SYNTHESIS OF (±)-3-DEMETHOXYERYTHRATIDINONE, AN ALKALOID OF ERYTHRINA LITHOSPERMA BLUME[1]

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 sythesis 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-7α-hydroxyerythrinan[a]

The 2,8-dioxo-7α-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 **3**[8], mp 118-120°C, in benzene with DBU at 160°C (sealed tube, 8h) afforded two demesylated products **4** [mp 133-135°C, δ5.87(1H, brs), 38%] and **5** [mp 200-202°C, δ5.87, 5.63 (each 1H, s), λmax. 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 $LiAlH_4$-$AlCl_3$[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}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.

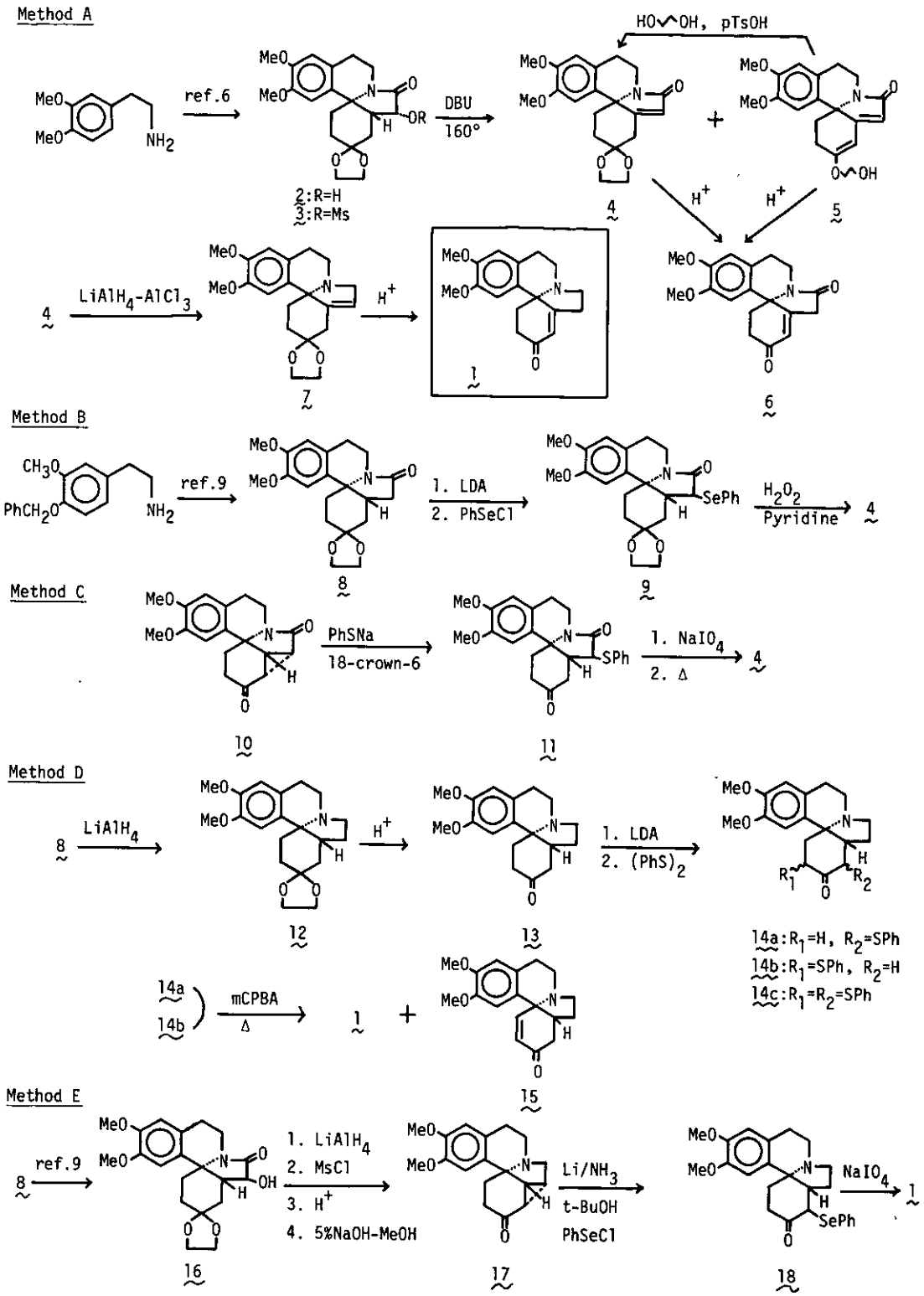
C. From 2,8-Dioxo-1,7-cycloerythrinan[a]

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 afforded a β-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-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
ref.6
DBU
160°
HO∧OH, pTsOH
2:R=H
3:R=Ms
4
5
6
7
1
LiAlH4-AlCl3
H+
Method B
ref.9
1. LDA
2. PhSeCl
H2O2
Pyridine
8
9
Method C
PhSNa
18-crown-6
1. NaIO4
2. Δ
10
11
Method D
LiAlH4
1. LDA
2. (PhS)2
12
13
14a:R1=H, R2=SPh
14b:R1=SPh, R2=H
14c:R1=R2=SPh
mCPBA
Δ
15
Method E
ref.9
1. LiAlH4
2. MsCl
3. H+
4. 5%NaOH-MeOH
Li/NH3
t-BuOH
PhSeCl
NaIO4
16
17
18

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 7β-hydroxy derivative **16**[9] by 5 steps (i. LDA, O_2, ii. $LiAlH_4$, iii. MsCl-pyridine, iv. H^+, v. 5%NaOH-MeOH) in 62% yield. Birch reduction of **17** followed by phenylselenylation (Li/NH_3, t-BuOH, PhSeCl in DME) resulted in α-phenylselenyl derivative **18** (23%). Oxidative elimination of the phenylselenyl group ($NaIO_4$ 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 avilability of the staring materials, simplicity of the procedures, and high over-all yields.

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REFERENCES AND NOTES

1. Synthesis of Erythrina and Related Alkaloids (10). Part (9): T. Sano, J. Toda, Y. Tsuda, and T. Ohshima, Heterocycles, 1984, 22, 49.
2. D.H.R. Barton, A.A.L. Gunatilaka, R.M. Letcher, A.M.F.T. Lobo, and Widdowson, J. C. S. Perkin I, 1973, 874.
3.a) A. Mondon and H.J. Nestler, Angew. Chem. Int. Ed., 1964, 3, 558.
b) Ibid., Chem. Ber., 1979, 112, 1329.
4. Synthesis of an 8-oxo-compound, erysotramidine: K. Ito, F. Suzuki, and M. Haruna, J. C. S. Chem. Comm., 1978, 733.
5. T. Sano, J. Toda, and Y. Tsuda, Heterocycles, 1982, 18, 229.
6. Y. Tsuda, Y. Sakai, K. Akiyama, and K. Isobe, Heterocycles, 1981, 16, 921.
7. The reported method (ref. 6) was improved in this time (use of DMSO-Ac_2O instead of Collins oxidation). Details will be reported in full paper.
8. All new compounds in this communication gave satisfactory elementary analyses or mass spectra together with satisfactory spectral data (^1H-NMR and IR).
9. M. Haruna and K. Ito, J. C. S. Chem. Comm., 1976, 345.
10. A. Mondon, H.G. Vilhauber, C. Fischer, M. Epe, B. Epe, and C. Wolff, Chem. Ber., 1979, 112, 1110.

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