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Two efficient methods for the conversion of camptothecin to mappicine ketone, an antiviral lead compound[1]

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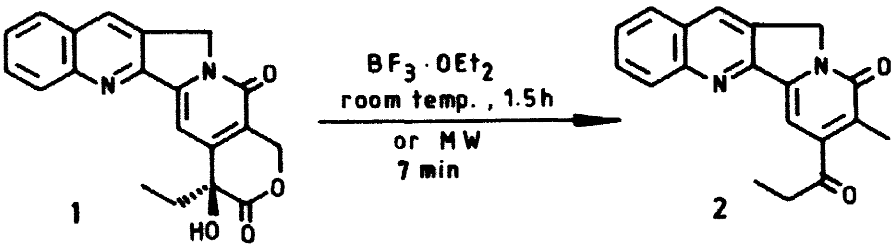
Abstract: Two simple and efficient methods for the conversion of the naturally occurring alkaloid, camptothecin to mappicine ketone, an antiviral lead compound, have been described. The first method involved the treatment of camptothecin with borontrifluoride etherate and the second method utilised the microwave irradiation of the alkaloid.

Camptothecin (**1**)[2], a naturally occurring pyrrolo-[3,4-b]- quinoline alkaloid, originally isolated from *Camptotheca acuminata* Decne (Nyssaceae) has been found to possess promising antineoplastic activity in animal tumour models[3]. The E-ring hydroxy lactone of the compound has been found to be most critical structural feature with respect to its antitumour activity[4]. The decarboxylated E-ring analogue of camptothecin, known as mappicine ketone (**2**), does not have an antitumour property[5]. However, the compound has recently been identified[5] as an antiviral lead. It exhibits potent activity against the herpesviruses (HSV-1 and HSV-2) and human cytomegalovirus (HCMV).

Mappicine ketone (**2**) was initially discovered[6] as the reaction product when camptothecin (**1**) was heated at 110-120^{0}C in the presence of sodium azide. Recently, several other methods for the semisynthesis and total synthesis of mappicine ketone and its analogues have been reported[5,7]. The natural occurrence of the compound **2** has been observed[8] in *Nothapodytes foetida* (Wight) Sleumer (Icacinaceae) along with other camptothecins. However, due to low abundance of the compound in the plant its isolation in large quantity is difficult. In continuation of our recent work[8b, c] on camptothecins we have developed two simple and efficient methods for the conversion of camptothecin (**1**) to mappicine ketone (**2**).



Camptothecin (**1**) was treated[9a] with borontrifluoride etherate in tetrahydrofuran at room temperature for 1.5h to obtain mappicine ketone (**2**) (yield 65%). The structure of the latter was settled by comparison of its physical and spectral properties with those reported[8a] in the literature and also by direct comparison with

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an authentic sample[8c]. This is the first report of the conversion of camptothecin (**1**) to mappicine ketone (**2**) by utilising a chemical reagent at room temperature. The recovered unreacted camptothecin (**1**) (27%) could again be utilised.

Alternatively, camptothecin (**1**) was irradiated[9b] without any solvent under microwave irradiation for 7 min to form mappicine ketone (**2**) (yield 96%). The conversion was rapid and inexpensive. This high-yield transformation did not form any undesirable side product. The experimental procedure is simple and the process is environmentally benign.

In conclusion, we have developed two simple, useful and efficient methods, one by using boron trifluoride etherate and other by utilising microwave irradiation, for the conversion of camptothecin to mappicine ketone, an antiviral lead compound. The application of microwave irradiation is the most convenient process for the preparation of this important antiviral molecule. The method was also found to be suitable for the preparation of the analogues of mappicine ketone as 9-methoxycamptothecin[8b] when irradiated under microwave irradiation (time 7 min.) afforded 9-methoxymappicine ketone[8c] (yield 95%).

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References and Notes

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9. a) Treatment of camptothecin with BF_3. OEt_2: Camptothecin (200mg) was added to THF (50ml) and the mixture was stirred at room temperature. BF_3. OEt_2 (2ml) dissolved in THF (10ml) was added dropwise to the stirred mixture under N_2 atmosphere during 10 min. The stirring was continued for 1.5h. The mixture was poured on ice chips and extracted with EtOAc (3×50ml). The extract was purified by column chromatography over silica gel using EtOAc as eluent. The reaction product was isolated and finally purified by crystallisation from $CHCl_3$ to afford mappicine ketone (114mg). Unreacted camptothecin (54mg) was recovered.
   b) Microwave irradiation of camptothecin: Camptothecin (200mg) was taken in an Erlenmeyer flask and placed in an alumina bath inside a commercial microwave oven (BPL BMO 700T). The compound was irradiated at full power (466 Watts) for 7 min. The reaction mixture was then purified by column chromatography and the isolated product was crystallised from $CHCl_3$ to yield mappicine ketone (168 mg).