

AN EFFICIENT SYNTHESIS OF (±)-3-DEMETHOXYERYTHRATIDINONE

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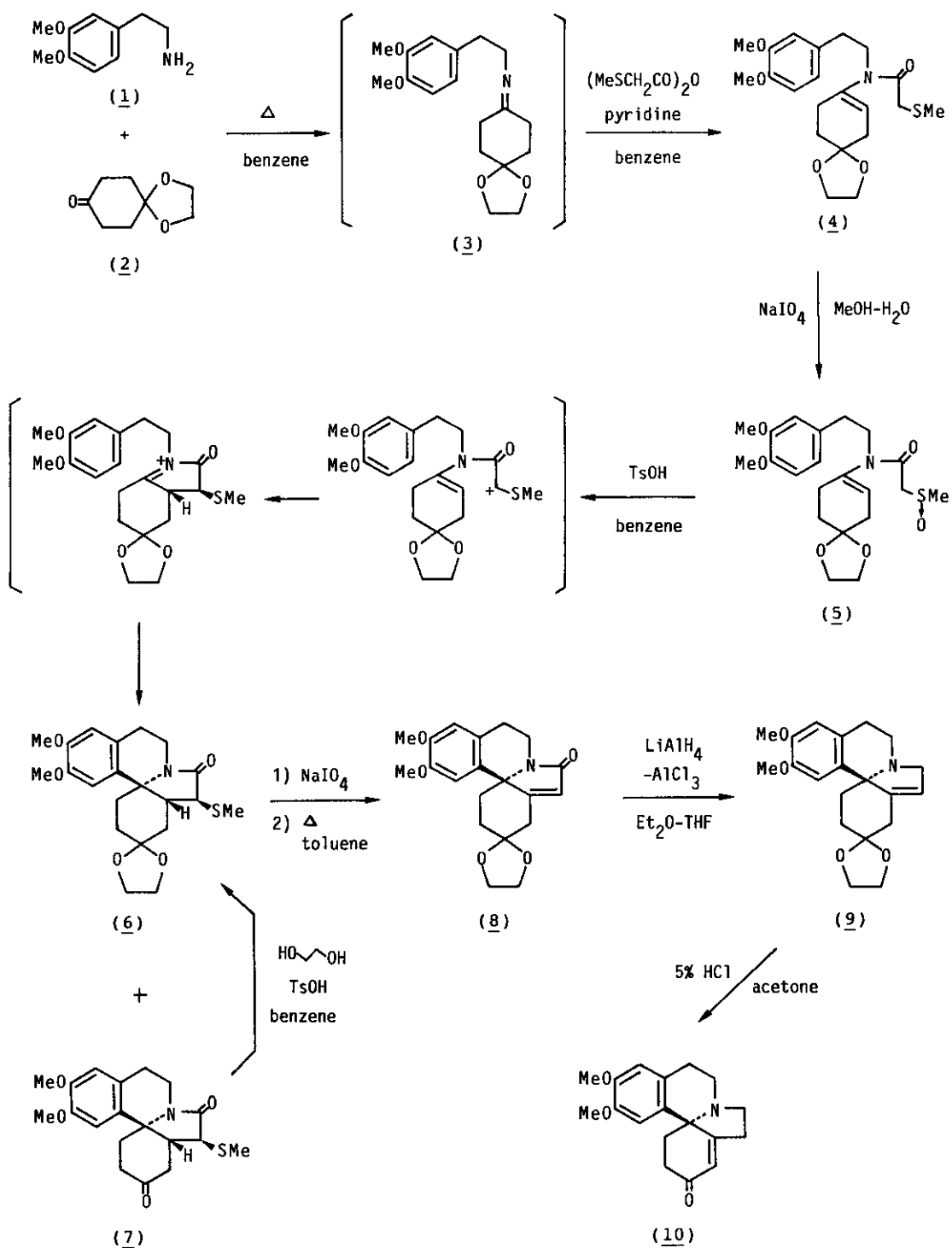
Abstract—(±)-3-Demethoxyerythratidinone (10), an alkaloid of Erythrina lithosperma, was synthesized in nine steps and 37% overall yield from homoveratrylamine and cyclohexane-1,4-dione monoethylene acetal.

Previous accounts from our laboratory have revealed a direct access to the erythrinan skeleton by acid-promoted double cyclization of N-arylethyl-N-(cyclohex-1-enyl)- α -sulfinylacetamides.¹ We have now applied this method to the total synthesis of (±)-3-demethoxyerythratidinone (10), an alkaloid isolated from Erythrina lithosperma in 1973 by Barton and colleagues.²

The key sulfoxide 5 was synthesized from homoveratrylamine (1) and cyclohexane-1,4-dione monoethylene acetal (2)³ in three steps. Thus, heating a mixture of 1 and 2 in benzene with azeotropic removal of water followed by treatment of the resulting imine 3 in situ with (methylthio)acetic anhydride⁴ and pyridine afforded the acylenamide 4, mp 89-90°C (from n-hexane-benzene), in 75% yield. Oxidation of 4 with sodium metaperiodate in aqueous methanol provided quantitatively the sulfoxide 5 as an oil.

Cyclization of 5 was effected by heating with 2 molar equiv. of p-toluenesulfonic acid in benzene with azeotropic removal of water for 10 min to give two erythrinan derivatives 6⁵ and 7⁶ in 19 and 53% yields, respectively. Reprotection of the ketone 7 with ethylene glycol by an usual manner gave quantitatively the acetal 6.

Oxidation of 6 with sodium metaperiodate followed by thermolysis of the resulting sulfoxide in refluxing toluene in the presence of NaHCO₃ for 7 h afforded, in 80% overall yield, the unsaturated lactam 8,⁷ mp 132-133°C (from ethyl ether), lit.⁸ 133-135°C.



According to the reported procedure,⁸ compound **8** was subjected to reduction with $\text{LiAlH}_4\text{-AlCl}_3$ in tetrahydrofuran-ethyl ether (5:2) at room temperature for 1 h to give the amine **9**.⁹ This compound was then deprotected with 5% HCl-acetone at 50°C to furnish, with concomitant migration of the double bond, (+)-3-demethoxyerythratidinone (**10**),¹⁰ mp 103-104°C (from benzene-light petroleum), lit.⁸ 101-102°C, in 86% yield from **8**. The ir (CHCl_3) and ^1H -nmr (CDCl_3) spectra of **10** were identical with those of a reference sample provided by Professor Tsuda.

Thus we succeeded in the synthesis of (+)-3-demethoxyerythratidinone (**10**) in nine chemical operations and 37% overall yield from homoveratrylamine (**1**) and cyclohexane-1,4-dione monoethylene acetal (**2**).

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5. mp 170-171°C (from *n*-hexane-ethyl acetate); ir (ν , cm^{-1} , CHCl_3) 1680; ^1H -nmr (δ , ppm, 300 MHz, CDCl_3) 1.72 (1H, ddd, $J=14.0$, 7.0, 4.5 Hz), 1.88 (1H, ddd, $J=14.0$, 8.2, 5.8 Hz), 2.03-2.11 (2H, m), 2.09 (3H, s, SMe), 2.26-2.30 (2H, m), 2.48 (1H, ddd, $J=9.5$, 5.5, 3.8 Hz), 2.76 (1H, ddd, $J=16.0$, 6.0, 3.8 Hz), 2.94 (1H, ddd, $J=16.5$, 10.0, 7.0 Hz), 3.26 (1H, dddd, $J=13.3$, 10.0, 5.8, 1.0 Hz), 3.86 (3H, s, OMe), 3.88 (3H, s, OMe), 3.91-4.06 (4H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 4.00 (1H, d, $J=5.0$ Hz, SCH), 4.14 (1H, ddd, $J=13.0$, 6.8, 4.0 Hz), 6.62 (1H, s, arom.), 6.83 (1H, s, arom.).
6. mp 112-113°C (from *n*-hexane-ethyl acetate); ir (ν , cm^{-1} , CCl_4) 1725 (six-

- membered ketone), 1695 (five-membered lactam); ^1H -nmr (δ , ppm, 60 MHz, CDCl_3) 2.06 (3H, s, SMe), 2.34 (4H, br s), 2.5-4.1 (7H, m), 3.85 (3H, s, OMe), 3.89 (3H, s, OMe), 4.15-4.65 (1H, m), 6.58 (1H, s, arom.), 6.68 (1H, s, arom.).
7. Ir (ν , cm^{-1} , CHCl_3) 1670; ^1H -nmr (δ , ppm, 60 MHz, CDCl_3) 1.2-4.5 (10H, m), 3.86 (3H, s, OMe), 3.88 (3H, s, OMe), 4.02 (4H, s, $\text{OCH}_2\text{CH}_2\text{O}$), 5.97 (1H, br s, C=CH), 6.72 (1H, s, arom.), 7.02 (1H, s, arom.).
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9. an oil; ^1H -nmr (δ , ppm, 60 MHz, CDCl_3) 1.5-4.2 (12H, m), 3.85 (6H, s, OMe x 2), 3.99 (4H, s, $\text{OCH}_2\text{CH}_2\text{O}$), 5.55-5.75 (1H, br, C=CH), 6.64 (1H, s, arom.), 7.0 (1H, s, arom.).
10. Ir (ν , cm^{-1} , CHCl_3) 1665, 1610, 1505, 1250; ^1H -nmr (δ , ppm, 60 MHz, CDCl_3) 2.0-3.7 (12H, m), 3.74 (3H, s, OMe), 3.85 (3H, s, OMe), 6.09 (1H, m, C=CH), 6.57 (1H, s, arom.), 6.66 (1H, s, arom.).

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