SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 17, pp. 3099–3110, 2004

Facile Syntheses of ABC Ring Skeleton of Camptothecin and Related Alkaloids

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ABSTRACT

Facile synthetic approaches toward the preparation of ABC ring of camptothecin and related alkaloids starting from cheaper and readily available chemical reagents.

Key Words: Camptothecin; Alkaloids; ABC ring skeleton.

Wall and coworkers[1] isolated Camptothecin (**1**), a potential anticancer chemotherapeutic agent, in the early 1960s from *Camptotheca acuminata*. Spanning four decades it has been the compound of choice for both medicinal as well as synthetic chemists. Nothapodytine B [Mappicine ketone (**2b**)]

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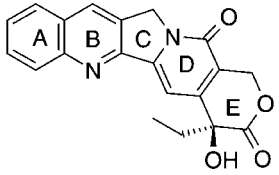
DOI: 10.1081/SCC-200028560 0039-7911 (Print); 1532-2432 (Online)

isolated recently from *Nothapodytes foetida*[2] (an oxidized derivative of Mappicine[3] and E-ring decarboxylated analogue of camptothecin) has been identified as an antiviral lead with reported selectivity against HSV-1, HSV-2, and HCMV.[4] Intense research on camptothecins has culminated in launching



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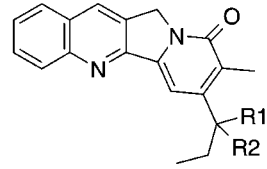
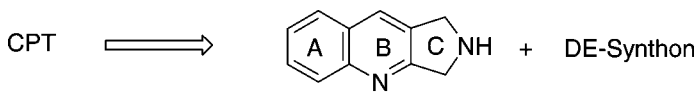


2 a) R1=H and R2=OH - mappicine
b) R1 = R2 = O -Nothapodytine B

two successful compounds in clinical practice (irinotecan and topotecan) and several other compounds in clinical development.[5] Given the current continued interest, many syntheses have been achieved, still there is an evident need for the development of a new synthetic route amenable to camptothecin and its analogues.

Several groups involved in the convergent synthesis of camptothecin and mappicine ketone identified the tricylic amine **3** as a key synthon for the construction of ABC ring system (Sch. 1).[6] Reports involving the preparation of this key intermediate have utilized chemical reagents, which are either expensive, unstable, low yielding, or pose handling problems.[6] These limitations are certainly a drawback during large-scale preparation of this tricyclic amine **3**. This implies that there is an evident need for new methods to synthesize this important intermediate. As a part of our research to explore new synthetic approaches toward camptothecin[7a,7b] and mappicine ketone,[7c] we decided to explore new synthetic sequences to provide the tricyclic amine **3** using simple and commercially available starting materials.

Meth-Cohn's quinoline aldheyde **4**[8] with a formyl group at 3-position and the handle at 2-position for the functionalization, i.e., C-C bond formation, given the flexibility and simplicity for the analogues preparation,[9] appealed to be the ideal starting material. This approach certainly circumvents the short-



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Scheme 1.

comings of the earlier approaches such as usage of 2-aminobenzaldehyde, regiochemistry problems encountered in Friedlander condensation, and the usage of expensive starting materials like acridine, propargyl amine, and dimethylacetylene dicarboxylate (DMAD).[6]

Thus, the formyl group of the iodoaldehyde **4** was protected as cyclic acetal **5** according to literature procedure (Sch. 2).[8] Quenching the lithio derivative of **5** with dimethyl formamide (DMF) provided the 3-oxolyl-2-formyl-quinoline (**6**) in 64% yield after column chromatography. Treatment of acetal **6** with 20% HCl in ether furnished dialdehyde **7**. Gratifyingly, the treatment of dialdehyde **7** with 0.6 equivalent of benzyl amine followed by the reduction (in the same pot) with sodium borohydride at 0°C and resulted in the formation of tricyclic amine **8** after usual work-up and column chromatography. The amine obtained was converted to its carbamate **9**[10] by refluxing with ethyl chloroformate whose deprotection to tricyclic amine **3** can be obtained by established protocol.[6e]

A much closer look at the tricyclic amine revealed another synthetic route starting from cheaper and readily available quinoline ester (Sch. 3).[11]

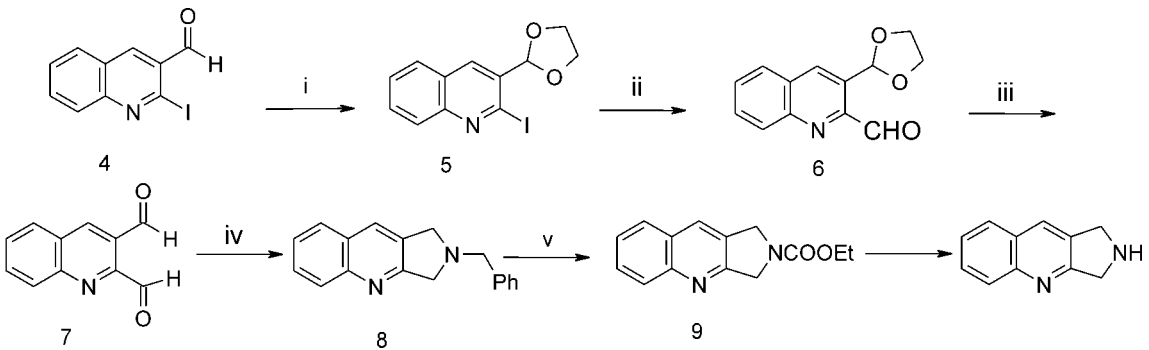
Reduction of the ester group in quinoline **10** with lithium aluminium hydride furnished the corresponding hydroxyquinoline **11** in 55% yield.[11] The oxidation of **11** with 13-chloroperbenzoic acid (MCPBA) at room temperature resulted in the formation of corresponding quinoline *N*-oxide **12** in very high yields. The same transformation was also achieved with peracetic acid as an oxidizing agent. Further treatment of quinoline *N*-oxide **12** with acetic anhydride followed by acetate hydrolysis furnished the diol **14** in good yields. The diol **14** obtained was converted to its dimesylate **15** as per Corey's protocol whose conversion to tricyclic amine can be obtained by literature reports.[6b,6c]

In conclusion, new and facile synthetic approaches toward the preparation of ABC ring of camptothecin and related alkaloids were achieved starting from cheaper and readily available chemical reagents.

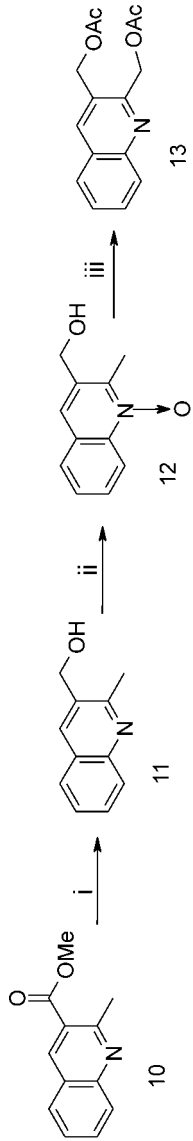
EXPERIMENTAL SECTION

General Remarks

All melting points reported are uncorrected and the temperature is expressed in degree scale. All solvents were distilled before use. Benzene, tetrahydro furan (THF), and diethyl ether were dried over sodium. Dimethyl formamide (DMF) was dried over calcium hydride. Petroleum ether refers to the fraction boiling in the range of 60°C–80°C. When chromatographic purification was done, SiO_2 (60–120 mesh size) or activated neutral alumina was used as stationary phase. The reaction progress was monitored



Scheme 2. Reagents and conditions: (i) ethylene glycol, PTSA, C_6H_6, azeotrope, 6 h, 90%; (ii)BuLi DMF, ether, −78°C, 1 h, 57%; (iii) 10% HCl, RT, 1 h, 92%; (iv) (a) $BnNH_2$, MeOH, RT, 1 h, (b) $NaBH_4$, MeOH, 0°C, 1 h, 80%, (v) ClCOOEt, C^6H_6, reflux, 2 h, 74%.



Scheme 3. Reagents and conditions: (i) LAH, THF, 0°C, 1 h, 55%; (ii) MCPBA, CH_3CN, RT, 12 h, 90%; (iii) Ac_2O, 130°C, 2 h, 75%; (iv) K_2CO_3, aq. MeOH, RT, 1/2 h, 80%, (v) MsCl, TEA, C_6H_6, 0°C, 1 h, 80%.

by the thin layer plates precoated with silica gel 60 $\mathbf{F}_{254}$ (Merck). Infrared (IR) spectra were recorded on Perkin Elmer infrared spectrophotometer model 683B or 1605 FTIR, and IR absorbance is expressed in cm^{-1}. The proton and carbon-13 NMR spectra were recorded on Bruker AC-200, MSL-300, and DRX-500 and chemical shifts are reported on δ scale. Mass spectra were recorded at an ionization energy 70 eV on Finnigan MAT-1020, automated GC/MS instrument, and on API Q STARPULSAR using electron spray ionization [(ESI), solvent medium-water, acetonitrile and ammonium acetate] technique and mass values are expressed as m/z. Elemental analyses (C, H, N) were obtained on a Carlo-Erber 1100 automatic analyzer.

3-[1,3] Dioxaolan-2-yl-2-iodo-quinoline [5]

A solution of 2-iodo-3-formyl quinoline (**4**) (28.3 g, 0.1 mol) in benzene (300 mL) containing ethylene glycol (18.62 g, 0.3 mol) and catalytic amount of PTSA was heated under reflux for 7 h with azeotropic removal of water. The cooled solution was treated with sat. $NaHCO_3$ solution (100 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to give **5** as a white solid (34.1 g, 90%), which was pure enough for further use.

Melting point	110°C
IR (Nujol): cm^{-1}	1625, 1555, 1310, 1175
^1H NMR ($CDC1_3$, 200 MHz): δ	4.14 (m, 4H), 5.99 (s, 1H), 7.54 (m, 1H), 7.7–7.82 (m, 2H), 8.02 (m, 1H), 8.15 (s, 1H)
Mass: m/z (%)	327 (M^+, 5), 235 (80), 204 (10), 200 (30), 190 (50), 163 (100), 148 (75), 127 (50), 101 (30)

3-[1,3] Dioxolan-2-yl-quinoline-2-carbaldehyde [6]

3-[1,3] Dioxolan-2y1-2-iodo-quinoline (**5**) (0.654 g, 2.88 mmol) in dry ether at −70°C under N_2 atmosphere was treated with *n*-BuLi (1.9 mL, 1.6 *M* sol in hexane, 3 mmol) with stirring, and after few minutes dry DMF was added. After reaching ambient temperature the solution was quenched with water and extracted with $CHCl_3$ (3 × 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude aldehyde, which was purified by column chromatography over silica gel using ethyl acetate-pet ether (3 : 7) as eluent to give pure **6** as a pale yellow solid in 64% yield (0.278 g).

Melting point	103°C
IR ($CHCl_3$): cm^{-1}	1685, 1617, 1560, 1145, 910

^{1}H NMR ($CDCl_3$, 200 MHz): δ	4.18 (m, 4H), 6.73 (s, 1H), 7.57 (t, 1H), 7.61 (t, 1H), 7.81 (d, $J = 8.3$ Hz, 1H), 8.25 (d, $J = 8.3$ Hz, 1H), 8.6 (s, 1H), 10.37(s, 1H)
Mass: m/z (%)	229 (M^+, 1), 228 (5), 200 (92), 169(30), 157(100), 129(100)

Quinoline-2, 3-dialdehyde [7]

The quinoline acetal **6** (0.460 g, 2 mmol) was suspended in a 1 : 2 mixture of aq HCl solution (5 mL, 2 *M*) and ether (10 mL) for 1 h. Ether layer was removed and the aqueous phase was rendered basic with saturated sodium bicarbonate solution and extracted with $CHCl_3$ (2 × 5 mL). The organic layer was dried over sodium sulfate, filtered, and evaporated under reduced pressure to give dialdehyde **7** as a yellow solid in 92% yeld (0.340 g).

Melting point	173°C–175°C
IR ($CHCl_3$): cm^{-1}	1705, 1680, 1620, 1575
^{1}H NMR($CDCl_3$, 200 MHz): δ	7.8 (m, 1H), 7.98 (m, 1H), 8.06 (m, 1H), 8.31 (m, 1H), 8.86 (s, 1H), 10.38 (s, 1H), 11.02 (s, 1H)
Mass (ESI): m/z	184 $(M-1)^+$

2-Benzyl-2,3-dihydro-lH-pyrrolo[3, 4-b]quinoline [8]

Quinoline dialdehyde **7** (1.85 g, 10 mmol) and benzylamine (0.645 g, 0.6 eq) were mixed in methanol (20 mL) at room temperature under nitrogen atmosphere and the mixture was further stirred for 1 h, until the aldimine formation was completed. The aldimine in methanol at 0°C was carefully treated with solid sodium borohydride (0.6 g, 1.6 mmol) and was stirred for 1 h. Methanol was reduced under reduced pressure, quenched with water, and extracted with chloroform (2 × 30 mL). The combined organic extracts were washed with saturated aq NaCl (10 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated and pure tricyclic amine **8** (80% yield, 2.10 g) was obtained by column chromatography over alumina using 20% pet ether-ethyl acetate as a white solid.

Melting point	116°C–118°C, lit[6g] mp-118°C
IR ($CHCl_3$): cm^{-1}	3340, 1540, 260
^{1}H NMR ($CDCl_3$, 200 MHz): δ	4.00, (s, 2H), 4.05 (s, 2H), 4.13 (s, 2H), 7.5–7.23 (m, 6H), 7.76 (m, 1H), 7.73 (m, 1H), 7.86 (s, 1H), 8.05 (d, 1H)
Mass: m/z (%)	260 $(M)^+$

N-Carbethoxy-2,3-dihydro-1H-(3, 4b)-quinoline [9]

To 0.35 g (1.23 mmol) of amine **8** was added (0.16 g, 1.53 mmol) of ethyl chloroformate in 25 mL of dry benzene. The mixture was refluxed under a nitrogen atmosphere for 2 h. After the completion of the reaction, benzene was removed on a rotary evaporator and the crude urethane was purified by column chromatography over silica gel using 25% pet ether-ethyl acetate as eluent to furnish 0.242 g (74% yield) of urethane **9** as a yellow solid.

Melting point	130°C–132°C, lit[6e] mp-134°C
IR ($CHCl_3$): cm^{-1}	1710
^1H NMR ($CDCl_3$, 500 MHz): δ	1.36 (t, $J = 7.1$ Hz, 3H), 4.25 (q, $J = 7.1$ Hz, 2H), 4.80 (s, 2H), 4.90 (s, zH), 7.5 (t, $J = 8.00$ Hz, 1H), 7.6 (t, $J = 8.00$ Hz, 1H) 7.7 (s, 1H), 7.9–8.1(m, 2H)
Mass (ESI): m/z	241 $(M+1)^+$

2-Methyl-3-hydroxymethylquinoline [11]

To the ester **10** (5 g, 24.8 mmol) dry THF (50 mL) was added slowly at 0°C to the suspension of LAH, (0.945 g, 24.8 mmol) in dry THF (20 mL). The reaction mixture was stirred for 1 h at 0°C, quenched with methanol, and the precipitate was filtered. The precipitate was washed with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Chromatography on silica gel (eluting with pet ether-EtOAc = 9 : 11) afforded the title compound **11** as a pale yellow solid (2.37 g, 55%).

Melting point	Above 240°C
IR (Nujol): cm^{-1}	3150, 2943, 2922, 1455
^1H NMR ($CDCl_3$, 200 MHz): ä	2.72 (s, 3H), 4.89 (s, 2H), 7.50 (m, 1H), 7.69 (m, 1H), 7.79 (d, $J = 8$ Hz, 1H), 8.03 (d, 1H, $J = 8.00$ Hz), 8.12 (s, 1H)
Mass: m/z (100%)	173 (M^+, 100), 155 (84), 144 (100), 131 (30), 115 (40), 103 (19), 89 (17), 77 (38), 63 (30)

2-Methyl-3-hydroxymethylquinoline 1-Oxide [12]

To the hydroxyquinoline **11** (2.5 g, 14.4 mmol) in acetonitrile (40 mL) was added 55% MCPBA (5 g, 16 mmol) dissolved in acetonitrile (15 mL) drop-wise. The reaction mixture was stirred overnight at room temperature. The solid obtained was filtered; washed with saturated Na_2SO_3 solution

(10 mL), $NaHCO_3$ solution (10 mL), and acetonitrile (10 mL); and dried under reduced pressure as a white solid. The crude quinoline *N*-oxide **12** thus obtained (2.45 g, 90% yield) was sufficiently pure for the subsequent reaction.

Melting point	191°C–193°C
IR (Nujol): cm^{-1}	2924, 2855, 1601, 1564, 1461, 1377
^1H NMR ($CDCl_3$, 200 MHz): ä	4.29 (s, 3H), 6.36 (s, 2H), 8.95 (m, 3H), 9.36 (m, 1H), 10.23 (d, 1H), $J = 10.00$ Hz)
^{13}C NMR (CD_3OD, 75 MHz): ä	148.59, 140.96, 136.29, 131.98, 129.54, 127.89, 119.7, 62.46, 14.33
Mass: m/z (%)	189 (M^+, 27), 172 (60), 155 (13), 144 (100), 128 (37), 115 (53), 102 (23), 89 (27), 77 (54)
Analysis expected	C 69.84, H 5.82, N 7.40
Observed	C 69.54, H 5.97, N 7.15

Acetic Acid 2-Acetoxymethyl-quinolin-3-ylmethyl ester [13]

To Ac_2O (15 mL) preheated at 110°C, quinoline *N*-oxide **12** (2 g, 10.6 mmol) was added. After stirring at the same temperature for 5 min, the reaction mixture was heated at 130°C for 90 min. Excess Ac_2O was removed under reduced pressure. The residue obtained was subjected to column chromatography on silica gel (eluting with 30% pet ether-EtOAc) afforded the title compound **13** as a colorless oil (2.17 g, 75%).

IR ($CHCl_3$): cm^{-1}	1374, 1744
^1H NMR ($CDCl_3$, 200 MHz): ä	1.98 (s, 3H), 2.02 (s, 3H), 5.17 (s, 2H), 5.29 (s, 2H), 7.38 (m, 1H), 7.55 (m, 2H), 7.94 (m, 2H)
^{13}C NMR($CDCl_3$, 50 MHz): ä	169.61, 153.91, 147.00, 136.82, 129.65, 129.14, 127.52, 127.26, 126.86, 65.51, 62.64, 20.48
Mass: m/z (%)	273 (M^+, 25), 230 (45), 170 (83), 143 (100), 130 (13), 115 (27)
Analysis expected	C 65.93 H 5.53 N 5.13
Observed	C 65.45 H 5.44 N 5.10

2-Hydroxymethyl-quinolin-3-yl-methanol [14]

To the diacetate **13** (1 g, 5.29 mmol) dissolved in aq MeOH (10 mL) was added K_2CO_3 (1.46 g, 10.58 mmol) at room temperature for 30 min. After the methanol was removed under reduced pressure, the residue was extracted with dichloromethane (3 × 20 mL). The organic layer was washed with

water, brine, dried over Na_2SO_4, and concentrated under vacuum. Column chromatography on silica gel (eluting with pet ether-EtOAc = 32 : 1) furnished the dihydroxy compound **14** as a pale yellow solid.

Melting point	118°C–120°C, lit[6b] 115°C–118°C
IR ($CHCl_3$): cm^{-1}	3202
^1H NMR ($CDCl_3$, 200 MHz): ä	1.77 (b, 1H), 4.83 (s, 2H), 4.93 (s, 2H), 7.56 (m, 1H), 7.73 (m, 1H), 7.84 (d, $J = 8.22$ Hz, 1H), 8.08 (d, $J = 8.22$ Hz, 2H), 8.18 (s, 1H)
Mass: m/z (%)	189 (M^+, 7), 171 (53), 160 (27), 143 (100), 130 (33), 115 (30), 103 (20)

Methanesulfonic Acid 2-Methanesulfonyloxymethyl-quinolin-3-ylmethyl Ester [15]

To a mixture of **14** (0.500 g, 2.7 mmol) and triethylamine (1.06 g, 10.5 mmol) in dry benzene at −5°C was added MsCl (0.909 g, 7.9 mmol) drop-wise. The reaction mixture was stirred at the same temperature for 2 h. The resulting mixture was washed with water (10 mL), saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue obtained was subjected to column chromatography on silica gel (eluting with 40% pet ether-EtOAc) afforded the title compound **15** as a colorless oil (0.73 g, 80% yield).

IR (CHC13): cm^{-1}	3020, 1604, 1497, 1360, 1215, 1175
^1H NMR ($CDCl_3$, 200 MHz): ä	3.07 (s, 3H), 3.10 (s, 3H), 5.47 (s, 2H), 5.54 (s, 2H), 7.57 (s, 1H), 7.7–7.84 (m, 2H), 8.04 (d, $J = 8.30$ Hz, 1H), 8.24 (s, 1H)

ACKNOWLEDGMENTS

Authors K. P, R. S, and M. S thank CSIR New Delhi for fellowship and funding from CSIR (New Delhi) under YSA (SPC) and DST scheme is gratefully acknowledged.

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Received in India May 18, 2004