

develop a more efficient strategy for synthesizing these carbazole alkaloids, we found that 3-oxygenated carbazoles have a methyl group at the 2-position. Based on this finding, we envisaged that an electrocyclic reaction of an allene intermediate (4) in retro-synthetic Scheme 1 might be more reactive than the reaction of the 2,3-bisvinylindole system^{3a,b} for producing poly-substituted carbazole alkaloids with a methyl group in the 2-position. A new type of allene intermediate (4) possessing an appropriate functional group would be generated from the 2-propargylindole derivative (5).

We started from the 2-formyl-3-iodoindole (6),¹⁰ prepared from 2-formylindole, for the synthesis of the precursor (5) (Scheme 2). The compound (6) was converted into the *N*-benzenesulfonylindole (7) by the usual way.^{3a,b} Cross-coupling reaction between 7 and the vinylstannane (8) in the presence of bis(triphenylphosphine)palladium (II) chloride (Pd(PPh₃)₂Cl₂) gave the 3-alkenylindole (9) (84%). Treatment of 9 with ethynyl magnesium bromide followed by treatment of the alcohol (10) with chloromethyl methyl ether (MOM-Cl), in order to avoid a formation of an enone-type compound during a generation of an allene intermediate,^{9a} produced the 3-alkenyl-2-propargylindole (5) (88% from 9).

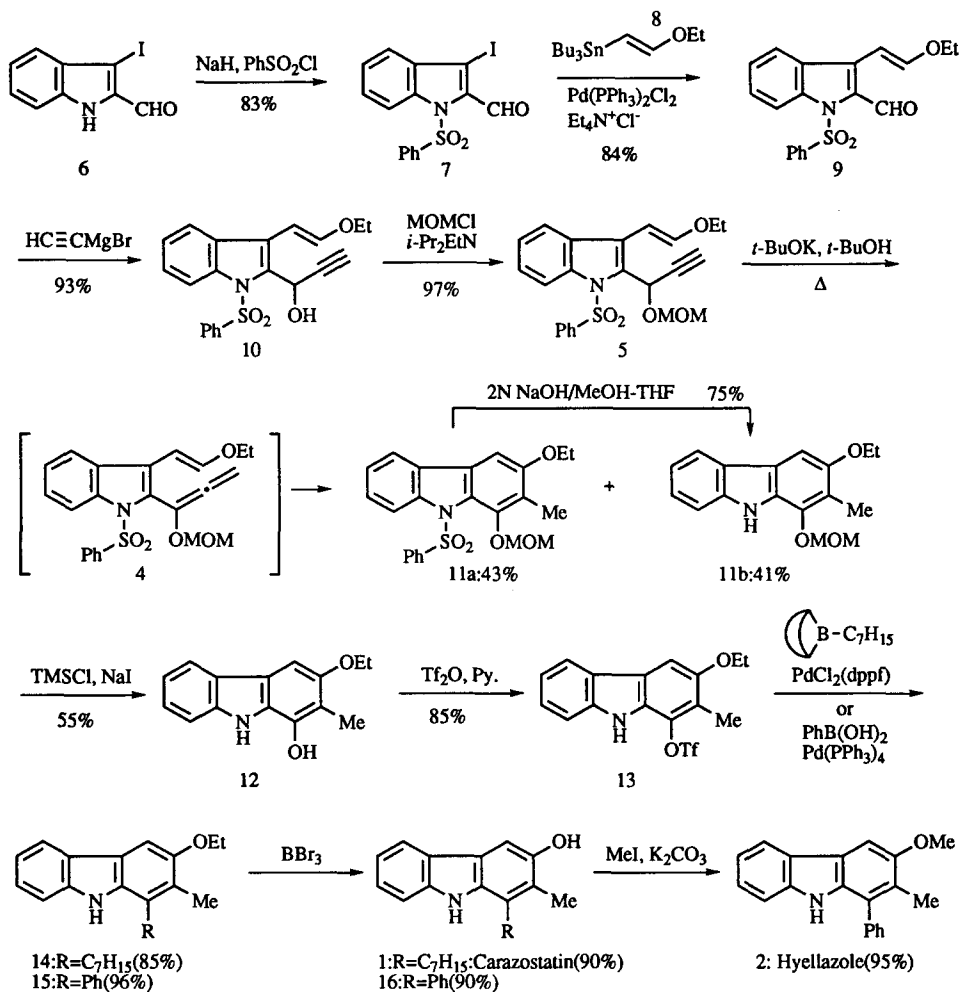
Heating of 5 in *t*-butanol in the presence of potassium *t*-butoxide according to the previously reported method for allene-generation¹¹ yielded the expected carbazole derivative (11a) (43%) together with the *N*-deprotected carbazole (11b) (41%). Although it is undeniable that this benzo-annulation proceeds through an ionic process,¹² at present it has been considered that it is initiated by a generation of an allene intermediate to undergo an electrocyclic reaction to give rise to the desired tri-substituted carbazole with a tautomeric process.

Hydrolysis of 11a with sodium hydroxide gave the carbazole (11b) (75%). Subsequent cleavage of the MOM-ether bond of 11b with the combination of trimethylsilyl chloride (TMSCl) and sodium iodide¹³ gave the 1-hydroxycarbazole (12) (55%). The phenol (12) was converted into the triflate (13) in order to introduce alkyl and phenyl groups at the 1-position of the carbazole ring. The triflate (13) was subjected to Suzuki cross-coupling reaction¹⁴ with 9-heptyl-9-borabicyclo[3,3,1]nonane (prepared from 9-BBN and 1-heptene) and with phenylboronic acid in the presence of palladium catalysts to yield the 1-heptylcarbazole (14) (85%) and the 1-phenylcarbazole (15) (96%), respectively.

Finally, cleavage of the ethyl ether group of 14 with boron tribromide (BBr₃) produced carazostatin (1) (90%). Cleavage of the ethyl ether group of 15 with BBr₃ followed by methylation of the phenol (16) yielded hyellazole (2) (89% from 15). The spectroscopic data and physical data of both synthetic materials¹⁵ were virtually identical with those reported for the natural products.^{2,3,6,7}

In conclusion, we have developed new total syntheses of carazostatin (1) and hyellazole (2) using a new type of allene-mediated electrocyclic reaction involving the indole 2,3-bond. In hyellazole, this key reaction provided more effective result than those of our previous synthesis.^{3a,b} This benzo-annulation may be a useful strategy for constructing highly-substituted carbazole alkaloids that possess a methyl group at the 2-position. Further studies are now in progress.

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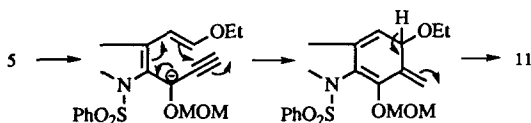


Scheme 2

References and Notes

- For recent reviews, see: (a) Chakraborty, D. P.; Roy, S. in *Prog. Chem. Org. Nat. Prod.*, Vol. 57; Herz, W.; Grisebach, H.; Kirby, G. W.; Tamm, C. Eds.; Springer: Wien, **1991**, p. 71. (b) D. P. Chakraborty, in *The Alkaloids*, Vol. 44; A. Brossi, Ed.; Academic: New York, **1993**, p. 257.
- For the isolation of hyellazole, see: Cardellina II, J. H.; Kirkup, M. P.; Moore, R. E.; Mynderse, J. S.; Seff, K.; Simmons, C. J. *Tetrahedron Lett.* **1979**, 4915.
- For previous syntheses of hyellazole, see: (a) Kano, S.; Sugino, E.; Hibino, S. *J. Chem. Soc. Chem. Commun.* **1980**, 1241. (b) Kano, S.; Sugino, E.; Shibuya, S.; Hibino, S. *J. Org. Chem.* **1981**, *46*, 3856. (c) Takano, S.; Suzuki, Y.; Ogasawara, K. *Heterocycles* **1981**, *16*, 1479. (d) Kawasaki, T.; Nonaka, Y.; Sakamoto, M. *J. Chem. Soc. Chem. Commun.* **1989**, 43. (e) Moody, C. J.; Shah, P. J. *Chem. Soc. Perkin Trans. 1* **1989**, 2463. (f) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.

- Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093. (g) Kawasaki, T.; Nonaka, Y.; Akahane, M.; Maeda, M.; Sakamoto, M. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1777. (h) Beccalli, E. M.; Marchesini, A.; Pilati, T. *J. Chem. Soc. Perkin Trans. 1* **1994**, 579. (i) Knölker, H.-J.; Baum, E.; Hopfmann, T. *Tetrahedron Lett.* **1995**, *36*, 5339.
4. For the isolation of carbazomycins, see: (a) Sakano, K.; Ishimaru, K.; Nakamura, S. *J. Antibiotics* **1980**, *33*, 683. (b) Sakano, K.; Nakamura, S. *J. Antibiotics* **1980**, *33*, 961. (c) Kaneda, M.; Sakano, K.; Nakamura, S.; Kushi, Y.; Iitaka, Y. *Heterocycles* **1981**, *15*, 993. (d) Yamasaki, K.; Kaneda, M.; Watanabe, K.; Ueki, Y.; Ishimaru, K.; Nakamura, S.; Nomi, R.; Yoshida, N.; Nakajima, T. *J. Antibiotics* **1983**, *36*, 552. (e) Kondo, S.; Katayama, M.; Marumo, S. *J. Antibiotics* **1986**, *39*, 727. (f) Naid, T.; Kitahara, T.; Kaneda, M.; Nakamura, S. *J. Antibiotics* **1987**, *40*, 157. (g) Kaneda, M.; Naid, T.; Kitahara, T.; Nakamura, S.; Hirata, T.; Suga, T. *J. Antibiotics* **1988**, *41*, 602.
5. For previous syntheses of carbazomycins, see reference 8.
6. For the isolation of carazostatin, see: Kato, S.; Kawai, H.; Kawasaki, T.; Toda, Y.; Urata, T.; Hayakawa, Y. *J. Antibiotics* **1989**, *42*, 1879.
7. For previous syntheses of carazostatin, see: (a) Jackson, P. M.; Moody, C. J. *Synlett* **1990**, 521. (b) Jackson, P. M.; Moody, C. J.; Mortimer, R. J. *J. Chem. Soc. Perkin Trans. 1* **1991**, 2941. (c) Shin, K.; Ogasawara, K. *Chem. Lett.* **1995**, 289. (d) Knölker, H.-J.; Hopfmann, T. *Synlett* **1995**, 981.
8. For recent reviews, see: (a) Pindur, U. *Chimia*, **1990**, *44*, 406. (b) Bergman, J.; Pelcman, B. *Pure Appl. Chem.* **1990**, *62*, 1967. (c) Knölker, H.-J. *Synlett* **1992**, 371. (d) Kawasaki, T.; Sakamoto, M. *J. Indian Chem. Soc.* **1994**, *71*, 443. (e) Moody, C. J. *Synlett* **1994**, 681. (f) Knölker, H.-J. in *Advances in Nitrogen Heterocycles* Moody, C. J. Ed.; JAI Press: Greenwich, CT(USA), **1995**, Vol. 1, p. 173. (g) Hibino, S.; Sugino, E. in *Advances in Nitrogen Heterocycles* Moody, C. J. Ed.; JAI Press: Greenwich, CT(USA), **1995**, Vol. 1, p. 205.
9. (a) Schuster, H. F.; Coppola, G. M. "Allenenes in Organic Synthesis" Wiley: New York, **1984**. (b) Turnbull, P.; Moore, H. W. *J. Org. Chem.* **1995**, *60*, 3274 and related references cited therein.
10. 2-Formyl-3-iodoindole (mp 193-194°C, 81%) was prepared from 2-formylindole by the following method: Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1990**, *36*, 2248.
11. Hayakawa, K.; Ohsuki, S.; Kanematsu, K. *Tetrahedron Lett.* **1986**, *27*, 4205.
- 12.



13. Rigby, J. H.; Wilson, J. Z. *Tetrahedron Lett.* **1984**, *25*, 1429.
14. (a) Ishiyama, T.; Kizaki, H.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1993**, *34*, 7595. (b) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201.
15. Carazostatin (**1**) mp: 159-160°C (lit^{7a}, 162-163°C); ¹H-nmr (400 MHz, CDCl₃): δ 0.90(3H, t, *J*=6.8 Hz), 1.20-1.50(8H, m), 1.60-1.69(2H, m), 2.38(3H, s), 2.89(2H, t, *J*=7 Hz), 7.17(1H, t, *J*=7 Hz), 7.31(1H, s), 7.33-7.46(2H, m), 7.74(1H, br s), 7.94(1H, d, *J*=7 Hz). Hyellazole (**2**) mp: 129-130°C (lit², 133-134°C); ¹H-nmr (400 MHz, CDCl₃): δ 2.21(3H, s), 4.00(3H, s), 7.18(1H, t, *J*=7 Hz), 7.25-7.57(7H, m), 7.51(1H, s), 7.60(1H, br s), 8.02(1H, d, *J*=7 Hz).