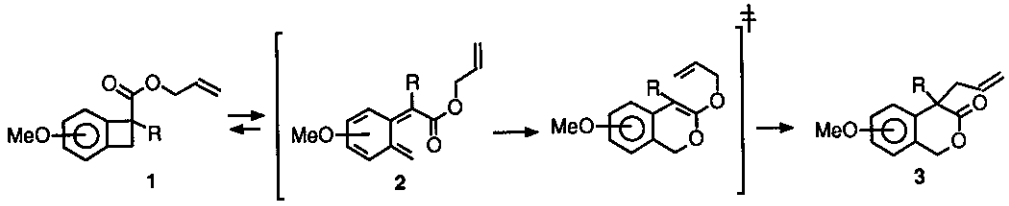
A SYNTHETIC APPROACH TO (±)-VINDOLINE[1]

Kozo Shishido[a], Hironori Komatsu[a], Keiichiro Fukumoto[a]*, and Tetsuji Kametani[b] †

[a]Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan
[b]Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

Abstract —— A synthesis of the potential intermediate of (±)-vindoline was achieved from the isochromanone (**6**), which was obtained by thermolysis of the benzocyclobutene (**5**).

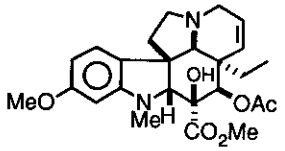
We have previously developed the tandem electrocyclic-[3,3]sigmatropic reaction of Z-o-quinodimethanes (**2**), generated in situ by thermolysis of the benzocyclobutenes (**1**), as an expedient, one-pot procedure forming 4,4-disubstituted isochroman-3-ones (**3**).[2] (Scheme 1)



Scheme 1

Since the products thus obtained have not only a quaternary carbon at the benzylic position but also suitably functionalized structure for assembling natural products, the methodology has successfully applied to the syntheses of Calabar bean alkaloids.[3] In this communication we describe an alternative use of the reaction for a synthetic approach to an indole alkaloid, vindoline (**4**).[4]

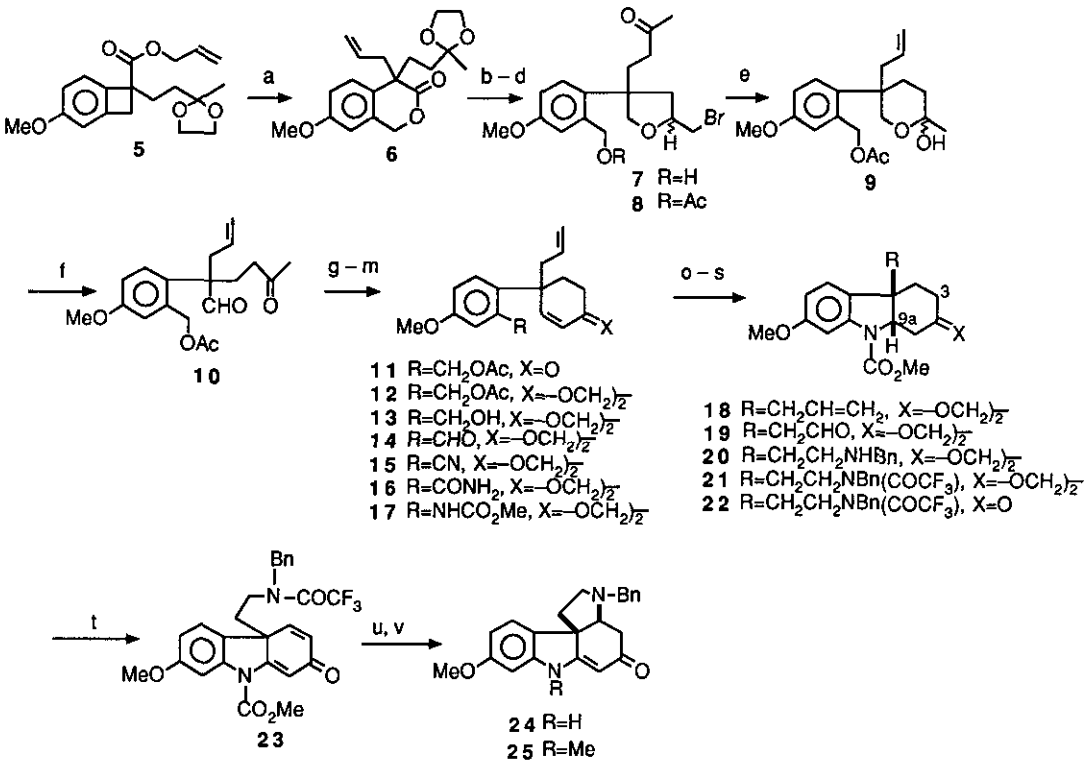
Figure



4

† Deceased October 11, 1988.

On heating a solution of the allyl ester (**5**), prepared from 1-cyano-4-methoxybenzocyclobutene by sequential alkylation (LDA, 2-(2-bromoethyl)-2-methyl-1,3-dioxolane[5]), hydrolysis (KOH, aq. EtOH), and esterification[6] (allyl alcohol, p-TsCl, 4-DMAP), in o-dichlorobenzene at 180°C for 8h, the isochromanone (**6**)[7] was obtained in 96 % yield. Reduction of **6** with $LiAlH_4$ gave the diol, which was treated with NBS to give the five-membered bromo ether (**7**) as a mixture of diastereomers. Under the reaction conditions, simultaneous hydrolysis of acetal moiety occurred. After protection of benzylic primary alcohol as the acetate, reduction of **8** with Zn-Cu couple afforded the hemiacetal (**9**) in 98 % yield from **6**. Oxidation of **9** with PCC followed by treatment of the resulting keto aldehyde (**10**) with pyrrolidine and benzoic acid gave the cyclohexenone (**11**). Sequential acetalization and hydrolysis of **11** afforded the alcohol (**13**), which was oxidized with MnO_2 to the corresponding aldehyde (**14**). Transformation of the formyl group in **14** to the carbamate (**17**)was accomplished by the following sequence of reactions. Treatment of **14** with the conditions of oxime formation followed by immediate dehydration with carbon disulfide[8] afforded the cyanide (**15**) in 61 % overall yield from **9**, which on treatment with sodium hydroxide and hydrogen peroxide gave the amide (**16**). The Hofmann rearrangement of **16** was carried out by the procedure of Radlick[9] to give the carbamate (**17**). Cyclization of **17** was accomplished by treatment with a catalytic amount of p-TsOH in the presence of 4 Å molecular sieves to form the tricyclic indoline (**18**) in 86% yield from **15**. The cis stereochemistry of the ring juncture was established by ^{1}H-nmr n.O.e., where irradiation of the allylic methylene protons induced 18.3 % enhancement of 9a-methine proton. Oxidative cleavage of the allylic double bond of **18** afforded the aldehyde (**19**), which was treated with benzylamine and sodium cyanoborohydride to give the secondary amine (**20**). After protection of the basic nitrogen as the trifluoroacetamide, the acetal moiety of **21** was hydrolyzed to give the ketone (**22**) in 71 % yield from **18**. With the tricyclic ketone (**22**) in hand, we next addressed the task of assembling the pyrrolidine ring. After numerous unsuccessful attempts to introduce a double bond at C-3 in **22** regioselectively followed by conjugate addition to construct the fourth ring, we were able to circumvent this problem by using the procedure developed by Barton.[10] Treatment of **22** with iodosobenzene and diphenyl diselenide in refluxing xylene gave the dienone (**23**)[11] as a 4:3 mixture of two amide rotamers in 69 % yield. Exposure of **23** to potassium carbonate in aqueous methanol gave the desired tetracyclic compound (**24**)[4] in 93 % yield as a single product. Subsequent N-methylation with methyl iodide and sodium hydride proceeded smoothly to give **25** in 91 % yield. The structure assignment of **25** is based on spectroscopic data[12], especially uv spectra, which indicate the characteristic absorption bands which agree well with those of N-acetyl derivative reported by Takano.[13] (Scheme 2)



Reagents: a) 180°C ; b) LAH; c) NBS, aq. THF; d) Ac_2O, pyridine; e) Zn–Cu; f) PCC; g) pyrrolidine, $PhCO_2H$; h) ethylene glycol, *p*–TsOH; i) LiOH, aq. MeOH; j) MnO_2; k) $NH_2OH \cdot HCl$, aq. NaOH then CS_2; l) aq. NaOH,30% H_2O_2; m) NaOMe, Br_2; o) *p*–TsOH, 4Å MS; p) $NaIO_4$, OsO_4; q) $PhCH_2NH_2$, $Na(CN)BH_3$; r) $(CF_3CO)_2O$, NEt_3; s) 10% HCl, THF; t) PhI=O, PhSeSePh; u) K_2CO_3, aq. MeOH; v) MeI, NaH

Scheme 2

In summary, a synthesis of the potential intermediate (25) for (±)-vindoline has been described. A further utility of the tandem methodology for the construction of Aspidosperma indole alkaloids has been exmplified.

REFERENCES AND NOTES

1. This paper is dedicated to Sir Derek H. R. Barton, Professor of Texas A & M University, on the occasion of his 70th birthday.
2. K. Shishido, E. Shitara, K. Fukumoto, and T. Kametani, J. Am. Chem. Soc., 1985, **107**, 5810; K. Shishido, K. Hiroya, K. Fukumoto, and T. Kametani, Tetrahedron Lett., 1986, **27**, 971.
3. K. Shishido, E. Shitara, H. Komatsu, K. Hiroya, K. Fukumoto, and T. Kametani, J. Org. Chem., 1986, **51**, 3007; K. Shishido, K. Hiroya, H. Komatsu, K. Fukumoto, and T. Kametani, J. Chem. Soc., Chem. Commun., 1986, 904; idem, J. Chem. Soc., Perkin Trans. 1, 1987, 2491.
4. For a recent synthesis of vindoline, see K. Cardwell, B. Hewitt, M. Ladlow,

and P. Magnus, J. Am. Chem. Soc., 1988, **110**, 2242, and references cited therein.

5. L. Willimann and H. Schinz, Helv. Chim. Acta, 1949, **32**, 2151.
6. G. F. Hennion and S. O. Barett, J. Am. Chem. Soc., 1957, **79**, 2146.
7. All new compounds exhibited satisfactory spectroscopic and analytical (combustion and/or high-resolution mass spectral) data consistent with the structures shown.
8. H. Shinozaki, M. Imaizumi, and M. Tajima, Chem. Lett., 1983, 929.
9. P. Radlick and L. R. Brown, Syn. Commun., 1974, 290.
10. D. H. R. Barton, C. R. A. Godfrey, J. W. Morzycki, W. B. Motherwell, and S. V. Ley, J. Chem. Soc., Perkin Trans. 1, 1982, 1947.
11. Colorless oil; ir($CHCl_3$)cm^{-1} 1736, 1692, 1656, 1637; m/z 500.1541 (M^+, calcd for $C_{26}H_{23}N_2O_5F_3$ m/z 500.1559); ^{1}H-nmr ($CDCl_3$, 500 MHz) δ 3.82(12/7H, s), 3.83(9/7H, s), 3.98(12/7H, s), 3.99(9/7H, s), 6.24(4/7H, dd, J=9.7 and 1.5 Hz), 6.29(3/7H, dd, J=9.7 and 1.5 Hz), 6.57(4/7H, d, J=1.5 Hz), 6.61(3/7H, d, J=1.5Hz), 6.64(4/7H, dd, J=8.5 and 2.5 Hz), 6.68(3/7H, dd, J=8.5 and 2.5 Hz), 7.08(4/7H, d, J=9.7 Hz), 7.14(3/7H, d, J=9.7 Hz), 7.09(4/7H, d, J=8.5 Hz), 7.10(3/7H, d, J=8.5 Hz), 7.50(4/7H, d, J=2.5 Hz), 7.56(3/7H, d, J=2.5 Hz).
12. Colorless oil; uv(EtOH)nm 240(log ε 3.91), 256(log ε 3.97), 337(log ε 4.09); ir($CHCl_3$)cm^{-1} 1587; m/z 360.1851(M^+, calcd for $C_{23}H_{24}N_2O_2$ m/z 360.1837); ^{1}H-nmr($CDCl_3$, 500 MHz) δ 3.13(3H, s), 3.81(3H, s,), 3.82(1H, d, J=13.0 Hz), 3.87(1H, d, J=13.0 Hz), 5.31(1H, s); ^{13}C-nmr($CDCl_3$, 125 MHz) δ 29.59(q), 33.82(t), 41.76(t), 49.05(t), 53.14(s), 55.01(t), 55.75(q), 64.58(d), 95.89(d), 96.15(d), 105.97(d), 124.29(d), 127.18(d), 128.47(d), 128.68(d), 129.92(s), 138.99(s), 145.94(s), 160.43(s), 173.29(s), 195.60(s).
13. S. Takano, K. Shishido, M. Sato, K. Yuta, and K. Ogasawara, J. Chem. Soc., Chem. Commun., 1978, 943; S. Takano, K. Shishido, T. Matsuzaka, M. Sato, and K. Ogasawara, Heterocycles, 1979, **13**, 307.

Received, 21st July, 1988