL) and dried with $MgSO_4$. After evaporation of the solvents under reduced pressure, the crude product was purified by flash chromatography (SiO_2, CH_2Cl_2/CH_3OH, 95:5) to afford alcohol **22** (153 mg, 95%) as a yellow powder. M.p. > 250 °C (EtOAc). IR: $\tilde{\nu}$ = 3398, 1653, 1617, 1589 cm^{-1}. MS (CI): *m*/*z* = 305 [MH^+]. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.58 (d, ^3J = 6.7, 3 H, -C*H*$_3$), 5.15 (q, ^3J = 6.7, 1 H, 17-H), 5.22 (s, 2 H, 5-H), 5.64 (d, ^3J = 11.1, 1 H, 21-H), 5.99 (d, ^3J = 17.3, 1 H, 21-H), 6.96 (dd, ^3J = 17.3; ^3J = 11.1, 1 H, 20-H), 7.45 (s, 1 H, 14-H), 7.62 (t, ^3J = 8.4, 1 H, 10-H), 7.77 (t, *J* = 8.2 Hz, 1 H, 11-H), 7.88 (d, ^3J = 8.4, 1 H, 9-H), 8.17 (d, ^3J = 8.2, 1 H, 12-H), 8.32 (s, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2, 49.8, 66.8, 99.8, 121.9, 127.8, 128.0, 128.1, 128.5, 129.5, 130.5, 131.0, 131.7, 143.2, 144.5, 148.8, 152.8, 161.5 ppm.

8-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-7-ethenylindolizino[1,2-*b*]-quinolin-9(11*H*)-one (23): Imidazole (289 mg, 4.25 mmol, 8 equivalents) and *tert*-butyldimethylsilyl chloride (318 mg, 2.1 mmol, 4 equivalents) were added to a solution of alcohol **20** (45 mg, 0.11 mmol) in anhydrous dimethylformamide (10 mL). The reaction mixture was stirred for 16 h at room temp. and then quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted twice with ethyl acetate (10 mL) and the combined organic layers were washed with brine and dried with $MgSO_4$. The solvents were evaporated under reduced pressure and the crude mixture was purified by flash chromatography (SiO_2, CH_2Cl_2/EtOAc, 80:20) to afford protected alcohol **23** (95 mg, 64%) as a yellow powder. IR: $\tilde{\nu}$ = 1654, 1612, 1595 cm^{-1}. HRMS (CI) calculated for $C_{25}H_{31}N_2O_2Si$ [MH^+]: *m*/*z* = 419.2155, found 419.2160 [MH^+]. ^1H NMR (300 MHz, $CDCl_3$): δ = −0.03 [s, 3 H, -Si(CH_3)C*H*$_3$], 0.10 [s, 3 H, -Si(CH_3)C*H*$_3$], 0.88 [s, 9 H, -SiC(C*H*$_3$)$_3$], 1.50 (d, ^3J = 6.7, 3 H, -CH_3), 5.22 (s, 2 H, 5-H), 5.53 (d, ^3J = 11.2, 1 H, 21-H), 5.76 (q, ^3J = 6.7, 1 H, 17-H), 5.99 (d, ^3J = 17.7, 1 H, 21-H), 7.45 (s, 1 H, 14-H), 7.61 (t, ^3J = 8.0, 1 H, 10-H), 7.78 (t, ^3J = 8.1, 1 H, 11-H), 7.83 (dd, ^3J = 17.7; ^3J = 11.2, 1 H, 20-H), 7.88 (d, ^3J = 8.4, 1 H, 9-H), 8.19 (d, ^3J = 8.3, 1 H, 12-H), 8.32 (s, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0, 18.0, 23.8, 25.7, 49.8, 64.9, 99.1, 118.5, 127.3, 127.9, 128.8, 129.4, 130.1, 130.6, 132.5, 142.7, 146.0, 148.6, 153.3, 160.4 ppm.

8-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-9-oxo-9*H*,11*H*-indolizino[1,2-*b*]quinoline-7-carbaldehyde (24): Sodium periodate (205 mg, 0.96 mmol, 4 equivalents) and osmium tetroxide (290 μL, 2.5 wt.% in 2-methylpropan-2-ol, 0.024 mmol, 0.1 equivalent) were added to a solution of protected alcohol **23** (100 mg, 0.24 mmol) in tetrahydrofuran/water (2:1, 7.5 mL). The reaction mixture was stirred at room temp. for 6 h and then quenched with saturated aqueous $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted twice with ethyl acetate (10 mL) and the combined organic layers were washed with brine and dried with $MgSO_4$. The solvents were evaporated under reduced pressure to give pure aldehyde **24** (95 mg, 94.5%) as a yellow powder. IR: $\tilde{\nu}$ = 1694, 1655, 1601 cm^{-1}. MS (CI): *m*/*z* = 421 [MH^+]. ^1H NMR (300 MHz, $CDCl_3$): δ = −0.01 [s, 3 H, -Si(CH_3)C*H*$_3$], 0.12 [s, 3 H, -Si(CH_3)C*H*$_3$], 0.87 [s, 9 H, -SiC(C*H*$_3$)$_3$], 1.64 (d, ^3J = 6.5, 3 H, -C*H*$_3$), 5.21 (s, 2 H, 5-H), 5.62 (q, ^3J = 6.5, 1 H, 17-H), 7.45 (s, 1 H, 14-H), 7.58 (t, ^3J = 8.0, 1 H, 10-H), 7.75 (t, ^3J = 8.1, 1 H, 11-H), 7.84 (d, ^3J = 8.2, 1 H, 9-H), 8.16 (d, ^3J = 8.3, 1 H, 12-H), 8.28 (s, 1 H, 7-H), 10.5 (s, 1 H, 20-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −0.8, 18.0, 25.7, 25.8, 50.3, 66.3, 97.9, 127.7, 128.0, 128.4, 129.7, 130.3, 130.7, 140.0, 142.3, 144.3, 148.7, 153.1, 160.2, 192.6 ppm.

8-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-7-(1-hydroxyprop-2-enyl)-indolizino[1,2-*b*]quinolin-9(11*H*)-one (25): Vinylmagnesium bromide solution in tetrahydrofuran (1 M, 833 μL, 0.833 mmol, 2.5 equivalents) was added dropwise at −78 °C under nitrogen to a solution of aldehyde **24** (140 mg, 0.33 mmol) in anhydrous tetrahydrofuran (5 mL). The reaction mixture was stirred for 3 h at −78 °C and then quenched with saturated aqueous NH_4Cl (4 mL). The aqueous layer was extracted twice with ethyl acetate (10 mL) and the combined organic layers were washed with brine and dried with $MgSO_4$. After evaporation of the solvents under reduced pressure, the crude mixture was purified by flash chromatography (SiO_2, CH_2Cl_2/EtOAc, 80:20) to afford allylic alcohols **25** (81 mg, 55%) as a diastereomeric mixture (*de*, 33%). Yellow powder. MS (CI): *m*/*z* = 449 [MH^+]. ^1H NMR (300 MHz, $CDCl_3$): **25a** major δ = 0.05 [s, 3 H, -Si(CH_3)C*H*$_3$], 0.13 [s, 3 H, -Si(CH_3)C*H*$_3$], 0.89 [s, 9 H, -SiC(C*H*$_3$)$_3$], 1.57 (d, ^3J = 6.7, 3 H, -C*H*$_3$), 5.21 (s, 2 H, 5-H), 5.32 (d, ^3J = 2.5, 1 H, 20-H), 5.43 (d, ^3J = 10.2, 1 H, 18-H), 5.79 (q, ^3J = 6.7, 1 H, 17-H), 6.03−6.20 (m, 2 H, 18-H), 7.38 (s, 1 H, 14-H), 7.57 (t, ^3J = 8.0, 1 H, 10-H), 7.75 (t, ^3J = 8.1, 1 H, 11-H), 7.84 (d, ^3J = 8.2, 1 H, 9-H), 8.17 (d, ^3J = 8.3, 1 H, 12-H), 8.32 (s, 1 H, 7-H) ppm. **25b** minor: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.07 [s, 3 H, -Si(CH_3)C*H*$_3$], 0.16 [s, 3 H, -Si(CH_3)C*H*$_3$], 0.91 [s, 9 H, -SiC(C*H*$_3$)$_3$], 1.62 (d, ^3J = 6.7, 3 H, -C*H*$_3$), 5.28 (d, ^3J = 2.5, 1 H, 20-H), 5.52 (d, ^3J = 10.2, 1 H, 18-H), 5.79 (q, ^3J = 6.7, 1 H, 17-H), 6.03−6.20 (m, 2 H, 18-H), 7.30 (s, 1 H, 14-H), 7.57 (t, ^3J = 8.0, 1 H, 10-H), 7.75 (t, ^3J = 8.1, 1 H, 11-H), 7.84 (d, ^3J = 8.2, 1 H, 9-H), 8.17 (d, ^3J = 8.3, 1 H, 12-H), 8.32 (s, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0, 18.1, 24.6, 25.5, 50.0, 65.8, 70.2, 101.6, 116.2, 127.5, 128.0, 128.7, 129.5, 130.2, 130.7, 132.6, 138.9, 142.5, 144.7, 149.2, 153.0, 160.2 ppm.

8-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-7-(1-hydroxypropyl)indol-izino[1,2-*b*]quinolin-9(11*H*)-one (26): Platinum(IV) oxide (Adam's catalyst, 5 mg) was added to a solution of alcohols **25** (42 mg, 0.093 mmol) in ethyl acetate (5 mL). The reaction mixture was stirred under hydrogen atmosphere (1 atm) for 2 h and the suspension was then filtered through a pad of Celite™. The Celite™ was rinsed twice with CH_2Cl_2/CH_3OH (10 mL) and the filtrate was evaporated under reduced pressure to give pure alcohols **26** (40 mg, quantitative) as a diastereomeric mixture (*de*, 33%). Yellow powder. MS (CI): *m*/*z* = 451 [MH^+]. ^1H NMR (300 MHz, $CDCl_3$): **26a** major δ = 0.11 [s, 6 H, -Si(C*H*$_3$)$_2$], 0.89 [s, 9 H, -SiC(C*H*$_3$)$_3$], 1.11 (t, ^3J = 7.2, 3 H, 11-H), 1.51 (d, ^3J = 6.7, 3 H, -C*H*$_3$), 1.70−1.95 (m, 2 H, 19-H), 5.22 (s, 2 H, 5-H), 5.25−5.35 (m, 1 H, 20-H), 5.7 (m, 1 H, 17-H), 7.38 (s, 1 H, 14-H), 7.57 (t, ^3J = 8.0, 1 H, 10-H), 7.75 (t, ^3J = 8.1, 1 H, 11-H), 7.81 (d, ^3J = 8.2, 1 H, 9-H), 8.17 (d, ^3J = 8.3, 1 H, 12-H), 8.3 (s, 1 H, 7-H) ppm. **26b** minor: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.13 [s, 6 H, -Si(C*H*$_3$)$_2$], 0.91 [s, 9 H, -SiC(C*H*$_3$)$_3$], 0.95 (t, ^3J = 7.2, 3 H, 18-H), 1.54 (d, ^3J = 6.7, 3 H, -C*H*$_3$), 1.70−1.95 (m, 2 H, 19-H), 5.22 (s, 2 H, 5-H), 5.25−5.35 (m, 1 H, 20-H), 5.7 (m, 1 H, 17-H), 7.32 (s, 1 H, 14-H), 7.57 (t, ^3J = 8.0, 1 H, 10-H), 7.75 (t, ^3J = 8.1, 1 H, 11-H), 7.81 (d, ^3J = 8.2, 1 H, 9-H), 8.17 (d, ^3J = 8.3, 1 H, 12-H), 8.3 (s, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0, 10.8, 18.1, 24.8, 25.7, 35.3, 50.2, 65.8, 71.1, 101.5, 127.6, 128.1, 128.6, 129.5, 130.2, 130.7, 140.1, 142.5, 144.7, 150.1, 153.5, 159.6 ppm.

8-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-7-propanoylindolizino[1,2-*b*]-quinolin-9(11*H*)-one (27): Dimethyl sulfoxide (41 μL, 0.578 mmol, 6.5 equivalents) was added at −60 °C under nitrogen to a solution of oxalyl chloride (24 μL, 0.275 mmol, 3.1 equivalents) in anhy-

drous dichloromethane (5 mL). The reaction mixture was stirred for 30 min, and alcohols **26** (40 mg, 0.089 mmol) in solution in anhydrous dichloromethane (2 mL) were then added dropwise by cannula. After stirring for 1 h at −60 °C, the reaction mixture was quenched with triethylamine (184 μL, 1.32 mmol, 15 equivalents) and the mixture was then allowed to warm to room temp. and stirred for 30 min. Brine (5 mL) was added and the aqueous layer was extracted twice with ethyl acetate (10 mL). The combined organic layers were washed with brine and then dried with $MgSO_4$. After evaporation of the solvents under reduced pressure, the crude product was purified by flash chromatography (SiO_2, CH_2Cl_2/EtOAc, 90:10) to afford ketones **27** (30 mg, 72% from **25**) as a yellow powder. MS (CI): *m*/*z* = 449 [MH^+]. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.10 [s, 6 H, -Si(CH_3)$_2$], 0.88 [s, 9 H, -SiC(CH_3)$_3$], 1.19 (t, ^3J = 7.4, 3 H, 18-H), 1.57 (d, ^3J = 6.7, 3 H, -CH_3), 2.82 (dq, ^2J = 15.8; ^3J = 7.4, 1 H, 19-H), 3.04 (dq, ^2J = 15.8, ^3J = 7.4, 1 H, 19-H), 5.21 (s, 2 H, 5-H), 5.34 (q, ^3J = 6.7, 1 H, 17-H), 7.01 (s, 1 H,14-H), 7.57 (t, ^3J = 8.0, 1 H, 10-H), 7.73 (t, ^3J = 8.1, 1 H, h-11), 7.82 (d, ^3J = 8.2, 1 H, 9-H), 8.12 (d, ^3J = 8.3, 1 H, 12-H), 8.32 (s, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 1.3, 7.7, 18.6, 24.1, 26.2, 37.2, 50.0, 66.9, 71.1, 99.2, 127.7, 128.0, 128.6, 129.6, 130.4, 130.9, 132.9, 143.9, 148.8, 149.3, 152.7, 159.5, 205.8 ppm.

7-[1-(*tert*-Butyldimethylsilyloxy)-8-[1-(*tert*-butyldimethylsilyloxy)-ethyl]-1-cyano]propylindolizino[1,2-*b*]quinolin-9(11*H*)-one (28): TMSCN (28 μL, 0.21 mmol, 3 equivalents), potassium cyanide (0.9 mg, 0.014 mmol, 0.2 equivalent), and then 18-crown-6 (3.5 mg, 0.013 mmol, 0.2 equivalent) were added under nitrogen at room temp. to a solution of ketones **27** (30 mg, 0.067 mmol) in anhydrous dichloromethane (5 mL). After stirring for 2 h at room temp., the reaction mixture was quenched with brine (5 mL) and the aqueous layer was extracted twice with ethyl acetate (10 mL). The combined organic layers were washed with brine (5 mL) and dried with $MgSO_4$. The solvents were evaporated under reduced pressure and the crude mixture was purified by flash chromatography (SiO_2, CH_2Cl_2/EtOAc, 90:10) to afford cyano compounds **28** (16 mg, 42%) as a diastereomeric mixture (*de*, 33%). Yellow powder. MS (CI): *m*/*z* = 548 [MH^+]. ^1H NMR (300 MHz, $CDCl_3$): **28a** major δ = 0.04 [s, 3 H, -Si(CH$_3$)CH_3], 0.26 [s, 3 H, -Si(CH$_3$)CH_3], 0.89 [s, 9 H, -SiC(CH_3)$_3$], 1.15 (t, ^3J = 7.4, 3 H, 18-H), 1.74 (d, ^3J = 6.7, 3 H, -CH_3), 2.05−2.25 (m, 2 H, 19-H), 5.24 (s, 2 H, 5-H), 5.79 (q, ^3J = 6.7, 1 H, 17-H), 7.61 (s, 1 H, 14-H), 7.61 (t, ^3J = 8.0, 1 H, 10-H), 7.78 (t, ^3J = 8.1, 1 H, 11-H), 7.88 (t, ^3J = 8.2, 1 H, 9-H), 8.20 (t, ^3J = 8.3, 1 H, 12-H), 8.33 (s, 1 H, 7-H) ppm. **28b** minor: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.10 [s, 3 H, -Si(CH$_3$)CH_3], 0.26 [s, 3 H, -Si(CH$_3$)CH_3], 0.85 [s, 9 H, -SiC(CH_3)$_3$], 1.08 (t, ^3J = 7.4, 3 H, 18-H), 1.83 (d, ^3J = 6.7, 3 H, -CH_3), 2.05−2.25 (m, 2 H, 19-H), 5.24 (s, 2 H, 5-H), 5.61 (q, ^3J = 6.7, 1 H, 17-H), 7.48 (s, 1 H, 14-H), 7.61 (t, ^3J = 8.0, 1 H, 10-H), 7.78 (t, ^3J = 8.1, 1 H, 11-H), 7.88 (t, ^3J = 8.2, 1 H, 9-H), 8.20 (t, ^3J = 8.3, 1 H, 12-H), 8.33 (s, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 1.0, 1.1, 8.8, 18.4, 24.6, 26.0, 37.0, 50.0, 66.5, 70.5, 97.5, 120.2, 127.6, 127.9, 128.0, 128.8, 129.9, 130.3, 130.7, 138.1, 143.8, 148.9, 151.2, 153.0, 159.9 ppm.

17-Methylcamptothecins (29): A saturated hydrogen chloride ethanol solution (0.5 mL) was added dropwise under nitrogen at room temp. to a solution of cyano compounds **28** (16 mg, 0.029 mmol) in absolute ethanol (0.5 mL). The reaction mixture was stirred at 90 °C for 30 min, allowed to cool to room temp., and then poured into ice-cooled brine (5 mL). The pH of the solution was adjusted to 6 by addition of few drops of saturated aqueous $NaHCO_3$ solution and the mixture was then extracted twice with dichloromethane (5 mL). The combined organic layers were dried with $MgSO_4$ and the solvents were evaporated under reduced pressure. Purification by flash chromatography afforded a diastereomeric mixture of 17-methylcamptothecins (**29a** and **29b**, 10 mg, 92%) in 33% *de*. Yellow powder. UV: λ_{max} (logε) = 220 (4.45), 255 (4.20), 358 (4.08), 370 (4.10) nm. IR: $\tilde{\nu}$ = 3690, 1710, 1660, 1602 cm^{-1}. HRMS (CI) calculated for $C_{21}H_{19}N_2O_4$ [MH^+]: *m*/*z* = 363.1345, found 363.1341 [MH^+]. **29a** major: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, ^3J = 7.4, 3 H, 18-H), 1.85−1.95 (m, 2 H, 19-H), 1.97 (d, ^3J = 6.7, 3 H, -CH_3), 5.26 (s, 2 H, 5-H), 5.71 (q, ^3J = 6.7, 1 H, 17-H), 7.63 (s, 1 H, 14-H), 7.63 (t, ^3J = 8.0, 1 H, 10-H), 7.81 (t, ^3J = 8.1, 1 H, 11-H), 7.90 (d, ^3J = 8.2, 1 H, 9-H), 8.22 (d, ^3J = 8.3, 1 H, 12-H), 8.36 (s, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.0, 21.0, 34.4, 50.1, 71.6, 72.3, 97.9, 123.0, 127.9, 128.0, 128.5, 129.8, 130.5, 131.0, 146.0, 148.6, 149.0, 152.5, 157.8, 172.9 ppm. **29b** minor: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.07 (t, ^3J = 7.4, 3 H, 18-H), 1.77 (d, ^3J = 6.7, 3 H, -CH_3), 1.85−1.95 (m, 2 H, 19-H), 5.26 (s, 2 H, 5-H), 5.81 (q, ^3J = 6.7, 1 H, 17-H), 7.61 (s, 1 H, 14-H), 7.63 (t, ^3J = 8.0, 1 H, 10-H), 7.81 (t, ^3J = 8.1, 1 H, 11-H), 7.90 (d, ^3J = 8.2, 1 H, 9-H), 8.20 (d, ^3J = 8.3, 1 H, 12-H), 8.35 (s, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.8, 20.8, 37.0, 49.9, 70.5, 72.3, 98.2, 123.2, 127.9, 128.0, 128.4, 129.8, 130.5, 131.0, 146.0, 147.9, 149.0, 152.5, 157.6, 173.2 ppm.

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