Synthesis of Quinoline Alkaloids

A Modular Approach to Oxoindolizino Quinolines: Efficient Synthesis of Mappicine Ketone (Nothapodytine B)**

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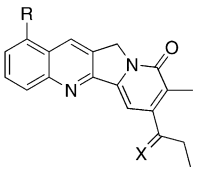
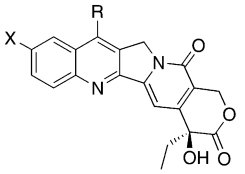
In memory of Patrick Léon

Oxoindolizino quinolines include the natural products mappicine ketone (nothapodytine B, **1a**),[1] nothapodytine A (**1b**),[1] mappicine (**1c**),[2] and camptothecin (**2a**),[3] as well as several chemotherapeutic derivatives of camptothecin, such as topotecan (**2b**) and irinotecan (**2c**).[3] While the



1a: Mappicine ketone (nothapodytine B) (R = H, X = O)
1b: Nothapodytine A (R = OCH_3, X = O)
1c: Mappicine (R = H, X = α-OH,β-H)

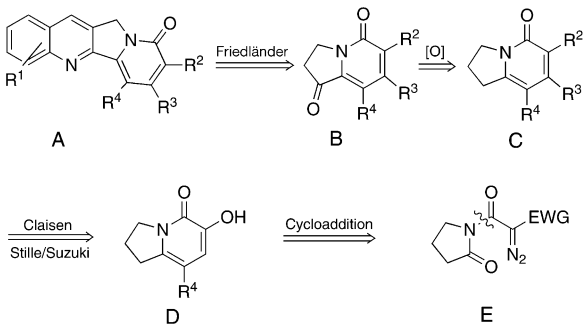


2a: Camptothecin (X = R = H)
2b: Topotecan (X = OH, R = $CH_2N(CH_3)_2 \cdot HCl$)
2c: Irinotecan (X = OCOPipPip, R = C_2H_5)

importance of these and related alkaloids has already fostered many synthetic approaches, beginning with that by Stork and Schultz[4] some 30 years ago, additional, and in particular, efficient and flexible routes remain highly desirable for discovering derivatives with improved biological profiles.

Our envisioned modular approach to these compounds is shown in retrosynthetic form in Scheme 1. A Friedländer condensation, which is ideal for accessing diversely substituted quinolines, was planned for the formation of the tetracyclic framework of the oxoindolizino quinolines.[5] The requisite ketones **B** were viewed as products of benzylic-type oxidation of pyridones **C**, which would originate from various Claisen and Stille/Suzuki transformations of hydroxypyridones **D**.[6] Hydroxypyridones **D** are easily available through cycloaddition of the isomünchnone dipoles derived from diazo imides **E**.[7]

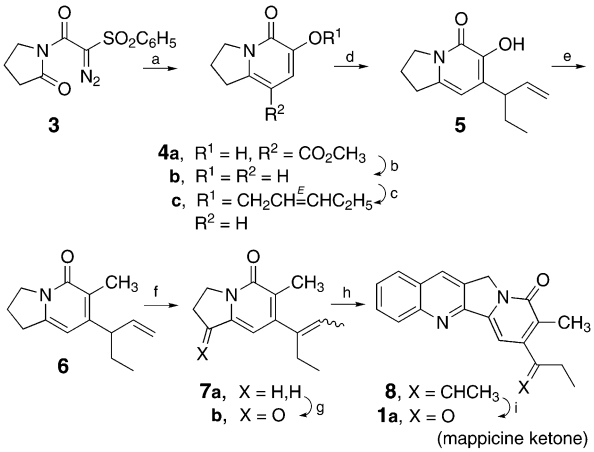
We now illustrate the feasibility of this general strategy by way of an effective synthesis of mappicine ketone (**1a**). Mappicine ketone, present in small amounts in *Nothapodytes foetida* (a plant found in India),[1] and formed by thermolysis of camptothecin,[8] displays strong, selective activity against



Scheme 1. Retrosynthesis of oxoindolizino quinolines **A**.

herpes viruses (HSV-1 and HSV-2, including Acyclovir-resistant forms) and human cytomegalovirus.[9,10]

The synthesis of **1a** began with the formation of the known adduct **4a** by cycloaddition of the carbonyl ylide derived from **3** with methyl acrylate (Scheme 2).[11] This



Scheme 2. Synthesis of **1a**. a) $[Rh(OCOCH_3)_2]_2$, $H_2C{=}CHCO_2CH_3$, C_6H_6, 90 °C, 14 h (81 %); b) 48 % aq HBr, 140 °C, 14 h (82 %); c) (*E*)-$BrCH_2CH{=}CHC_2H_5$, Cs_2CO_3, DMF, 70 °C, 1 h; d) C_6H_5Cl, reflux, 24 h (74 %, 2 steps); e) $C_6H_5NTf_2$, $N(C_2H_5)_3$, CH_2Cl_2, 0→20 °C, 18 h (94 %); $Sn(CH_3)_4$, $[PdCl_2\{P(C_6H_5)_3\}_2]$, LiCl, DMF, 110 °C, 2 h (89 %); f) $RhCl_3$, C_2H_5OH, 100 °C, 0.5 h (91 %); g) NaHMDS, O_2, $P(OC_2H_5)_3$, THF, −78 °C, 2 h (76 %); PDC, 4 Å molecular sieves, CH_2Cl_2, 0 °C, 2 h (81 %); h) *o*-$NH_2C_6H_4CHO$, *p*-TsOH, $C_6H_5CH_3$, reflux, 20 h (73 %); i) O_3, CH_2Cl_2-CH_3OH, −78 °C; $(CH_3)_2S$, −78→20 °C, 16 h (60 %). NaHMDS = sodium hexamethyldisilazide, PDC = pyridinium dichromate.

multistep sequence proceeded smoothly and in high yield when catalyzed by rhodium(II) acetate. Hot aqueous hydrobromic acid then effected decarbomethoxylation of **4a** to give **4b** in 82 % yield.[11] Etherification of **4b** with commercially available (*E*)-1-bromo-2-pentene and cesium carbonate in dimethylformamide produced the expected substitution product, which cleanly underwent Claisen rearrangement[6a] in refluxing chlorobenzene to afford the desired derivative **5** in 74 % overall yield. This transformation is a rare example of a Claisen rearrangement in a hydroxypyridone system.[12]

The α-hydroxypyridone **5** was converted into its triflate derivative under standard conditions. This was followed by Stille coupling[6b] with tetramethyltin to provide α-methyl-

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pyridone **6** in 84% yield. In the presence of rhodium(III) chloride in hot ethanol,[13] **6** rapidly isomerized to olefin **7a** (91%). The success of this key transformation derives from the carbon symmetry of the β substituent in pyridone **6**. Oxidation[14] of **7a** in two steps then selectively generated the Friedländer substrate **7b**, which reacted with *o*-aminobenzaldehyde to give oxoindolizino quinoline **8** in 73% yield. Pleasingly, ozone in dichloromethane/methanol at −78 °C accomplished selective double-bond cleavage in **8** to provide mappicine ketone (m.p. 233–234 °C), with spectroscopic and chromatographic properties identical to those of the naturally derived material (m.p. 231–232 °C).[8b]

In summary, a concise, efficient synthesis of mappicine ketone has been used to demonstrate a modular approach to oxoindolizino quinolines. By virtue of the variations that are possible in the substituents R^1–R^4 (Scheme 1), a wide range of new camptothecinoids should be easily available for biological testing. Continuing efforts are being directed toward the preparation of irinotecan and derivatives by this approach.

Experimental Section

8: A mixture of ketone **7b** (200 mg, 0.86 mmol), *o*-aminobenzaldehyde (126 mg, 1.04 mmol), and *p*-toluenesulfonic acid monohydrate (8 mg, 0.04 mmol) in toluene (10 mL) was refluxed (Dean–Stark trap) for 20 h. The solvent was then removed under reduced pressure, and the crude product was purified by column chromatography on silica gel to yield 200 mg (73%) of quinoline **8** as a mixture of *E* and *Z* isomers. FTIR: $\tilde{\nu}$ = 1650, 1590, 1375, 1226, 968, 834, 755, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, major isomer): δ = 8.31 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.76 (m, 1H), 7.59 (m, 1H), 7.12 (s, 1H), 5.41 (q, J = 6.9 Hz, 1H), 5.25 (s, 2H), 2.45 (q, J = 7.6 Hz, 2H), 2.21 (s, 3H), 1.79 (d, J = 6.9 Hz, 3H), 0.94 ppm (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, major isomer): δ = 162.0, 153.7, 153.5, 148.8, 141.5, 140.9, 130.7, 130.2, 129.5, 128.9, 128.1, 127.9, 127.3, 126.8, 124.2, 103.2, 49.8, 23.7, 14.2, 13.3, 12.5 ppm; HRMS calcd for $[C_{21}H_{20}N_2O+H]^+$: 317.1654; found: 317.1661.

Selected data for other compounds: **4c**: FTIR: $\tilde{\nu}$ = 1653, 1599, 1285, 1248, 1219, 1185, 1054 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 6.60 (d, J = 7.4 Hz, 1H), 5.89 (d, J = 7.4 Hz, 1H), 5.88 –5.72 (m, 1H), 5.65–5.54 (m, 1H), 4.41 (d, J = 5.9 Hz, 2H), 4.01 (t, J = 7.1 Hz, 2H), 2.93 (t, J = 7.7 Hz, 2H), 2.14–2.04 (m, 2H), 2.02–1.98 (m, 2H), 0.92 ppm (t, J = 7.5, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 157.4, 146.7, 140.9, 137.1, 123.5, 116.5, 99.0, 69.7, 48.6, 30.7, 25.1, 22.0, 13.0 ppm; HRMS calcd for $[C_{13}H_{17}NO_2+H]^+$: 220.1338; found: 220.1319. **5**: m.p. 120–121 °C; FTIR: $\tilde{\nu}$ = 3245, 1662, 1634, 1595, 1291, 1237 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 6.68 (br s, 1H), 5.94 (s, 1H), 5.91–5.82 (m, 1H), 5.09–5.01 (m, 2H), 4.11 (t, J = 7.2 Hz, 2H), 3.55 (q, J = 7.4 Hz, 1H), 2.96 (t, J = 7.6 Hz, 2H), 2.21–2.11 (m, 2H), 1.73–1.55 (m, 2H), 0.85 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 157.0, 141.0, 139.7, 138.3, 131.4, 115.0, 100.8, 48.5, 43.9, 30.7, 26.4, 22.3, 11.9 ppm; HRMS calcd for $[C_{13}H_{17}NO_2+H]^+$: 220.1338; found: 220.1345. **6**: m.p. 76–77 °C; FTIR: $\tilde{\nu}$ = 1641, 1581, 1537, 1184, 1009, 920, 824, 756, 680 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.95 (s, 1H), 5.86–5.74 (m, 1H), 5.09–4.98 (m, 2H), 4.10 (t, J = 7.3 Hz, 2H), 3.38 (q, J = 7.4, 1H), 2.99 (t, J = 7.7 Hz, 2H), 2.17–2.07 (m, 2H), 2.11 (s, 3H), 1.73–1.52 (m, 2H), 0.85 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 162.4, 152.0, 145.9, 139.8, 122.6, 115.2, 99.8, 48.7, 47.0, 31.5, 27.0 , 21.5, 11.9, 11.7 ppm; HRMS: calcd for $[C_{14}H_{19}NO+H]^+$: 218.1545; found: 218.1558. **7a**: m.p. 74–75 °C; FTIR: $\tilde{\nu}$ = 1646, 1570, 1541, 1314, 1209, 1168, 1050, 947, 834, 772, 665 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, major isomer): δ = 5.86 (s, 1H), 5.25 (q, J = 6.9 Hz, 1H), 4.10 (t, J = 7.2 Hz, 2H), 2.99 (t, J = 7.4 Hz, 2H), 2.30 (q, J = 7.5 Hz, 2H), 2.18–2.08 (m, 2H), 2.02 (s, 3H), 1.72 (d, J = 6.9 Hz, 3H), 0.87 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, major isomer): δ = 162.8, 153.1, 145.4, 141.3, 123.2, 120.2, 102.9, 48.8, 31.5, 23.8, 21.7, 13.7, 13.3, 12.5 ppm; HRMS: calcd for $[C_{14}H_{19}NO+H]^+$: 218.1545; found: 218.1561. **7b**: m.p. 70–71 °C; FTIR: $\tilde{\nu}$ = 1735, 1644, 1603, 1360, 1314, 1267, 1200, 1116, 838, 763, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, major isomer): δ = 6.68 (s, 1H), 5.32 (q, J = 6.8 Hz, 1H), 4.25 (t, J = 6.9 Hz, 2H), 2.85 (t, J = 6.9 Hz, 2H), 2.34 (q, J = 7.6 Hz, 2H), 2.16 (s, 3H), 1.75 (d, J = 6.8 Hz, 3H), 0.87 ppm (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, major isomer): δ = 197.2, 162.0, 152.3, 140.0, 135.9, 133.2, 124.9, 105.9, 41.8, 33.8, 23.6, 14.7, 13.3, 12.3 ppm; HRMS: calcd for $[C_{14}H_{17}NO_2+H]^+$: 232.1338; found: 232.1329. **1a**: m.p. 233–234 °C; FTIR: $\tilde{\nu}$ = 3087, 1702, 1654, 1619, 1599, 1379, 1185, 933, 838, 762 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, major isomer): δ = 8.34 (s, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.79 (m, 1H), 7.62 (m, 1H), 7.22 (s, 1H), 5.27 (s, 2H), 2.88 (q, J = 7.3 Hz, 2H), 2.28 (s, 3H), 1.23 ppm (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 205.5, 161.7, 152.9, 148.8, 148.2, 143.4, 131.0, 130.4, 129.6, 128.6, 128.1, 128.0, 127.7, 127.0, 97.9, 50.2, 36.0, 13.6, 7.8 ppm; HRMS: calcd for $[C_{19}H_{16}N_2O_2+H]^+$: 305.1290; found: 305.1313.

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