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Synthesis of New Camptothecin Analogues with the E-Lactone Ring Replaced by α,β-Cyclohexenone

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The total synthesis of racemic camptothecin analogues **12a** and **12b**, in which the E-lactone ring has been replaced by an α,β-cyclohexenone ring and the ethyl and hydroxy substituents have been retained, was achieved by first preparing the ABCD fragments **31a** and **31b**, which were then converted into the tetracyclic triol **36a** and **36b** by osmium-mediated dihydroxylation. Compounds **36a** and **36b** were oxidized in one-pot reactions, followed by intramolecular aldol condensation to furnish the desired pentacyclic **12a** and **12b**, which retained topoisomerase I inhibitory activity and exhibited cytotoxicity to tumor cell growth in culture.

Introduction

The natural antitumor alkaloid (20*S*)-camptothecin (**1**, CPT, Figure 1), is a pentacyclic pyranoindolizino[1,2-*b*]-quinoline derivative isolated from *Camptotheca acuminata* (Nyssaceae) by Wall and co-workers in 1966.[1] The chemical and biological properties of CPT and its analogues have been studied in great detail.[2–5] Phase I and II clinical trials of this natural alkaloid were carried out with its water-soluble sodium salt (CPT-Na salt), in which the E-lactone ring had been cleaved by sodium hydroxide, but were abandoned because of low efficacy and excess non-specific toxicity (bone marrow and bladder).[6]

Numerous structure–activity studies (SARs) have identified several design principles for CPT analogues and have also established a direct correlation between the ability of CPT derivatives to stabilize the covalent topoisomerase I (Topo I)-DNA intermediate and their ability to kill cancer cells.[7,8] Several CPT derivatives with substituent(s) on the AB ring system exhibit significant enzyme inhibitory activity and antitumor efficacy. Among them, topotecan (**2**), SN-38 (**3**), and irinotecan (**4**) have been clinically approved for the treatment of cancers (Figure 1).[9]

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Studies on the mechanism of action of CPT showed that this agent rapidly blocks both DNA and RNA synthesis in treated cells, and it has emerged as a potent anticancer compound.[10–12] The sole intracellular target for CPT and its derivatives is Topo I;[13,14] in vitro studies showed that CPT and its analogues inhibited plasmid relaxation by human Topo I and increased the yield of covalent intermediates when the reaction was stopped with SDS.[7,11,14] A hypothetical CPT binding model based on crystallographic information and SARs has been proposed by Redinbo et al.,[15] demonstrating that a hydrogen-bonding network could be established between the Asp^{533} and Arg^{364} side chains and the (20*S*)-OH and lactone moieties of CPT. Mutation of the Phe^{361} and Gly^{363} residues is likely to mediate CPT resistance by disruption the conformation of the loop that holds Arg^{364}. The studies further confirmed that the alteration of the CDE rings of CPT severely affects its ability to bind with Topo I and thus decreases its cytotoxicity. In contrast, modifications in the AB ring, especially at C-7, C-9, and C-10, are generally well tolerated and in many cases enhance the potency of CPT analogues in both in vitro and in vivo studies.[10] Furthermore, substantial evidence indicates that CPT binds reversibly only after cleavage and covalent attachment for the enzyme to the DNA.[16]

In spite of the importance of the conformation of the E-ring of CPT for enzyme inhibition and cytotoxicity, a CPT analogue containing a seven-membered β-hydroxylactone, homocamptothecin (hCPT, **10**, Figure 1), was synthesized by Lavergne et al.[17–19] Like CPT, hCPT contains an asymmetric tertiary alcohol moiety and displays stereoselective inhibition of Topo I, while being more potent than CPT. hCPTs fluorinated in the A-ring were found to have potent cytotoxicity against the A427 and PC3 tumor cell lines and

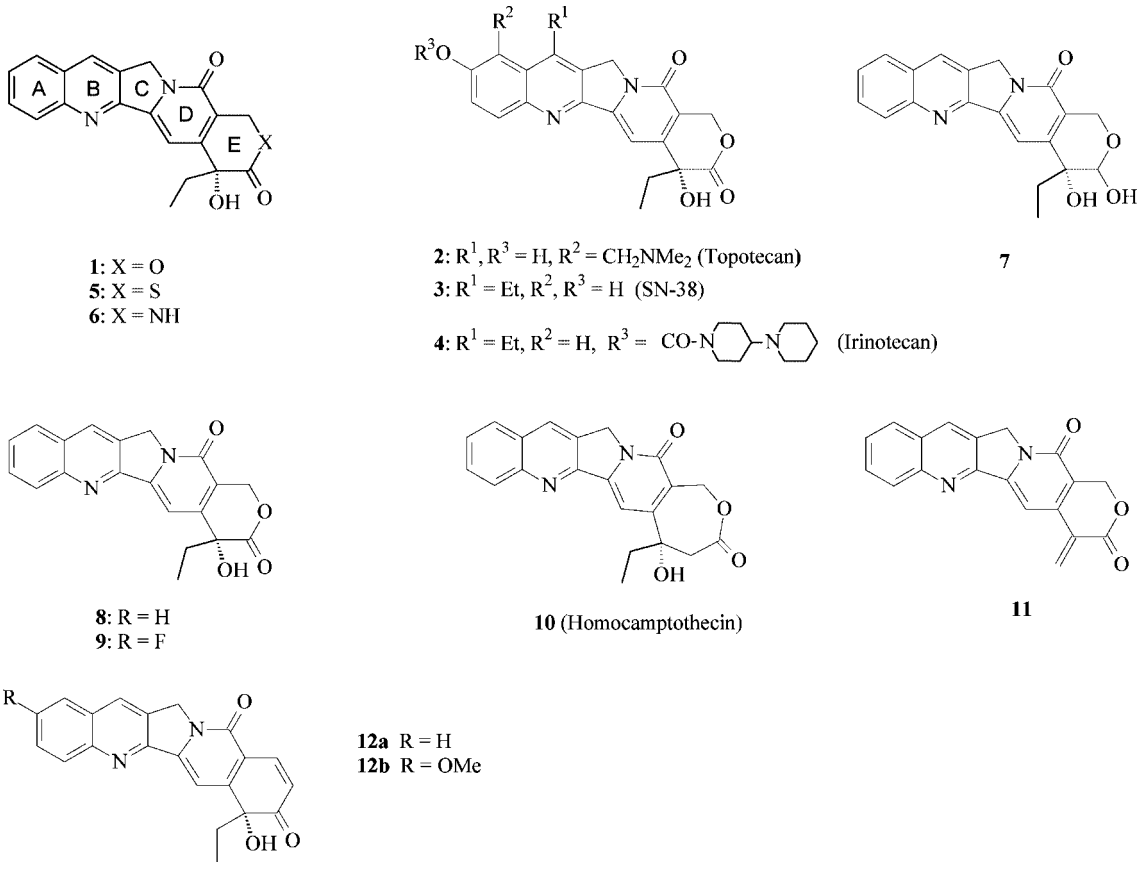
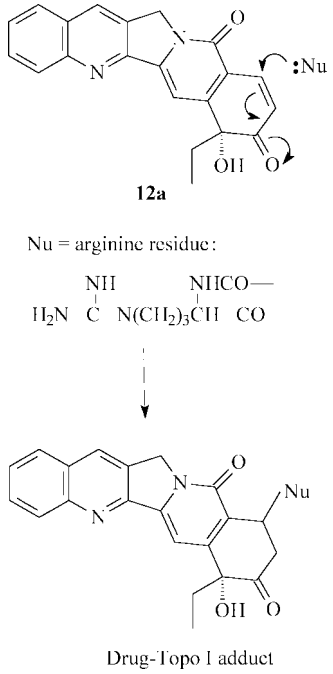


Figure 1. Structures of camptothecin derivatives.

were more efficacious than CPT against HT-29 xenografts in vivo. The homologation of the lactone E-ring reinforces the stability of the lactone,[17] although the replacement of the CPT lactone E-ring with a homologous seven-member lactone ring was found to have changed the sequence specificity of the drug-induced DNA cleavage by Topo I,[20] suggesting that the hCPT-Topo I binding site may differ from that of the proposed model for CPT. The results showed that the β-hydroxylactone ring in hCPT played an important and positive role in the poisoning of Topo I.[21]

To elaborate the actual CPT-Topo I binding site, it is worthwhile to synthesize CPT analogues with covalent bond formation potential, so that a nucleophile generated from enzyme or DNA can bind with CPT covalently. Danishefsky et al.[22] synthesized the 18-noranhydrocamptothecin analogue **11** (Figure 1), bearing an exocyclic methylene group on the E-ring. Designed as an alkylating agent, compound **11** exhibited CPT-like inhibition of Topo I, although its cytotoxicity was significantly reduced in relation to CPT. To design and synthesize CPT analogues with covalent bond formation capability, we replaced the E-ring of CPT with an α,β-cyclohexenone moiety, so that the nucleophilic guanidine function of the Arg^{364} residue in the enzyme might attack the α,β-cyclohexenone moiety through Michael addition to form the drug-Topo I adduct (Scheme 1). The target compounds **12a** and **12b** may facilitate study of the drug-Topo I binding site, and their total synthesis is described here.

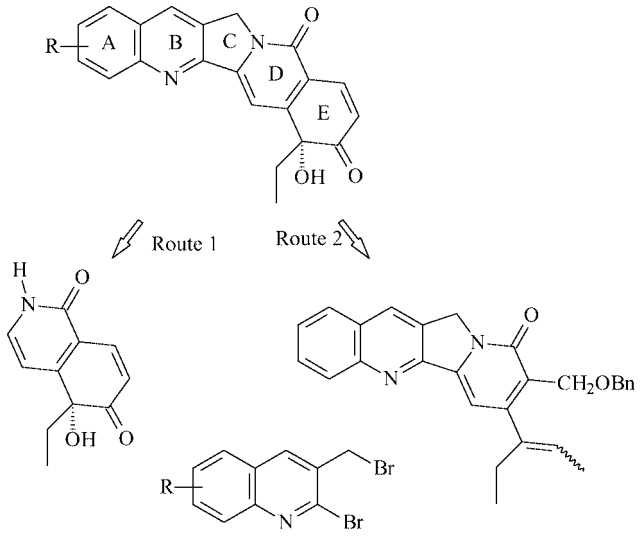


Scheme 1. Covalent bond formation capability of **12a** with topoisomerase I.

Results and Discussion

The novel structure and biological activity of (20*S*)-CPT have sustained a high level of interest in the total synthesis

of this agent.[23–25] Consideration of the synthesis of compounds **12a** and **12b** indicates that one might be able to construct this target compound either by applying the shortest asymmetric synthesis of CPT suggested by Comins,[26] involving the formation of the C-ring by connecting the A,B and D,E fragments through an *N*-alkylation and a key intramolecular Heck ring-closure (Scheme 2), or by first synthesizing the ABCD fragment, followed by formation of the E-ring.



Scheme 2. Retrosynthesis of new CPT analogues.

Asymmetric dihydroxylation has been applied to prepare optically active α-hydroxy lactones (E-ring) for use in CPT synthesis: Curran et al.[27] synthesized three classes of olefins – endocyclic ketene acetals (**13**, Figure 2), endocyclic enol ethers (**14**), and exocyclic α,β-unsaturated lactones (**15**) – that were used for a model study of E-ring construction. It was found that the dihydroxylation of **13** with commercially available AD-mix-β by the standard procedure was slow, but acceptable rates were obtained. A marked improvement in enantioselectivity, together with a high yield, was obtained when the endocyclic enol ether **14** was treated with AD-mix-β, whilst studies on the dihydroxylation of exocyclic olefins **15** showed disappointing results with the (*E*) isomer but dihydroxylation of the (*Z*) isomer to give the desired (20*S*) configuration in 50% yield and with 99% *ee* when the compounds were treated with AD-mix-α. Independently, Fang et al.[28] reported that the DE ring fragment could be obtained from the endocyclic enol ether (**16**) through dihydroxylation with AD-mix-α, whilst Henegar et al.[29] later developed a new synthetic strategy for preparing CPT analogues from the key intermediate **17**, which was a good substrate for osmium-mediated dihydroxylation (OsO_4/$Me_3NO{\cdot}2H_2O$), a high yield of diol being obtained.

In view of the synthesis of the target compound by synthetic route 1, the key step for the successful synthesis of **12a** was the stereoselective formation of compound **23** (Scheme 4).

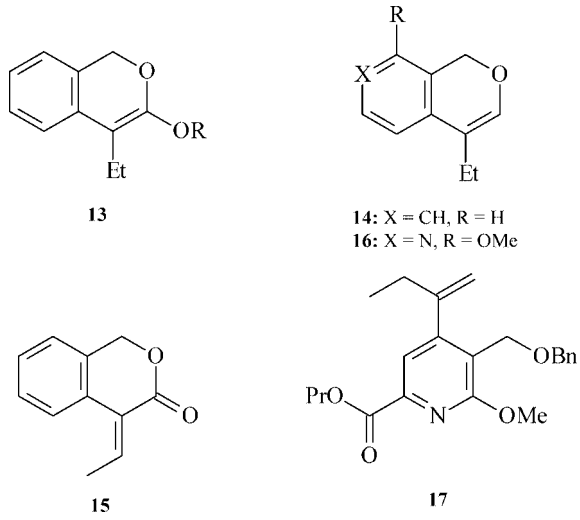
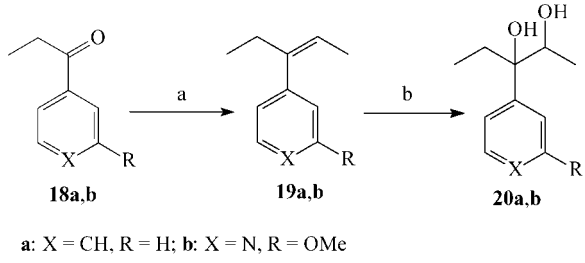


Figure 2. Structures of olefins used for model studies and construction of the DE-ring of camptothecin.

Our model studies showed that (*Z*)-3-phenylpent-2-ene (**19a**) or a 4-((*E*/*Z*)-1-ethylpropenyl)-2-methoxypyridine mixture (**19b**, 5:95) could be dihydroxylated by treatment with AD-mix-α to give the desired diols **20a** and **20b** in excellent yields (Scheme 3 and Table 1, Entries 1, 2) under standard Sharpless AD reaction conditions.[30]



a: X = CH, R = H; **b**: X = N, R = OMe

Scheme 3. Model studies on dihydroxylation of olefins **19a** and **19b**. Reagents and conditions: a) Ph_3PEtBr $KN(SiMe_3)_2$, THF, –80 °C to room temp., 2 h, **19a**: 81%; **19b**: 95%. b) AD-mix-α, $MeSO_2NH_2$, *t*BuOH, H_2O, 0 °C, **20a**: 10 h, 99%; **20b**: 18 h, 94%.

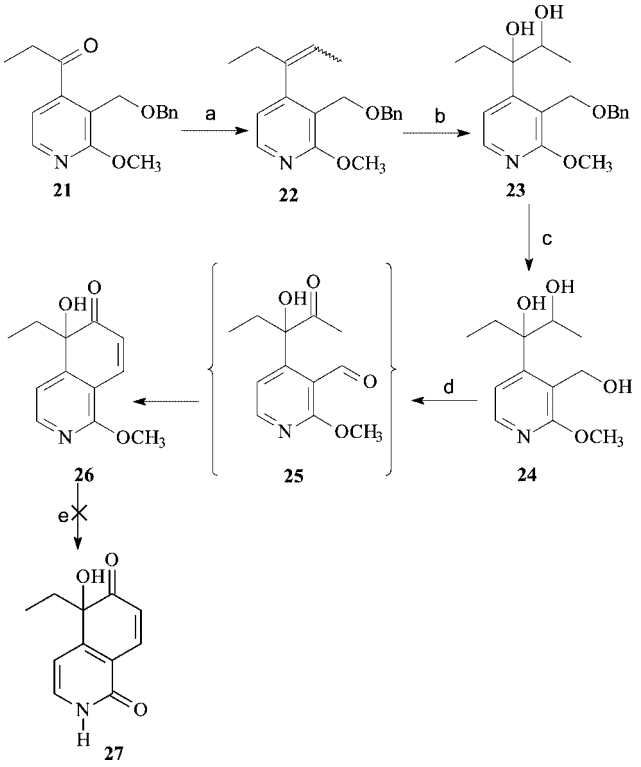
The model studies encouraged us to prepare the 4-(1-ethylpropenyl)pyridine derivative **22** from the known ketone **21**[18] by a Wittig reaction with ethyltriphenylphosphonium ylide (Scheme 4).

The product **22** was obtained in good yield as an isomeric mixture with an (*E*/*Z*) ratio of 10:90, but attempts to convert the olefin **22** into diol **23** by Sharpless catalytic asymmetric dihydroxylation with AD-mix-α or -β[30] (Table 1, Entry 3) failed. We found that the dihydroxylation of **22** could be only achieved by treatment with 5 mol% osmium tetraoxide in the presence of 3 equiv. of trimethylamine *N*-oxide in *tert*-butyl alcohol at room temperature, the desired diol **23** then being obtained only in a moderate yield (Table 1, Entry 4) even after extension of the reaction time (5–10 d). ^1H NMR spectral analysis showed that the (*E*) olefin **22** was converted into diol **23** more rapidly, since the recovered starting material was only (*Z*)-**22**. In an investigation to optimize the content of (*E*)-**22** in the isomeric mixture under various reaction conditions, we found that

Table 1. Dihydroxylation of various olefins for E-ring construction.

Entry	Substrate (*E*/*Z* ratio)[a]	Reaction time [d]	Method[b]	Product	Yield [%][c]
1	**19a** (1:100)	1	A	**20a**	99
2	**19b** (5:95)	1	A	**20b**	94
3	**22** (1:9)	1	A	n.r.[d]	
4	**22** (1:9)	5	B	**23**	68.5 (7.7)
5	**31a** (2:8)	1	A	n.r.	
6	**31a** (2:8)	5	C	**32a**	20.5 (71.8)
7	**34a** (2:8)	1	A	n.r.	
8	**34a** (3:7)	1.5	D	**35a**	45.2 (36.7)
9	**34b** (3:7)	4	D	**35b**	20.1 (17.5)

[a] Determined by ^{1}H NMR spectroscopy. [b] Reagents and conditions A: AD-mix-α or β, $MeSO_2NH_2$, *t*BuOH, H_2O (1:1, v/v).[30] Reagents and conditions B: OsO_4 (0.05 equiv.), $Me_3NO{\cdot}2H_2O$ (3 equiv.), *t*BuOH. Reagents and conditions C: OsO_4 (1 equiv.), $Me_3NO{\cdot}2H_2O$ (3 equiv.), THF. Reagents and conditions D: OsO_4 (0.3 equiv.), $Me_3NO{\cdot}2H_2O$ (2 equiv.), THF. [c] Numbers in parentheses are the percentage of recovered (*Z*)-olefin. [d] n.r.: no reaction.



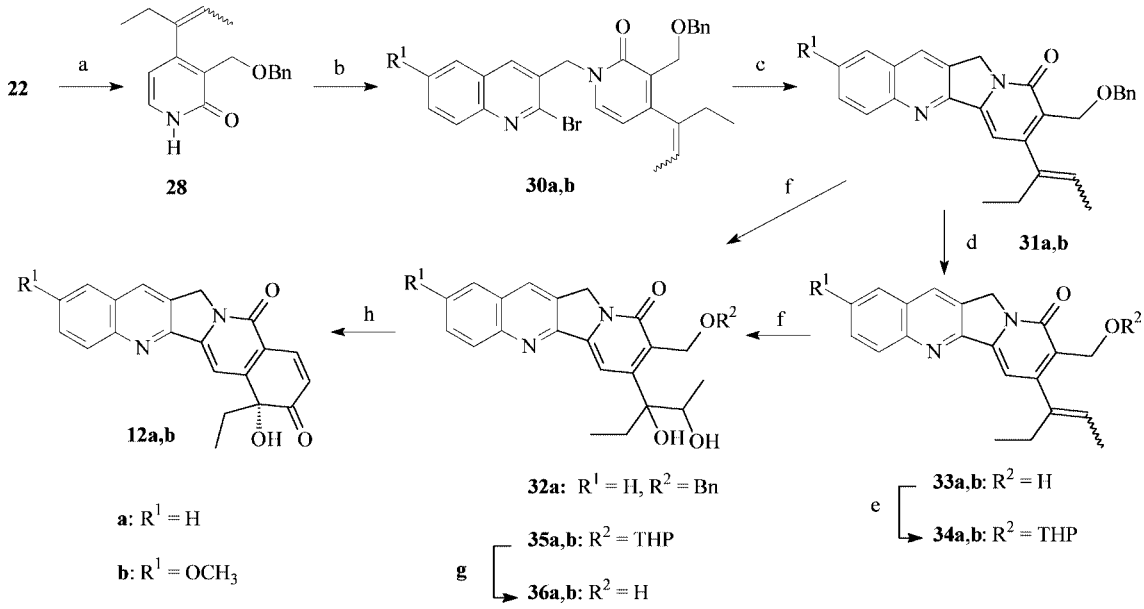
Scheme 4. Preparation of isoquinolinone **26**. Reagents and conditions: a) Ph_3PEtBr, $KN(SiMe_3)_2$, THF, –85 °C to room temp., 4 h, 96% or Ph_3PEtBr, $LiN(SiMe_3)_2$, ether, –80 °C to room temp., 22 h, 35%. b) OsO_4, $Me_3NO{\cdot}2H_2O$, *t*BuOH, room temp., 5 d, 69%. c) H_2, Pd/C (cat.), MeOH, room temp., 2 h, 98%. d) MnO_2/C, CH_3COOH, CH_2Cl_2, room temp., 4 h, 85%. e) TMSCl, NaI, MeCN, room temp.

the amount of (*E*)-**22** was increased to the ratio of *E*/*Z* = 3:7 when LiHMDS was employed as a base in ethereal solution, but that the total yield of the product was low (34.5%), unreacted ketone **21** also being recovered (60%). The benzyl protecting group in diol **23** was carefully removed by catalytic hydrogenation (10% Pd/C, H_2) to give triol **24** in good yield (98%), and compound **24** was then converted into 5*H*-isoquinoline-6-one **26** in good yield (92%) by treatment with freshly prepared "active" MnO_2 on carbon[31] in CH_2Cl_2 in the presence of acetic acid. Apparently, the one-pot synthesis of **26** from triol **24** was achieved through oxidation to give intermediate **25** and simultaneous intramolecular aldol-crotonic condensation under the acid catalysis conditions. These results shed light on the successes of the synthesis of **12a** by the first synthetic route. Unfortunately, though, in our attempts to convert **26** into the desired 1*H*,5*H*-isoquinoline-1,6-dione **27**, to be used for the condensation with the AB fragment, we found that **26** was unstable under acidic conditions, treatment of **26** with acid (such as HCl or TMSI) for demethylation resulting in the formation of a complex mixture of products.

The strategy for the synthesis of **12a** was then switched to the second synthetic route, involving the initial construction of the ABCD fragment, followed by the formation of the E-ring as shown in Scheme 5.

Compound **22** was treated with TMSCl/NaI in dry CH_3CN to afford pyridone **28** (Scheme 5), which was then treated with dibromoquinoline **29a**[26] to yield **30a**. Subsequent ring-closure of **30a** under Heck conditions afforded the tetracyclic **31a**. In our attempts to transform compound **31a** into triol **36a** by the same procedure as used for the synthesis of triol **21**, we found that the process was unsuitable, since the dihydroxylation of **31a** took place only over a long period of time (about 5 d), resulting in a low yield of diol **32a** (21%), together with unreacted **31a** and side-products (Table 1, Entry 6). In addition, the catalytic debenzylation of **32a** yielded a complex mixture of products, suggesting that the benzyl function in **31a** was not a suitable protecting group for preparing triol **36a**, so we replaced the benzyl group with THP as the protecting function and synthesized compound **34a**. The result was that all the (*E*)-**34a** and some of the (Z)-**34a** were dihydroxylated (OsO_4/$Me_3NO{\cdot}2H_2O$) to give diol **35a** (45%), whilst unreacted (*Z*)-**34a** (36.7%) was recovered from the reaction mixture after column chromatography (Table 1, Entry 8). On removal of the THP protecting group under acidic conditions, compound **35a** was converted into triol **36a** (70%), which was then smoothly transformed in a one-pot reaction to give the desired racemic pentacyclic **12a** in good yield by treatment with MnO_2 in acetic acid through oxidation and ring-closure. By following the same synthetic route, we also prepared (7*RS*)-7-ethyl-7-hydroxy-2-methoxy-7*H*,12*H*-5,11a-diazadibenzo[*b*,*h*]fluorene-8,11-dione (**12b**).

This study showed that the dihydroxylation of olefins **22**, **31a**, **34a**, and **34b** proceeded in the presence of sufficient amount OsO_4 (0.05 to 1 equiv.) although they did not undergo dihydroxylation with AD-mix-α (Table 1, Entries 3, 5, 7). The slow reaction rates and low yields of the dihydroxylations of these olefins can mainly be accounted for by the configurations of the olefins – low ratios of (*E*) isomers in the mixtures – as we found that the (*E*) isomers were transformed into the corresponding diols, while the recovered starting materials were the unreacted (*Z*) forms.



Scheme 5. Completion of the synthesis of **12a** and **12b**. Reagents and conditions: a) TMSCl, NaI, MeCN, room temp., 30 h, 84%. b) **29a**[26] or **29b**,[32] *t*BuOK, DME, reflux, **30a**: 5 h, 98%; **30b**: 6 h, 90%. c) $Pd(OAc)_2$, PPh_3, KOAc, MeCN, reflux, **31a**: 12 h, 99%; **31b**: 30 h, 75%. d) BBr_3, CH_2Cl_2, –80 °C, 3 h, **33a**: 77%, **33b**: 56%. e) THP, *p*TsA(cat), CH_2Cl_2, room temp., 5 h, 99%. f) OsO_4, $Me_3NO{\cdot}2H_2O$, THF, room temp., **32a**: 21%, **35a**: 45%, **35b**: 20%. g) *p*TsA(cat), CH_3OH, room temp., 5 h, **36a**: 70%, **36b**: 71%. h) MnO_2/C, CH_3COOH (cat), CH_2Cl_2, room temp., **12a**: 85%, **12b**: 17%.

Apparently, the benzyloxymethyl group at C-3 of the pyridine affected the stereoselectivity in the formation of the olefins, and consequently affected the dihydroxylation.

It is of great interest to note that compounds **12a** and **12b** exhibited potent CPT-like inhibitory effect against topoisomerase I and induced enzyme-mediated DNA cleavage. An antitumor study revealed that both compounds were significantly less potent than CPT against human nasopharyngeal carcinoma and human lymphoblastic leukemia cell growth in vitro, with IC_{50} values in a range of 1–3 μM.

Conclusions

In summary, we have modified the camptothecin E-ring by replacing the lactone ring with an α,β-cyclohexenone moiety, whilst retaining the ethyl and hydroxy functions. Although compounds **12a** and **12b** exhibited CPT-like inhibitory effect against topo I and induced enzyme-mediated DNA cleavage, in vitro antitumor studies revealed both compounds to be significantly less active then CPT.

Experimental Section

General Methods: THF, ether, and DME were distilled from sodium–benzophenone, and acetonitrile and CH_2Cl_2 were distilled from P_2O_5 immediately prior to use. The reactions were conducted under argon. Melting points were determined on a Fargo melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were determined on Bruker 400, 500, and 600 MHz spectrometers in $CDCl_3$ or [D_6]DMSO solution at 25 °C; chemical shifts are expressed in ppm downfield from internal standard TMS. Column chromatography was carried out over silica gel G60 (70–230 mesh, ASTM; Merck). Thin-layer chromatography was performed on silica gel G60 F_{254} (Merck) plates with short-wavelength UV light for visualization. Elemental analyses were done on a Heraeus CHN-O Rapid instrument.

(*Z*)-3-Phenylpent-2-ene (19a): A solution of $KN(SiMe_3)_2$ in THF (1 M, 93 mL) was added to a suspension of ethyltriphenylphosphonium bromide (18.56 g, 100 mmol) in anhydrous THF (300 mL). The mixture was stirred at room temperature for 0.5 h (red color of mixture) and was then chilled to –80 °C, and propiophenone (**18a**, 9.57 mL, 9.66 g, 72 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 1.5 h. The reaction was quenched by dropwise addition of HCl (1 N, 100 mL), the layers were separated, the water layer was extracted with diethyl ether (3×25 mL), and the organic layer and extracts were combined, dried ($MgSO_4$), and concentrated. The obtained oil was chromatographed on a silica gel column (6×30 cm, hexane), and the fractions containing the desired compound **19a** were combined and concentrated to dryness under reduced pressure to give **19a** (8.51 g, 80.8%) as a clear oil. ^1H NMR ($CDCl_3$): δ = 0.94 (dt, J = 2.0 and 7.6 Hz, 3 H, Me), 1.55 (d, J = 6.4 Hz, 3 H, Me), 2.34 (q, J = 7.7 Hz, 2 H, CH_2), 5.52 (q, J = 6.4 Hz, 1 H, CH=), 7.13–7.33 (m, 5 H, PhH) ppm. A comparison of the ^1H NMR spectrum of the product with the data in ref.[33] showed that only the (*Z*) isomer of **19a** had been isolated.

4-(1-Ethylpropenyl)-2-methoxypyridine (19b): Compound **19b** was obtained from **18b**[18] (0.33 g, 2 mmol) by the same procedure as used for the synthesis of **19a**, with use of HMPA (5 equiv.) as cosolvent, as a mixture of (*E*/*Z*) isomers (5:95, ^1H NMR). Yield 0.34 g (94.8%), as a clear oil. ^1H NMR ($CDCl_3$) (*E*) isomer: δ = 0.95 (t, J = 7.4 Hz, 3 H, Me), 1.57 (d, J = 6.9 Hz, 3 H, Me), 2.30 (q, J = 7.4 Hz, 2 H, CH_2), 3.95 (s, 3 H, MeO), 5.56 (q, J = 6.9 Hz, 1 H, CH=), 6.53 (s, 1 H, C3-H), 6.68 (dd, J = 1.1 and 5.2 Hz, 1 H, C5-H), 8.12 (d, J = 5.2 Hz, 1 H, C6-H) ppm; (*Z*) isomer: δ = 0.99 (t, J = 7.3 Hz, 3 H, Me), 1.81 (d, J = 7.0 Hz, 3 H, Me), 2.47 (q, J = 7.3 Hz, 2 H, CH_2), 3.94 (s, 3 H, MeO), 5.94 (q, J = 6.9 Hz,

1 H, CH=), 6.53 (s, 1 H, C3-H), 6.86 (dd, J = 1.5 and 5.3 Hz, 1 H, C5-H), 8.06 (d, J = 5.2 Hz, 1 H, C6-H) ppm. $C_{11}H_{15}NO\cdot0.35H_2O$ (183.55): calcd. C 72.10, H 8.62, N 7.62; found C 72.40, H 8.68, N 7.35.

3-Phenylpentane-2,3-diol (20a): A mixture of **19a** (0.73 g, 5 mmol), AD-mix-α (7 g), and $MeSO_2NH_2$ (0.475 g, 5 mmol) in *t*BuOH/H_2O (1:1, 50 mL) was stirred for 10 h at 0 °C. The reaction was quenched at 0 °C by addition of sodium sulfite (7.5 g) and the system was then allowed to warm to room temperature and stirred for 0.5 h. The *t*BuOH and water layers were separated, the aqueous layer was extracted with EtOAc (4×5 mL), and the *t*BuOH layer and EtOAc extracts were combined, washed with KOH (2 N, 2×10 mL), dried ($MgSO_4$), and concentrated. Compound **20a** was purified by silica gel column chromatography (3×25 cm), being eluted (0.891 g, 99%) from EtOAc/hexane (1:2, v/v) as a clear oil. ^{1}H NMR ($CDCl_3$): δ = 0.74 (t, J = 6.9 Hz, 3 H, Me), 0.94 (d, J = 6.9 Hz, 3 H, Me), 1.84 (d, J = 5.9 Hz, 1 H, exchangeable, OH), 1.98 (m, 2 H, CH_2), 2.35 (s, 1 H, exchangeable, OH), 3.94 (m, 1 H, CHO), 7.22–7.38 (m, 5 H, PhH) ppm. $C_{11}H_{16}O_2$ (180.24): calcd. C 73.30, H 8.95; found C 73.28, H 8.99.

3-(2-Methoxypyridin-4-yl)pentane-2,3-diol (20b): Compound **20b** was obtained from **19b** (0.177 g, 1 mmol) by the same procedure as used for the synthesis of **20a**, with use of AD-mix-α for 18 h at 0 °C. Yield 0.198 g (93.8%), m.p. 60–63 °C as a mixture of diastereomers (2:8, ^{1}H NMR). ^{1}H NMR ([D$_6$]DMSO), major diastereomer: δ = 0.56 (t, J = 7.4 Hz, 3 H, Me), 0.78 (d, J = 6.3 Hz, 3 H, Me), 1.73 and 1.94 (each: sext, J = 7.4 and 14.8 Hz, 1 H, CH_2), 3.71 (quint, J = 6.1 Hz, 1 H, CHO), 3.82 (s, 3 H, MeO), 4.48 (s, 1 H, exchangeable, OH), 4.64 (d, J = 5.9 Hz, 1 H, exchangeable, OH), 6.78 (d, J = 0.8 Hz, 1 H, C3-H), 6.92 (dd, J = 1.4 and 5.4 Hz, 1 H, C5-H), 8.04 (dd, J = 0.4 and 5.4 Hz, 1 H, C6-H) ppm; minor diastereomer: δ = 0.63 (t, J = 7.3 Hz, 3 H, Me), 0.85 (d, J = 6.3 Hz, 3 H, Me), 1.69 and 1.88 (each: m, J = 7.2 Hz, 1 H, CH_2), 3.69 (m, 1 H, CHO), 3.82 (s, 3 H, MeO), 4.67 (s, 1 H, exchangeable, OH), 4.68 (d, J = 5.2 Hz, 1 H, exchangeable, OH), 6.82 (dd, J = 2.4 and 2.6 Hz, 1 H, C3-H), 7.02 (dd, J = 1.4 and 5.5 Hz, 1 H, C5-H), 8.02 (d, J = 5.5 Hz, 1 H, C6-H) ppm. $C_{11}H_{17}NO_3\cdot0.4H_2O$ (218.46): calcd. C 60.48, H 8.21, N 6.41; found C 60.12, H 8.32, N, 6.17.

3-Benzyloxymethyl-4-[(*E*/*Z*)-1-ethylpropenyl]-2-methoxypyridine (22). Method 1: A mixture of ethyltriphenylphosphonium bromide (16.27 g, 43.8 mmol) in dried THF (90 mL) containing anhydrous HMPA (22 mL, 217.5 mmol) was cooled to 5 °C under argon. A solution of potassium bis(trimethylsilyl)amide (8.50 g, 42.6 mmol) in anhydrous THF (50 mL) was added dropwise to the above mixture over 20 min and the system was then stirred at room temperature for 15 min. The resulting red mixture was cooled to –85 °C and a solution of ketone **21**[18] (6.95 g, 24.4 mmol) in anhydrous THF (6 mL) was added dropwise with vigorous stirring, after which the reaction mixture was allowed to warm to room temperature and continuously stirred for 2 h. The reaction mixture was quenched by addition of saturated NH_4Cl aqueous solution (15 mL, 61 mmol), the resulting precipitate was filtered, and the water layer was separated and extracted with diethyl ether (3×10 mL). The combined organic extracts were washed successively with brine and water and dried (Na_2SO_4), and the solvents were evaporated in vacuo to dryness. The residue was chromatographed on a silica gel column with EtOAc/hexanes (1:10, v/v) as the eluent. Fractions containing the product **22** were combined and concentrated to dryness under reduced pressure to give **22** (6.923 g, 95.6%) as an oil. The ratio of (*E*) and (*Z*) isomers (1:9) was determined by ^{1}H NMR spectral analysis. ^{1}H NMR ($CDCl_3$) (*E*) isomer: δ = 0.85 (t, J = 7.8 Hz, 3 H, Me), 1.73 (d, J = 7.1 Hz, 3 H, Me), 2.37 (q, J = 7.6 Hz, 2 H, CH_2), 3.96 (s, 3 H, OMe), 4.41 (m, 2 H, CH_2Py), 4.59 (s, 2 H, CH_2Ph), 5.48 (m, 1 H, CH=), 6.65 (d, J = 6.0 Hz, 1 H, C5-H), 7.21–7.43 (m, 5 H, ArH), 8.01 (d, J = 5.5 Hz, 1 H, C6-H) ppm; (*Z*) isomer: δ = 0.97 (t, J = 7.3 Hz, 3 H, Me), 1.36 (d, J = 7.6 Hz, 3 H, Me), 2.24 (m, 2 H, CH_2), 3.99 (s, 3 H, OMe), 4.41 (dd, J = 8.4 Hz, 2 H, CH_2Py), 4.56 (s, 2 H, CH_2Ph), 5.54 (m, 1 H, CH=), 6.57 (d, J = 5.1 Hz, 1 H, C5-H), 7.21–7.43 (m, 5 H, ArH), 8.07 (d, J = 5.5 Hz, 1 H, C6-H) ppm. $C_{19}H_{23}NO_2$ (297.38): calcd. C 76.74, H 7.80, N 4.71; found C 76.42, H 7.48, N 4.55.

Method 2: The procedure for the synthesis of **22** by Method 2 was similar to that of Method 1: the reaction was carried out in anhydrous ether and lithium bis(trimethylsilyl)amide was used instead of potassium bis(trimethylsilyl)amide. Compound **22** was prepared from ketone **21** (14.27 g, 50.0 mmol). The reaction mixture was worked up in the usual way and the residue was chromatographed on a silica gel column. Compound **22** (5.18 g, 34.8%) was eluted from EtOAc/hexane (3:97, v/v) as an oil (*E*/*Z*, 3:7, determined by ^{1}H NMR) and the starting material **21** was eluted from EtOAc/hexane (1:9, v/v), 8.89 g (59.8%).

3-(3-Benzyloxymethyl-2-methoxypyridin-4-yl)pentane-2,3-diol (23): A mixture of **22** (2.38 g, 8.0 mmol), OsO_4 (0.102 g, 0.4 mmol), and $Me_3NO\cdot2H_2O$ (2.67 g, 24 mmol) in *t*BuOH (16 mL) was stirred at room temperature. The reaction was monitored by TLC (EtOAc/hexane, 4:6, v/v). After the mixture had been stirred for 5 d the starting material **22** had not been consumed. The reaction mixture was quenched by addition of aqueous $NaHSO_3$ (39%, 16 mL) and was then stirred at room temperature for 1 h and diluted with water (30 mL), and the water layer was separated. The aqueous layer was extracted with EtOAc (4×5 mL), and the *t*BuOH layer and EtOAc extracts were combined and stirred with Celite (2 g) for 1 h. After filtration, the solid cake was washed with ethyl acetate (2×5 mL), the combined filtrate and washings were evaporated in vacuo to dryness, and the residue was dissolved in EtOAc (100 mL), dried with $MgSO_4$, and concentrated to dryness under reduced pressure. The oil residue was chromatographed on a silica gel column, unreacted **22** being eluted in EtOAc/hexane (1:10, v/v), followed by product **23** (1.35 g, 68.5%) as a clear oil and as a mixture of diastereomers (3:7, ^{1}H NMR). ^{1}H NMR ([D$_6$]DMSO) major diastereomer: δ = 0.58 (t, J = 7.6 Hz, 3 H, Me), 0.77 (d, J = 6.1 Hz, 3 H, Me), 1.95 (m, 2 H, CH_2), 3.85 (s, 3 H, OMe), 4.00 (m, 1 H, CH), 4.37 (s, 1 H, exchangeable, OH), 4.53 and 4.56 (each: d, J = 12.2 Hz, 1 H, CH_2-Ph), 4.67 and 4.71 (each: d, J = 9.9 Hz, 1 H, CH_2-Py), 4.75 (d, J = 5.6 Hz, 1 H, exchangeable, OH), 7.15 (br d, J = 5.5 Hz, 1 H, C5-ArH), 7.25–7.38 (m, 5 H, ArH), 8.03 (d, J = 5.5 Hz, 1 H, C6-ArH) ppm; minor diastereomer: δ = 0.64 (t, J = 7.6 Hz, 3 H, Me), 0.97 (d, J = 6.3 Hz, 3 H, Me), 1.66 (m, 2 H, CH_2), 3.85 (s, 3 H, OMe), 3.89 (m, 1 H, CH), 4.37 (s, 1 H, exchangeable, OH), 4.52 (s, 2 H, CH_2-Ph), 4.70 (s, 2 H, CH_2-Py), 4.91 (d, J = 9.9 Hz, 1 H, OH), 7.10 (br d, J = 5.5 Hz, 1 H, C5-H), 7.25–7.38 (m, 5 H, ArH), 8.01 (d, J = 5.5 Hz, 1 H, C6-ArH) ppm. $C_{19}H_{25}NO_4$ (331.4): calcd. C 68.86, H 7.60, N 4.23; found C 68.56, H 7.63, N 4.13.

3-(3-Hydroxymethyl-2-methoxypyridin-4-yl)pentane-2,3-diol (24): A mixture of diol **23** (2.891 g, 8.72 mmol) and Pd/C in methanol (5%, 50 mL) was hydrogenated at 1 atmosphere for 1.6 h. The mixture was filtered through a pad of Celite, the solid cake was washed with MeOH, and the combined filtrate and washings were concentrated under reduced pressure to give an oil, which was recrystallized from $CHCl_3$/hexane to afford **24** (2.064 g, 98.1%), m.p. 101–104 °C. ^{1}H NMR ([D$_6$]DMSO) major diastereomer: δ = 0.60 (t, J = 7.4 Hz, 3

H, Me), 0.80 (d, J = 6.4 Hz, 3 H, Me) 1.93 (m, 2 H, CH_2), 3.85 (s, 3 H, OMe), 3.94 (m, 1 H, CH), 4.66 (brs, 1 H, CH_2O), 4.72 (brt, J = 5.6 Hz, exchangeable, 1 H, OH), 4.77 (brd, J = 5.4 Hz, exchangeable, 1 H, OH), 4.91 (brs, 1 H, exchangeable, OH), 6.97 (d, J = 5.4 Hz, 1 H, C5-ArH), 7.97 (d, J = 5.4 Hz, 1 H, C6-H) ppm; minor diastereomer: δ = 0.65 (t, J = 7.4 Hz, 3 H, Me), 0.97 (d, J = 6.3 Hz, 3 H, Me) 1.93 (m, 2 H, CH_2), 3.84 (s, 3 H, OMe), 4.02 (m, 1 H, CH), 4.66 (brs, 1 H, CH_2O), 4.72 (brt, J = 5.6 Hz, exchangeable, 1 H, OH), 4.77 (brd, J = 5.4 Hz, exchangeable, 1 H, OH), 4.91 (brs, 1 H, exchangeable, OH), 7.03 (d, J = 5.4 Hz, 1 H, C5-ArH), 7.88 (d, J = 5.4 Hz, 1 H, C6-ArH) ppm. $C_{12}H_{19}NO_4$ (241.28): calcd. C 59.73, H 7.94, N 5.80; found C 59.95, H 7.86, N 5.71.

5-Ethyl-5-hydroxy-1-methoxy-5*H*-isoquinoline-6-one (26): Freshly prepared active MnO_2 (14.62 g) on carbon was added to a solution of triol **24** (1.18 g, 4.87 mmol) in a mixture of CH_2Cl_2 (90 mL) and acetic acid (4.5 mL).[31] The mixture was stirred at room temperature and the reaction was monitored by TLC ($CH_3OH/CHCl_3$, 1:10, v/v). After having been stirred for 2 h, the solid in the mixture was filtered through a pad of Celite and the solid cake was washed with CH_2Cl_2 (2×15 mL). The filtrate and washings were combined and successively washed with water (2×15 mL), $NaHCO_3$ (8%, 2×10 mL), brine (10 mL), and water (10 mL), and dried ($MgSO_4$), and the solvents were evaporated in vacuo to dryness. The product was purified by flash chromatography ($CH_3OH/CHCl_3$, 1:5, v/v) to give **26** (0.983 g, 92.1%); m.p. 68–69 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 0.72 (t, J = 7.4 Hz, 3 H, Me), 1.92 (m, 2 H, CH_2), 3.92 (s, 3 H, OMe), 4.81 (d, J = 13.0 Hz, 1 H, CH), 4.95 (d, J = 13.0 Hz, 1 H, CH), 6.52 (brs, 1 H, OH), 6.99 (d, J = 5.2 Hz, 1 H, C5-ArH), 8.14 (d, J = 5.2 Hz, 1 H, C6-ArH) ppm. $C_{12}H_{13}NO_3 \cdot 0 \cdot 13\,H_2O$ (221.58): calcd. C 61.82, H 6.44, N 6.32; found C 61.62, H 6.51, N 6.52.

3-Benzyloxymethyl-4-(1-ethylpropenyl)-1*H*-pyridin-2-one (28): A mixture of **22** (5.95 g, 20 mmol) and TMSI [freshly generated from TMSCl (7.62 mL, 60 mmol) and NaI (9 g, 60 mmol)] in anhydrous CH_3CN (100 mL) was stirred at –10 °C for 10 min and was then allowed to warm to room temperature. After having been stirred for an additional 30 h, the reaction mixture was quenched with aqueous $NaHSO_3$ solution (39%, 30 mL) and stirred with EtOAc (30 mL). The organic layer was separated, the water layer was extracted with ethyl acetate (4×15 mL), and the combined organic extracts were successively washed with saturated $NaHCO_3$ solution (15 mL), $Na_2S_2O_3$ (1 M, 15 mL), and brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography (CH_3OH/CH_2Cl_2, 2:98, v/v) to give **28** (7.637 g, 84.4%) as syrup. Compound **28** was a mixture of (*E*) and (*Z*) isomers (3:7) as determined by ^{1}H NMR spectral analysis. ^{1}H NMR ([D$_6$]DMSO) (*E*) isomer: δ = 0.88 (t, J = 7.5 Hz, 3 H, Me), 1.70 (d, J = 6.9 Hz, 3 H, Me), 2.33 (q, J = 7.5 Hz, 2 H, CH_2), 4.42 (s, 2 H, CH_2Py), 4.63 (s, 2 H, CH_2Ph), 5.57 (qt, J = 0.7 and 6.9 Hz, 1 H, CH=), 6.07 (d, J = 6.6 Hz, 1 H, C5-ArH), 7.23–7.40 (m, 6 H, ArH), 13.00 (brs, 1 H, exchangeable, NH) ppm; (*Z*) isomer: δ = 0.98 (t, J = 7.5 Hz, 3 H, Me), 1.42 (dt, J = 1.5 and 6.8 Hz, 3 H, Me), 2.22 (qt, J = 1.4 and 7.5 Hz, 2 H, CH_2), 4.33 and 4.43 (each: d, J = 9.4 Hz, 1 H, CH_2Py), 4.60 (dd, J = 11.3 Hz, 2 H, CH_2Ph), 5.45 (qt, J = 1.5 and 6.8 Hz, 1 H, CH=), 5.98 (d, J = 6.6 Hz, 1 H, C5-ArH), 7.23–7.40 (m, 6 H, ArH), 13.00 (brs, 1 H, exchangeable, NH) ppm. $C_{18}H_{21}NO_2 \cdot 0.2\,H_2O$ (286.96): calcd. C 75.34, H 7.52, N 4.88; found C 75.60, H 7.43, N 4.81.

3-Benzyloxymethyl-1-(2-bromoquinolin-3-ylmethyl)-4-(1-ethylpropenyl)-1*H*-pyridin-2-one (30a): Potassium *tert*-butoxide (3.37 g, 30 mmol) was added in one portion to a stirring solution of **28** (6.819 g, 24 mmol) in anhydrous DME (300 mL) and the mixture was then stirred under argon at room temperature for 1 h. Compound **29a**[26] (7.525 g, 25 mmol) was then added to the above mixture in one portion. After having been heated at reflux for 5 h it was allowed to cool to room temperature and the solvents were evaporated in vacuo to dryness. The residue was mixed with a saturated solution of NH_4Cl (50 mL) and then with diethyl ether (100 mL), the ethereal layer was separated, and the water layer was extracted with diethyl ether (3×20 mL). The combined ethereal extracts was washed with water (3×20 mL) and dried (Na_2SO_4), and the solvents were evaporated in vacuo to dryness. The product **30a** was purified by column chromatography (EtOAc/hexane, 1:5, v/v). Yield 10.42 g (86.2%) as a mixture of (*E*) and (*Z*) isomers (3:7), m.p. 85–93 °C. ^{1}H NMR ($CDCl_3$) (*E*) isomer: δ = 0.90 (t, J = 7.4 Hz, 3 H, Me), 1.72 (d, J = 6.9 Hz, 3 H, Me), 2.35 (q, J = 7.4 Hz, 2 H, CH_2), 4.43 (s, 2 H, CH_2Py), 4.64 (s, 2 H, CH_2Ph), 5.36 (s, 2 H, CH_2N), 5.62 (q, J = 6.9 Hz, 1 H, CH=), 6.07 (d, J = 7.0 Hz, 1 H, C5-ArH), 7.40 (d, J = 7.0 Hz, 1 H, C6-ArH), 7.56 (ddd, J = 1.0 and 7.0 Hz, 1 H, C6′-ArH), 7.72 (ddd, J = 1.4, 6.8, and 8.4 Hz, 1 H, C7′-ArH), 7.80 (d, J = 8.0 Hz, 1 H, C5′-ArH), 7.79 (d, J = 8.5 Hz, 1 H, C8′-ArH), 8.10 (s, 1 H, C4′-ArH); (*Z*) isomer: δ = 1.00 (t, J = 7.4 Hz, 3 H, Me), 1.45 (dt, J = 1.6 and 6.9 Hz, 3 H, Me), 2.24 (qt, J = 1.6 and 7.4 Hz, 2 H, CH_2), 4.35 and 4.44 (each: brd, J = 8.5 Hz, 1 H, CH_2Py), 4.61 (brd, J = 6.5 Hz, 2 H, CH_2Ph), 5.39 (s, 2 H, CH_2N), 5.48 (qt, J = 1.6 and 6.9 Hz, 1 H, CH=), 5.97 (d, J = 7.0 Hz, 1 H, C5-ArH), 7.46 (d, J = 7.0 Hz, 1 H, C6-ArH), 7.56 (ddd, J = 1.0 and 7.0 Hz, 1 H, C6′-ArH), 7.72 (ddd, J = 1.4, 6.8, and 8.4 Hz, 1 H, C7′-ArH), 7.79 (dd, J = 1.2 and 8.0 Hz, 1 H, C5′-ArH), 8.02 (d, J = 8.6 Hz, 1 H, C8′-ArH), 8.13 (s, 1 H, C4′-ArH) ppm. $C_{28}H_{27}BrN_2O_2$ (503.42): calcd. C 66.80, H 5.41, N 5.56; found C 66.82, H 5.49, N 5.60.

3-Benzyloxymethyl-1-(2-bromo-6-methoxyquinolin-3-ylmethyl)-4-(1-ethylpropenyl)-1*H*-pyridin-2-one (30b): Compound **30b** (6.68 g, 89.6%) was obtained from **28** (3.77 g, 13.3 mmol) and **29b**[32] (4.40 g, 14 mol) by the same procedure as used for the synthesis of **30a**, as a mixture of (*E*) and (*Z*) isomers (3:7), m.p. 81–90 °C. ^{1}H NMR ($CDCl_3$) (*E*) isomer: δ = 0.90 (t, J = 7.8 Hz, 3 H, Me), 1.73 (d, J = 6.7 Hz, 3 H, Me), 2.36 (q, J = 7.4 Hz, 2 H, CH_2), 3.89 (s, 3 H, OMe), 4.45 (s, 2 H, CH_2Py), 4.65 (s, 2 H, CH_2Ph), 5.35 (s, 2 H, CH_2N), 5.63 (q, J = 7.0 Hz, 1 H, CH=), 6.06 (d, J = 7.0 Hz, 1 H, C5-ArH), 7.08 (d, J = 2.7, 1 H, C5′-ArH), 7.22–7.39 (m, 6 H, C7′-ArH and Ph), 7.41 (d, J = 7.0 Hz, 1 H, C6-ArH), 7.90 (d, J = 9.0 Hz, 1 H, C8′-ArH), 8.04 (s, 1 H, C4′-ArH) ppm; (*Z*) isomer: δ = 1.01 (t, J = 7.4 Hz, 3 H, Me), 1.45 (dt, J = 1.6 and 6.7 Hz, 3 H, Me), 2.25 (qt, J = 1.6 and 7.4 Hz, 2 H, CH_2), 3.88 (s, 3 H, OMe), 4.36 and 4.46 (each: brs, 1 H, CH_2Py), 4.65 (brd, J = 5.7 Hz, 2 H, CH_2Ph), 5.37 (d, J = 10.0 Hz, 2 H, CH_2N), 5.48 (qt, J = 1.6 and 6.7 Hz, 1 H, CH=), 5.96 (d, J = 7.0 Hz, 1 H, C5-ArH), 7.05 (d, J = 2.7 Hz, 1 H, C5′-ArH), 7.22–7.39 (m, 6 H, Ph and C7′-ArH), 7.49 (d, J = 7.0 Hz, 1 H, C6-ArH), 7.91 (d, J = 9.0 Hz, 1 H, C8′-ArH), 8.10 (s, 1 H, C4′-ArH) ppm. $C_{29}H_{29}BrN_2O_2 \cdot 0.9\,H_2O$ (533.66): calcd. C 63.37, H 5.65, N 5.10; found C 63.58, H 5.66, N 4.97.

8-Benzyloxymethyl-7-(1-ethylpropenyl)-11*H*-indolizino[1,2-*b*]quinolin-9-one (31a): A mixture of **30a** (2.517 g, 5 mmol), $Pd(OAc)_2$ (0.112 g, 0.5 mmol), PPh_3 (0.262 g, 1 mmol), and freshly dried potassium acetate (1.472 g, 15 mmol) in anhydrous acetonitrile (150 mL) was stirred under argon at room temperature for 2 h and was then heated at reflux for 12 h. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was dissolved in $CHCl_3$ (50 mL), filtered through a pad of Celite, and washed with $CHCl_3$ (3×15 mL). The combined filtrate and washing were evaporated to dryness in vacuo, and the product was purified by column chromatography (MeOH/EtOAc/hexanes 1:10:15,

v/v/v) to afford **31a** (2.04 g, 96.3%), as a mixture of (*E*) and (*Z*) isomers (3:7), and recrystallized from EtOAc, m.p. 215–217 °C. ^{1}H NMR ($CDCl_3$) (*E*) isomer: δ = 0.88 (t, *J* = 7.2 Hz, 3 H, Me), 1.77 (d, *J* = 6.9 Hz, 3 H, Me), 2.49 (q, *J* = 7.4 Hz, 2 H, CH_2), 4.55 (m, 2 H, CH_2Py), 4.70 (s, 2 H, CH_2Ph), 5.67 (q, *J* = 6.9 Hz, 1 H, CH_2), 7.16 (s, 1 H, C6-ArH), 7.26–7.40 (m, 5 H, Ph), 7.63 (m, 1 H, C2-ArH), 7.80 (m, 1 H, C3-ArH), 7.92 (m, 1 H, C4-ArH), 8.20 (m, 1 H, C1-ArH), 8.35 (s, 1 H, C12-ArH) ppm; (*Z*) isomer: δ = 1.06 (t, *J* = 7.2 Hz, 3 H, Me), 1.48 (dt, *J* = 1.4 and 6.8 Hz, 3 H, Me), 2.35 (qt, *J* = 1.4 and 7.4 Hz, 2 H, CH_2), 4.45 and 4.57 (each: d, *J* = 9.7 Hz, 1 H, CH_2Py), 4.67 (each: d, *J* = 11.7 Hz, 1 H, CH_2Ph), 5.57 (qt, *J* = 1.5 and 6.9 Hz, 1 H, CH_2), 7.07 (s, 1 H, C6-ArH), 7.26–7.40 (m, 5 H, Ph), 7.63 (ddd, *J* = 1.2 and 6.9 Hz, 1 H, C2-ArH), 7.80 (ddd, *J* = 1.4 and 6.9, 1 H, C3-ArH), 7.92 (dd, *J* = 1.4 and 6.9 Hz, 1 H, C4-ArH), 8.20 (dd, *J* = 1.2 and 6.9 Hz, 1 H, C1-ArH), 8.37 (s, 1 H, C12-ArH) ppm. $C_{28}H_{26}N_2O_2$ (422.51): calcd. C 79.59, H 6.20, N 6.63; found C 79.68, H 6.26, N 6.62.

8-Benzyloxymethyl-7-(1-ethylpropenyl)-2-methoxy-11*H*-indolizino-[1,2-*b*]quinolin-9-one (31b): Compound **31b** was obtained from **30b** (5.89 g, 11 mmol) by the same procedure as used for the synthesis of **31a**. Yield 3.72 g (74.7%); m.p. 162–164 °C as a mixture of (*E*) and (*Z*) isomers (3:7). ^{1}H NMR ($CDCl_3$) (*E*) isomer: δ = 0.94 (t, *J* = 7.4 Hz, 3 H, Me), 1.77 (d, *J* = 7.0 Hz, 3 H, Me), 2.48 (q, *J* = 7.4 Hz, 2 H, CH_2), 3.967 (s, 3 H, OMe), 4.54 (s, 2 H, CH_2Py), 4.70 (s, 2 H, CH_2Ph), 5.25 (d, *J* = 0.8 Hz, 2 H, CH_2N), 5.66 (q, *J* = 6.7 Hz, 1 H, CH=), 7.09 (s, 1 H, C6-ArH), 7.15 (d, *J* = 3.1 Hz, 1 H, C1-ArH), 7.24–7.38 (m, 5 H, Ph), 7.42 (d, *J* = 9.0 Hz, 1 H, C3-ArH), 8.08 (d, *J* = 9.0 Hz, 1 H, C4-ArH), 8.23 (s, 1 H, C12-ArH) ppm; (*Z*) isomer: δ = 1.05 (t, *J* = 7.4 Hz, 3 H, Me), 1.48 (dt, *J* = 1.2 and 7.0 Hz, 3 H, Me), 2.34 (qt, *J* = 1.2 and 7.4 Hz, 2 H, CH_2), 3.971 (s, 3 H, OMe), 4.44 and 4.54 (each: d, *J* = 9.8 Hz, 1 H, CH_2Py), 4.67 (d, *J* = 3.5 Hz, 2 H, CH_2Ph), 5.27 (s, 2 H, CH_2N), 5.55 (qt, *J* = 1.6 and 7.0 Hz, 1 H, CH=), 7.00 (s, 1 H, C6-ArH), 7.17 (d, *J* = 3.0 Hz, 1 H, C1-ArH), 7.24–7.38 (m, 5 H, Ph), 7.42 (d, *J* = 9.0 Hz, 1 H, C3-ArH), 8.08 (d, *J* = 9.0 Hz, 1 H, C4-ArH), 8.25 (s, 1 H, C12-H) ppm. $C_{29}H_{28}N_2O_3$ (452.53): calcd. C 76.97, H 6.24, N 6.19; found C 77.15, H 6.38, N 6.36.

8-Benzyloxymethyl-7-(1-ethyl-1,2-dihydroxypropyl)-11*H*-indolizino-[1,2-*b*]quinolin-9-one (32a): A solution of OsO_4 (0.508 g, 2 mmol) in THF (3 mL) was added to a mixture of **31a** (0.845 g, 2 mmol) and $(CH_3)_3NO{\cdot}2H_2O$ (0.67 g, 6 mmol) in THF (45 mL). The mixture was stirred at room temperature for 5 d (**31a** was not consumed completely) and was then quenched by addition of aq. $NaHSO_3$ (39%, 4 mL) and water (10 mL). The mixture was stirred with Celite (2 g) for 1 h and then filtered, the solid cake was washed with ethyl acetate (2 × 5 mL), the filtrate and washing were combined and dried (Na_2SO_4), and the solvents were evaporated to dryness. The residue was chromatographed on a silica gel column (3 × 30 cm), the starting material **31a** [0.453 g, 53.6%, only (*Z*) isomer (^{1}H NMR)] being eluted ($CHCl_3$), followed by the product ($CH_3OH/CHCl_3$ 1:50). Yield 0.787 g (26.7%), m.p. 179–192 °C (recrystallized from $CHCl_3$/hexane) as a mixture of diastereomers (4:6, ^{1}H NMR). ^{1}H NMR ($CDCl_3$) major diastereomer: δ = 0.80 (t, *J* = 7.3 Hz, 3 H, Me), 1.01 (d, *J* = 5.9 Hz, 3 H, Me), 2.00 and 2.26 (each: m, 1 H, CH_2), 2.10 (brs, 1 H, exchangeable, OH), 4.13 (q, *J* = 5.9 Hz, 1 H, CH), 4.69 (dd, *J* = 11.0 Hz, 2 H, CH_2Py), 5.10 and 5.19 (each: d, *J* = 10.3 Hz, 1 H, CH_2Ph), 5.29 (s, 2 H, CH_2N), 5.53 (brs, 1 H, exchangeable, OH), 7.12 (s, 1 H, C6-ArH), 7.26–7.42 (m, 5 H, Ph), 7.65 (m, 1 H, C2-ArH), 7.82 (m, 1 H, C3-ArH), 7.91 (d, *J* = 8.1 Hz, 1 H, C1-ArH), 8.23 (d, *J* = 8.1 Hz, 1 H, C4-ArH), 8.38 (s, 1 H, C12-ArH) ppm; minor diastereomer: δ = 0.81 (t, *J* = 7.3 Hz, 3 H, Me), 1.30 (d, *J* = 5.9 Hz, 3 H, Me), 1.82 (m, 2 H, CH_2), 2.10 (brs, 1 H, exchangeable, OH), 4.23 (q, *J* = 5.9 Hz, 1 H, CH), 4.70 (m, 2 H, CH_2Py), 5.16 and 5.21 (each: d, *J* = 10.3 Hz, 1 H, CH_2Ph), 5.29 (d, *J* = 6.6 Hz, 1 H, CH_2N), 7.12 (s, 1 H, C6-ArH), 7.26–7.42 (m, 5 H, Ph), 7.64 (m, 1 H, C2-ArH), 7.79 (m, 1 H, C3-ArH), 7.91 (d, *J* = 8.1 Hz, 1 H, C1-ArH), 8.21 (d, *J* = 8.1 Hz, 1 H, C4-ArH), 8.35 (s, 1 H, C12-ArH) ppm. $C_{28}H_{28}N_2O_4{\cdot}0.5H_2O$ (465.53): calcd. C 72.24, H 6.28, N 6.02; found C 71.98, H 6.32, N 5.94.

7-(1-Ethylpropenyl)-8-hydroxymethyl-11*H*-indolizino[1,2-*b*]quinolin-9-one (33a): BBr_3 (5.2 g, 20.7 mmol) was added at –80 °C to a stirring solution of **31a** (3.50 g, 8.28 mmol) in dried CH_2Cl_2 (110 mL) and the reaction mixture was stirred at –80 °C for 1 h. The reaction was quenched by dropwise addition of saturated aqueous $NaHCO_3$ (60 mL) and the reaction mixture was then allowed to warm to –10 °C and neutralized with aqueous Na_2CO_3 solution (10%). The water layer was separated and extracted with CH_2Cl_2 (4 × 10 mL), the combined organic layer and extracts were washed with brine (10 mL) and dried (Na_2SO_4), and the solvents were evaporated to dryness in vacuo. The residue was chromatographed on a silica gel column (5.5 × 30 cm) with $CHCl_3$ as the eluent. The product (2.12 g, 77%) was eluted with $CH_3OH/CHCl_3$ (1:20, v/v) as a mixture of (*E*) and (*Z*) isomers (3:7); m.p. 204–206 °C (dec.). ^{1}H NMR ([D$_6$]DMSO) (*E*) isomer: δ = 0.92 (t, *J* = 7.6 Hz, 3 H, Me), 1.80 (d, *J* = 7.0 Hz, 3 H, Me), 2.50 (q, *J* = 7.6 Hz, 2 H, CH_2), 4.42 (m, 2 H, CH_2O), 4.75 (s, exchangeable, 1 H, OH), 5.27 (s, 1 H, CH_2N), 5.57 (q, *J* = 6.5 Hz, 1 H, CH_2), 6.97 (s, 1 H, C6-ArH), 7.71 (m, 1 H, C2-ArH), 7.86 (m, 1 H, C3-ArH), 8.12 (m, 1 H, C4-ArH), 8.15 (m, 1 H, C1-ArH), 8.68 (s, 1 H, C12-ArH) ppm; (*Z*) isomer: δ = 1.01 (t, *J* = 7.3 Hz, 3 H, Me), 1.45 (dt, *J* = 1.5 and 6.8 Hz, 3 H, Me), 2.36 (qt, *J* = 1.5 and 7.6 Hz, 2 H, CH_2), 4.29 and 4.44 (each: dd, *J* = 5.9 and 11.7 Hz, 1 H, CH_2), 4.70 (t, *J* = 5.6 Hz, 1 H, exchangeable, OH), 5.30 (s, 1 H, CH_2N), 5.62 (qt, *J* = 1.2 and 7.0 Hz, 1 H, CH_2N), 6.88 (s, C6–1 H, ArH), 7.63 (m, *J* = 1.2 and 6.8 Hz, 1 H, C2-ArH), 7.86 (m, *J* = 1.5 and 6.8 Hz, 1 H, C3-ArH), 8.13 (d, *J* = 9.4 Hz, 1 H, C4-ArH), 8.15 (d, *J* = 9.1 Hz, 1 H, C1-ArH), 8.69 (s, 1 H, C12-ArH) ppm. $C_{21}H_{20}N_2O_2$ (332.39): calcd. C 75.88, H 6.06, N, 8.43; found C 75.77, H 6.12, N 8.26.

7-(1-Ethylpropenyl)-8-hydroxymethyl-2-methoxy-11*H*-indolizino-[1,2-*b*]quinolin-9-one (33b): Compound **33b** was obtained from **31b** (3.25 g, 7.17 mmol) by the same procedure as used for the synthesis of **33a**. Yield 1.46 g (56%) as a mixture of (*E*) and (*Z*) isomers (3:7); m.p. 184–189 °C. ^{1}H NMR ([D$_6$]DMSO), (*E*) isomer: δ = 0.92 (t, *J* = 7.8 Hz, 3 H, Me), 1.80 (d, *J* = 6.4 Hz, 3 H, Me), 2.49 (q, *J* = 7.8 Hz, 2 H, CH_2), 3.94 (s, 3 H, OMe), 4.41 (d, *J* = 6.0 Hz, 2 H, CH_2O), 4.72 (t, *J* = 6.0 Hz, 1 H, exchangeable, OH), 5.22 (s, 1 H, CH_2N), 5.56 (q, *J* = 6.4 Hz, 1 H, CH_2), 6.87 (s, 1 H, C6-ArH), 7.49 (dd, *J* = 3.1 and 9.3 Hz, 1 H, C3-ArH), 7.51 (d, *J* = 3.1 Hz, 1 H, C1-ArH), 8.01 (d, *J* = 7.8 Hz, 1 H, C4-ArH), 8.51 (s, 1 H, C12-ArH) ppm; (*Z*) isomer: δ = 1.01 (t, *J* = 7.3 Hz, 3 H,Me), 1.45 (d, *J* = 6.9 Hz, 3 H, Me), 2.35 (qt, *J* = 1.4 and 7.3 Hz, 2 H, CH_2), 3.94 (s, 3 H, OMe), 4.29 and 4.43 (each: dd, *J* = 6.0 and 11.5 Hz, 1 H, CH_2O), 4.68 (t, *J* = 6.0 Hz, 1 H, exchangeable, OH), 5.26 (s, 1 H, CH_2N), 5.61 (qt, *J* = 1.4 and 6.9 Hz, 1 H, CH=), 6.79 (s, 1 H, C6-ArH), 7.49 (dd, *J* = 3.1 and 9.3, 1 H, C3-ArH), 7.51 (d, *J* = 3.1 Hz, 1 H, C1-ArH), 8.03 (d, *J* = 9.2 Hz, 1 H, C4-H), 8.53 (s, 1 H, C12-ArH) ppm. $C_{22}H_{22}N_2O_3$ (362.42): calcd. C 72.91, H 6.12, N 7.73; found C 73.14, H 5.90, N 7.48.

7-(1-Ethylpropenyl)-8-(tetrahydropyran-2-yloxymethyl)-11*H*-indolizino[1,2-*b*]quinolin-9-one (34a): A mixture of **33a** (1.308 g, 3.93 mmol), 3,4-dihydro-2*H*-pyran (1.65 g, 19.7 mmol), and *p*-toluenesulfonic acid monohydrate (2 mg) in anhydrous CH_2Cl_2 (25 mL) was stirred under argon atmosphere for 3 h. The reaction mixture was neutralized by addition of triethylamine (3 drops) and was then

evaporated to dryness in vacuo. The residue was chromatographed on a silica gel column (4×29 cm) with $CH_3OH/CHCl_3$ (1:50, v/v) and the product **34a** was obtained as crystals (1.62 g, 99%) as a mixture of diastereomers, m.p. 185–189 °C. ^1H NMR ($CDCl_3$): δ = 0.99–1.11 (m, 3 H, Me), 1.48–1.83 (m, 3 H, Me), 1.5–1.9 (m, 6 H, THP), 2.34–2.55 (m, 1 H, CH_2), 3.62 (m, 1 H, OCH, THP), 4.03 (m, 1 H, OCH, THP), 4.34–4.78 (m, 2 H, $ArCH_2O$), 4.87–4.95 (m, 1 H, OCH, THP), 5.27–5.32 (m, 2 H, CH_2N), 5.60–5.65 (m, 1 H, CH=), 7.07–7.18 (m, 1 H, C6-ArH), 7.64 (m, 1 H, C2-ArH), 7.80 (m, 1 H, C3-ArH), 7.92 (d, J = 7.7 Hz, 1 H, C4-ArH), 8.20 (d, J = 8.4 Hz, 1 H, C1-ArH), 8.37 (s, 1 H, C12-ArH) ppm. $C_{26}H_{28}N_2O_3{\cdot}H_2O$ (434.52): calcd. C 71.87, H 6.96, N 6.45; found C 72.01, H 6.94, N 6.08.

7-(1-Ethylpropenyl)-2-methoxy-8-(tetrahydropyran-2-yloxymethyl)-11*H*-indolizino[1,2-*b*]quinolin-9-one (34b): Compound **34b** (1.42 g, 3.92 mmol) was obtained from **33b** by the same procedure as used for the synthesis of **34a**. Yield 1.75 g (99%) as a mixture of diastereomers; m.p. 177–180 °C. ^1H NMR ($CDCl_3$): δ = 0.97–1.11 (m, 3 H, Me), 1.47–1.83 (m, 3 H, Me), 1.5–1.9 (m, 6 H, THP), 2.34–2.54 (m, 1 H, CH_2), 3.60 (m, 1 H, OCH, THP), 3.98 (s, 3 H, MeO), 4.00–4.13 (m, 1 H, OCH, THP), 4.33–4.76 (m, 2 H, $ArCH_2O$), 4.88–4.94 (m, 1 H, OCH, THP), 5.25–5.28 (m, 2 H, CH_2N), 5.60–5.65 (m, 1 H, CH=), 7.01–7.17 (m, 1 H, C6-ArH), 7.44–7.50 (m, 2 H, C1-ArH, C3-H), 8.08 (d, J = 9.6 Hz, 1 H, C4-ArH), 8.24 (s, 1 H, C12-ArH) ppm. $C_{27}H_{30}N_2O_4{\cdot}0.5\,H_2O$ (455.54): calcd. C 71.19, H 6.86, N 6.15; found C 71.01, H 6.94, N 6.08.

7-(1-Ethyl-1,2-dihydroxypropyl)-8-(tetrahydropyran-2-yloxymethyl)-11*H*-indolizino[1,2-*b*]quinolin-9-one (35a): A solution of OsO_4 (0.64 g, 2.52 mmol) in THF (2 mL) was added to a mixture of **34a** (3.554 g, 8.4 mmol) and $(CH_3)_3NO{\cdot}2\,H_2O$ (1.87 g, 16.8 mmol) in THF (60 mL). The mixture was stirred at room temperature for 36 h (the olefin **34a** was not consumed completely), the reaction was quenched by addition of a solution of Na_2SO_3 (1.2 g) in water (30 mL), the mixture was stirred with celite (2 g) for 1 h and then filtered, and the solid cake was washed with ethyl acetate (5×10 mL). The filtrate and washing were combined and dried (Na_2SO_4), the solvents were evaporated to dryness, and the residue was chromatographed on a silica gel column (6×30 cm). The starting material **34a** [0.505 g, 36.7%, only (*Z*) isomer (^1H NMR)] was eluted ($CHCl_3$), followed by the product ($CH_3OH/CHCl_3$ 1:50). Yield 0.672 g (45.2%), m.p. 175–188 °C, as a mixture of diastereomers. ^1H NMR ($CDCl_3$): δ = 0.80–1.12 (m, 3 H, Me), 1.45–1.63 (m, 7 H, Me, THP), 1.65–1.73 (m, 1 H, THP), 1.73–1.87 (m, 1 H, THP), 2.26–2.39 (m, 1 H, CH_2), 3.47–3.61 (m, 1 H, OCH, THP), 4.21–4.41, (m, 2 H, OCH), 4.50–4.70 (m, 2 H, OCH, THP), 4.72 (s, 1 H, exchangeable, OH), 4.76–4.86 (m, 1 H, THP), 4.91 (s, 2 H, CH_2N), 5.56 (m, 1 H, THP), 6.76, (s, 1 H, C6-ArH), 7.56 (m, 1 H, C2-ArH), 7.71 (m, 1 H, C3-ArH), 7.83 (d, J = 8.2 Hz, 1 H, C4-ArH), 8.05 (d, J = 8.2 Hz, 1 H, C1-ArH), 8.36 (m, 1 H, C12-ArH) ppm. $C_{18}H_{21}NO_2{\cdot}0.2\,H_2O$ (286.96): calcd. C 75.34, H 7.52, N 4.88; found C 75.46, H 7.43, N 4.91.

7-(1-Ethyl-1,2-dihydroxypropyl)-8-(tetrahydropyran-2-yloxymethyl)-2-methoxy-11*H*-indolizino[1,2-*b*]quinolin-9-one (35b): Compound **35b** was obtained from **34b** (1.75 g, 3.92 mmol) by the same procedure as used for the synthesis of **35a**. Yield 0.38 g (20.1%), m.p. 211–215 °C, as a mixture of diastereomers. ^1H NMR ([D$_6$]DMSO): δ = 0.68–0.82 (m, 3 H, Me), 0.88–1.09 (m, 3 H, Me), 1.35–1.80 (m, 4 H, THP), 1.85–2.18 (m, 4 H, THP and CH_2), 3.51 (m, 1 H, OCH, THP), 3.94 (s, 3 H, MeO), 4.00 (m, 1 H, OCH), 4.71–4.91 (m, 1 H, OCH, THP), 5.11–5.17 (m, 1 H, THP), 5.23 (s, 2 H, CH_2N), 7.35–7.55 (m, 3 H, C6-ArH, C3-ArH, and OH), 8.07 (d, J = 9.5 Hz, 1 H, C4-ArH), 8.32–8.53 (m, 1 H, C12-ArH) ppm. $C_{27}H_{32}N_2O_6$ (480.55): calcd. C 67.48, H 6.71, N 5.83; found C 67.68, H 6.85, N 5.69.

7-(1-Ethyl-1,2-dihydroxypropyl)-8-hydroxymethyl-11*H*-indolizino-[1,2-*b*]quinolin-9-one (36a): *p*-Toluenesulfonic acid monohydrate (2 mg) was added to a solution of **35a** (0.481 g, 1.07 mmol) in CH_3OH (35 mL). The reaction mixture was stirred at ambient temperature for 7 h and was then quenched by addition of NH_4OH (25%, 100 μL). The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (2×30 cm) with $CH_3OH/CHCl_3$ (1:50, v/v) to afford **36a** (0.272 g, 69.5%), m.p. 192–196 °C (recrystallized from $CHCl_3$/hexane) as a mixture of diastereomers (4:6, ^1H NMR). ^1H NMR ([D$_6$]DMSO) major diastereomer: δ = 0.74 (t, J = 7.6 Hz, 3 H, Me), 0.95 (d, J = 6.3 Hz, 3 H, Me), 2.03 (m, 2 H, CH_2), 4.06 (m, 1 H, CH), 4.70–5.1 (m, 4 H, CH_2O and 2×OH, exchangeable), 5.25 (s, 2 H, CH_2N), 5.49 (brs, 1 H, exchangeable, OH), 7.36 (brs, 1 H, C6-ArH), 7.70 (m, 1 H, C2-ArH), 7.85 (m, 1 H, C3-ArH), 8.11 (d, J = 8.2 Hz, 1 H, C1-ArH), 8.17 (d, J = 8.6 Hz, 1 H, C4-ArH), 8.66 (s, 1 H, C12-ArH) ppm; minor diastereomer: δ = 0.79 (t, J = 7.6 Hz, 3 H, Me), 1.09 (d, J = 6.3 Hz, 3 H, Me), 1.74 and 2.14 (each: m, 1 H, CH_2), 3.93 (m, 1 H, CH), 5.24 (s, 2 H, CH_2N), 7.44 (s, 1 H, C6-H) ppm; signals from protons of CH_2OH, OH and *A*,*B* rings of molecule overlapped with signals from the protons of major diastereomer. $C_{21}H_{22}N_2O_4{\cdot}H_2O$ (384.42): calcd. C 65.61, H 6.29, N 7.29; found C 65.69, H 6.03, N 7.20.

7-(1-Ethyl-1,2-dihydroxypropyl)-8-hydroxymethyl-2-methoxy-11*H*-indolizino[1,2-*b*]quinolin-9-one (36b): Compound **36b** was obtained from **35b** (0.209 g, 0.43 mmol) by the same procedure as used for synthesis of **36a**. Yield 0.122 g (70.8%), as a mixture of diastereomers (1:1), m.p. 216–218 °C (recrystallized from $CHCl_3$/hexane). ^1H NMR ([D$_6$]DMSO): δ = 0.73 and 0.78 ppm (each: t, J = 7.4 Hz, 3 H, Me), 0.93 and 1.07 (each: d, J = 6.3 Hz, 3 H, Me), 1.72 and 2.13 (each: m, 1 H, CH_2), 2.01 (m, 2 H, CH_2), 3.94 (s, 3 H, MeO), 4.04 (m, 1 H, CH), 4.68–5.1 (m, 4 H, CH_2O and 2×OH, exchangeable), 5.22 and 5.23 (each: s, 2 H, CH_2N), 7.28 and 7.36 (each: brs, 1 H, exchangeable, OH), 7.51 (m, 4 H, C6-ArH and C3-ArH), 8.06 (d, J = 9.4 Hz, 2 H, C4-ArH), 8.53 (s, 2 H, C12-ArH). $C_{22}H_{24}N_2O_5$ (396.43): calcd. C 66.65, H 6.10, N 7.07; found C 66.58, H 6.18, N 7.01.

(7*RS*)-7-Ethyl-7-hydroxy-7*H*,12*H*-5,11a-diazadibenzo[*b*,*h*]fluorene-8,11-dione (12a): Active MnO_2 on carbon, prepared by Caprino's method,[31] was added to a solution of **36a** (0.22 g, 0.6 mmol) and acetic acid (0.5 mL) in CH_2Cl_2 (170 mL). The reaction mixture was heated at reflux under argon for 36 h and filtered while hot through a pad of Celite, and the solid cake was washed with a hot $CH_3OH/CHCl_3$ solution (10 mL). The filtrate and washings were combined and the solvents were evaporated to dryness. The residue was chromatographed on silica gel column (1.5×30 cm) with $CH_3OH/CHCl_3$ (1:25) to afford (**7*RS*)-12a** (0.161, g 85.2%), m.p. 188–190 °C (dec., recrystallized from $CHCl_3$/hexane). ^1H NMR ([D$_6$]DMSO): δ = 0.80 (t, J = 7.4 Hz, 3 H, Me), 2.01 (m, 2 H, CH_2), 4.84 and 4.98 (each: d, J = 14.1 Hz, 1 H, CH=CH), 5.28 (s, 2 H, CH_2N), 6.72 (brs, 1 H, exchangeable, OH), 7.18 (s, 1 H, C6-ArH), 7.71 (ddd, J = 1.2 and 7.4 Hz, 1 H, C2-ArH), 7.86 (ddd, J = 1.6 and 7.0 Hz, 1 H, C3-ArH), 8.11 (d, J = 7.4 Hz, 1 H, C1-ArH), 8.15 (d, J = 8.6 Hz, 1 H, C4-ArH), 8.69 (s, 1 H, C14-ArH) ppm. $C_{21}H_{16}N_2O_3$ (384.42): calcd. C 73.24, H 4.68, N 8.13; found C 73.27, H 4.76, N 7.97.

(7*RS*)-7-Ethyl-7-hydroxy-2-methoxy-7*H*,12*H*-5,11a-diazadibenzo-[*b*,*h*]fluoren-8,11-dione (12b): Compound (**7*RS*)-12b** was obtained from **36b** (0.117 g, 0.29 mmol) by the same procedure as used for the synthesis of **12a**. Yield 0.019 g (17.2%), m.p. 178–180 °C (dec.,

recrystallized from $CHCl_3$/hexane). ^1H NMR ([D_6]DMSO): δ = 0.79 (t, J = 7.4 Hz, 3 H, Me), 2.00 (m, 2 H, CH_2), 3.95 (s, 3 H, MeO), 4.82 and 5.27 (each: d, J = 13.7 Hz, 1 H, CH=CH), 5.27 (s, 2 H, CH_2N), 6.65 (br s, 1 H, exchangeable, OH), 7.11 (s, 1 H, C6-ArH), 7.53 (m, 2 H, C1, C3-ArH), 8.07 (d, J = 8.9 Hz, 1 H, C4-ArH), 8.56 (s, 1 H, C14-ArH) ppm. $C_{22}H_{18}N_2O_4$ (374.38): calcd. C 70.68, H 4.85, N 7.48; found C 70.75, H 4.98, N 7.32.

Supporting Information (see footnote on the first page of this article): ^{13}C NMR spectra of compound **22**, **34a**, **12a**.

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