A REGIOSPECIFIC SYNTHESIS OF CARBAZOLES *VIA* CONSECUTIVE PALLADIUM-CATALYZED CROSS-COUPLING AND ARYNE-MEDIATED CYCLIZATION[1]

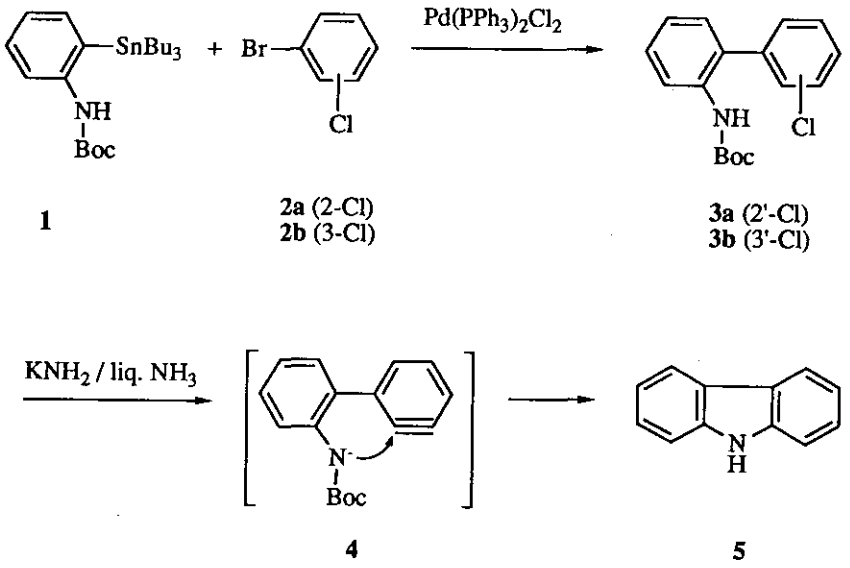
Masatomo Iwao,*[,a] Hirokazu Takehara,[b] Sunao Furukawa,[b] and Mitsuaki Watanabe*[,c]

[a]Faculty of Liberal Arts, [b]School of Pharmaceutical Sciences, and [c]Center for Instrumental Analysis, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852, Japan

Abstract- A regiospecific synthesis of carbazoles has been developed using palladium-catalyzed cross-coupling of *N*-(*tert*-butoxycarbonyl)-2-tributylstannylanilines with 2- or 3-bromochlorobenzene followed by aryne-mediated cyclization as the key reactions. The carbazole alkaloids, glycozolinine and glycozolidine, were synthesized using this procedure.

Since the first discovery of murrayanine in 1965,[2] a number of carbazole alkaloids have been isolated from higher plants, microorganisms, and marine sources.[3] Some of the alkaloids and their synthetic analogues exhibit significant biological activities, such as antimicrobial,[4] antiviral,[5] and cytotoxic properties.[6] Major synthetic approaches to the carbazole skeleton include a) reductive cyclization of 2-nitrobiphenyls,[7] b) thermal,[8] photolytic,[9] and palladium-promoted[10] cyclization of diphenylamines, c) dehydrogenation of 1,2,3,4-tetrahydrocarbazoles which are usually prepared by Fischer indole synthesis,[11] and d) syntheses from indole precursors.[12] In the syntheses of highly substituted carbazole alkaloids, however, many of these methods have problems, such as lengthy steps in the preparation of appropriate precursors, non-regioselectivity of the cyclization steps, and harsh reaction conditions. In this communication, we report a short and regiospecific synthesis of the carbazoles[13] from easily accessible stannylaniline and bromochlorobenzene precursors using palladium-catalyzed cross-coupling[14] and aryne-mediated cyclization[15] as key reactions.

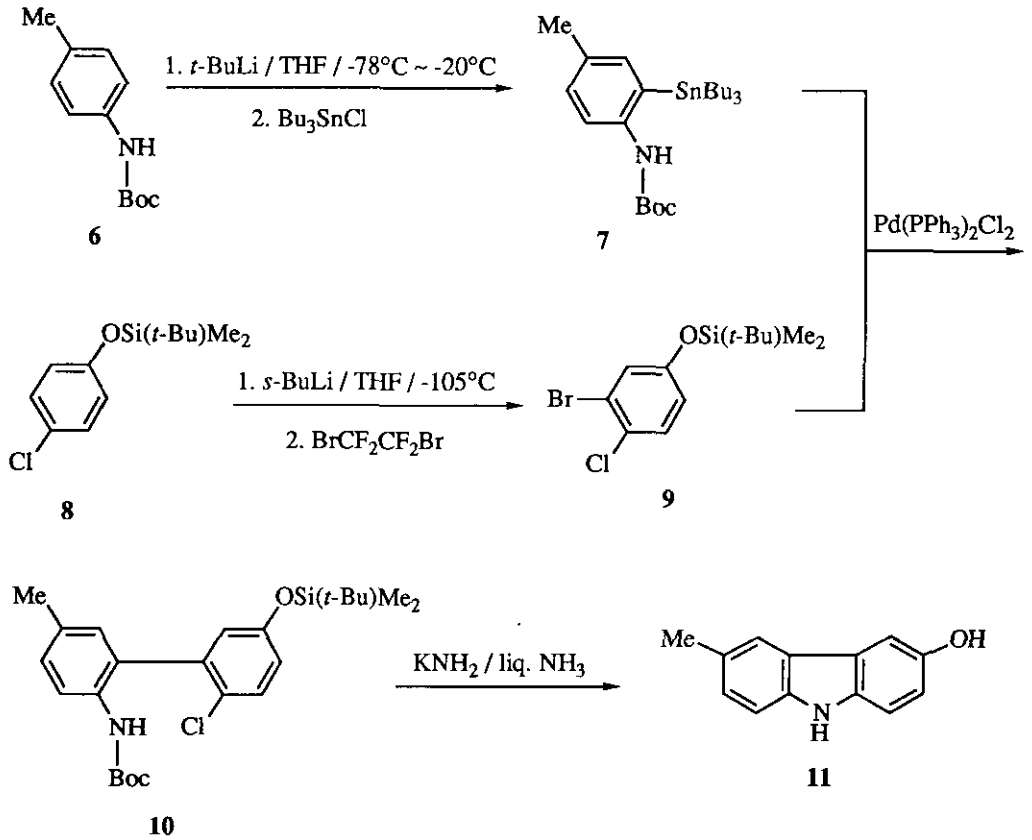
The stannane (**1**),[16] which was prepared in 80% yield by *ortho*-lithiation of *N*-(*tert*-butoxycarbonyl)aniline under the standard conditions[17] (2.5 equiv. *t*-BuLi / THF / -78°C ~ -20°C) followed by stannylation with Bu_3SnCl, was coupled with 2-bromochlorobenzene (**2a**) in the presence of 5 mol % of $Pd(PPh_3)_2Cl_2$ in toluene at 110°C for 25 h to give *N*-(*tert*-butoxycarbonyl)-2-(2'-chlorophenyl)aniline (**3a**) in 74% yield (**Scheme 1**). The reaction proceeded in DMF under milder conditions (90°C, 25 h) affording **3a** in 76% yield. In a similar manner (5 mol % of $Pd(PPh_3)_2Cl_2$ / DMF / 90°C / 25 h), **1** was coupled with 3-bromochlorobenzene (**2b**) to furnish *N*-(*tert*-butoxycarbonyl)-2-(3'-chlorophenyl)aniline (**3b**) in 80% yield. Treatment of **3a** with excess KNH_2 (10 equiv.) in liq. NH_3 at -33°C for 3 h afforded carbazole (**5**) in 99% yield *via* the aryne intermediate (**4**). The *tert*-butoxycarbonyl group was cleaved under the highly nucleophilic reaction conditions. Under similar reaction conditions, **3b** cyclized to **5** in 70% yield. The lower yield of the cyclization of **3b** compared to **3a** may be due to simultaneous formation of the isomeric aryne intermediate (3',4'-aryne).



Scheme 1

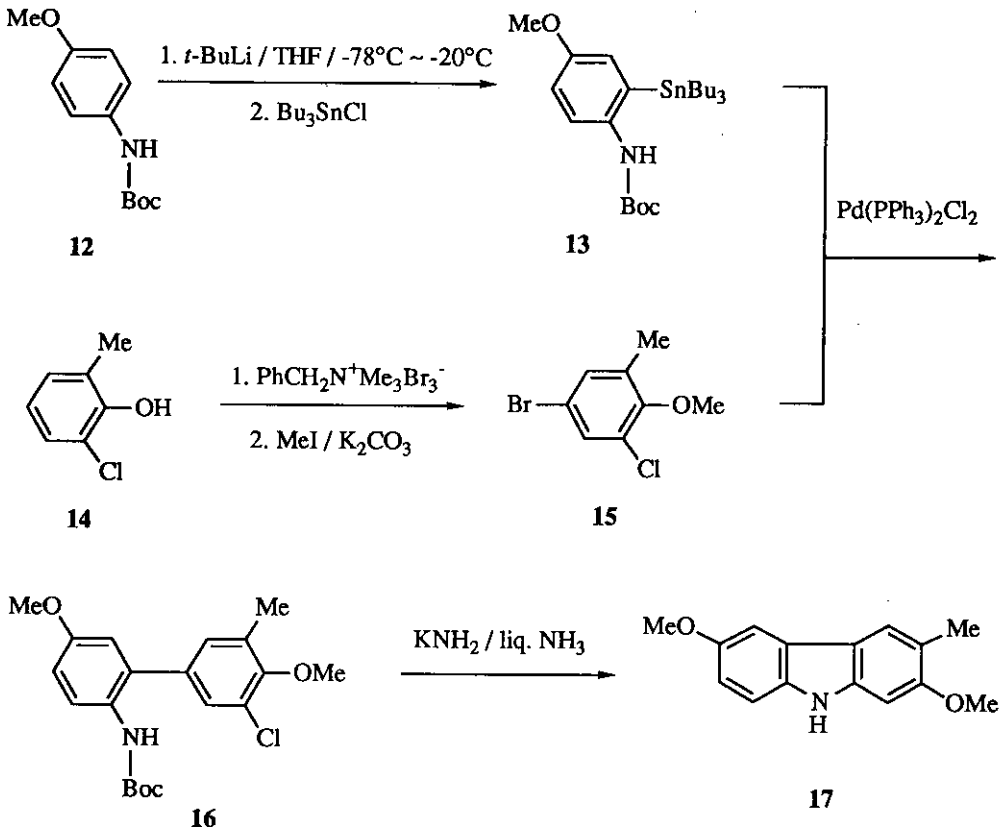
The utility of this carbazole synthesis was demonstrated in the preparation of carbazole alkaloids, glycozolinine (**11**)[18] and glycozolidine (**17**).[19] The synthesis of glycozolinine (**11**) is shown in **Scheme 2**. *Ortho*-lithiation of *N*-(*tert*-butoxycarbonyl)-4-methylaniline (**6**) followed by a reaction with Bu_3SnCl afforded the stannane (**7**)[16] in 62% yield. Another *ortho*-lithiation of 1-(*tert*-butyldimethylsilyloxy)-4-chlorobenzene (**8**) (1.2 equiv. *s*-BuLi / THF / -105°C / 2 h)[20] and subsequent reaction with 1,2-dibromo-1,1,2,2-tetrafluoroethane[21] gave the bromide

(**9**) in 95% yield. Cross-coupling of **7** with **9** (5 mol % of $Pd(PPh_3)_2Cl_2$ / DMF / 90°C / 25 h) furnished the biphenyl (**10**) in 65% yield. Treatment of **10** with KNH_2 (10 equiv.) in liq. NH_3 overnight[22] gave glycozolinine (**11**)[23] in 54% yield. During the cyclization both the *tert*-butoxycarbonyl and *tert*-butyldimethylsilyl groups were cleaved.



Scheme 2

The synthesis of glycozolidine (**17**) is shown in **Scheme 3**. The stannane (**13**)[16] was prepared from *N*-(*tert*-butoxycarbonyl)-4-methoxyaniline (**12**) in 63% yield in a similar manner as described for **1** and **7**. The bromide (**15**) was synthesized from 2-chloro-6-methylphenol (**14**) by sequential bromination ($PhCH_2N^+Me_3Br_3^-$ / CH_2Cl_2-MeOH / room temperature / 5 h)[24] and methylation (MeI / K_2CO_3 / acetone / reflux / 4 h) in 96% overall yield. Coupling of **13** with **15** (5 mol % of $Pd(PPh_3)_2Cl_2$ / DMF / 90°C / 25 h) gave the biphenyl (**16**) in 56% yield. Cyclization of **16** (10 equiv. of KNH_2 / liq. NH_3 / -33°C / 3 h) furnished glycozolidine (**17**)[25] in 99% yield.



Scheme 3

In summary, we have developed a new and efficient route for the regiospecific preparation of substituted carbazoles . Since this is based on the easy availability of the stannane and bromochlorbenzene precursors using directed *ortho*-lithiation and conventional bromination strategies, its further application for the synthesis of a wide range of carbazole alkaloids may be anticipated.

REFERENCES AND NOTES

1. Part of this work has been presented at 22nd Congress of Heterocyclic Chemistry, Sendai, Japan, 1-P-03 (abstract pp. 33-36), October 7-9, 1991.
2. D. P. Chakraborty, B. K. Barman, and P. K. Bose, *Tetrahedron* , **1965**, *21*, 681.
3. For reviews of carbazole alkaloids, see: a) R. S. Kapil, 'The Alkaloids: The Carbazole Alkaloids,' Vol. 13, ed. by R. H. F. Manske, Academic Press, Inc., New York, 1971, pp. 273-302; b) D. P.

Chakraborty, *Fortch. Chem. Org. Naturst.*, **1977**, *34*, 299; c) D. P. Chakraborty, *Planta Med.*, **1980**, *39*, 97; c) D. P. Chakraborty, *Trans. Bose Res. Inst.*, **1984**, *47*, 49; d) H.-P. Husson, 'The Alkaloids: Simple Indole Alkaloids Including β-Carbolines and Carbazoles,' Vol. 26, ed. by A. Brossi, Academic Press, Inc., Orland, 1985, pp. 1-51; e) P. Bhattacharyya and D. P. Chakraborty, *Fortch. Chem. Org. Naturst.*, **1987**, *52*, 159.

4. a) K. Sakano, K. Ishimaru, and S. Nakamura, *J. Antibiotics*, **1980**, *33*, 683; b) K. Sakano and S. Nakamura, *J. Antibiotics*, **1980**, *33*, 961; c) S. Nakamura, *Trans. Bose Res. Inst.*, **1984**, *47*, 69.
5. M. R. TePaske, J. B. Gloer, D. T. Wicklow, and P. F. Dowd, *J. Org. Chem.*, **1989**, *54*, 4743.
6. a) L. M. Rice and K. R. Scot, *J. Med. Chem.*, **1970**, *13*, 308; b) M. Fiebig, J. M. Pezzuto, D. D. Soejarto, and A. D. Kinghorn, *Phytochem.*, **1985**, *24*, 3041; c) M. R. Tepaske, J. B. Gloer, D. T. Wicklow, and P. F. Dowd, *Tetrahedron Lett.*, **1989**, *30*, 5965.
7. a) J. I G. Cadogan, *Synthesis* **1969**, *1*, 11; b) S. P. Kureel, R. S. Kapil, and S. P. Popli, *J. Chem. Soc., Chem. Commun.*, **1969**, 1120. c) S. P. Kureel, R. S. Kapil, and S. P. Popli, *Chem. and Ind.*, **1970**, 1262. d) R. B. Sharma and R. S. Kapil, *Chem. and Ind.*, **1982**, 268.
8. a) A. Islam, P. Bhattacharyya, and D. P. Chakraborty, *J. Chem. Soc., Chem. Commun.*, **1972**, 537; b) P. Bhattacharyya, A. R. Mitra, and D. P. Chakraborty, *J. Indian Chem. Soc.*, **1976**, *53*, 321.
9. W. Carruthers, *J. Chem. Soc., Chem. Commun.*, **1966**, 272.
10. a) B. Akermark, L. Eberson, E. Jonsson, and E. Pettersson, *J. Org. Chem.*, **1975**, *40*, 1365; b) H. Furukawa, C. Ito, M. Yogo, and T.-S. Wu, *Chem. Pharm. Bull.*, **1986**, *34*, 2672.
11. a) J. D. Crum and P. W. Sprague, *J. Chem. Soc., Chem. Commun.*, **1966**, 417; b) D. P. Chakraborty and B. K. Chowdhury, *J. Org. Chem.*, **1968**, *33*, 1265; c) D. P. Chakraborty, K. C. Das, and B. K. Chowdhury, *Phytochem.*, **1969**, *8*, 773.
12. For a review, see: J. Bergman and B. Pelcman, *Pure and Appl. Chem.*, **1990**, *62*, 1967.
13. A procedure for the synthesis of azacarbazoles which is conceptually similar to our carbazole synthesis has been published very recently: P. Pocca, F. Marsais, A. Godard, and G. Queguiner, *Tetrahedron*, **1993**, *49*, 49. This paper prompted us to report our results.
14. For a review of tin-based palladium-catalyzed cross-coupling reactions, see: T. N. Mitchell, *Synthesis*, **1992**, 803. The cross-coupling reactions of *N*-(*tert*-butoxycarbonyl)-2-trimethylstannylanilines have been reported: a) F. G. Salituro and I. A. McDonald, *J. Org. Chem.*, **1988**, *53*, 6138; b) E. Gómez-

Bengona and A. M. Echavarren, *J. Org. Chem.*, **1991**, *56*, 3497; b) N. Tamayo, A. M. Echavarren, and M. C. Paredes, *J. Org. Chem.*, **1991**, *56*, 6488.

15. For a review, see: S. V. Kessar, 'Comprehensive Organic Synthesis: Nucleophilic Coupling with Arynes,' Vol. 4, ed. by B. M. Trost and I. Fleming, Pergamon Press plc, Oxford, 1991, pp. 483-515.
16. The stannanes (**1**), (**7**), and (**13**) should be purified by flash chromatography over alumina (hexane-ethyl acetate 20:1). Chromatography over silica gel caused considerable loss of tributylstannyl group.
17. a) J. M. Muchowski and M. C. Venuti, *J. Org. Chem.*, **1980**, *45*, 4798; b) P. Stanetty, H. Koller, and M. Mihovilovic, *J. Org. Chem.*, **1992**, *57*, 6833.
18. a) S. Mukherjee, M. Mukherjee, and S. N. Ganguly, *Phytochem.*, **1983**, *22*, 1064. The same alkaloid has been named glycozolinol by another research group, see: b) P. Bhattacharyya, T. Sarkar, A. Chakraborty, and B. K. Chowdhury, *Indian J. Chem.*, **1984**, *23B*, 49.
19. a) D. P. Chakraborty and B. P. Das, *Science and Culture (India)*, **1966**, *32*, 181; b) D. P. Chakraborty, B. P. Das, and S. P. Basak, *The Plant Biomedical Journal (India)*, **1974**, *1*, 73.
20. M. Iwao, *J. Org. Chem.*, **1990**, *55*, 3622.
21. X. Wang and V. Snieckus, *Tetrahedron Lett.*, **1991**, *32*, 4879.
22. Ammonia was spontaneously evaporated overnight. When the reaction mixture was quenched after 3 h at -33°C, only the desilylated starting material was recovered.
23. Glycozolinine (**11**): mp 235-238°C (ether) (lit.,[18a] mp 231-232°C); ir (KBr) 3390, 1615, 1575, 1460, 1400, 1320, 1250, 1200, 1140, 935, 865, 800, 575, 450 cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6) δ 2.43 (s, 3H), 6.85 (dd, 1H, *J*=8.7 and 2.5 Hz), 7.13 (d, 1H, *J*=7.9 Hz), 7.23 (d, 1H, *J*=8.7 Hz), 7.28 (d, 1H, *J*=7.9 Hz), 7.35 (d, 1H, *J*=2.5 Hz), 7.75 (s, 1H), 8.87 (s, 1H, exchanged with D_2O), 10.71(s, 1H, exchanged with D_2O); ms *m/z* 197 (M^+). *Anal.* Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.26; H, 5.61; N, 7.17.
24. S. Kajigaeshi, T. Kakinami, H. Tokiyama, T. Hirakawa, and T. Okamoto, *Chem. Lett.*, **1987**, 627.
25. Glycozolidine (**17**): mp 166-167°C (ether-hexane) (lit.,[19a,b] mp 161-162°C); ir (KBr) 3400, 3000, 2940, 2830, 1630, 1580, 1490, 1470, 1430, 1320, 1295, 1275, 1220, 1200, 1170, 1135, 1110, 1030, 815, 775, 460 cm^{-1}; ^1H nmr (400 MHz, DMSO-d_6) δ 2.27 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 6.88 (dd, 1H, *J*=8.6 and 2.7 Hz), 6.91 (s, 1H), 7.29 (d, 1H, *J*=8.6 Hz), 7.51 (d, 1H, *J*=2.7 Hz), 7.79 (s, 1H), 10.77 (s, 1H, exchanged with D_2O); ms *m/z* 241 (M^+). *Anal.* Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.39; H, 6.31; N, 5.78.

Received, 8th February, 1993