

SYNTHESIS OF (±)-3-DEMETHOXYERYTHRATIDINONE, AN ALKALOID OF
ERYTHRINA LITHOSPERMA BLUME¹

Yoshisuke Tsuda* and Akira Nakai^a

Faculty of Pharmaceutical Sciences, Kanazawa University, 13-1
Takara-machi, Kanazawa 920, Japan

Kazuo Ito,* Fumio Suzuki, and Mitsumasa Haruna^b

Faculty of Pharmacy, Meijo University, Yagoto, Tempaku-ku,
Nagoya 468, Japan

Abstract—3-Demethoxyerythratidinone, an alkaloid of Erythrina lithosperma Blume was synthesized in a racemic form by five different routes.

3-Demethoxyerythratidinone 1, an alkaloid isolated from Erythrina lithosperma Blume in 1973 by Barton et al.,² is one of the simplest erythrynan alkaloid which belongs to an alkenoid type. Although the syntheses of the dienoid type aromatic erythrinan alkaloids, erysotrine and erythraline, have been achieved,^{3,4,5} total synthesis of the alkenoid type alkaloid has not been appeared so far. Here we describe five different synthetic routes to the titled alkaloid.

A. From 2,8-Dioxo-7 α -hydroxyerythrinan^a

The 2,8-dioxo-7 α -hydroxyerythrinan ethyleneacetal 2 is conveniently available from homoveratrylamine by 7 step reactions in over-all yield of 65%.^{6,7} Methanesulfonylation of 2 and heating of the resulting mesylate 3⁸, mp 118-120°C, in benzene with DBU at 160°C (sealed tube, 8h) afforded two demesylated products 4 [mp 133-135°C, δ 5.87 (1H, brs), 38%] and 5 [mp 200-202°C, δ 5.87, 5.63 (each 1H, s), λ max. 233 and 285 nm, 51%], the both of which gave the same enone 6 (δ 6.11, 1H, t, J=2 Hz) on acid hydrolysis and compound 5 gave compound 4 on heating with ethylene glycol in the presence of p-TsOH (100%). Thus 3 was convertible to a single product 4 in 90% yield by two successive treatments,

demesylation and acetalization.

Reduction of 4 with $\text{LiAlH}_4\text{-AlCl}_3$ ⁴ in THF followed by acid hydrolysis (2% HCl-acetone, 50°C) of the resulting amine 7 (δ 5.53, 1H, m) furnished, with concomitant migration of the double bond, (+)-demethoxyerythratidinone 1, mp 101-102°C (picrate, mp 250-252°C), in 77% yield. Identity of this with the natural product was confirmed by comparisons of IR(CHCl_3) and $^1\text{H-NMR}$ (CDCl_3) spectra with the authentic sample provided by Prof. Barton.

B. From 2,8-Dioxoerythrinan^b

The intermediate 4 in the above synthesis was prepared by a different route from the 2,8-dioxoerythrinan ethyleneacetal 8 which is available from 4-benzyloxy-3-methoxyphenylethylamine by 5 steps.⁹

The compound 8 was phenylselenylated to 9, oil, on treatment with LDA then with PhSeCl (93%). Oxidative elimination of phenylselenyl group from 9 (15% H_2O_2 in CH_2Cl_2 -pyridine) resulted in 4 (100%) which was identical with the specimen obtained above.

C. From 2,8-Dioxo-1,7-cycloerythrinan^a

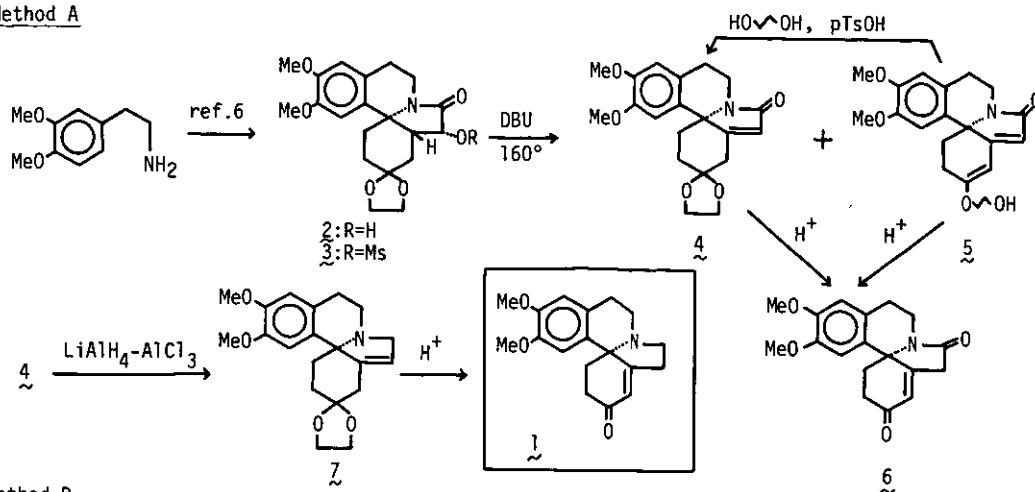
Treatment of the 2,8-dioxo-1,7-cycloerythrinan 10^{5,7,10} with PhSnA in the presence of 18-crown-6 resulted in electrophilic opening of the conjugated cyclopropane ring to afford a 6-SPh substituted product 11, gum, though the yield was not satisfactory (~10%). Oxidation of this with NaIO_4 and heating of the resulting sulfoxide in benzene with ethylene glycol and $p\text{-TsOH}$ resulted in syn-elimination of the sulfoxide group with concomitant ethyleneacetalization thus giving rise to 4 identical with the compound obtained in method A.

D. From 2-Oxo-erythrinan^b

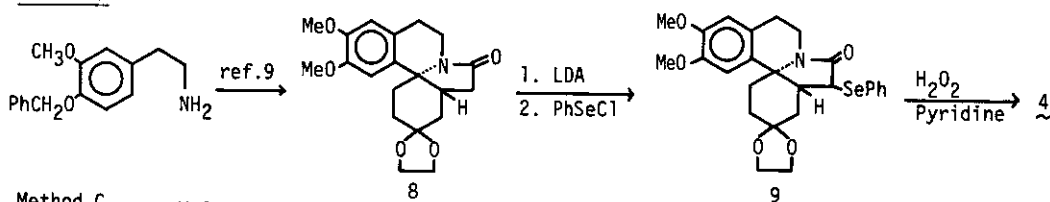
The following two methods utilize the 2-oxo derivative of erythrinan or 1,7-cycloerythrinan.^{4,9}

The erythrinan-2-one 13, oil, is available from 8 by LiAlH_4 reduction followed by acid deacetalization. Treatment of 13 with LDA followed by phenylsulfenylation with PhSSPh resulted in a mixture of mono-(14a and 14b, 62.7%) and di-(14c, 6%) phenylsulfides. The inseparable mixture of 14a and 14b was oxidized with mCPBA and the resulting sulfoxides were heated under reflux in CCl_4 for 18 h to afford 1 (48%) and 15 (3.3%), which were separated by silica gel chromatography. Identity of 1 with demethoxyerythratidinone was again confirmed by spectral comparisons with the authentic specimen.

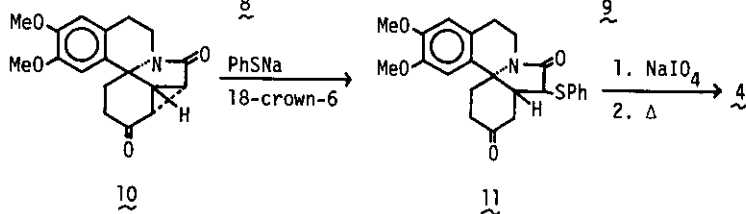
Method A



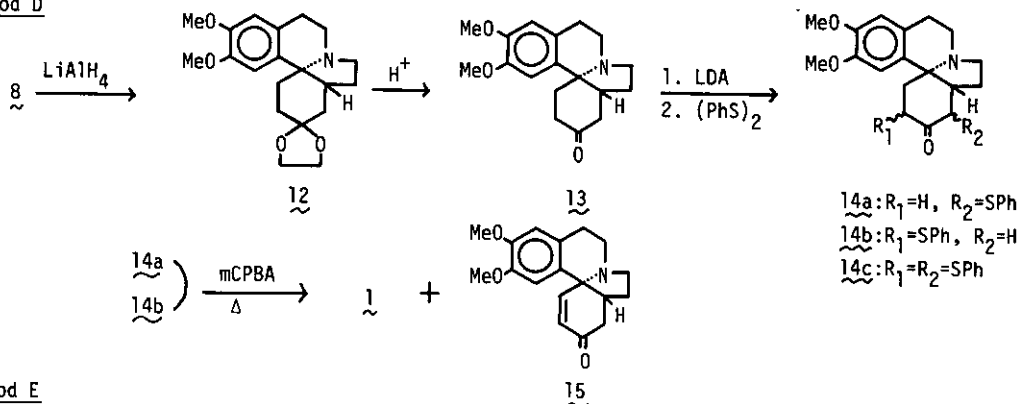
Method B



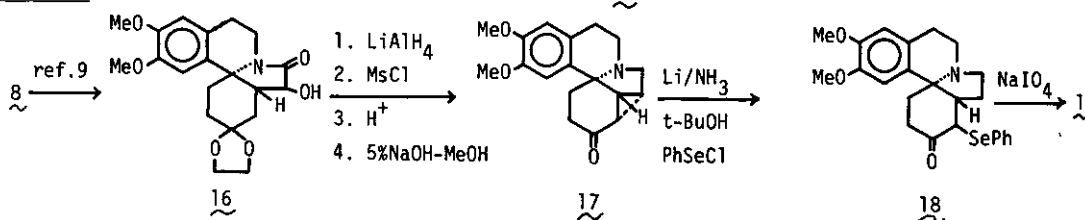
Method C



Method D



Method E



E. From 2-Oxo-1,7-cycloerythrinan^b

The 2-oxo-1,7-cycloerythrinan **17**, mp 205-207°C, is available from compound **8** through 7 β -hydroxy derivative **16**⁹ by 5 steps (i. LDA, O₂, ii. LiAlH₄, iii. MsCl-pyridine, iv. H⁺, v. 5%NaOH-MeOH) in 62% yield. Birch reduction of **17** followed by phenylselenylation (Li/NH₃, t-BuOH, PhSeCl in DME) resulted in α -phenylselenyl derivative **18** (23%). Oxidative elimination of the phenylselenyl group (NaIO₄ in THF) from **18** gave an unsaturated ketone which was identical with demethoxyerythratidinone **1** in spectral data.

Among the above described five methods, methods A and B are the most practical ones for availability of the starting materials, simplicity of the procedures, and high over-all yields.

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7. The reported method (ref. 6) was improved in this time (use of DMSO-Ac₂O instead of Collins oxidation). Details will be reported in full paper.
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