A NEW ROUTE FOR THE TRICYCLIC INDOLE SYSTEM: A USEFUL INTERMEDIATE FOR ERGOT ALKALOIDS[1]

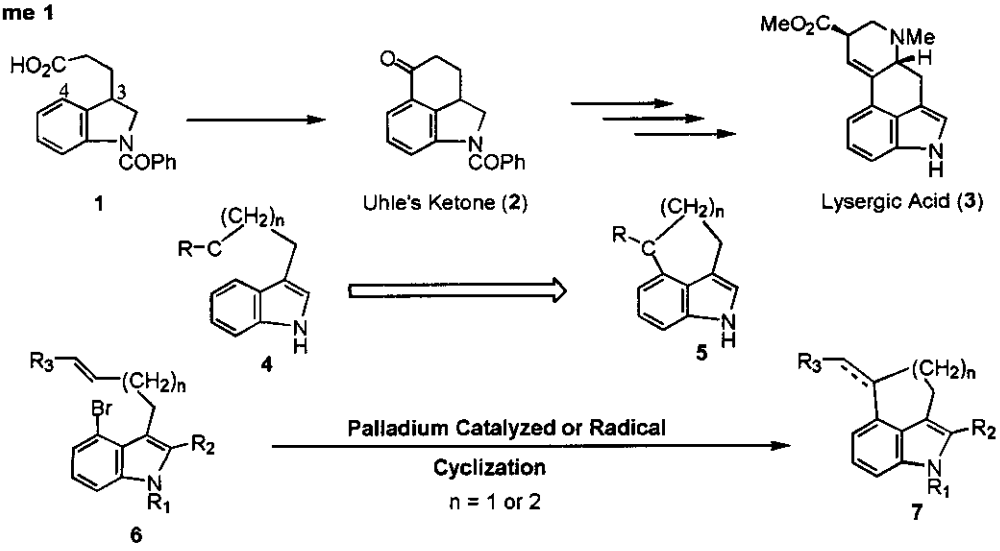
Yuusaku Yokoyama,* Hiroaki Matsushima, Mitsuru Takashima, Tomoko Suzuki, and Yasuoki Murakami*

School of Pharmaceutical Sciences, Toho University
2-2-1, Miyama, Funabashi, Chiba 274, Japan

Abstract - Cyclization of 4-bromoindole derivatives which have α,β-unsaturated esters or aldehydes in the C_3-side chain, were accomplished using intramolecular palladium-catalyzed cyclization (Heck reaction) or radical cyclization using Bu_3SnH and AIBN. A cyclohexa[*c,d*]indole system was formed by the radical reaction, while a cyclohepta[*c,d*]indole system was obtained using the Heck reaction.

Intramolecular cyclization of the C_3-side chain at the C_4-position of indoline derivative (**1**) to make a tricyclic system such as Uhle's ketone (**2**) is an important step for the total synthesis of lysergic acid (**3**).[2] Many attempts for the similar cyclization of indole derivatives (**4**) have been made using various methods (Heck reaction,[3] photo-reaction,[4] Friedel-Crafts acylation,[5] or other electrophilic reactions[6]) Although there have been many successful examples of the formation of cyclohepta- (**5**; n=2) or cycloocta[*c,d*]indole

Scheme 1

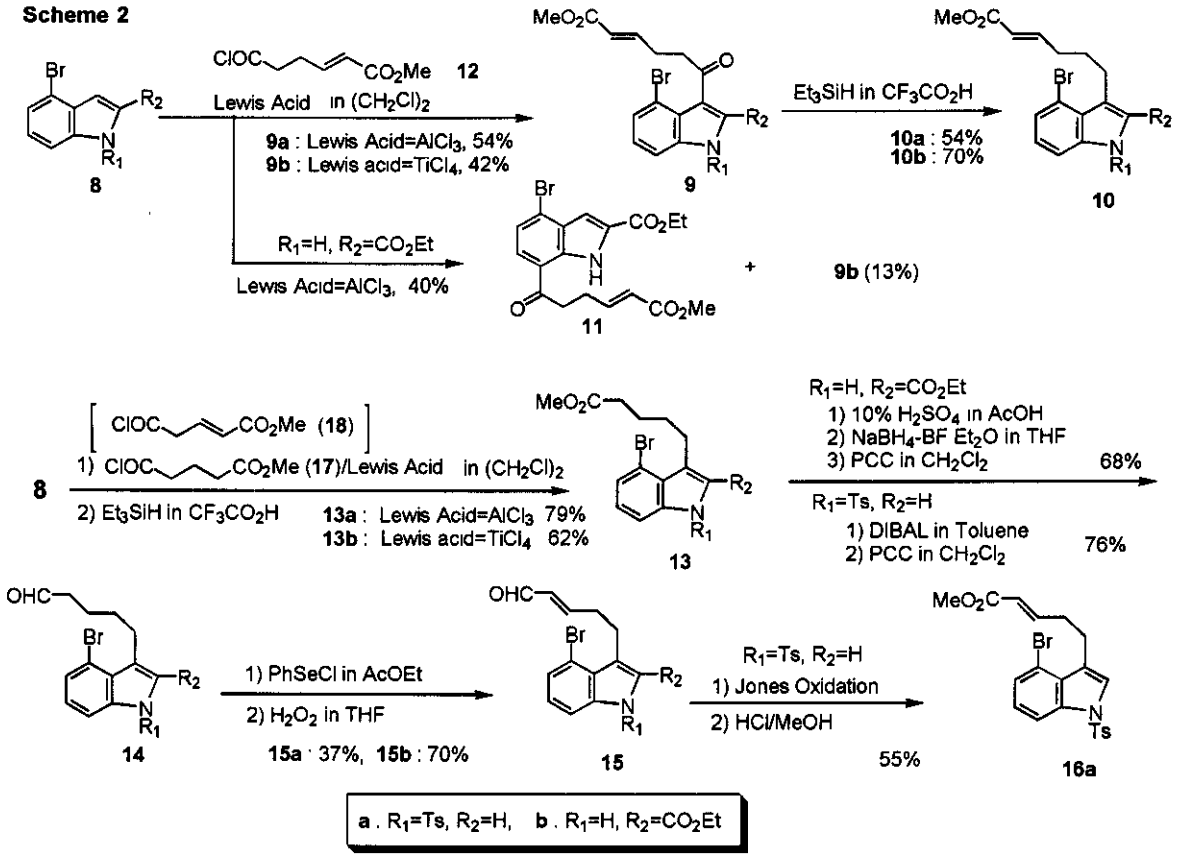


This paper is dedicated to the memory of the late Professor Shun-ichi Yamada.

(**5**; n=3)[3b] or the corresponding aza derivatives,[4, 6] only few studies have reported[5, 7] the formation of cyclohexa[*c,d*]indole skeletons (**5**; n=1). The present report involves a new methodology for the synthesis of the tricyclic system (**7**) using intramolecular Pd-catalyzed vinylation (Heck reaction) or radical reaction of 4-bromoindole derivatives (**6**) which have an α,β-unsaturated ester or aldehyde in the C_3-side chain.

Various α,β-unsaturated carbonyl compounds (**10, 15,** and **16a**) were prepared from 4-bromo-1-tosyl- (**8a**) and 4-bromo-2-ethoxycarbonylindoles (**8b**) (Scheme 2). With respect to the preparation of **10**, which is a starting material for cycohepta[*c,d*]indole, Friedel-Crafts acylation of **8** with acid chloride[8] (**12**) was carried out. Interestingly, the regioselectivity of the acylation[9] varied with the combination of indoles (**8a, b**) and Lewis acids. The acylation of *N*-tosylindole (**8a**) with $AlCl_3$ gave the C_3-acylated product (**9a**), while the acylation of 2-ethoxycarbonylindole (**8b**) with $AlCl_3$ gave the undesired C_7-acylated product (**11**) as the main product. The desired C_3-acylated product (**9b**) was obtained using $TiCl_4$ as the Lewis acid. The reduction of the acylated products (**9**) with Et_3SiH gave the desired substrates (**10a, b**). The preparation of the substrates (**15** and **16a**) for the cyclohexa[*c,d*]indoles was rather tedious. Because the required acid chloride (**18**) was not commercially available, the saturated acid chloride (**17**) was used for the Friedel-Crafts acylation. The acylation and reduction of the carbonyl group proceeded smoothly to give the saturated esters (**13**). Introduction of a conjugate double bond to

Scheme 2



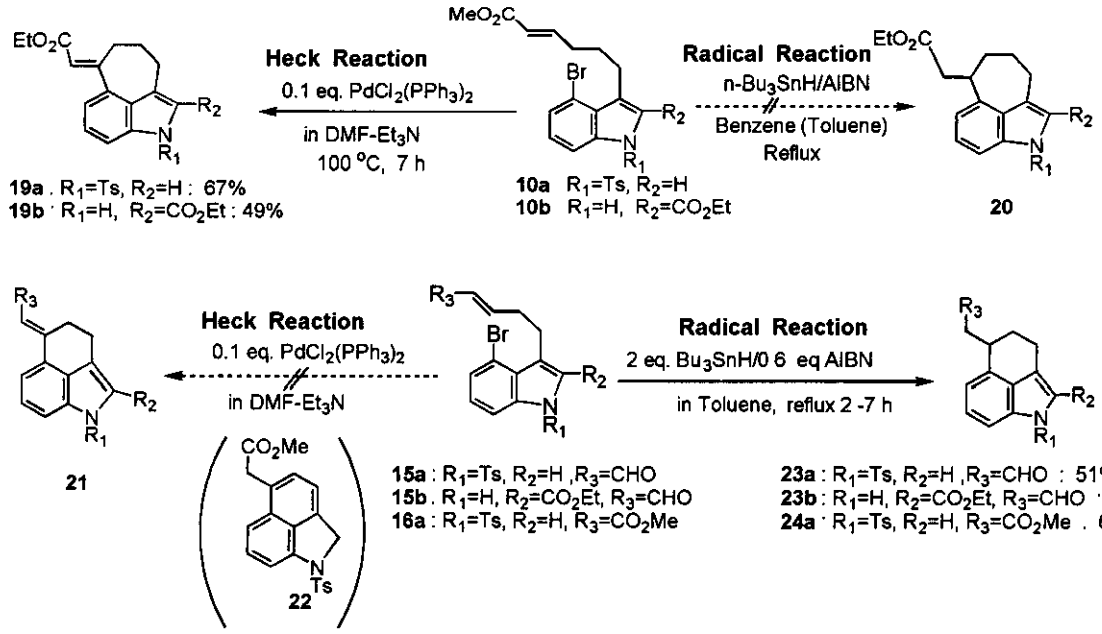
the esters (**13**) was unsuccessful. Therefore, the ester group was converted to an aldehyde (**14**) and the double bond was then introduced by selenenylation followed by *syn*-elimination of selenides to give the conjugated aldehydes (**15**). The *N*-tosyl derivative (**15a**) was converted to the ester (**16a**) using Jones oxidation and subsequent esterification.

The cyclizations of **10, 15**, and **16a** were carried out using Heck and radical reactions. The general procedure was as follows. The Heck reaction was achieved by heating a mixture of 0.1 eq. $PdCl_2(PPh_3)_2$ and starting material in DMF-Et_3N, and the radical reaction was carried out by refluxing the mixture of starting material and Bu_3SnH and AIBN in toluene. Scheme 3 shows the results of the cyclization.

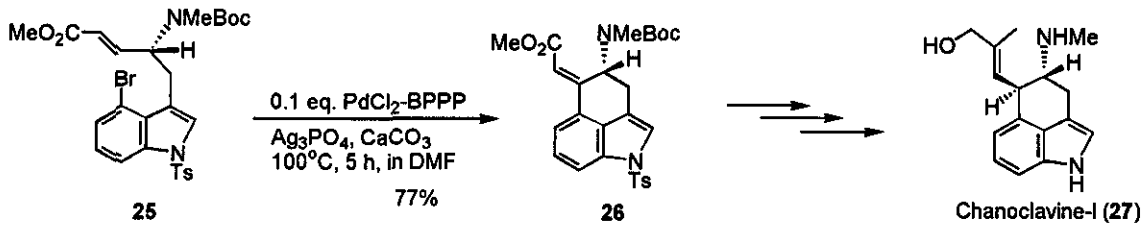
The kind of substituent of the indole ring, namely *N*-tosyl group or 2-ethoxycarbonyl group, did not affect the results of cyclization. However, the reactivity depended on the length of the side chain and the method used to achieve the cyclization. Heck reaction of **10a, b** afforded the cyclohepta[*c,d*]indole (**19a, b**) in moderate yields, whereas that of **15a, b** or **16a** did not give the desired cyclohexa[*c,d*]indole (**21**) but formed many unidentified products and naphthalene derivative (**22**), which may have formed from the cyclized product (**21**) *via* isomerization of the double bond. In contrast, the radical cyclization of **15a, b** and **16a** resulted in good to moderate yields of cyclohexa[*c,d*]indole (**23a, b** and **24a**), while reaction of **10a** and **b** did not give any desired product.

Hegedus has reported[3a] the cyclization of 3-allyl-4-bromo-*N*-tosylindole under Heck conditions to give a naphthalene derivative and Horwell has reported[3c] the Pd-catalyzed cyclization of α-allyl-4-bromotryptophan to give a mixture of cycloocta- and cyclohepta[*c,d*]indole. Those results were compatible with our results for the cylization of **10a, b** and **16a** under Heck conditions. However, we have reported[7] that the Heck reaction of the α,β-unsaturated ester of a 4-bromotryptophan analogue (**25**) gave the cyclohexa[*c,d*]indole system (**26**), a key intermediate for the synthesis of optically active

Scheme 3



Scheme 4



chanoclavine-I (**27**), but that the radical reaction of the same compound (**25**) did not afford the cyclized product under similar conditions. The above results[7] are in conflict with the results of the present cyclization of **15a, b** and **16**. One possible reason for this conflict may be an instability of the formyl group of **15a, b** under Heck conditions. However, it is not clear why the product was not obtained by the reaction of **25** under radical conditions.

REFERENCES AND NOTES

1. This paper is the "Synthetic Studies on Indoles and Related Compounds 45." Part 44 : H. Suzuki, Y. Ebihara, Y. Yokoyama, and Y. Murakami, *Heterocycles, submitted.*
2. a) E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, G. E. Jones, and R. B. Woodward, *J. Am. Chem. Soc.*, **1956**, *78*, 3087. b) H G. Floss, *Tetrahedron*, **1976**, *32*, 873. c) I. Ninomiya and T. Kiguchi, 'The Alkaloids: Ergot Alkaloids' Chapter 1, Vol. 38, ed. by A. Brossi ; Academic Press, Inc., London, 1990, pp. 1-156
3. a) P. J. Harrington and L. S. Hegedus, *J. Org. Chem.*, **1984**, *49*, 2657. b) L. S. Hegedus, M.R. Sestrick, E.T. Michaelson, and P. J. Harrington, *J. Org. Chem.*, **1989**, *54*, 4141. b) D. C. Horwell, P. D. Nichols, G. S. Ratcliffe, and E. Roberts, *J. Org. Chem.*, **1994**, *59*, 4418.
4. a) N. G. Anderson and R. G. Lawton, *Tetrahedron Lett.*, **1977**, 1843. b) S. E. Klohr and J. M. Cassady, *Synth. Comm.*, **1988**, *18*, 671. c) M. Mascal, C. J. Moody, A. M. Z. Slawin, and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 823.
5. K. Teranishi, S. Hayashi, S. Nakatsuka, and T. Goto, *Synthesis*, **1995**, 506.
6. S. Nakatsuka, H. Miyazaki, and T. Goto, *Chemistry Lett.*, **1981**, 407.
7. Y. Yokoyama, K. Kondo, M. Mitsuhashi, and Y. Murakami, *Tetrahedron Lett.*, **1996**, *37*, 9309.
8. Corresponding acid was prepared from *trans*-2-butene-1,4-dicarboxylic acid in 3 steps according to the previously reported method. Y. Kato and T. Wakabayshi, *Synth. Comm.*, **1977**, *7*, 125 and J. A. Elvidge, R. P. Linstead, B. A. Orkin, P. Sims, H. Baer, and D. B. Pattison, *J. Chem. Soc.*, **1950**, 2228.
9. We have reported that regioselectivities of Friedel-Crafts acylation of ethyl indole-2-carboxylate were affected by the combination of Lewis acid and solvents or by the structure of acid chloride. M. Tani, T. Aoki, S. Ito, S. Matsumoto, M. Hideshima, K. Fukushima, R. Nozawa, T. Maeda, M. Tashiro, Y. Yokoyama, and Y. Murakami, *Chem. Pharm. Bull.*, **1990**, *38*, 3261; Y. Murakami, M. Tani, K. Tanaka, and Y. Yokoyama, *Chem. Pharm. Bull.*, **1988**, *36*, 2023.

Received, 4th March, 1997