TOTAL SYNTHESIS OF (+)-ERYSOTRINE *VIA* ASYMMETRIC DIELS-ALDER REACTION UNDER SUPER HIGH PRESSURE[1]

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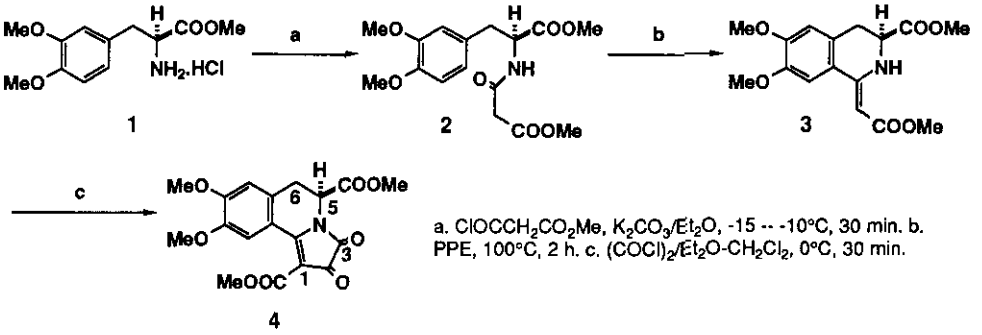
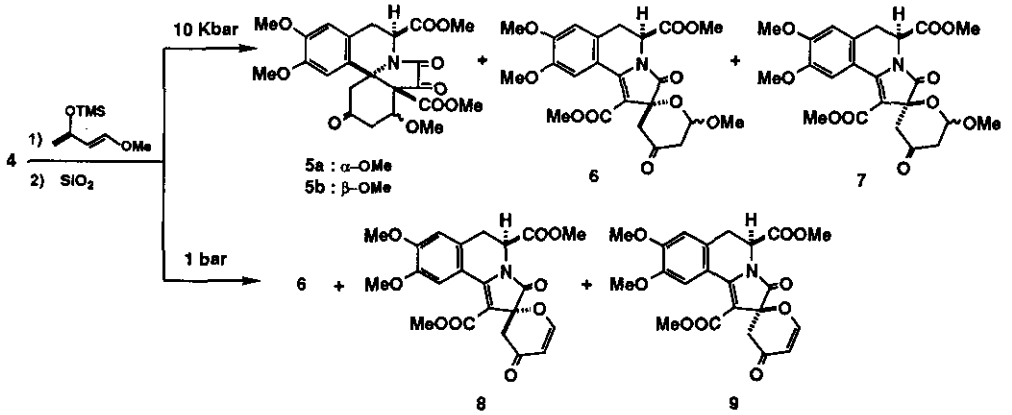
Abstract—— The first total synthesis of (+)-erysotrine in a chiral form was achieved through application of Diels-Alder reaction of a chiral dioxopyrroline with 1-methoxy-3-trimethylsilyloxybutadiene under a 10 Kbar pressure.

An effective synthetic route to erythrinan alkaloids using Diels-Alder reaction of an isoquinolinopyrrolinedione with a 1,3-*O*-disubstituted butadiene as a key step was reported.[2] In the present communication, we wish to report the first total synthesis of (+)-erysotrine from an L-DOPA derivative utilizing asymmetric Diels-Alder reaction under super high pressure. The chiral dienophile, dioxopyrroline (**4**), was prepared as follows (Scheme 1). Condensation of (*S*)-3,4-dimethoxyphenylalanine methyl ester hydrochloride (**1**)[3] with methyl chloroformylacetate gave the amide (**2**),[4] mp 95-95.5°C, in 97% yield. Treatment of **2** with polyphosphate ester (PPE) at 100 °C for 2 h afforded **3**,[4] mp 139.5-141°C (98%). Condensation of **3** with oxalyl chloride in Et_2O-CH_2Cl_2 at 0°C gave the pyrrolinedione (**4**)[4] (99%), mp. 223-224 °C, carrying a COOMe group at C-5. An X-ray analysis of **4** revealed that ring B of this compound is of half-chair conformation and the methoxycarbonyl group is in axial orientation.

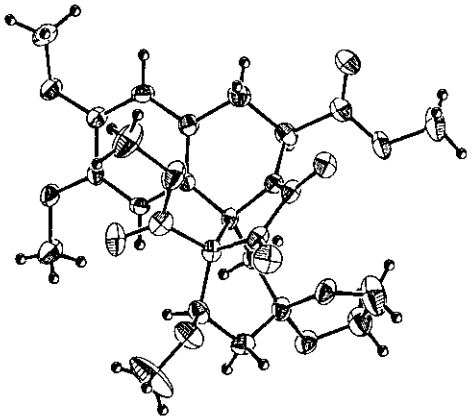


Scheme 1

Diels-Alder reaction of **4** with 1-methoxy-3-trimethylsilyloxybutadiene (5 equiv.) in dichloromethane at 130°C for 1 h under an ordinary pressure (1 bar) (followed by treatment with silica gel) produced only *one*-adducts, **6** (gum, 13%),[5] **8** (gum, 45%),[5] and **9** (mp 192-193°C, 14%).[5] On the other hand, when this reaction was carried out under a pressure of 10 Kbar, the desired *ene*-adduct (**5**) was obtained in 40-50% yield together with *one*-adducts, **6** (gum, *ca.* 20%) and **7**[5] (gum, trace). The ratio of *cis-endo* isomer (**5a**)[6] (mp 177-179°C) *vs* *cis-exo* isomer (**5b**)[6] (mp 206-207°C) in the reation mixture, calculated from the peak areas of aromatic proton signals, was variable (2/1-1/12) depending on the reaction time. The *ene*-adducts (**5a**) and (**5b**) were converted to the ethyleneacetals (**10a**)[6] (mp 246-247°C) and (**10b**)[6] (gum) on heating with ethylene glycol in benzene under catalysis of *p*-toluenesulfonic acid, respectively, and the structure of **10a** was proved by an *X*-ray analysis (Figure 1).

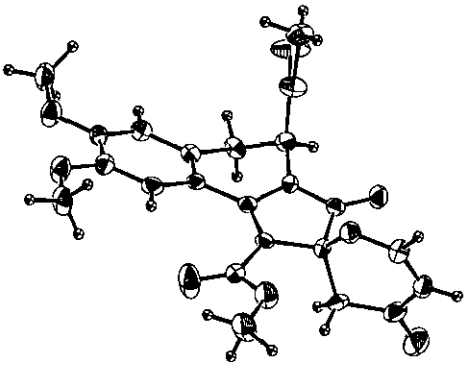


Scheme 2



Crystal data: orthorhombic, space group $p2_12_12_1$, a=14.841(4), b=14.920(3), c=11.247(2)Å, V=2490.4(9)Å^3, Z=4, Dc=1.39g/cm^3, *R*=0.039.

Figure 1 ORTEP drawing of **10a**



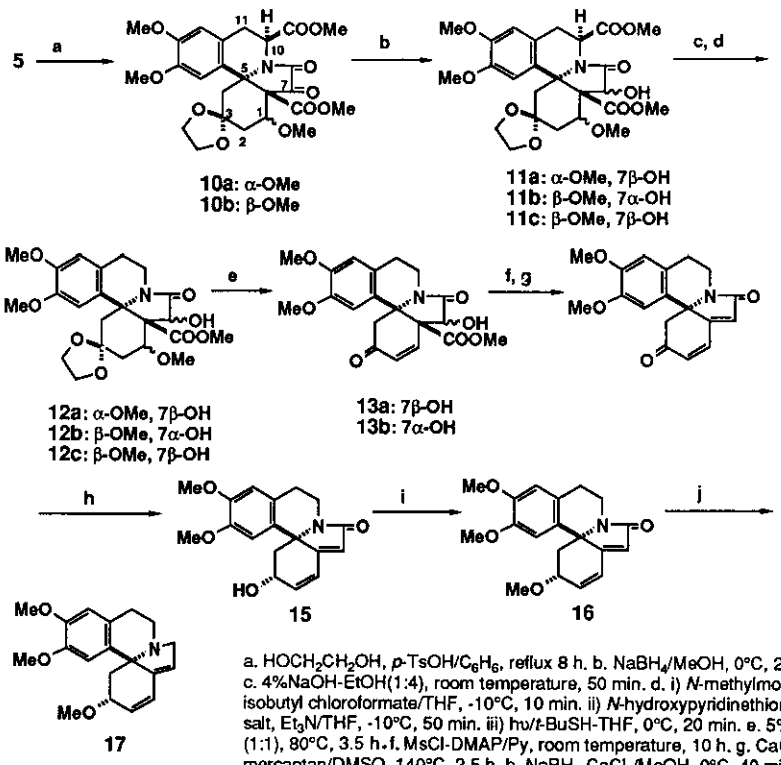
Crystal data: monoclinic, space group $p2_1$, a=6.021(2), b=10.295(2), c=16.696Å, b=93.62(2)°, V=1032.8(5)Å^3, Z=2, Dc=1.43g/cm^3, *R*=0.038.

Figure 2 ORTEP drawing of **9**

The above remarkable difference between the Diels-Alder reaction at 1 bar and that at 10 Kbar may be explained by the following assumption that a super high pressure might force reactants to take the smallest molecular volume at a transition state, thus giving rise to the product of small molecular volume. Apparently, the *ene*-adducts have smaller molecular volume than the *one*-adducts. This explanation leads to the suggestion that both faces of **4** are hindered for Diels-Alder reaction at 1 bar, probably by the presence of 5β-COOMe and 6α-H.

For transformation of the above adduct to the natural alkaloid, (+)-erysotrine, a mixture of **10a** and **10b** derived from a mixture of **5a** and **5b** (2:1) was reduced with sodium borohydride in methanol at 0 °C to give the alcohol (**11**).[7] Alkaline hydrolysis of the mixture of **11** followed by application of Barton's decarboxylation method[8] to the resulting carboxylic acid afforded **12** (a mixture of **12a**, **12b**, and **12c**) which was converted to a mixture of the enones (**13a** and **13b**),[7] by acid hydrolysis. The ^{1}H-nmr spectrum of **13a** was identical with that of the corresponding racemic compound.[2] Mesylation of the mixture of **13**

followed by decarbomethoxylation with $CaCl_2$/DMSO[9] gave the dienone (**14**), mp 196-197°C, $[\alpha]_D$ +217° (*c*=0.26, $CHCl_3$), as a single product in overall yield of 51% from **5**. The ir and nmr spectra of **14** were identical with those reported for the racemic compound.[2] Conversion of **14** to (+)-erysotrine (**17**) was performed as reported in the racemic compound.[2] $NaBH_4$-$CeCl_3$ reduction[10] of **14** gave the 3α-alcohol (**15**), mp 214-216°C, $[\alpha]_D$ +182° (*c*=0.25, $CHCl_3$), as a major product together with the 3β-alcohol, mp 82-83°C. Methylation of **15** gave (+)-erysotramidine (**16**), oil, $[\alpha]_D$ +148° (*c*=1.2, $CHCl_3$) [lit. oil, $[\alpha]_D$ +121° ($CHCl_3$)],[11] in 85% yield. This was further converted to the amine (**17**) (94%), mp 95-98°C. Identity of **17** with the natural (+)-erysotrine was confirmed by converting to the picrate, mp 163-164°C, $[\alpha]_D$ +143° (*c*=0.14, EtOH), whose mp, $[\alpha]_D$, and the spectral data were identical with those of (+)-erysotrine picrate [mp 162-163°C, $[\alpha]_D$ +142° (EtOH)].[12] Thus, the first total synthesis of erysotramidine and erysotrine in optically active forms was accomplished.



a. $HOCH_2CH_2OH$, *p*-TsOH/C_6H_6, reflux 8 h. b. $NaBH_4$/MeOH, 0°C, 20 min. c. 4%NaOH-EtOH(1:4), room temperature, 50 min. d. i) *N*-methylmorpholine, isobutyl chloroformate/THF, -10°C, 10 min. ii) *N*-hydroxypyridinethione sodium salt, Et_3N/THF, -10°C, 50 min. iii) hν/*t*-BuSH-THF, 0°C, 20 min. e. 5%HCl-THF (1:1), 80°C, 3.5 h. f. MsCl-DMAP/Py, room temperature, 10 h. g. $CaCl_2$-*t*-heptyl-mercaptan/DMSO, 140°C, 2.5 h, h. $NaBH_4$-$CeCl_3$/MeOH, 0°C, 40 min. i. MeI, KOH, Et_4NBr/THF, room temperature, 34 h. j. $LiAlH_4$-$AlCl_3$(1:3)/Et_2O-THF, 0°C, 40 min.

Scheme 3

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4. **2**: Ir($CHCl_3$) 1735, 1670 cm^{-1}. $[\alpha]_D$ +55° (*c*=0.56, $CHCl_3$). **3**: Ir(KBr) 1737, 1662 cm^{-1}. $[\alpha]_D$ -171° (*c*=0.5, $CHCl_3$). **4**: Red prisms, Ir(KBr): 1761, 1731, 1706 cm^{-1}. $[\alpha]_D$ -92° (*c*=1.0, $CHCl_3$).
5. **6**: A mixture of stereoisomers, pale red gum. Ir($CHCl_3$) 1737, 1695cm^{-1}. δ ArH 7.85, 6.69; OMe 3.94, 3.90, 3.76, 3.58, 3.55 and ArH 7.84, 6.68; OMe 3.94, 3.90, 3.81, 3.59, 3.45. **7**: Pale red gum. Ir($CHCl_3$) 1735, 1693 cm^{-1}. δ ArH 8.34, 6.70; OMe 3.95, 3.93, 3.68, 3.62, 3.52. The stereochemistry of these compounds is tentative. **8**: Red gum. Ir($CHCl_3$) 1740, 1690, 1679, 1599 cm^{-1}. δ ArH 8.04, 6.63; COCH=CH 7.22, 5.44 (d, *J*=6 Hz); OMe 3.88, 3.86, 3.74. **9**: Orange prisms, mp 192-193°C. Ir($CHCl_3$) 1740, 1690, 1679, 1600 cm^{-1}. δ ArH 8.45, 6.64; COCH=CH 7.28, 5.44 (d, *J*=6.5 Hz); OMe 3.88, 3.72, 3.55. The structure of **9** was determined by an X-ray analysis (Figure 2).
6. **5a**: Colorless needles. $[\alpha]_D$-147° (*c*=0.24, $CHCl_3$). δ ArH 6.64, 6.06; C_1-H 4.64 (t, *J*=3 Hz); OMe 3.87, 3.85, 3.72, 3.36, 3.08. **5b**: Colorless needles. $[\alpha]_D$-221° (*c*=0.17, $CHCl_3$). δ ArH 7.25, 6.62; C_1-H 4.58, (t, *J*=3 Hz); OMe 3.87, 3.85, 3.82, 3.73, 3.11. **10a**: Colorless prisms. Ir($CHCl_3$) 1773, 1749, 1719 cm^{-1}. δ ArH 6.82, 6.60; C_1-H 4.48 (dd, *J*=10, 6.4 Hz); OMe 3.90, 3.86, 3.84, 3.49, 3.21. **10b**: Colorless gum. Ir($CHCl_3$) 1775, 1745, 1718 cm^{-1}. δ ArH 7.52, 6.59; C_1-H 4.43 (br d, *J*=5.3 Hz); OMe 3.86, 3.85, 3.82, 3.61, 3.16.
7. Reduction of **10a** gave the 7β-alcohol (**11a**) as a single product, while that of **10b** gave a 4:1 mixture of **11b** and **11c**. **11a**: Colorless gum. Ir($CHCl_3$) 3500, 1735, 1710 cm^{-1}. δ ArH 7.08, 6.56; C_7-H 4.90. **11b**: δ ArH 6.82, 6.54; C_7-H 4.82. **11c**: δ ArH 7.59, 6.53; C_7-H 4.52. **13a**: Colorless needles, mp 209.5-211°C. $[\alpha]_D$ +73°(*c*=1.4, $CHCl_3$). Ir(KBr) 3315, 1730, 1720, 1672 cm^{-1}. δ ArH 6.55, 6.47; COCH=CH 7.57, 6.46 (d, *J*=10 Hz); C_7-H 4.78; OMe 3.83, 3.67, 3.29. **13b**: Colorless prisms, mp 217-219°C. $[\alpha]_D$+131°(*c*=0.39, $CHCl_3$). Ir(KBr) 3255, 1736, 1690, 1670 cm^{-1}. δ ArH 6.56, 6.55; COCH=CH 7.15, 6.56

(d, J=10.5 Hz); C_7-H 4.53; OMe 3.83, 3.70, 3.26.

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