A New Efficient Synthesis of the 3-Methoxycarbazole Alkaloid Hyellazole

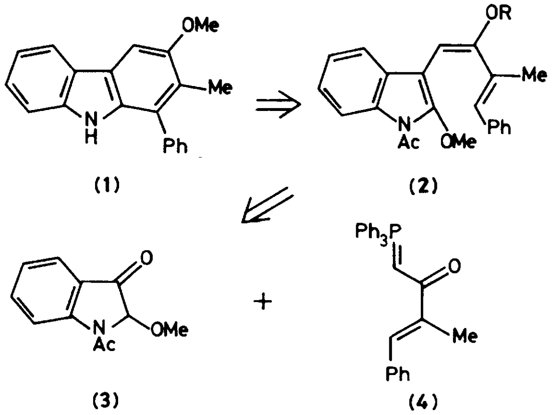
Tomomi Kawasaki, Yoshinori Nonaka, and Masanori Sakamoto*

Meiji College of Pharmacy, 1-35-23 Nozawa, Setagaya-ku, Tokyo 154, Japan

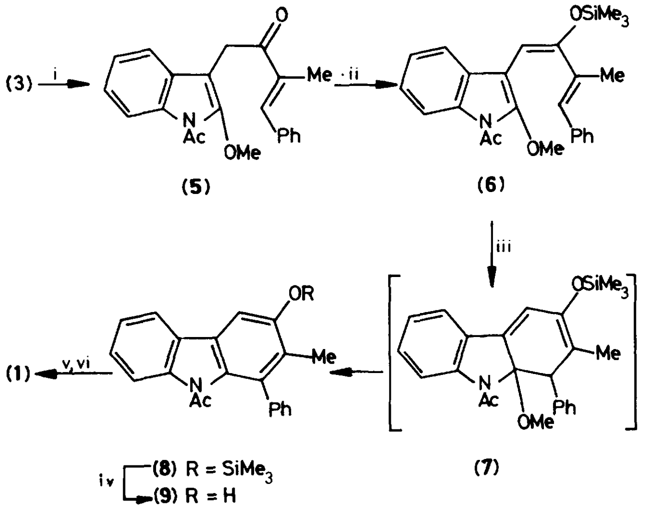
A short synthesis of hyellazole (**1**) based on a new method of benzannelation of indoles which involves cyclization of 3-buta-1,3-dienylindole (**6**) is described.

Current interest in the chemistry of polysubstituted 3-methoxycarbazoles such as hyellazole,[1] carbazomycins,[2] and so on[3] has continued to grow because of their physiological activities. Although 3-methoxycarbazoles have been synthesized by electrocyclic closure of 3-(β-methoxyvinyl)-2-vinylindoles[4] and Diels–Alder reaction of 3-(β-methoxyvinyl)indoles with dienophiles in the presence of dehydrogenating agents,[5] in the dehydrogenation step the methoxy group is concomitantly lost to give 3-demethoxycarbazoles. We now report a new synthesis of a 3-methoxycarbazole alkaloid, hyellazole (**1**), based on the strategy shown in Scheme 1. This approach, which involves a ring closure of a 3-buta-1,3-dienylindole (**2**) without the loss of the methoxy group at the 3-position of hyellazole (**1**) has surprisingly found little use in the carbazole synthesis to date.[6]

The starting 2-methoxyindolin-3-one (**3**) is readily available by our previously described method.[7] The phosphonium ylide



Scheme 1



Scheme 2. *Reagents and conditions:* i, (**4**), dioxane, reflux, 7 h; ii, Me$_3$SiI, HMDS, CH$_2$Cl$_2$, −20 °C, then room temp., 2 h; iii, decaline, reflux, 5.5 h; iv, Bu$_4$N$^+$F$^-$, aq. tetrahydrofuran, 0 °C, 10 min.; v, Me$_2$SO$_4$, 50%NaOH, Bu$_4$N$^+$HSO$_4^-$ (cat.), C$_6$H$_6$, room temp., 10 min.; vi, 50% NaOH, Bu$_4$N$^+$HSO$_4^-$ (cat.), C$_6$H$_6$, reflux, 1.5 h.

(**4**) was prepared by the usual procedure[8] from triphenylphosphine and 1-chloro-3-methyl-4-phenylbut-3-en-2-one.[9] Wittig reaction of (**3**) with (**4**) gave the 3-(2-oxobut-3-enyl)indole (**5**) in 74% yield,†‡ which was treated with trimethylsilyl iodide in the presence of hexamethyldisilazane (HMDS) to provide the desired 3-buta-1,3-dienylindole (**6**) in 80% yield. On heating (**6**), an electrocyclic reaction occurred leading to intermediate (**7**) from which methanol was spontaneously liberated to give the 3-hydroxycarbazole (**9**) and its silylate (**8**) in 13% and 53% yields, respectively, of which the latter was treated with tetrabutylammonium fluoride (TBAF) to afford (**9**) in 81% yield. Methylation of (**9**) with dimethyl sulphate and sodium hydroxide at room temperature followed by standard deacetylation gave hyellazole (**1**) in 72% yield. This synthetic carbazole derivative was spectroscopically identical with natural hyellalzole.[1]

Received, 8th August 1988; Com. 8/03244K

References

1 J. H. Cardellina, II, M. P. Kirkup, R. E. Moore, J. S. Mynderse, K. Seff, and C. J. Simmons, *Tetrahedron Lett.*, 1979, 4915.

2 T. Naid, T. Kitahara, M. Kaneda, and S. Nakamura, *J. Antibiot.*, 1987, **40**, 157; S. Kondo, M. Katayama, and S. Marumo, *ibid.*, 1986, **39**, 727; H.-P. Hussom, *The Alkaloids*, 1985, **26**, 17.

3 D. P. Chakraborty, *Fortshr. Chem. Org. Naturst.*, 1977, **34**, 299.

4 S. Kano, E. Sugino, S. Shibuya, and S. Hibino, *J. Org. Chem.*, 1981, **46**, 3856.

5 U. Pinder and L. Pfeuffer, *Heterocycles*, 1987, **26**, 325; L. Pfeuffer and U. Pinder, *Helv. Chim. Acta*, 1987, **70**, 1419.

6 J. A. Joule, *Adv. Heterocycl. Chem.*, 1984, **35**, 83.

7 C.-S. Cheng, T. Suzuki, T. Kawasaki, and M. Sakamoto, *Chem. Pharm. Bull.*, 1984, **32**, 3945.

8 A. W. Johnson, 'Ylid Chemistry,' Academic Press, New York, 1966, p. 16.

9 J. A. Moore, *J. Org. Chem.*, 1955, **20**, 1607.

10 R. J. Sundberg, 'The Chemistry of Indoles,' Academic Press, New York, 1970, p. 364.

---

† All compounds gave satisfactory elemental analyses and spectral data.

‡ Although 1-acetylindolin-3-ones are enolizable ketones which rarely react with nucleophiles,[10] (**3**), for which enolization is remarkably hindered by its 2-methoxy group reacts smoothly with (**4**).