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# Total Synthesis of Mimocin, an Isoquinolinequinone Antibiotic<sup>1)</sup>

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Mimocin, which is an isoquinolinequinone antibiotic, was synthesized starting from 2,3,6-trimethoxytoluene.

**Keywords**—mimocin; antibiotic; Bischler–Napieralski reaction; dimethylaluminum amide; oxidative demethylation

Kubo and co-workers<sup>2)</sup> isolated mimocin (**1**), a new isoquinolinequinone antibiotic exhibiting strong activity against *Bacillus subtilis* and *Candida albicans*, from the fermentation broth of *Streptomyces lavendulae*, and synthesized it starting from 7-methoxy-5,8-isoquinoline-dione.

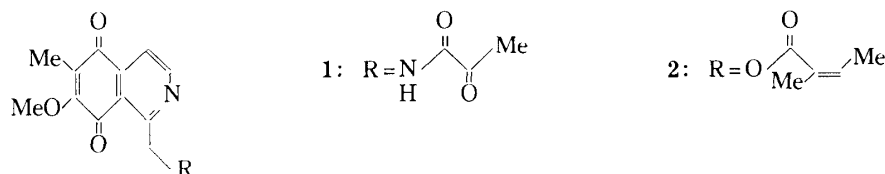


Fig. 1

In the course of our synthetic studies on marine natural products,<sup>3)</sup> we became interested in the structural similarity between mimocin (**1**) and renierone (**2**),<sup>4)</sup> isolated by Faulkner and co-worker as an antimicrobial substance from a marine sponge *Reniera sp.*, and in their antimicrobial activities. This paper describes an alternative synthesis of mimocin (**1**).

Our synthetic approach to mimocin (**1**) was initiated by formylation of 2,3,6-trimethoxytoluene (**3**)<sup>5)</sup> with hexamethylenetetramine and trifluoroacetic acid, giving an aldehyde (**4**) in 58% yield. The structure of **4** was determined by inspection of the nuclear magnetic resonance (NMR) spectral data of **4** and its isomer (**5**), which was obtained by formylation of 2,4-dimethoxy-3-methylphenol<sup>5)</sup> with hexamethylenetetramine and trifluoroacetic acid<sup>6)</sup> followed by methylation with methyl iodide and potassium carbonate. The aromatic protons appeared at  $\delta$  7.25 and 7.03 ppm in the NMR spectra of **4** and **5**, respectively.

The obtained aldehyde (**4**) was condensed with nitromethane in the presence of ammonium acetate<sup>7)</sup> to furnish a  $\beta$ -nitrostyrene derivative (**6**) in 77% yield, and this was reduced to an amine (**7**) with lithiumaluminum hydride-aluminum chloride in ether in 84% yield. Treatment of the amine (**7**) with ethyl oxalyl chloride in the presence of triethylamine in ether afforded an amide ester (**8**) in 91% yield, which was subjected to Bischler–Napieralski reaction. The amide ester (**8**) was allowed to react with polyphosphate ester<sup>8)</sup> in the absence of any solvent at 110–120°C for 9.5 h, furnishing a ring-closed ester (**9**) in 55% yield; the reaction with phosphoryl chloride in toluene at refluxing temperature resulted in a lower yield (26%). Heating of the ester (**9**) in the presence of 5% Pd/C in decalin at 160–170°C for 3 h gave the isoquinoline ester (**10**) in 60% yield.

Next the transformation of the ester group in **10** to an aminomethyl group was investigated. Firstly, treatment of the ester (**10**) with methanolic ammonia in a sealed tube at 100°C to obtain an amide (**12**) resulted in recovery of the starting material. However, Weinreb

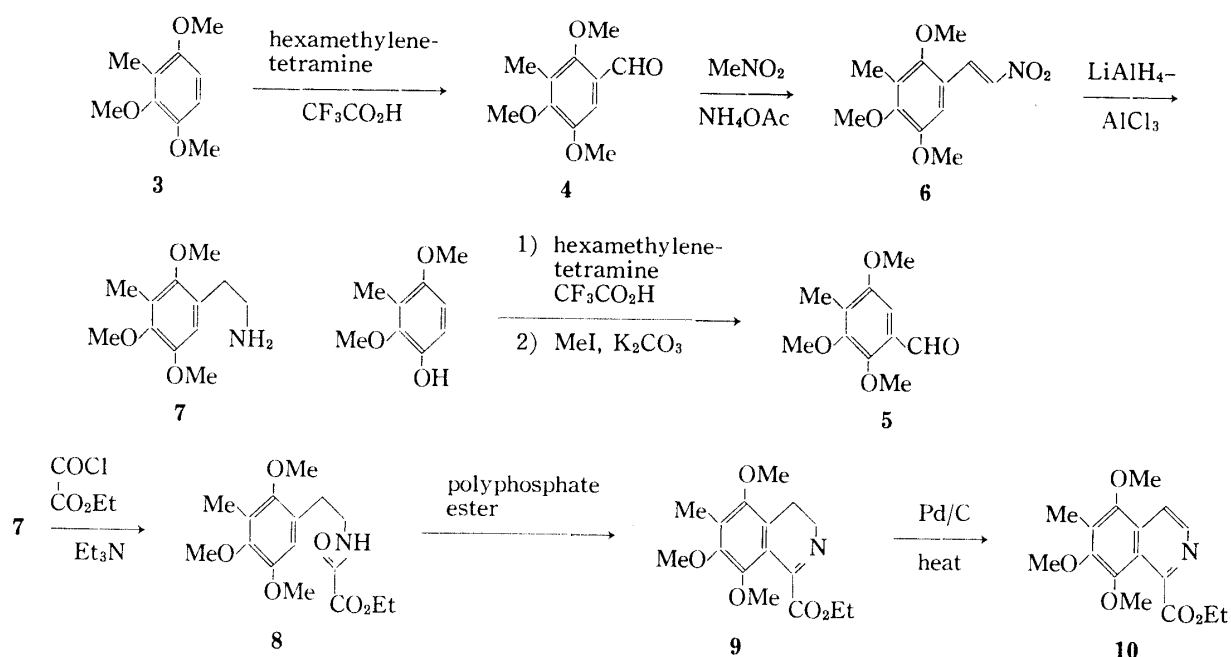


Chart 1

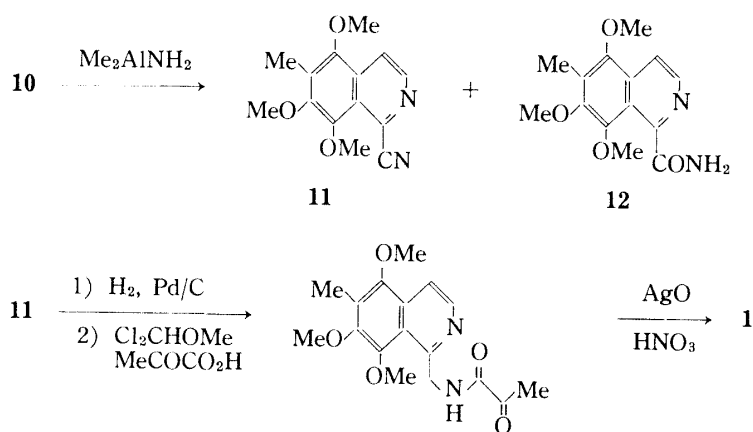


Chart 2

and co-workers<sup>9)</sup> reported that dimethylaluminum amides react in high yield under very mild conditions with a wide variety of esters to produce carboxamides. We therefore tried to apply this reagent to the above transformation.

Reaction of the ester (**10**) with dimethylaluminum amide in methylene chloride at refluxing temperature produced a mixture of a nitrile (**11**) and the amide (**12**) in 32% and 13% yields, respectively. When the reaction was carried out in benzene at refluxing temperature for 1.5 d, the nitrile (**11**) was obtained in 83% yield along with a small amount of the amide (**12**) (9% yield).<sup>10)</sup> The nitrile (**11**) was then hydrogenated over 5% Pd/C in methanol containing hydrogen chloride to give the desired aminomethylisoquinoline derivative as a dihydrochloride which, without isolation, was treated with 1,1-dichlorodimethyl ether and pyruvic acid<sup>11)</sup> in the absence of any solvent to afford an amide (**13**) in 43% yield from **11**. For oxidative demethylation<sup>12a)</sup> of the amide (**13**) at the final step of mimocin synthesis, silver oxide-nitric acid oxidation<sup>12a)</sup> and ceric ammonium nitrate oxidation<sup>12b)</sup> were examined. The former gave a better result in this isoquinoline system. Thus, treatment of the amide (**13**) with silver oxide-nitric acid in dioxane at room temperature for 15 min furnished mimocin (**1**) in 53% yield. The infrared (IR) and NMR spectra of natural mimocin (**1**) and synthetic mimocin were identi-

cal. This represents a total synthesis of mimocin in moderate overall yield starting from 2,3,6-trimethoxytoluene. The ester (**10**) is an useful intermediate for the synthesis of renierone (**2**) and related compounds.<sup>4,13)</sup>

### Experimental

The boiling and melting points are uncorrected. IR spectra were measured with a Hitachi EPI-S infrared spectrometer and NMR spectra were taken on a JEOL JNM-FX 200 (200 MHz) spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were measured with Hitachi M-70 and JEOL D-300 spectrometers.

**3-Methyl-2,4,5-trimethoxybenzaldehyde (4)**—Dried hexamethylenetetramine (56 g, 0.4 mol) was added to a solution of 2,3,6-trimethoxytoluene (**3**) (66.188 g, 0.3637 mol) in trifluoroacetic acid (500 ml) with stirring at room temperature, and the whole was heated to reflux and maintained under these conditions for 3 h. After being cooled to room temperature, the mixture was diluted with water, stirred for 15 min and extracted four times with chloroform. The organic extracts were washed three times with water and saturated brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to afford 89.677 g of a viscous oil, 15 g of which was purified by  $\text{SiO}_2$  column chromatography (benzene-methanol=100:1) to furnish 7.405 g (58%) of **4** as crystalline masses. mp 51–53°C (recrystallized from hexane). The 2,4-dinitrophenylhydrazone of **4** was prepared by the usual method. mp 190–192°C (recrystallized from ethanol). IR  $\nu_{\text{max}}^{\text{neat}}$   $\text{cm}^{-1}$ : 1675, 1587, 1463, 1385, 1325, 1280, 1240, 1203, 1120, 1075, 990, 850. NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.23 (3H, s,  $\text{ArCH}_3$ ), 3.85, 3.89 and 3.92 (each 3H, s,  $3 \times \text{OCH}_3$ ), 7.25 (1H, s, ArH), 10.32 (1H, s, CHO). Anal. Calcd for  $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}_7$  (as 2,4-DNP): C, 52.30; H, 4.66; N, 14.35. Found: C, 52.43; H, 4.75; N, 14.33.

**4-Methyl-2,3,5-trimethoxybenzaldehyde (5)**—A mixture of 2,4-dimethoxy-3-methylphenol<sup>5)</sup> (1.0 g, 5.95 mmol) and hexamethylenetetramine (0.917 g, 6.55 mmol) in trifluoroacetic acid (8 ml) was treated in the same manner as described above to afford 2-hydroxy-3,5-dimethoxy-4-methylbenzaldehyde, which was then reacted with methyl iodide in the presence of  $\text{K}_2\text{CO}_3$  in acetone in the usual way to give **5** as an oil. IR  $\nu_{\text{max}}^{\text{neat}}$   $\text{cm}^{-1}$ : 1680, 1595, 1465, 1405, 1385, 1330, 1280, 1200, 1130, 1080, 1025, 920, 850, 735. NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.20 (3H, s,  $\text{ArCH}_3$ ), 3.84, 3.87 and 3.96 (each 3H, s,  $3 \times \text{OCH}_3$ ), 7.03 (1H, s, ArH), 10.34 (1H, s, CHO).

**3-Methyl-2,4,5-trimethoxy- $\beta$ -nitrostyrene (6)**—Ammonium acetate (5.1 g, 97% purity, 64 mmol) was added to a solution of **4** (10.755 g, 51.2 mmol) in nitromethane (40 ml) at room temperature, and the whole was heated and refluxed for 30 min. After being cooled, the mixture was diluted with methylene chloride, washed with water and dried over  $\text{Na}_2\text{SO}_4$ . Removal of the solvent gave 14.704 g of crystalline masses, which were recrystallized from methylene chloride-hexane to afford 9.23 g (77%) of **6** as prisms. mp 121–123°C. IR  $\nu_{\text{max}}^{\text{neat}}$   $\text{cm}^{-1}$ : 3100, 1620, 1595, 1325, 1225, 1130, 1085, 995, 970, 835. NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.23 (3H, s,  $\text{ArCH}_3$ ), 3.75 (3H, s,  $\text{OCH}_3$ ), 3.90 (6H, s,  $2 \times \text{OCH}_3$ ), 6.87 (1H, s, ArH), 7.70 (1H, d,  $J=14$  Hz,  $\text{ArCH}=\text{CHNO}_2$ ), 8.22 (1H, d,  $J=14$  Hz,  $\text{ArCH}=\text{CHNO}_2$ ). Anal. Calcd for  $\text{C}_{12}\text{H}_{15}\text{NO}_5$ : C, 56.90; H, 5.98; N, 5.53. Found: C, 56.69; H, 5.93; N, 5.72.

**3-Methyl-2,4,5-trimethoxyphenethylamine (7)**—A solution of  $\text{AlCl}_3$  (484 mg, 3.62 mmol) in ether (2 ml) was added to a suspension of  $\text{LiAlH}_4$  (137 mg, 3.62 mmol) in ether (10 ml) with cooling under an  $\text{N}_2$  atmosphere. Next, a solution of **6** (833 mg, 3.29 mmol) in ether (5 ml) was added with stirring and cooling. The whole was warmed up to room temperature and stirred for 1.5 h at this temperature. After being cooled with ice, the mixture was diluted with water and then 6 N HCl, and the ether layer was separated. The ether layer was washed with 6 N HCl. The original water layer and the washing were combined and made basic by addition of KOH pellets with ice-cooling. The alkaline solution was extracted three times with ether and the organic layer was washed with saturated brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to give 625 mg (84%) of **7** as an oil. This oil was relatively unstable and was used without further purification for the next reaction after taking its IR spectrum. IR  $\nu_{\text{max}}^{\text{neat}}$   $\text{cm}^{-1}$ : 3375, 3300, 1593, 1483, 1230, 1113, 1080, 1005, 830.

**Ethyl N-[2-(3-Methyl-2,4,5-trimethoxyphenyl)ethyl]oxamate (8)**—A solution of ethyl oxalyl chloride (14.185 g, 0.1 mol) in dry ether (50 ml) was added to a solution of **7** (19.486 g, 86.6 mmol) and triethylamine (14.48 ml, 0.1 mol) in dry ether (190 ml) with stirring and ice-cooling. After being allowed to warm to room temperature, the mixture was stirred at this temperature for 3 h and then allowed to stand overnight. Water was added to the mixture and the organic layer was separated then washed with water. The original water layer and the washing were combined and washed with ether. The original ether layer and the washing were combined and washed with saturated  $\text{NaHCO}_3$  and saturated brine. After being dried over  $\text{Na}_2\text{SO}_4$ , the ether layer was concentrated *in vacuo* to give 29.479 g of a brown viscous oil, which was purified by  $\text{SiO}_2$  column chromatography (benzene-ethyl acetate=2:1) to furnish 25.677 g (91%) of **8** as an oil. bp 214–215°C (0.1 mmHg). IR  $\nu_{\text{max}}^{\text{neat}}$   $\text{cm}^{-1}$ : 3300, 1730, 1680, 1290, 1215, 1105, 1075, 1000. NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.37 (3H, t,  $J=7$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.22 (3H, s,  $\text{ArCH}_3$ ), 2.85 (2H, t,  $J=6$  Hz,  $\text{ArCH}_2\text{CH}_2\text{NHCO}$ ), 3.52 (2H, t,  $J=6$  Hz,  $\text{ArCH}_2\text{CH}_2\text{NHCO}$ ), 3.72, 3.81 and 3.83 (each 3H, s,  $3 \times \text{OCH}_3$ ), 4.35 (2H, q,  $J=7$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 6.62 (1H, s, ArH), 7.65 (1H, br s, NH). Exact mass Calcd for  $\text{C}_{16}\text{H}_{23}\text{NO}_6$ : 305.1463. Found: 305.1493.

**Ethyl 3,4-Dihydro-6-methyl-5,7,8-trimethoxy-1-isoquinolinecarboxylate (9)**—The amide ester (8) (8.123 g, 25 mmol) was mixed with 64.2 g of polyphosphate ester, prepared according to the literature,<sup>8)</sup> and the mixture was heated on an oil bath at 110–120°C for 9.5 h. The reaction mixture was poured into water and the resulting solution was stirred at room temperature for 30 min and then extracted with chloroform. The aqueous layer was made basic with ammonium hydroxide and extracted four times with chloroform. The organic extract was washed with saturated brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent *in vacuo* gave 940 mg of a black oil. The original chloroform extract was washed with saturated brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to leave 8.128 g of an oil, which was combined with the above black oil. Purification of the oily product by SiO<sub>2</sub> column chromatography (benzene–ethyl acetate=2:1) afforded 4.205 g (55%) of **9** as an oil. bp 194–195°C (0.1 mmHg). IR  $\nu_{\text{max}}^{\text{neat}}$  cm<sup>-1</sup>: 1733, 1613, 1570, 1465, 1405, 1327, 1250, 1135, 1115, 1075, 1015. NMR (CDCl<sub>3</sub>)  $\delta$ : 1.40 (3H, t,  $J=7$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.23 (3H, s, ArCH<sub>3</sub>), 2.70 (2H, dd,  $J=8, 10$  Hz, ArCH<sub>2</sub>CH<sub>2</sub>N=), 3.68, 3.79 and 3.82 (each 3H, s, 3  $\times$  OCH<sub>3</sub>), 3.6–3.9 (2H, m, ArCH<sub>2</sub>CH<sub>2</sub>N=), 4.38 (2H, q,  $J=7$  Hz, OCH<sub>2</sub>CH<sub>3</sub>). Exact mass Calcd for C<sub>16</sub>H<sub>21</sub>NO<sub>5</sub>: 307.1418. Found: 307.1395.

**Ethyl 6-Methyl-5,7,8-trimethoxy-1-isoquinolinecarboxylate (10)**—A mixture of **9** (8.341 g, 27.17 mmol) and 5% Pd/C (7.0 g) in decalin (85 ml) was heated on an oil bath at 160–170°C for 3 h. After being cooled to room temperature, the mixture was filtered and the catalyst was washed with methanol and acetone. The filtrate and the washing were combined and concentrated *in vacuo* to give an oil, which was purified by SiO<sub>2</sub> column chromatography (benzene–ethyl acetate=7:3) to furnish 4.974 g (60%) of **10** as a viscous oil. IR  $\nu_{\text{max}}^{\text{neat}}$  cm<sup>-1</sup>: 1735, 1610, 1580, 1445, 1385, 1270, 1243, 1135, 1095, 1055, 995. NMR (CDCl<sub>3</sub>)  $\delta$ : 1.45 (3H, t,  $J=7$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.40 (3H, s, ArCH<sub>3</sub>), 3.85, 3.92 and 3.94 (each 3H, s, 3  $\times$  OCH<sub>3</sub>), 4.52 (2H, q,  $J=7$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 7.81 (1H, d,  $J=6$  Hz, ArCH=CHN=), 8.45 (1H, d,  $J=6$  Hz, ArCH=CHN=). Exact mass Calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>5</sub>: 305.1263. Found: 305.1266.

**6-Methyl-5,7,8-trimethoxy-1-isoquinolinecarbonitrile (11)**—Ammonia (gas) was introduced into a solution of trimethylaluminum (15% hexane solution, 10.2 ml, 21.13 mmol) in dry benzene (55 ml) with stirring and ice-cooling. When the solution was saturated with ammonia, the ice bath was removed and the solution was allowed to warm to room temperature. The solution was then stirred at room temperature for 20 min, while further ammonia was introduced slowly. A solution of **10** (2.578 g, 8.45 mmol) in dry benzene (8 ml) was added to the above solution with stirring at room temperature and the whole was heated to reflux and held under these conditions for 1.5 d. The mixture was cooled to room temperature and 2 N HCl solution was added. The benzene layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layer was washed with saturated brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent *in vacuo* gave 1.818 g (83%) of **11** as a viscous oil, which crystallized on standing. Recrystallization of this product from ethanol–hexane afforded prisms which melted at 95.5–97.5°C. IR  $\nu_{\text{max}}^{\text{Nujol}}$  cm<sup>-1</sup>: 2180, 1605, 1572, 1555, 1330, 1102, 1065, 990. NMR (CDCl<sub>3</sub>)  $\delta$ : 2.41 (3H, s, ArCH<sub>3</sub>), 3.89, 4.02 and 4.08 (each 3H, s, 3  $\times$  OCH<sub>3</sub>), 7.99 (1H, d,  $J=6$  Hz, ArCH=CHN=), 8.56 (1H, d,  $J=6$  Hz, ArCH=CHN=). Anal. Calcd for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C, 65.09; H, 5.47; N, 10.85. Found: C, 65.08; H, 5.52; N, 10.89.

The above acidic aqueous layer was made basic with KOH and extracted three times with chloroform. The extract was washed with saturated brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent furnished crystalline masses, which were recrystallized from benzene–methanol to give 208 mg (9%) of 6-methyl-5,7,8-trimethoxy-1-isoquinolinecarboxamide (**12**). mp 219–223°C (dec.). IR  $\nu_{\text{max}}^{\text{Nujol}}$  cm<sup>-1</sup>: 3380, 3270, 1660, 1605, 1315, 1095, 998. NMR (CDCl<sub>3</sub>)  $\delta$ : 2.34 (3H, s, ArCH<sub>3</sub>), 3.81 (3H, s, OCH<sub>3</sub>), 3.85 (6H, s, 2  $\times$  OCH<sub>3</sub>), 6.1 (2H, br s, CONH<sub>2</sub>), 7.75 (1H, d,  $J=5$  Hz, ArCH=CHN=), 8.35 (1H, d,  $J=5$  Hz, ArCH=CHN=). Anal. Calcd for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>: C, 60.85; H, 5.85. Found: C, 61.15; H, 6.20.

**6-Methyl-1-pyruvamidomethyl-5,7,8-trimethoxyisoquinoline (13)**—A solution of **11** (318 mg, 1.23 mmol) in methanol (10 ml) containing conc. HCl (1 ml) was stirred with 5% Pd/C (300 mg) under an H<sub>2</sub> atmosphere. When hydrogen uptake ceased, the catalyst was filtered off and washed with methanol. The filtrate and washing were combined and concentrated *in vacuo* to give crude 1-aminomethyl-5,7,8-trimethoxy-6-methylisoquinoline dihydrochloride, which was not isolated and was used immediately for the next reaction after being dried by azeotropic distillation with benzene. 1,1-Dichlorodimethyl ether (0.334 ml, 3.7 mmol) was added to the amine dihydrochloride obtained above, then pyruvic acid (0.8 ml, 11.5 mmol) was added with stirring at room temperature. The whole was heated to 60°C for 30 min. The reaction mixture was diluted with water under ice-cooling and made basic with K<sub>2</sub>CO<sub>3</sub> solution. The basic solution was extracted three times with chloroform and the extract was washed with saturated brine then dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent *in vacuo* afforded 413 mg of a viscous oil, which was purified by SiO<sub>2</sub> column chromatography (benzene–ethyl acetate=3:1) to give 174 mg (43%) of **13** as crystals. Recrystallized from ethanol–hexane. mp 148–151°C. IR  $\nu_{\text{max}}^{\text{Nujol}}$  cm<sup>-1</sup>: 3300, 1717, 1677, 1300, 1068, 1002. NMR (CDCl<sub>3</sub>)  $\delta$ : 2.40 (3H, s, ArCH<sub>3</sub>), 2.56 (3H, s, COCH<sub>3</sub>), 3.87, 3.94 and 4.03 (each 3H, s, 3  $\times$  OCH<sub>3</sub>), 5.18 (2H, d,  $J=6$  Hz, ArCH<sub>2</sub>NH), 7.74 (1H, d,  $J=5$  Hz, ArCH=CHN=), 8.38 (1H, d,  $J=5$  Hz, ArCH=CHN=), 9.13 (1H, br s, ArCH<sub>2</sub>NHCO). Exact mass Calcd for C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>: 332.1372. Found: 332.1382.

**Micocin (1)**—HNO<sub>3</sub> (6 M, 0.2 ml) was added to a mixture of **13** (66.4 mg, 0.2 mmol), AgO (100 mg, 0.8 mmol) and dry dioxane (2 ml) with stirring at room temperature. The whole was stirred at room temperature for 15 min. A mixture of chloroform (6 ml) and water (14 ml) was added to the reaction mixture

and the chloroform layer was separated. The aqueous layer was extracted twice with chloroform. The combined organic layer was washed with saturated brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to give a crystalline mass, which was purified by chromatography on  $\text{SiO}_2$  preparative layer plates using a mixture of benzene-ethyl acetate=2:1 as a developing solvent. A yellow band was extracted with ethyl acetate and the solvent was evaporated off *in vacuo* to give 32 mg (53%) of **1**, which was recrystallized from chloroform-hexane as needles. mp 189–190°C (lit.<sup>2)</sup> mp 189–191°C). IR  $\nu_{\text{max}}^{\text{CHCl}_3}$   $\text{cm}^{-1}$ : 3350, 1722, 1670, 1572, 1512, 1305, 1115, 982. NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.09 (3H, s,  $\text{ArCH}_3$ ), 2.52 (3H, s,  $\text{COCH}_3$ ), 4.17 (3H, s,  $\text{OCH}_3$ ), 5.10 (2H, d,  $J=5$  Hz,  $\text{ArCH}_2\text{NH}$ ), 7.92 (1H, d,  $J=5$  Hz,  $\text{ArCH=CHN=}$ ), 8.60 (1H, br s,  $\text{NH-}$ ), 8.94 (1H, d,  $J=5$  Hz,  $\text{ArCH=CHN=}$ ). Exact mass Calcd for  $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_5$ : 302.0903. Found: 302.0935.

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