Successive Diarylation at the Carbon Positions (2/4 and 2/5) of 1*H*-Imidazole and its Application to the Total Synthesis of Nortopsentin D

Ikuo Kaswasaki, Masayuki Yamashita and Shunsaku Ohta*

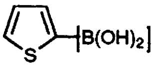
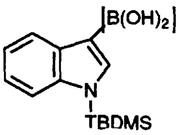
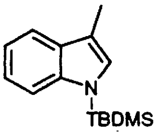
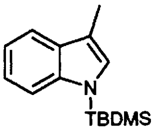
Kyoto Pharmaceutical University, Misasagi, Yamashinaku, Kyoto 607, Japan

Nortopsentin D, an antifungal 2,4-diindolylimidazole, is synthesized by use of a successive and regioselective diarylation, in which *N*-protected 2,4,5-tri- and 4,5-di-bromoimidazole derivatives are treated with *N*-silylated 3-indolylboric acid in the presence of a palladium(o) catalyst.

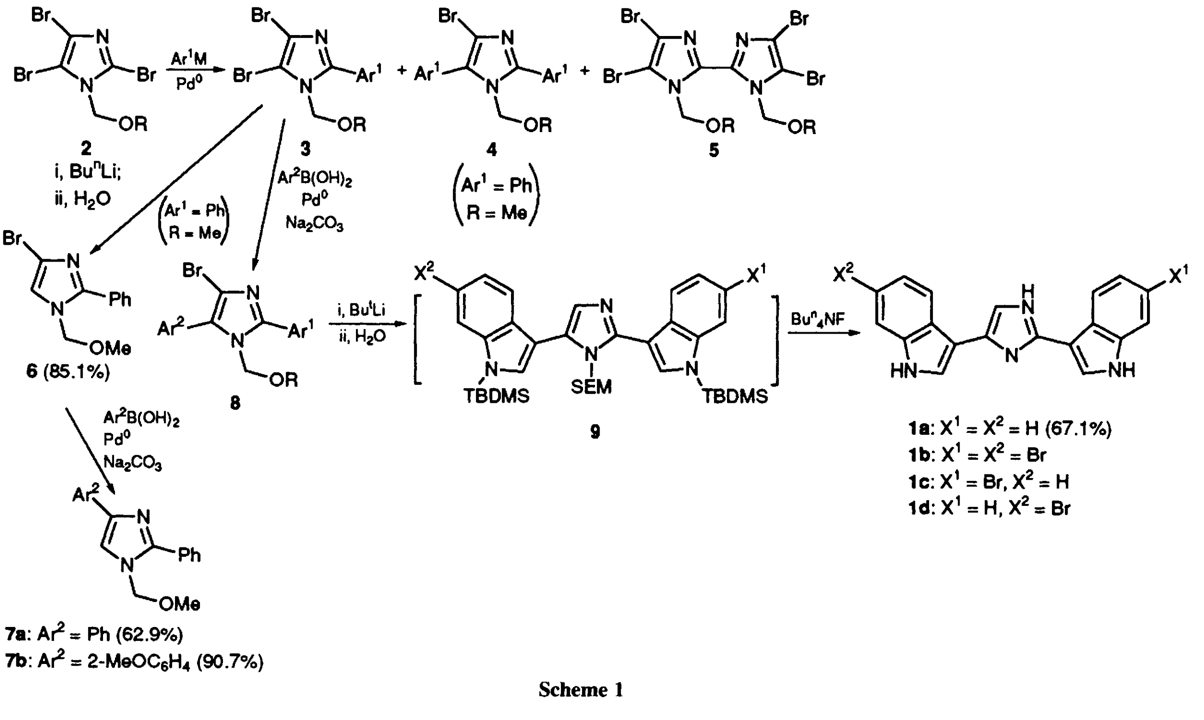
Nortopsentins **1a**–**1d**, 2,4-di(3-indolyl)-1*H*-imidazole and its derivatives, are antifungal marine alkaloids, which were isolated from a sponge.[1] Regioselective introduction of carbogenic substituents into the 4- and/or 5-position(s) of the imidazole nucleus is still an interesting subject in the field or organic synthesis,[2] and in particular selective arylation of the positions has been an undeveloped area.

As shown in Table 1 (runs 1–7), we found that the cross-coupling of the tribromoimidazoles **2**[3] with aryl metal reagents at the 2-position proceeded satisfactorily when an

Table 1 Cross-coupling of **2** and **3** with ArM

Run	$Ar^1[M]$ (equiv.)	$Ar^2B(OH)_2$ (equiv.)	R	Reaction time/h	Yield of product(s) (%)
1	Ph[ZnCl] (1)	—	Me	5	45.0[a] (**3a**), 8.9[b] (**5**)
2	Ph[MgBr] (1)	—	Me	10	14.5[a] (**3a**), 27.3[b] (**5**)
3	$Ph[B(OH)_2]$ (1)	—	Me	8	94.4[b] (**3a**)
4	$Ph[B(OH)_2]$ (2)	—	Me	15	64.5[a] (**3a**), 30.0[b] (**4**)
5	$2\text{-}MeOC_6H_4[B(OH)_2]$ (1)	—	Me	8	92.0[b] (**3b**)
6	 (1)	—	Me	8	79.5[b] (**3c**)
7	 (1)	—	$(CH_2)_2SiMe_3$	8	88.5[b] (**3d**)
8	Ph	Ph (1)	Me	10	70.9[b] (**8a**)
9	Ph	$2\text{-}MeOC_6H_4$ (1)	Me	10	71.5[b] (**8b**)
10		 (1)	$(CH_2)_2SiMe_3$	10	68.3[b] (**8c**)

[a] Determined by GLC with an internal standard. [b] Isolated yield.



Scheme 1

equimolar amount of arylboric acid was used in the presence of a catalytic amount of $Pd^0(PPh_3)_4$ and sodium carbonate.[4] Introduction of a second aryl group into the 5-position of the 2-arylimidazoles **3** also proceeded in a similar manner to give **8** in moderate yields (runs 8–10). These successive diarylations *i.e.* **2** → **8** could also be conveniently performed in a single reaction vessel (one-pot procedure).

The bromine atom at the 5-position of **3a** was removed by lithiation followed by quenching with water[2d] to give **6** in 85.1% yield. Introduction of the aryl group into the 4-position of **6** similarly proceeded under the conditions of run 3 to give 2,4-diarylimidazoles **7a** (62.9%) and **7b** (90.7%).

The bromine atom and the silyl protecting group of **8c** were removed by treatment with *n*-butyllithium–water and then with tetrabutylammonium fluoride to give nortopsentin D **1a** in 67.1% yield.[5]

Received, 14th February 1994; Com. 4/00894D

References

1 S. Sakemi and H. H. Sun, *J. Org. Chem.*, 1991, **56**, 4304; H. H. Sun, S. Sakemi, S. Gunasekera and Y. Kashman, *US Pat.*, 4,970,226 [*Chem. Abstr.*, 1991, **115**, 35701z].

2 (*a*) S. Ohta, T. Yamamoto, I. Kawasaki, M. Yamashita, H. Katsuma, R. Nasako, K. Kobayashi and K. Ogawa, *Chem. Pharm. Bull.*, 1992, **40**, 2681; (*b*) S. Ohta, T. Yamamoto, I. Kawasaki, M. Yamashita, Y. Nagashima and T. Yoshikawa, *Chem. Pharm. Bull.*, in the press; (*c*) B. Iddon and B. L. Lim, *J. Chem. Soc., Perkin Trans. 1*, 1983, 271, 279, 735; (*d*) B. Iddon, N. Kahn and B. L. Lim, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1445, 1453; (*e*) A. J. Carpenter and D. J. Chadwick, *Tetrahedron*, 1986, **42**, 2351; (*f*) R. M. Turner, S. D. Lindell and S. V. Ley, *J. Org. Chem.*, 1991, **56**, 5739; (*g*) S. Knapp, J. Albaneze and H. J. Schugar, *J. Org. Chem.*, 1993, **58**, 997; (*h*) J. F. O'Connell, J. Paquette, W. E. Yelle, W. Wang and H. Rapopport, *Synthesis*, 1988, 767; (*i*) B. H. Lipshuz and W. Hagen, *Tetrahedron Lett.*, 1992, **33**, 5865.

3 K.-E. Stensiö, K. Wahrberg and R. Wahren, *Acta Chem. Scand.*, 1973, **27**, 2179; B. Iddon, N. Kahn and B. L. Lim, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1437.

4 A. Alvarez, A. Guzmán, A. Ruiz, E. Velarde and J. M. Muchowski, *J. Org. Chem.*, 1992, **57**, 1653.