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Enantioselective Synthesis of (*S*)- and (*R*)-Mappicines and their Analogues[1]

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Abstract: The naturally occurring alkaloids, camptothecin and mappicine ketone were converted to racemic mappicine acetate which was enantioselectively hydrolyzed to (*S*)- and (*R*)-mappicines in high optical purity using baker's yeast and a lipase, Amano PS. Treatment of the racemic acetate with baker's yeast afforded (*S*)-mappicine while with Amano PS yielded (R)-mappicine. 9-Methoxycamptothecin and 9-methoxymappicine ketone underwent similar conversion to (*S*)- and (R)-9-methxymappicines.

INTRODUCTION

Indian *Nothapodytes foetida* (Wight) Sleumer (Icacinaceae) (formerly, *Mappia foetida* Miers) has been found to contain different bioactive constituents including camptothecin (**1**)[2-4] and 9-methoxycamptothecin (**2**),[2-4] two potent antitumour agents, and mappicine ketone (**3**),[5] an antiviral lead compound. The same plant produces 9-methoxymappicine ketone (**4**),[5] (*S*)-mappicine (**5**)[6,7] and (*S*)-9-methoxymappicine (**6**)[7] in low yields. Due to their interesting chemical structures and important biological properties, the synthesis and transformations of camptothecins as well as of mappicine ketone and mappicines have been undertaken in recent years. In continuation of our current investigation on camptothecins[3-5,7,8] we have developed a simple and efficient conversion of such compounds to (*S*)-and (*R*)-mappicines and their analogues. (*R*)-mappicine (**10**) has not yet been reported from a natural source. However, (*S*)- and (*R*)-mappicines and their analogues may be utilized for bioevaluation and their bioactivity may be compared. Only one method has so far been reported[8] for the transformation of camptothecin (**1**) to (*S*)-mappicine (**5**) but no method has yet been known for the preparation of (*R*)-mappicine from camptothecin. Here we report the enantioselective synthesis of (*S*)-and (*R*)-mappicines and their analogues from camptothecins.

RESULTS AND DISCUSSION

During our present study camptothecin (**1**) was converted to (*S*)- and (*R*)-mappicines *via* mappicine ketone (**3**) which was prepared[5] by microwave irradiation of **1**. The irradiation time was short (7 min) and the yield of the product (**3**) was very high (96%). Naturally occurring mappicine ketone could also be directly used. Sodium borohydride reduction of **3** afforded a racemic alcohol (**7**) whose spectral properties were found to be identical to those of naturally occurring mappicine.[6,7,9] Acetylation of the racemic alcohol with acetic anhydride and pyridine yielded a racemic acetate **8** which was enantioselectively hydrolyzed using baker's yeast or a lipase Amano PS.

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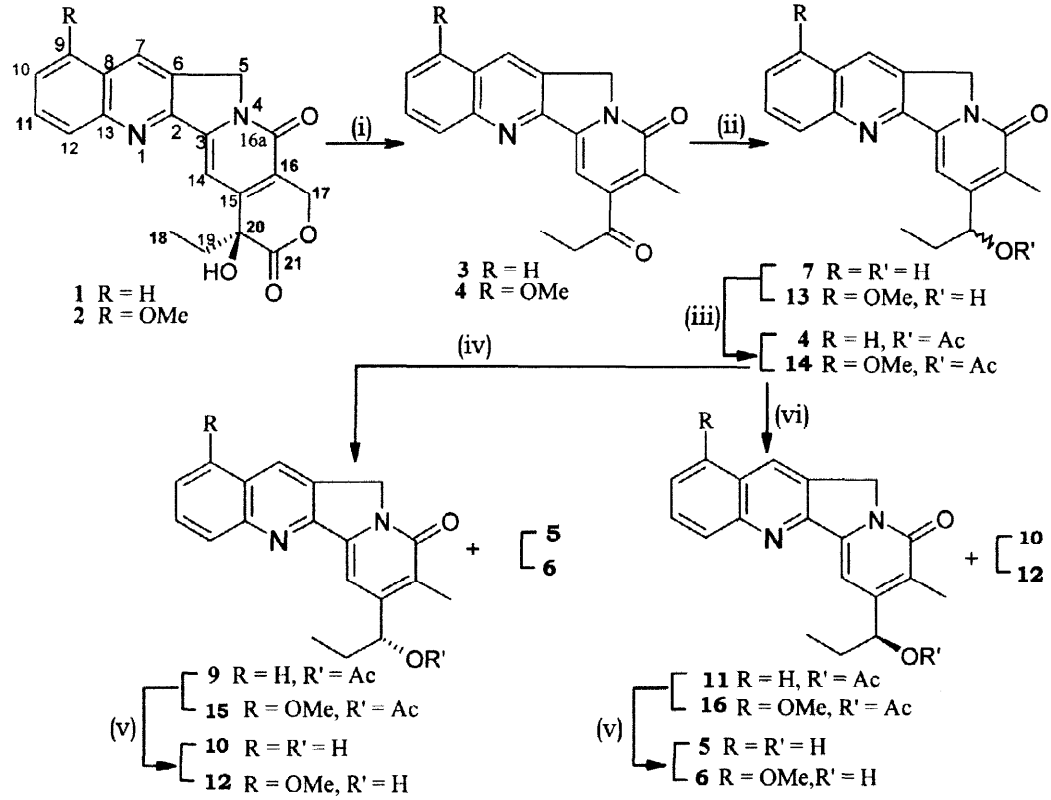
Treatment of **8** with beaker's yeast afforded (*S*)-mappicine (**5**) (yield 48%) in high optical purity[6,7,9] ($[\alpha]^{25}_D$ -12.03 (c 0.73, $CHCl_3$-MeOH, 1:1), ee 97%). The unchanged (*R*)-mappicine acetate (**9**) was next hydrolyzed chemically by refluxing with 10% aqueous potassium carbonate solution to give (*R*)-mappicine (**10**) (yield 48% from **8**; ($[\alpha]^{25}_D$ +12.05 (c 0.58, $CHCl_3$-MeOH, 1:1), ee 97%). Hydrolysis of **8** with the lipase Amano PS in phosphate buffer (pH 7.2) gave a different result. The product was identified as (*R*)-mappicine (**10**) (yield 47%, $[\alpha]^{25}_D$ +11.41 (c 0.82, $CHCl_3$-MeOH, 1:1), ee 92%). The unchanged (*S*)-mappicine acetate (**11**) was then hydrolyzed chemically to (*S*)-mappicine (**5**) (yield 47% from **8**, $[\alpha]^{25}_D$ -11.40 (c 0.72, $CHCl_3$-MeOH,1:1), ee 92%). The structures and configuration of both the products **5** and**10** were established by comparison of their optical and spectral properties to those of the naturally occurring (*S*)-mappicine.[6,7,9]



Reagents and conditions: (i) M.W, 7 min (ii) $NaBH_4$, MeOH, room temp. 2h (iii) Ac_2O, pyridine, room temp. over night (iv) Baker's yeast, 192 h (v) 10% aq K_2CO_3, reflex, 2h (vi) lipase Amano PS, phosphate buffer (pH 7.2), THF, 72h.

9-Methoxycamptothecin (**2**) and 9-methoxymappicine ketone (**4**) were also transformed to (*S*)-and (*R*)-9-methoxymappicines (**6** and **12** respectively) by a similar method as described above. 9-Methoxymappicine ketone (**4**) was prepared[5] by microwave irradiation of the first compound **2** or the naturally occurring **4**[7] was directly utilized for transformation. The compound **4** was reduced with sodium borohydride to produce a racemic alcohol **13**, which on acetylation afforded racemic 9-methoxymappicine acetate (**14**). The last compound was enantioselectively hydrolyzed by baker's yeast to (*S*)-9-methoxymappicine (**6**)[7,9] (yield 47%, $[\alpha]^{25}_D$ -9.17 (c 0.52, $CHCl_3$-MeOH, 1:1), ee 95%) and by Amano PS to (*R*)-9-methoxymappicine (**12**) (yield 45%, $[\alpha]^{25}_D$ +8.40 (c 0.78,

$CHCl_3$-MeOH, 1:1),ee 87%). The unchanged 9-methoxymappicine acetate (**15**) in the first case was hydrolyzed by 10% aqueous K_2CO_3 solution to (*R*)-9-methoxymappicine (**12**) and the unchanged acetate (**16**) in the second case to (*S*)-9-methoxymappicine (**6**). The optical and spectral properties of **6** and **12** were compared to those of naturally occurring (*S*)-9-methoxymappicine.[7,9]

In summary, we have developed for the first time a simple, useful and efficient method for the conversion of naturally abundant camptothecin to both (*S*)- and (*R*)-mappicines simultaneously in high optical purity. Enantioselective hydrolysis of the intermediate racemic acetate of mappicine by using two different biocatalysts, baker's yeast and the lipase Amano PS has been employed to get the desired enantiomers. The method is suitable for the transformation of other naturally occurring camptothcins[7,10] to their corresponding (*S*)- and (*R*)-mappicines analogues which may be utilized for bioevaluation.

EXPERIMENTAL

M.p.s were measured in a Buchi-510 apparatus and are uncorrected. Spectra were recorded with the following instruments: UV, Shimadzu 240 spectrophotometer; IR, Nicolet 740 FTIR spectrophotometer; ^{1}H NMR, Varian Gemini 200 MHz and MS, VG Micromass 7070H (70 eV). Optical rotations were determined with a Jasco DIP 360 digital polarimeter. Column chromatography was performed on silica gel (BDH, 100-200 mesh) and TLC with silica gel G. The spots were detected under UV light and in an iodine chamber.

***Microwave irradiation of camptothecin* (1)**

Camptothecin (**1**, 500 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 watt) for 7 min. The reaction mixture was removed from the oven and cooled to room temperature. The mixture was shaken with $CHCl_3$ (30 ml) and filtered. The filtrate was concentrated and purified by column chromatography over silica gel using EtOAc as eluent to yield mappicine ketone (**3**, 420 mg, 96%) as a pale yellow solid, m.p. 214-215°C ($CHCl_3$) [lit.[11] 210-215°C ($CHCl_3$)]; IR. 1694, 1653, 1596 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.37 (1H,s, H-7), 8.18 (1H, dd, J = 8.6, 1.4Hz, H-12), 7.91 (1H, dd, J = 8.6, 1.4Hz, H-9), 7.82 (1H, dd, J = 8.6, 1.4Hz, H-11), 7.63 (1H, dt, J = 8.6, 1.4Hz, H-10), 7.22 (1H, s, H-14), 5.29 (2H, s, H_2-5), 2.89 (2H, q, J = 7.0Hz, H_2-19), 2.30 (3H, s, Me-17), 1.28 (3H, t, J = 7.0Hz, Me-18); MS: m/z (%) 304 ($M^{+\cdot}$,22), 289 (7), 248 (18), 219 (20), 191 (2), 125 (8). Found, C: 74.88; H: 5.32; N: 9.31. $C_{19}H_{16}N_2O_2$ requires C: 74.98; H: 5.30; N: 9.20%. The structure of compound **3** was confirmed from its spectral data and by direct comparison with an authentic sample.[5]

***Microwave irradiation of 9-methoxycamptothecin* (2)**

9-Methoxycamptothcin (**2**, 500 mg) was also irradiated under microwave irradiation for 7 min following the method described above to produce 9-methxymappicine ketone (**4**, 414 mg, 94%) as a pale yellow solid, m.p. 236-237°C ($CHCl_3$) [lit.[11] 235-238°C ($CHCl_3$)]; IR: 1691, 1652, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.76 (1H,s, H-7), 7.80-7.62 (2H, m, H-11 and H-12), 7.21 (1H, s, H-14), 6.92 (1H, dd, J = 6.0, 2.5Hz), 5.24 (2H, s, H_2-5), 4.06 (3H, s, -OMe), 2.90 (2H, q, J = 7.0Hz, H_2-19), 2.28 (3H, s, Me-17), 1.27 (3H, t, J = 7.0Hz, Me-18); MS: m/z (%) 334 ($M^{+\cdot}$, 100), 319 (42), 279 (44), 234 (12), 207 (10). Found, C: 71.78; H: 5.42; N: 8.30. $C_{20}H_{18}N_2O_3$ requires C: 71.84; H: 5.43; N: 8.38%. A direct comparison of the compound with an authentic sample of 9-methxymappicine ketone[5] confirmed the structure of the former.

Reduction of mappicine ketone (3) with $NaBH_4$

Mappicine ketone (**3**, 400 mg) was dissolved in MeOH (20 ml) and cooled in ice. The solution was treated with $NaBH_4$ (200 mg) in small portions. The mixture was kept

overnight. MeOH was removed under reduced pressure and water (40 ml) was added to the reaction mixture. The mixture was extracted with EtOAc (3x30 ml). The extract was concentrated and purified by column chromatography using EtOAc as eluent to afford racemic mappicine (**7**, 364 mg, 91%) as a pale yellow solid, m.p. 248-249°C (MeOH), $[\alpha]^{25}_D \pm 0$ (c 0.76, $CHCl_3$-MeOH, 1:1); IR: 3457, 1665, 1600 cm^{-1}; ^1H NMR ($CDCl_3$-CD_3OD): δ 8.38 (1H, s, H-7), 8.12 (1H, dd, J = 8.5, 1.4Hz, H-12), 7.88 (1H, dd, J = 8.5, 1.4Hz, H-9), 7.77 (1H, dt, J = 8.5, 1.4Hz, H-11), 7.63-7.54 (2H, m, H-10 and H-14), 5.23 (2H, s, H_2-5), 4.86 (1H, t, J = 6.5Hz, H-20), 2.22 (3H, s, Me-17), 1.86-1.60) (2H, m, H_2-19), 1.03 (3H, t, J = 7.0Hz, Me-18); MS: m/z (%) 306(M^+, 43), 291(12), 277(38), 248(23), 219(18), 191(5), 167(12), 140(17). Found, C: 74.68; H: 5.76; N: 9.22. $C_{19}H_{18}N_2O_2$ requires C: 74.49; H: 5.92; N: 9.14%. The structure of the product **7** was established from its spectral properties as well as by direct comparison with an authentic sample of (*S*)-mappicine.[7,9]

Reduction of 9-methoxymappicine ketone (4) with $NaBH_4$

9-Methoxymappicine ketone (**4**, 400 mg) dissolved in MeOH (20 ml) was reduced with $NaBH_4$ (200 mg) following the method described above to form racemic 9-methoxymappicine (**13**, 360 mg, 90%) as a pale yellow solid, m.p. 247-248°C (MeOH), $[\alpha]^{25}_D \pm 0$ (c 0.67, $CHCl_3$-MeOH, 1:1); IR: 3446, 1650, 1577 cm^{-1}; ^1H NMR ($CDCl_3$-CD_3OD): δ 8.82 (1H, s, H-7), 8.15 (1H, s, -OH), 7.72-7.68 (2H, m, H-11 and H-12), 7.67 (1H, s, H-14), 7.04 (1H, dd, J = 6.0, 2.5Hz, H-10), 5.21 (2H, s, H_2-5), 4.77 (1H, dd, J= 7.5, 5.5Hz, H-20), 2.15 (3H, s, Me-17), 1.72-1.58 (2H, m, H_2-19), 0.98 (3H, t, J = 7.0Hz, Me-18); MS: m/z(%) 336(M^+, 10), 319(6), 256(8), 239(5), 213(8), 193(7). Found, C: 71.38; H: 5.87; N: 8.47. $C_{20}H_{20}N_2O_3$ requires C: 71.41; H: 5.99; N: 8.33%. The structure of **13** was established from its spectroscopic data as well as by direct comparison with an authentic sample of 9-methoxymappicine.[7,9]

Acetylation of racemic mappicine (7)

To racemic mappicine (**7**, 300 mg) acetic anhydride (20 ml) and pyridine (1 ml) were added. The mixture was kept overnight. This was poured on water (50 ml) and extracted with EtOAc (3x50 ml). The extract was washed with water (3x50 ml), concentrated and purified by column chromatography using EtOAc as eluent to obtain the acetylated product **8** (282 mg, 83%) as a viscous mass, $[\alpha]^{25}_D \pm 0$ (c 0.57, $CHCl_3$); IR: 1733, 1655, 1598 cm-1; ^1H NMR ($CDCl_3$): δ 8.29 (1H, s, H-7). 8.19 (1H, dd, J = 8.5, 1.5Hz, H-12), 7.85 (1H, dd, J = 8.5, 1.5Hz, H-9), 7.78 (1H, dt, J=8.5, 1.5Hz, H-11), 7.61 (1H, dd, J = 8.5, 1.5Hz, H-10), 7.29 (1H, s, H-14), 5.86 (1H, dd, J=7.5, 5.5Hz, H-20), 5.20 (2H, s, H_2-5), 2.32 (3H, s, -OAc), 2.18 (3H, s, Me-17), 2.02-1.78 (2H, m, H_2-19), 1.02 (3H, t, J = 7.0Hz, Me-18); MS: m/z (%) 348(M^+, 35), 305(14), 288(100), 273(73), 290(18). Found, C: 72.36; H: 5.68; N: 8.18. $C_{21}H_{20}N_2O_3$ requires C: 72.40, H: 5.79; N: 8.04%.

Acetylation of racemic 9-methoxymappicine (13)

Racemic 9-methoxymappicine (**13**, 300 mg) was acetylated with acetic anhydride (20 ml) and pyridine (1 ml) by the method described above to form the acetylated product **14** (278 mg, 82%) as a viscous mass, $[\alpha]^{25}_D \pm 0$ (c 0.68, $CHCl_3$); IR: 1736, 1654, 1617 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.79 (1H, s, H-7), 7.80-7.67 (2H, m, H-11 and H-12), 7.42 (1H, s, H-14), 6.93 (1H, dd, J = 6.0, 2.5Hz, H-10), 5.88(1H, dd, J = 7.5, 5.5Hz, H-20), 5.24 (2H, s, H_2-5), 4.02 (3H, s, -OMe), 2.27 (3H, s, -OAc), 2.13(3H, s, Me-17), 1.70-1.59 (2H, m, H_2-19), 0.98 (3H, t, J=7.0Hz, Me-18); MS: m/z (%) 378(M^+, 20), 335(12), 320(43), 319(45), 306(48), 279(20), 206(14). Found, C: 69.89; H: 5.80; N: 7.36. $C_{22}H_{22}N_2O_4$ requires C: 69.83; H: 5.86; N: 7.40%.

Treatment of racemic mappicine acetate (8) with baker's yeast

Baker's yeast (*Saccharomyces cerevisiae*) (2g) was added to a vigorously stirred solution of sucrose (1.5 g) in tap water (200 ml). The mixture was stirred for 1h at room

temperature. Racemic mappicine acetate (**8**, 100 mg) was added and fermenting baker's yeast [1.5 g in a solution of sucrose (750 mg) in tap water (50 ml)] was added during 72h and the suspension was stirred for another 120h at room temperature. The reaction mixture was extracted with EtOAc (3x100 ml). The concentrated extract was purified by column chromatography using EtOAc to produce (*S*)-mappicine (**5**, 42 mg, 48%) as a pale yellow solid, m.p. 250-251°C (MeOH), $[\alpha]^{25}_D$ -12.03 (c 0.73, $CHCl_3$-MeOH, 1:1) [lit.[8] m.p. 252-253°C (MeOH), $[\alpha]^{25}_D$ -12.40 (c 0.91, $CHCl_3$-MeOH, 4:1)] and the unchanged (*R*)-acetate (**9**, 48 mg, 48%). The spectral (IR, ^{1}H NMR and MS) properties of **5** were found to be identical to those reported above for racemic mappicine. Found, C: 74.62; H: 5.73; N: 9.21. $C_{19}H_{18}N_2O_2$ requires C: 74.49; H: 5.92; N: 9.14%. The product **5** was directly compared with an authentic sample of naturally occurring (*S*)-mappicine.[7-9]

Treatment of racemic 9-methoxymappicine acetate (14) with baker's yeast

Racemic 9-methoxymappicine acetate (**14**, 100 mg) was also treated with bakers yeast (6.5 g) following the method described above to yield (*S*)-9-methoxymappicine (**6**, 41 mg, 47%) as a pale yellow solid, m.p. 248-249°C (MeOH), $[\alpha]^{25}_D$ - 9.17 (c 0.52, $CHCl_3$-MeOH, 1:1) [lit.[7] m.p. 249-251°C (MeOH), $[\alpha]^{25}_D$ -9.65 (c 0.62, $CHCl_3$-MeOH, 4:1) and the unchanged (*R*)-acetate (**15**, 47 mg, 47%). The spectral (IR, ^{1}H NMR and MS) data of **6** were similar to those reported above for racemic 9-methoxymappicine. Found, C: 71.32; H: 5.84; N: 8.28. $C_{20}H_{20}N_2O_3$ requires C: 71.41; H: 5.99; N: 8.33%. A direct comparison of the product **6** with an authentic sample of naturally occurring (*S*)-9-methoxymappicine[7,9] confirmed the structure of the former.

Alkaline hydrolysis of the acetate 9

Acetate **9** (40 mg) dissolved in MeOH (5 ml) was added to 10% aqueous K_2CO_3 solution (20 ml) and refluxed for 2h. The mixture was cooled and neutralized with 2(N) HCl. This was extracted with EtOAc (3x20ml) and washed with water (3X50 ml). The concentrated extract was purified by column chromatography using EtOAc as eluant to afford (*R*)-mappicine (**10**, 34 mg, 97%) as a pale yellow solid, m.p.248-249°C (MeOH), $[\alpha]^{25}_D$ +12.05 (c 0.58, $CHCl_3$-MeOH 1:1). Found, C: 74.47; H: 5.94; N: 9.25. $C_{19}H_{18}N_2O_2$ requires C: 74.49; H: 5.92; N: 9.14%. The spectral (IR; ^{1}H NMR and MS) properties of **10** were identical to those of racemic and (*S*)-mappicines.

Alkaline hydrolysis of the acetate 15

Acetate **15** (40 mg) dissolved in MeOH (5 ml) was hydrolyzed by refluxing with 10% aqueous K_2CO_3 solution for 2h to yield (*R*)-9-methoxymappicine (**12**, 35 mg, 98%) as a pale yellow solid, m.p. 247-248°C (MeOH), $[\alpha]^{25}_D$ +9.15 (c 0.62, $CHCl_3$-MeOH, 1:1). Found, C: 71.35; H: 5.82; N: 8.42. $C_{20}H_{20}N_2O_3$ requires C: 71.43; H: 5.95; N: 8.33%. The spectroscopic (IR, ^{1}H NMR and MS) data were identical to those of racemic and (*S*)-9-methoxymappicines.

Treatment of racemic mappicine acetate (8) with lipase

Racemic mappicine acetate (**8**, 100 mg) was dissolved in anhydrous THF (20 ml). To the solution phosphate buffer (pH 7.2, 10 ml) and the lipase Amano PS (*Pseudomonas cepacia*) (25 mg) were added. The reaction was monitored by TLC under UV light. After 72h the mixture was filtered and the filtrate extracted with EtOAc (3x20 ml). The concentrated extract was purified by column chromatography using EtOAc as eluent to afford (*R*)-mappicine (**10**, 41 mg, 47%) as a pale yellow solid, m.p. 248-249°C (MeOH), $[\alpha]^{25}_D$ +11.41 (c 0.82, $CHCl_3$-MeOH, 1:1) and the unchanged (*S*)-acetate (**11**, 47 mg, 47%). The spectral (IR, ^{1}H NMR and MS) properties of **10** were similar to those of racemic and (*S*)-mappicines. Found, C: 74.66; H: 5.72; N: 9.23. $C_{19}H_{18}N_2O_2$ requires C: 74.49; H: 5.92; N: 9.14%.

Treatment of racemic 9-methoxymappicine acetate* (14) *with lipase

Racemic 9-methoxymappicine acetate (**14**, 100 mg) was also treated with Amano PS (25 mg) following the above mentioned method to produce (*R*)-9-methoxymappicine (**12**, 39 mg, 45%)as a pale yellow solid, m.p. 247-248°C (MeOH), $[\alpha]^{25}_{D}$ +8.40 (c 0.78, $CHCl_3$-MeOH, 1:1) and the unchanged (*S*)-acetate (**16**, 45 mg, 45%). The spectral (IR ^{1}H NMR and MS) data of **12** were identical to those of (*S*)- and racemic 9-methoxymappicines. Found, C: 71.37; H: 5.83; N: 8.24. $C_{20}H_{20}N_2O_3$ requires C: 71.41; H: 5.99; N: 8.33%.

***Alkaline hydrolysis of the acetate* 11**

Acetate **11** (40 mg) dissolved in MeOH (5 ml) was refluxed with 10% aqueous K_2CO_3 solution (20 ml) for 2h. Usual work-up (discussed above) afforded (*S*)-mappicine (**5**, 35 mg, 99%) as a pale yellow solid, m.p. 249-250°C (MeOH), $[\alpha]^{25}_{D}$ -11.40 (c 0.72, $CHCl_3$-MeOH, 1:1). [lit.[8] m.p. 252-253°C (MeOH), $[\alpha]^{25}_{D}$ -12.40 (c 0.91, $CHCl_3$-MeOH, 4:1)]. Found, C: 74.53; H: 5.92; N: 9.18. $C_{19}H_{18}N_2O_2$ requires C: 74.49; H: 5.92; N: 9.14%. The spectral (IR, ^{1}H NMR and MS) properties of the product were identical to those reported above for racemic and (*S*)-mappicines. A direct comparison of the product with an authentic sample of naturally occurring (*S*)-mappicine[7,9] confirmed the structure of the former.

***Alkaline hydrolysis of the acetate* 16**

Acetate **16** (40 mg) dissolved in MeOH (5 ml) was hydrolyzed by refluxing with 10% aqueous K_2CO_3 solution for 2h to produce (*S*)-9-methoxymappicine (**6**, 34 mg, 96%) as a pale yellow solid, m.p. 248-249°C (MeOH), $[\alpha]^{25}_{D}$ -8.38 (c 0.68, $CHCl_3$-MeOH, 1:1) [lit.[7] m.p.249-251°C (MeOH),$[\alpha]^{25}_{D}$ -9.65 (c 0.62, $CHCl_3$-MeOH, 4:1)]. Found, C: 71.48; H: 5.82; N: 8.41. $C_{20}H_{20}N_2O_3$ requires C: 71.41; H: 5.99; N: 8.33%. The spectral (IR ^{1}H NMR and MS) date of the product were directly compared with those of an authentic sample of (*S*)-9-methoxymappicne[7,9].

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