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Toward new camptothecins. Part 4: On the reactivity of nitro and amino precursors of aza analogs of 5-methoxycarbonyl camptothecin

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Abstract—In the context of formation of new aza analogs of camptothecin, nitration then reduction of condensed pyridones was realized, leading to new derivatives of pyrrolo-aza-indoles. Treatment of these compounds with hydrobromic acid led to new structure rearrangements while oxidation of the α-position was unsuccessful. Mechanisms of formation of the new products are discussed.

1. Introduction

The 2-pyridone unit is a key structural feature of a number of biologically active compounds.[1] Some pyridones act as antiviral,[2] or as herbicides,[3] pesticides,[4] fungicides,[5] antibiotics,[6] or antioxidant agents.[7] On the other hand, it can be found in the toxin ricinine,[8] the psychoactive huperzine A,[9] or in the lead anticancer alkaloid camptothecin (Fig. 1).

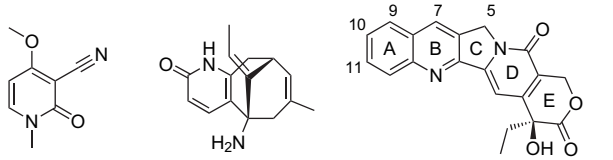

Figure 1. Structures of some active pyridones.

The isolation and structure of camptothecin were reported in 1966 by Wall[10a] and many reviews, devoted to this compound, revealed its paramount importance.[10b,c,12] Interest in this cytotoxic drug and semisynthetic analogs was stimulated when its mode of action was discovered. When the cleavable complex between topoisomerase I and DNA is stabilized by camptothecin, collision of the replication fork with this reversible complex[11] leads to cell death by preventing DNA religation.[12] Irinotecan and topotecan have emerged from bioavaibility and tolerance studies, and are used in cancer treatment.[13] Recently, the crystal structure of the DNA–topoisomerase I–camptothecin complex was solved and two models of camptothecin–DNA–topoisomerase I interaction were formulated.[14] In the camptothecin series, structure–activity relationships are well established in regard to modifications in A, B, C, and D rings. They also indicated the ability of substituents in positions 7, 9, 10, and 11 to maintain or improve biological activity. The need for a hydroxy lactone ring E has been established as a golden rule[15] and, for instance, lactams **1** (Fig. 2) possess poor activity.[16] However, this dogma fell with the discovery of other compounds stabilizing the complex between DNA and topoisomerase I in the same way as camptothecin: the homocamptothecins such as the diflomotecan, or the cyclopentanones such as S39625 are now in clinical phase.[17] The luotonin is also now known to exhibit one tenth of the camptothecin topo I inhibitory activity (Fig. 2).[18]

The targets of the present work were lactams **2** designed to explore the potential of aza analogs of cyclopentanones such as S39625 (Fig. 2). We have already described the synthesis of 5-methoxycarbonyl camptothecin **3** from DL methyl pyroglutamate **4**.[19c] A key intermediate of this reaction scheme was ketone **5**, obtained by oxidation of enamine **6** (Scheme 1). Interest in the methoxycarbonyl group of **2** came from its position face to face with the major groove

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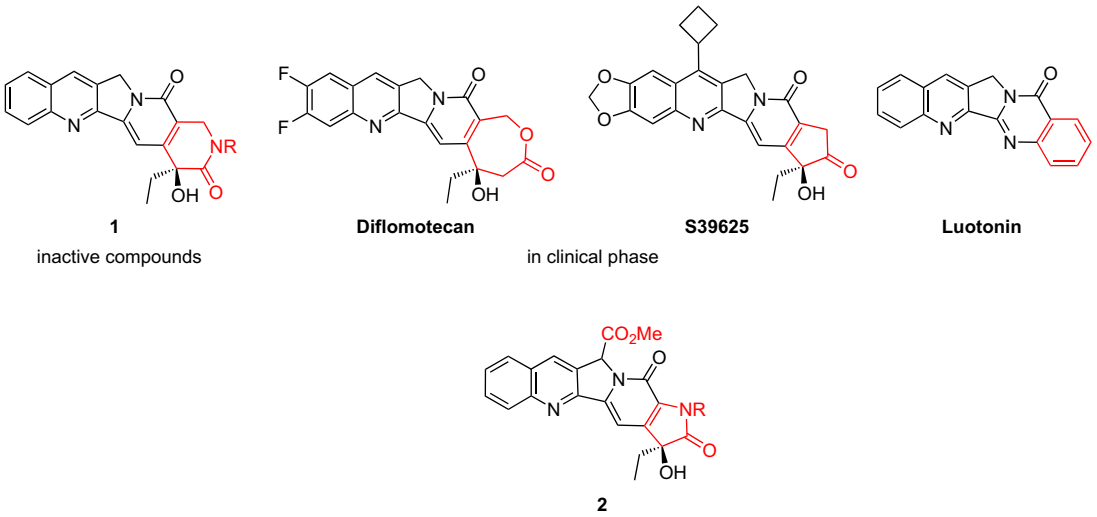
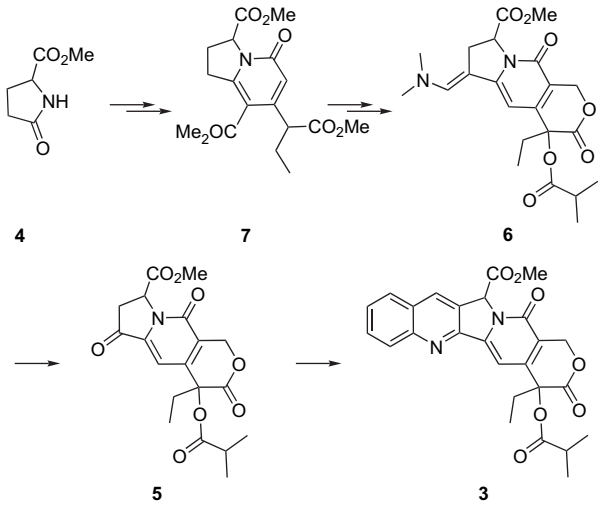


Figure 2. Camptothecin analogs.

in the potential complex with DNA and topo I. It can probably be replaced easily by a hydrogen,[19a] thereby increasing the size of the library of compounds to be tested biologically.



Scheme 1. Synthesis of 5-methoxycarbonyl camptothecin analog.

2. Results and discussion

2.1. Synthesis of nitro compounds and treatment of products in acidic media

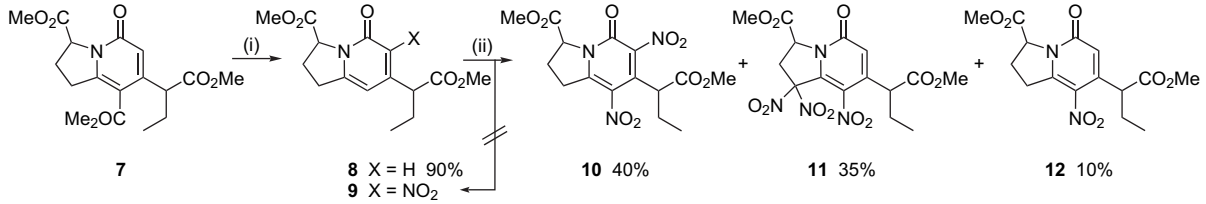
As a first approach to the reaction of nitration, pyridone **8**[19a] was submitted to the action of $AcONO_2$, although the preferential reactivity of these condensed pyridones toward electrophiles in the *para* position of the carbonyl was known.[20] Compound **9** nitrated at the *ortho* position was not observed in the reaction media, and only products **10**–**12** were isolated by chromatography on SiO_2. The syntheses of mono and dinitro products **10** and **12** were not unexpected, but formation of the *gem* disubstituted compound **11** was interesting, highlighting the particular reactivity at the α-position of condensed pyridones (Scheme 2).

Because mono nitropyridone **9** was not formed during this first reaction, nitration of triester **7** was now realized. Only small amounts of nitrated triester **13** were isolated after using 63% HNO_3/AcOH or HNO_3/H_2SO_4; however, HNO_3/TFAA[21] led to 79% of **13**, and HNO_3/Ac_2O[22] gave quantitative yield of the same product (Scheme 3).

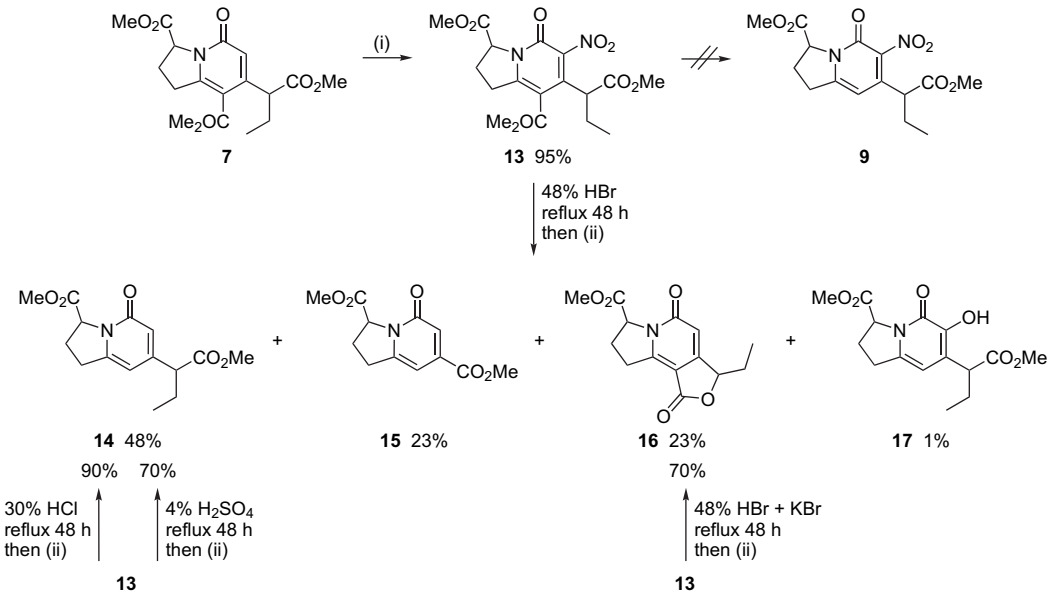
Removal of the aromatic methoxycarbonyl group of **13** was then studied. Such a decarboxylation of esters of condensed pyridones is well known, realized by reflux in 48% HBr. Thereby triester **13** was treated in these conditions (Scheme 3). The remaining ester functions were hydrolyzed in the course of the reaction and the compounds need to be reesterified; that was realized with MeOH, while drying the ternary azeotrope H_2O/MeOH/$CHCl_3$ on molecular sieves.[19a] Compounds **14**–**17** were obtained with a 95% total yield.

2.2. Formation of pyridone 14

Removal of the nitro group of the previous nitropyridone **13** is only a consequence of the reversibility of the reaction of electrophiles with aromatics. An interesting result is the better



Scheme 2. Reaction conditions: (i) (a) 48% HBr, reflux, 5 h; (b) MeOH, $MeSO_3H$, $CHCl_3$, molecular sieves 3 Å, reflux, 48 h;[19a] (ii) Ac_2O/63% HNO_3, 60 °C, 2 h.

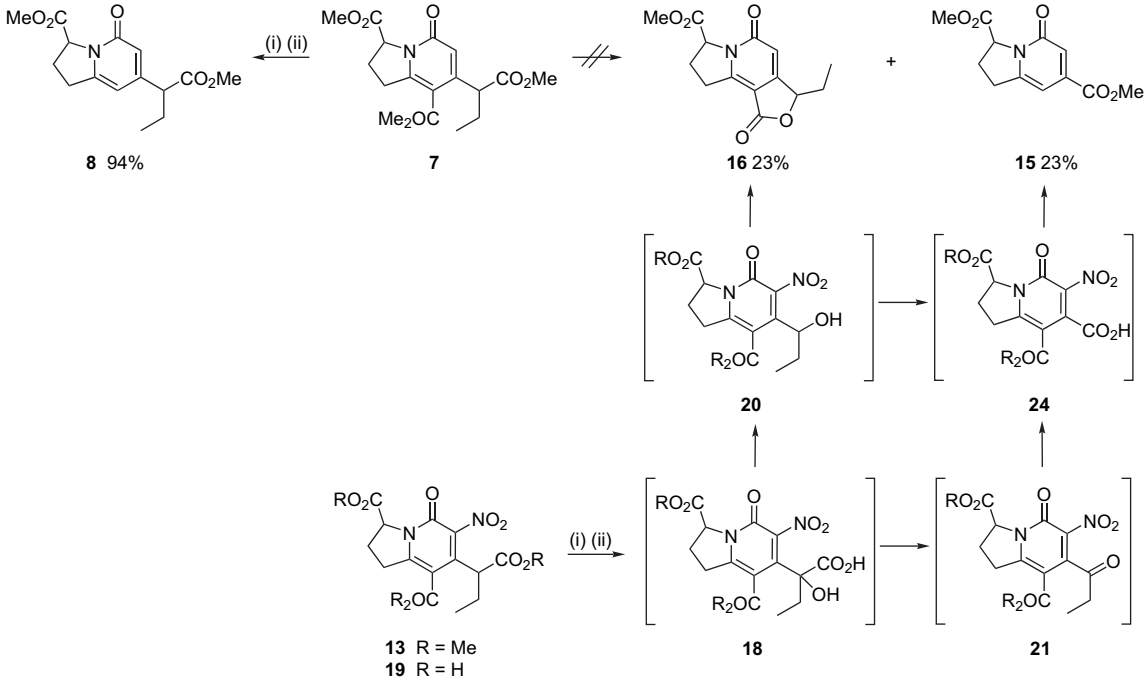


Scheme 3. Reaction conditions: (i) Ac_2O/63% HNO_3, 60 °C, 1 h; (ii) MeOH, $MeSO_3H$, $CHCl_3$, molecular sieves 3 Å, reflux, 48 h.

yield of **14** obtained by using 30% HCl. This led very cleanly to 90% of **14**, while 4% H_2SO_4 gave 70% of the same product, accompanied by low amounts of diester **15** and lactone **16**. These better yields were not caused by the rise in the acidity because 30% HCl is less acidic than 48% HBr. So this increase in **14** was due to the decrease in the formation of the other by-products. This interpretation of the results was validated when KBr was added to HBr, leading to the preferential formation of lactone **16**, to the disadvantage of **14** (Scheme 3).

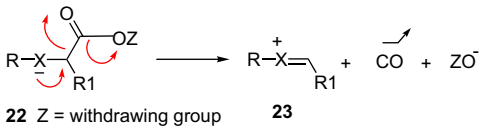
2.3. Formation of oxidized products 15 and 16

Pyridones **15** and **16** came from an oxidation of the lateral chain of **13**. In a possible mechanism that was due to oxygen dissolved in hydrobromic acid[23] even when the reactions were performed under nitrogen. Because triester **7** (or the corresponding triacid) was not oxidized in the same conditions[19] (Scheme 4), the nitro group of **13** was necessary for the oxidation to occur. As the presence of KBr increased the yield in lactone **16** (Scheme 3), the Br^- anion probably mediated this reaction. Alcohol **18** was thus obtained more easily from triester **13** or triacid **19** (Scheme 4). In this product, the hydroxyacid chain was substituted in the α-position of the acid by the strongly withdrawing nitropyridone group. Decarboxylation of acid **18**, then cyclization of alcohol **20** led to lactone **16**. On the other hand, alcohol **18** can evolve to ketone **21**. Indeed, decarbonylation of α-amino (amido, oxo) acid derivatives **22** to give oxonium ions **23** is



Scheme 4. Reaction conditions: (i) 48% HBr, reflux, 5 h; (ii) MeOH, $MeSO_3H$, $CHCl_3$, molecular sieves 3 Å, reflux, 48 h.[19a]

a well-known reaction[24] (Scheme 5). When R=H (**22**), the oxonium formed was the protonated form of ketone **21**. Another oxidation step changed the ethyl ketone chain of **21** to a new carboxylic acid **24**; protolysis of the nitro group, decarboxylation of the *para*-carboxyacid, and reesterification led then to pyridone **15**.



Scheme 5. Oxonium ions.

2.4. Formation of oxidized products 17

A first light on the reaction mechanism leading to compound **17** was obtained in the following reaction: in the hope to clarify the possible influence of ester groups, triester **13** was first heated in sodium hydroxide. The resulting crude product was heated at reflux in 48% HBr then reesterified in the usual way. Only new pyridone **25** was isolated in 30% yield, without traces of phenol **17**. A possible mechanism involves initial nucleophilic attack of the hydroxyl ion on the carbon carrying the nitro function, with formation of the anionic σ^H adduct **26** (Meisenheimer complex). Upon reflux in HBr, the pyridone ring of triacid **27** would be open, to give ketone **28** (drawn in its enolic form in Scheme 6). Recyclization, oxidative aromatization, and decarboxylation would then furnish diacid **29**, whose esterification gave **25**.

In this process, the crucial need for the aromatic carboxylic group of **27** to open the pyridone ring was highlighted by the fact that analog **30**, obtained from saponification of diester **17**, does not evolve toward **25** (Scheme 6).

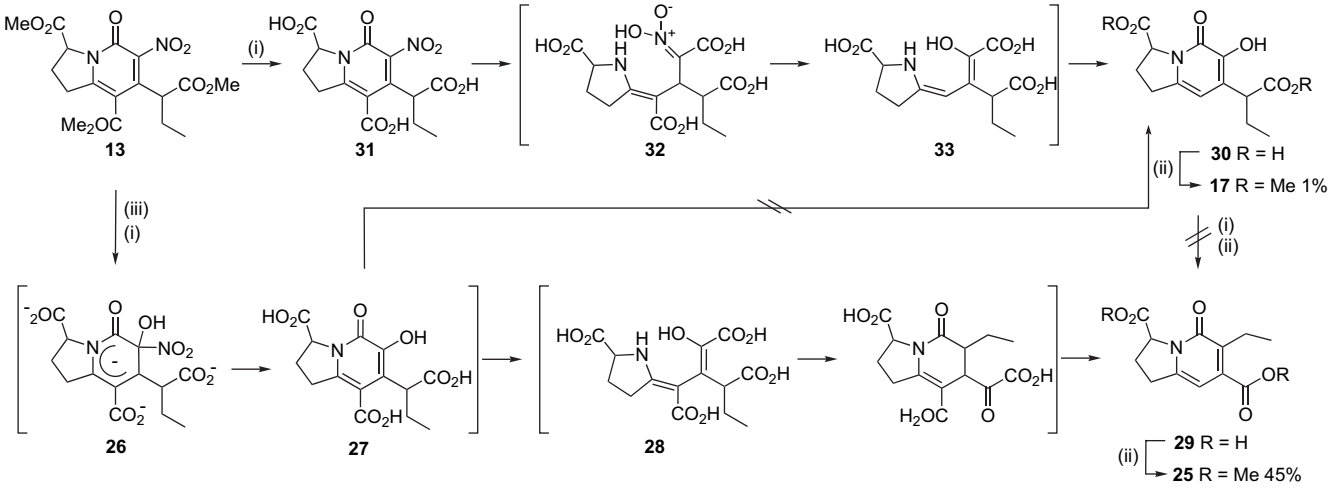
Formation of compound **17** can now be described as the opening of the pyridone ring of triacid **31** then hydrolysis of nitro compound **32** to give ketone **33** (these two compounds are drawn in their enolic forms in Scheme 6). Because **33**, unlike **28**, did not yield diester **25**, the decarboxylation of **32** occurred before hydrolysis of the nitro group.

2.5. Reduction then decarboxylation of nitropyridone 13

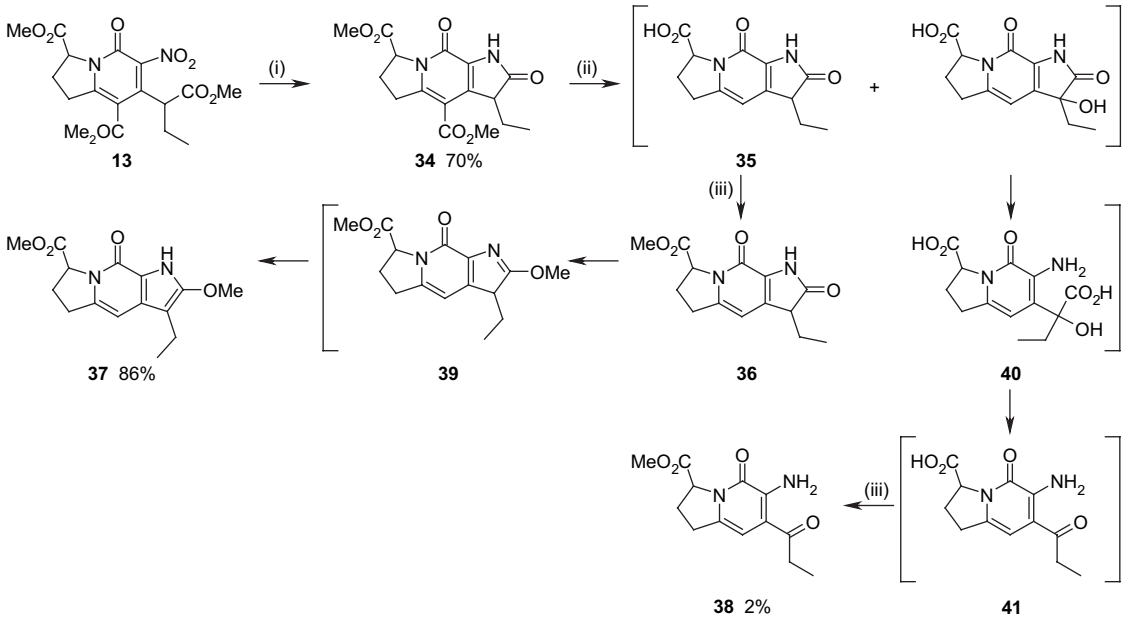
Because decarboxylation of triester **13** does not yield the required nitropyridone, it was decided to perform this step after reduction of the nitro function. Treatment of **13** either with Pd/C or with Zn/HBr yields 83 or 70%, respectively, of azaindolinedione **34**, thus furnishing the E ring of compound **2**. Decarboxylation of **34** was realized as previously by reflux in 48% HBr then reesterification of acid **36** with MeOH. Ester **36** was not obtained, but methoxyazaindolinone **37** was isolated in 86% yield, accompanied by 2% of amine **38**. Iminoether **39**, formed from **36** and MeOH/H^+, could be an intermediate in the formation of **37**. On the other hand, oxidation of heterocycle **35** or of the aminoacid obtained from hydrolysis of the lactam ring of **35**, probably yielded **40**. As shown in Scheme 7, loss of carbon monoxide would then lead to aminoketones **41** then **38**. Acid **35** was characterized by NMR, but was not isolated; if needed, it will be necessary to proceed to its esterification by using other methods that the reflux in MeOH/H^+.

2.6. Attempts to introduce a ketone group in C ring

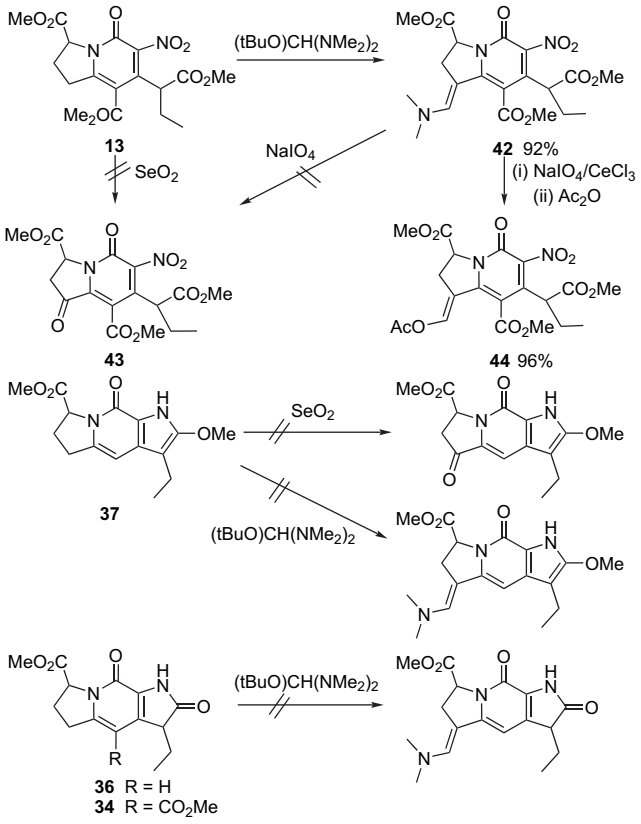
Many reactions were performed in the aim to introduce a ketone functionality in the pyrrolidine C ring. Some of them are reported in Scheme 8; the use of selenium oxide was earlier reported by Danishefsky[20] in his synthesis of camptothecin, and we have already described the oxidation of enedimethylamines in the same context.[19] Only one result needs some comments: heating nitropyridone **13** with Bredereck's reagents easily gave 92% of enamine **42**. Oxidation of this compound by $NaIO_4$ led to entire degradation of the reaction medium. Because that could be caused by oxidative cleavage of the enol form of ketone **43**, stabilization of the keto form was attempted by complexation with $CeCl_3$. The obtained mixture led rapidly to a very complex NMR spectrum (there were three asymmetric centers in the new product obtained) but some peaks could originate from an aldehyde or its enol form. The crude mixture was then



Scheme 6. Reaction conditions: (i) 48% HBr, reflux, 5 h; (ii) MeOH, $MeSO_3H$, $CHCl_3$, molecular sieves 3 Å, reflux, 48 h; (iii) NaOH, reflux 6 h.



Scheme 7. (i) Zn/HBr/MeOH, 20 °C; 1 h; (ii) 48% HBr, reflux, 24 h; (iii) MeOH, $MeSO_3H$, $CHCl_3$, molecular sieves 3 Å, reflux, 48 h.



Scheme 8. α-Oxidation of C ring.

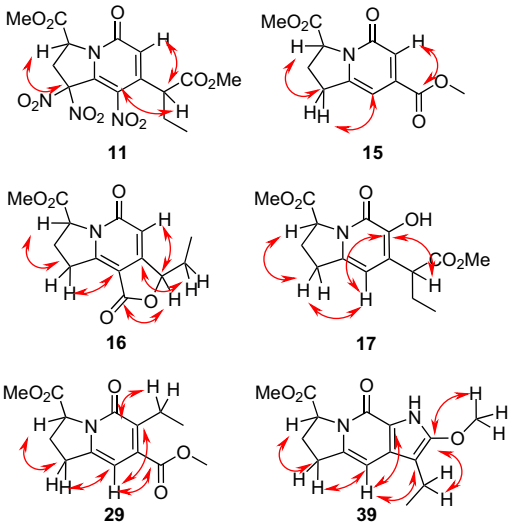


Figure 3. ^{1}H NMR spectra of pyridones **11**, **15**–**17**, **29**, and **39** and assignments determined by 2D NMR techniques: COSY, NOESY, HMBC, and HSQC.

treated by acetic anhydride, giving a quantitative yield of enol acetate **44**.

2.7. NMR spectra of new compounds

Many of the new products obtained in this study were unexpected compounds. Elucidation of their structures was carried out by NMR, mass spectrometry (LC–MS), infra-red and elemental analyses. Some of ^{1}H NMR spectra as well as HMBC and HSQC correlations are reported in Figure 3.

3. Conclusion

Introduction of the ketone functionality in the pyrrolidine C ring of the key precursors of aza analogs of 5-methoxycarbonyl camptothecin was unsuccessful. Thus it will be necessary to use other methods than nitration to obtain these compounds. However, some of the new products described in this study could give dipeptide analog scaffolds useful in the field of rigid β-turn peptidomimetics (Fig. 4).[25]

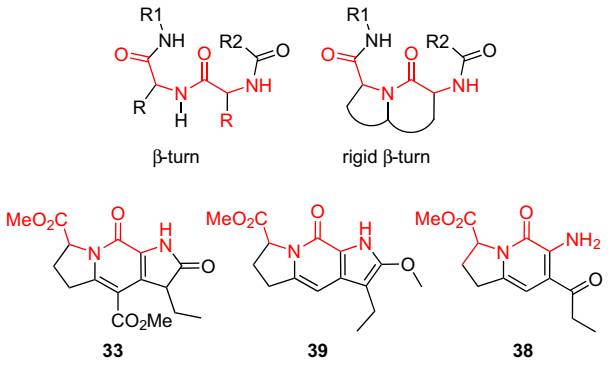


Figure 4. Analogy between **34**, **38**, and **39** and rigid β-turn peptidomimetics.

4. Experimental section

4.1. General

Melting points were determined using an Electrothermal apparatus and are uncorrected. ^{1}H 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. APCI$^+$ (atmospheric pressure chemical ionization) mass spectra were obtained on an LC–MS system Thermo Electron Surveyor MSQ. Microanalyses were performed by the 'Service de Microanalyses' of LSEO, Université de Bourgogne, Dijon, France. All products are obtained as mixtures of diastereoisomers.

4.2. Nitration of pyridone 8

Nitric acid (63%, 2 mL) was slowly added to a solution of pyridone **8** (900 mg, 3 mmol) in acetic anhydride (11 mL) at 0 °C. The mixture was stirred at 60 °C for 1 h and the solvent was evaporated. The residue was diluted with EtOAc (50 mL) and washed with satd aqueous $NaHCO_3$ (50 mL). The aqueous phase was extracted with EtOAc (3×30 mL) and the combined organic layers were dried by $MgSO_4$ then evaporated. The residue was purified by chromatography on SiO_2 (heptane/EtOAc, 100/0% to 0/100%), to give compounds **10**–**12**.

4.2.1. Methyl 7-(1-(methoxycarbonyl)propyl)-1,2,3,5-tetrahydro-6,8-dinitro-5-oxoindolizine-3-carboxylate (10). Recrystallized from methanol/ether; yellow powder; 40% yield; TLC R_f (EtOAc)=0.7; mp 65–67 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.92, 0.93 (2t, J=7.5 and 7.5 Hz, 3H, $CHCH_2CH_3$), 1.52–1.78 (m, 2H, $CHCH_2CH_3$), 2.20–2.69 (m, 2H, CH_2CH_2CH), 3.44–3.78 (m, 3H, CH_2CH_2CH, $CHCH_2CH_3$), 3.65 (s, 3H, CO_2CH_3), 5.19, 5.22 (2dd, J=9.6, 3.3 Hz and J=8.0, 1.6 Hz, 1H, CH_2CH_2CH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.2 (CH_3), 25.0 (CH_2), 25.4 (CH_2), 33.4 (CH_2), 48.7 (CH), 52.2 (CH_3), 53.0 (CH_3), 62.3 (CH), 118.2 (C), 146.0 (C), 153.3 (C), 159.2 (C), 169.3 (C), 171.3 (C), 171.6 (C); IR: ν cm^{-1} 1745, 1680, 1534, 1338. Anal. Calcd for $C_{15}H_{17}O_9N_3$: C, 47.00; H, 4.47; N, 10.96. Found: C, 46.92; H, 4.66; N, 10.63.

4.2.2. Methyl 7-(1-(methoxycarbonyl)propyl)-1,2,3,5-tetrahydro-1,1,8-trinitro-5-oxoindolizine-3-carboxylate (11). Recrystallized from EtOAc/ether; yellow powder; 10% yield; mp 105–107 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.81, 0.83 (2t, J=7.3 Hz and J=7.3 Hz, 3H, CH_2CH_3), 1.71–2.20 (m, 2H, CH_3CH_2CH), 3.65, 3.67 (2s, 3H, CO_2CH_3), 3.68 (t, J=7.3 Hz, 1H, $CHCH_2CH_3$), 3.75, 3.76 (2s, 3H, CO_2CH_3), 3.78–4.14 (m, 2H, CH_2CH), 5.43, 5.45 (2dd, J=9.5, 1.7 Hz and J=9.4, 1.6 Hz, 1H, CH_2CH_2CH), 7.3, 7.31 (2s, 1H, CH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.6 (CH_3), 24.4 (CH_2), 24.8 (CH_2), 35.5 (CH), 47.9 (CH_3), 53.0 (CH_3), 106.4 (C), 119.4 (C), 139.6 (CH), 139.7 (C), 144.9 (C), 151.8 (C), 167.7 (C), 170.4 (C); IR: ν cm^{-1} 1741, 1683, 1632, 1543, 1358; LC–MS (APCI$^+$) m/z 429 (MH$^+$). Anal. Calcd for $C_{15}H_{16}N_4O_{11}$: C, 42.06; H, 3.77; N, 13.08. Found: C, 42.38; H, 3.80; N, 13.48.

4.2.3. Methyl 7-(1-(methoxycarbonyl)propyl)-1,2,3,5-tetrahydro-8-nitro-5-oxoindolizine-3-carboxylate (12). Recrystallized from methanol/ether; yellow powder; 35% yield; TLC R_f (EtOAc)=0.8; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.99, 1 (2t, J=7.5 Hz and J=7.5 Hz, 3H, CH_2CH_3), 1.75–2.27 (m, 1H, CH_2CH_2CH), 2.3–2.7 (m, 1H, CH_2CH_2CH), 3.55–3.67 (m, 2H, CH_2CH_2CH), 3.71 (s, 3H, CO_2CH_3), 3.83 (s, 3H, CO_2CH_3), 3.92, 3.94 (2t, J=7.1 Hz and J=7.2 Hz, 1H, $CHCH_2CH_3$), 5.18 (dd, J=9.3, 3.4 Hz, 1H, CH_2CH_2CH), 6.44 (s, 1H, CH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.8 (CH_3), 24.9 (CH_2), 27.3 (CH_2), 29.4 (CH_2), 45.1 (CH), 52.0 (CH_3), 52.8 (CH_3), 61.2 (CH), 100.6 (CH), 126.7 (C), 138.3 (C), 141.7 (C), 156.5 (C), 170.1 (C), 173.6 (C). Anal. Calcd for $C_{15}H_{18}O_7N_2$: C, 53.25, H, 5.36, N, 8.28. Found: C, 53.11; H, 5.42; N, 8.08.

4.3. Dimethyl 7-[1-(methoxycarbonyl)propyl]-6-nitro-5-oxo-1,2,3,5-tetrahydro-3,8-indolizinedicarboxylate (13)

Nitric acid (63%, 90 mL, 0.6 mol) was slowly added to a solution of compound **7** (70 g, 0.2 mol) in acetic anhydride (1 L) at 0 °C. The mixture was stirred at 60 °C for 1 h and the solvent was evaporated. The residue was diluted with EtOAc (50 mL) and washed by satd aqueous $NaHCO_3$ (50 mL). The aqueous phase was extracted with EtOAc (3×30 mL) and the combined organic layers were dried ($MgSO_4$). The residue obtained upon evaporation was crystallized from methanol/ether; yellow powder; 95% yield; TLC R_f (EtOAc)=0.6; mp 147–149 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.92, 0.95 (2t, J=7.3 Hz and J=7.6 Hz, 3H, CH_2CH_3), 1.5–1.7 (m, 2H, $CHCH_2CH_3$), 2.25–2.65 (m, 2H, CH_2CHCO), 3.35–3.65 (m, 3H, $CHCH_2CH_3$, CH_2CH_2CH), 3.68, 3.69 (2s, 3H, CO_2CH_3), 3.79, 3.80 (2s, 3H, CO_2CH_3), 3.83, 3.84 (2s, 3H, CO_2CH_3), 5.2, 5.24 (2dd, J=9.6, 3.5 Hz and J=9.6, 2.9 Hz, 1H, $NCHCO_2CH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.6 (CH_3), 23.7 (CH_2), 24.1 (CH_2), 25.5 (CH_2), 33.3 (CH_2), 48.1 (CH), 52.1 (CH_3), 52.4 (CH_3), 53.3 (CH_3), 62.6 (CH), 104.6 (C), 144.0 (C), 152.7 (C), 157.3 (C), 164.6 (C), 169.1 (C), 170.4 (C); IR: ν cm^{-1} 1740, 1723, 1660, 1605, 1533, 1433. Anal. Calcd for $C_{17}H_{20}O_9N_2$: C, 51.51; H, 5.02; N, 6.79. Found: C, 51.52; H, 5.09; N, 7.07.

4.4. Decarboxylation of nitro compound 13

A stirred solution of pyridone **7** (1 g, 2.5 mmol) in 48% hydrobromic acid (50 mL) was heated at 130 °C for 48 h then evaporated. Methanesulfonic acid (0.10 mg) in methanol (200 mL) and chloroform (200 mL) were added to the

residue, and the mixture 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 aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$) then evaporated. The residue was purified by chromatography on SiO_2 (heptane/EtOAc, 100/0% to 0/100%) to give pyridones **14**–**17**.

4.4.1. Methyl 7-[1-(methoxycarbonyl)propyl]-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (14). Recrystallized from EtOAc; white powder; 48% yield; TLC R_f (EtOAc)=0.45; mp 65–67 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91, 0.92 (2t, J=7.2 Hz and J=7.6 Hz, 3H, $CHCH_2CH_3$), 1.7–2.1 (m, 2H, $CHCH_2CH_3$), 2.2–2.6 (m, 2H, CH_2CH_2CH), 2.9–3.2 (m, 2H, CH_2CH_2CH), 3.28 (t, J=7.7 Hz, 1H, $CHCH_2CH_3$), 3.69, 3.69 (2s, 3H, CO_2CH_3), 3.8 (s, 3H, CO_2CH_3), 5.08, 5.09 (2dd, J=9.1, 2.9 Hz and J=5.9, 3.2 Hz, 1H, CH_2CH_2CH), 6.15 (s, 1H, ArH), 6.3 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.8 (CH3), 25.5 (CH_2), 26.1 (CH_2), 30.3 (CH_2), 52.1 (CH), 52.6 (CH3), 52.9 (CH3), 60.9 (CH), 101 (CH), 116.4 (CH), 150 (C), 152.6 (C), 161.3 (C), 170.4 (C), 172.8 (C); IR: ν cm^{-1} 1727, 1657, 1589, 1532, 1432, 1204; Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.49; H, 5.91; N, 5.17. Found: C, 61.49; H, 6.78; N, 5.17.

4.4.2. Dimethyl 1,2,3,5-tetrahydro-5-oxoindolizine-3,7-dicarboxylate (15). White powder; 23% yield; TLC R_f (EtOAc)=0.4; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.24–2.74 (m, 2H, CH_2CH_2CH), 3.03–3.36 (m, 2H, CH_2CH_2CH), 3.79 (s, 3H, CO_2CH_3), 3.9 (s, 3H, CO_2CH_3), 5.13 (dd, J=9.4, 3.1 Hz, 1H, CH_2CH_2CH), 6.63, 7.03 (2s, ArH, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8.4 (CH_3), 25.8 (CH_2), 27.4 (CH_2), 29.5 (CH_2), 52.9 (CH_3), 61.6 (CH), 81.2 (CH), 102.3 (C), 108.7 (CH), 155.1 (C), 159.3 (C), 161.1 (C), 167.4 (C), 169.6 (C); LC–MS (APCI$^+$) m/z 251 (MH^+). Whatever the purification method, this product was always contaminated with 10% of **14**.

4.4.3. Methyl 3-ethyl-1,3,5,7,8,9-hexahydro-1,5-dioxofuro[3,4-*g*]indolizine-7-carboxylate (16). Recrystallized from EtOAc/ether; white powder; 23% yield; TLC R_f (EtOAc)=0.4; mp 112–114 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.03 (t, J=7.4 Hz, 3H, $CHCH_2CH_3$), 1.69–2.16 (m, 2H, $CHCH_2CH_3$), 2.36–2.75 (m, 2H, CH_2CH_2CH), 3.34–3.69 (m, 2H, CH_2CH_2CH), 3.82 (s, 3H, CO_2CH_3), 5.17 (dd, J=9.6, 3.2 Hz, 1H, CH_2CH_2CH), 5.31, 5.34 (2dd, J=7.0, 1.4 Hz and J=7.0, 1.4 Hz, 1H, $CHCH_2CH_3$), 6.29 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8.4 (CH_3), 25.8 (CH_2), 27.4 (CH_2), 29.5 (CH_2), 52.9 (CH_3), 61.6 (CH), 81.2 (CH), 102.3 (C), 108.7 (CH), 155.1 (C), 159.3 (C), 161.1 (C), 167.4 (C), 169.6 (C); IR: ν cm^{-1} 1742, 1677; LC–MS (APCI$^+$) m/z 278 (MH^+). Anal. Calcd for $C_{14}H_{15}O_5N$: C, 60.65; H, 5.45; N, 5.05. Found C, 60.60; H, 5.60; N, 5.08.

4.4.4. Methyl 7-(1-(methoxycarbonyl)propyl)-1,2,3,5-tetrahydro-6-hydroxy-5-oxoindolizine-3-carboxylate (17). Recrystallized from EtOAc; white cotton; 1% yield; TLC R_f (EtOAc)=0.55; mp 172–174 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91, 0.93 (2t, J=7.4 Hz and J=7.4 Hz, 3H, $CHCH_2CH_3$), 1.59–1.85 (m, 1H, $CHCH_2CH_3$), 1.9–2.15 (m, 1H, $CHCH_2CH_3$), 2.23–2.65 (m, 2H, CH_2CH_2CH), 3.68, 3.7 (2s, CO_2CH_3, 3H), 3.8, 3.81 (2s, CO_2CH_3, 3H), 3.93, 3.95 (2t, J=7.7 Hz and J=7.7 Hz, 1H, $CHCH_2CH_3$), 5.11, 5.13 (2dd, J=7.4, 1.8 Hz and J=7.4, 1.8 Hz, 1H, CH_2CH_2CH), 6.16 (m, 1H, ArH), 6.96 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.8 (CH_3), 24.9 (CH_2), 27.3 (CH_2), 29.4 (CH_2), 45.1 (CH), 52.0 (CH_3), 52.8 (CH_3), CH (61.2), 100.6 (CH), 126.7 (C), 138.3 (C), 141.7 (C), 156.5 (C), 170.1 (C), 173.6 (C); IR: ν cm^{-1} 1751, 1734, 1677, 1340, 1211; LC–MS (APCI$^+$) m/z 310 (MH^+). Anal. Calcd for $C_{15}H_{19}O_6N$: C, 8.25; H, 6.19; N, 4.53. Found: C, 58.25; H, 6.24; N, 4.74.

4.5. Dimethyl 6-ethyl-5-oxo-1,2,3,5-tetrahydroindolizine-3,7-dicarboxylate (29)

A stirred solution of pyridone **7** (500 mg, 1, 3 mmol) in 30% sodium hydroxide (20 mL) was heated at 70 °C for 16 h. The mixture was acidified by 48% hydrobromic acid (50 mL) and was heated at 130 °C for 48 h then evaporated. Methanesulfonic acid (0.10 mg) in methanol (200 mL) and chloroform (200 mL) were added to the residue, and the mixture 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 aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$) then evaporated. The residue obtained upon evaporation was crystallized from methanol/ether; yellow powder; 45% yield; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.14 (t, J=7.4 Hz, 3H, CH_2CH_3), 2.22–2.61 (m, 2H, $CHCH_2CH_2$), 2.97–3.30 (m, 2H, CH_2CH_2CH), 3.80 (s, 3H, CO_2CH_3), 3.90 (s, 3H, CO_2CH_3), 5.11 (dd, J=9.3 Hz and J=3.5 Hz, 1H, CH_2CH_2CH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.4 (CH_3), 21.7 (CH_2), 26.3 (CH_2), 30.3 (CH_2), 52.4 (CH_3), 52.7 (CH_3), 61.6 (CH), 99.9 (CH), 133.9 (C), 138.9 (C), 146.9 (C), 161.4 (C), 167.3 (C), 170.4 (C); LC–MS (APCI$^+$) m/z 280 (MH^+). Anal. Calcd for $C_{14}H_{17}O_5N$: C, 60.21; H, 6.14; N, 5.02. Found: C, 59.67; H, 6.21; N, 4.89.

4.6. Methyl 3-ethyl-2,9-dioxo-2,3,5,6,7,9-hexahydro-1*H*-pyrrolo[2,3-*f*]indolizine-4,7-dicarboxylate (34)

Zinc dust (600 mg) was slowly added to a stirring solution of pyridone **7** (400 mg, 1 mmol) in HBr (48%, 25 mL) and methanol (2 mL). After 1 h, the mixture was filtered on Celite and the filtrate was diluted with satd aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted by EtOAc (3×100 mL) and the combined organic layers were dried. Residue obtained upon evaporation was purified by crystallization in methanol. Recrystallized from methanol; white powder; 70% yields; TLC R_f (EtOAc)=0.56; mp 174–176 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.83 (t, J=7.3 Hz, 3H, CH_2CH_3), 1.93–2 (m, 2H, $CHCH_2CH_3$), 2.3–2.66 (m, 2H, CH_2CHCO), 3.48–3.66 (m, 2H, CH_2CH_2CH), 3.83 (s, 3H, CO_2CH_3), 3.85–3.88 (m, 4H, CO_2CH_3 and $CHCH_2CH_3$), 5.27 (dd, J=3.3, 9.5 Hz, 1H, $NCHCO_2CH_3$), 8.6 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.2 (CH_3), 23.4 (CH_2), 26.0 (CH_2), 32.5 (CH_2), 50.7 (CH), 51.7 (CH_3), 53.0 (CH_3), 61.6 (CH), 104.4 (C), 130.5 (C), 135.6 (C), 151.2 (C), 151.4 (C), 164.7 (C), 169.9 (C), 178.6 (C); IR: ν cm^{-1} 3224, 1729, 1717, 1653, 1576, 1537, 1438, 1212. Anal. Calcd for $C_{15}H_{17}O_9N_3$: C, 47.00, H, 4.47, N, 10.96. Found: C, 46.92; H, 4.66; N, 10.63.

4.7. Decarboxylation of compound 34

A stirred solution of pyridone **34** (6 g, 18 mmol) in 48% hydrobromic acid (120 mL) was heated at 130 °C for 24 h then evaporated. Methanesulfonic acid (0.25 mg) in methanol (200 mL) and chloroform (200 mL) were added to the residue and the solution was refluxed for 48 h while drying the solvent by condensing it in a Soxhlet-type apparatus containing 3 Å molecular sieves (50 g). Dilute $NaHCO_3$ (200 mL) was added to the residue obtained upon evaporation and the solution was extracted with dichloromethane (2×400 mL). The combined organic layers were dried ($MgSO_4$) then evaporated. The residue was purified by chromatography on SiO_2 (heptane/EtOAc, 100/0% to 0/100%) to give pyridones **37** and **38**.

4.7.1. Methyl 3-ethyl-5,6,7,9-tetrahydro-2-methoxy-9-oxo-1*H*-pyrrolo[2,3-*f*]indolizine-7-carboxylate (37). Recrystallized from methanol/ether; gray powder; 97% yield; TLC R_f (EtOAc)=0.15; mp 235–237 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.16 (t, J=7.5 Hz, 3H, CH_2CH_3), 2.22–2.62 (m, 2H CH_2CH_2CH), 2.52 (q, J=7.5 Hz, 2H, CH_2CH_3), 2.97–3.32 (m, 2H, CH_2CH_2CH), 3.74 (s, 3H, CO_2CH_3), 4.08 (s, 3H, OCH_3), 5.17 (dd, J=9.4, 2.6 Hz, 1H, CH_2CH_2CH), 6.37 (t, J=1.4 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15 (CH_2), 15.8 (CH_3), 27.4 (CH_2), 29.6 (CH_2), 52.5 (CH_3), 59.3 (CH_3), 60.5 (CH), 95.7 (CH), 99.4 (C), 114.2 (C), 133.5 (C), 139.7 (C), 152.0 (C), 152.5 (C), 171.5 (C); IR: ν cm^{-1} 1750, 1663, 1587, 1567, 1198; LC–MS (APCI$^+$) m/z 291 (MH^+). Anal. Calcd for $C_{15}H_{18}O_4N_2\cdot H_2O$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.25; H, 6.24; N, 9.60.

4.7.2. Methyl 6-amino-1,2,3,5-tetrahydro-5-oxo-7-propionylindolizine-3-carboxylate (38). Yellow foam; 2% yield; TLC R_f (EtOAc)=0.6; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.19 (t, J=1.4 Hz, 3H, CH_2CH_3), 2.22–2.61 (m, 2H CH_2CH_2CH), 2.52 (q, J=7.4 Hz, 2H, CH_2CH_3), 2.90–3.22 (m, 2H, CH_2CH_2CH), 3.79 (s, 3H, CO_2CH_3), 5.11 (dd, J= 9.0, 3.1 Hz, 1H, CH_2CH_2CH), 6.4 (t, J=1.6 Hz, 1H, ArH), 7.24 (br s, 2H, NH_2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8.1 (CH_3), 27.0 (CH_2), 28.8 (CH_2), 32.6 (CH_2), 52.6 (CH_3), 60.9 (CH), 99.4 (CH), 112.7 (C), 131.3 (C), 140.4 (C), 157.2 (C), 170.3 (C), 202.0 (C). Anal. Calcd for $C_{14}H_{17}O_4N$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.64; H, 6.42; N, 10.02.

4.8. Dimethyl (1*E*)-7-(1-(methoxycarbonyl)propyl)-1-((dimethylamino)methylene)-1,2,3,5-tetrahydro-6-nitro-5-oxoindolizine-3,8-dicarboxylate (42)

A stirred mixture of triester **13** (300 mg, 0.75 mmol) and Bredereck's reagent (210 mg, 1.05 mmol) was heated at 110 °C for 3 h (N_2). The residue obtained upon evaporation was diluted in water (40 mL) then extracted by dichloromethane (2×100 mL). The residue was dissolved in dichloromethane, Celite was added, and the solvent was evaporated. The powder was placed in a thimble of a Soxhlet apparatus then extracted with ether for 48 h. Recrystallized from ether; orange powder; 92% yield; TLC R_f (EtOAc)= 0.45; mp 177–179 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.93, 0.95 (2t, J=7.4 Hz and J=7.5 Hz, 3H, $CHCH_2CH_3$), 1.46–1.77 (m, 1H, $CHCH_2CH_3$), 2.09–2.34 (m, 1H, $CHCH_2CH_3$), 3.07 (s, 6H, $N(CH_3)_2$), 3.08–3.47 (m, 2H, CH_2CH), 3.52, 3.53 (2t, J=6.3 Hz and J=6.3 Hz, 3H, $CHCH_2CH_3$), 5.03, 5.05 (2dd, J=10.9, 2.1 Hz and J=10.7, 1.8 Hz, 1H, CH_2CH_2CH), 6.66, 6.78 (2t, J=1.4 Hz and J=1.3 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.4 (CH_3), 23.0 (CH_2), 23.2 (CH_2), 42.8 (CH_3), 30.8 (CH_3), 47.7 (CH), 52.2 (CH_3), 52.5 (CH_3), 52.9 (CH_3), 59.6 (CH), 95.2, 95.5 (C), 109.7 (C), 144.5 (C), 145.6 (CH), 145.7 (C), 167.7 (C), 169.4 (C), 170.7 (C), 171.2 (C); IR: ν cm^{-1} 1745, 1657, 1632, 1500, 1350. Anal. Calcd for $C_{20}H_{25}O_9N_3$: C, 53.21; H, 5.58; N, 9.31. Found: C, 53.20; H, 5.65; N, 9.27.

4.9. Dimethyl 7-(1-(methoxycarbonyl)propyl)-1-(acetoxymethylene)-1,2,3,5-tetrahydro-6-nitro-5-oxoindolizine-3,8-dicarboxylate (44)

Cerium trichloride (8 mg, 0.055 mmol) was added to a stirred solution of enamine **41** (50 mg, 0.11 mmol) in acetonitrile (0.1 mL), EtOAc (0.1 mL), and sodium metaperiodate in water (0.1 mL, 0.055 mmol). The mixture was stirred for 15 min then aqueous $NaHCO_3$ (1 mL) was added and the mixture was extracted by dichloromethane (2×10 mL). The combined organic layers were dried then evaporated. The residue was dissolved in a mixture of acetic anhydride (5 mL) and sodium acetate (3 mg, 0.022 mmol) and the solution was refluxed for 48 h. The residue obtained upon evaporation was diluted in water (3 mL) then was extracted with dichloromethane (2×10 mL). The combined organic layers were dried by $MgSO_4$ then evaporated; 96% yield; brown oil; TLC R_f (EtOAc)=0.7; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.93, 0.96 (2t, J=7.4 Hz and J=7.5 Hz, 3H, $CHCH_2CH_3$), 1.51–1.77 (m, 1H, $CHCH_2CH_3$), 1.96–2.37 (m, 1H, $CHCH_2CH_3$), 2.27 (s, 3H, $COCH_3$), 3.04–3.39 (m, 2H, CH_2CH), 3.5 (t, J=7.0 Hz, 3H, $CHCH_2CH_3$), 3.69, 3.72 (2s, 3H, CO_2CH_3), 3.83, 3.84 (2s, 3H, CO_2CH_3), 3.87, 3.88 (2s, 3H, CO_2CH_3), 5.15 (dd, J=8.3, 1.4 Hz, 1H, CH_2CH_2CH), 7.95, 8.05 (2s, 1H, CH). This product was analyzed only by NMR.

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