SHORT PAPER

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Chemoenzymatic synthesis of (S)- and (R)-mappicines and their analogues†

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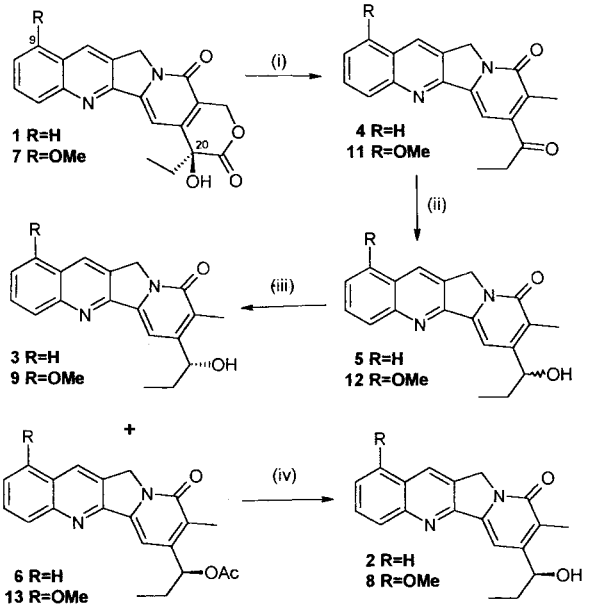
The natural alkaloids, camptothecin and mappicine ketone were converted into racemic mappicine which on treatment with vinyl acetate in presence of the lipase *Candida cylindracea* (CCL) afforded (*S*)-mappicine acetate and (R)-mappicine. The acetate was chemically hydrolysed to (*S*)-mappicine. 9-Methoxycamtpothecin and 9-methoxymappicine ketone were similarly converted into (*S*)- and (*R*)-9-methoxymappicines.

In continuation of our work[2] on the naturally occurring alkaloid, camptothecin (**1**)[3], a potent antitumour agent and its various analogues we have recently developed an efficient chemoenzymatic conversion of the former into (*S*)- and (*R*)-mappicines. (*S*)-Mappicine [**2**, ($[\alpha]^{25}_D$ –12.40° (c 0.91, $CHCl_3$–MeOH, 1:1)] is also a natural antitumour compound [2c,4,5] but (*R*)-mappicine (**3**) has not yet been reported from a natural source[3]. Camptothecin (**1**) was at first converted into mappicine ketone (**4**) by our recently developed method[2b] utilizing microwave irradiation. Natural mappicine ketone[2a,b] could also directly be used for transformation. The ketone **4** was reduced with $NaBH_4$ to form reacemic mappicine (**5**). The latter was treated with vinyl acetate in the presence of the lipase *Candida cylindracea* (CCL). (*R*)-Mappicine [**3**, $[\alpha]^{25}_D$ +12.02° (c 0.94, $CHCl_3$–MeOH, 1:1), ee 97%] remained unchanged. The product (*S*)-mappicine acetate (**6**) was hydrolysed by refluxing with 10% aqueous K_2CO_3 solution to produce (*S*)-mappicine [**2**, $[\alpha]^{25}_D$ –12.01° (c 0.92, $CHCl_3$–MeOH, 1:1), ee 97%].The structures and stereochemistry of both the compounds **2** and **3** were settled by comparison of their optical and spectral properties to those of the natural (*S*)-mappicine.[2c,4]

Naturally occurring 9-methoxycamptothecin (**7**)[2a] was similarly converted into (*S*)- and (*R*)-9-methoxymappicines (**8** and **9** respectively). (*S*)-9-Methoxymappicine [**8**, $[\alpha]^{25}_D$ –9.65° (c 0.62, $CHCl_3$-MeOH, 1:1)] is a natural alkaloid.[2d] To prepare **8** and **9** the compound **7** was at first irradiated[2b] under microwave irradiation to form 9-methoxymappicine ketone (**11**). The naturally occurring ketone **11**[2a,b] was also directly used for conversion. The compound on reduction with $NaBH_4$ afforded racemic 9-methoxymappicine (**12**). The latter was then treated with vinyl acetate in presence of CCL. (*R*)-9-Methoxymappicine (**9**, $[\alpha]^{25}_D$ +9.16° (c 0.65, $CHCl_3$-MeOH, 1:1), ee 95%) remained here intact. The product (*S*)-9-methoxymappicine acetate (**13**) was refluxed with 10% aqueous K_2CO_3 solution to form (*S*)-9-methoxymappicine (**8**, $[\alpha]^{25}_D$ –9.14° (c 0.61 $CHCl_3$–MeOH, 1:1), ee 95%). The optical and spectral properties of **8** and **9** were compared to those of the naturally occurring (*S*)-9-methoxymappicine.[2d]

In conclusion we have developed an efficient chemoenzymatic synthesis of (*S*)- and (*R*)-mappicines and their analogues. The compounds were obtained in high optical purity. The enantioselective esterification of racemic mappicines in presence of the lipase CCL has been utilized here for the first time to produce the chiral mappicines. The compounds which were prepared may be used for bioevaluation.



Reagents and Conditions: (i) M.W., 7 min (ii) $NaBH_4$, MeOH, room temp., 2h (iii)  , CCL, room temp., 7 days (iv) aq K_2CO_3, reflux, 2h

Experimental

Reduction of mappicine ketone with $NaBH_4$: Mappicine ketone (**4**, 200mg) was dissolved in MeOH (20 ml) and cooled in ice. $NaBH_4$ (200 mg) was added to the solution in portions. The mixture was kept overnight. MeOH was removed and water (30 ml) was added. The mixture was extracted with EtOAc (3 × 30 ml). The concentrated extract was purified by column chromatography using EtOAc as eluent to yield racemic mappicine[2c] (**5**, 185 mg, yield 92%), m.p. 247–248^0 (MeOH).

Reduction of 9-methoxymappicine ketone with $NaBH_4$: 9-Methoxymappicine ketone (**11**, 200mg) dissolved in MeOH (20 ml) was reduced with $NaBH_4$ (200 mg) following the method described above to produce racemic 9-methoxymappcine[2c] (**12**, 183 mg, yield 91%), m.p. 245–246^0 (MeOH).

Treatment of racemic mappicine with vinyl acetate in presence of CCL: Racemic mappicine (**5**, 100 mg) was added to $CHCl_3$ (100 ml) and shaken. Vinyl acetate (0.5 ml) and the lipase CCL (50 mg) were added. The reaction mixture was monitored by TLC under UV light. After 7 days the mixture was filtered off and purified by column chromatography using EtOAc as eluent to afford (*S*)-mappicine acetate[2c] (**6**, 47mg, yield 41%) and (*R*)-mappicine[2c] (**3**, 42 mg, yield 42%), m.p. 248–249° (MeOH).

Treatment of racemic 9-methoxymappicine with vinyl acetate in presence of CCL: Racemic 9-methoxymappicine (**12**, 100 mg) in $CHCl_3$ (100 ml) was treated with vinyl acetate (0.5 ml) in presence of CCL (50 mg) following the method mentioned above to yield (*S*)-9-methoxymappicine acetate[2d] (**13**, 45 mg, 40%) and (*R*)-9-methoxymappicine[2c] (**9**, 41 mg, 41%), m.p. 247–248° (MeOH).

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Alkaline hydrolysis of (S)-mappicine acetate: (*S*)-Mappicine acetate (**6**, 40 mg) dissolved in MeOH (5 ml) was hydrolyzed by refluxing with 10% aqueous K_2CO_3 solution for 2h to produce (*S*)-mappicine[4] (**2**, 34 mg, yield 97%), m.p. 251–252° (MeOH).

Alkaline hydrolysis of (S)-9-methoxymappicine acetate: (*S*)-9-Methoxymappcine acetate (**13**, 40 mg) dissolved in MeOH (5 ml) was refluxed with 10% aqueous K_2CO_3 solution for 2h to yield (*S*)-9-methoxymappicine[2d] (**8**, 34 mg, yield 95%), m.p. 246–247° (MeOH).

The structures and stereochemistry of all the known compounds were established by comparison of their physical and spectral properties to those reported for the compounds in the literature.

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