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Total Syntheses of Carazostatin and Hyellazole by Allene-Mediated Electrocyclic Reaction

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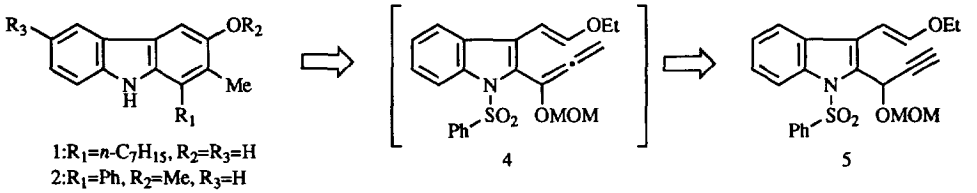
Abstract: The free radical scavenger carazostatin and the marine alkaloid hyellazole have been synthesized by a new type of allene-mediated electrocyclic reaction involving the indole 2,3-bond as a key step.

Over the past 15 years, new poly-substituted carbazole alkaloids have been found by several groups.[1] Hyellazoles were isolated from the blue-green algae *Hyella caespitosa* by Moore in 1979, representing the first carbazole alkaloids of marine origin.[2,3] The carbazomycins, isolated from *Streptoverticillium ehimense* by Nakamura in 1980, possess antibiotic, weak antibacterial and anti-yeast activities.[4,5] Hayakawa (1989) isolated carazostatin which is a free radical scavenger produced by *Streptomyces chromofuscus* .[6,7] These novel alkaloids attracted considerable interest from synthetic organic chemists because of their potential biological activities.[8] In this paper we describe novel total syntheses of carazostatin (**1**) and hyellazole (**2**) by a new type of allene-mediated electrocyclic reaction involving the indole 2,3-bond.[9]



1:R_1=*n*-C_7H_{15}, R_2=R_3=H
2:R_1=Ph, R_2=Me, R_3=H
3:R_1=Ph, R_2=Me, R_3=Cl

4 5

Scheme 1

We developed the first total synthesis of hyellazole (**2**) and 6-chlorohyellazole (**3**) by means of the thermal electrocyclic reaction of the 2,3-bisvinylindoles in 1980-1981.[3a,b] In the course of our attempt to

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 ($Pd(PPh_3)_2Cl_2$) 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-generation[11] yielded the expected carbazole derivative (**11a**) (43%) together with the *N*-deprotected carbazole (**11b**) (41%). Although it is undeniable that this benzo-annelation 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 trimethysilyl chloride (TMSCl) and sodium iodide[13] 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 reaction[14] 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 (BBr_3) produced carazostatin (**1**) (90%). Cleavage of the ethyl ether group of **15** with BBr_3 followed by methylation of the phenol (**16**) yielded hyellazole (**2**) (89% from **15**). The spectroscopic data and physical data of both synthetic materials[15] 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-annelation 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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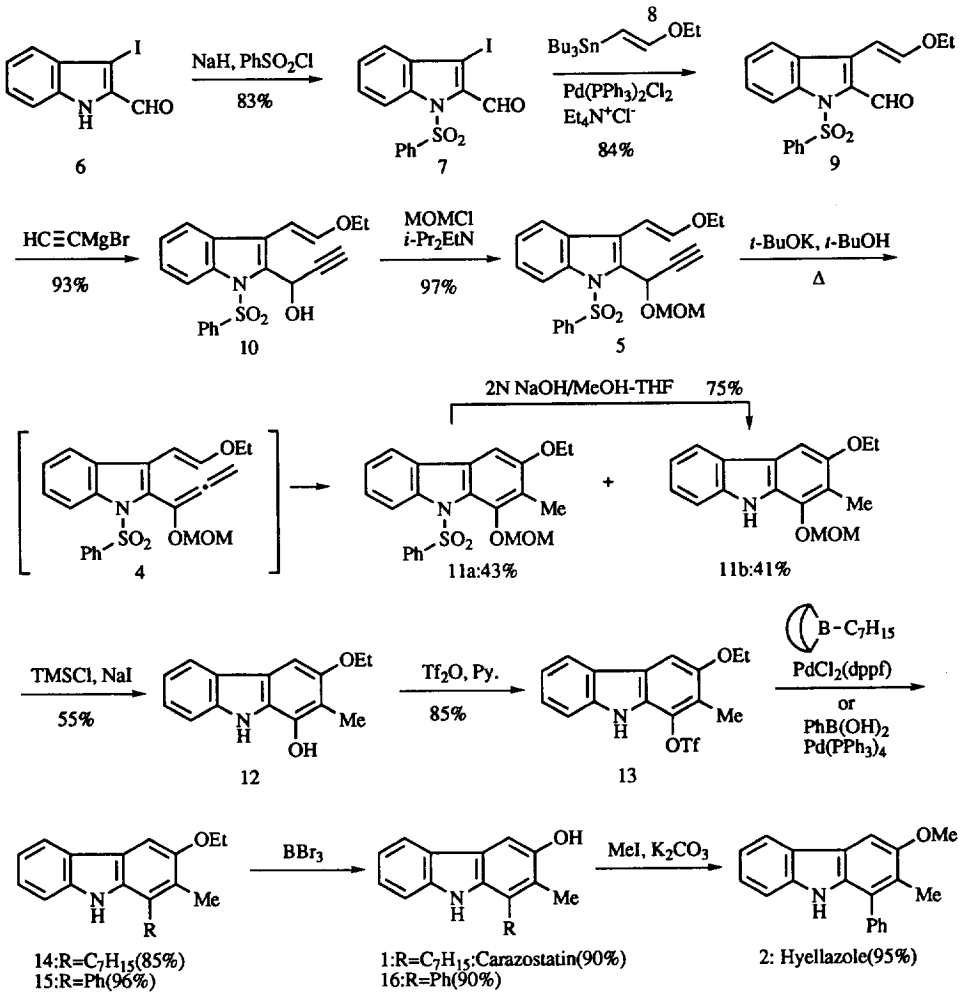
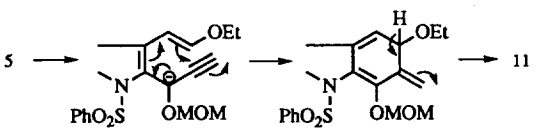


Scheme 2

References and Notes

1. 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.
2. 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.
3. 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. "Allenes 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); ^{1}H-nmr (400 MHz, $CDCl_3$): 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 (lit[2], 133-134°C); ^{1}H-nmr (400 MHz, $CDCl_3$): 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).

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