

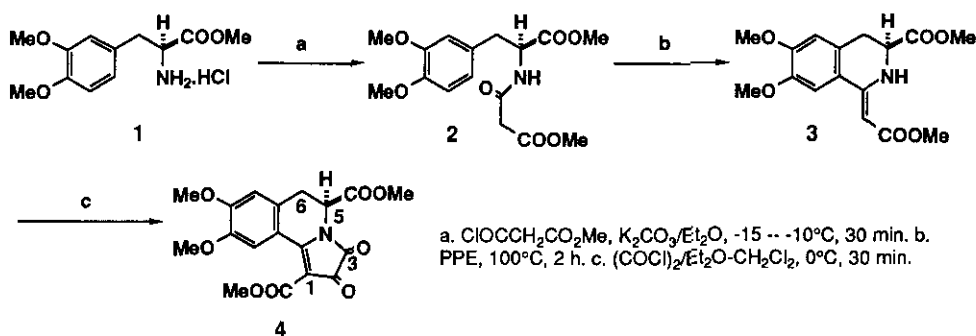
TOTAL SYNTHESIS OF (+)-ERYSOTRINE VIA ASYMMETRIC DIELS-ALDER REACTION UNDER SUPER HIGH PRESSURE¹

Yoshisuke Tsuda*^a, Shinzo Hosoi,^a Nobuya Katagiri,^b Chikara Kaneko,^b
and Takehiro Sano^c

*Faculty of Pharmaceutical Sciences,^a Kanazawa University, 13-1 Takara-machi,
Kanazawa 920, Japan, Pharmaceutical Institute,^b Tohoku University, Aobayama,
Sendai 980, Japan, and Showa College of Pharmaceutical Sciences,^c 3-3165
Higashi-tamagawagakuen, Machida, Tokyo 194, Japan*

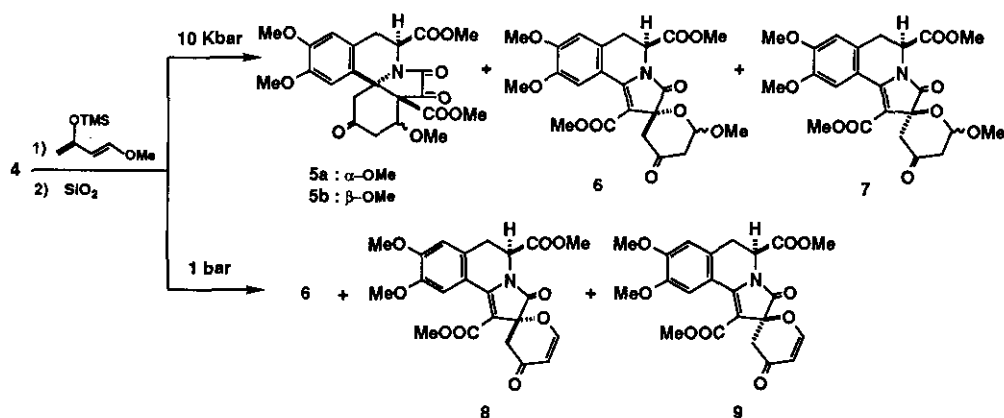
Abstract—— The first total synthesis of (+)-erysotrine in a chiral form was achieved through application of Diels-Alder reaction of a chiral dioxopyrroline with 1-methoxy-3-trimethylsilyloxybutadiene under a 10 Kbar pressure.

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 Et₂O-CH₂Cl₂ 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.

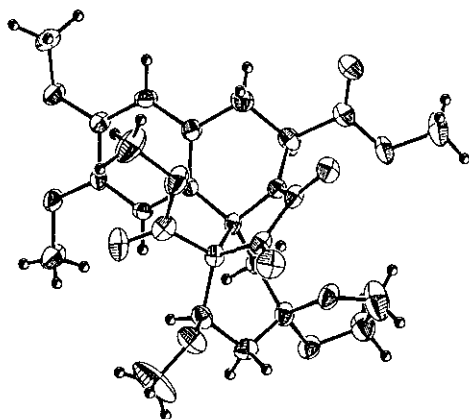


Scheme 1

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 $192\text{--}193^\circ\text{C}$, 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 $177\text{--}179^\circ\text{C}$) vs *cis-exo* isomer (**5b**)⁶ (mp $206\text{--}207^\circ\text{C}$) in the reaction 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 $246\text{--}247^\circ\text{C}$) 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).

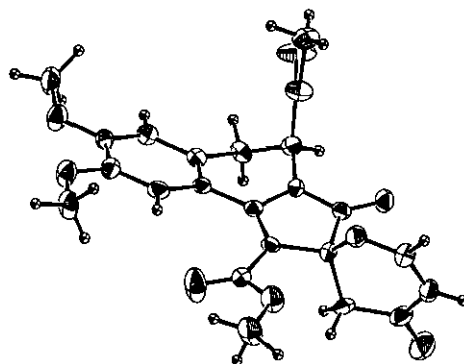


Scheme 2



Crystal data: orthorhombic, space group $p2_12_12_1$, $a=14.841(4)$, $b=14.920(3)$, $c=11.247(2)\text{\AA}$, $V=2490.4(9)\text{\AA}^3$, $Z=4$, $D_c=1.39\text{g/cm}^3$, $R=0.039$.

Figure 1 ORTEP drawing of **10a**



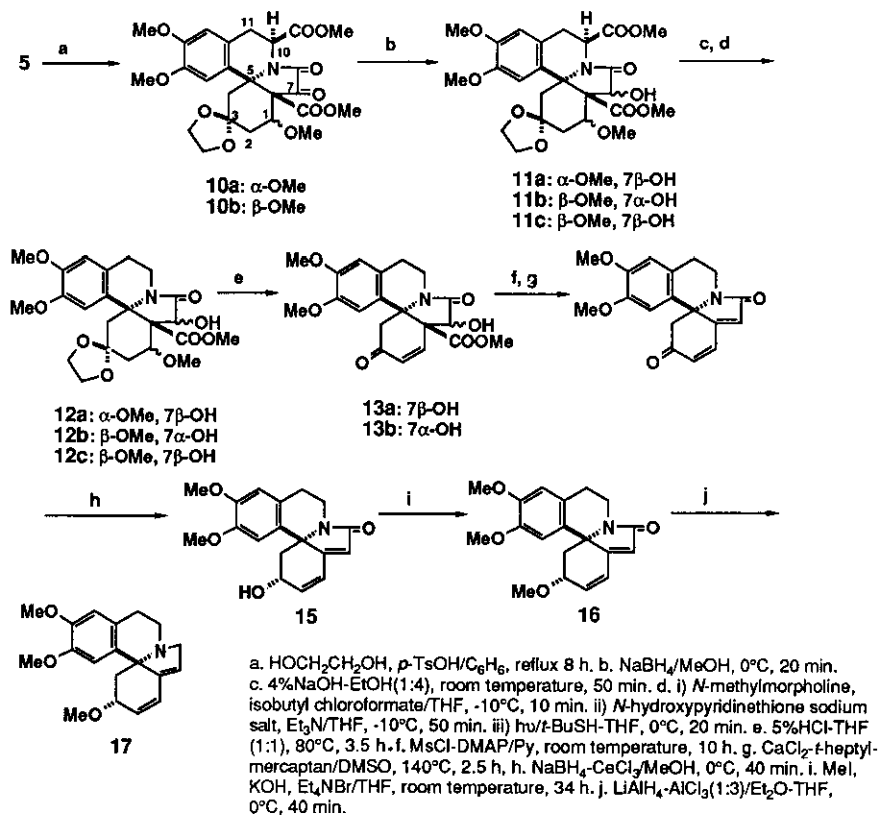
Crystal data: monoclinic, space group $p2_1$, $a=6.021(2)$, $b=10.295(2)$, $c=16.696\text{\AA}$, $b=93.62(2)^\circ$, $V=1032.8(5)\text{\AA}^3$, $Z=2$, $D_c=1.43\text{g/cm}^3$, $R=0.038$.

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 $5\beta\text{-COOMe}$ and $6\alpha\text{-H}$.

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 method⁸ 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 ^1H -nmr spectrum of **13a** was identical with that of the corresponding racemic compound.² Mesylation of the mixture of **13**

followed by decarbomethoxylation with $\text{CaCl}_2/\text{DMSO}$ ⁹ gave the dienone (**14**), mp 196-197°C, $[\alpha]_D +217^\circ$ ($c=0.26$, 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 $\text{NaBH}_4\text{-CeCl}_3$ reduction¹⁰ of **14** gave the 3 α -alcohol (**15**), mp 214-216°C, $[\alpha]_D +182^\circ$ ($c=0.25$, CHCl_3), as a major product together with the 3 β -alcohol, mp 82-83°C. Methylation of **15** gave (+)-erysotramidine (**16**), oil, $[\alpha]_D +148^\circ$ ($c=1.2$, CHCl_3) [lit. oil, $[\alpha]_D +121^\circ$ (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, $[\alpha]_D +143^\circ$ ($c=0.14$, EtOH), whose mp, $[\alpha]_D$, and the spectral data were identical with those of (+)-erysotrine picrate [mp 162-163°C, $[\alpha]_D +142^\circ$ (EtOH)].¹² Thus, the first total synthesis of erysotramidine and erysotrine in optically active forms was accomplished.



Scheme 3

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1. Synthesis of *Erythrina* and Related Alkaloids. Part XXXI.
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4. **2**: Ir(CHCl₃) 1735, 1670 cm⁻¹. [α]_D +55° (c=0.56, CHCl₃). **3**: Ir(KBr) 1737, 1662 cm⁻¹. [α]_D -171° (c=0.5, CHCl₃). **4**: Red prisms, Ir(KBr): 1761, 1731, 1706 cm⁻¹. [α]_D -92° (c=1.0, CHCl₃).
5. **6**: A mixture of stereoisomers, pale red gum. Ir(CHCl₃) 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(CHCl₃) 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(CHCl₃) 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(CHCl₃) 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. [α]_D-147° (c=0.24, CHCl₃). δ ArH 6.64, 6.06; C₁-H 4.64 (t, J=3 Hz); OMe 3.87, 3.85, 3.72, 3.36, 3.08. **5b**: Colorless needles. [α]_D-221° (c=0.17, CHCl₃). δ ArH 7.25, 6.62; C₁-H 4.58, (t, J=3 Hz); OMe 3.87, 3.85, 3.82, 3.73, 3.11. **10a**: Colorless prisms. Ir(CHCl₃) 1773, 1749, 1719 cm⁻¹. δ ArH 6.82, 6.60; C₁-H 4.48 (dd, J=10, 6.4 Hz); OMe 3.90, 3.86, 3.84, 3.49, 3.21. **10b**: Colorless gum. Ir(CHCl₃) 1775, 1745, 1718 cm⁻¹. δ ArH 7.52, 6.59; C₁-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(CHCl₃) 3500, 1735, 1710 cm⁻¹. δ ArH 7.08, 6.56; C₇-H 4.90. **11b**: δ ArH 6.82, 6.54; C₇-H 4.82. **11c**: δ ArH 7.59, 6.53; C₇-H 4.52. **13a**: Colorless needles, mp 209.5-211°C. [α]_D +73°(c=1.4, CHCl₃). Ir(KBr) 3315, 1730, 1720, 1672 cm⁻¹. δ ArH 6.55, 6.47; COCH=CH 7.57, 6.46 (d, J=10 Hz); C₇-H 4.78; OMe 3.83, 3.67, 3.29. **13b**: Colorless prisms, mp 217-219°C. [α]_D+131°(c=0.39, CHCl₃). 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); C₇-H 4.53; OMe 3.83, 3.70, 3.26.

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