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Received February 22, 2002

Dimethyl 7-methoxycarbonylmethyl-5-oxo-1,2,3,5-tetrahydro-indolizine-3,8-dicarboxylate was synthesized starting from methyl pyroglutamate. A study was made of the reactions of this highly functionalized pyridone with ethyl iodide, selenium oxide, isoamyl nitrite and formaldehyde. Literature reports that reaction of 4-(1-carbomethoxypropyl)-5-carbomethoxy-1,6-cyclopentano-2-pyridone with formaldehyde lead to a 95% yield of a monolactone (**26**) precursor of camptothecin. Our experiments resulted in 15 % of this monolactone and 40% of a new dilactone (**27**).

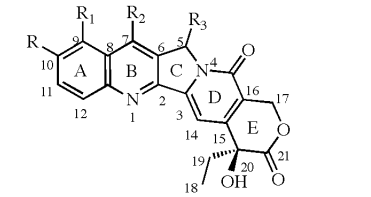
J. Heterocyclic Chem., **40**, 45 (2003).

The isolation and structure of camptothecin **1** were reported in 1966 by Wall [1]. Interest in this cytotoxic drug and its hemisynthetic analogs was stimulated when their mode of action was discovered. The cleavable complex between topoisomerase I and DNA is stabilized by camptothecin and collision of the replication fork with this reversible complex [2] leads to cell death by preventing DNA religation [3]. The crystal structure of the DNA - topoisomerase I - camptothecin complex was resolved and two models of camptothecin - DNA - topoisomerase I interaction were proposed [4].

Irinotecan and topotecan have emerged from these studies and are used in cancer treatment [5]. In the camptothecin series, structure-activity relationships are well established for modifications in rings A, B, D and E. They also indicate the necessity for a hydroxy lactone ring [6] and the capacity of substituents in positions 7, 9, 10 and 11 to maintain or improve biological activity. However contradictory results have been observed concerning the position 5, as hydroxy, methoxy or oxycarbonyl groups introduced in this position generally result in inactive products [7], while some 5-methylenecarbonyl substituents are tolerated and the inhibitory function is maintained [8] (Scheme 1).

As part of a program focusing on potential anticancer agents [9], it was necessary to clarify the influence of an oxygenated substituent on position 5 of ring C. Our study began with the synthesis of camptothecin derivative **2**, substituted by a carboxylic ester at position 5. Many total syntheses of camptothecin have already been published

Scheme 1



1 camptothecin R, R_1, R_2, R_3 = H

irinotecan R_1, R_2, R_3 = H, R =

topotecan R_2, R_3 = H R = OH R_1 = CH_2NMe_2

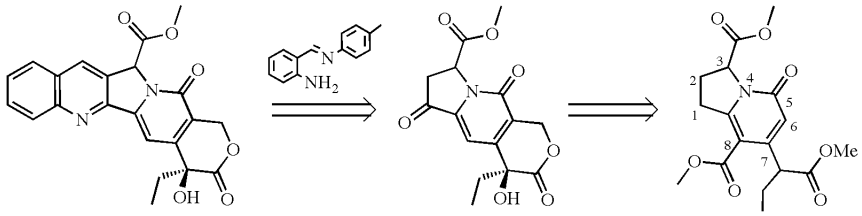
[10] and our aim was to apply our knowledge of the chemistry of pyroglutamic acid [11a] and indolizines [11b-d] to the general approach of Danishefsky [12] reported in the retrosynthetic pathway of Scheme 2.

Application of this strategy is dependent on the synthesis of pyridone **3**, which should easily be converted into the camptothecin analog **2**. Thus it was necessary to introduce a heteroatom such as oxygen or bromine into position 1 and a hydroxymethyl group into position 6 of pyridone **4** or of one of its precursors (Scheme 2).

Synthesis of the new pyridone **9** was performed in the first part of this work, followed by a study of the chemical reactivity of heterocycles **4** and **9**, with compound **3** as an ultimate target.

Methyl pyroglutamate (**5**) [13] was reacted with dimethyl sulfate to give iminoether **6** [14]. Condensation of **6** with Meldrum's acid produced a good yield of enam-

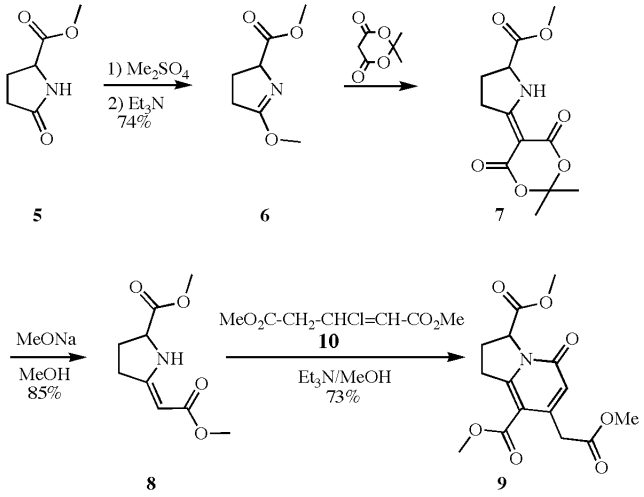
Scheme 2



2 **3** **4**

inoester **7** [14] whose reaction with sodium methylate gave product **8** [11c,15]. Pyridone **9** was then obtained in 73% yield by reacting dimethyl 3-chloroglutaconate **10** with diester **8** and triethylamine in refluxing methanol. The use of ethanol as the solvent for this reaction [12] led to the transesterification of one methyl ester group (Scheme 3).

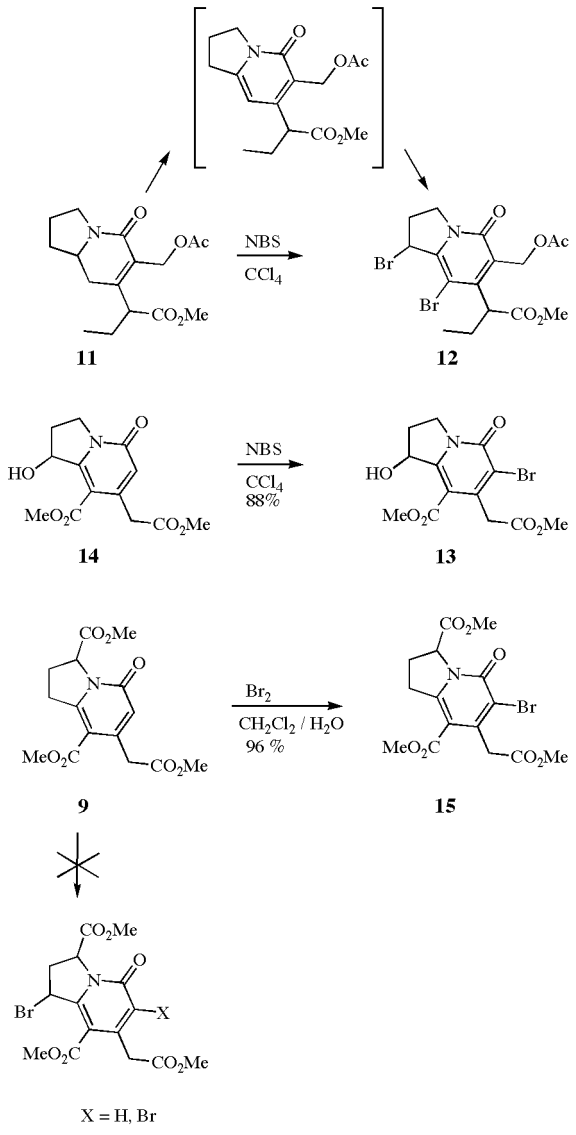
Scheme 3



5 **6** **7** **8** **9**

Some aspects of the chemistry of pyridone **9** were then briefly examined mainly to explore the possibility of introducing a heteroatom into position 1 of indolizin-5-one. Reaction of *N*-bromosuccinimide with dihydropyridone **11** was known to lead to such a product, giving the dibromo compound **12** [16], while monobromo product **13** was obtained from pyridone **14** [12c]. When heterocycle **9** was treated with *N*-bromosuccinimide (carbon tetrachloride/benzoyl peroxide) or with bromine (ultraviolet light/carbon tetrachloride or dichloromethane/water/potassium hydrogenocarbonate or sodium hydride/dimethoxyethane), only mono bromopyridone **15** was isolated in 96% yield (Scheme 4).

Scheme 4



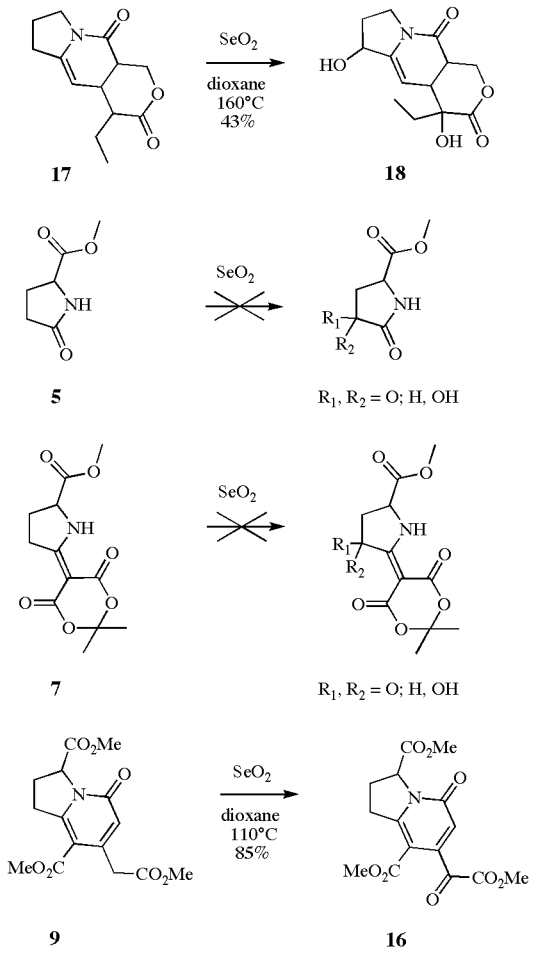
11 **12** **14** **13** **9** **15**

X = H, Br

Oxidized derivatives of heterocycle **9** are also of interest. Because selenium dioxide reacts easily with lactone **17** to give dialcohol **18** [12], we submitted the precursors of compound **9**, methyl pyroglutamate **5** and Meldrum's ester **7**, to the action of this reagent. No reaction was observed with esters **5** or **9**, while triester **9** gave a good yield of ketoester **16** which may be a key compound opening the way to an asymmetric synthesis of camptothecin precursor **3** (Scheme 5).

Another attempt to introduce a heteroatom into the same benzylic position 1 (product **19**) was performed by reacting isoamyl nitrite with triester **9**. In the presence of

Scheme 5

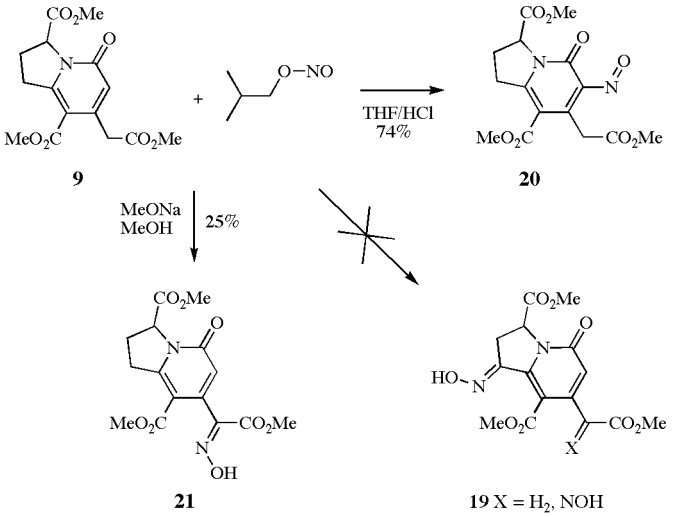


hydrochloric acid, only the nitroso compound **20** was obtained in 74% yield, although this was variable, while in a basic medium (MeONa/MeOH), a small amount of oxime **21** was formed (Scheme 6).

In a last part of this work, an ethyl group was easily introduced into compound **9**, resulting in triester **4**, obtained as a mixture of diastereoisomers. In this series, the best yield (71%) was obtained by using sodium hydride and ethyl iodide at room temperature in tetrahydrofuran.

We did not manage to form the lactone ring of **2** by reacting pyridone **4** with formaldehyde according to the conditions described for diester **22** (Scheme 8) (paraformaldehyde, sulfuric acid, water and dioxane) [12b] or using some variations (paraformaldehyde, trioxane or dimethoxymethane, sulfuric or triflic acid in dioxane, zinc chloride in acetic and hydrochloric acids or tin chloride [18] and chlorotrimethylsilane in methylene dichloride [19]) (Scheme 7). Reactions of triester **9** with formaldehyde were also tested using various experimental conditions [20]. Compound **23** was never isolated, but

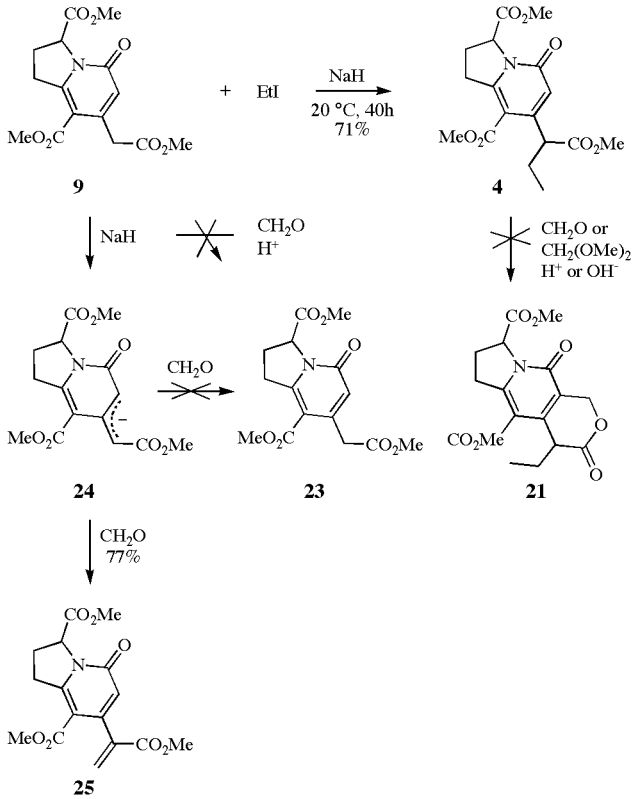
Scheme 6



interestingly, anion **24** gave a 77% yield of the methylene product **25** (Scheme 7).

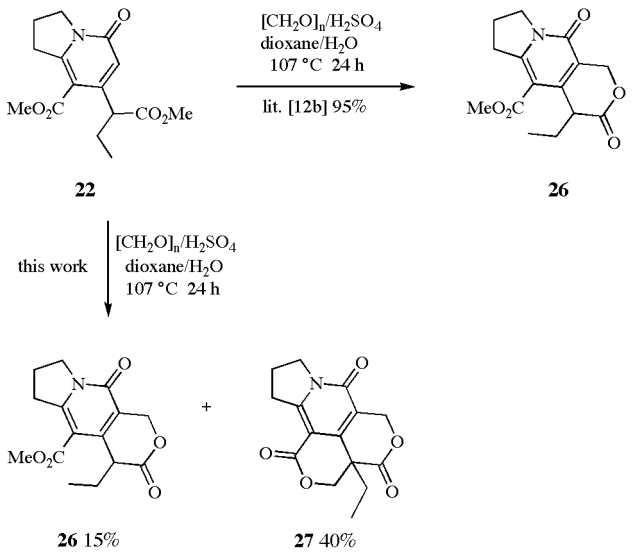
Given the poor results obtained for the synthesis of lactone **21** or **23**, we returned to the original Danishefsky synthesis of lactone **26** [12] in the hope to observe a procedure subtlety allowing success in our lactone synthesis. Lactone **26** was never obtained at a yield of more than 15% (lit. [12b]: 95%), but a new by-product, dilactone **27** was also

Scheme 7



isolated in 40% yield (Scheme 8). It should be noted that it is almost impossible to distinguish compounds **26** and **27** by thin-layer chromatography (9/1 dichloromethane/ methanol; **26**: rf = 0.68; **27**: rf = 0.65) The incorporation of an additional formaldehyde unit in a position adjacent to a lactone carbonyl group has already been reported in pyridones lacking a carbonyl ester in position 5 [21].

Scheme 8



In conclusion, we have described medium to high yield synthesis of new highly functionalized pyridones and we have studied their reactions with brominating and oxidizing agents. Despite the fact that their reaction with formaldehyde failed to give the desired lactones, some of these compounds could be useful for further syntheses of camptothecin derivatives.

EXPERIMENTAL

Melting points were determined on an 'Electrothermal' apparatus and are uncorrected. The ir spectra were recorded on a 'Perkin-Elmer' 700 spectrometer and the nmr spectra on a Varian 'Gemini 2000' at 200 MHz for ^{1}H and 50 MHz for ^{13}C, using tetramethylsilane as an internal reference. Elemental analyses were performed by the «Service Central de Microanalyses» (CNRS, Vernaison, France).

Dimethyl 7-[1-(Methoxycarbonyl)propyl]-5-oxo-1,2,3,5-tetrahydroindolizine-3,8-dicarboxylate (**4**).

Triester **9** (7 g, 21.6 mmol) was added to a suspension of sodium hydride (0.573 g, 23.8 mmol) in tetrahydrofuran (190 ml). After 20 min, ethyl iodide (5.7 ml, 65 mmol) was added and the mixture was stirred for 40 hours. After adding methanol (45 ml), the solution was evaporated. Methylene dichloride was added and the solution was washed twice with hydrochloric acid solution (100 ml, 0.1 *N*). The organic phase was dried (sodium sulfate), filtered and concentrated. The residue crystallized from acetone, giving 71% yield of pyridone **4** as a mixture of two diastereoisomers, mp 90 °C (acetone); ir (potassium bromide): ν cm^{-1} 1740, 1720, 1660 (C=O), 1580, 1520, 1420 (C=C), 1200 (C-O); ^{1}H nmr (deuteriochloroform): δ ppm 0.94 and 0.95 (2t, J = 7.4 Hz, 3 H), 1.65-1.87 (m, 1 H), 1.98-2.18 (m, 1 H), 2.18-2.60 (m, 2 H), 3.38-3.50 (m, 2 H), 3.66 (s, 3 H), 3.78 (s, 3 H), 3.82 (s, 3 H), 4.03 and 4.04 (2t, J = 7.3 Hz, 1 H), 5.12 (dd, J = 6.9, 3.4 Hz, 1 H), 6.39 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ ppm 12.4, 25.5, 33.3, 49.6, 49.8, 51.7, 52.0, 52.8, 61.6, 107.0, 117.3, 152.1, 155.8, 160.1, 165.4, 169.7, 172.5.

Anal. Calcd. for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.99; O, 31.87. Found: C, 58.34; H, 6.07; N, 3.82; O, 31.71.

Dimethyl 7-Methoxycarbonylmethyl-5-oxo-1,2,3,5-tetrahydroindolizine-3,8-dicarboxylate (**9**).

A stirred mixture of diester **8** (20 g, 0.1 mol), glutaconate [22] **10** (27 g, 0.14 mol) and triethylamine (23.7 ml, 0.17 mol) in methanol (100 ml) was refluxed for 28 hours. The solution was evaporated, ethyl acetate (200 ml) was added and triethylamine hydrochloride was filtered. Part of the solvent was evaporated and the residue crystallized at 0 °C. The solid obtained was recrystallized from ethyl acetate to give compound **9**, in 73% yield, mp 83 °C (ethyl acetate); ir (potassium bromide) ν cm^{-1} 1750, 1710, 1680 (C=O), 1600, 1520, 1440 (C=C), 1220 (C-O); ^{1}H nmr (deuteriochloroform): δ ppm 2.21-2.80 (m, 2H), 3.40-3.60 (m, 2H), 3.70 (s, 3H), 3.78 (s, 6H), 3.60 (d, J = 16.5 Hz, 1 H), 4.00 (d, J = 16.5 Hz, 1 H), 5.13 (dd, J = 9.1, 5.1 Hz, 1 H), 6.27 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ ppm 28.5, 36.5, 44.1, 54.6, 55.0, 55.8, 64.6, 109.6, 123.2, 150.6, 159.9, 163.0, 168.2, 172.7, 173.3.

Anal. Calcd. for $C_{15}H_{17}NO_7$: C, 55.73; H, 5.30; N, 4.33; O, 34.64. Found: C, 55.73; H, 5.30; N, 4.39; O, 34.88.

Dimethyl 6-Bromo-7-methoxycarbonylmethyl-5-oxo-1,2,3,5-tetrahydroindolizine-3,8-dicarboxylate (**15**).

Bromine (0.17 g, 1.1 mmol) was added to triester **9** (0.21 g, 0.65 mmol) and potassium hydrogenocarbonate (0.13 g, 1.3 mmol) in methylene dichloride (3 ml) and water (4 ml). The mixture was stirred for 15 hours, methylene dichloride (15 ml) was added, the aqueous layer extracted with methylene dichloride (15 ml). The combined organic phases were dried (sodium sulfate), filtered and concentrated. The residue was subjected to flash chromatography (50/50, heptane/ethyl acetate) to give compound **15**, in 96% yield, mp 110 °C (ethyl acetate); ir (potassium bromide): ν cm^{-1} 1740, 1730, 1720 (C=O), 1590, 1500, 1430 (C=C), 1200 C-O); ^{1}H nmr (deuteriochloroform): δ ppm 2.18-2.60 (m, 2 H), 3.36-3.49 (m, 2 H), 3.67 (s, 3 H), 3.73 (s, 3 H), 3.76 (s, 3 H), 4.13 (s, 2 H), 5.12 (dd, J = 9.7, 3.2 Hz, 1 H); ^{13}C nmr (deuteriochloroform): δ ppm 25.4, 33.2, 37.6, 51.8, 52.1, 52.8, 53.3, 62.6, 107.0, 125.2, 143.3, 153.8, 156.4, 165.1, 169.5.

Anal. Calcd. for $C_{15}H_{16}BrNO_7$: C, 44.80; H, 4.01; Br, 19.87; N, 3.48; O, 27.85. Found: C, 44.97; H, 4.19; N, 3.44; O, 28.21.

Dimethyl 7-Methoxyoxalyl-5-oxo-1,2,3,5-tetrahydroindolizine-3,8-dicarboxylate (**16**).

A stirred mixture of **9** (0.2 g, 0.62 mmol) and selenium dioxide (0.14 g, 1.2 mmol) in dioxane (7.3 ml) was heated in a sealed tube at 110 °C for 48 hours. The solution was filtered, the solid was washed with methylene chloride, and the organic phases were concentrated. The solid residue was then chromatographed (ethyl acetate/heptane, 60/40) to give **16** as a white solid in 85%

yield, mp 132 °C (ethyl acetate); ir (potassium bromide): ν cm^{-1} 1740, 1720, 1680 (C=O), 1600, 1520, 1440 (C=C), 1200 (C-O); ^{1}H nmr (deuteriochloroform): δ ppm 2.30-2.65 (m, 2 H), 3.40-3.76 (m, 2 H), 3.81 (s, 6 H), 3.91 (s, 3 H), 5.17 (dd, J = 9.8, 3.4 Hz, 1 H), 6.44 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ ppm 28.5, 32.7, 36.1, 55.4, 56.0, 56.3, 64.9, 106.9, 120.4, 153.2, 160.5, 162.9, 165.6, 172.3, 186.9.

Anal. Calcd. for $C_{15}H_{15}NO_8$: C, 53.42; H, 4.48; N, 4.15; O, 37.95. Found: C, 53.74; H, 4.41; N, 4.51; O, 37.72.

Dimethyl 7-Methoxycarbonylmethyl-6-nitroso-5-oxo-1,2,3,5-tetrahydroindolizine-3,8-dicarboxylate (**20**).

A mixture of **9** (0.21 g, 0.65 mmol), and isoamyl nitrite (0.3 ml, 2.23 mmol) in 36% hydrochloric acid (0.1 ml) and tetrahydrofuran (3 ml) was stirred at room temperature for 15 hours. The mixture was concentrated, the residue poured into brine and the aqueous phase extracted with dichloromethane (2 x 50 ml). The combined organic phases were dried (sodium sulfate), filtered and concentrated. The residue was then subjected to flash chromatography (ethyl acetate/heptane, 70/30) to give **20** as a yellow oil in 74% yield; ir (potassium bromide): ν cm^{-1} 1750, 1720, 1670 (C=O), 1580, 1520, 1440 (C=C), 1200 (C-O); ^{1}H nmr (deuteriochloroform): δ ppm 2.22-2.64 (m, 2 H), 3.43-3.56 (m, 2 H), 3.72 (s, 3 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 4.14 (s, 2 H), 5.19 (dd, J = 9.5, 3.2 Hz, 1 H); ^{13}C nmr (deuteriochloroform): δ ppm 28.4, 36.2, 40.6, 54.9, 55.1, 55.9, 56.3, 65.6, 110.1, 128.2, 146.3, 156.8, 159.4, 168.1, 172.5.

Anal. Calcd. for $C_{15}H_{16}N_2O_8$: C, 51.14; H, 4.58; N, 7.95; O, 36.33. Found: C, 50.74; H, 4.76; N, 8.29; O, 36.08.

Dimethyl 7-[1-(Methoxycarbonyl)vinyl]-5-oxo-1,2,3,5-tetrahydroindolizine-3,8-dicarboxylate (**25**).

Triester **9** (0.59 g, 1.82 mmol) and paraformaldehyde (1.64 g, 55 mmol) were added to a suspension of sodium hydride (0.048 g, 2 mmol) in dioxane (10 ml). The mixture was stirred at room temperature for 48 hours. Methanol (5 ml) was added, the solution was concentrated and the residue was dissolved in dichloromethane (120 ml). The solution was extracted with 0.1 *N* hydrochloric acid and the organic phase was dried (sodium sulfate), filtered and concentrated. The residue was then subjected to flash chromatography (ethyl acetate/heptane, 70/30) to give compound **25** as a yellow oil in 77% yield; ir (potassium bromide): ν cm^{-1} 1750, 1730, 1700, 1660; ^{1}H nmr (deuteriochloroform): δ ppm 2.25-2.61 (m, 2 H), 3.35-3.69 (m, 2 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 3.81 (s, 3 H), 5.15 (dd, J = 9.9, 3.5 Hz, 1 H); 5.78 (d, J = 1 Hz, 1 H), 6.34 (s, 1 H), 6.35 (d, J = 1 Hz, 1 H); ^{13}C nmr (deuteriochloroform): δ ppm 25.5, 33.1, 51.5, 52.1, 52.9, 61.6, 106.2, 119.1, 126.2, 141.0, 150.5, 156.5, 160.5, 165.2, 165.6, 170.0.

Anal. Calcd. for $C_{16}H_{17}NO_7$: C, 57.31; H, 5.11; N, 4.18; O, 33.40. Found: C, 57.51; H, 5.27; N, 4.43; O, 33.11.

Methyl 4-Ethyl-3,10-dioxo-3,4,6,7,8,10-hexahydro-1*H*-pyrano[3,4-*f*]indolizine-5-carboxylate (**26**) and 3a-Ethyl-3,3a,6,8,9,10-hexahydro-2,5-dioxa-7a-azacyclopenta[a]phenalene-1,4,7-trione (**27**).

A teflon sealed tube containing pyridone **22** (1 g, 3.4 mmol), paraformaldehyde (1 g, 20.4 mmol), dioxane (5 ml) and concentrated sulfuric acid (0.2 ml) was heated at 107 °C for 24 hours. After cooling, dioxane was evaporated, dichloromethane (100 ml) was added and the organic phase was washed with a potassium carbonate solution. The aqueous phase was extracted with methylene dichloride (2 x 100 ml). The combined organic extracts were dried over magnesium sulfate. After evaporation of the solvents, chromatography of the residue on silica gel and elution with 9.9/0.1 dichloromethane/methanol first gave 15% of lactone **26**, identical to the product previously described [12b], then 40% of dilactone **27**, mp = 88-90 °C, ir (potassium carbonate): ν cm^{-1} 1649, 1723; ^{1}H nmr (deuteriochloroform): 1.06 (t, J = 7.6 Hz, 3 H), 1.99 (m, 2 H), 4.33 (d, J = 12.2 Hz, 1 H), 4.67 (d, J = 12.2 Hz, 1 H), 5.21 (d, J = 16.0 Hz, 1 H), 5.45 (d, J = 16.0 Hz, 1 H).

Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84; O, 27.65. Found: C, 62.34; H, 5.09; N, 4.99; O, 27.51.

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