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Synthesis of indolizinoquinolinones through three- and four-component domino Knoevenagel / hetero-Diels–Alder reactions: novel access to (+)-camptothecin

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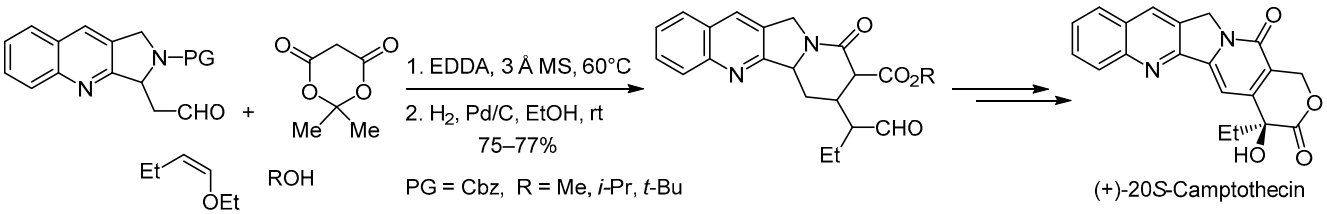


The fused heterocyclic indolizinoquinolinone system is a key structural feature of several highly bioactive alkaloids, including camptothecin. Camptothecin has been efficiently obtained by a three- or four-component domino Knoevenagel / hetero-Diels–Alder reaction of aldehyde, Meldrum's acid, and enol ether in the presence or absence of alcohol, followed by reductive cleavage of the amine protecting group. The obtained products were further transformed along several different routes leading to camptothecin.

Keywords: alkaloids, camptothecin, indolizinoquinolinones, domino reactions, hetero-Diels–Alder reaction, natural product synthesis, oxidation.

Indolizinoquinolinones are tetracyclic quinoline derivatives containing two nitrogen atoms. Their structural motif is well known and is present in several bioactive compounds.[1] The best known compound of this type is the natural alkaloid (+)-camptothecin (**1a**) and its semisynthetic analogs topotecan (**2**) and irinotecan (**3**) (Fig. 1).[2] Several other related compounds are currently under clinical investigation.[3] Irinotecan (**3**) and topotecan (**2**) are important drugs for the treatment of cancer.[4,5] Their mode of action is based on the inhibition of topoisomerase I, which is responsible for unwinding DNA during the cell division.[6]

Here we describe efficient syntheses of indolizinoquinolinones by three- and four-component domino Knoevenagel / hetero-Diels–Alder reactions, which were used in the preparation of (+)-camptothecin (**1a**).

A domino reaction can be defined as a process consisting of two or more bond-forming transformations under identical reaction conditions, in which the latter transformations take place at the functionalities obtained in the former reactions.[7] One, two, three, or more compounds can be involved in such processes. Thus, multicomponent reactions are usually domino reactions. This strategy has numerous advantages over the usual stepwise procedures, since it allows for minimization of the generated waste, conservation of resources, and general reduction of the cost of manufacturing, thus providing environmental and commercial advantages. Moreover, it allows planning synthesis *via* unstable intermediates. In addition to the definition of domino reactions, we have also classified the reactions according to the mechanisms of the single steps

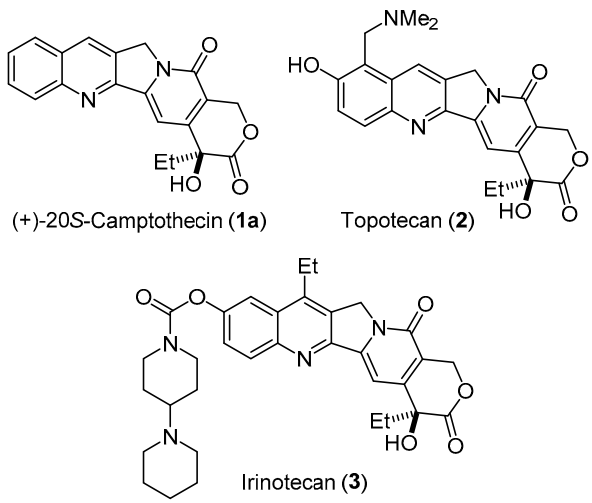


Figure 1. Camptothecin (**1**) and related compounds **2**, **3**.

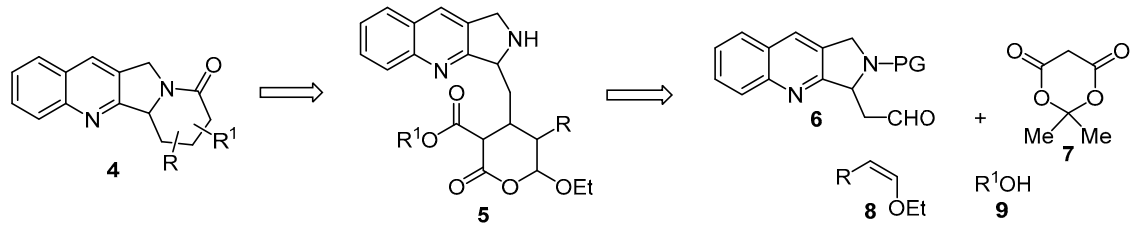


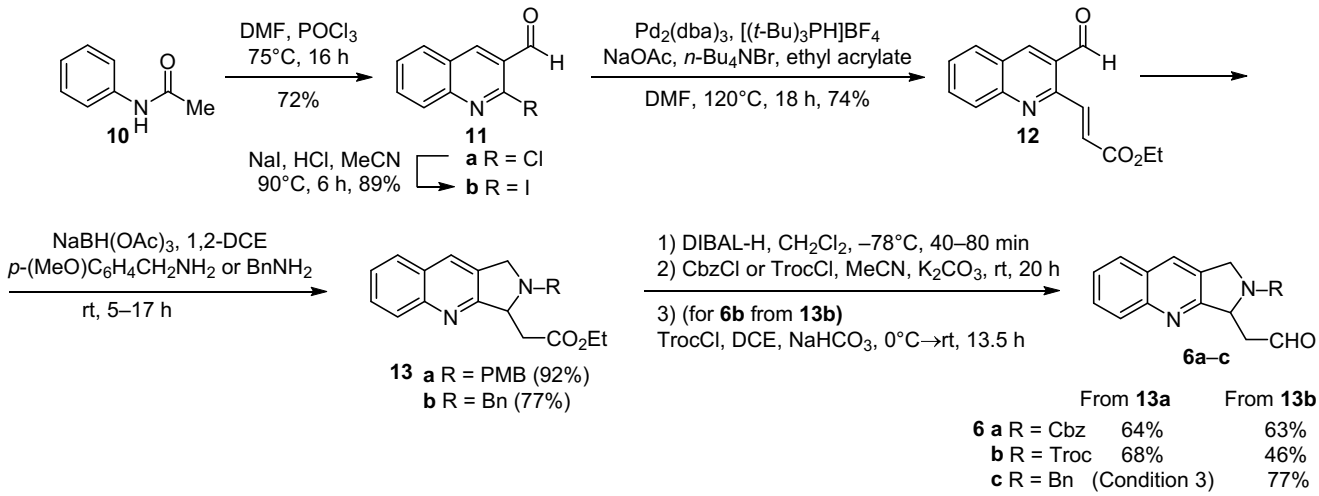
Figure 2. Retrosynthetic analysis of indolizinoquinolinone **4** synthesis.

in the process. Recently we have developed several Pd-catalyzed domino reactions for the synthesis of natural products as well as molecules designed as optical switches.[8] For the synthesis of indolizinoquinolinones **4**, we used a combination of an anionic condensation and a cycloaddition reaction. The retrosynthetic analysis of indolizinoquinolinone **4** led to the substituted pyrroloquinoline **5**, which is easily accessible from aldehyde **6**, Medrum's acid (**7**), enol ether **8**, and alcohol **9** in the case of a four-component reaction or without the alcohol in the case of a three-component reaction (Fig. 2). Pyrroloquinoline **5** can undergo lactam formation as in indolizinoquinolinones **4** by a reaction between the secondary amine and the lactone moiety.

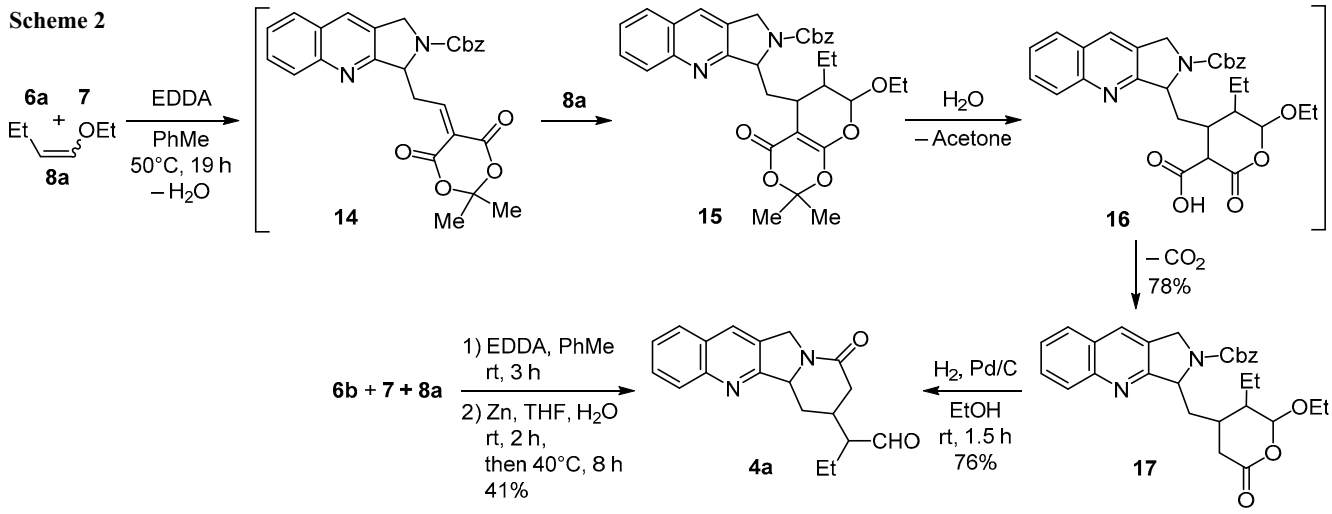
Thus, our selected starting materials for the domino process were the *N*-protected pyrroloquinolinecarbaldehydes **6**, which can be obtained from *N*-acetylaniline (**10**) by a reaction with DMF and $POCl_3$ giving 2-chloro-3-quinoline carbaldehyde (**11a**) according to a procedure described by Meth-Cohn[9] (Scheme 1). Then compound **11a**, using the Heck reaction with ethyl acrylate in the presence of $Pd_2(dba)_3$ and $[(t\text{-}Bu)_3PH]BF_4$ as a bulky ligand and NaOAc or $n\text{-}Bu_4NBr$ as bases, provided product **12** in 74% yield. The reaction did not proceed with $Pd(OAc)_2$ in the presence of $P(o\text{-}Tol)_3$, while other ligands and bases gave lower yields. In order to improve the yield, we transformed the chloride **11a** into iodide **11b** by a reaction with NaI[9,16] and treated it with ethyl acrylate in the presence of $Pd(OAc)_2$ and $P(o\text{-}Tol)_3$ in DMF at 120°C for 6 h. However, the yield of product **12** did not exceed 65% and the product could not be effectively purified. Compound **12** was used in a reductive amination step followed by an intramolecular 1,4-addition with $NaBH(OAc)_3$ and either *p*-methoxybenzylamine or benzylamine to give the desired pyrroloquinolines **13a** and **13b** in 92 and 77% yields, respectively. Reduction of the ester moiety in compounds **13a**,**b** using DIBAL-H in dichloromethane followed by an exchange of the benzyl protecting group by reaction with CbzCl or 2,2,2-trichloroethyl chloroformate (TrocCl) gave product **6a** in 64 or 63% yield and product **6b** in 68 or 46% yield, respectively, depending on the reagent and the starting material.

Pyrroloquinolines **6a**,**b** were then used at first in three-component domino Knoevenagel / hetero-Diels–Alder reactions with Meldrum's acid (**7**) and 1-ethoxy-1-butene (**8a**) (Scheme 2). Since the reactions led to mixtures of diastereomers, the products were not purified and were reduced with either hydrogen on Pd catalyst or Zn to give the desired indolizinoquinolinone **4a** as a mixture of diastereomers. When using pyrroloquinoline **6a**, the reaction was performed in toluene at 50°C for 19 h. First, the 1-oxa-1-butadiene **14** was formed in a Knoevenegel condensation in the presence of a catalytic amount of ethylenediammonium diacetate (EDDA). Compound **14** then underwent the hetero-Diels–Alder reaction with enol ether **8a** present in the reaction mixture, producing cycloadduct **15**. This compound was not stable and reacted with the water formed in the condensation step, producing a malonic acid derivative which lost carbon dioxide to give the desired compound **17**. In this transformation it can not be excluded that the non-isolated intermediate **15** underwent an electrocyclic ring opening with the extrusion of acetone to first give a ketene, which then reacted with water to afford intermediate **16**.

Scheme 1



Scheme 2



Usually oxabutadienes react with enol ethers only at higher temperatures, but intermediate **14** had a rather low-energy LUMO due to the second carbonyl moiety, which allowed a reaction at around 50°C or even at room temperature. The crude product **17** was hydrogenated without isolation using Pd on carbon, producing indolizinoquinolinone **4a** in 76% yield (Scheme 2). The Cbz group was first removed during this process and the formed secondary amine reacted with the lactone moiety to give a lactam.

In a similar way as described for the reaction of compound **6a**, the Troc-protected pyrroloquinoline **6b** led to product **4a** upon treatment of the initially formed cycloadduct with Zn (Scheme 2). The domino reaction in that case took place already at 20°C.

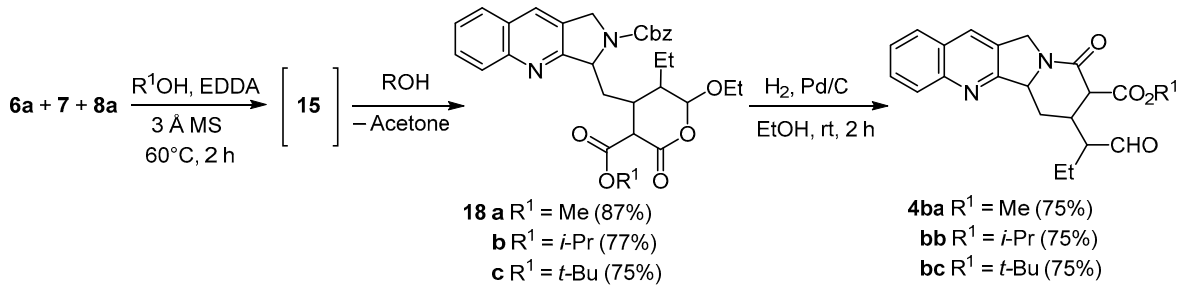
It should be noted that the *N*-benzyl-protected pyrroloquinoline **6c** did not undergo the described domino reactions, probably due to the higher nucleophilicity of the tertiary amino group.

The domino reaction can also be performed as a four-component synthesis, using various alcohols such as methanol, isopropanol, and *t*-butanol. Thus, the reaction of aldehyde **6a**, Meldrum's acid (**7**), and 1-ethoxy-1-butene (**8a**) in methanol as solvent led *via* intermediate **15** to the diastereomeric mixture **18a** in a 87% yield, which was hydrogenated on Pd/C catalyst, giving 75% of product **4ba** as a mixture of diastereomers (Scheme 3). When the reaction was performed in isopropanol, the corresponding compound **4bb** was formed in 75% yield. Compound **4bc** was obtained in 75% yield with *t*-butanol as solvent. The NMR spectra of all three compounds showed a multitude of peaks due to the existence of eight diastereomers.

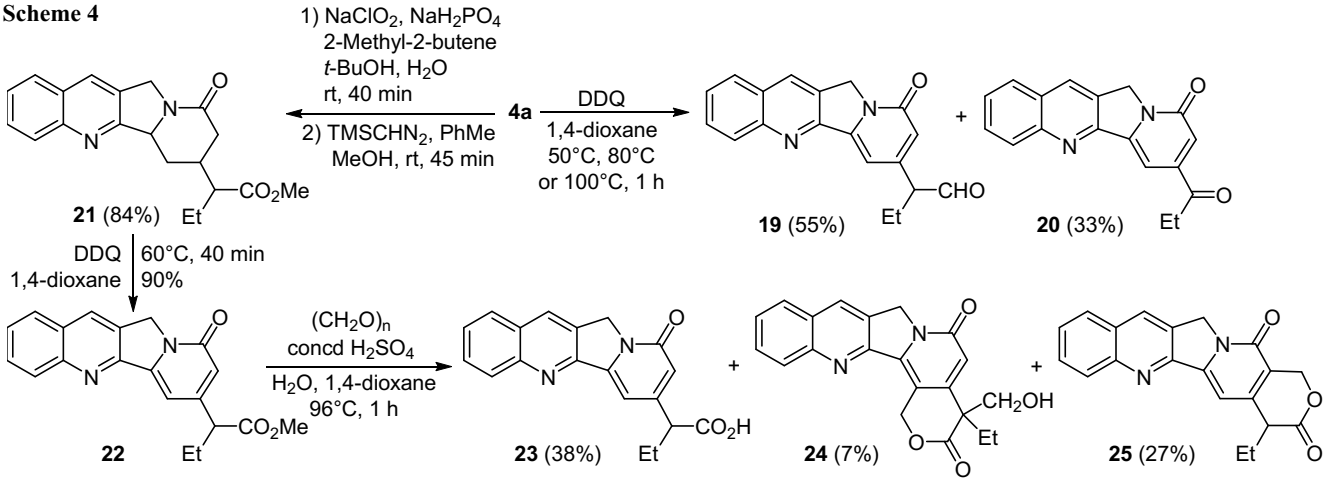
Indolizinoquinolinones **4a** and **4ba** were used for further transformations and also for the synthesis of camptothecin (**1**). The oxidation of lactam **4a** containing an aldehyde side chain with DDQ in 1,4-dioxane at 50, 80, or 100°C led to pyridone **19** bearing intact aldehyde functionality in 55% yield and ketone **20** in 33% yield (Scheme 4). On the other hand, the aldehyde moiety in compound **4a** could be oxidized at first using the Pinnick procedure with $NaClO_2$ to obtain the corresponding acid, which was then transformed into methyl ester **21** using $TMSCHN_2$. Oxidation with DDQ in 1,4-dioxane led to the desired pyridone **22** in 90% yield. The introduction of a hydroxymethyl group in intermediate **22** on the way to camptothecin (**1**) was, however, less successful. Thus, employing the Danishefsky method[10] using paraformaldehyde gave the desired product **25** in merely 27% yield after purification by chromatography. Unfortunately, product **25** still contained a few percent of an impurity that could only be removed by repeated chromatography with a reduction of the yield to 9%. In addition to product **25**, also acid **23** and compound **24** containing a free hydroxymethyl group were isolated. Other approaches for the introduction of CH_2X groups like the Bredereck procedure[11] or a modified Mannich reaction[12] did not work at all. Compound **25** served as a direct precursor of camptothecin (**1**), which was obtained from compound **25** by using well-known oxidative methods.[13]

Aldehyde **4ba**, obtained in a four-component domino reaction from aldehyde **6**, Meldrum's acid (**7**), enol ether **8a**, and methanol could also be oxidized using the Pinnick procedure to give carboxylic acid **26** in a quantitative yield (Scheme 5). It should be noted that the reaction did not always produce quantitative yield. For the formation of the

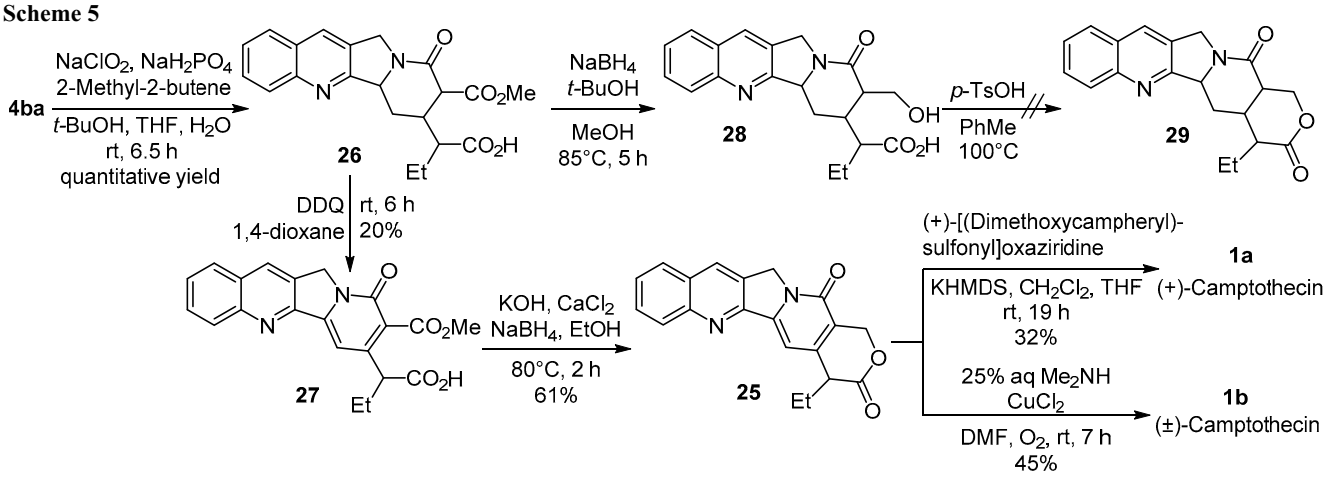
Scheme 3



Scheme 4



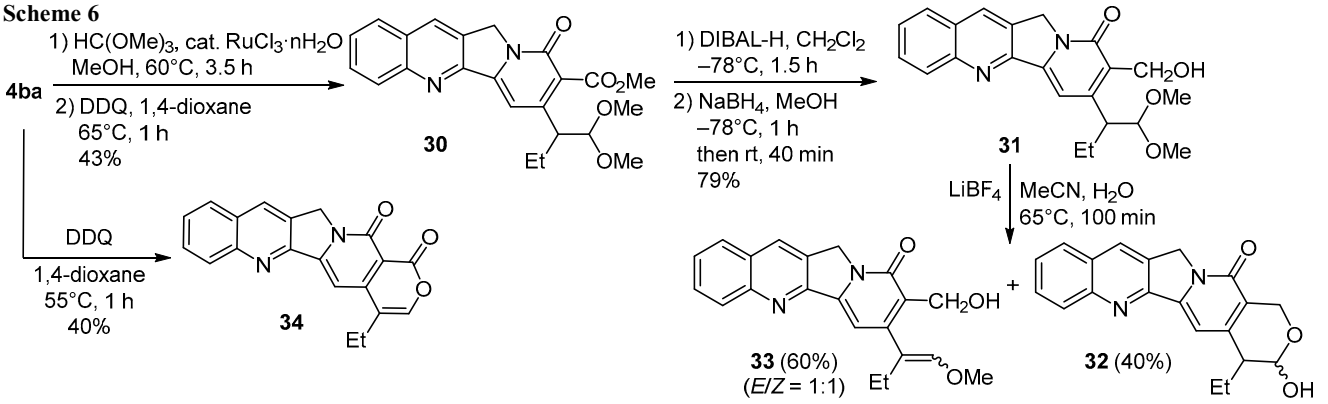
Scheme 5



lactone ring of camptothecin (**1**), we first reduced the ester moiety of compound **26** to create a hydroxymethyl group. The best results were obtained by using an excess of $NaBH_4$ in *t*-BuOH–MeOH at 85°C, leading to compound **28** as a single product. Other reducing agents, such as $LiBH_4$, DIBAL-H, or $NaBH(OMe)_3$, and different reaction conditions were less successful. Unfortunately, all attempts to cyclize compound **28** to lactone **29** were not fruitful. We therefore transformed compound **26** into the corresponding pyridone **27** with 20% yield using DDQ in 1,4-dioxane at room temperature. In order to improve the yield, we investigated the reaction using about 20 different oxidizing and dehydrating reagents, but DDQ proved to be the best choice. Fortunately, the formation of lactone **25** from compound **27** could be easily achieved in 61% yield using *in situ* prepared calcium borohydride. The transformation of lactone **25** into racemic and enantiomerically enriched camptothecin **1a** and **1b** was achieved using previously published procedures[13] with similar results.

The acetalization of compound **4ba** using trimethyl orthoformate in the presence of $RuCl_3$ catalyst followed by dehydration with DDQ led to pyridone **30** in 43% yield over two steps (Scheme 6). Compound **30** was then reduced by a two-step procedure first with DIBAL-H and

Scheme 6



then with $NaBH_4$ in methanol to allow a reduction of the partially formed aldehyde to give alcohol **31**. Moreover, 6% of the starting material could be recovered. The treatment of acetal **31** with $LiBF_4$[14] in a mixture of acetonitrile–water led to enol ether **33** in 60% yield and lactol **32** in 40% yield. Both compounds have been used in enantioselective synthesis of camptothecin (**1a**).[13g,15] Another interesting transformation is the oxidation of compound **4ba** using DDQ in 1,4-dioxane, which led to the pyrone **34** in 40% yield.

In conclusion, we have described an efficient strategy for the construction of indolizinoquinolinone heterocycles using three- and four-component domino reactions, which are based on Knoevenagel condensation and hetero-Diels–Alder reactions. The obtained indolizinoquinolinones could be transformed to 20-deoxycamptothecin by different routes.

Experimental

IR spectra were recorded using a Bruker Vector 22 spectrometer. Liquid substances were measured as a thin film between NaCl plates and solids in KBr pellets. UV spectra were recorded using a Perkin Elmer Lambda 2 spectrometer in the wavelength range of 180–450 nm. ^1H and ^{13}C NMR spectra were acquired on Varian spectrometers Mercury 300 (300 and 75 MHz, respectively), Unity 300 (300 and 75 MHz, respectively), Inova 500 (500 and 125 MHz, respectively), and Inova 600 (600 and 150 MHz, respectively), using TMS or the respective solvent signals as internal standard. Regular and high-resolution mass spectra (EI ionization) were recorded on a Finnigan MAT 95 instrument. ESI mass spectra were recorded on Finnigan TSQ 7000 or LCQ instruments. ESI-HRMS analyses were performed also on a Bruker APEX IV FT-ICR mass spectrometer. Optical rotation values were measured with a PerkinElmer 241 polarimeter. Column chromatography was performed with Merck silica gel 60 with a particle size of 0.040−0.063 mm and alumina (activated, neutral, 50–200 μm) from Acros. Thin-layer chromatography was performed on precoated Merck F-254 silica gel plates. In addition to the UV detection, vanillin–sulfuric acid or $KMnO_4$ stains were used. Commercially available substances were used directly without purification, unless otherwise stated.

Ethyl (*E*)-3-(3-formylquinolin-2-yl)acrylate (12). $Pd_2(dba)_3$ (7.20 mg, 7.83 μmol, 1.5 mol %) and $[(t\text{-}Bu)_3PH]BF_4$ (9.10 mg, 31.3 μmol, 6.0 mol %) were added to a degassed suspension of chloroquinoline **11a** (100 mg, 522 μmol, 1.0 equiv), NaOAc (47.0 mg, 574 μmol, 1.1 equiv), $n\text{-}Bu_4NBr$ (168 mg, 522 μmol, 1.0 equiv), and ethyl acrylate (78.5 mg, 85.0 μl, 783 μmol, 1.5 equiv) in DMF (1 ml), and the mixture was stirred at 120°C (preheated oil bath) for 18 h. After cooling to room temperature, Et_2O (15 ml) and H_2O (15 ml) were added and the organic phase was separated. The aqueous phase was extracted with Et_2O (2×15 ml), the combined organic layers were washed with saturated aqueous NaCl solution (15 ml), dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. Silica gel column chromatography (pentane–EtOAc, 4:1) afforded compound **12**. Yield 99.0 mg (74%), yellow solid. R_f 0.29 (petroleum ether – EtOAc, 4:1). UV spectrum (MeCN), λ_{max}, nm (log ε): 207.5 (4.33), 271.0 (4.71). IR spectrum (KBr), ν, cm^{-1}: 2727, 1714, 1370, 1294, 1193, 1166, 988, 794. ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.38 (3H, t, J = 7.2, CH_3); 4.33 (2H, q, J = 7.2, CH_2); 7.29 (1H, d, J = 15.6, CH=C<u>H</u>CO_2Et); 7.65 (1H, ddd, J = 8.1, J = 6.9, J = 1.2, H-6); 7.89 (1H, ddd, J = 8.1, J = 6.9, J = 1.2, H-7); 7.97 (1H, dd, J = 8.1, J = 1.2, H-5); 8.14 (1H, dd, J = 8.1, J = 1.2, H-8); 8.64 (1H, s, H-4); 8.66 (1H, d, J = 15.6, C<u>H</u>=CHCO_2Et); 10.42 (1H, s, CHO). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: 14.2; 60.8; 126.9; 127.1; 127.5; 128.2; 128.9; 129.9; 133.1; 138.9; 142.7; 149.3; 151.6; 166.4; 190.6. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 182 $[M–CO_2Et]^+$ (100), 255 $[M]^+$ (10). Found, *m*/*z*: 256.09687 $[M+H]^+$. $C_{15}H_{13}NO_3$. Calculated, *m*/*z*: 256.09682.

Ethyl 2-[2-(4-methoxybenzyl)-2,3-dihydro-1*H*-pyrrolo-[3,4-*b*]quinolin-3-yl]acetate (13a). A solution of compound **12** (2.11 g, 8.26 mmol, 1.0 equiv) in 1,2-DCE (45 ml) was added dropwise over 30 min at room temperature to a mixture of 4-methoxybenzylamine (1.80 g, 12.40 mmol, 1.5 equiv) and $NaBH(OAc)_3$ (2.80 g, 13.20 mmol, 1.6 equiv) in 1,2-DCE (30 ml). After 5 h, saturated aqueous Na_2CO_3 solution (30 ml) and water (30 ml) were added, the aqueous phase was extracted with CH_2Cl_2 (2×50 ml), and the combined organic layers were dried over Na_2SO_4. After the removal of solvent, the residue was purified by column chromatography on neutral alumina (pentane–EtOAc, 6:1), providing product **13a**. Yield 2.86 g (92%), yellow solid. R_f 0.20 (pentane–EtOAc, 8:1, neutral alumina) or 0.45 (pentane–EtOAc, 4:1, silica gel). IR spectrum (KBr), ν, cm^{-1}: 1730 (C=O), 1514 (CH_3), 1248 (CH_2), 1161, 1034 (C–O), 749 (CH_2). UV spectrum (MeCN), λ_{max}, nm (log ε): 195.5 (4.75), 209.5 (4.75), 230.5 (4.69), 274.5 (3.75), 306.5 (3.63), 319.5 (3.71). ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.20 (3H, t, J = 7.2, $CH_2C\underline{H}_3$); 2.97 (1H, dd, J = 15.7, J = 5.9) and 3.25 (1H, dd, J = 15.7, J = 4.8, 2-CH_2); 3.61–3.75 (2H, m, 1'-CH_A, $C\underline{H}_AC_6H_4(p\text{-}OCH_3)$); 3.80 (3H, s, OCH_3); 4.11–4.27 (4H, m, $CO_2C\underline{H}_2CH_3$, 1'-CH_B, $C\underline{H}_BC_6H_4(p\text{-}OCH_3)$); 4.52 (1H, m_c, 3'-CH); 6.84–6.92 (2H, m, *m*-H $C_6H_4(p\text{-}OCH_3)$); 7.28–7.36 (2H, m, *o*-H $C_6H_4(p\text{-}OCH_3)$); 7.46 (1H, m_c, H-7'); 7.63 (1H, m_c, H-6'); 7.73 (1H, d, J = 8.0, H-8'); 7.79 (1H, s, H-9'); 8.04 (1H, d, J = 8.5, H-5'). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: 14.1; 38.8; 55.1; 55.3; 57.9; 60.3; 65.0; 113.7; 125.9; 127.6; 128.6; 129.0; 129.9; 130.6; 131.1; 147.8; 158.8; 164.3; 172.0. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 121 $[CH_2C_6H_4(p\text{-}OCH_3)]^+$ (100), 255 $[M–CH_2C_6H_4(p\text{-}OCH_3)]^+$ (34), 376 $[M]^+$ (6).

Ethyl 2-(2-benzyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-3-yl)acetate (13b). Benzylamine (5.56 ml, 5.46 g, 50.9 mmol, 1.1 equiv) was added to a solution of acrylic acid ester **12** (11.80 g, 46.3 mmol, 1.0 equiv) in 1,2-DCE (116 ml) and stirred at room temperature for 30 min. Then $NaBH(OAc)_3$ (10.80 g, 50.9 mmol, 1.1 equiv) was added and the mixture was stirred at room temperature for 17 h. Saturated aqueous $NaHCO_3$ solution (100 ml) was added, the organic phases were separated, the aqueous phase was extracted with CH_2Cl_2 (2×100 ml). The combined organic

phases were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. Silica gel column chromatography (pentane–EtOAc, 6:1 → 4:1) afforded the desired product **13b**. Yield 12.1 g (77%), orange oil. R_f 0.45 (petroleum ether – EtOAc, 4:1). IR spectrum (NaCl), ν, cm^{-1}: 3061, 2980, 2801, 1732, 1504, 1161, 750. UV spectrum (MeCN), λ_{max}, nm (log ε): 209.0 (4.74), 230.5 (4.57), 234.0 (4.54). ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.21 (3H, t, *J* = 7.2, CH_3); 2.98 (1H, dd, *J* = 15.6, *J* = 6.0) and 3.27 (1H, dd, *J* = 15.6, *J* = 4.8, 2-CH_2); 3.69–3.76 (2H, m, CH_2Ph); 4.16 (2H, q, *J* = 7.2, CH_2); 4.20 (1H, d, *J* = 13.2) and 4.32 (1H, d, *J* = 13.2, 3'-CH_2); 4.56 (1H, t, *J* = 5.4, 1'-CH); 7.25–7.44 (5H, m, H Ph); 7.48 (1H, ddd, *J* = 8.1, *J* = 7.2, *J* = 1.2, H-6'); 7.64 (1H, ddd, *J* = 8.1, *J* = 7.2, *J* = 1.2, H-7'); 7.74 (1H, dd, *J* = 8.1, *J* = 1.2, H-5'); 7.81 (1H, s, H-4'); 8.05 (1H, d, *J* = 8.1, H-8'). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: 14.1; 38.9; 55.5; 58.7; 60.3; 65.2; 126.0; 127.2; 127.7 (2C); 128.4; 128.7 (2C); 128.8; 129.1; 131.1; 138.7; 147.9; 164.3; 172.1. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 255 $[M–CH_2C_6H_4]^+$ (82), 259 $[M–CH_2CO_2C_2H_5]^+$ (100), 346 $[M]^+$ (21). Found, *m*/*z*: 347.17523 $[M+H]^+$. $C_{22}H_{22}N_2O_2$. Calculated, *m*/*z*: 347.17540.

Benzyl 3-(2-oxoethyl)-1,3-dihydro-2*H*-pyrrolo[3,4-*b*]-quinoline-2-carboxylate (6a). From compound **13a**: DIBAL-H (1.0 M in CH_2Cl_2, 6.0 ml, 1.1 equiv) was added dropwise to a solution of compound **13a** (2.15 g, 5.71 mmol, 1.0 equiv) in CH_2Cl_2 (60 ml) at –78°C. After 40 min, further DIBAL-H (1.0 M in CH_2Cl_2, 0.80 ml, 0.1 equiv) was added and stirred for another 40 min. Methanol (2 ml) and water (10 ml) were added, the mixture was brought to 0°C and Et_2O (200 ml) was added. The organic phase was subsequently washed with aqueous NaOH solution (1 M, 2×60 ml), water (60 ml), and saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The resulting dark oil (1.90 g) was dissolved in MeCN (40 ml), cooled to 0°C, then K_2CO_3 (0.16 g, 1.16 mmol, 0.2 equiv) and CbzCl (1.44 g, 1.20 ml, 8.44 mmol, 1.5 equiv) were added. The mixture was stirred for 30 min at 0°C and then at room temperature for 13 h. Thereafter, CbzCl (1.44 g, 1.20 ml, 8.44 mmol, 1.5 equiv) was added and the reaction mixture was stirred for 3 h. The solid K_2CO_3 was removed by filtration, washed with EtOAc, and the filtrate was concentrated. The residue was purified twice by column chromatography on silica gel (CH_2Cl_2–Et_2O, 6:1, then, pentane–EtOAc, 6:1) to obtain aldehyde **6a**. Yield 1.27 g (64% over two steps), white solid.

From compound **13b**: DIBAL-H (1.0 M in CH_2Cl_2, 0.6 ml, 1.2 equiv) was added dropwise to a solution of compound **13a** (200 mg, 0.57 mmol, 1.0 equiv) in CH_2Cl_2 (6 ml) at –78°C. Reaction mixture was stirred at same temperature for 80 min. Methanol (0.3 ml) and water (1 ml) were added, the mixture was brought to 0°C and Et_2O (50 ml) was added. The organic phase was subsequently washed with aqueous 1 M NaOH solution (2 × 10 ml), water (20 ml), and saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The resulting dark oil (180 mg) was dissolved in MeCN (5 ml), cooled to 0°C, then K_2CO_3 (15 mg, 0.107 mmol, 0.2 equiv) and CbzCl (134 mg, 0.11 ml, 0.78 mmol, 1.5 equiv) were added. The mixture was stirred for 30 min at 0°C and then at room temperature for 13 h. Thereafter, CbzCl (134 mg, 0.11 ml, 0.78 mmol, 1.5 equiv) was added and the reaction mixture was stirred for 3 h. The solid K_2CO_3 was removed by filtration, washed with EtOAc, and the filtrate was concentrated. The residue was purified by twofold column chromatography on silica gel (CH_2Cl_2–Et_2O, 6:1, then, pentane–EtOAc, 6:1) to obtain aldehyde **6a**. Yield 123 mg (63% over two steps), white solid. R_f 0.30 (CH_2Cl_2–Et_2O, 6:1) or 0.58 (pentane–EtOAc, 1:1). IR spectrum (NaCl), ν, cm^{-1}: 2955 (CH), 2879, 2841 (CHO), 1713 (C=O), 1405 (CH_2), 1099, 1025 (C–O), 758, 695 (CH_2). UV spectrum (MeCN), λ_{max}, nm (log ε): 209.0 (4.77), 226.0 (4.55), 229.0 (4.55), 281.5 (3.54), 287.0 (3.53), 293.5 (3.56), 299.5 (3.57), 306.0 (3.71), 312.5 (3.65), 320.0 (3.86). ^1H NMR spectrum (600 MHz, $CDCl_3$, rotamer A/B = 0.38:0.62), δ, ppm (*J*, Hz): 3.14 (0.38H, dd, *J* = 17.5, *J* = 4.2) and 3.30 (0.38H, dd, *J* = 17.5, *J* = 4.2, 2-CH_2, rotamer A); 3.21 (0.62H, dd, *J* = 17.5, *J* = 4.2) and 3.54 (0.62H, dd, *J* = 17.5, *J* = 4.2, 2-CH_2, rotamer B); 4.82–5.04 (2H, m, 1'-CH_2); 5.11–5.21 (1H, m) and 5.21–5.31 (1H, m, CH_2Ph); 5.41–5.50 (1H, m, 3'-CH); 7.30–7.44 (5H, m, H Ph); 7.48–7.57 (1H, m, H-7'); 7.63–7.72 (1H, m, H-6'); 7.75–7.84 (1H, m, H-8'); 7.96 (1H, s, H-9'); 7.97–8.06 (1H, m, H-5'); 9.65 (0.38H, s, CHO, rotamer A); 9.80 (0.62H, s, CHO, rotamer B). ^{13}C NMR spectrum (150 MHz, $CDCl_3$, rotamer A/B), δ, ppm: 47.3; 48.3; 49.9; 50.3; 58.4; 58.9; 67.2; 67.4; 126.5 (2C); 127.4; 127.7 (2C); 127.9; 128.0; 128.1; 128.2 (2C); 128.4 (2C); 128.5; 128.8; 129.7; 129.3; 129.5; 135.9; 136.2; 148.0; 154.5; 154.7; 160.7; 161.0; 199.2; 199.5. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 303 $[M–CH_2CHO]^+$ (49), 347 $[M+H]^+$ (100). Found, *m*/*z*: 347.1390 $[M+H]^+$. $C_{21}H_{18}N_2O_3$. Calculated, *m*/*z*: 347.1390.

2,2,2-Trichloroethyl 3-(2-oxoethyl)-1,3-dihydro-2*H*-pyrrolo[3,4-*b*]quinoline-2-carboxylate (6b). From compound **13a**: DIBAL-H (1.0 M in CH_2Cl_2, 0.600 ml, 1.12 equiv) was added dropwise to a solution of compound **13a** (202 mg, 0.537 mmol, 1.00 equiv) in CH_2Cl_2 (5.5 ml) at –78°C. The mixture was stirred at this temperature for 40 min. The reaction was terminated by adding saturated aqueous sodium potassium tartrate solution (4.5 ml). The mixture was warmed to 0°C, then Et_2O (40 ml) and water (10 ml) were added. The organic phase was subsequently washed with aqueous 1 N NaOH solution (2×20 ml), water (20 ml), and saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The light-brown oil obtained was mixed with MeCN (10 ml) and K_2CO_3 (15.0 mg, 0.109 mmol, 0.202 equiv). TrocCl (0.116 g, 74.0 ml, 0.550 mmol, 1.02 equiv) was added to this mixture at –47°C. After 1 h, the mixture was warmed to 0°C and stirred for 2 h. K_2CO_3 was removed by filtration. After the mother liquor was concentrated, the residue was purified by silica gel column chromatography (pentane–EtOAc, 3:1) to afford aldehyde **6b**. Yield 142 mg (68% over two steps), white solid. R_f 0.31 (pentane–EtOAc, 3:1).

From compound **13b**: DIBAL-H (1.0 M in CH_2Cl_2, 0.61 ml, 1.4 equiv) was added dropwise to a solution of compound

13b (200 mg, 0.577 mmol, 1.00 equiv) in CH_2Cl_2 (5.5 ml) at –78°C. The mixture was stirred at this temperature for 40 min. The reaction was terminated by adding saturated aqueous sodium potassium tartrate solution (4.5 ml). The mixture was warmed to 0°C, then Et_2O (40 ml) and water (10 ml) were added. The organic phase was subsequently washed with 1 N aqueous NaOH solution (2×20 ml), water (20 ml), and saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The light-brown oil obtained was mixed with DCE (10 ml) and cooled to 0°C; $NaHCO_3$ (111 mg, 1.32 mmol, 2.32 equiv) and TrocCl (134 mg, 87.0 ml, 0.63 mmol, 1.1 equiv) were added to this mixture and stirred at 0°C for 2.5 h. Thereafter, TrocCl (342 mg, 0.22 ml, 1.61 mmol, 2.8 equiv) was added and the reaction mixture was stirred at room temperature for 11 h. $NaHCO_3$ was removed by filtration. After the mother liquor was concentrated, the residue was purified by silica gel column chromatography (pentane–EtOAc, 3:1) to afford aldehyde **6b**. Yield 102 mg (46% over two steps), white solid. IR spectrum (NaCl), ν, cm^{-1}: 2951 (C–H), 1720 (C=O), 1405 (CH_2), 1124, 1059 (C–O), 858, 817 (C–Cl), 755, 709 (CH_2). UV spectrum (MeCN), λ_{max}, nm (log ε): 208.0 (4.71), 225.0 (4.51), 281.5 (3.56), 287.0 (3.56), 293.0 (3.59), 299.5 (3.59), 306.0 (3.71), 312.5 (3.65), 319.5 (3.85). ^{1}H NMR spectrum (600 MHz, $CDCl_3$, rotamer A/B = 0.56:0.44), δ, ppm (*J*, Hz): 3.26 (0.56H, dd, *J* = 17.9, *J* = 4.7, 2-CH_A, rotamer A); 3.39 (0.44H, dd, *J* = 17.9, *J* = 3.5, 2-CH_A, rotamer B); 3.58 (1H, dd, *J* = 17.9, *J* = 4.7, 2-CH_B); 4.75 (0.56H, d, *J* = 12.0, O$C\underline{H}_AH_B$, rotamer A); 4.81 (0.44H, d, *J* = 12.0, O$C\underline{H}_AH_B$, rotamer B); 4.86–4.97 (1.44H, m, O$CH_A\underline{H}_B$, 1'-CH_A); 4.98–5.08 (1.56H, m, 1'-CH_A, 1'-CH_B); 5.45 (0.56H, m_c, 3'-CH, rotamer A); 5.49 (0.44H, m_c, 3'-CH, rotamer B); 7.49–7.57 (1H, m, H-7'); 7.65–7.72 (1H, m, H-6'); 7.81 (1H, d, *J* = 8.2, H-8'); 7.98–8.06 (2H, m, H-5',9'); 9.74 (0.44H, s, CHO, rotamer B); 9.77 (0.56H, s, CHO, rotamer A). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: 46.9; 47.7; 50.2; 50.8; 58.6; 59.1; 74.9; 75.0; 95.3; 95.4; 126.7; 127.5; 127.8 (2C); 127.9; 128.1; 128.9 (2C); 129.5; 129.6; 129.7 (2C); 148.1 (2C); 152.7; 152.9; 160.3; 160.8; 198.8; 199.0. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 342.9 $[M–CH_2CHO]^+$ (100), 344.9 (96), 387.0 $[M+H]^+$ (42), 389.0 (40). Found, *m*/*z*: 342.9803, 344.9773 $[M–CH_2CHO]^+$, 387.0065, 389.0035 $[M+H]^+$. $C_{16}H_{13}Cl_3N_2O_3$. Calculated, *m*/*z*: 342.9802, 344.9772, 387.0064, 389.0035.

2-(2-Benzyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-3-yl)-acetaldehyde (6c). DIBAL-H (1.0 M in CH_2Cl_2, 38.4 ml, 1.1 equiv) was added dropwise over 30 min to a solution of ethyl ester **13b** (12.1 g, 34.9 mmol) in CH_2Cl_2 (58 ml) at –78°C, while cooling with dry ice. $Na_2SO_4·10H_2O$ (12 g) was added, the cooling bath was removed, and the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered through Celite, washed with CH_2Cl_2 (300 ml), and the filtrate was concentrated under reduced pressure. Column chromatography on deactivated silica gel (pentane–EtOAc, 3:1) afforded the title compound **6c**. Yield 8.11 g (77%), brown solid. R_f 0.39 (pentane–EtOAc, 2:1). IR spectrum (KBr), ν, cm^{-1}: 3061, 2801, 1722, 1504, 1415, 1315, 1146, 750. UV spectrum (MeCN), λ_{max}, nm (log ε): 209.5 (4.70), 230.5 (4.56), 234.0 (4.52). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.15 (1H, ddd, *J* = 16.8, *J* = 5.4, *J* = 3.9) and 3.31 (1H, ddd, *J* = 16.8, *J* = 3.9, *J* = 1.2, 2-CH_2); 3.67 (1H, d, *J* = 12.9) and 4.30 (1H, d, *J* = 12.9, C$\underline{H}_2$Ph); 3.74 (1H, d, *J* = 13.8) and 4.21 (1H, d, *J* = 13.8, 3'-CH_2); 4.48 (1H, t, *J* = 3.9, 1'-CH); 7.26–7.39 (5H, m, H Ph); 7.51 (1H, ddd, *J* = 8.1, *J* = 6.9, *J* = 1.2, H-6'); 7.68 (1H, ddd, *J* = 8.1, *J* = 6.9, *J* = 1.2, H-7'); 7.77 (1H, dd, *J* = 8.1, *J* = 1.2, H-5'); 7.86 (1H, s, H-4'); 8.07 (1H, d, *J* = 8.1, H-8'); 9.73 (1H, dd, *J* = 3.9, *J* = 1.2, CHO). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: 45.4; 55.5; 58.0; 63.8; 126.3; 127.4; 127.7; 127.8; 128.5; 128.8; 129.0 (2C); 129.1; 131.1; 138.1; 147.9; 163.8; 201.7. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 325 $[M+Na]^+$ (16), 335 $[M+CH_3OH+H]^+$ (100), 691 $[2M+2CH_3OH+Na]^+$ (20). Found, *m*/*z*: 325.13119 $[M+Na]^+$. $C_{20}H_{18}N_2O$. Calculated, *m*/*z*: 325.13113.

Benzyl 3-[(2-ethoxy-3-ethyl-6-oxotetrahydro-2*H*-pyran-4-yl)methyl]-1,3-dihydro-2*H*-pyrrolo[3,4-*b*]quinoline-2-carboxylate (17). A mixture of compound **6a** (769 mg, 2.22 mmol, 1.0 equiv), Meldrum's acid (**7**) (320 mg, 2.22 mmol, 1.0 equiv), EDDA (16.0 mg, 89.0 μmol, 4 mol %), and enol ether **8a** (889 mg, 8.88 mmol, 4.0 equiv) in toluene (22 ml) was heated at 50°C for 19 h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (pentane–EtOAc, 2:1) to obtain the domino reaction product **17**. Yield 846 mg (78%), light-yellow solid. R_f 0.27 (pentane–EtOAc, 2:1). ^{1}H NMR spectrum (300 MHz, $CDCl_3$, selected signals), δ, ppm (*J*, Hz): 3.41–3.62 (1H, m) and 3.79–4.02 (1H, m, O$C\underline{H}_2CH_3$); 4.68–4.88 (1H, m, N$C\underline{H}_AH_B$); 4.92–5.41 (5H, m, N$CH_A\underline{H}_B$, CH_2Ph, H-6,3''); 7.29–7.50 (5H, m, H Ph); 7.55 (1H, m_c, H-7''); 7.71 (1H, m_c, H-6''); 7.81 (1H, d, *J* = 7.9, H-8''); 7.94–8.13 (2H, m, H-5'',9''). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 489 $[M+H]^+$ (100). Found, *m*/*z*: 489.2383 $[M+H]^+$. $C_{29}H_{32}N_2O_5$. Calculated, *m*/*z*: 489.2384.

2-(9-Oxo-5b,6,7,8,9,11-hexahydroindolizino[1,2-*b*]-quinolin-7-yl)butanal (4a). Single-step synthesis from the domino product **17**. A suspension of compound **17** (330 mg, 0.675 mmol, 1.0 equiv) and 10% palladium on carbon (72 mg) in ethanol (30 ml) was stirred at room temperature under an H_2 atmosphere for 1.5 h. The reaction mixture was then filtered on a Celite pad, concentrated, and the residue was purified by silica gel column chromatography (EtOAc–NEt_3, 20:1) to afford the desired aldehyde **4a**. Yield 158 mg (76%), light-brown solid.

Two-step synthesis from aldehyde **6b**. A mixture of vinyl ether **8a** (84 mg, 0.84 mmol, 2.0 equiv), EDDA (5 mg, 0.03 mmol, 0.07 equiv), compound **6b** (160 mg, 0.42 mmol, 1.0 equiv), and Meldrum's acid (**7**) (61 mg, 0.42 mmol, 1.0 equiv) in toluene (5 ml) was stirred at room temperature for 3 h. Concentration of the reaction mixture under reduced pressure afforded the crude domino product (243 mg) as a yellow solid. A portion of the crude product (36 mg) was added to a suspension of Zn powder (186 mg, 2.84 mmol, 6.7 equiv) in THF (3 ml) and water (0.5 ml). After stirring at room temperature for 2 h, the reaction mixture was heated at 40°C for 8 h. After cooling to room

temperature, the reaction mixture was filtered on a Celite pad and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (pentane–EtOAc, 2:1), giving aldehyde **4a**. Yield 7.8 mg (41% over two steps), light-brown solid. R_f 0.35 (EtOAc–NEt_3, 20:1). ^{1}H NMR spectrum (300 MHz, $CDCl_3$, selected signals, 4 diastereomers A:B:C:D = 1:1:1:1), δ, ppm (*J*, Hz): 0.86–1.07 (3H, m, CH_3); 1.63–1.92 (2H, m, $C\underline{H}_2CH_3$); 4.58–4.76 (1H, m, 11'-CH); 4.85–5.04 (1H, m, 5'b-CH); 5.15 (0.25H, d, ^2J = 7.8, 11'-CH, diastereomer A); 5.21 (0.25H, d, ^2J = 7.7, 11'-CH, diastereomer B); 5.31 (0.50H, d, ^2J = 16.3, 11'-CH, diastereomers C and D); 7.56 (1H, m_c, H-2'); 7.72 (1H, m_c, H-3'); 7.83 (1H, d, ^3J = 8.1, H-1'); 8.00–8.15 (2H, m, H-4',12'); 9.67–9.76 (1H, m, CHO). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: 11.3 (2C); 11.4; 11.6; 19.0; 19.2; 19.7; 19.8; 161.4; 161.5; 162.0; 162.1; 168.1 (2C); 169.6; 169.8; 203.4; 203.6; 203.7. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 309 $[M+H]^+$ (100), 331 $[M+Na]^+$ (98). Found, *m*/*z*: 309.1597 $[M+H]^+$, 331.1417 $[M+Na]^+$. $C_{19}H_{20}N_2O_2$. Calculated, *m*/*z*: 309.1597, 331.1417.

Synthesis of compounds 18a–c (General method). A mixture of aldehyde **6a** (5.66 g, 16.3 mmol, 1.0 equiv), Meldrum's acid (**7**) (2.58 g, 17.9 mmol, 1.1 equiv), enol ether **8a** (6.31 ml, 4.90 g, 48.9 mmol, 3.0 equiv), 3 Å molecular sieves (1.5–3.0 g), and EDDA (150 mg) in the appropriate alcohol, MeOH, 2-PrOH, or *t*-BuOH (2 ml/mmol), was stirred for 2 h in a pressure flask at 60°C, using a pre-heated oil bath. After cooling to room temperature, the molecular sieves were removed by filtration, washed with CH_2Cl_2 (75 ml), and the filtrate was concentrated under reduced pressure. Silica gel column chromatography (pentane–EtOAc, 2:1) afforded the target compounds **18a–c**.

Benzyl 3-{[2-ethoxy-3-ethyl-5-(methoxycarbonyl)-6-oxotetrahydro-2*H*-pyran-4-yl]methyl}-1,3-dihydro-2*H*-pyrrolo[3,4-*b*]quinoline-2-carboxylate (18a). Yield 7.74 g (87%), pale-yellow, crystalline solid. R_f 0.41, 0.44 (petroleum ether–EtOAc, 2:1). IR spectrum (KBr), ν, cm^{-1}: 3433, 2961, 1707, 1403, 1106, 756. UV spectrum (MeCN), λ_{max}, nm (log ε): 208.5 (4.76), 229.5 (4.57). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 569 $[M+Na]^+$ (34), 1115 $[2M+Na]^+$ (100). Found, *m*/*z*: 547.24390 $[M+H]^+$. $C_{31}H_{34}N_2O_7$. Calculated, *m*/*z*: 547.24388.

Benzyl 3-{[2-ethoxy-3-ethyl-5-(isopropoxycarbonyl)-6-oxotetrahydro-2*H*-pyran-4-yl]methyl}-1,3-dihydro-2*H*-pyrrolo[3,4-*b*]quinoline-2-carboxylate (18b). Yield 382 mg (77%), orange crystalline solid. R_f 0.28, 0.35 (pentane–EtOAc, 2:1). IR spectrum (KBr), ν, cm^{-1}: 2977, 1707, 1403, 1354, 1106, 980, 756, 699. UV spectrum (MeCN), λ_{max}, nm (log ε): 208.5 (4.80), 229.5 (4.59), 319.5 (3.84). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 597 $[M+Na]^+$ (80), 1172 $[2M+Na]^+$ (100). Found, *m*/*z*: 597.2579 $[M+Na]^+$. $C_{33}H_{38}N_2O_7$. Calculated, *m*/*z*: 597.2571.

Benzyl 3-{[3-(*tert*-butoxycarbonyl)-6-ethoxy-5-ethyl-2-oxotetrahydro-2*H*-pyran-4-yl]methyl}-1,3-dihydro-2*H*-pyrrolo[3,4-*b*]quinoline-2-carboxylate (18c). Yield 3.80 g (75%), pink crystalline solid. R_f 0.23, 0.31 (pentane–EtOAc, 2:1). IR spectrum (KBr), ν, cm^{-1}: 2975, 1707, 1403, 1106, 978, 755. UV spectrum (MeCN), λ_{max}, nm (log ε): 208.5 (4.80), 226.5 (4.58), 229.0 (4.58), 319.5 (3.84). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 611 $[M+Na]^+$ (100), 1200 $[2M+Na]^+$ (97), 1789 $[3M+Na]^+$ (40). Found, *m*/*z*: 611.2725 $[M+Na]^+$. $C_{34}H_{40}N_2O_7$. Calculated, *m*/*z*: 611.2728.

Synthesis of compounds 4ba, 4bb, and 4bc (General method). A suspension of the appropriate lactone **18a–c** (150 mg, 364 mg, 650 mg) and 10% palladium on carbon (38 mg, 91 mg, 163 mg) in EtOH (1 ml per 0.1 mmol of lactone) was stirred at room temperature under an H_2 atmosphere for 2 h. The reaction mixture was filtered through Celite, washed with CH_2Cl_2, and the filtrate was concentrated under reduced pressure. Silica gel column chromatography (pentane–EtOAc, 1:1 + 1% NEt_3) afforded the target compounds.

Methyl 9-oxo-7-(1-oxobutan-2-yl)-5b,6,7,8,9,11-hexahydroindolizino[1,2-*b*]quinoline-8-carboxylate (4ba). Yield 75.0 mg (75%), brown solid. R_f 0.31–0.51 (EtOAc). IR spectrum (KBr), ν, cm^{-1}: 3424, 2959, 1737, 1651, 1409, 1165, 759. UV spectrum (MeCN), λ_{max}, nm (log ε): 208.5 (4.65), 230.5 (4.56). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 389 $[M+Na]^+$ (100), 421 $[M+Na+CH_3OH]^+$ (100), 787 $[2M+Na+CH_3OH]^+$ (91), 1186 $[3M+Na+2CH_3OH]^+$ (13). Found, *m*/*z*: 389.1468 $[M+Na]^+$. $C_{21}H_{22}N_2O_4$. Calculated, *m*/*z*: 389.1472.

Isopropyl 9-oxo-7-(1-oxobutan-2-yl)-5b,6,7,8,9,11-hexahydroindolizino[1,2-*b*]quinoline-8-carboxylate (4bb). Yield 186 mg (75%), orange solid. R_f 0.54–0.77 (EtOAc). IR spectrum (KBr), ν, cm^{-1}: 2977, 1730, 1656, 1455, 1408, 1314, 1174, 1106, 757. UV spectrum (MeCN), λ_{max}, nm (log ε): 208.5 (4.70), 230.0 (4.58), 319.0 (3.82). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 417 $[M+Na]^+$ (57), 449 $[M+CH_3OH+Na]^+$ (100), 843 $[2M+CH_3OH+Na]^+$ (86), 875 $[2M+2MeOH+Na]^+$ (83), 1302 $[3M+3MeOH+Na]^+$ (9). Found, *m*/*z*: 417.1776 $[M+Na]^+$. $C_{23}H_{26}N_2O_4$. Calculated, *m*/*z*: 417.1785.

***tert*-Butyl 9-oxo-7-(1-oxobutan-2-yl)-5b,6,7,8,9,11-hexahydroindolizino[1,2-*b*]quinoline-8-carboxylate (4bc)**. Yield 344 mg (77%), orange solid. R_f 0.50–0.67 (EtOAc). IR spectrum (KBr), ν, cm^{-1}: 2974, 1727, 1666, 1455, 1408, 1152, 862, 755. UV spectrum (MeCN), λ_{max}, nm (log ε): 208.5 (4.70), 230.0 (4.58), 305.0 (3.72), 319.0 (3.82). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 431 $[M+Na]^+$ (56), 463 $[M+CH_3OH+Na]^+$ (100), 872 $[2M+CH_3OH+Na]^+$ (73), 904 $[2M+2CH_3OH+Na]^+$ (79), 1312 $[3M+2CH_3OH+Na]^+$ (26). Found, *m*/*z*: 431.1943 $[M+Na]^+$. $C_{24}H_{28}N_2O_4$. Calculated, *m*/*z*: 431.1941.

Oxidation of compound 4a. DDQ (57 mg, 0.25 mmol, 2.0 equiv) was added to a solution of aldehyde **4a** (39 mg, 0.13 mmol, 1.0 equiv) in 1,4-dioxane (1.3 ml). The mixture was subsequently stirred at 50, 80, and 100°C in each case for 1 h, during which precipitate was formed. After cooling to room temperature, the precipitate was filtered off and washed with CH_2Cl_2. The mother liquor was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 20:1). Two fractions, ketone **19** and aldehyde **20** were obtained.

2-(9-Oxo-9,11-dihydroindolizino[1,2-*b*]quinolin-7-yl)-butanal (19). Yield 21 mg (55%), light-yellow solid. R_f 0.21 (CH_2Cl_2–MeOH, 20:1). ^{1}H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.00 (3H, t, *J* = 7.4);

1.82–1.98 (1H, m); 2.20 (1H, m); 3.46 (1H, m); 5.29 (2H, s); 6.62 (1H, d, *J* = 1.4); 7.21 (1H, d, *J* = 1.4); 7.66 (1H, m); 7.83 (1H, m); 7.94 (1H, d, *J* = 8.2); 8.22 (1H, d, *J* = 8.6); 8.40 (1H, s); 9.76 (1H, d, *J* = 1.7). ^{13}C NMR spectrum (125 MHz, $CDCl_3$) δ, ppm: 11.7; 22.3; 49.8; 60.5; 101.1; 120.1; 127.9; 128.1 (2C); 128.8; 129.6; 130.5; 131.1; 146.4; 148.8; 150.6; 152.6; 161.2; 199.1. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 305 $[M+H]^+$ (100), 327 $[M+Na]^+$ (55). Found, *m*/*z*: 305.1284 $[M+H]^+$, 327.1104 $[M+Na]^+$. $C_{19}H_{16}N_2O_2$. Calculated, *m*/*z*: 305.1284, 327.1104.

7-Propionylindolizino[1,2-*b*]quinolin-9(11*H*)-one (20). Yield 21 mg (55%), brown solid. R_f 0.35 (CH_2Cl_2–MeOH, 20:1). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.26 (3H, t, *J* = 7.2); 3.01 (2H, q, *J* = 7.2); 5.24 (2H, s); 7.16 (1H, d, *J* = 1.4); 7.60–7.68 (2H, m, H-8); 7.81 (1H, m); 7.89 (1H, d, *J* = 8.1); 8.20 (1H, d, *J* = 8.5); 8.34 (1H, s). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 291 $[M+H]^+$ (100). Found, *m*/*z*: 291.1126 $[M+H]^+$. $C_{18}H_{14}N_2O_2$. Calculated, *m*/*z*: 291.1128.

Methyl 2-(9-oxo-5b,6,7,8,9,11-hexahydroindolizino[1,2-*b*]-quinolin-7-yl)butanoate (21). A mixture of compound **4a** (96 mg, 0.31 mmol, 1.0 equiv) and 2-methyl-2-butene (2.5 ml) in *t*-BuOH (6 ml) and water (1.5 ml) at room temperature was treated with $NaH_2PO_4 \cdot H_2O$ (0.43 g, 3.1 mmol, 10.0 equiv) and $NaClO_2$ (80% assay, 0.35 g, 3.1 mmol, 10.0 equiv). Water (8 ml) was added after 40 min, and the aqueous phase was extracted with CH_2Cl_2 (3×20 ml); the combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to give the intermediate carboxylic acid (0.11 mg) as a white solid. The carboxylic acid (0.11 mg) was taken up in methanol (2.8 ml) and toluene (10 ml), then $TMSCHN_2$ (2 M solution in Et_2O, 0.20 ml, 0.40 mmol, 1.3 equiv) was added dropwise at room temperature. After stirring for 45 min, the reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc–NEt_3, 200:9) to afford methyl ester **21**. Yield 88 mg (84% over two steps), white solid. R_f 0.38 (EtOAc–NEt_3, 20:1). ^{1}H NMR spectrum (300 MHz, $CDCl_3$, selected signals, 4 diastereomers A:B:C:D = 1:1:1:1), δ, ppm (*J*, Hz): 0.95 (3H, m_c, $CH_2C\underline{H}_3$); 1.64–1.89 (2H, m, $C\underline{H}_2CH_3$); 3.72 (0.75H, s, CO_2CH_3, diastereomer A); 3.74 (0.75H, s, CO_2CH_3, diastereomer B); 3.75 (0.75H, s, CO_2CH_3, diastereomer C); 3.77 (0.75H, s, CO_2CH_3, diastereomer D); 4.66 (1H, m_c, 11'-CH); 4.83–5.03 (1H, m, 5'b-CH); 5.16 (0.25H, d, *J* = 5.4, 11'-CH, diastereomer A); 5.21 (0.25H, d, *J* = 5.4, 11'-CH, diastereomer B); 5.30 (0.50H, d, *J* = 16.5, 11'-CH, diastereomers C and D); 7.56 (1H, m_c, H-2'); 7.72 (1H, m_c, H-3'); 7.83 (1H, d, *J* = 7.9, H-1'); 8.04–8.12 (2H, m, H-4',12'). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, selected signals), δ, ppm: 11.7 (3C); 11.8; 22.6; 22.8; 23.0; 23.3; 161.6; 161.7; 162.2; 162.3; 168.4; 169.8; 169.9; 174.8; 174.9; 175.1. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 339 $[M+H]^+$ (100). Found, *m*/*z*: 339.1702 $[M+H]^+$, 361.1521 $[M+Na]^+$, 377.1259 $[M+K]^+$. $C_{20}H_{22}N_2O_3$. Calculated, *m*/*z*: 339.1703, 361.1522, 377.1262.

Methyl 2-(9-oxo-9,11-dihydroindolizino[1,2-*b*]quinolin-7-yl)butanoate (22). Methyl ester **21** (52 mg, 0.16 mmol, 1.0 equiv) and DDQ (80 mg, 0.35 mmol, 2.2 equiv) were dissolved in 1,4-dioxane (1.5 ml) and heated at 60°C for 40 min. After cooling to room temperature, the precipitate was removed by filtration, washed with CH_2Cl_2, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc–NEt_3, 20:1), giving ester **22**. Yield 48 mg (90%), light-yellow solid. R_f 0.32 (EtOAc–MeOH, 20:1). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.93 (3H, t, *J* = 7.3, $CH_2C\underline{H}_3$); 1.79–1.97 (1H, m) and 2.05–2.22 (1H, m, $C\underline{H}_2CH_3$); 3.45 (1H, t, *J* = 7.7, 2-CH); 3.69 (3H, s, $CO_2C\underline{H}_3$); 5.18 (2H, s, 11'-CH_2); 6.61 (1H, t, *J* = 1.3, H-8'); 7.27 (1H, d, *J* = 1.3, H-6'); 7.58 (1H, m_c, H-2'); 7.76 (1H, m_c, H-3'); 7.86 (1H, d, *J* = 8.2, H-1'); 8.16 (1H, d, *J* = 8.6, H-4'); 8.30 (1H, s, H-12'). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 335.1 $[M+H]^+$ (100). Found, *m*/*z*: 335.1390 $[M+H]^+$. $C_{20}H_{18}N_2O_3$. Calculated, *m*/*z*: 335.1390.

Synthesis of compounds 23 and 24 from compound 22. A mixture of compound **22** (0.11 g, 0.33 mmol, 1.0 equiv), concd. sulfuric acid (66 mg), paraformaldehyde (78 mg), and water (0.40 ml) in 1,4-dioxane (11 ml) in a pressure flask was heated at 95°C for 17 h. After cooling to room temperature, half-saturated NaCl solution (10 ml) was added and the aqueous phase was extracted with CH_2Cl_2 (3×25 ml). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (10 ml). The insoluble solid was filtered off and washed with CH_2Cl_2. Further drying of the solid under reduced pressure gave carboxylic acid **23** (40 mg, 0.12 mmol, 38%) as a yellow solid. The mother liquor was concentrated and the residue was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 20:1). Two fractions were obtained, respectively, lactone **25** (26 mg, 78 μmol, 27%) as a yellow solid and alcohol **24** (8.2 mg, 23 μmol, 7%) as a yellow oil.

2-(9-Oxo-9,11-dihydroindolizino[1,2-*b*]quinolin-7-yl)-butanoic acid (23). Yield 40 mg (38%), yellow solid. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.91 (3H, t, *J* = 7.2); 1.67–1.86 (1H, m); 1.93–2.10 (1H, m); 3.48–3.61 (1H, m); 5.22 (2H, s); 6.50 (1H, d, *J* = 1.0); 7.16 (1H, d, *J* = 1.0); 7.70 (1H, m); 7.85 (1H, m); 8.07–8.22 (2H, m); 8.67 (1H, s); 11.98 (1H, br. s). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 321 (100) $[M+H]^+$. Found, *m*/*z*: 321.1233 $[M+H]^+$. $C_{19}H_{16}N_2O_3$. Calculated, *m*/*z*: 321.1233.

4-Ethyl-4-(hydroxymethyl)-1,8-dihydro-3*H*-pyrano-[4',3':7,8]indolizino[1,2-*b*]quinoline-3,6(4*H*)-dione (24). Yield 8.2 mg (7%), yellow oil. R_f 0.23 (CH_2Cl_2–MeOH, 20:1). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.88 (3H, t, *J* = 7.2); 1.84–2.01 (1H, m); 2.06–2.25 (1H, m); 4.02 (1H, d, *J* = 10.4); 4.32 (1H, d, *J* = 10.4); 5.07 (2H, m); 6.13 (1H, d, *J* = 15.4); 6.33 (1H, d, *J* = 15.4); 6.67 (1H, s); 7.54 (1H, m_c); 7.65–7.84 (2H, m); 8.03–8.22 (2H, m). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 363 (100) $[M+H]^+$. Found, *m*/*z*: 363.1339 $[M+H]^+$. $C_{21}H_{18}N_2O_4$. Calculated, *m*/*z*: 363.1339.

2-[8-(Methoxycarbonyl)-9-oxo-5b,6,7,8,9,11-hexahydro-indolizino[1,2-*b*]quinolin-7-yl]butanoic acid (26). A solution of $NaClO_2$ (827 mg, 9.14 mmol, 10.0 equiv) and $NaH_2PO_4 \cdot H_2O$ (1.01 g, 7.31 mmol, 8.0 equiv) in H_2O

(5 ml) was added dropwise to a solution of aldehyde **4ba** (335 mg, 0.914 mmol, 1.0 equiv) and 2-methyl-2-butene (385 mg, 583 μl, 5.48 mmol, 6.0 equiv) in *t*-BuOH–THF (10 ml, 1:1) and the mixture was subsequently stirred at room temperature for 6.5 h. Then H_2O (50 ml) was added and the mixture was acidified with 2 M aqueous HCl to achieve pH 1. The aqueous phase was extracted with CH_2Cl_2 (2×50 ml), the combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure, giving the title compound **26** as pale-yellow solid. Yield 348 mg (100%). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 405 $[M+Na]^+$ (78), 787 $[2M+Na]^+$ (100), 1169 $[3M+Na]^+$ (16).

2-[8-(Methoxycarbonyl)-9-oxo-9,11-dihydroindolizino-[1,2-b]quinolin-7-yl]butanoic acid (27). A mixture of methyl ester **26** (350 mg, 0.914 mmol, 1.0 equiv) and DDQ (415 mg, 1.83 mmol, 2.0 equiv) in 1,4-dioxane (6 ml) was stirred at room temperature for 6 h. The precipitated hydroquinone was removed by filtration, washed with CH_2Cl_2 (50 ml), and the filtrate was concentrated under reduced pressure. Silica gel column chromatography (CH_2Cl_2–MeOH, 100:1 + 1% AcOH → 50:1 + 1% AcOH) and recrystallization from MeOH gave the title compound **27**. Yield 70.0 mg (20%), pale-yellow solid. R_f 0.28 (CH_2Cl_2–MeOH, 25:1 + 1 % AcOH). IR spectrum (KBr), ν, cm^{-1}: 3433, 2964, 1726, 1649, 1580, 1403, 1196, 1133, 770. UV spectrum (MeCN), λ_{max}, nm (log ε): 195.5 (4.40), 217.0 (4.50), 253.0 (4.42), 287.5 (3.74), 364.5 (4.22). ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.90 (3H, t, *J* = 7.5, 4-CH_3); 1.73–1.90 (1H, m) and 1.99–2.15 (1H, m, 3-CH_2); 3.48 (1H, t, *J* = 7.5, 2-CH); 3.86 (3H, s, CO_2CH_3); 5.25 (2H, s, 11'-CH_2); 7.18 (1H, s, H-6'); 7.71 (1H, t, *J* = 7.5, H-2'); 7.86 (1H, t, *J* = 7.5, H-3'); 8.11 (1H, d, *J* = 7.5, H-1'); 8.19 (1H, d, *J* = 7.5, H-4'); 8.67 (1H, s, H-12'); 12.79 (1H, br. s, CO_2H). ^{13}C NMR spectrum (125 MHz, DMSO-d_6), δ, ppm: 11.8; 25.2; 49.8; 50.3; 52.2; 97.7; 124.1; 127.6; 127.8; 128.3; 128.8; 129.9; 130.2; 131.3; 146.2; 147.7; 149.6; 151.8; 156.9; 166.1; 172.5. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 357 $[M–CO_2+Na]^+$ (93), 401 $[M+Na]^+$ (100). Found, *m*/*z*: 401.1097 $[M+Na]^+$. $C_{21}H_{18}N_2O_5$. Calculated, *m*/*z*: 401.1108.

4-Ethyl-1,12-dihydro-14*H*-pyrano[3',4':6,7]indolizino-[1,2-*b*]quinoline-3,14(4*H*)-dione (25). A solution of methyl ester **27** (30.0 mg, 0.0792 mmol, 1.0 equiv) in EtOH (1 ml) was treated by first adding KOH (4.4 mg, 0.0792 mmol, 1.0 equiv), followed by $CaCl_2$ (13.0 mg, 0.119 mmol, 1.5 equiv) and $NaBH_4$ (9.0 mg, 0.238 mmol, 3.0 equiv), and the mixture was stirred at 80°C for 2 h. After cooling to room temperature, aqueous 2 M HCl solution (2 ml) was added and the mixture was stirred at room temperature for 2 h. Water (25 ml) was then added and the aqueous phase was extracted with CH_2Cl_2 (3×25 ml). The combined organic phases were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. Silica gel column chromatography (CH_2Cl_2–MeOH, 100:1) afforded the desired compound **25**. Yield 16.0 mg (61%), pale-yellow solid. R_f 0.53 (CH_2Cl_2–MeOH, 10:1). IR spectrum (KBr), ν, cm^{-1}: 1741, 1654, 1601, 1231, 1052, 761. UV spectrum (MeCN), λ_{max}, nm (log ε): 196.0 (4.44), 218.5 (4.55), 245.5 (4.39), 252.5 (4.46), 288.0 (3.81), 363.0 (4.26). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.06 (3H, t, *J* = 7.5, 18-CH_3); 2.01–2.13 (2H, m, 19-CH_2); 3.59 (1H, t, *J* = 6.6, 20-CH); 5.25 (2H, s, 5-CH_2); 5.36 (1H, d, *J* = 16.2) and 5.53 (1H, d, *J* = 16.2, 22-CH_2); 7.13 (1H, s, H-14); 7.63 (1H, ddd, *J* = 8.1, *J* = 6.9, *J* = 1.2, H-10); 7.80 (1H, ddd, *J* = 8.4, *J* = 6.9, *J* = 1.5, H-11); 7.90 (1H, d, *J* = 8.1, H-9); 8.17 (1H, dd, *J* = 8.4, H-12); 8.35 (1H, s, H-7). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: 11.3; 25.2; 45.8; 49.9; 66.0; 99.6; 120.6; 128.0; 128.1; 128.5; 129.6; 130.6; 131.1; 145.9; 147.1; 148.8; 152.3; 157.8; 170.9. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 371 $[M+K]^+$ (100), 387 $[M+Na]^+$ (32), 719 $[2M+CH_3OH+Na]^+$ (50). Found, *m*/*z*: 333.1232 $[M+H]^+$. $C_{20}H_{16}N_2O_3$. Calculated, *m*/*z*: 333.1234.

4-Ethyl-4-hydroxy-1,12-dihydro-14*H*-pyrano[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,14(4*H*)-dione ((*rac*)-camptothecin (1b)). $CuCl_2·2H_2O$ (50 mg, 0.37 mmol) and aqueous 40% Me_2NH solution (60 μl, 0.37 mmol) were added to a solution of 4-ethyl-1,12-dihydro-14*H*-pyrano-[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*)-dione (**25**) (30.0 mg, 0.0903 mmol) in DMF (10 ml), and O_2 was passed through the reaction mixture for 7 h at room temperature. The pH value was adjusted to 5–6 by adding 2 M HCl. Water (25 ml) was then added and the aqueous phase was extracted with CH_2Cl_2 (5×25 ml). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Silica gel column chromatography (CH_2Cl_2–MeOH, 100:1) afforded the desired compound **1b**. Yield 14.0 mg (45%), pale-yellow solid. R_f 0.45 (CH_2Cl_2–MeOH, 10:1). IR spectrum (KBr), ν, cm^{-1}: 3274, 1755, 1651, 1584, 1460, 1158, 1040, 768. UV spectrum (MeCN), λ_{max}, nm (log ε): 195.5 (4.39), 218.5 (4.50), 252.5 (4.41), 288.0 (3.75), 362.5 (4.22). ^{1}H NMR spectrum (600 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.89 (3H, t, *J* = 7.4, 18-CH_3); 1.88 (2H, m_c, 19-CH_2); 5.29 (2H, s, 5-CH_2); 5.43 (2H, d, *J* = 1.2, 22-CH_2); 6.47 (1H, s, OH); 7.36 (1H, s, H-14); 7.71 (1H, t, *J* = 7.2, H-10); 7.87 (1H, ddd, *J* = 9.0, *J* = 7.2, *J* = 1.2, H-11); 8.12 (1H, d, *J* = 7.2, H-9); 8.17 (1H, d, *J* = 9.0, H-12); 8.69 (1H, s, H-7). ^{13}C NMR spectrum (125 MHz, DMSO-d_6), δ, ppm: 7.6; 30.2; 50.1; 65.1; 72.2; 96.5; 119.0; 127.5; 127.9; 128.4; 129.0; 129.7; 130.3; 131.5; 145.4; 147.9; 149.9; 152.5; 156.8; 172.3. Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 349 $[M+H]^+$ (6), 371 $[M+Na]^+$ (14), 719 $[2M+Na]^+$ (100). Found, *m*/*z*: 349.1181 $[M+H]^+$. $C_{20}H_{16}N_2O_4$. Calculated, *m*/*z*: 349.1183.

(*S*)-4-Ethyl-4-hydroxy-1,12-dihydro-14*H*-pyrano[3',4':6,7]-indolizino[1,2-*b*]quinoline-3,14(4*H*)-dione ((+)-camptothecin (1a)). KHMDS (0.5 M in toluene, 100 μl, 49.6 μmol, 1.1 equiv) was added dropwise to a cold (−78°C) solution of 4-ethyl-1,12-dihydro-14*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]-quinoline-3,14(4*H*)-dione (**25**) (15.0 mg, 45.1 μmol, 1.0 equiv) in CH_2Cl_2 (750 μl). Subsequently, (+)-[(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine (30.0 mg, 0.104 mmol, 2.3 equiv) in THF (750 μl) was added and the reaction mixture was allowed to warm to room temperature over 19 h. Saturated aqueous NH_4Cl solution (25 ml) was added, and the aqueous phase was extracted with EtOAc (3×25 ml).

The combined organic layers were washed with saturated aqueous Na_2SO_3 solution (25 ml) and saturated aqueous NaCl solution (25 ml), dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. Silica gel column chromatography (CH_2Cl_2–MeOH, 100:1) provided the title compound **1**. Yield 5 mg, (32%), pale-yellow solid. $[\alpha]_D^{20}$ +14.4° (*c* 0.34, $CHCl_3$–MeOH, 4:1). HPLC (Chiralpak IA, (*n*-hexane–MeOH–CH_2Cl_2 4:2:1)–CH_2Cl_2, 80:20, flow rate 0.6 ml/min, 254 nm): t_R 13.7 min (*R*)-(**1**), t_R 14.6 min (*S*)-(**1**), 37% *ee*. ($[\alpha]_D^{20}$ +14.2° (*c* 0.34, $CHCl_3$–MeOH, 4:1)[13b]). The remaining analytical data correspond to the racemic compound.

Methyl 7-(1,1-dimethoxybutan-2-yl)-9-oxo-9,11-dihydro-indolizino[1,2-*b*]quinoline-8-carboxylate (30). A mixture of compound **4ba** (10 mg, 27 μmol, 1.0 equiv), $RuCl_3 \cdot nH_2O$ (2 mg, 9.6 μmol), trimethyl orthoformate (3.5 mg, 33 μmol, 1.2 equiv) in methanol (1 ml) was stirred in a pressure flask at 60°C for 3.5 h. Aqueous 5% $NaHCO_3$ solution (5 ml) was added, the aqueous phase was extracted with CH_2Cl_2 (3×10 ml), and the combined organic layers were dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel column chromatography (pentane–EtOAc, 1:1) to give the acetal intermediate. Yield 6.0 mg (54%), white solid. A mixture of the acetal (14 mg, 34 μmol, 1.0 equiv) and DDQ (15 mg, 68 μmol, 2.0 equiv) in 1,4-dioxane (2 ml) was stirred at 65°C for 1 h. After cooling to room temperature, the precipitate was removed by filtration, washed with CH_2Cl_2, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc–NEt_3, 20:1) to obtain compound **30**. Yield 11 mg (79%), yellow solid. R_f 0.38 (EtOAc–NEt_3, 20:1). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.87 (3H, t, *J* = 7.4, $CH_2C\underline{H}_3$); 1.70–1.88 (1H, m) and 1.88–2.06 (1H, m, 2'-CH_2); 3.04–3.16 (1H, m, 1'-CH); 3.32 (3H, s, OCH_3); 3.41 (3H, s, OCH_3); 3.96 (3H, s, CO_2CH_3); 4.58 (1H, d, *J* = 6.5, $C\underline{H}(OCH_3)_2$); 5.28 (2H, s, 11-CH_2); 7.34 (1H, s, H-6); 7.66 (1H, m_c, H-2); 7.83 (1H, m_c, H-3); 7.93 (1H, d, *J* = 8.1, H-1); 8.23 (1H, d, *J* = 8.5, H-4); 8.38 (1H, s, H-12). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 431.1 $[M+Na]^+$ (100). Found, *m*/*z*: 409.1757 $[M+H]^+$, 431.1576 $[M+Na]^+$, 447.1316 $[M+K]^+$. $C_{23}H_{24}N_2O_5$. Calculated, *m*/*z*: 409.1758, 431.1577, 447.1316.

7-(1,1-Dimethoxybutan-2-yl)-8-(hydroxymethyl)-indolizino[1,2-*b*]quinolin-9(11*H*)-one (31). DIBAL-H (1.0 M in CH_2Cl_2, 54 μl, 54 μmol, 2.0 equiv) was added dropwise to a solution of compound **30** (11 mg, 27 μmol, 1.0 equiv) in dichloromethane (1.5 ml) at −78°C and stirred at this temperature for 1.5 h. Subsequently, methanol (2 ml) and $NaBH_4$ (12 mg, 0.32 mmol, 12 equiv) were added at −78°C and stirred for 1 h. The reaction mixture was warmed to room temperature and stirred for 40 min. Aqueous 1 M NaOH solution (5 ml) was added, the aqueous phase was extracted with CH_2Cl_2 (3×10 ml), and the combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by silica gel column chromatography (EtOAc–MeOH, 20:1), providing alcohol **31**. Yield 7.3 mg (71%), yellow solid. R_f 0.20 (EtOAc–MeOH, 30:1). IR spectrum (KBr), ν, cm^{-1}: 3355 (O–H), 2961 (C–H), 1653 (C=O), 1589, 1455, 1401 (CH_3, CH_2), 1143, 1066 (C–O), 754, 724 (CH_3, CH_2). UV spectrum (MeCN), λ_{max}, nm (log ε): 197.5 (4.47), 220.5 (4.53), 244.5 (4.42), 252.5 (4.46), 290.0 (3.83), 332.5 (3.92), 367.5 (4.25). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.84 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 1.71–1.91 (1H, m) and 1.91–2.10 (1H, m, 2'-CH_2); 3.23–3.38 (4H, m, H-1', OCH_3); 3.45 (3H, s, OCH_3); 4.00 (1H, m_c, OH); 4.58 (1H, d, *J* = 7.4, $C\underline{H}(OCH_3)_2$); 4.69–4.80 (1H, m) and 4.89–5.01 (1H, m, $C\underline{H}_2OH$); 5.27 (2H, s, 11-CH_2); 7.30 (1H, s, H-6); 7.64 (1H, m_c, H-2); 7.81 (1H, m_c, H-3); 7.92 (1H, d, *J* = 8.1, H-1); 8.22 (1H, d, *J* = 8.5, H-4); 8.36 (1H, s, H-12). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 381 $[M+H]^+$ (100). Found, *m*/*z*: 381.1808 $[M+H]^+$, 403.1628 $[M+Na]^+$. $C_{22}H_{24}N_2O_4$. Calculated, *m*/*z*: 381.1808, 403.1628.

Synthesis of compounds 32 and 33. A mixture of compound **31** (3.2 mg, 8.4 μmol, 1.0 equiv) and $LiBF_4$ (6.7 mg, 71 μmol, 8.5 equiv) in MeCN–H_2O (50:1, 0.3 ml) was stirred at room temperature for 30 min and then at 65°C for 70 min. After slight cooling, $LiBF_4$ (5.8 mg, 62.0 μmol, 7.4 equiv) and a mixture of MeCN–H_2O (50:1, 0.1 ml) were added. The reaction mixture was then stirred at 65°C for 30 min. Aqueous 5% $NaHCO_3$ solution (1 ml) was added, the aqueous phase was extracted with CH_2Cl_2 (3×10 ml), and the combined organic layers were dried over anhydrous Na_2SO_4. After the removal of solvent, the residue was purified by silica gel column chromatography (EtOAc–NEt_3, 40:3 → EtOAc–MeOH, 20:1), providing two products – enol ether **33** and lactol **32**.

4-Ethyl-3-hydroxy-1,3,4,12-tetrahydro-14*H*-pyrano-[3',4':6,7]indolizino[1,2-*b*]quinolin-14-one (32). Yield 1.1 mg (40%), light-yellow solid, R_f 0.13 (EtOAc–NEt_3, 20:1) or 0.22 (EtOAc–MeOH, 40:1). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.07 (3H, t, *J* = 7.5, $CH_2C\underline{H}_3$); 1.80 (2H, m_c, $C\underline{H}_2CH_3$); 2.67 (1H, t, *J* = 6.6, 4-CH); 2.97 (1H, br. s, OH); 4.85 (2H, m_c, 1-CH_2); 5.24 (2H, s, 12-CH_2); 5.35–5.44 (1H, m, 3-CH); 7.19 (1H, s, H-5); 7.63 (1H, m_c, H-9); 7.80 (1H, m_c, H-8); 7.91 (1H, d, *J* = 8.3, H-10); 8.20 (1H, d, *J* = 8.6, H-7); 8.34 (1H, s, H-11). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 335 $[M+H]^+$ (100). Found, *m*/*z*: 335.1390 $[M+H]^+$. $C_{20}H_{18}N_2O_3$. Calculated, *m*/*z*: 335.1390.

8-(Hydroxymethyl)-7-(1-methoxybut-1-en-2-yl)-indolizino[1,2-*b*]quinolin-9(11*H*)-one (33). Yield 1.7 mg (60%), white solid, R_f 0.31 (EtOAc–NEt_3, 20:1). ^{1}H NMR spectrum (300 MHz, $CDCl_3$, isomer A/B ratio 1:1), δ, ppm (*J*, Hz): 1.04–1.17 (3H, m, $CH_2C\underline{H}_3$); 1.72–1.87 (1.5H, m, 2'-CH_2, isomer A and 2'-$C\underline{H}_AH_B$, isomer B); 2.62 (0.5H, m_c, 2'-$CH_A\underline{H}_B$, isomer B); 2.89 (1H, br. s, OH); 3.50 (1.5H, s, OCH_3, isomer A); 3.54 (1.5H, s, OCH_3, isomer B); 4.65 (0.5H, dd, *J* = 17.1, *J* = 1.4, $C\underline{H}_AH_BOH$, isomer A); 4.77–4.95 (2.5H, m, $CH_A\underline{H}_BOH$, isomer A and $C\underline{H}OCH_3$); 5.25 (2H, s, 11-CH_2); 7.19 (0.5H, s, H-6, isomer A); 7.32 (0.5H, s, H-6, isomer B); 7.63 (1H, m_c, H-2); 7.81 (1H, m_c, H-3); 7.92 (1H, d, *J* = 8.1, H-1); 8.20 (1H, d, *J* = 8.5, H-4); 8.35 (1H, s, H-12). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 349 $[M+H]^+$ (100). Found, *m*/*z*: 349.1547 $[M+H]^+$. $C_{21}H_{20}N_2O_3$. Calculated, *m*/*z*: 349.1546.

4-Ethyl-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-1,14(12*H*)-dione (34). A mixture of compound **4ba** (58 mg, 0.16 mmol, 1.0 equiv) and DDQ (72 mg, 0.32 mmol, 2.0 equiv) in 1,4-dioxane (1.6 ml) was stirred at 55°C for 1 h. After cooling to room temperature, the precipitate was removed by filtration, washed with 1,4-dioxane, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc–NEt_3, 20:1), providing compound **34**. Yield 21 mg (40%), light-yellow solid. R_f 0.19 (EtOAc–NEt_3, 20:1). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.35 (3H, t, *J* = 7.5, $CH_2C\underline{H}_3$); 2.68 (2H, q, *J* = 7.5, $C\underline{H}_2CH_3$); 5.39 (2H, s, 12-CH_2); 7.32 (1H, s, H-3); 7.35 (1H, s, H-5); 7.72 (1H, m_c, H-9); 7.87 (1H, m_c, H-8); 7.97 (1H, d, *J* = 8.1, H-10); 8.27 (1H, d, *J* = 8.5, H-7); 8.43 (1H, s, H-11). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 331 $[M+H]^+$ (100), 353 $[M+Na]^+$ (20). Found, *m*/*z*: 331.1078 $[M+H]^+$, 353.0897 $[M+Na]^+$. $C_{20}H_{14}N_2O_3$. Calculated, *m*/*z*: 331.1077, 353.0896.

The Supplementary information file containing NMR spectra of the synthesized compounds is available from the journal website at http://link.springer.com/journal/10593http://hgs.osi.lv.

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