TANDEM MICHAEL ADDITION–[3,3] SIGMATROPIC REARRANGEMENT PROCESSES —A CONCISE ROUTE TO FUNCTIONALIZED 3-ALKOXYCARBONYLINDOLES —

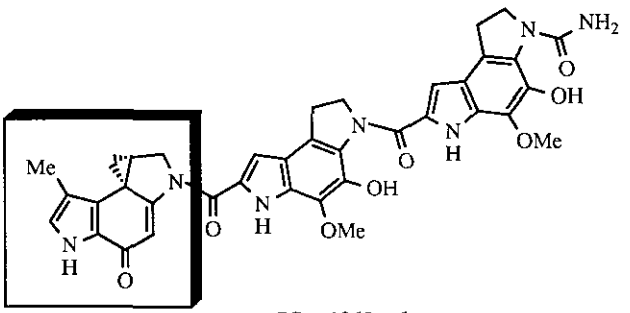
Masahiro Toyota and Keiichiro Fukumoto*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Abstract — The synthesis of methyl indole-3-carboxylate (**4**) and methyl 6-methoxyindole-3-carboxylate (**7**) by tandem Michael addition–[3,3] sigmatropic rearrangement reaction is described.

Not surprisingly, numerous synthetic methods of indole skeleton have been reported,[1] however, little is known about the efficient ones for the construction of 3-alkoxycarbonylindole containing oxygen function on benzene part of the indole nucleus.[2] We now wish to present a novel approach, *i.e.*, tandem Michael addition–[3,3] sigmatropic rearrangement reaction, to synthesize those kind of compounds. Since methyl 6-methoxylindole-3-carboxylate (**7**) might be a suitable starting material for the construction of the CPI (cyclopropylpyrroloindole) unit of antitumor antibiotic CC-1065 (**1**) which was about 400 *times more potent than adriamycin against L1210 leukemia cell in vitro*,[3] first of all we explored a new method to get (**7**)(Scheme 1).

Scheme 1



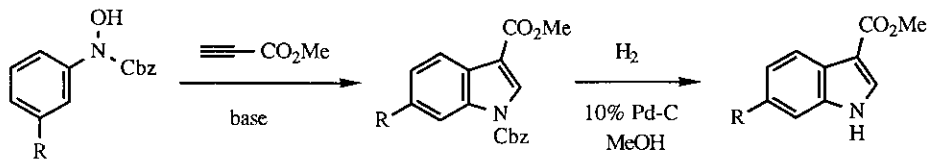
CPI unit

CC - 1065 **1**

As a model experiment of tandem Michael addition–[3,3] sigmatropic rearrangement reaction, indolization of N-phenylbenzohydroxamic acid (**2**)[4] with methyl propiolate was examined under a variety of conditions. The desired methyl 1-carbobenzyloxyindole-3-carboxylate (**3**),[5] mp 89.0 - 91.0 °C, was produced at room temperature under an atmosphere of argon. Some of the conditions and yields examined for indolization of the compound (**2**) with methyl propiolate are listed in the Table. Best result, 89%, was obtained on the reaction using N,N-diisopropylethylamine as base in nitromethane. In order to establish the structure of the product (**3**), the compound (**3**) was quantitatively transformed into well-known methyl indole-3-carboxylate (**4**), mp 149.5 - 150.5 °C (lit.[6] 147.0 - 148 °C), by a catalytic hydrogenation in the presence of 10% palladium-charcoal.

Regioselective tandem Michael addition—[3,3] sigmatropic rearrangement reaction of benzyl N-hydroxy-N-(3-methoxyphenyl)carbamate (**5**),[5] prepared from *m*-nitroanisole, also afforded the indole derivative (**6**)[5] as a single regioisomer.[7] In the same manner as previously, the catalytic hydrogenation of (**6**) gave rise to the compound (**7**) in 92% yield (Scheme 2).

Scheme 2



2 R = H **3** R = H **4** R = H

5 R = OMe **6** R =OMe **7** R =OMe

Table

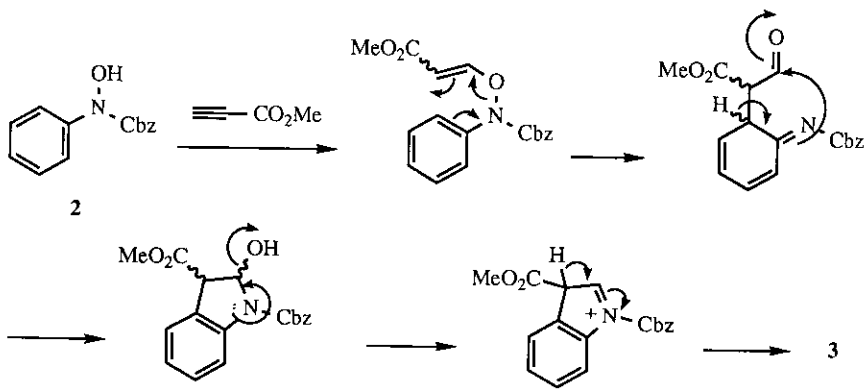
Conditions and Yields of Tandem Michael Addition–[3, 3] Sigmatropic Rearrangement Reaction of Compound **2**

entry	base	solvent	yield (%)
1	Et_3N	C_6H_6	25
2	NMM[a]	C_6H_6	31
3	$^iPr_2NEt$	C_6H_6	65
4[b]	$^iPr_2NEt$	CH_2Cl_2	66
5[b]	$^iPr_2NEt$	MeCN	78
6[b]	$^iPr_2NEt$	$MeNO_2$	89

a ; N-methylmorpholine b ; 2.0 eq. of methyl propiolate was used.

As the most plausible mechanism[4] that is accountable for the observations, we propose a tandem Michael addition—[3,3] sigmatropic rearrangement process shown in Figure 1.

Figure 1



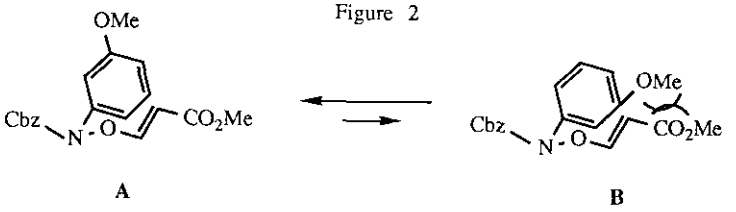
ACKNOWLEDGMENT

A part of this work was financially supported by Grant-in-Aid for Special Project from the Ministry of Education, Science and Culture of Japan.

REFERENCES AND NOTES

1. B. Robinson, "The Fischer Indole Synthesis", John Wiley and Sons, New York, 1982.
2. a; S. Nakatsuka, O. Asao, K. Ueda, and T. Goto, Heterocycles, 1978, 26, 1471. b; Y. Murakami, H. Takahashi, Y. Nakazawa, M. Koshimizu, T. Watanabe, and Y. Yokoyama, Tetrahedron Lett., *1989*, 30, *2099*, and *references cited therein.*
3. D. H. Swenson, W. C. Krueger, A. H. Lin, S. L. Schpoc, and L. H. Li, Cancer Res., 1981, 22, 857.
4. a; T. Sheradsky, E. Nov, S. Segal, and A. Frank, J. Chem. Soc., Perkin Trans. 1, 1977, 1827. b; P. Martin, Tetrahedron Lett., 1987, 28, 1645.
5. All compounds have been characterized by elemental analyses and/or high resolution mass spectra. Spectral data are recorded below: **3:** Ir ($CHCl_3$) 1745 and 1710 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$) 3.92 (3H, s, OMe), 5.48 (2H, s, OCH_2Ar), 7.33 - 7.51 (7H, m, ArH), 8.16 (1H, dd, J =2.0 and 8.0 Hz, 4-H), 8.20 (1H, br d, J = 8.0 Hz, 7-H), 8.30 (1H, s, 2-H). **5:** Ir (neat) 3300 (OH), 1700 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$) 3.73 (3H, s, OMe), 5.25 (2H, s, CH_2Ar), 6.73(1H, br dd, J = 2.0 and 8.0 Hz, 4-H), 7.06 (1H, t, J = 8.0 Hz, 2-H), 7.08 (1H, br dt, J = 2.0 and 8.0 Hz, 6-H), 7.23 (1H, t, J = 8.0 Hz, 5-H), 7.39 (1H, br s, OH). **6:** Ir ($CHCl_3$)1745 and 1705cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$) 3.83 (3H, s, ArOMe), 3.93 (3H, s, CO_2Me), 5.50 (2H,s, CH_2Ar), 6.96 (1H, dd, J = 2.2 and 8.8 Hz, 5-H),7.37 - 7.51 (5H, m, ArH), 7.74 (1H, br s, 7-H), 8.00 (1H, d, J = 8.8 Hz, 4-H), 8.19 (1H, s, 2-H). **7:** Ir ($CHCl_3$) 1695 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$) 3.82 (3H,s, ArOMe), 3.92 (3H, s, CO_2Me), 6.86 (1H, d, J = 2.2 Hz, 7-H), 6.93 (1H, dd, J = 2.2 and 8.8Hz, 5-H), 7.79 (1H, d, J = 3.0 Hz, 2-H), 8.04 (1H, d, J = 8.8 Hz, 4-H), 8.71 (1H, br s, 1-H).
6. P. E. Peterson, J. P. Wolf III, and C. Niemann, J. Org. Chem., 1958, 23, 303.
7. The steric congestion in the transition state **B** makes it less favorable than the alternative transition state **A** which gives rise to the desired product (**6**)(Figure 2).

Figure 2



A **B**

Received, 1st June, 1990