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A Convergent Total Synthesis of Mappicine Ketone: A Leading Antiviral Compound

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Abstract : An efficient total synthesis of the naturally occuring mappicine ketone **1** and mappicine **2** are described. The approach is based on the assembly of tricyclic amine **5** with pseudo acid chloride **20**. A Friedlander condensation is utilized for the construction of the ABC skeleton and a periselective Diels-Alder approach is utilized for the preparation of the pseudo acid chloride.

INTRODUCTION

Mappicine ketone (MPK) **1** is an oxidized form of the natural alkaloid mappicine **2**, isolated from *Mapia foetida* Miers[1] and an E-ring decarboxylated analogue of 20-(*S*)-camptothecin (CPT) **3**, which is the parent member of an important family of anticancer agents.[2] MPK has recently been identified as an antiviral agent with selective activities against HSV-1, HSV-2, and human cytomagalovirus (HCMV).[3]

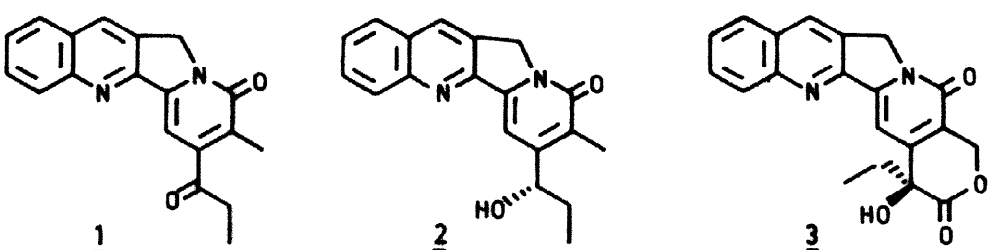

Fig. 1

Though CPT is available in quantity from natural sources, MPK has only been isolated in low content which prohibits further studies. Hence, recent efforts have described improvements in the degradation of CPT,[4] as well as the development of a total synthesis of MPK[5] and related analogues.[3] To fulfill the desire of expanding SAR studies within the MPK series, it is necessary to develop a more generalised synthetic route. Herein, we report an elegant approach for the total synthesis of mappicine ketone and racemic mappicine.

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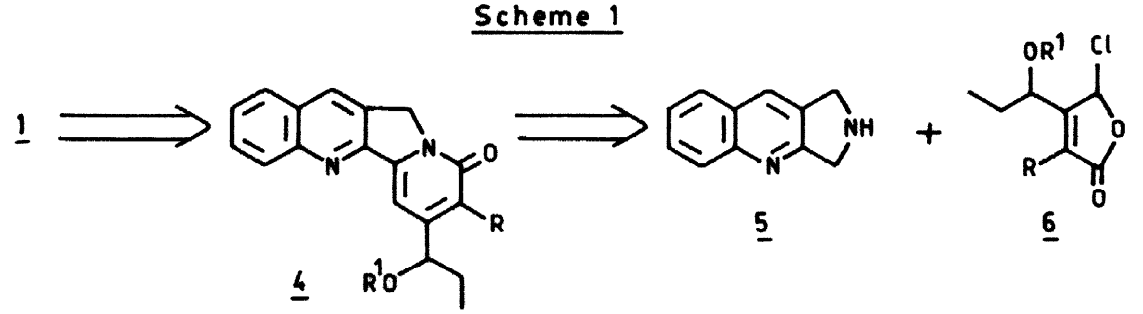
RESULTS AND DISCUSSION

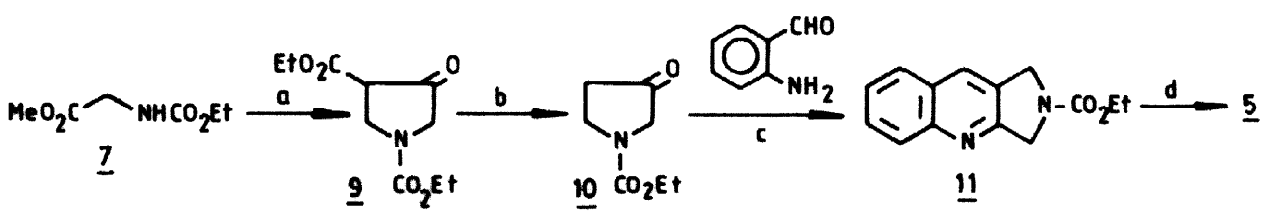
On the basis of our own work[6] in the area of the total synthesis of CPT, we developed a convergent retrosynthetic route to mappicine ketone as shown in Scheme 1. This strategy revealed that the pseudo acid halide **6** could be assembled with tricyclic amine **5** to give a key retron **4** which could be successfully converted into mappicine ketone.

Scheme 1



The tricyclic amine was synthesized successfully starting from cheaply available glycine (Scheme 2). Accordingly, *N*-carbethoxymethyl ester derivative of glycine **7**[7a] underwent one pot Michael addition as well as Dieckmann cyclization with ethyl acrylate **8** to afford **9**. Compound **9** after decarboxylation provided **10** which was subjected to Friedlander condensation with 2-amino benzaldehyde to produce the key intermidiate **11**.[7b] Compound **11** on basic hydrolysis of the carbamate group gave the crucial tricyclic amine **5** quantitatively.[7b]

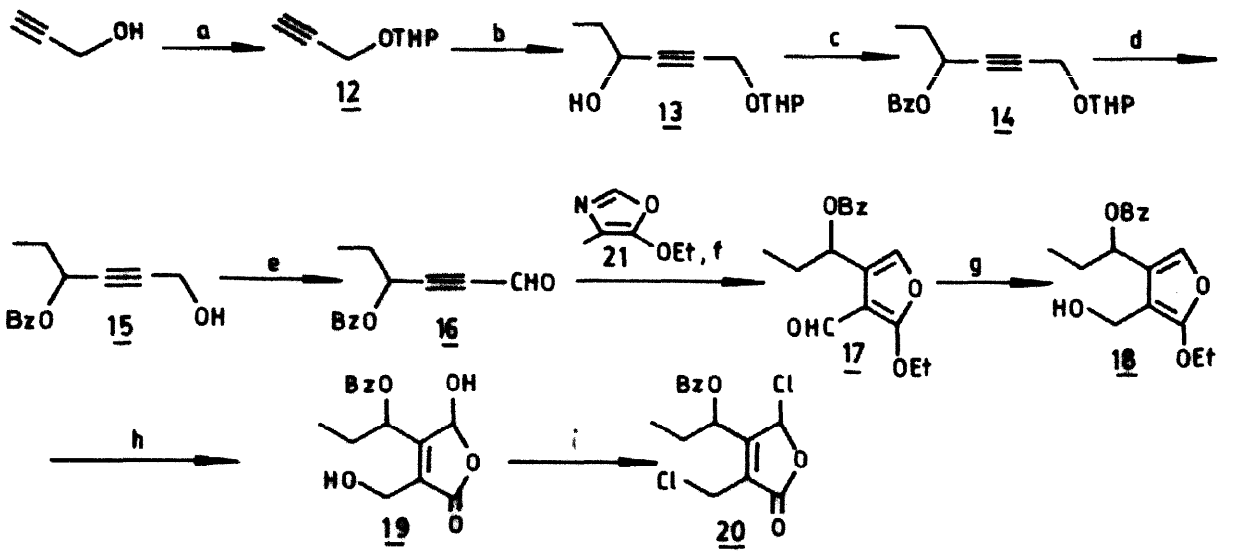
Scheme 2



Reagents and conditions : a) NaH, benzene, rt, 12 h and then CH_2=CH-CO_2Et **8**, reflux, 2 h (85%); b) 6 N HCl : H_2O (1 : 15), reflux, 4 h (92%); c) ref. 7b; d) ref. 7b.

On the other hand, for the preparation of the pseudo acid halide part (Scheme 3), commercially available propargyl alcohol was protected as its pyranyl ether derivative **12** which was then alkylated with propionaldehyde to give **13**. Protection of the secondary alcohol group as its benzoate ester and deprotection of the pyranyl group provided **15** via **14**. Conventional PCC oxidation of **15** furnished aldehyde **16** which underwent a Diels-Alder reaction with the well known diene unit[8] oxazole **21** to give periselective adduct **17**. This adduct was reduced to alcohol **18** with $NaBH_4$. Alcohol **18** was converted into the crucial butenolide unit **19** using active MnO_2 and conc. HCl in THF, a methodology developed by our group.[9] Compound **19** was then treated with $SOCl_2$ to get the desired pseudo acid chloride **20** as the key intermediate.

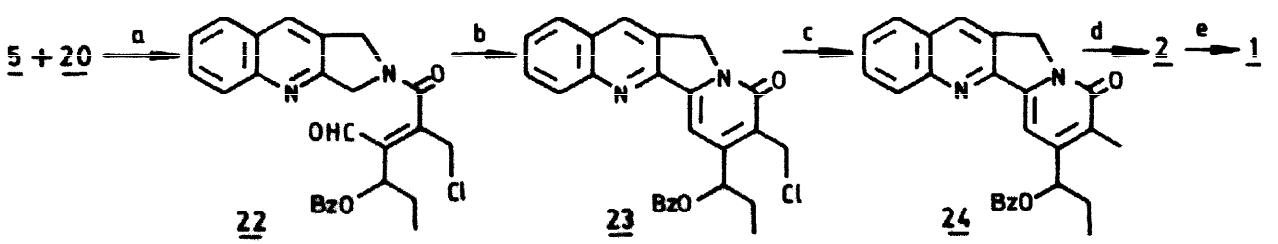
Scheme 3



Reagents and conditions: a) DHP, DCM, PTSA (cat), rt, 3 h (93%); b) EtMgBr, THF, propionaldehyde, rt, 14 h (86%); c) BzCl, Et_3N, DMAP (cat), DCM, rt, 1 h (88%); d) PTSA (cat), MeOH, rt, 3 h (72%); e) PCC, DCM, rt, 3 h (70%); f) tolune, reflux, 12 h (65%); g) $NaBH_4$, MeOH, rt, 1 h (82%); h) MnO_2, 35% HCl, -10 °C, 30 min (65%); i) $SOCl_2$, DMF (cat), $CHCl_3$, rt, 3 h (80%).

After successful preparation of **5** and **20**, the main target was to couple them to get the ABCD ring skeleton of MPK (**Scheme 4**). The tricyclic amine **5** was coupled with **20** using 10% pyridine-acetonitrile media[10] which provided the aldehyde **22**. Compound **22** after cyclization using 20% sodium acetate-acetic acid gave the key retron **23**. Our next crucial job was to introduce the methyl group at the C-8-position of MPK. Reductive dechlorination of **23** under catalytic hydrogenation conditions using 10% $Pd(OH)_2/C$ as catalyst in ethanol provided the benzoate derivative of mappicine **24**. The benzoate group was removed using NaOMe in methanol to furnish mappicine **2** which was oxidised with PCC[5d] to give the target molecule **1**.

Scheme 4



Reagents and conditions: a) pyridine : acetonitrile (1 : 9), rt, 12 h (40%); b) NaOAc, AcOH, rt, 20 h (40%); c) $Pd(OH)_2/C$, H_2, NaOAc, EtOH, rt, 24 h (68%); d) NaOMe (cat), MeOH, rt, 10 h (66%); e) PCC, celite, DCM, rt, 12 h (60%).

In conclusion, we have developed an elegant synthetic route for the total synthesis of MPK. This strategy can be utilized for the preparation of several MPK analogues for SAR studies. Work in this direction is currently underway.

EXPERIMENTAL

Melting points were recorded on a Buchi R-535 apparatus and are uncorrected. Moisture and air sensitive reactions were carried out under nitrogen atmosphere using dry solvents, prepared by standard procedure. IR spectra were recorded on a Perkin-Elmer infrared 683 spectrophotometer with NaCl optics. ^{1}H NMR spectra were recorded on Varian Unity 400 or Varian Gemini 200 spectrometers. The samples were recorded in $CDCl_3$ using tetramethylsilane as the internal standard and are given on the δ scale. Mass measurements were carried out on a CEC-21-110B double focussing mass spectrometer operating at 70 eV and are given in the mass units (m/z). TLC was performed on 0.25 mm E.Merck precoated silica plates (60F-254). All the products were purified by column chromatography on silica gel (100-200 mesh).

Diethyl 4-oxotetrahydro-1H-1,3-pyrroledicarboxylate (9):

60% dispersion of sodium hydride (37.78 g, 1.49 mol) in mineral oil was taken in dry benzene (150 mL) and to this, compound **7** (100 g, 0.62 mol) in dry benzene (300 mL) was added dropwise with stirring. During addition, the reaction mixture was initially heated at 100 °C to initiate the reaction. The heating was then removed and the refluxing condition was maintained by the slow addition of compound **7**. The reaction mixture was stirred at room temperature for 12 h. Ethyl acrylate **8** (70 g, 0.70 mol) was added slowly over a period of 30 min and refluxed for 2 h. The reaction mixture was then quenched with water and extracted with benzene (4x500 mL). The organic layer was washed with water, brine and dried (Na_2SO_4). Removal of organic solvent under reduced pressure gave crude material which after column chromatography (using 40% ethyl acetate in hexane) on silica gel furnished compound **9** (120.9 g, 85 % yield) as a white solid, mp 52-54 °C, lit.[7a] mp 59-62 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.12-1.38 (m, 6H), 4.02-4.34 (m, 9H); IR (KBr) : 1750, 1710 cm^{-1}; EIMS (m/z) : 229 (M^+), 184; HRMS calcd. for $C_{10}H_{15}NO_5$ 229.0950, found 229.0959.

Ethyl 3-oxotetrahydro-1H-1-pyrrolecarboxylate (10):

A mixture of compound **9** (60 g, 0.38 mol), 6 N HCl (10 mL) and water (150 mL) was refluxed for 4 h. Water was removed under reduced pressure and the resultant residue was diluted with ethyl acetate (500 mL). The organic layer was washed with water, brine and dried (Na_2SO_4). Removal of organic solvent gave crude material which after column chromatography (using 30% ethyl acetate in hexane) on silica gel afforded **10** (37.84 g, 92 % yield) as a liquid. ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.24 (t, J= 7.9 Hz, 3H), 2.56 (t, J= 9.2 Hz, 2H), 3.64-3.82 (m, 4H), 4.10 (q, J= 7.9 Hz, 2H); IR (neat) : 2985, 1737, 1707 cm^{-1}; EIMS (m/z) : 157 (M^+), 129, 112; HRMS calcd. for $C_7H_{11}NO_3$ 157.0739, found 157.0742.

Ethyl 2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-2-carboxylate (11):

Compound **11** was prepared following literature procedure[7b] as a yellow solid in 88% yield, mp 130 °C, lit[7b] mp 134 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.35 (t, J= 6.7 Hz, 3H), 4.28 (q, J= 6.7 Hz, 2H), 4.88 (s, 4H), 7.42-8.10 (m, 5H); IR (KBr) : 1710, 1620 cm^{-1}; EIMS (m/z) : 242 (M^+), 213, 169, 140; HRMS calcd. for $C_{14}H_{14}N_2O_2$ 242.1055, found 242.1060.

2,3-Dihydro-1H-pyrrolo[3,4-b]quinoline (5):

Compound **5** was prepared following literature procedure[7b] as a buff coloured solid in 83% yield, mp 96 °C, lit.[7b] mp 101-103 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.1 (br s, 1H), 4.35 (s, 2H), 4.4 (s, 2H), 7.44-8.05

(m, 5H); IR (KBr) : 3250, 1553 cm^{-1}.

2-(2-Propynyloxy)tetrahydro-2H-pyran (12):

In a 1000 mL two necked round bottomed flask equipped with a calcium chloride guard tube and a dropping funnel, freshly distilled propargyl alcohol (56 g, 1.0 mol) and catalytic amount of PTSA (2 g) were taken in dry DCM (300 mL). The reaction mixture was cooled to 0 °C and to it , DHP (98.5 mL, 1.1 mol) was added dropwise through the dropping funnel. After the addition was over, the reaction mixture was brought to room temperature and stirred for 3 h. Then the reaction mixture was diluted with DCM (500 mL) and the organic layer was washed successively with aq. $NaHCO_3$ solution, water, brine and dried (Na_2SO_4). Concentration and purification over silica gel column chromatography (using 10% ethyl acetate in hexane) gave **12** (130 g, 93 % yield) as a liquid. ^1H NMR ($CDCl_3$, 200 MHz) : δ 1.42-1.90 (m, 6H), 2.32 (br s, 1H), 3.45-3.58 and 3.72-3.90 (2m, 2H), 4.22 (s, 2H), 4.8 (br s, 1H); IR (neat) : 3286, 2940, 2126 cm^{-1}.

6-Tetrahydro-2H-2-pyranyloxy-4-hexyn-3-ol (13):

To a suspension of Mg (10.285 g, 0.428 mol) in THF (100 mL), ethyl bromide (33.36 mL, 0.428 mol) in THF (50 mL) was added dropwise under nitrogen atmosphere. After the addition was over, the reaction mixture was stirred for 1 h. To this Grignard reagent, compound **12** (50 g, 0.357 mol) in THF (150 mL) was added dropwise at -10 °C. After 1 h, catalytic amount of cuprous iodide (0.34 g, 0.005 mol) was added to the reaction mixture and it was stirred for another 3 h at room temperature. Then it was again cooled to -10 °C using freezing mixture and to this, propionaldehyde (39.33 mL, 0.535 mol) in THF (50 mL) was added in a dropwise fashion. After addition, the reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched with saturated NH_4Cl solution and the THF layer was separated and the aqueous layer was extracted with ether (4x100 mL): The combined organic layer was washed with water and brine and dried over Na_2SO_4 and the solvent was rotary evaporated to give the crude material which after column chromatography (using 25% ethyl acetate in hexane) provided **13** (60.8 g, 86 % yield) as a liquid. ^1H NMR ($CDCl_3$, 200 MHz) : δ 1.00 (t, J= 8.0 Hz, 3H), 1.44-1.95 (m, 8H), 3.42-3.58 and 3.72-3.90 (2m, 2H), 4.22-4.29 (m, 2H), 4.29-4.38 (m, 1H), 4.8 (br s, 1H); IR (neat) : 3421, 2944, 1022 cm^{-1}; EIMS (m/z) : 198 (M^+), 113; HRMS calcd. for $C_{11}H_{18}O_3$ 198.1256, found 198.1252.

2-(4-Phenylcarbonyloxy-2-hexynyloxy)tetrahydro-2H-pyran (14):

Alcohol **13** (100 g, 0.505 mol) in dry DCM (600 mL) was taken in a 2 litre round bottomed flask. To this solution, dry triethylamine (109.3 mL, 0.757 mol) and DMAP (3.08 g, 0.025 mol) were added. The reaction mixture was cooled to 0 °C and to this cold solution, benzoyl chloride (70.12 mL, 0.606 mol) was added in a dropwise manner under nitrogen atmosphere. The reaction mixture was stirred for 1 h at room temperature and then diluted with DCM (600 mL). The organic layer was washed with aq. $NaHCO_3$ solution, water and brine and dried (Na_2SO_4). Concentration of organic solvent provided the crude material which after silica gel column chromatography (using 15% ethyl acetate in hexane) afforded **14** (134 g, 88 % yield) as a liquid. ^1H NMR ($CDCl_3$, 400 MHz) : δ 1.10 (t, J= 8.0 Hz, 3H), 1.50-1.85 (m, 6H), 1.95 (m, 2H), 3.50 and 3.82 (2m, 2H), 4.30 (ABq, J= 16 Hz, 2H), 4.8 (br s, 1H), 5.60 (t, J= 5.6 Hz, 1H), 7.41 (m, 2H), 7.55 (m, 1H), 8.05 (m, 2H); IR (neat) : 2930, 2272, 1716 cm^{-1}; CIMS (m/z) : 303 (M+1), 219, 201; HRMS calcd. for $C_{18}H_{23}O_4$ 303.1596, found 303.1590.

1-Ethyl-4-hydroxy-2-butynyl benzoate (15):

Compound **14** (32 g, 0.105 mol) was taken in dry methanol (200 mL). To this solution, PTSA (1.006 g, 0.0053 mol) was added and it was stirred for 3 h at room temperature. Methanol was evaporated under vacuum

and the residue was diluted with DCM (700 mL). DCM layer was washed with aq. $NaHCO_3$ solution, water and brine and dried (Na_2SO_4). Evaporation of organic solvent on a rotary evaporator and column chromatography (using 25% ethyl acetate in hexane) provided the compound **15** (16.63 g, 72 % yield) as a liquid. ^1H NMR ($CDCl_3$, 400 MHz) : δ 1.10 (t, J= 8.3 Hz, 3H), 1.92 (m, 2H), 4.3 (s, 2H), 5.58 (t, J= 5.6 Hz, 1H), 7.42 (m, 2H), 7.58 (m, 1H), 8.05 (m, 2H); IR (neat) : 3432, 2815, 1718 cm^{-1}; CIMS (m/z) : 219 (M+1), 201; HRMS calcd. for $C_{13}H_{15}O_3$ 219.1021, found 219.0989.

1-Ethyl-3-formyl-2-propynyl benzoate (16):

Compound **16** (10 g, 0.045 mol) was taken in dry DCM (200 mL) and cooled to 0 °C. PCC (14.86 g, 0.068 mol) was added portionwise to this and it was stirred for 3 h under nitrogen atmosphere. After the reaction was over (monitored by TLC), the reaction mixture was diluted with ether (500 mL) and it was filtered through short silica gel column. The filtrate was concentrated and subjected to silica gel column chromatography (using 12% ethyl acetate in hexane) to obtain **16** (6.94 g, 70 % yield) as a liquid. ^1H NMR ($CDCl_3$, 400 MHz) : δ 1.18 (t, J= 7.6 Hz, 3H), 2.02 (m, 2H), 5.72 (t, J= 5.7 Hz, 1H), 7.48 (m, 2H), 7.58 (m, 1H), 8.05 (m, 2H), 9.25 (s, 1H); IR (neat) : 2970, 2245, 1718, 1694 cm^{-1}; CIMS (m/z) 217 (M+1), 188; HRMS calcd. for $C_{13}H_{13}O_3$ 217.0865, found 217.0874.

5-Ethoxy-4-formyl-3-(1-phenylcarbonyloxypropyl)furan (17):

Aldehyde **16** (6 g, 0.028 mol) and oxazole **21** (3.56 g, 0.028 mol) were taken in dry toluene (50 mL) and refluxed overnight under nitrogen atmosphere. Toluene was removed from the reaction mixture and the residue was subjected to column chromatography (using 14% ethyl acetate in hexane) to provide compound **17** (5.45 g, 65 % yield) as a liquid. ^1H NMR ($CDCl_3$, 400 MHz) : δ 1.0 (t, J= 7.1 Hz, 3H), 1.50 (t, J= 8.9 Hz, 3H), 1.96-2.18 (m, 2H), 4.42 (q, J= 8.9 Hz, 2H), 6.19 (t, J= 6.3 Hz, 1H), 6.82 (s, 1H), 7.42 (m, 2H), 7.58 (m, 1H), 8.05 (m, 2H), 9.80 (s, 1H); IR (neat) : 1713, 1666 cm^{-1}; EIMS (m/z) : 302 (M^+), 197, 180; HRMS calcd. for $C_{17}H_{18}O_5$ 302.1154, found 302.1172.

5-Ethoxy-4-hydroxymethyl-3-(1-phenylcarbonyloxypropyl)furan (18):

Compound **17** (4 g, 0.013 mol) was taken in dry methanol (20 mL) and cooled to 0 °C under nitrogen atmosphere. To this well stirred solution, $NaBH_4$ (0.603 g, 0.016 mol) was added and stirring was continued for additional 1 h at room temperature. The reaction mixture was quenched with water and it was extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with water, brine and dried (Na_2SO_4). After evaporation of organic solvent, the crude compound was purified by column chromatography (using 20% ethyl acetate in hexane) to get **18** (3.30 g, 82 % yield) as a liquid. ^1H NMR ($CDCl_3$, 200 MHz) : δ 1.08 (t, J= 6.8 Hz, 3H), 1.36 (t, J= 8.2 Hz, 3H), 1.88-2.10 (m, 2H), 4.20 (q, J= 8.2 Hz, 2H), 4.65-4.90 (ABq, J= 18.2 Hz, 2H), 6.05 (t, J= 6.4 Hz, 1H), 6.90 (s, 1H), 7.48-7.60 (m, 3H), 7.95-8.05 (m, 2H); IR (neat) : 3400, 1710 cm^{-1}; EIMS (m/z) : 304 (M^+), 182; HRMS calcd. for $C_{17}H_{20}O_5$ 304.1311, found 304.1313.

2-Hydroxy-4-hydroxymethyl-5-oxo-3-(1-phenylcarbonyloxypropyl)-2,5-dihydrofuran (19):

8.58 mL of 35 % HCl was taken in a round bottomed flask and it was cooled to -10 °C using ice-salt mixture. To this well stirred acid solution, **18** (2.5 g, 0.0082 mol) in THF (10 mL) and active MnO_2 (2.86 g, 0.033 mol) was added simultaneously. After the addition was over, the reaction mixture was stirred for another 30 min and then it was diluted with ether (200 mL). Ether layer was washed successively with water, brine and dried (Na_2SO_4). After concentration on a rotary evaporator, the residue was subjected to silica gel column chromatography (using 40% ethyl acetate in hexane) to provide compound **19** (1.56 g, 65% yield) as a liquid. ^1H NMR ($CDCl_3$, 200 MHz) : δ 1.08 (2t, J_1= J_2= 6.8 Hz, 3H), 1.88-2.20 (m, 2H), 4.38 and 4.80 (2m, 2H), 5.80

and 6.06 (2m, 1H), 5.95 and 6.16 (2 br s, 1H), 7.36-7.65 (m, 3H), 7.95-8.06 (m, 2H); IR (neat) : 3412 (br), 2925, 1766, 1718 cm^{-1}; EIMS (m/z) : 292 (M^+), 275, 259, 105; HRMS calcd. for $C_{15}H_{16}O_6$ 292.0947, found 292.0938.

2-Chloro-4-chloromethyl-5-oxo-3-(1-phenylcarbonyloxypropyl)-2,5-dihydrofuran (20):

To a well stirred solution of compound **19** (1.56 g, 0.0053 mol) in dry chloroform (15 mL), catalytic amount of DMF was added and to this thionyl chloride (0.86 mL, 0.0118 mol) was added dropwise under nitrogen atmosphere. The reaction mixture was stirred till the starting material was disappeared as judged by TLC. Then it was diluted with chloroform (50 mL) and the chloroform layer was washed with water, brine and dried (Na_2SO_4). The organic solvent was rotary evaporated and the residue was subjected to column chromatography (using 15% ethyl acetate in hexane) to obtain **20** (1.41 g, 80% yield) as a liquid. ^1H NMR ($CDCl_3$, 200 MHz) : δ 1.16 (2t, $J_1 = J_2 = 7.2$ Hz, 3H), 2.15 (m, 2H), 4.35 (m, 2H), 5.45 and 6.15 (2m, 1H), 6.45 and 6.78 (2s, 1H), 7.42-7.66 (m, 3H), 7.99-8.12 (m, 2H); IR (neat) : 1788, 1718 cm^{-1}; EIMS (m/z) : 293 (M-Cl) ; FABMS (m/z) : 329 (M+1), 293; HRMS calcd. for $C_{15}H_{14}O_4Cl$ 293.0581, found 293.0578.

2-(2-Chloromethyl-3-formyl-4-phenylcarbonyloxy-2-hexenoyl)-2,3-dihydro-1H-pyrrolo[4,3-b]quinoline (22):

Compound **5** (400 mg, 2.35 mmol) was taken in a mixture of anhydrous acetonitrile (2 mL) and pyridine (0.5 mL). To this, compound **20** (418 mg, 1.27 mmol) in dry acetonitrile (3 mL) was added with stirring perfectly under nitrogen atmosphere. Stirring was continued for 12 h at room temperature. Organic solvent was removed under vacuum and the residue was diluted with DCM (50 mL). Organic layer was washed with water, brine and dried (Na_2SO_4). Organic solvent was evaporated to get **22** (0.217 mg, 40% yield) which was treated for the next reaction without any purification.

3-Chloromethyl-4-oxo-2-(1-phenylcarbonyloxypropyl)-4,6-dihydroindolizino[1,2-b]quinoline (23):

Acetic acid (5 mL) and sodium acetate (1 g) were added successively to compound **22** (217 mg, 0.50 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 20 h. Then it was diluted with DCM (50 mL) and neutralised with saturated aq. solution of $NaHCO_3$. Organic layer was separated and washed successively with water and brine and dried (Na_2SO_4). Concentration of organic solvent and purification over column chromatography (using 2% MeOH in DCM) provided **23** (83 mg, 40% yield) as a pasty material. ^1H NMR ($CDCl_3$, 200 MHz) : δ 1.25 (t, J= 7.2 Hz, 3H), 2.3 (m, 2H), 4.25-4.45 (m, 2H), 5.19-5.38 (m, 2H), 5.90-6.05 (m, 1H), 7.3-8.6 (m, 11H); IR (KBr) : 1710, 1660 cm^{-1}; FABMS (m/z) : 338 (M-PhCHO), 310; HRMS calcd. for $C_{19}H_{15}N_2O_2Cl$ 338.0822, found 338.0829.

3-Methyl-4-oxo-2-(1-phenylcarbonyloxypropyl)-4,6-dihydroindolizino[1,2-b]quinoline (24):

Compound **23** (83 mg, 0.188 mmol) was taken in dry ethanol. Catalytic amount 10% $Pd(OH)_2/C$ (20 mg) and anhydrous sodium acetate (23 mg, 0.28 mmol) was added to it. The reaction mixture was stirred under hydrogen atmosphere for 24 h. Catalyst was filtered off and the filtrate was concentrated under vacuum to get crude material which was charged on silica gel column chromatography (using 2% methanol in DCM) to furnish **24** (52 mg, 68 % yield) as a yellow solid, mp 172 °C. ^1H NMR ($CDCl_3$, 200 MHz) : δ 1.14 (t, J= 6.7 Hz, 3H), 2.05 (m, 2H), 3.05 (s, 3H), 5.30 (br s, 2H), 6.55 (m, 1H), 7.32-8.4 (m, 11H); IR ($CHCl_3$) : 1728, 1655 cm^{-1}; FABMS (m/z) : 411 (M+1); HRMS calcd. for $C_{26}H_{23}N_2O_3$ 411.1709, found 411.1715.

2-(1-Hydroxypropyl)-3-methyl-4,6-dihydroindolizino[1,2-b]quinolin-4-one (2):

To a well stirred solution of compound **24** (52 mg, 0.13 mmol) in dry MeOH, catalytic amount of NaOMe was added under nitrogen atmosphere. The reaction mixture was stirred for 10 h. After completion of reaction

(as judged by TLC) methanol was removed and the residue was diluted with chloroform (50 mL). Organic layer was washed with water, brine and dried (Na_2SO_4). Organic solvent was removed and the residue was column chromatographed (using 4% MeOH in $CHCl_3$) to furnish compound **2** (25 mg, 66% yield) as a yellow solid, mp 268-269 °C, lit.[5b] mp 271-273 °C. ^1H NMR (d_6-DMSO, 200 MHz) : δ 0.95 (t, J= 7.5 Hz, 3H), 1.75 (m, 2H), 2.52 (s, 3H), 5.05 (m, 1H), 5.26 (br s, 2H), 7.45-8.50 (m, 6H); IR (KBr) : 3265, 1660 cm^{-1}; CIMS (m/z) : 307 (M+1); HRMS calcd. for $C_{19}H_{19}N_2O_2$ 307.1447, found 307.1438.

1-(3-Methyl-4-oxo-4,6-dihydroindolizino[1,2-b]quinolin-2-yl)-1-propanone (1):

A solution of **2** (25 mg, 0.08 mmol) in dry DCM (2 mL) was added to a mixture of PCC (35 mg, 0.16 mmol) and celite (50 mg) in DCM (2 mL). The reaction mixture was stirred overnight at room temperature then filtered over a short pad of silica gel and eluted with chloroform/acetone (1 :1). The organic solvent was then concentrated and subjected to column chromatography (using 3% methanol in DCM) to get the product which was furthur purified by preparative TLC using 3% methanol in DCM as eluent to provide **1** (15 mg, 60% yield) as a yellow solid, mp 235-236 °C, lit.[5b] mp 237-238 °C. ^1H NMR ($CDCl_3$-d_6-DMSO, 200 MHz) : δ 0.98 (t, J= 7.1 Hz, 3H), 1.90 (q, J= 7.1 Hz, 2H), 2.55 (s, 3H), 5.3 (s, 2H), 7.55-8.55 (m, 6H); IR (KBr) : 2918, 1710, 1651 cm^{-1}; EIMS (m/z) : 304 (M^+), 289, 248; HRMS calcd. for $C_{19}H_{16}N_2O_2$ 304.1212, found 304.1200.

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REFERENCES

1. Govindachari, T. R.; Ravindranath, K. R.; Viswanathan, N. *J. Chem. Soc. Perkin Trans. 1* **1974**, 1215.

2. (a) *Camptothecin : New Anticancer Agents*, Potmesil, M. and Pinedo, H. Eds.; CRC, Boca Raton, FL, **1995**. (b) Luzzio, M. J.; Besterman, J. M.; Emerson, D. L.; Evans, M. G.; Lackey, K.; Leitner, P. L.; Mcintyre, G.; Morton, B.; Myers, P. L.; Peel, M.; Sisco, J. M.; Sternbach, D. D.; Tong, W. -Q.; Truesdale, A.; Uehling, D. E.; Vuong, A.; Yates, J. *J. Med. Chem.* **1995**, *38*, 395.

3. (a) Pendrak, I.; Barney, S.; Wittrock, R.; Lambert, D. M.; Kingsbury, W. D. *J. Org. Chem.* **1994**, *59*, 2623. (b) Pendrak, I.; Wittrock, R.; Kingsbury, W. D. *J. Org. Chem.* **1995**, *60*, 2912.

4. (a) Fortunak, J. M. D.; Mastrocola, A. R.; Mellinger, M.; Wood, J. L. *Tetrahedron Lett.* **1994**, *35*, 5763. (b) Kingsbury, W. D. *Tetrahedron Lett.* **1988**, *29*, 6847. (c) Das, B.; Madhusudhan, P.; Kashinatham, A. *Tetrahedron Lett.* **1998**, *39*, 431.

5. (a) Kametani, T.; Takeda, H.; Nemoto, H.; Fukumoto, K. *Heterocycles*, **1975**, *3*, 167. (b) Kametani, T.; Takeda, H.; Nemoto, H.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1825. (c) Comins, D. L.; Saha, J. K. *J. Org. Chem.* **1996**, *61*, 9623. (d) Josein, H.; Curran, D. P. *Tetrahedron*, **1997**, *53*, 8881. (e) Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **1998**, *120*, 1218.

6. Rama Rao, A. V.; Yadav, J. S.; Valluri, M. *Tetrahedron Lett.* **1994**, *35*, 3613.

7. a) Kuhn, R.; Osswald, G.; *Chem Ber*, **1956**, *89*, 1423. b) Zalkow, L. H.; Nabors, J. B.; French, K.; Bisarya, S. C. *J. Chem. Soc. (c)*, **1971**, 3551.

8. Turchi, I. J.; Dewar, M. J. S.; *Chem. Rev.* **1975**, *75*, 389.

9. Yadav, J. S.; Valluri, M.; Rama Rao, A. V. *Tetrahedron Lett.* **1994**, *35*, 3609.

10. Corey, E. J.; Crouse, D. N.; Anderson, J. E. *J. Org. Chem.* **1975**, *40*, 2140.