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THE FIRST CONVERSION OF CAMPTOTHECIN TO (*S*)-MAPPICINE BY AN EFFICIENT CHEMOENZYMATIC METHOD[1]

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Abstract: Camptothecin has been converted for the first time to (*S*)-mappicine via mappicine ketone, which is the sole product of the microwave irradiation of camptothecin. Baker's yeast reduction of mappicine ketone yielded (*S*)-mappicine in high optical purity.

(*S*)-Mappicine (**1**) was isolated[2] in very low yield from *Nothapodytes foetida* (Wight) Sleumer (Icacinaceae) [formerly, *Mappia foetida* Miers] along with other camptothecins of promising antitumour activity. The compound, **1** has been prepared[2,3] in racemic form from camptothecin (**2**), the major constituent of the plant, by several workers. However, the conversion of the latter to (*S*)-mappicine (**1**) has not previously been achieved though an unsuccessful attempt of such conversion has been described.[2a] Different methods[4] for the total synthesis of (±)-mappicine have been developed and two methods[5] for the total synthesis of (*S*)-mappicine (**1**) have also recently been reported. As the compound **1** is structurally related[2a,3a,4c,5] to various antitumour and antiviral camptothecins detailed biological studies on this molecule are needed and an useful method for its preparation is required.

As a result of our current interest in camptothecins[2b,6] coupled with our recent biochemical studies on natural products[7] we have discovered an efficient chemoenzymatic process for the conversion of camptothecin (**2**) to (*S*)-mappicine (**1**). Camptothecin (**2**) was at first converted[8a] to mappicine ketone (**3**) by our recently developed method[6c] by utilizing microwave irradiation of the former. The irradiation time is short (7 min.) and the yield of the product (**3**) is very high (96%). In the second step, mappicine ketone (**3**) was treated[8b] with baker's yeast in phosphate buffer solution of pH 7.2 to produce (*S*)-mappicine (**1**) in 74% yield and 86% ee.

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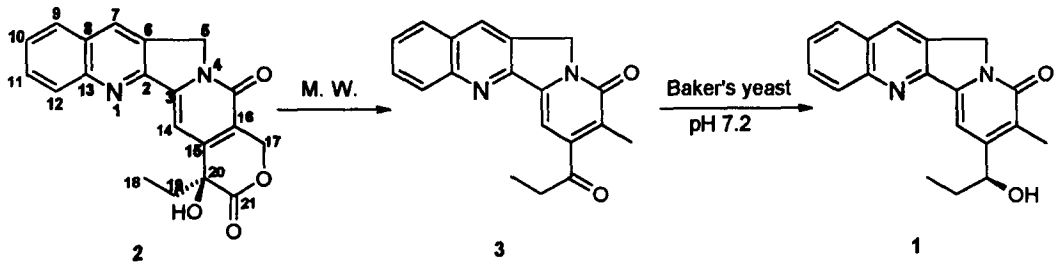

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In conclusion, we have developed for the first time a simple, useful and efficient chemoenzymatic process for the conversion of camptothecin to (*S*)-mappicine. The process is suitable for transformation of other naturally occurring camptothecins [2a,6a,9] to their corresponding (*S*)-mappicine analogues which may be utilized for bioevaluation.

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8. a) Microwave irradiation of camptothecin (**2**): Camptothecin (**2**) (200 mg) 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 taken out from the oven and was cooled to the room temperature. This was shaken with CH_2Cl_2 (10 ml) and filtered. The concentrated filtrate was purified by column chromatography over silica gel, the column being eluted with solvents of increasing polarity using hexane, EtOAc and MeOH. The fractions eluted with EtOAc-MeOH (99:1) afforded a solid which was crystallized from MeOH to yield mappicine ketone (**3**) (168 mg), mp 231-232°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.37 (1H, s, H-7), 8.18 (1H, dd, J=8.6, 1.4 Hz, H-12), 7.91 (1H, dd, J=8.6, 1.4 Hz, H-9), 7.82 (1H, dt, J=8.6, 1.4 Hz, H-11), 7.63 (1H, dt, J=8.6, 1.4 Hz, H-10), 7.22 (1H s, H-14), 5.29 (2H, br s, H-5), 2.89 (2H, q, J=7.0 Hz, H-19), 2.30 (3H, s, Me-17), 1.28 (3H, t, J=7.0 Hz, Me-18); EIMS m/z (rel. intensity) 304 ($M^{+\cdot}$, 22), 289 (7), 248 (18), 219 (20), 191 (2), 125 (8). The structure of the compound **3** was established from its physical and spectral properties which were found to be identical to those of an authentic sample of mappicine ketone[2b]
b) Treatment of mappicine ketone (**3**) with baker's yeast: Baker's yeast (*Saccharomyces cerevisiae*) (2 g) was added to a vigorously stirred solution of sucrose (1.5 g) in tap water (200 ml). Phosphate buffer solution of pH 7.2 (20 ml) was added. The suspension was stirred for 1 h at room temperature. Mappicine ketone (**3**) (100mg) was added and stirring was continued. Three portions of fermenting baker's yeast [1.5 g in a solution of sucrose (750 mg) in tap water (50 ml)] were added during 72 h and the suspension was stirred for another 120 h at room temperature. The

mixture was extracted with EtOAc (3×100 ml). The extract was dried, concentrated and purified by column chromatography over silica gel. The fractions eluted with EtOAc-MeOH (97:3) yielded (*S*)-mappicine (**1**) (75 mg), mp 250-251°C (MeOH), $[\alpha]_D^{20}$ –10.66° (c 0.8562, $CHCl_3$-MeOH, 4:1); ^1H NMR ($CDCl_3$-CD_3OD, 200 MHz) δ 8.38 (1H, s, H-7), 8.12 (1H, dd, J=8.5, 1.4 Hz, H-12), 7.88 (1H, dd, J=8.5, 1.4 Hz, H-9), 7.77 (1H,dt, J=8.5, 1.4 Hz, H-11), 7.63-7.54 (2H, m, H-10, H-14), 5.23 (2H, br s, H-5), 4.86 (1H, t, J=6.5 Hz, H-20), 2.22 (3H, s, Me-17), 1.86-1.60 (2H, m, H-19), 1.03 (3H, t, J=7.0Hz, Me-18); EIMS m/z (rel. intensity) 306 ($M^{+\cdot}$, 43), 291 (12), 277 (38), 248 (23), 219 (18), 191 (5), 167 (12), 140 (17). The structure of the product (**1**) was settled by comparison of its physical and spectral properties with those reported[2a,5] in the literature and also by direct comparison with an authentic sample of (*S*)-mappicine[2b].

The recovered unreacted mappicine ketone (**3**) (12 mg) could again be utilized for baker's yeast reduction.

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