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Total synthesis of nothapodytine B and (±)-mappicine

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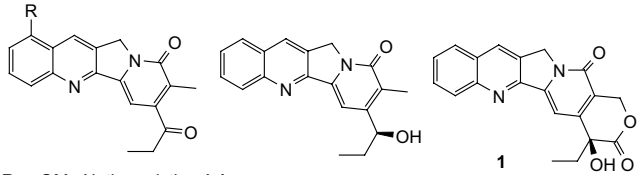
Abstract—A novel, efficient total synthesis of the naturally occurring antiviral nothapodytine B (**2**, mappicine ketone) is reported. The approach is based on the successful implementation of the Johnson orthoester rearrangement of allylic alcohol **7** for assembly of a pyridone D ring precursor with the necessary functionalities. Nothapodytine B is converted into mappicine **3** by $NaBH_4$ reduction.

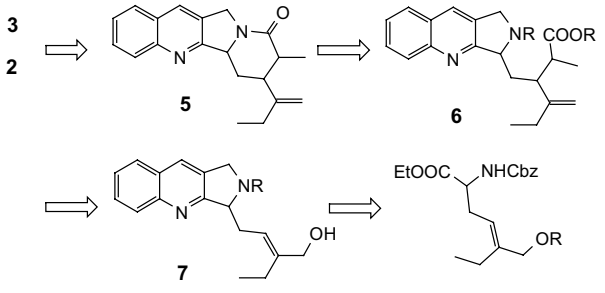
Nothapodytine A (**1**), and B (**2**), have recently been isolated from *Nothapodytis foetida*.[1] Structurally nothapodytine B (**2**) is an E-ring decarboxylated analogue of camptothecin (**4**),[2] a topoisomerase inhibitor whose derivatives are antitumour lead compounds, and an oxidized derivative of mappicine (**3**).[3]



Both **1** and **2** exhibit significant cytotoxicity against the human KB cell line and antiviral activity against the herpes viruses HSV-1, HSV-2 and human cytomegalovirus including those resistant to acyclovir.[4] The impressive biological activity of these alkaloids and low abundance coupled with the possibility of obtaining better antiviral leads by preparing substituted analogues has attracted considerable attention towards their synthesis. As a result, recent efforts have been directed to improve the degradation chemistry of camptothecin[5] and towards the development of novel synthetic routes to nothapodytine B[6] as well as related analogues.[4] Attracted by its impressive biological activity coupled with our interest in the parent molecule of this family that is, camptothecin,[7] we set out to develop a synthesis and herein we delineate a novel and efficient approach to **2** and **3**. We envisaged that a Johnson orthoester rearrangement[8] of **7** would place the requisite functional groups and appendages onto the tricyclic synthon for further elaboration to the pyridone ring, a new pyridone approach, as shown in our retrosynthetic analysis in Scheme 1.

The allylic alcohol **7** was synthesized from readily available starting materials as shown in Scheme 2.

Accordingly, allylation of O'Donnell's Schiff's base **8** with chlorocompound **9**, prepared from propargyl alcohol according to modification of the reported procedure,[9] under phase transfer conditions in the presence of TBABr afforded the allylglycine **10** after the usual workup followed by hydrolysis of the alkylated Schiff's



Scheme 1.

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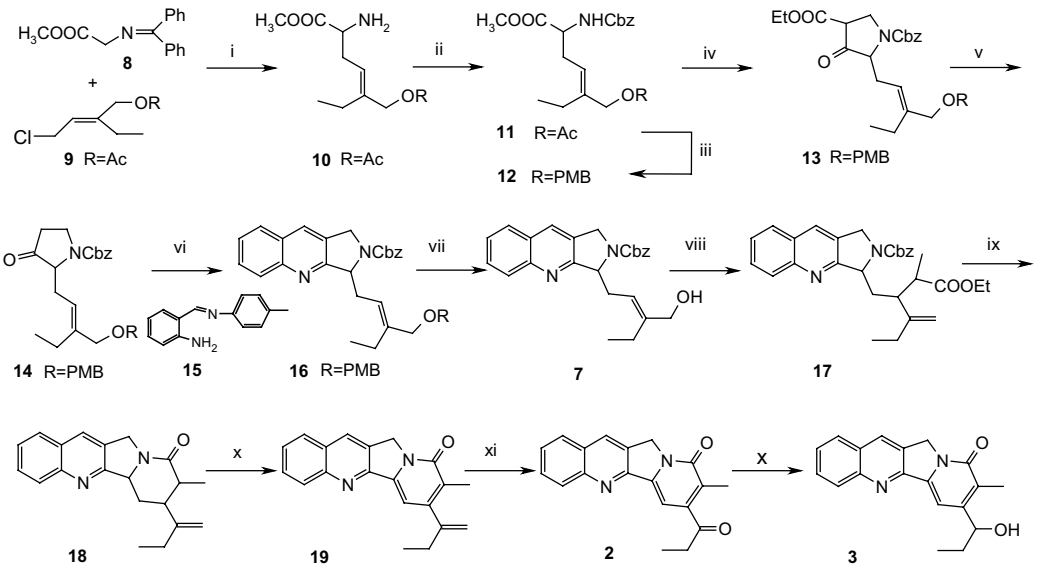

Scheme 2. Reagents and conditions: (i) (a) TBABr, KI, K_2CO_3, CH_3CN, reflux; (b) 10% HCl, 0.5 h, 86%; (ii) CbzCl, K_2CO_3, DCM, 96%; (iii) (a) K_2CO_3, CH_3OH, 95%; (b) *p*-$MeOC_6H_4CH_2O$–C(=NH)CCl_3, $BF_3{\cdot}OEt_2$ (cat.), rt, 3 h, 81%; (iv) NaH, ethyl acrylate, reflux, 2.5 h, 66%; (v) NaCl, DMSO; (vi) *p*-TSA, toluene, reflux 3 h, 69% (over two steps); (vii) DDQ, DCM, 90%; (viii) triethyl orthopropionate, CH_3CH_2COOH (cat.), 130 °C, 2 h, 92%; (ix) (a) TMSI, pyridine, rt, 1 h, 81%; (b) EtOH, NaOAc, reflux, 85%; (x) DDQ, dioxane, reflux, 80%; (xi) O_3, DMS, CH_2Cl_2, 76%, (x) $NaBH_4$, MeOH, 69%.

base. Amine **10** thus obtained was protected as its benzyloxy carbamate **11** employing potassium carbonate as the base in anhydrous dichloromethane. Next, the acetate protecting group was replaced with a PMB group. Hydrolysis of the acetate in the presence of K_2CO_3 in methanol and treatment of the resulting allylic alcohol with PMB trichloroacetimidate furnished carbamate **12**.

The Michael induced ring closure,[10] originally employed for the pyrrolidinone construction with ethyl acrylate afforded β-ketoester **13**, which was decarboxylated under Krapcho's conditions to give pyrrolidinone **14**. Friedlander condensation of pyrrolidone **14** with Schiff's base **15** furnished quinoline **16.** The deprotection of the PMB ether with DDQ afforded the allylic alcohol **7**.

To our delight, allylic alcohol **7** underwent facile rearrangement with triethyl orthopropionate in the presence of propionic acid (cat.) to furnish the α,β-unsaturated ester **17** as a mixture of diastereoisomers. The carbamate functionality of **17** was removed with TMSI/pyridine to yield a secondary amine, which readily underwent lactamization in refluxing ethanol in the presence of KOAc to give the tetrahydropyridone **18**. Oxidation of the tetrahydropyridone **18** with DDQ afforded pyridone **19**. Controlled ozonolysis of the olefin **19** completed the synthesis of nothapodytine B **2**.

Reduction of the ketone group of **2** with $NaBH_4$ afforded (±)-mappicine **3**. The spectral data of compounds **2** and **3** were in complete agreement with reported data.[11,12]

In conclusion, a novel and efficient total synthesis of nothapodytine B and (±)-mappicine based on the implementation of a new pyridone approach was accomplished and suggests straightforward extensions to the synthesis of camptothecin and related analogues. The total synthesis of camptothecin and homocamptothecin is underway employing this strategy.

Acknowledgements

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12. Selected spectroscopic data for compound **17** (mixture of diastereomers): **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.09 (m, 2H), 7.95–7.75 (m, 2H), 7.47 (t, $J = 8.3$ Hz, 1H), 7.34 (m, 5H), 5.29–5.25 (m, 4H), 4.95–4.27 (m, 2H), 3.89 (m, 2H), 2.5–2.2.5 (m, 3H), 2.24–1.75 (m, 4H), 1.25–0.71 (m, 9H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 175.07 (C), 173.08 (C), 161.91 (C), 154.63 (C), 149.78 (C), 148.16 (CH), 147.8 (C), 136.51 (C), 136.17 (C), 128.97 (2CH), 128.72 (CH), 128.28 (2CH), 127.87 (CH), 127.47 (CH), 127.32 (CH), 110.62 (CH_2), 67.86 (CH_2), 60.26 (CH), 59.97 (CH), 59.61 (CH_2), 50.31 (CH_2), 44.39 (CH), 42.74 (CH), 32.78 (CH_2), 27.08 (CH_2), 13.99 (CH_3), 11.98 (CH_3), 8.70 (CH_3). **Mass**: m/z (%): 486 (M^+, 5), 424 (5), 385 (5), 351 (10), 306 (18), 277 (8), 249 (23), 224 (16), 197 (8), 169 (95), 91 (100), 67 (10). Compound **18**: **^{1}H NMR** (200 MHz, $CDCl_3$): δ: 8.24–8.14 (m, 2H), 7.87 (d, $J = 8.3$ Hz, 1H), 7.53 (t, $J = 5.8$ Hz, 1H), 7.63 (t, $J = 8.3$ Hz, 1H), 5.5–4.5 (m, 5H), 2.90–2.5 (m, 2H), 2.47 (m, 1H), 2.25–1.83 (m, 3H), 1.4–1.1 (m, 6H). **^{13}C NMR** (50 MHz, $CDCl_3$): δ: 178.41 (C), 168.63 (C), 148.52 (C), 132.91 (C), 129.09 (2CH), 126.78 (C), 127.69 (CH), 127.43 (C), 125.96 (2CH), 101.78 (CH_2), 58.01 (CH), 49.1 (CH_2), 47.28 (CH), 41.2 (CH), 32.93 (CH_2), 27.08 (CH), 13.98 (CH_3) 12.17 (CH_3). **Mass**: m/z (%): 306 (M^+, 5), 289 (15), 277 (4), 249 (50), 224 (74), 196 (25), 182 (65), 169 (100), 140 (60), 128 (30), 115 (35), 81 (40), 67 (60). Compound **19**: **^{1}H NMR** (200 MHz, $CDCl_3$): δ: 8.31 (s, 1H), 8.17 (d, $J = 8.3$ Hz, 1H), 7.89 (d, $J = 8.3$ Hz, 1H), 7.81 (t, $J = 7.3$ Hz, 1H), 7.59 (t, $J = 7.3$ Hz, 1H), 7.18 (s, 1H), 5.28 (s, 1H), 5.27 (s, 2H), 4.98 (s, 1H), 2.44 (q, $J = 7.9$ Hz, 2H), 2.24 (s, 3H), 1.1 (t, $J = 7.9$ Hz, 3H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 161.87 (C), 153.42 (C), 152.61 (C), 149.45 (C), 148.82 (C), 141.88 (C), 130.70 (CH), 130.15 (CH), 129.59 (CH), 128.79 (CH), 128.02 (C), 127.32 (CH), 127.02 (C), 126.40 (C), 113.50 (CH_2) 102.62 (CH), 50.01 (CH_2), 29.62 (CH_2), 14.03 (CH_3), 12.23 (CH_3). **Mass**: m/z (%): 302 (M^+, 50), 287 (100), 273 (14), 243 (25), 218 (24), 128 (25), 77 (35).