AN EFFICIENT SYNTHESIS OF (±)-3-DEMETHOXYERYTHRATIDINONE

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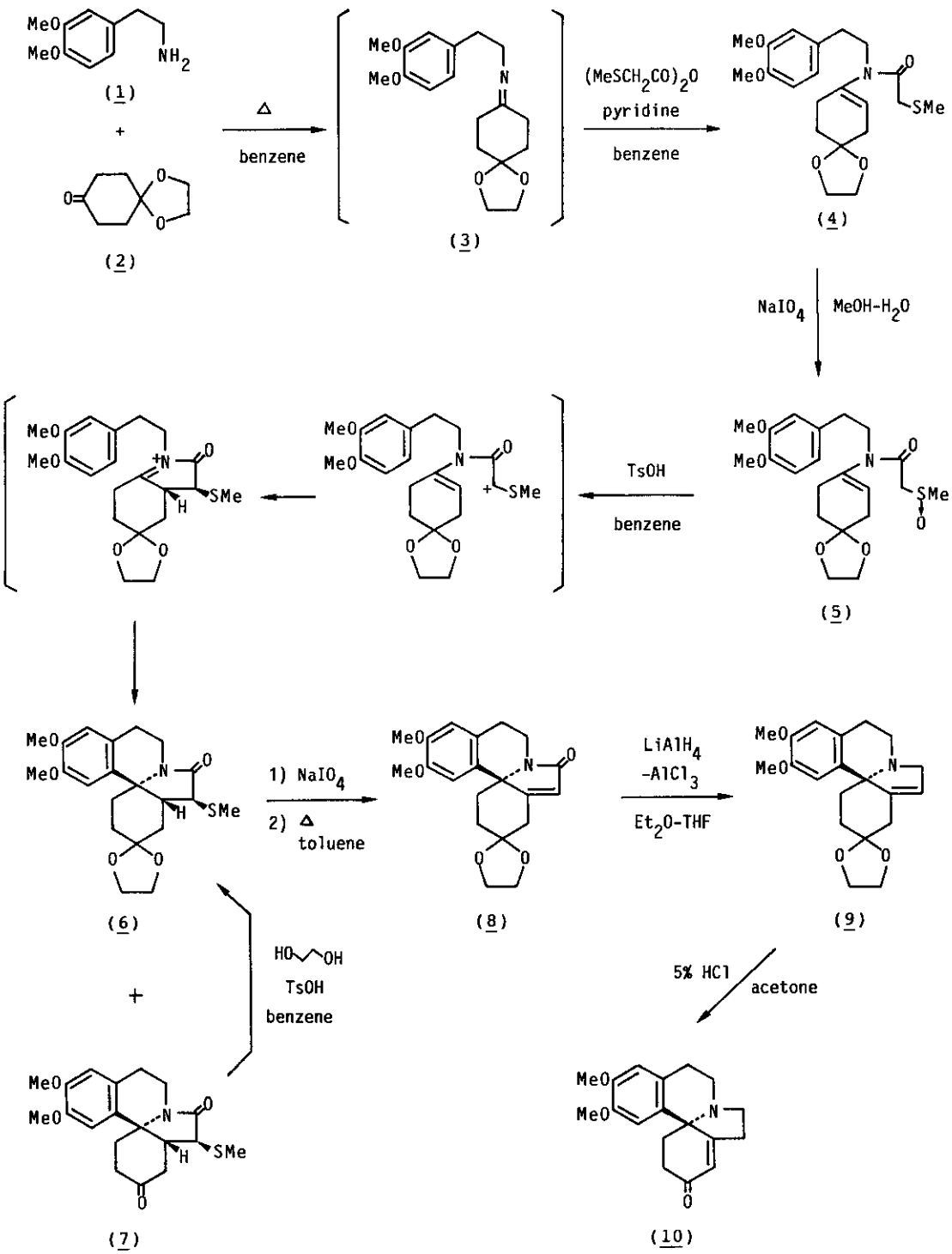
Abstract—(±)-3-Demethoxyerythratidinone (**10**), an alkaloid of Erythrina lithosperma, was synthesized in nine steps and 37% overall yield from homoveratrylamine and cyclohexane-1,4-dione monoethylene acetal.

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 anhydride[4] 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 **6**[5] and **7**[6] 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 $NaHCO_3$ 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.


MeO
MeO
NH2
(1)
+
O
O
O
(2)
Δ
benzene
(3)
(MeSCH2CO)2O
pyridine
benzene
SMe
(4)
NaIO4
MeOH-H2O
TsOH
benzene
(5)
SMe
H
(6)
1) NaIO4
2) Δ
toluene
(8)
LiAlH4
-AlCl3
Et2O-THF
(9)
HO OH
TsOH
benzene
(7)
5% HCl
acetone
(10)

According to the reported procedure,[8] compound **8** was subjected to reduction with $LiAlH_4$-$AlCl_3$ 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 ^{1}H-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; ^{1}H-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, OCH_2CH_2O), 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); ^{1}H-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; ^{1}H-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, OCH_2CH_2O), 5.97 (1H, br s, C=CH), 6.72 (1H, s, arom.), 7.02 (1H, s, arom.).

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9. an oil; ^{1}H-nmr (δ, ppm, 60 MHz, $CDCl_3$) 1.5-4.2 (12H, m), 3.85 (6H, s, OMe x 2), 3.99 (4H, s, OCH_2CH_2O), 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; ^{1}H-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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