CHIRAL SYNTHESIS OF *ENANTIO*-TYPE ERYTHRINAN ALKALOIDS UTILIZING ASYMMETRIC ACYLATION AND KINETIC RESOLUTION OF DIASTEREOMERS[1)]

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Chiral synthesis of an erythrinan alkaloid, (-)-3-demethoxyerythratidinone (11), as well as a versatile intermediate, the 1,7-cycloerythrinan derivative (14) (both are of *enantio*-type) was achieved using asymmetric acylation and kinetic resolution starting from the L-dopa derivative (1).

KEYWORDS chiral synthesis; *Erythrina* alkaloid; 3-demethoxyerythratidinone; *enantio*-type alkaloid; asymmetric acylation; kinetic resolution; cyclization

Erythrinan alkaloids have been successfully synthesized in racemic forms by one of the following three routes: (1) Diels-Alder route,[2)] (2) intramolecular cyclization route,[3), 4)] and (3) photochemical route.[5)] Recently a chiral synthesis of the natural alkaloid, (+)-erysotrine, was also reported by utilizing the first route under a super high pressure.[6)] In this communication, we describe the chiral synthesis of erythrinan alkaloids by the second route, which gave the alkaloids of *enantio*-type preferentially.

(*S*)-(+)-Amine **1**[7)] derived from L-dopa was condensed with ethyl 5,5-ethylenedioxy-2-oxocyclohexanecarboxylate to afford the enamino-ester **2**[7)] in 94 % yield. Treatment of **2** with oxalyl chloride gave the dioxopyrrolines **3** as a mixture of diastereomers, **3a** and **3b**[7)]. The yield and diastereomeric excess (de)[8)] of the products were dependent on the reaction conditions (solvent and temperature), and the best result was obtained by the reaction in Et_2O at -15°C: 90% yield and 60% de for the (6*R*)-isomer **3a** (for the absolute configuration, see below). The reaction proceeds in two steps: *N*-acylation followed by *C*-acylation. Asymmetric induction occurs at the second step. Although the energy difference between two transition states, A and B, is not *a priori* evaluated, the above result shows that the *si*-face attack (A) is preferred to the *re*-face attack (B).

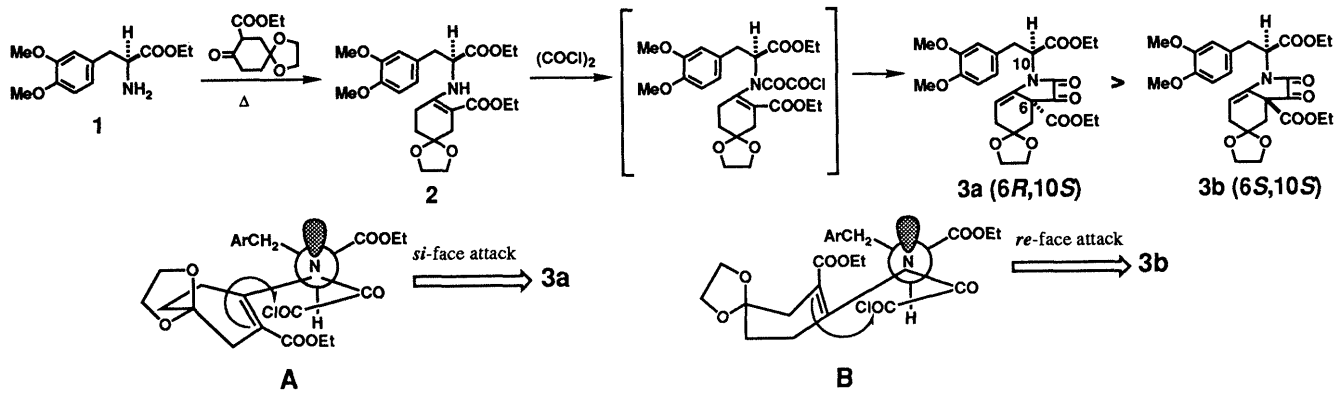


Chart 1

A mixture of the dioxopyrrolines **3** was reduced by $NaBH_4$ and then cyclized by BF_3•Et_2O in CH_2Cl_2 to afford a mixture of erythrinans, **5a** and **5b**,[9)] (93 % from **3**, 60% de) . Treatment of **5** with 5%HCl-acetone (1:1) at room temperature for 3 h resulted in partial hydrolysis of the ethylene acetal group to give a mixture of acetals **5**[7)] (62%) and the ketones **6**[7)] (17 %), which were easily separated by column chromatography. Interestingly, the de of the acetals **5** and ketones **6** was revealed to be 82% and 0%, respectively, indicating that the minor (5*R*,6*S*,7*S*,10*S*)-isomer was more rapidly hydrolyzed than the major (5*S*,6*R*,7*R*,10*S*)-isomer was. Thus the de of the 5*S*-isomer could be raised to 82% from the original 60% by the kinetically controlled hydrolysis of the acetal

mixture. This large difference in the hydrolysis rates between **5a** and **5b** may be attributed to the conformational difference of the diastereomers. Assuming that C_{10}-COOEt groups in both isomers are equatorially oriented, the (5*R*,6*S*,7*S*,10*S*)-isomer would have severe steric interaction between the ethylene acetal and C_6-COOEt groups, thus destabillizing the compound.

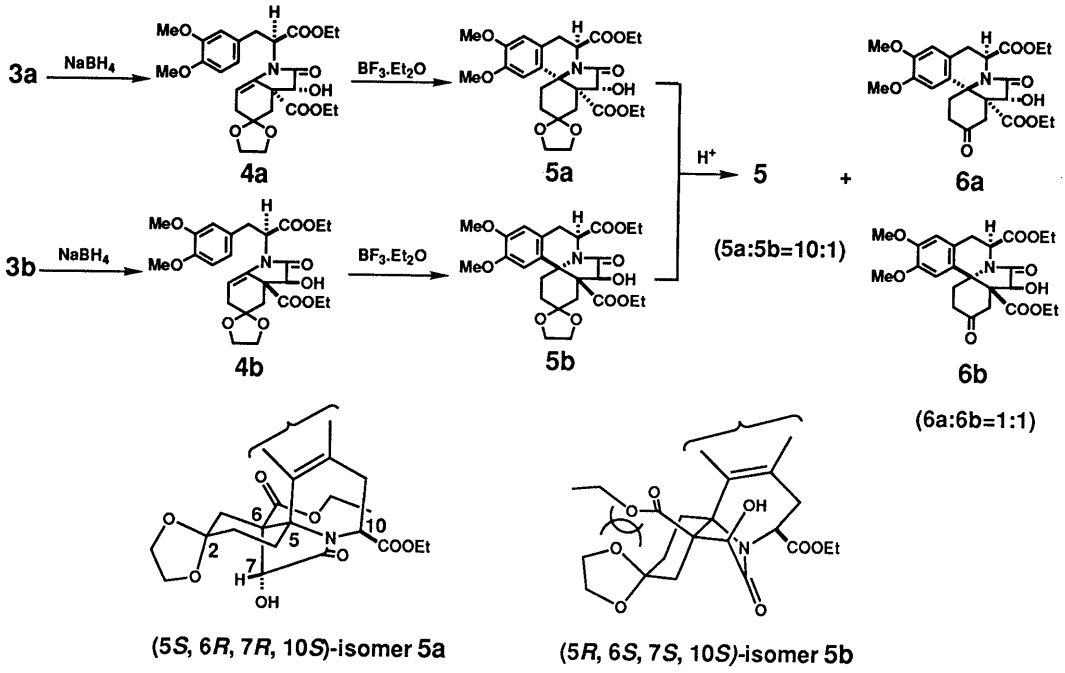
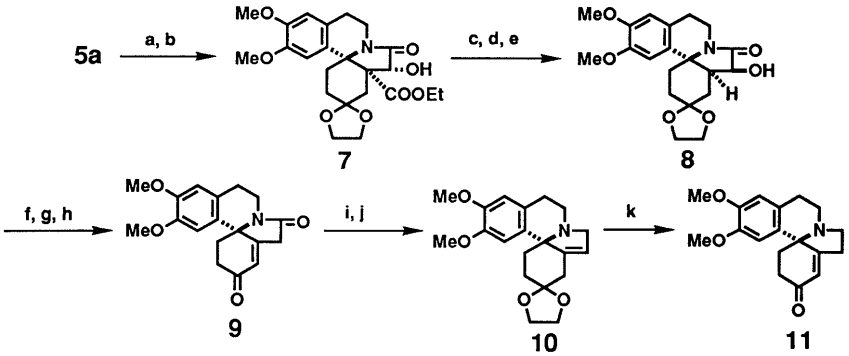


Chart 2

Alkaline hydrolysis of **5a** (80% de) followed by decarboxylation of the resulting acid by Barton's method[10] gave the decarboxylated product **7** which was identical with the corresponding racemic compound[3] in the ^{1}H-NMR spectra and TLC behavior. Compound **7** was converted to (-)-3-demethoxyerythratidinone **11** in the manner reported for the racemate[3] (Scheme is shown in Chart 3). The final product **11** (obtained in 15 % yield from **5**) was identical with the alkaloid, (+)-3-demetoxyerythratidinone,[11] in the spectral data and TLC behavior except that it had an opposite sign in the optical rotation ($[\alpha]_D^{20}$ -236°, *c*=0.8, $CHCl_3$),[12] thus indicating that the present synthesis gave the erythrinan of *enantio*-type.

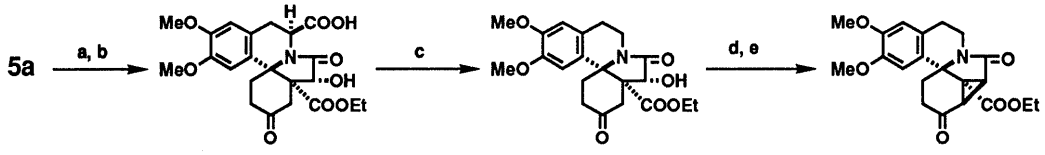


a. 5% NaOH-EtOH (1:1), r. t.; b. i) *N*-methylmorpholine, isobutyl chloroformate/THF, -10°C, ii) *N*-hydroxypyridinethione sodium salt, Et_3N/THF, -10°C , iii) hυ/*t*-BuSH-THF, 0°C; c. DMSO-Ac_2O, r.t.; d. $MgCl_2$-HMPA, 140°C; e. $NaBH_4$/EtOH-THF (1:1), 0°C; f. MsCl-DMAP/Py, r.t.; g. DBU/benzene,160°C; h. 10% HCl-acetone (1:1), 60°C; i. ethylene glycol, *p*-TsOH/benzene, reflux; j. $LiAlH_4$-$AlCl_3$ (3:1)/ Et_2O-THF, 0°C; k. 5% HCl-acetone (3:5), 80°C.

Chart 3

Next, we converted **5a** to the 1,7-cycloerythrinan derivative **14**, a key intermediate to dienoid type erythrinan alkaloids. Acid

deacetalization of **5a** followed by alkaline hydrolysis and decarboxylation by Barton's method gave the ketone **13** {60 % yield from **5**, colorless prisms from MeOH-Et_2O, mp 263-265°C, $[\alpha]_D^{26}$ +117° (*c*=0.18, $CHCl_3$)}, which was identical with the corresponding racemate[3] (mp 237-239°C) except for the $[\alpha]_D$ and mp. Methanesulfonylation of **13** followed by demethanesulfonylation with DBU, as in the racemate,[3] gave (-)-**14** (92 %, mp 184-186°C, $[\alpha]_D^{28}$ -28°, *c*=0.75, $CHCl_3$). Since (±)-**14** was already converted to (±)-erysotrine,[4] the same sequence of reactions would give the corresponding alkaloid of *enantio*-type.



a. 5%HCl-acetone (1:1), 50°C; b. 5%NaOH-EtOH (1:2), r.t.; c. i) *N*-methylmorpholine, isobutyl chloroformate/THF, -10°C, ii) *N*-hydroxypyridinethione sodium salt, Et_3N/THF, -10°C, iii) hυ/ *t*-BuSH-THF, 0°C; d. MsCl/Py, r.t.; e. DBU/toluene, reflux.

Chart 4

The present synthesis indicates that, starting from the same chiral precursor (*S*)-(+)-**1**, it is possible to synthesize both enantiomers of aromatic-type *Erythrina* alkaloid in chiral forms: Diels-Alder method gives the alkaloids of (+)-series and intramolecular cyclization method gives those of (-)-series. (*R*)-(-)-Amine **1** should therefore give the reversal result.

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7) (*S*)-(+)-**1**: oil. $[\alpha]_D^{24}$ +5.3° (*c*=1.0, EtOH). δ NH_2 1.75 (brs); OMe 3.86, 3.87; ArH 6.73 (brs), 6.74 (dd, *J*=8, 2 Hz), 6.81 (d, *J*=8 Hz). (-)-**2**: oil. $[\alpha]_D^{24}$ -92° (*c*=0.98, $CHCl_3$). IR ($CHCl_3$): 1727, 1639, 1591. δ OMe 3.85, 3.86; ArH 6.77 (m); NH 9.36 (d, *J*=8.8 Hz). **3**: δ ($COOCH_2CH_3$): for **3a**, 1.19, 1.21; for **3b**, 1.17, 1.26. **5**: gum, IR ($CHCl_3$): 1728, 1700. δ for **5a**, OMe 3.84, 3.86; H-7 5.28 (s), ArH 6.70, 6.78 ; for **5b**, OMe 3.84, 3.85; H-7 5.14; ArH 6.62, 6.67. **6**: gum. IR ($CHCl_3$): 1716. δ for **6a**, OMe 3.82, 3.87; H-7 4.51; ArH 6.61, 6.67; for **6b**, OMe 3.83, 3.86; H-7 4.30; ArH 6.54, 6.62.

8) Diastereomers in this paper were not separated chromatographically. The de's of the mixture were calculated from the ^{1}H-NMR spectra.

9) Previous studies for the compounds which lack C_{10}-COOEt group (ref. 3) revealed that $NaBH_4$ reduction of C_7-ketone gave the alcohol *cis* to C_6-COOEt group and the following Lewis acid catalyzed cyclization always gave A/B *cis*-fused erythrinans. Therefore each stereoisomer **3a** or **3b** gives the single product, **5a** or **5b**, respectively.

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12) The optical purity calculated from this value was 72% ee.

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