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Towards new camptothecins. Part 3: Synthesis of 5-methoxycarbonyl camptothecin☆

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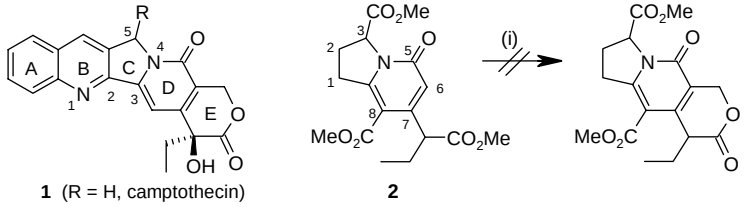
Abstract—The synthesis of two camptothecin analogs substituted by a carbonyl function on position 5 of cycle C was realized. New conditions were studied to obtain the E-lactone ring of these heterocycles. These compounds were obtained from the reaction of Bredereck's reagent with indolizines derived from pyroglutamic acid. This yielded dimethylaminovinyl groups whose oxidation by $NaIO_4$ yielded ketones. The indolizinones obtained were reacted in Friedlander condition, to give the scaffold of the desired camptothecins.

1. Introduction

In the context of the synthesis of new camptothecins **1** substituted in position 5, we chose to use the general method of Danishefsky.[1] In previous paper in this series,[2a] we solved the problem of the introduction of a ketone function in position 1 of indolizines **2** derived from pyroglutamic acid. The next crucial point now was the formation of the E ring. We have already shown[2b] that this lactone ring cannot be obtained by reacting formaldehyde with indolizines **2** under Danishefsky conditions (Scheme 1). Herein, we report on attempts to obtain the lactone ring E by using an intramolecular cyclization of intermediates **3** or **4**, then a successful Mannich reaction of pyridone **2**, in conditions different from the previous ones (Scheme 2). Transformation of the compound thus obtained led to a camptothecin analog, although in low yields.

2. The intramolecular approach

Considering the poor yields of the classical Mannich condensation,[2b] we thought that an intramolecular reaction could allow the synthesis of the cycle E. This can be obtained by cyclizing sulfonium **3a** (Pummerer reaction)[3] or oxonium **3b** (Mannich reaction)[4] salts, or by attack of the pyridone ring on a methyl ester substituted by a chloride or sulfinate leaving group (Scheme 2). In order to obtain these intermediates, it was necessary to differentiate the three appended carbonyl groups located on the pyrrolo–pyridone scaffold **2**. Because saponification of heterocycle **2** (R=H, Et) (Scheme 1) was not selective and led to hydrolysis of the two aliphatic esters groups, we used the carboxamides **5** and **6** (Scheme 3) as the starting compounds.



1 (R = H, camptothecin) **2**

Scheme 1. Reaction conditions: (i) CH_2O, dioxane, H_2O, H_2SO_4.

☆ Part 2 in this series: see Ref. 2a.

Keywords: Camptothecins; Mannich reaction; Bredereck's reagent.
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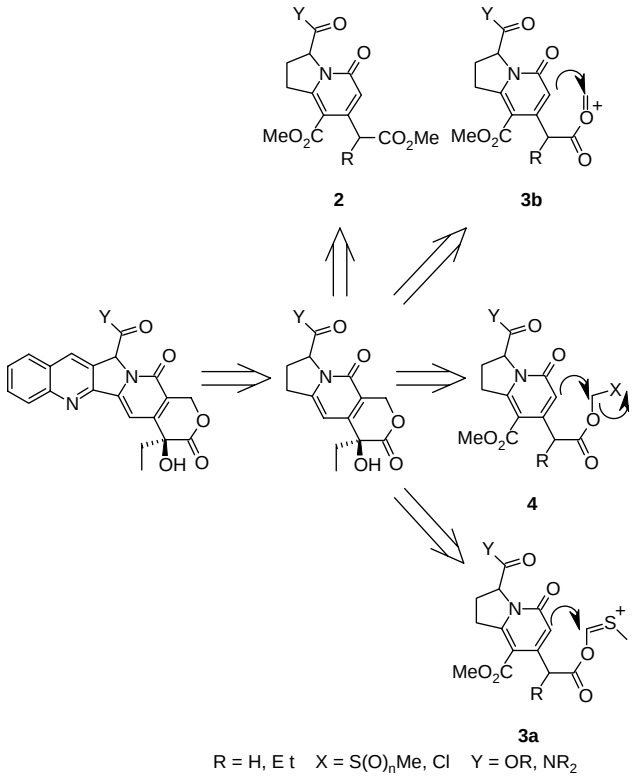
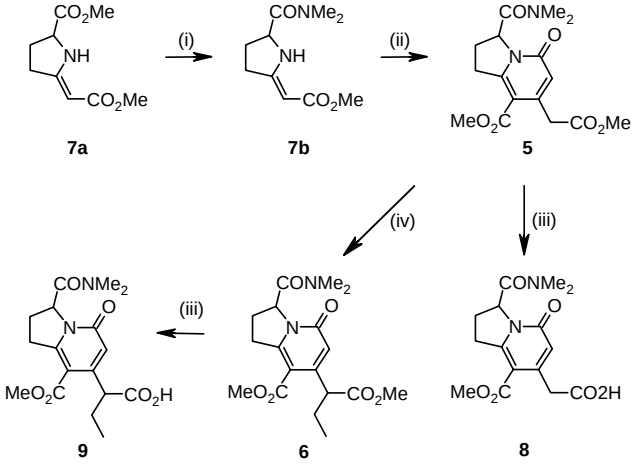


Scheme 2. Retrosynthetic approach towards modified camptothecins.



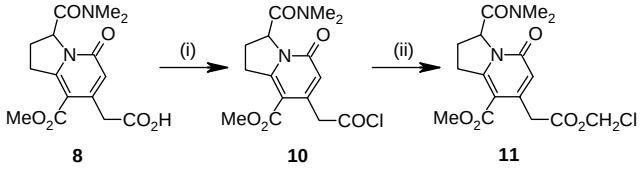
Scheme 3. Reaction conditions: (i) Me_2NH, MeOH (77%);[2a] (ii) dimethyl 3-chloroglutaconate, Et_3N, MeOH (95%);[2a] (iii) NaOH, 20 °C, 30 min (**8** 89%, **9** 78%); (iv) EtI, NaH, THF (78%).[2a]

2.1. Synthesis of acids 8 and 9

Amides **5** and **6** were obtained from enaminoesters **7a**,**b** as already described.[2a] The aliphatic ester group of these heterocycles was selectively saponified at room temperature by a dilute sodium hydroxide solution. Afterward, acidification gave very good yields in acids **8** and **9** (Scheme 3). It is worthy to note that the reaction of ester **5** with potassium trimethylsilanolate[5] reaches also the aromatic ester group to give a mixture of mono and diacids.

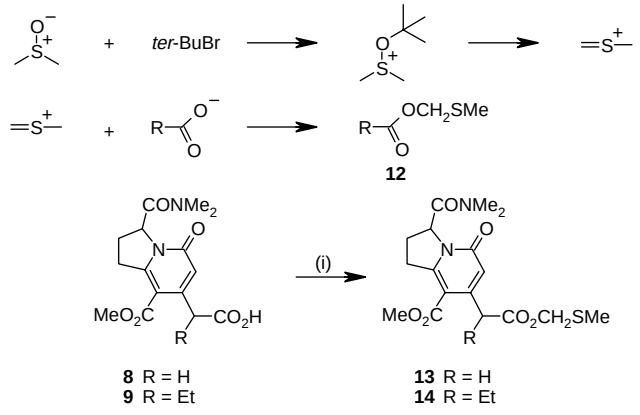
2.2. Synthesis of functionalized esters

It is well known that acid chlorides react with formaldehyde, in the presence of a Lewis acid, giving chloromethyl esters.[6] Thus, acid **8** was reacted with oxalyl chloride to give compound **10** in quantitative yield. Reaction of chloride **10** with formaldehyde and $AlCl_3$ as catalyst led to chloromethyl ester **11** in an unoptimized yield of 20% (Scheme 4). This reaction did not succeed when zinc chloride or boron trifluoride etherate was used as catalyst.



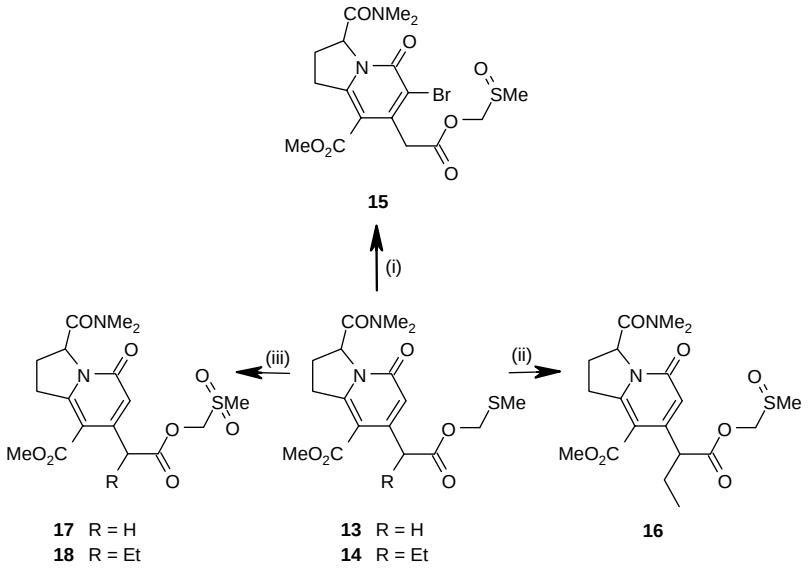
Scheme 4. Reaction conditions: (i) $(ClCO)_2$, $CHCl_3$, DMF cat., 20 °C, 30 min (100%); (ii) CH_2O, $AlCl_3$, PhCl, reflux, 24 h (20%).

Reaction of DMSO with *tert*-BuBr in the presence of a base yields a methylenesulfonium cation that can be trapped by a carboxylate ion to give methylsulfanylmethyl esters **12** (Scheme 5).[7] Following this method, esters **13** and **14** were easily obtained in 77–84% yields starting from acids **8** and **9**. Though the reaction can be performed at room temperature in pure DMSO,[7] the use of DMSO diluted in another solvent (CH_2Cl_2) improved the yield in the extraction step. It was then necessary to proceed under reflux conditions.



Scheme 5. Reaction conditions: (i) DMSO, *tert*-BuBr, $NaHCO_3$, (**13**: 20 °C, 24 h, 84%, **14**: 12 h, reflux, 77%).

Taking into account that sulfoxide function could generate a thionium in acid medium (Pummerer reaction), the sulfoxidation of substrates **13** and **14** was investigated. Thus, oxidation of a sulfur atom can be obtained with bromine,[8] but the ring bromination of pyridone also occurred, and ester **13** then gave bromopyridone **15** (because of the acidity if the $ArCH_2CO$ group, treatment of this compound with a base was not attempted). Sodium periodate and magnesium monoperoxyphtalate (MMPP) are more selective reagents, providing, respectively, very good yields in sulfoxide **16** or sulfones **17** and **18** (Scheme 6).



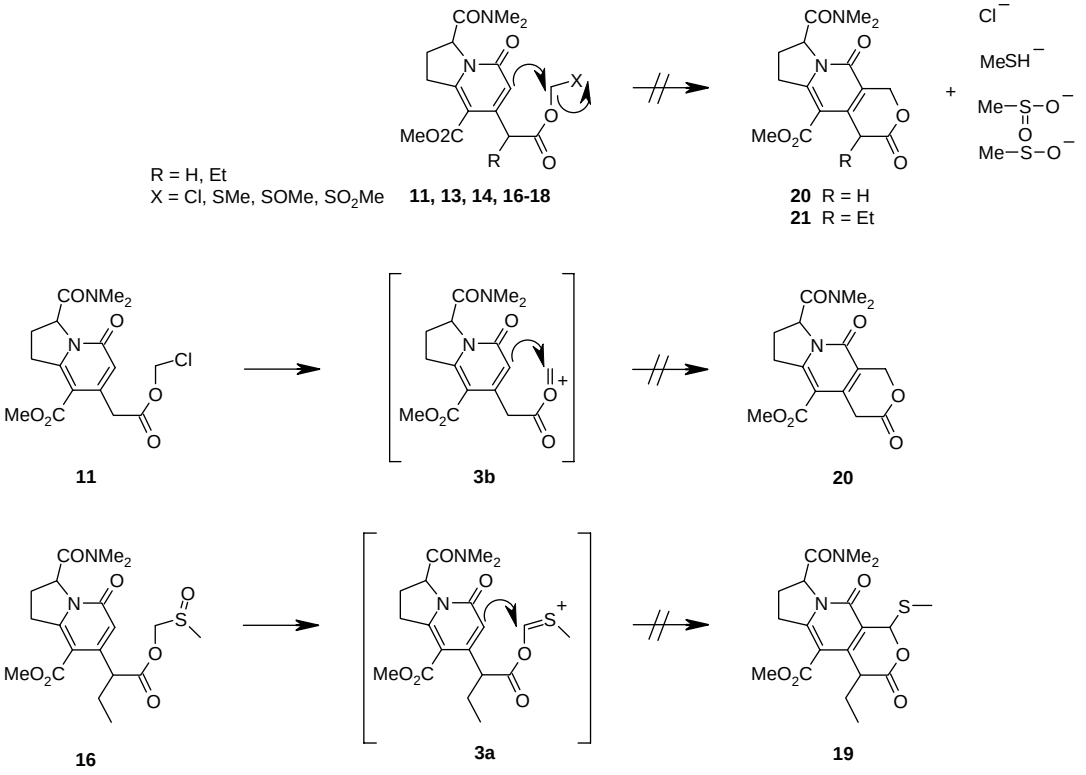
Scheme 6. Reaction conditions: (i) Br_2, $KHCO_3$, H_2O, CH_2Cl_2, 20 °C, 15 h (92%); (ii) $NaIO_4$, H_2O, MeOH, 20 °C, 12 h (86%); (iii) MMPP, MeOH, 20 °C, 12 h (**17**: 98%, **18**: 92%).

2.3. Attempts for the formation of cycle E

Formation of the wanted lactone ring E from previous functionalized esters can be envisaged by a direct attack of the pyridone ring on a C-leaving group, with loss of chloride, methanethiolate, methanesulfenate or methane–sulfinate ion. In another reaction mechanism, treatment of chloromethyl ester **11** with a Lewis acid[6] or sulfoxide **16** with TFAA or Ac_2O and PTSA,[9] could lead to a sulfonium **3a** or oxonium **3b** cation, to give lactones **19** or **20** (Scheme 7). All our attempts to carry out these processes only led to mixtures of many unidentified products.

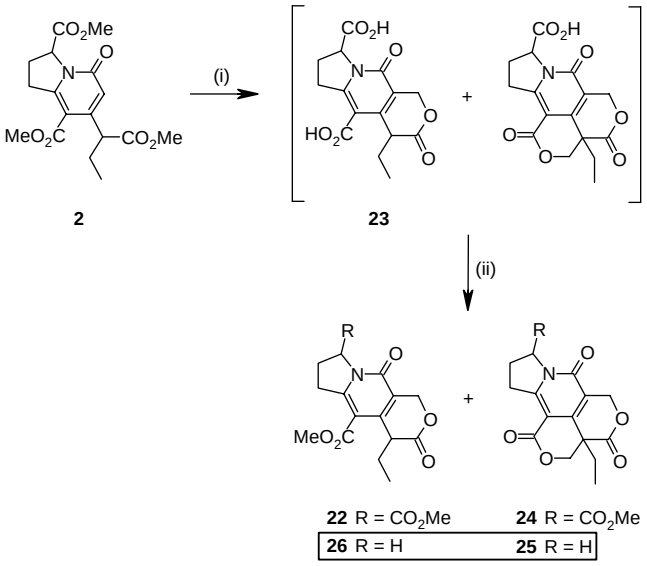
3. The bimolecular approach

At the beginning of this work, it was though necessary to introduce the 5-carboxamide group at the start of the reaction sequence, in order to differentiate the two aliphatic carboxyl functions. In a bimolecular approach it was not



Scheme 7. Attempted formation of the lactone ring E.

necessary to distinguish these groups, and the starting material was now indolizine **2** (Scheme 8).



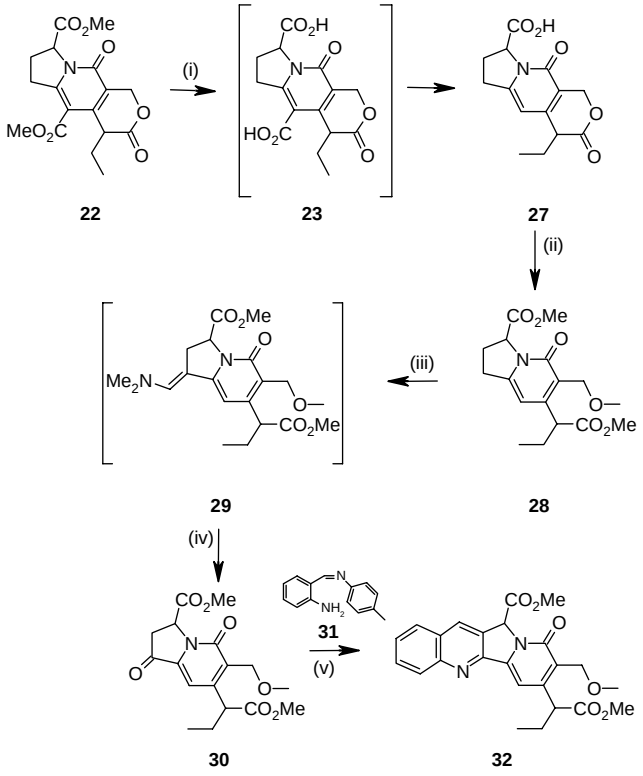
Scheme 8. Reaction conditions: (i) CH_2O, AcOH, 34% HCl, 80 °C, 24 h; (ii) MeOH, $CHCl_3$, H^+, reflux, 24 h (**22**: 84% from **2**, **24**: 0–6% from **2**).

3.1. Mannich reaction of indolizinone 4

We have already described how reaction of formaldehyde with a diastereoisomer mixture of tetrahydroindolizinone **2**[2] in the general conditions of Danishefsky[1,10] (CH_2O, H_2SO_4, dioxane, H_2O, reflux 24 h) does not give lactone **22**.[2b] We now tried other general conditions for Mannich reactions that use aqueous formaldehyde in a mixture of AcOH and concentrated HCl.[11] In that case, a hydroxymethyl group was indeed introduced in the pyridone ring, but a great part of the mixture of products obtained was hydrolyzed, mainly leading to hydroxyacids. To decrease the water content of the reaction mixture, aqueous formaldehyde was replaced by polyoxymethylene. Under these conditions, lactone **23** was formed in very good yield. Due to the difficulties encountered during its purification, it was transformed into the corresponding methyl esters **22**. The esterification was realized in 84% reproducible yield with MeOH under the ternary Azeotropic conditions (H_2O/MeOH/$CHCl_3$).[2a,12] gave a lactone **22**. It should be noted that this product was often accompanied by a small amount of di-lactone **24**, analog to compound **25** (R=H) that was obtained[2b] in attempts to reproduce the synthesis of heterocycle **26** described earlier (Scheme 8).[1]

3.2. Synthesis of 5-methoxycarbonyl camptothecin analog 32

Reflux of diester **22** in 48% HBr[1] led to the hydrolysis of the ester functions followed by a decarboxylation of the aromatic acid as in **23** (Scheme 9). Lactone **27** was thus obtained in 92% yield. It was necessary to esterify again the free acid group before performing the next step.[13] When the esterification was performed in our usual conditions (MeOH, $CHCl_3$, H^+),[2a,12] opening of the lactone ring occurred and 64% of ether **28** was isolated. Ether **28** was an

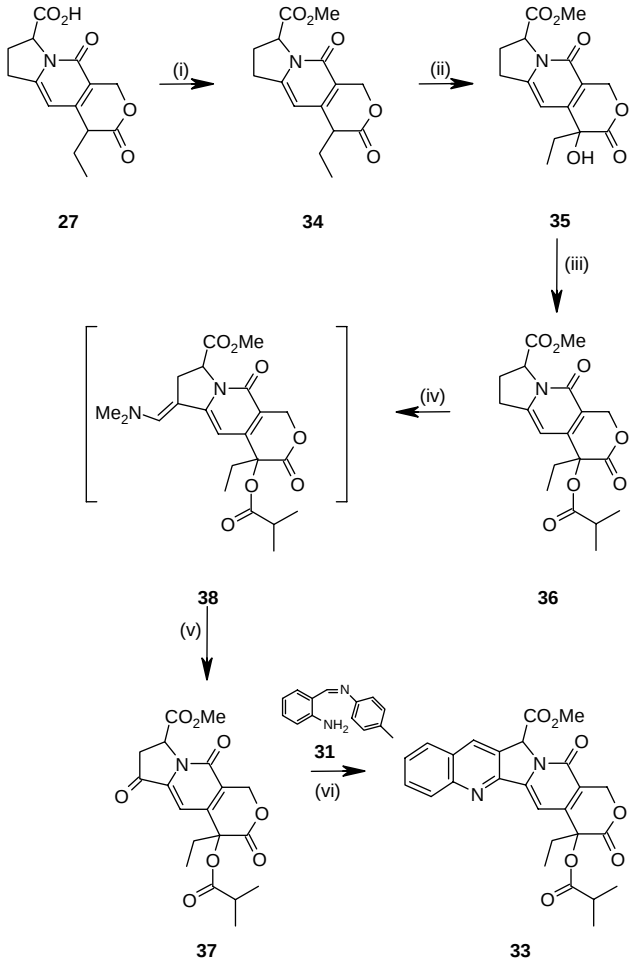


Scheme 9. Reaction conditions: (i) 48% HBr, reflux, 5 h (92%); (ii) MeOH, $CHCl_3$, CH_3SO_3H cat., reflux, 48 h (64%); (iii) *tert*-BuOCH$(NMe_2)_2$, 110 °C, 2 h; (iv) $NaIO_4$, THF, 20 °C, 30 min (80% from **28**); (v) AcOH, reflux, 1 h (70%).

important product because it allowed to test again our synthesis of a ketone group in such indolizines,[1b] and it can also increase the knowledge of the 'crucial' necessity[14] of the E lactone ring of camptothecin analogs. For that reason and following the method developed previously,[2a] reaction of pyridone **28** with Bredereck's reagent {*tert*-BuOCH$(NMe_2)_2$},[15] then $NaIO_4$ oxidation[16] of the intermediate enamide **29** were completed, resulting in 80% yield of ketone **30**. Friedlander reaction[1,17,18] of imine **31**[19,20] with heterocycle **30** in AcOH[1,2a] gave ultimately deoxycamptothecin analog **32** in 70% yield, thus validating this part of the reaction scheme (Scheme 9).

3.3. Formation of 5-methoxycarbonyl camptothecin analog 33

With this sequential protocol in hand, camptothecin analog **33** was now synthesized from the same pyridone **27**. Reaction of this acid, first with oxalyl chloride, then with MeOH, furnished 71% yield of ester **34**. Introduction of the important ternary alcohol group[14a,21] was performed following the method of Wall,[18] by bubbling oxygen in a methanol solution of ethyl lactone **34**, in the presence of potassium carbonate as a base. This led to 95% of lactone **35**. This alcohol was then esterified with isobutyric anhydride in pyridine, giving 73% yield of ester **36**. Formation of this ester was realized not only to protect the hydroxyl group during the next steps, but also to decrease the opening of the lactone ring of camptothecin **33** during the biological screening[22] (Scheme 10).



Scheme 10. Reaction conditions: (i) $(COCl)_2$, CH_2Cl_2, 20 °C, 3 h then MeOH, 20 °C, 3 h (71%); (ii) O_2, K_2CO_3, MeOH, 20 °C, 24 h (95%); (iii) $(i\text{-PrCO})_2O$, Py, 85 °C, 5 h (73%); (iv) *tert*-$BuOCH(NMe_2)_2$, 110 °C, 2 h; (v) $NaIO_4$, THF, 20 °C, 30 min (42% from **36**); (vi) AcOH, reflux, 1 h 67%.

Formation of ketone **37** was obtained following the same method as for pyridone **30**, by reacting the mixture of diastereoisomers of diester **36** first with Bredereck's reagent to give **38**, then with $NaIO_4$. Ketone **37** was thus obtained in 42% crude yield. That compound proved to be rather unstable; after purification by chromatography on a silica gel column, a very low amount of **37** was treated with imine **31** in AcOH, to give the camptothecin analog **33** in 67% yield. Due to the very low amount of **33** isolated, identification of this compound was performed only through NMR and mass spectrometry (Scheme 10).

4. Conclusion

The new camptothecin analog **33** (as a mixture of diastereoisomers) was isolated in low yield of (11%) from pyridone **2**, but the yield from **2** to **32** was of 27%. This justifies that the new methodologies reported herein can be utilized in the camptothecin field, at least when intermediates ketones are stable enough. To be noted in these syntheses are the new conditions for Mannich reaction that lead to high yields, and a new method for the introduction of a keto group in tetrahydroindolizinones. The use of these reaction sequences for the synthesis of other camptothecin analogs, whose biological properties will be tested, will be reported in due course.

5. Experimental

5.1. Materials

Melting points were determined using an Electrothermal apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained on a Varian Gemini 2000 at 200 and 50 MHz, respectively. IR spectra were obtained in ATR mode on a FTIR Bruker Tensor 27. Thin-layer chromatographies were performed on precoated Kieselgel $60F_{254}$ plates. Microanalyses were performed by the 'Service de Microanalyses' of LSEO, Université de Bourgogne, Dijon, France or by the 'Service Central de Microanalyses' of CNRS in Vernaison, France. Methyl pyroglutamate used was racemic.

5.1.1. [3-[(Dimethylamino)carbonyl]-8-(methoxycarbonyl)-5-oxo-1,2,3,5-tetrahydro-7-indolizinyl]acetic acid (8). A stirred mixture of ester **5** (5 g, 0.015 mol) and sodium hydroxide (0.71 g, 0.018 mol) in water (20 mL) was stirred for 30 min. Upon acidification (concd HCl) acid **8** was obtained as a white powder in 89% yield, mp (H_2O): 155–156 °C; TLC R_f (CH_2Cl_2/MeOH, 90:10): 0.20; IR: ν cm^{-1} 3541, 3430, 1753, 1709, 1639, 1608, 1540, 1128; ^1H NMR (D_2O): δ ppm 2.17–2.32 (m, 1H, CH_2CH), 2.53–2.73 (m, 1H, CH_2CH), 2.98 (s, 3H, NCH_3), 3.23 (s, 3H, NCH_3), 3.35–3.67 (m, 2H, CH_2CH_2), 3.83 (s, 3H, CO_2CH_3), 3.91 (s, 2H, CH_2CO), 5.65 (dd, J=9.3, 2.3 Hz, 1H, C*H*CO), 6.42 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ ppm 24.9 (CH_2), 30.2 (CH_2), 35.7 (CH_3), 36.8 (CH_3), 41 (CH_2), 48.7 (CH_3), 60.7 (CH), 116.0 (CH), 118.8 (C), 150.1 (C), 151.2 (C), 151.7 (C), 170.8 (C), 173.1 (C), 177.9 (C). Anal. Calcd for $C_{15}H_{18}N_2O_6$, H_2O: C, 52.94; H, 5.92; N, 8.23. Found: C, 53.16; H, 6.15; N, 8.17.

5.1.2. 2-[3-[(Dimethylamino)carbonyl]-8-(methoxycarbonyl)-5-oxo-1,2,3,5-tetrahydro-7-indolizinyl]-butanoic acid (9). A mixture of diester **6** (2 g, 5.5 mmol) and NaOH (0.24 g, 6.1 mmol) in water (20 mL) was stirred at room temperature for 30 min. The solution was acidified until pH 4 with HCl then the solution was extracted six times with dichloromethane (6×50 mL). The combined organic phases were dried (Na_2SO_4) then evaporated, giving the mixture of diastereoisomers **9** as a white powder (78%), mp (acetone): 157–159 °C; TLC R_f (CH_2Cl_2/MeOH, 80:20): 0.27; IR: ν cm^{-1} 3430, 1728, 1656, 1640, 1567, 1523, 1441, 1209; ^1H NMR ($CDCl_3$): δ ppm 0.96 and 0.97 (2t, J= 7.4 Hz, 3H, CH_2CH_3), 1.59–1.87 (m, 1H, CH_2CH$_3$), 1.98–2.28 (m, 2H, CH_2CH$_2$, CH_2CH$_3$), 2.28–2.52 (m, 1H, CH_2CH$_2$), 2.99 and 3.00 (2s, 3H, NCH_3), 3.21 (s, 3H, NCH_3), 3.33–3.75 (m, 2H, CH_2CH$_2$), 3.84 and 3.87 (2s, 3H, CO_2CH_3), 3.90 and 4.09 (dd, J=7.6, 6.6 Hz and dd, J=8.0, 6.0 Hz, 1H, C*H*CH$_2$), 5.49 and 5.54 (dd, J=5.9, 2.3 Hz and dd, J=5.9, 2.2 Hz, 1H, C*H*CH$_2$), 6.48 and 6.49 (2s, 1H, Ar*CH*); ^{13}C NMR ($CDCl_3$): δ ppm 12.4 (CH_3), 25.5 ($2CH_2$), 33.7 (CH_3), 36.0 (CH_2), 37.2 (CH_3), 50.0 (CH), 51.7 (CH_3), 59.5 (CH), 107.3 (C), 117.1 (CH), 152.8 (C), 157.0 (C), 160.8 (C), 166.1 (C), 168.8 (C), 175.0 (C). Anal. Calcd for $C_{17}H_{22}N_2O_6$, $0.5H_2O$: C, 56.82; H, 6.45; N, 7.79. Found: C, 56.45; H, 6.73; N, 7.41.

5.1.3. Methyl 7-[2-(chloromethoxy)-2-oxoethyl]-3-[(dimethylamino)carbonyl]-5-oxo-1,2,3,5-tetrahydro-8-indolizinecarboxylate (11). Oxalyl chloride (0.2 mL, 0.29 g, 2.29 mmol) was added with a syringe to a stirred mixture of acid **8** (0.5 g, 1.55 mmol) and DMF (3 drops) in chloroform (10 mL). The solution was stirred for 30 min then evaporated. Chlorobenzene (10 mL), paraformaldehyde (0.1 g, 3.67 mmol) then $AlCl_3$ (1.2 g, 8.8 mmol) were added to the solution. After reflux for 24 h, dichloromethane (100 mL) and water (10 mL) were added. The organic phase was dried (Na_2SO_4) then evaporated leading to compound **11** (~20%) as an impure oil, which was used directly in the next step; ^{1}H NMR ($CDCl_3$): δ ppm 1.84–2.20 (m, 1H, CH_2CH$_2$), 2.30–2.58 (m, 1H, CH_2CH$_2$), 3.00 (s, 3H, NCH_3), 3.23 (s, 3H, NCH_3), 3.52–3.69 (m, 2H, CH_2CH$_2$), 3.70 (d, J=16.5 Hz, 1H, CH_2CO), 3.79 (s, 3H, CO$_2$CH_3), 4.02 (d, J=16.5 Hz, 1H, CH_2CO), 5.31 (dd, J=9.6, 2.2 Hz, 1H, CHCO), 5.73 (s, 2H, CH_2Cl), 6.28 (s, 1H, ArCH); ^{13}C NMR ($CDCl_3$): δ ppm 25.4 (CH_2), 34.1 (CH_2), 36.0 (CH_3), 37.2 (CH_3), 41.3 (CH_2), 51.7 (CH_3), 59.6 (CH), 77.05 (CH_2), 106.0 (C), 120.5 (CH), 146.7 (C), 158.7 (C), 160.3 (C), 165.5 (C), 168.4 (C), 168.8 (C).

5.1.4. Methyl 3-[(dimethylamino)carbonyl]-7-{2-[(methylsulfanyl)methoxy]-2-oxoethyl}-5-oxo-1,2,3,5-tetrahydro-8-indolizinecarboxylate (13). *tert*-Butyl bromide (7 mL, 62 mmol) in dimethyl sulfoxide (200 mL) was added to a stirred suspension of acid **8** (2 g, 6.2 mmol) and sodium hydrogencarbonate (5.2 g, 62 mmol). The mixture was stirred at room temperature for 24 h then water (100 mL) was added. The aqueous phase was extracted with dichloromethane (2×150 mL). The combined organic phases were washed with brine (3×100 mL), then dried (Na_2SO_4) and evaporated. The oil obtained crystallized from ethyl acetate, giving amide **13** as a white powder (84%), mp (EtOAc): 72–74 °C; TLC R_f (MeOH/CH_2Cl_2, 5:95): 0.42; IR: ν cm^{-1} 1745, 1710, 1660, 1590, 1515, 1440, 1150; ^{1}H NMR ($CDCl_3$): δ ppm 2.13–2.29 (m, 1H, CH_2CH$_2$), 2.24 (s, 3H, SCH_3), 2.30–2.51 (m, 1H, CH_2CH$_2$), 3.00 (s, 3H, NCH_3), 3.23 (s, 3H, NCH_3), 3.55–3.69 (m, 2H, CH_2CH$_2$), 3.67 (d, J=16.9 Hz, 1H, CH_2CO), 3.80 (s, 3H, CO$_2$CH_3), 4.01 (d, J=16.9 Hz, 1H, CH_2CO), 5.17 (s, 2H, OCH_2S), 5.52 (dd, J=9.5, 2.3 Hz, 1H, CHCO), 6.33 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ ppm 15.3 (CH_3), 25.3 (CH_2), 33.9 (CH_2), 35.8 (CH_3), 37.0 (CH_3), 41.4 (CH_2), 51.4 (CH_3), 59.4 (CH), 68.5 (CH_2), 106.2 (C), 120.0 (CH), 147.4 (C), 158.2 (C), 160.2 (C), 165.5 (C), 168.7 (C), 169.8 (C). Anal. Calcd for $C_{17}H_{22}N_2O_6S$: C, 53.39; H, 5.80; N, 7.32; S, 8.38. Found: C, 53.31; H, 6.13; N, 7.63; S, 8.04.

5.1.5. Methyl 3-[(dimethylamino)carbonyl]-7-(1-{[(methylsulfanyl)methoxy]carbonyl}propyl)-5-oxo-1,2,3,5-tetrahydro-8-indolizinecarboxylate (14). *tert*-Butyl bromide (6.4 mL, 57 mmol) in dimethyl sulfoxide (10 mL, 11 g, 141 mmol) was added to a stirred suspension of acid **9** (2 g, 5.7 mmol) and sodium hydrogencarbonate (4.8 g, 57 mmol) in dichloromethane (30 mL). The mixture was refluxed for 12 h, cooled at room temperature then water (50 mL) was added. The aqueous phase was extracted with dichloromethane (5×100 mL). The combined organic phases were washed with brine (3×100 mL) then dried (Na_2SO_4) and evaporated. The oil obtained crystallized from ethyl acetate, giving amide **14** as a white powder (77%), mp (EtOAc): 83–85 °C; TLC ($C_{18}SiO_2$) R_f (MeOH/H_2O, 60:40): 0.4; IR: ν cm^{-1} 1746, 1712, 1659, 1589, 1519, 1439, 1152; ^{1}H NMR ($CDCl_3$): δ ppm 0.97 (t, J=7.3 Hz, 3H, CH$_2$CH_3), 1.65–1.86 (m, 1H, CH_2CH$_3$), 1.98–2.31 (m, 2H, CH_2CH$_3$, CH_2CH$_2$), 2.18 (s, 3H, SCH_3), 2.31–2.53 (m, 1H, CH_2CH), 3.00 (s, 3H, NCH_3), 3.23 (s, 3H, NCH_3), 3.34–3.73 (m, 2H, CH_2CH$_2$), 3.83 (s, 3H, CO$_2$CH_3), 4.08 (t, J=7.0 Hz, 1H, CHCO$_2$), 5.06 (d, J=11.8 Hz, 1H, OCH_2S), 5.18 (d, J=11.8 Hz, 1H, OCH_2S), 5.49 (dd, J=9.3, 2.2 Hz, 1H, CHCON), 6.38 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ ppm 12.4 (CH_3), 15.3 (CH_3), 25.5 (CH_2), 33.9 (CH_2), 36.0 (CH_3, CH_2), 37.2 (CH_3), 50.1 (CH_3), 51.6 (CH), 59.4 (CH), 66.6 (CH_2), 106.6 (C), 117.4 (CH), 152.0 (C), 157.3 (C), 160.4 (C), 165.8 (C), 168.8 (C), 171.9 (C). Anal. Calcd for $C_{19}H_{26}N_2O_6S$: C, 55.59; H, 6.38; N, 6.82; S, 7.81. Found: C, 55.75; H, 6.51; N, 6.93; S, 7.35.

5.1.6. Methyl 6-bromo-3-[(dimethylamino)carbonyl]-7-{2-[(methylsulfinyl)methoxy]-2-oxoethyl}-5-oxo-1,2,3,5-tetrahydro-8-indolizinecarboxylate (15). Bromine (0.017 g, 0.20 mmol) in dichloromethane (2.2 mL) was added to amide **13** (0.050 g, 0.11 mmol) and potassium hydrogenocarbonate (0.040 g, 0.40 mmol) in methylene dichloride (2 mL) and water (2 mL). The mixture was stirred for 15 h, methylene dichloride (10 mL) was added, and the aqueous layer was extracted with methylene dichloride (10 mL). The combined organic phases were dried (Na_2SO_4), then evaporated giving 92% of **15** as a mixture of two isomers (purity estimated by NMR ~95%); this compound was only checked by NMR. ^{1}H NMR ($CDCl_3$): δ ppm 2.13–2.33 (m, 1H, CH_2CH$_2$), 2.33–2.51 (m, 1H, CH_2CH$_2$), 2.66 and 2.67 (2s, 3H, SCH_3), 3.00 (s, 3H, NCH_3), 3.26 (s, 3H, NCH_3), 3.38–3.78 (m, 2H, CH_2CH$_2$), 3.82 and 3.83 (2s, 3H, CO$_2$CH_3), 4.30 (s) and 4.31 (d, J=1.0 Hz) (2H, CH_2CO), 5.02 and 5.03 (2d, J=10.4 Hz, 1H, OCH_2S), 5.10 and 5.12 (2d, J=10.4 Hz, 1H, OCH_2S), 5.57 (dd, J=9.6 Hz, 1H, CHCO); ^{13}C NMR ($CDCl_3$): δ ppm 25.5 (CH_2), 34.3 (CH_2), 36.0 (CH_3), 36.1 (CH_3), 37.3 (CH_3), 40.9 (CH_2), 52.1 (CH_3), 60.7 (CH), 78.6 (CH_2), 107.0 and 107.1 (C), 118.4 (C), 145.2 and 145.3 (C), 156.2 and 156.9 (2C), 165.2 and 165.3 (C), 168.1 (C), 168.7 and 169.8 (C).

5.1.7. Methyl 3-[(dimethylamino)carbonyl]-7-(1-{[(methylsulfanyl)methoxy]carbonyl}propyl)-5-oxo-1,2,3,5-tetrahydro-8-indolizinecarboxylate (16). Sodium periodate (1.25 g, 5.84 mmol) was added to a stirred solution of amide **14** (2 g, 4.87 mmol) in a mixture of methanol (30 mL) and water (30 mL). After stirring at room temperature for 12 h solvents were evaporated and the residue was dissolved in dichloromethane (100 mL). The solution was washed with water (50 mL), the aqueous phase was extracted with dichloromethane (3×50 mL), the combined organic phases were dried (Na_2SO_4) then evaporated. The residue crystallized from ethyl acetate, giving a mixture of three isomers of **16** as a white powder (86%), mp (EtOAc): 142–144 °C; TLC ($C_{18}SiO_2$) R_f (MeOH/H_2O, 60:40): 0.51; IR: ν cm^{-1} 1746, 1716, 1644, 1591, 1523, 1436, 1187, 1016; ^{1}H NMR ($CDCl_3$): δ ppm 0.96 and 0.97 (t, J=7.4 Hz, 3H, CH_3CH$_2$), 1.65–1.91 (m, 1H, CH$_3$CH_2), 2.01–2.28 (m, 2H, CH$_3$CH_2, CH$_2$CH_2), 2.28–2.49 (m, 1H, CH$_2$CH_2), 2.56, 2.58 and 2.60 (3s, 3H, SCH_3), 3.00 and 3.01 (2s, 3H, NCH_3), 3.23 (s, 3H, NCH_3), 3.36–3.74 (m, 2H, CH_2CH$_2$), 3.81, 3.82 and 3.83 (3s, 3H,

CO_2CH_3), 4.14 and 4.17 (2t, $J=6.8$ Hz, 1H, $CHCO_2$), 4.87, 4.98, 5.03, 5.06 (4d, $J=10.3$ Hz, 2H, OCH_2S), 5.50 (dd, $J=$ 9.4, 2.2 Hz, 1H, CHCON), 6.33, 6.34 and 6.36 (3s, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ ppm 12.2 and 12.3 (CH_3), 24.9 and 25.3 and 25.4 (CH_2), 34.0 (CH_2), 35.9 ($2CH_3$, CH_2), 37.1 (CH_3), 49.6 (CH), 50.5 and 51.7 (CH_3), 59.5 (CH), 78.3 and 78.7 (CH_2), 105.8 and 106.1 (C), 117.5 and 118.1 (CH), 151.1 and 151.3 (C), 157.7 and 157.8 (C), 160.2 (C), 165.7 (C), 168.6 (C), 171.0 and 171.2 (C). Anal. Calcd for $C_{19}H_{26}N_2O_7S$: C, 53.51; H, 6.14; N, 6.57; S, 7.52. Found: C, 53.14; H, 6.40; N, 6.21; S, 7.15.

5.1.8. Methyl 3-[(dimethylamino)carbonyl]-7-{2-[(methylsulfonyl)methoxy]-2-oxoethyl}-5-oxo-1,2,3,5-tetrahydro-8-indolizinecarboxylate (17). The synthesis of this compound was performed from compound **13**, using the same method as for **18**. The product crystallized from ethyl acetate, giving sulfone **17** as a white powder (95%), mp (EtOAc): 136–138 °C; TLC ($C_{18}SiO_2$) R_f (MeOH/H_2O, 60:40): 0.5; IR: ν cm^{-1} 1770, 1710, 1675, 1645, 1595, 1525, 1445, 1100; ^{1}H RMN ($CDCl_3$): δ ppm 2.12–2.29 (m, 1H, CH_2CH_2), 2.29–2.55 (m, 1H, CH_2CH_2), 2.98 (s, 3H, SCH_3), 3.00 (s, 3H, NCH_3), 3.20 (s, 3H, NCH_3), 3.52–3.67 (m, 2H, CH_2CH_2), 3.77 (d, $J=17.3$ Hz, 1H, CH_2CO), 3.79 (s, 3H, CO_2CH_3), 4.09 (d, $J=17.3$ Hz, 1H, CH_2CO), 5.03 (d, $J=12.6$ Hz, 1H, OCH_2S), 5.12 (d, $J=12.6$ Hz, 1H, OCH_2S), 5.52 (dd, $J=9.6$, 2.1 Hz, 1H, CHCO), 6.28 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ ppm 24.4 (CH_2), 33.4 (CH_2), 35.0 (CH_{32}), 36.2 (CH_3), 38.6 (CH_3), 39.9 (CH_3), 50.8 (CH_3), 58.8 (CH), 74.4 (CH_2), 104.6 (C), 119.5 (CH), 145.8 (C), 157.9 (C), 159.2 (C), 164.8 (C), 167.8 (C), 168.0 (C). Anal. Calcd for $C_{17}H_{22}N_2O_8S$, $3/2H_2O$: C, 46.25; H, 5.71; N, 6.35; S, 7.26. Found: C, 46.67; H, 5.37; N, 6.36; S, 7.69.

5.1.9. Methyl 3-[(dimethylamino)carbonyl]-7-(1-{[(methylsulfonyl)methoxy]carbonyl}propyl)-5-oxo-1,2,3,5-tetrahydro-8-indolizinecarboxylate (18). Magnesium monoperoxyphtalate (1.27 g, 2.58 mmol) was added to a stirred solution of amide **14** (1 g, 2.35 mmol) in methanol (15 mL). After stirring at room temperature for 12 h solvent was evaporated, and the residue was dissolved in dichloromethane (100 mL). The solution was washed with water (50 mL), the aqueous phase was extracted with dichloromethane (3×50 mL) and the combined organic phases were dried (Na_2SO_4) then evaporated. The residue crystallized from ethyl acetate, giving sulfone **18** as a white powder (92%), mp (EtOAc): 161–163 °C; TLC ($C_{18}SiO_2$) R_f (MeOH/H_2O, 60:40): 0.54; IR: ν cm^{-1} 1746, 1717, 1644, 1590, 1523, 1436, 1277, 1186; ^{1}H RMN ($CDCl_3$): δ ppm 0.96 and 0.97 (2t, $J=7.4$ Hz, 3H, CH_3CH_2), 1.70–1.94 (m, 1H, CH_3CH_2), 2.05–2.30 (m, 2H, CH_3CH_2, CH_2CH_2), 2.30–2.56 (m, 1H, CH_2CH_2), 2.90 and 2.93 (2s, 3H, SCH_3), 3.00 (s, 3H, NCH_3), 3.23 and 3.26 (2s, 3H, NCH_3), 3.39–3.72 (m, 2H, CH_2CH_2), 3.80 and 3.82 (2s, 3H, CO_2CH_3), 4.12 and 4.14 (2t, $J=7.3$ Hz, 1H, $CHCO_2$), 5.02 and 5.03 (2s, 2H, OCH_2S), 5.51 and 5.57 (2dd, $J=9.5$, 2.0 Hz, 1H, CHCON), 6.35 and 6.38 (2s, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ ppm 12.2 (CH_3), 24.8 and 25.3 (CH_2), 34.1 (CH_2), 35.9 ($2CH_3$), 37.1 (CH_2), 39.6 (CH_3), 50.1 (CH), 51.7 (CH_3), 59.6 (CH), 75.3 (CH_2), 105.8 (C), 118.0 (CH), 150.9 (C), 158.0 (C), 160.2 (C), 165.8 (C), 168.6 (C), 170.3 (C). Anal. Calcd for $C_{19}H_{26}N_2O_8S$: C, 51.57; H, 5.92; N, 6.33; S, 7.25. Found: C, 51.65; H, 6.04; N, 6.75; S, 7.10.

5.1.10. Dimethyl 4-ethyl-3,10-dioxo-3,4,6,7,8,10-hexahydro-1*H*-pyrano[3,4-*f*]indolizine-5,8-dicarboxylate (22) and methyl 3a-ethyl-1,4,7-trioxo-3a,4,7,8,9,10-hexahydro-1*H*,3*H*,6*H*-2,5-dioxa-7a-azacyclopenta[*a*]phenalene-8-carboxylate (24). A stirred mixture of triester **2** (5 g, 14.2 mmol), acetic acid (15 mL), 34% HCl (5 mL) and paraformaldehyde (1.28 g, 42.6 mmol) was heated at 80 °C for 24 h then the solution was evaporated giving crude acid **23**. The residue was dissolved in methanol (300 mL) and chloroform (200 mL). Methane sulfonic acid (2 drops) was added and the solution was refluxed for 24 h while drying the distillate by condensing it in a soxhlet-type apparatus containing 3 Å molecular sieves (50 g). Dichloromethane (200 mL) was added to the residue obtained upon evaporation, and the solution was washed with a $NaHCO_3$ solution. The organic phase was dried then evaporated. The residue was dissolved in hot ethyl acetate and crystallization gave lactone **22** as a white mixture of diastereoisomers (84%), mp (EtOAc): 145–147 °C; TLC R_f (EtOAc): 0.7; IR: ν cm^{-1} 1745, 1715, 165, 1595, 1545, 1440, 1205; ^{1}H NMR ($CDCl_3$): ppm 1.10 and 1.11 (2t, $J=7.4$ Hz, 3H, CH_3CH_2), 1.73–2.05 (m, 2H, CH_3CH_2), 2.25–2.44 (m, 1H, CH_2CH_2), 2.44–2.65 (m, 1H, CH_2CH_2), 3.41–3.64 (m, 2H, CH_2CH_2), 3.81 and 3.82 (2s, 3H, $CHCO_2CH_3$), 3.87 (s, 3H, $ArCO_2CH_3$), 4.34 and 4.42 (2dd, $J=9.3$, 4.9 Hz, 1H, $ArCHCH_2$), 5.07–5.24 (m, 2H, $ArCH_2O$, $CHCO_2$), 5.45 and 5.49 (2d, $J=15.9$ Hz, 1H, $ArCH_2O$); ^{13}C NMR ($CDCl_3$): δ ppm 11.7 (CH_3), 24.9 and 25.0 (CH_2), 25.2 and 25.4 (CH_2), 33.4 (CH_2), 44.0 and 44.2 (CH), 51.8 (CH_3), 52.8 (CH_3), 61.7 (CH), 64.4 (CH_2), 104.8 (C), 118.7 (C), 147.9 and 148.0 (C), 156.6 (C), 156.9 and 157.2 (C), 164.6 (C), 169.5 and 169.8 (C), 170.8 and 170.9 (C). Anal. Calcd for $C_{17}H_{19}NO_7$: C, 58.45; H, 5.48; N, 4.01. Found: C, 58.49; H, 5.68; N, 4.29.

The ethyl acetate solution remaining after crystallization of lactone **22** was purified by chromatography on SiO_2 column (EtOAc), giving dilactone **24** as a white mixture of diastereoisomers (up to 6%), mp (EtOAc): 162–164 °C; TLC R_f (EtOAc): 0.63; IR: ν cm^{-1} 1745, 1725, 1655, 1565, 1525, 1435, 1205; this compound was not submitted to elemental analysis; ^{1}H NMR ($CDCl_3$): δ ppm 1.10 and 1.12 (2t, $J=7.6$ Hz, 3H, CH_2CH_3), 1.78–2.17 (m, 2H, CH_2CH_3), 2.29–2.51 (m, 1H, CH_2CH_2), 2.51–2.74 (m, 1H, CH_2CH_2), 3.15–4.04 (m, 2H, CH_2CH_2), 3.83 (s, 3H, CO_2CH_3), 4.35 and 4.42 (2dd, $J=11.9$, 0.6 Hz, 1H, OCH_2), 4.72 and 4.73 (2d, $J=11.9$ Hz, 1H, OCH_2), 5.12–5.24 (m, 1H, $CHCO_2$), 5.22 and 5.25 (2dt, $J=16.0$, 1.2 Hz, 1H, $ArCH_2$), 5.46 and 5.49 (2d, $J=16.0$ Hz, 1H, $ArCH_2$); ^{13}C NMR ($CDCl_3$): δ ppm 9.1 and 11.6 (CH_3), 25.6 and 25.7 (CH_2), 26.8 and 27.3 (CH_2), 32.4 and 32.7 (CH_2), 42.4 and 42.5 (C), 53.0 and 53.2 (CH_3), 61.9 and 62.1 (CH), 65.7 (CH_2), 68.6 (CH_2), 98.5 and 98.6 (C), 115.6 (C), 146.7 and 146.8 (C), 156.9 and 157.3 (C), 160.7 and 161.7 (C), 168.5 and 168.7 (C), 169.6 and 169.7 (C), 170.1 (C).

5.1.11. 4-Ethyl-3,10-dioxo-3,4,6,7,8,10-hexahydro-1*H*-pyrano[3,4-*f*]indolizine-8-carboxylic acid (27). A stirred solution of lactone **22** (5 g, 14.2 mmol) in 48% hydrobromic acid (30 mL) was heated at 135 °C for 5 h then evaporated. The residue crystallized from acetone, giving 92% of acid **27** as white crystals, mp (acetone): 203–205 °C; TLC R_f (CH_3OH): 0.6; IR: ν cm^{-1} 1745, 1740, 1645, 1575, 1545, 1470, 1445, 1205; ^{1}H NMR (DMSO-d_6): δ ppm 0.96 and

0.98 (2t, $J=7.3$ Hz, 3H, CH_2CH_3), 1.93 (quint, $J=7.2$ Hz, 2H, CH_2CH_3), 2.14–2.31 (m, 2H, CH_2CH_2), 3.14 (dd, $J=9.1$, 6.1 Hz, 2H, CH_2CH_2), 3.60 (t, $J=6.6$ Hz, 1H, $CHCH_2$), 4.97 and 4.99 (2dd, $J=9.7$, 3.0 Hz, 1H, $CHCO_2$), 5.16 (d, $J=15.3$ Hz, 1H, CH_2O), 5.31 (d, $J=15.3$ Hz, 1H, CH_2O), 6.28 (s, 1H, Ar*H*); ^{13}C NMR (DMSO-d_6): δ ppm 11.1 and 11.3 (CH_3), 23.2 (CH_2), 25.7 (CH_2), 30.2 (CH_2), 44.7 (CH), 61.2 (CH), 64.9 (CH_2), 99.4 (CH), 116.5 and 116.6 (C), 147.4 (C), 151.3 (C), 157.2 (C), 171.0 (C), 171.3 (C). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.45; N, 5.05. Found: C, 60.27; H, 5.62; N, 5.04.

5.1.12. Methyl 7-[1-(methoxycarbonyl)propyl]-6-(methoxymethyl)-5-oxo-1,2,3,5-tetrahydro-3-indolizinecarboxylate (28). A stirred solution of acid **27** (3 g, 10.8 mmol) and methanesulfonic acid (0.44 g, 0.3 mL, 4.6 mmol) in methanol (300 mL) and chloroform (200 mL) was refluxed for 48 h while drying the solvent by condensing it in a soxhlet-type apparatus containing 3 Å molecular sieves (50 g). Dichloromethane (200 mL) was added to the residue obtained upon evaporation, and the solution was washed with a $NaHCO_3$ solution. The organic phase was dried then evaporated. The residue was purified by chromatography on SiO_2 column (EtOAc), giving the diester **28** as a colorless oil (64%); TLC R_f (EtOAc): 0.63; IR: ν cm^{-1} 1740, 1655, 1600, 1545, 1435, 1205; ^{1}H NMR ($CDCl_3$): 0.91 and 0.93 (2t, $J=7.5$ Hz, 3H, CH_3CH_2), 1.55–1.83 (m, 1H, CH_3CH_2), 1.91–2.16 (m, 1H, CH_3CH_2), 2.16–2.37 (m, 1H, CH_2CH_2), 2.37–2.63 (m, 1H, CH_2CH_2), 3.06 (ddd, $J=16.6$, 8.2, 4.3 Hz, 1H, CH_2CH_2), 3.18 (dd, $J=16.6$, 8.2 Hz, 1H, CH_2CH_2), 3.33 and 3.34 (2s, 3H, OCH_3), 3.67 and 3.68 (2s, 3H, $ArCHOCH_3$), 3.78 (s, 3H, CH_2CHOCH_3), 3.91 and 3.92 (2t, $J=7.6$ Hz, 1H, ArC*H*), 4.48 and 4.49 (2d, $J=11.0$ Hz, 1H, $ArCH_2$), 4.56 and 4.59 (2d, $J=11.0$ Hz, 1H, $ArCH_2$), 5.05 and 5.06 (2dd, $J=9.3$, 3.6 Hz, 1H, NC*H*), 6.22 and 6.24 (2s, 1H, ArC*H*); ^{13}C NMR ($CDCl_3$): δ ppm 11.6 and 11.7 (CH_3), 25.2 and 25.4 (CH_2), 25.7 (CH_2), 30.1 (CH_2), 47.9 (CH), 51.6 and 51.7 (CH_3), 52.2 (CH_3), 57.3 and 57.4 (CH_3), 61.1 (CH), 64.2 (CH_2), 99.7 (CH), 122.8 and 122.9 (C), 149.0 (C), 151.9 and 152.0 (C), 160.9 (C), 170.2 (C), 172.9 and 173.0 (C). Anal. Calcd for $C_{17}H_{23}NO_6$, $0.5H_2O$: C, 58.95; H, 6.98; N, 4.04. Found: C, 58.80; H, 6.61; N, 4.06.

5.1.13. Methyl 7-[1-(methoxycarbonyl)propyl]-6-(methoxymethyl)-1,5-dioxo-1,2,3,5-tetrahydro-3-indolizinecarboxylate (30). A stirred mixture of diester **28** (1 g, 5.9 mmol) and Bredereck's reagent (1.44 g, 8.3 mmol) was heated to 110 °C for 2 h (N_2), giving formation of enamine **29**. After cooling at room temperature, tetrahydrofuran (10 mL) and water (10 mL) were added. When a homogenous solution was obtained, sodium metaperiodate (3.8 g, 17.7 mmol) was added and the mixture was stirred for 30 min. The solid was filtered then washed with dichloromethane. The filtrate was extracted with dichloromethane, the combined organic phases were dried (Na_2SO_4) then evaporated. The residue was purified by chromatography on SiO_2 column (EtOAc), giving ketone **30** as an orange oil in a crude yield of 80%; TLC R_f (EtOAc): 0.57; due to its low stability this compound was analyzed only by NMR; ^{1}H NMR ($CDCl_3$): 0.91 and 0.95 (2t, $J=7.3$ Hz, 3H, CH_2CH_3), 1.60–1.96 (m, 1H, CH_2CH_3), 1.99–2.22 (m, 1H, CH_2CH_3), 2.84 (dd, $J=19.5$, 3.7 Hz, 1H, $COCH_2$), 3.19 and 3.20 (2dd, $J=19.5$, 9.3 Hz, 1H, $COCH_2$), 3.36 and 3.38 (2s, 3H, OCH_3), 3.68 and 3.70 (2s, 3H, $ArCHCO_2CH_3$), 3.83 and 3.84 (2s, 3H, $NCHCO_2CH_3$), 4.01 and 4.03 (2t, $J=7.6$ Hz, 1H, ArC*H*), 4.55 and 4.56 (2d, $J=11.3$ Hz, 1H, CH_2O), 4.63 and 4.65 (2d, $J=11.3$ Hz, 1H, CH_2O), 5.18 and 5.19 (2dd, $J=9.3$, 3.7 Hz, 1H, NC*H*), 7.00 and 7.02 (2s, 1H, Ar*H*).

5.1.14. Methyl 7-[1-(methoxycarbonyl)propyl]-8-(methoxymethyl)-9-oxo-9,11-dihydroindolizino[1,2-*b*]-quinoline-11-carboxylate (32). A stirred solution of ketone **30** (1 g, 2.85 mmol) and imine **31** (0.72 g, 3.42 mmol) in acetic acid (10 mL) was refluxed for 1 h (N_2). After cooling at room temperature, water (50 mL) was added then the solution was extracted with methylene dichloride. The organic phase was washed with brine then with a solution of $NaHCO_3$. After drying (Na_2SO_4), the solution was evaporated and the residue was purified by chromatography on SiO_2 column (EtOAc), giving the diester **32** as a white powder (70%), mp (EtOAc): 221–222 °C; TLC R_f (EtOAc): 0.56; IR: ν cm^{-1} 1735, 1660, 1615, 1535, 1435, 1205; ^{1}H NMR ($CDCl_3$): δ ppm 0.97 and 1.02 (2t, $J=7.3$ Hz, 3H, CH_2CH_3), 1.79–2.03 (m, 1H, CH_2CH_3), 2.12–2.36 (m, 1H, CH_2CH_3), 3.41 and 3.42 (2s, 3H, CH_2OCH_3), 3.71 and 3.74 (2s, 3H, CO_2CH_3), 3.84 and 3.85 (2s, 3H, $ArCO_2CH_3$), 4.09 and 4.10 (2t, $J=7.4$ Hz, 1H, CH_2CH), 4.65 and 4.66 (2d, $J=11.0$ Hz, 1H, OCH_2), 4.73 and 4.74 (2d, $J=11.0$ Hz, 1H, OCH_2), 6.06 and 6.07 (2d, $J=1.2$ Hz, 1H, NC*H*), 7.39 and 7.41 (2s, 1H, CHAr*H*), 7.65 (td, $J=6.9$, 1.3 Hz, 1H, Ar*H*), 7.83 (td, $J=6.9$, 1.6 Hz, 1H, Ar*H*), 7.93 (dd, $J=8.2$, 1.2 Hz, 1H, Ar*H*), 8.22 (br d, $J=8.6$ Hz, 1H, Ar*H*), 8.42 (br s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ ppm 11.9 and 12.1 (CH_3), 25.5 and 25.7 (CH_2), 48.7 (CH), 52.1 and 52.2 (CH_3), 53.3 (CH_3), 57.9 and 58.0 (CH_3), 62.6 (CH), 64.6 and 64.7 (CH_2), 100.4 (CH), 127.5 (C), 127.6 (C), 127.8 (CH), 128.2 (CH), 129.7 (CH), 130.8 (CH), 130.9 (CH), 144.2 (2C), 149.3 (C), 152.6 (2C), 160.6 (C), 166.5 (C), 172.8 (C). Anal. Calcd for $C_{24}H_{24}N_2O_6$, $0.5H_2O$: C, 64.71; H, 5.66; N, 6.29. Found: C, 64.45; H, 5.43; N, 6.21.

5.1.15. Methyl 4-ethyl-4-(isobutyryloxy)-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-12-carboxylate (33). A stirred solution of ketone **37** (0.1 g, 0.25 mmol) and imine **31** (0.065 g, 0.3 mmol) in acetic acid (1 mL) was refluxed for 1 h (N_2). After cooling at room temperature, water (5 mL) was added then the solution was extracted with dichloromethane. The organic phases were washed with brine then with a solution of $NaHCO_3$. After drying (Na_2SO_4) the solution was evaporated and the residue purified by chromatography on SiO_2 column (EtOAc) giving the diester **32** as a orange oil at 67% yield of crude compound; identification of **32** was obtained through NMR and mass spectra; TLC R_f (EtOAc): 0.53; MS (CI): $m/z=477$ [$M^+ + 1$]; ^{1}H RMN ($CDCl_3$): δ ppm 1.01 and 1.05 (2t, $J=7.4$ Hz, 3H, CH_2CH_3), 1.28 and 1.30 (2d, $J=6.8$ Hz, 6H, $C(CH_3)_2$), 2.20–2.30 (m, 2H, CH_2CH_3), 3.05–3.22 (m, 1H, $CH(CH_3)_2$), 3.80 and 3.83 (2s, 3H, CO_2CH_3), 5.37 and 5.41 (2d, $J=17.5$ Hz, 1H, CH_2O), 5.65 and 5.68 (2d, $J=17.5$ Hz, 1H, CH_2O), 6.07 and 6.09 (2d, $J=1.3$ Hz, 1H, CHCO), 7.17 and 7.18 (2s, 1H, CHAr*H*), 7.69 (td, $J=7$, 1.3 Hz, 1H, Ar*H*), 7.86 (td, $J=6.7$, 1.8 Hz, 1H, Ar*H*), 7.95 (br d, $J=8.0$ Hz, 1H, Ar*H*), 8.22 (br d, $J=8.4$ Hz, 1H, Ar*H*), 8.46 (br s, 1H, Ar*H*).

5.1.16. Methyl 4-ethyl-3,10-dioxo-3,4,6,7,8,10-hexahydro-1*H*-pyrano[3,4-*f*]indolizine-8-carboxylate (34). Oxalyl chloride (2.3 mL, 27 mmol) was dropped at room temperature into a stirred suspension of acid **27** (5 g, 18 mmol) in dichloromethane (20 mL) then the mixture was stirred for 3 h. Toluene (50 mL) was added and the solution was evaporated. Dichloromethane (30 mL) was added, then methanol (5 mL) in dichloromethane (20 mL) was dropped into the solution. After stirring for 3 h the solution was evaporated and dichloromethane (50 mL) was added. The solution was washed with a solution of $NaHCO_3$. The organic phase was dried then evaporated. The residue crystallized from toluene, giving lactone **34** as a white powder (71%), mp (toluene): 143–145 °C; TLC R_f (EtOAc): 0.34; IR: ν cm^{-1} 1745, 1660, 1600, 1570, 1435, 1210; ^1H NMR ($CDCl_3$): 1.02 and 1.05 (t, $J=7.3$ Hz, 3H, CH_2CH_3), 1.85–2.05 (m, 2H, CH_2CH_3), 2.25–2.43 (m, 1H, CH_2CH_2), 2.43–2.67 (m, 1H, CH_2CH_2), 3.00–3.31 (m, 2H, CH_2CH_2), 3.38 and 3.41 (t, $J=7.3$ Hz, 1H, ArCH), 3.81 and 3.82 (2s, 3H, CO_2CH_3), 5.11 and 5.14 (2dd, $J=9.3$, 3.4 Hz, 1H, NCH), 5.23 and 5.24 (2d, $J=15.7$ Hz, 1H, CH_2O), 5.39 and 5.40 (2d, $J=15.7$ Hz, 1H, CH_2O, ArH), 6.03 (br s, 1H); ^{13}C NMR ($CDCl_3$): 11.2 and 11.4 (CH_3), 24.8 and 24.9 (CH_2), 26.2 and 26.3 (CH_2), 30.4 (CH_2), 45.6 and 46.0 (CH), 52.9 (CH_3), 61.1 (CH), 65.7 (CH_2), 100.2 and 100.4 (CH), 117.5 and 117.7 (C), 147.4 and 147.6 (C), 150.3 (C), 157.9 (C), 170.2 and 170.3 (C), 171.0 and 171.1 (C). Anal. Calcd for $C_{15}H_{17}NO_5$, $0.5H_2O$: C, 59.99; H, 6.04; N, 4.66. Found: C, 60.28; H, 6.43; N, 4.31.

5.1.17. Methyl 4-ethyl-4-hydroxy-3,10-dioxo-3,4,6,7,8,10-hexahydro-1*H*-pyrano[3,4-*f*]indolizine-8-carboxylate (35). Potassium carbonate (0.95 g, 6.8 mmol) was added to a stirred solution of lactone **34** (2 g, 6.8 mmol) in methanol (20 mL) then oxygen was slowly bubbled into the mixture for 24 h. Neutralization was obtained by adding 1 N HCl and the resulting solution was extracted with dichloromethane. The organic phase was dried (Na_2SO_4) then evaporated. The residue crystallized from ethyl acetate, giving alcohol **35** as a white powder (95%), mp (EtOAc): 146–148 °C; TLC R_f (EtOAc/MeOH, 90:10): 0.48; IR: ν cm^{-1} 3385, 1745, 1655, 1565, 1435, 1210; ^1H NMR ($CDCl_3$): δ ppm 0.97 and 0.99 (2t, $J=7.3$ Hz, 3H, CH_2CH_3), 1.79 and 1.80 (2b quint, $J=7.3$ Hz, 2H, CH_2CH_3), 2.25–2.43 (m, 1H, CH_2CH_2), 2.43–2.69 (m, 1H, CH_2CH_2), 3.02–3.39 (m, 2H, CH_2CH_2), 3.69 (s, 1H, OH, deuterium oxide exchangeable), 3.80 and 3.82 (2s, 3H, CO_2CH_3), 5.12 and 5.16 (2dd, $J=9.4$, 3.4 Hz, 1H, NCH), 5.16 (d, $J=16$ Hz, 1H, CH_2O), 5.54 and 5.57 (2d, $J=16$ Hz, 1H, CH_2O), 6.51 (br s, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ ppm 7.7 (CH_3), 26.2 and 26.4 (CH_2), 30.6 (CH_2), 31.1 and 31.3 (CH_2), 52.8 (CH_3), 61.3 (CH), 66.0 (CH_2), 72.6 (C), 98.1 and 98.2 (CH), 115.8 and 115.9 (C), 150.3 (C), 150.8 and 150.9 (C), 157.7 (C), 170.0 and 170.3 (C), 173.8 and 173.9 (C). Anal. Calcd for $C_{15}H_{17}NO_6$, $0.5H_2O$: C, 56.96; H, 5.74; N, 4.43. Found: C, 56.87; H, 5.48; N, 4.43.

5.1.18. Methyl 4-ethyl-4-(isobutyryloxy)-3,10-dioxo-3,4,6,7,8,10-hexahydro-1*H*-pyrano[3,4-*f*]indolizine-8-carboxylate (36). A mixture of isobutyric anhydride (4 mL, 3.8 g, 24.1 mmol) and pyridine (4 mL) was stirred for 10 min then alcohol **35** (1 g, 3.2 mmol) was added and the solution was heated at 85 °C for 5 h. After cooling at room temperature, the mixture was neutralized with $NaHCO_3$ solution then extracted with dichloromethane. The organic phase was dried (Na_2SO_4) then evaporated. The residue crystallized from diethyl ether, giving **36** as a white powder (73%), mp 152–154 °C; TLC R_f (EtOAc) 0.55; IR: ν cm^{-1} 1760, 1740, 1665, 1600, 1570, 1470, 1215; ^1H NMR ($CDCl_3$): δ ppm 0.91 and 0.98 (2t, $J=7.3$ Hz, 3H, CH_2CH_3), 1.19 and 1.22 (2d, $J=7.0$ Hz, 3H, $C(CH_3)_2$), 1.23 and 1.24 (2d, $J=7.0$ Hz, 3H, $C(CH_3)_2$), 1.86–2.07 (m, 1H, CH_2CH_3), 2.07–2.24 (m, 1H, CH_2CH_3), 2.24–2.44 (m, 1H, CH_2CH_2), 2.44–2.62 (m, 1H, CH_2CH_2), 2.62–2.76 (m, 1H, $CH(CH_3)_2$), 2.96–3.14 (m, 1H, CH_2CH_2), 3.14–3.32 (m, 1H, CH_2CH_2), 3.80 and 3.82 (2s, 3H, CO_2CH_3), 5.07 and 5.08 (2dd, $J=9.2$, 3.7 Hz, 1H, NCH), 5.20 and 5.22 (2dt, $J=16.7$, 1.2 Hz, 1H, CH_2O), 5.49 and 5.51 (2d, $J=16.7$ Hz, 1H, CH_2O), 5.99 (t, $J=1.2$ Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ ppm 7.4 and 7.5 (CH_3), 18.4 (CH_3), 18.5 (CH_3), 26.1 and 26.3 (CH_2), 30.6 (CH_2), 31.3 and 31.6 (CH_2), 33.5 (CH), 52.8 (CH_3), 61.1 and 61.2 (CH), 66.5 and 66.6 (CH_2), 75.2 and 75.4 (C), 95.9 and 96.0 (CH), 117.5 (C), 146.1 (C), 150.0 and 150.2 (C), 157.5 (C), 167.4 (C), 169.7 (C), 175.0 (C). Anal. Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.19; H, 6.41; N, 3.62.

5.1.19. Methyl 4-ethyl-4-(isobutyryloxy)-3,6,10-trioxo-3,4,6,7,8,10-hexahydro-1*H*-pyrano[3,4-*f*]indolizine-8-carboxylate (37). A stirred mixture of diester **36** (1 g, 2.6 mmol) and Bredereck's reagent (0.65 g, 3.7 mmol) was heated at 110 °C for 2 h (N_2), giving enamine **38**. After cooling at room temperature, tetrahydrofuran (10 mL) and water (10 mL) were added. When a homogenous solution was obtained, sodium metaperiodate (0.65 g, 3.7 mmol) was added and the mixture was stirred for 30 min. The solid was filtered then washed with methylene dichloride. The aqueous phase was extracted with methylene dichloride, and the combined organic phases were dried (Na_2SO_4) then evaporated. The residue was purified by chromatography on SiO_2 column (EtOAc), giving ketone **37** as a brown oil (42%); TLC R_f (EtOAc): 0.51; because of its low stability, this compound was characterized only by NMR ^1H NMR ($CDCl_3$): δ ppm 0.95 and 0.97 (2t, $J=7.3$ Hz, 3H, CH_3CH_2), 1.29 and 1.31 (2d, $J=6.9$ Hz, 3H, $C(CH_3)_2$), 1.35 and 1.37 (2d, $J=6.9$ Hz, 3H, $C(CH_3)_2$), 1.82–2.04 (m, 2H, CH_3CH_2), 2.57–2.71 (m, 1H, $CH(CH_3)_2$), 3.33–3.90 (m, 2H, $COCH_2$), 3.81 and 3.83 (2s, 3H, CO_2CH_3), 5.09 and 5.10 (2dd, $J=9.3$, 3.3 Hz, 1H, NCH), 5.40–5.70 (m, 2H, CH_2O), 6.80 (s, 1H, ArH).

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