A New Method for the Stereocontrolled Synthesis of Dienamine Derivatives Using (Naphthalene)chromium Tricarbonyl Catalyzed Isomerization

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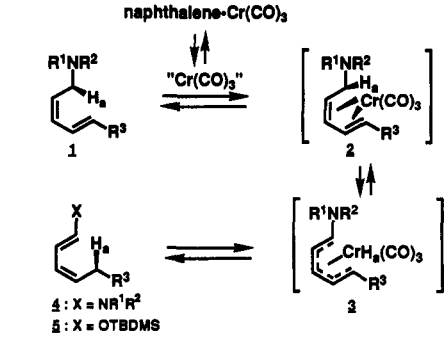
Dienamine derivatives are frequency utilized in organic synthesis such as Diels–Alder reaction,[1] and a variety of methods for the synthesis of dienamine derivatives have been developed to date.[2] However, stereocontrolled synthesis of dienamine derivatives of type 4, which would find application in synthesis, has not been reported.[3] In this paper, we report a stereocontrolled synthesis of dienamine derivatives of type 4 starting with butadiene derivatives (type 1).

We had already developed a stereocontrolled synthesis of silyl dienol ethers of type 5 starting with butadiene derivatives by (naphthalene)chromium tricarbonyl catalyzed isomerization.[4] In addition, this unique isomerization capability of (naphthalene)$Cr(CO)_3$ had been also applied to a stereocontrolled synthesis of aryl-substituted exocyclic olefins.[5] It was envisioned that treatment of butadiene derivatives of type 1[6] with a catalytic amount of (naphthalene)$Cr(CO)_3$ in acetone at 20 °C would afford dienamine derivatives of type 4 stereospecifically in excellent yields on the basis of the following matters. That is, effective isomerization of allylic amines to enamines is well-known,[7] and (naphthalene)$Cr(CO)_3$-catalyzed isomerization should proceed via U-shaped η^5-intermediates 3 formed stereospecifically by the oxidative addition of a C–H_a bond to "$Cr(CO)_3$" as shown in Scheme I. When

Scheme I



Scheme II

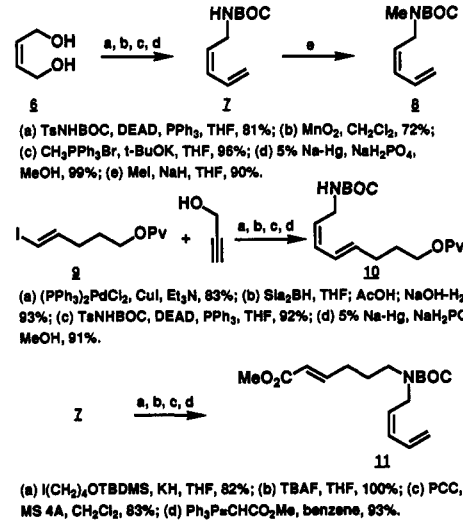
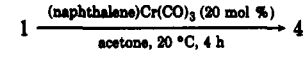
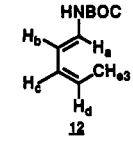
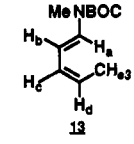
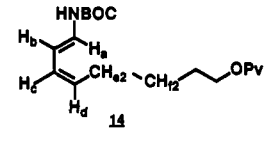
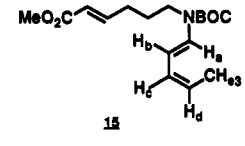


Table I. Isomerization of Butadiene Derivatives of Type 1



substrates	dienamine derivatives	yield (%)
7		94
8		89
10		88
11		97

(1) (a) Oppolzer, W.; Frōstl, W. *Helv. Chim. Acta* **1975**, *58*, 590. (b) Oppolzer, W.; Frōstl, W.; Weber, H. P. *Ibid.* **1975**, *58*, 593. (c) Oppolzer, W.; Flaskamp, E. *Ibid.* **1977**, *60*, 204. (d) Overman, L. E.; Taylor, G. F.; Houk, K. N.; Domelsmith, L. N. *J. Am. Chem. Soc.* **1978**, *100*, 3182. (e) Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179. (f) Oppolzer, W.; Bieber, L.; Francotte, E. *Tetrahedron Lett.* **1979**, 4537. (g) Stork, G.; Morgans, D. J., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 7110. (h) Danishefsky, S.; Hershenson, F. M. *J. Org. Chem.* **1979**, *44*, 1180. (i) Overman, L. E.; Petty, C. B.; Doedens, R. J. *Ibid.* **1979**, *44*, 4183. (j) Overman, L. E.; Fukaya, C. *J. Am. Chem. Soc.* **1980**, *102*, 1454. (k) Keck, G. E.; Boden, E.; Sonnewald, U. *Tetrahedron Lett.* **1981**, *22*, 2615. (l) Schmidt, R. R.; Wagner, A. *Ibid.* **1983**, *24*, 4661. (m) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35. (n) Magnus, P.; Cairns, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 217. (o) Hayakawa, K.; Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1987**, *28*, 5895. (p) Martin, S. F.; Li, W. *J. Org. Chem.* **1989**, *54*, 265. (q) Yasukouchi, T.; Kanematsu, K. *J. Chem. Soc., Chem. Commun.* **1989**, 953. (r) Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1989**, *30*, 6559.

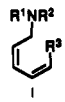
(2) (a) Oppolzer, W.; Frōstl, W. *Helv. Chim. Acta* **1975**, *58*, 587. (b) Overman, L. E.; Clizbe, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 2352, 8295. (c) Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164. (d) Oppolzer, W.; Bieber, L.; Francotte, E. *Tetrahedron Lett.* **1979**, 981. (e) Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139. (f) Berthon, L.; Uguen, D. *Tetrahedron Lett.* **1985**, *26*, 3975. (g) Bochu, C.; Couture, A.; Grandclaudon, P. *J. Org. Chem.* **1988**, *53*, 4852.

(3) Kanematsu and his co-workers have reported one example of the synthesis of the dienamine derivative (type 4). See: ref 1r.

(4) Sodeoka, M.; Yamada, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1990**, *112*, 4906.

(5) (a) Sodeoka, M.; Satoh, S.; Shibasaki, M. *J. Am. Chem. Soc.* **1988**, *110*, 4823. (b) Shibasaki, M.; Sodeoka, M.; Ogawa, Y. *J. Org. Chem.* **1984**, *49*, 4096. (c) Shibasaki, M.; Sodeoka, M. *J. Synth. Org. Chem. Jpn.* **1985**, *43*, 877.

(6) Dienamine derivatives of type i should afford 4 stereospecifically in lower yields than 1. See: ref 4.



i

(7) (a) Kumobayashi, H.; Akutagawa, S.; Otsuka, S. *J. Am. Chem. Soc.* **1978**, *100*, 3949. (b) Laguzza, B. C.; Ganem, B. *Tetrahedron Lett.* **1981**, 1483. (c) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc.* **1984**, *106*, 5208. (d) Inoue, S.; Takaya, H.; Tani, K.; Otsuka, S.; Sato, T.; Noyori, R. *J. Am. Chem. Soc.* **1990**, *112*, 4897.

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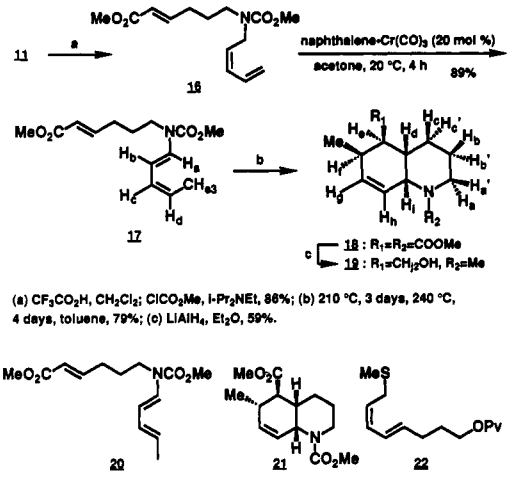
we initiated the present project, however, the effect of a nitrogen functionality on the isomerization catalyzed by (naphthalene)$Cr(CO)_3$ was virtually unknown.

Treatment of the butadiene derivative **7**, prepared from *cis*-2-butene-1,4-diol (**6**) in a four-step process (55% overall yield), with 20 mol % of (naphthalene)$Cr(CO)_3$ in degassed acetone at 20 °C for 4 h provided the dienamine derivative **12** as the sole product in 94% yield. The dienamine derivative **12** could be isolated by silica gel column chromatography without any isomerization. The stereochemical homogeneity of **12** was confirmed by the ^{13}C NMR and the stereochemical assignment followed from the ^1H NMR, which showed J_{ab} = 13.9 Hz and J_{cd} = 10.7 Hz. Furthermore, in NOE experiments, irradiation of H_c showed an enhancement of H_a and H_d and irradiation of H_e showed an enhancement of H_b and H_d. The N-methylated butadiene derivative **8** obtainable from **7** in 90% yield was also transformed into the dienamine derivative **13** stereospecifically in 89% yield under the similar reaction conditions. The stereochemistry of **13** was unequivocally determined from the ^1H NMR spectrum. In addition, the isomerization of the diene **10**, obtainable from the alkenyl iodide **9** in a four-step process (65% overall yield), afforded the dienamine derivative **14** as the sole product in 88% yield, whose stereochemistry was also determined from the ^1H NMR spectrum. Finally, it is worthy of note that the diene **11** bearing an α,β-unsaturated ester group, obtainable from **7** in a four-step process (63% overall yield), was also converted to the dienamine derivative **15** as the sole product in 94% yield. The stereochemical assignment followed from the ^1H NMR spectrum (Scheme II, Table I).

In order to demonstrate the synthetic utility of dienamine derivatives of type **4**, the intramolecular Diels–Alder reaction was undertaken. First of all, the intramolecular Diels–Alder reaction of **15** was carried out in toluene at 220 °C, resulting in the formation of many products probably due to the thermal instability of a BOC group. In order to overcome this problem, the butadiene derivative **16** protected as a methyl carbamate was next prepared in 86% yield from **11**. Isomerization of **16** with 20 mol % of (naphthalene)$Cr(CO)_3$ in degassed acetone at 20 °C for 4 h produced the dienamine derivative **17** as the sole product in 89% yield. The stereochemical assignment for **17** followed from the ^1H NMR, which showed J_{ab} = 14.3 Hz and J_{cd} = 10.6 Hz. The dienamine derivative **17** was then subjected to the intramolecular Diels–Alder reaction by heating in toluene (210 °C, 3 days, and 240 ° C, 4 days, sealed tube), affording the *cis*-octahydroquinoline derivative **18** exclusively in 79% yield. The stereochemical homogeneity of **18** was confirmed by ^{13}C NMR and the stereochemistry was speculated by ^1H NMR. In NOE experiments, irradiation of H_d showed an enhancement of H_c (2%) and H_i (5%), and irradiation of H_h showed an enhancement of H_g (3%), H_i (2%), and H_a (1%). In addition, irradiation of H_e showed an enhancement of CH_3 (1%), H_f (3%), and H_c (2%) and the coupling constant between H_e and H_f was 3.0 Hz. In order to confirm the stereochemistry of **18**, **18** was reduced with $LiAlH_4$ to give **19**. The ^1H NMR of **19** showed J_{di} = ~0 Hz, indicating the conformation of **19**. Furthermore, NOE was observed between H_i and CH_3 and H_e and H_f (NOESY). Considering that the intramolecular Diels–Alder reaction of **20**, easily obtainable by a conventional method, should afford the *cis*-octahydroquinoline derivative **21**, the previous result is noteworthy (Scheme III).[8]

(8) For the synthesis of *cis*-octahydroquinoline derivatives by the intramolecular Diels–Alder reaction, see: refs 1a and 1b.

Scheme III



Furthermore, in order to extend the utility of (naphthalene)$Cr(CO)_3$-catalyzed isomerization of conjugated dienes, reaction of the butadiene derivative **22**[9] having a sulfide functionality was undertaken. However, unexpectedly, treatment of **22**, obtainable from **9** in a four-step process, with 20 mol % of (naphthalene)$Cr(CO)_3$ in degassed acetone at 20 °C or 20 mol % of (methyl benzoate)$Cr(CO)_3$ in degassed THF at 120 °C (sealed tube) resulted in the complete recovery of **22**. It seems likely that softer S coordinates to "$Cr(CO)_3$" more tightly than O and/or N.[10,11]

In conclusion, we have succeeded in synthesizing dienamine derivatives of type **4** stereospecifically for the first time. Furthermore, the dienamine derivative **17** was successfully converted to the *cis*-octahydroquinoline derivative **18** just by heating, demonstrating the synthetic utility of dienamine derivatives of type **4**. We believe that the combination of the present methodology with high-pressure techniques in Diels–Alder reactions[12] should prove valuable for the construction of cyclohexenes having a nitrogen substituent, hydroquinolines, and hydroindoles.

Experimental Section

General. Reactions were carried out in dry solvents under an argon atmosphere. Solvents were distilled before use as follows: acetone from $KMnO_4$; tetrahydrofuran (THF) and ether from sodium benzophenone ketyl; dichloromethane (CH_2Cl_2) and benzene from calcium hydride; methanol and toluene from sodium. Melting points are uncorrected.

Satisfactory IR, ^1H NMR, and MS data were obtained on all intermediates described herein using chromatographically homogeneous samples.

***tert*-Butyl *N*-((*Z*)-4-Hydroxy-2-butenyl)-*N*-(*p*-toluenesulfonyl)carbamate.** To a stirred solution of (*Z*)-2-butene-

(9) The stereochemistry of the diene **21** was unequivocally determined from the ^1H NMR spectrum.

(10) Ho, T.-L. *Tetrahedron* **1985**, *41*, 1.

(11) It was also found that the corresponding sulfoxide did not afford the isomerized product.

(12) (a) Smith, A. B., III; Liverton, N. J.; Hrib, N. J.; Sivaramakrishnan, H.; Winzenberg, K. *J. Am. Chem. Soc.* **1986**, *108*, 3040. (b) Kozikowski, A. P.; Nieduzak, T. R.; Konoike, T.; Springer, J. P. *Ibid.* **1987**, *109*, 5167. (c) Engler, T. A.; Naganathan, S.; Takusagawa, F.; Yohannes, D. *Tetrahedron Lett.* **1987**, *28*, 5267. (d) Sera, A.; Ohara, M.; Kubo, T.; Itoh, K.; Yamada, H.; Mikata, Y.; Kaneko, C.; Katagiri, N. *J. Org. Chem.* **1988**, *53*, 5460. (e) Katagiri, N.; Akatsuka, H.; Kaneko, C.; Sera, A. *Tetrahedron Lett.* **1988**, *29*, 5397. (f) Engler, T. A.; Sampath, U.; Naganathan, S.; Velde, D. V.; Takusagawa, F.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 5712. (g) Rigby, J. H.; Kierkus, P. Ch. *J. Am. Chem. Soc.* **1989**, *111*, 4125. (h) Rigby, J. H.; Kierkus, P. Ch.; Head, D. *Tetrahedron Lett.* **1989**, *30*, 5073.

1,4-diol (0.36 mL, 4.38 mmol) in THF (10 mL) was added TsNHBOC (500 mg, 1.85 mmol) and PPh_3 (580 mg, 2.21 mmol) at room temperature. The solution was cooled to 0 °C, and DEAD (0.35 mL, 2.22 mmol) was added at the same temperature. The reaction mixture was stirred at room temperature for 12 h, quenched by the addition of H_2O at 0 °C, and extracted with ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated to give an oily residue, which was purified by silica gel column chromatography (ethyl acetate–hexane–methylene chloride (1:3:1)) to give *tert*-butyl *N*-((*Z*)-4-hydroxy-2-butenyl)-*N*-(*p*-toluenesulfonyl)carbamate (508 mg, 81%, based on TsNHBOC) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.20 (s, 9 H), 2.04 (b s, 1 H), 2.46 (s, 3 H), 4.31 (d, J = 6.4 Hz, 2 H), 4.58 (d, J = 6.7 Hz, 2 H), 5.73 (dt, J = 10.9, 6.7 Hz, 1 H), 5.97 (dt, J = 10.9, 6.4 Hz, 1 H), 7.32 (d, J = 8.5 Hz, 2 H), 7.83 (d, J = 8.5 Hz, 2 H); IR (neat) 3410, 2990, 1725, 1595, 1355, 1150 cm^{-1}; MS m/z 285 ($M^+ - CH_2{=}CMe_2$), 223 (M^+ – Boc – OH), 216, 155 (Ts), 91, 57 (b p, ^{t}Bu); HRMS ($M^+ - CH_2{=}CMe_2$) calcd for $C_{12}H_{15}O_5NS$ 285.0671, found 285.0668.

***tert*-Butyl *N*-((*Z*)-3-Formyl-2-propenyl)-*N*-(*p*-toluenesulfonyl)carbamate.** To a stirred solution of *tert*-butyl *N*-((*Z*)-4-hydroxy-2-butenyl)-*N*-(*p*-toluenesulfonyl)carbamate (53 mg, 0.16 mmol) in CH_2Cl_2 (6.5 mL) was added MnO_2 (473 mg, 5.44 mmol) at 0 °C, and the reaction mixture was stirred for 1 h at the same temperature, diluted with ether, and filtered through a pad of Celite. The filtrate was concentrated to give an oily residue, which was purified by silica gel column chromatography (ether–hexane (2:3)) to give *tert*-butyl *N*-((*Z*)-3-formyl-2-propenyl)-*N*-(*p*-toluenesulfonyl)carbamate (38 mg, 72%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.12 (s, 9 H), 1.87 (s, 3 H), 4.78 (dd, J = 6.7, 1.5 Hz, 2 H), 5.75 (ddt, J = 11.2, 6.3, 1.5 Hz, 1 H), 6.25 (dt, J = 11.2, 6.7 Hz, 1 H), 6.77 (d, J = 8.1 Hz, 2 H), 7.79 (d, J = 8.1 Hz, 2 H), 9.95 (d, J = 6.3 Hz, 1 H); IR (neat) 2990, 2870, 1730, 1685, 1600, 1360, 1160 cm^{-1}; MS m/z 283 ($M^+ - CH_2{=}CMe_2$), 239 ($M^+ - CH_2{=}CMe_2 - CO_2$), 155 (Ts), 91, 84, 57 (b p, ^{t}Bu); HRMS ($M^+ - CH_2{=}CMe_2 - CO_2$) calcd for $C_{11}H_{13}O_3NS$ 239.0616, found 239.0598.

***tert*-Butyl *N*-((*Z*)-2,4-Pentadienyl)-*N*-(*p*-toluenesulfonyl)carbamate.** A suspension of methyltriphenylphosphonium bromide (6.61 g, 18.5 mmol) and potassium *tert*-butoxide (1.94 g, 17.3 mmol) in THF (120 mL) was stirred for 1 h at 0 °C–room temperature. To the resulting ylide solution was then added *tert*-butyl *N*-((*Z*)-3-formyl-2-propenyl)-*N*-(*p*-toluenesulfonyl)carbamate (3.92 g, 11.6 mmol) in THF (80 mL) at 0 °C, and the reaction mixture was stirred for 0.5 h at room temperature, quenched by the addition of saturated aqueous NH_4Cl (0 °C), and extracted with ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated to give the residue, which was purified by silica gel column chromatography (ethyl acetate–hexane (1:8)) to afford *tert*-butyl *N*-((*Z*)-2,4-pentadienyl)-*N*-(*p*-toluenesulfonyl)carbamate (3.74 g, 96%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.34 (s, 9 H), 2.43 (s, 3 H), 4.62 (dd, J = 7.1, 1.2 Hz, 2 H), 5.24 (dd, J = 10.0, 1.8 Hz, 1 H), 5.30 (dd, J = 16.6, 1.8 Hz, 1 H), 5.55 (b dt, J = 10.8, 7.1 Hz, 1 H), 6.17 (b dt, J = 11.0, 10.8 Hz, 1 H), 6.83 (dddd, J = 16.6, 11.0, 10.0, 1.0 Hz, 1 H), 7.28 (d, J = 8.6 Hz, 2 H), 7.78 (d, J = 8.6 Hz, 2 H); IR (neat) 2990, 1730, 1595, 1355, 1150 cm^{-1}; MS m/z 281 ($M^+ - CH_2{=}CMe_2$), 155 (Ts), 126 (b p), 91, 82, 57 (^{t}Bu); HRMS ($M^+ - CH_2{=}CMe_2$) calcd for $C_{13}H_{15}O_4NS$ 281.0722, found 281.0745.

***tert*-Butyl *N*-((*Z*)-2,4-Pentadienyl)carbamate (7).** To a stirred solution of *tert*-butyl *N*-((*Z*)-2,4-pentadienyl)-*N*-(*p*-toluenesulfonyl)carbamate (305 mg, 0.91 mmol) and sodium dihydrogen phosphate (5.43 g, 45.3 mmol) in methanol (20 mL) was added 5% Na–Hg (8.33 g, 18.1 mmol) at 0 °C, and the reaction mixture was stirred for 1 h at the same temperature, quenched by the addition of H_2O (0 °C), stirred for 15 min, and filtered through a pad of Celite. After evaporation of methanol, the aqueous layer was extracted with ether, and the combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated to give the residue, which was purified by silica gel column chromatography (ether–hexane–methylene chloride (1:7:1)) to afford 7 (164 mg, 99%) as a colorless solid: ^1H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 3.89 (b dd, J = 7.0 Hz, 2 H), 4.49 (b s, 1 H), 5.19 (dd, J = 9.8, 1.8 Hz, 1 H), 5.25 (dd, J = 16.4, 1.8 Hz, 1 H), 5.44 (b dt, J = 10.5, 7.0 Hz, 1 H), 6.09 (dd, J = 11.0, 10.5 Hz, 1 H), 6.64 (dddd, J = 16.4, 11.0, 9.8, 1.0 Hz, 1 H); IR ($CHCl_3$) 3460, 2980, 1705, 1500, 1365, 1160 cm^{-1}; MS m/z 183 (M^+), 127 ($M^+ - CH_2{=}CMe_2$), 82 (M^+ – Boc), 66, 57 (b p, ^{t}Bu); HRMS ($M^+ - CH_2{=}CMe_2$) calcd for $C_6H_9O_2N$ 127.0633, found 127.0647. The analytical sample was recrystallized from hexane: mp 60.5–61.5 °C. Anal. Calcd for $C_{10}H_{17}O_2N$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.48; H, 9.31; N, 7.52.

***tert*-Butyl *N*-Methyl-*N*-((*Z*)-2,4-pentadienyl)carbamate (8).** To a stirred suspension of NaH (60% mineral oil dispersion, 13 mg, 0.33 mmol) in THF (0.2 mL) was added 7 (50 mg, 0.27 mmol) in THF (0.2 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 0.5 h. To this resulting suspension was then added CH_3I (22 μL, 0.35 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h, quenched by the addition of saturated aqueous NH_4Cl, and extracted with ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (ether–hexane (1:7)) to give 8 (49 mg, 90%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 2.81 (s, 3 H), 3.99 (d, J = 7.0 Hz, 2 H), 5.18 (b d, J = 10.1 Hz, 1 H), 5.26 (dd, J = 16.9, 1.8 Hz, 1 H), 5.43 (b dt, J = 11.0, 7.0 Hz, 1 H), 6.14 (dd, J = 11.0, 11.0 Hz, 1 H), 6.65 (dddd, J = 16.9, 11.0, 10.1, 1.0 Hz, 1 H); IR (neat) 3090, 2980, 1695, 1590, 1480, 1390, 1360, 1160 cm^{-1}; MS m/z 197 (M^+), 141 ($M^+ - CH_2{=}CMe_2$), 96, 82, 57 (b p, ^{t}Bu); HRMS (M^+) calcd for $C_{11}H_{19}O_2N$ 197.1416, found 197.1388.

5-(Trimethylsilyl)-4-pentyn-1-ol. To a stirred solution of 4-pentyn-1-ol (2.6 mL, 28.2 mmol) in THF (60 mL) was added BuLi (1.57 M THF solution, 37.7 mL, 59.2 mmol) at –78 °C, and the reaction mixture was stirred for 15 min at the same temperature. To this resulting suspension was then added TMSCl (9.0 mL, 70.9 mmol) at –78 °C, and the reaction mixture was stirred at room temperature for 2 h, quenched by the addition of 10% aqueous HCl (10 mL) at 0 °C, stirred for 15 min, and extracted with ether. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (ether–hexane (2:3)) to give the 5-(trimethylsilyl)-4-pentyn-1-ol (4.08 g, 93%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.12 (s, 9 H), 1.57 (s, 1 H), 1.67–1.86 (m, 2 H), 2.32 (t, J = 6.9 Hz, 2 H), 3.74 (t, J = 6.1 Hz, 2 H); IR (neat) 3330, 2960, 2900, 2180, 1250 cm^{-1}; MS m/z 156 (M^+), 141 (M^+ – Me), 123 (M^+ – Me – H_2O), 83 (M^+ – TMS), 75 (b p); HRMS (M^+ – Me) calcd for $C_7H_{13}OSi$ 141.0736, found 141.0733.

(*E*)-5-Iodo-4-pentenol. To a stirred solution of 5-(trimethylsilyl)-4-pentyn-1-ol (6.62 g, 38.6 mmol) in ether (200 mL) was added DIBAH (0.92 M hexane solution, 100 mL, 92.0 mmol) at –20 °C, and the reaction mixture was stirred for 18 h at room temperature. To this resulting solution was then added I_2 (29.4 g, 116 mmol) in THF–CH_2Cl_2 (50:150 mL) at –78 °C, and the reaction mixture was stirred for 30 min at the same temperature and quenched by the addition of 6 N aqueous NaOH at –78 °C. The whole reaction mixture was stirred for 30 min at 0 °C and extracted with ether. The combined organic extracts were washed with 10% aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4), and concentrated to give the crude silyl iodide (14.1 g).

To a stirred solution of sodium methoxide (16.7 g , 309 mmol) in methanol (95 mL) was added the crude silyl iodide (14.1 g) in methanol (55 mL) at room temperature, and the reaction mixture was refluxed for 2.5 h and quenched by the addition of H_2O (0 °C). After evaporation of methanol, the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (ether–hexane (1:2)) to give (*E*)-5-iodo-4-pentenol (4.43 g, 54%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.35 (s, 1 H), 1.51–1.80 (m, 2 H), 2.05–2.27 (m, 2 H), 3.64 (t, J = 6.2 Hz, 2 H), 6.00 (dt, J = 14.2, 1.3 Hz, 1 H), 6.50 (dt, J = 14.2, 7.0 Hz, 1 H); IR (neat) 3330, 3060, 2950, 1610 cm^{-1}; MS m/z 213 (M^+ + H), 212 (M^+), 193 (M^+ – OH), 149 (b p), 85 (M^+ – I); HRMS (M^+) calcd for C_5H_9OI 211.9698, found 211.9698.

(*E*)-5-(Pivaloyloxy)-1-pentenyl Iodide (9). To a stirred solution of (*E*)-5-iodo-4-pentenol (257 mg, 1.21 mmol) in CH_2Cl_2 (5 mL) was added pivaloyl chloride (0.30 mL, 2.44 mmol) and pyridine (0.49 mL, 6.06 mmol) at 0 °C. The reaction mixture was stirred for 3 h at room temperature, quenched by the addition

of H_2O, and extracted with ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (ether–hexane (1:8)) to give **9** (338 mg, 94%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.20 (s, 9 H), 1.66–1.89 (m, 2 H), 2.05–2.28 (m, 2 H), 4.06 (t, J = 6.4 Hz, 2 H), 6.05 (dt, J = 14.4, 1.2 Hz, 1 H), 6.55 (dt, J = 14.4, 6.8 Hz, 1 H); IR (neat) 3050, 2970, 1730, 1600, 1480, 1280, 1150 cm^{-1}; MS m/z 296 (M^+), 211 (M^+ – Pv), 194 (M^+ – ^{t}BuCOOH), 57 (b p, ^{t}Bu); HRMS (M^+) calcd for $C_{10}H_{17}O_2I$ 296.0273, found 296.0298.

(*E*)-8-(Pivaloyloxy)-4-octen-2-ynol. To a stirred solution of **9** (35 mg, 0.12 mmol) in Et_3N (0.65 mL) was added propargyl alcohol (14 μL, 0.24 mmol), $(PPh_3)_2PdCl_2$ (0.8 mg, 1.1 μmol), and CuI (0.5 mg, 2.6 μmol) at room temperature, and the reaction mixture was degassed through four freeze–pump–thaw cycles, stirred for 4 h at room temperature, filtered through a pad of Celite, washed with ethyl acetate, and diluted with H_2O. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (ether–hexane (2:3)) to give (*E*)-8-(pivaloyloxy)-4-octen-2-ynol (22 mg, 83%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.20 (s, 9 H), 1.58 (s, 1 H), 1.66–1.89 (m, 2 H), 2.10–2.33 (m, 2 H), 4.06 (t, J = 6.3 Hz, 2 H), 4.37 (d, J = 2.0 Hz, 2 H), 5.52 (dtt, J = 15.8, 2.0, 2.0 Hz, 1 H), 6.16 (dt, J = 15.8, 6.9 Hz, 1 H); IR (neat) 3440, 3020, 2980, 2210, 1725, 1480, 1280, 1160 cm^{-1}; MS m/z 224 (M^+), 223 (M^+ – H), 206 (M^+ – H_2O), 167 (M^+ – ^{t}Bu), 122 (M^+ – ^{t}BuCOOH), 57 (b p, ^{t}Bu); HRMS (M^+ – H) calcd for $C_{13}H_{19}O_3$ 223.1334, found 223.1306.

(2*Z*,4*E*)-8-(Pivaloyloxy)-2,4-octadienol. To a stirred solution of (*E*)-8-(pivaloyloxy)-4-octen-2-ynol (1.00 g, 4.46 mmol) in THF (5 mL) was added disiamylborane (0.96 M THF solution, 9.3 mL, 8.93 mmol) at 0 °C, and the reaction mixture was stirred for 2 h at the same temperature and quenched by the addition of CH_3COOH (2.0 mL, 34.9 mmol). The whole reaction mixture was heated at 65 °C for 5 h. After addition of 30% H_2O_2 (5.4 mL, 47.6 mmol) and 6 N NaOH (7.3 mL, 43.8 mmol) at 0 °C, the mixture was stirred for 20 min at the same temperature and extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (ether–hexane (2:3)) to give (2*Z*,4*E*)-8-(pivaloyloxy)-2,4-octadienol (942 mg, 93%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.20 (s, 9 H), 1.52 (b s, 1 H), 1.75 (tt, J = 7.0, 6.5 Hz, 2 H), 2.20 (b dt, J = 7.0, 7.0 Hz, 2 H), 4.07 (t, J = 6.5 Hz, 2 H), 4.30 (dd, J = 7.0, 1.2 Hz, 2 H), 5.53 (b dt, J = 11.0, 7.0 Hz, 1 H), 5.74 (dt, J = 15.1, 7.0 Hz, 1 H), 6.07 (b dd, J = 11.0, 11.0 Hz, 1 H), 6.34 (dddt, J = 15.1, 11.0, 1.2, 1.2 Hz, 1 H); IR (neat) 3400, 3030, 2970, 1725, 1650, 1480, 1280, 1160 cm^{-1}; MS m/z 226 (M^+), 208 (M^+ – H_2O), 169 (M^+ – ^{t}Bu), 124 (M^+ – ^{t}BuCOOH), 57 (b p, ^{t}Bu); HRMS (M^+) calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1540.

***tert*-Butyl *N*-[(2*Z*,4*E*)-8-(Pivaloyloxy)-2,4-octadienyl]-*N*-(*p*-toluenesulfonyl)carbamate.** To a stirred solution of (2*Z*,4*E*)-8-(pivaloyloxy)-2,4-octadienol (97 mg, 0.43 mmol), TsNHBOC (174 mg, 0.64 mmol), and PPh_3 (168 mg, 0.64 mmol) in THF (5 mL) was added DEAD (0.1 mL, 0.63 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h, and quenched by the addition of H_2O. The aqueous layer was extracted with ether, and the combined ether extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate–hexane (1:7)) to give *tert*-butyl *N*-[(2*Z*,4*E*)-8-(pivaloyloxy)-2,4-octadienyl]-*N*-(*p*-toluenesulfonyl)carbamate (189 mg, 92%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.20 (s, 9 H), 1.34 (s, 9 H), 1.71–2.04 (m, 2 H), 2.19–2.27 (m, 2 H), 2.43 (s, 3 H), 4.07 (t, J = 6.4 Hz, 2 H), 4.60 (dd, J = 7.1, 1.0 Hz, 2 H), 5.42 (b dt, J = 11.0, 7.1 Hz, 1 H), 5.78 (dt, J = 14.9, 7.0 Hz, 1 H), 6.12 (b dd, J = 11.0, 11.0 Hz, 1 H), 6.52 (dddt, J = 14.9, 11.0, 1.0, 1.0 Hz, 1 H); IR (neat) 3040, 2990, 1725, 1650, 1600, 1480, 1380, 1280, 1155 cm^{-1}; MS m/z 423 (M^+ – CH_2=CMe_2), 321, 224, 106 (b p), 57 (^{t}Bu); HRMS (M^+ – CH_2=CMe_2) calcd for $C_{21}H_{29}O_6NS$ 423.1716, found 423.1744.

***tert*-Butyl *N*-[(2*Z*,4*E*)-8-(Pivaloyloxy)-2,4-octadienyl]-carbamate (10).** To a stirred solution of *tert*-butyl *N*-[(2*Z*,4*E*)-8-(pivaloyloxy)-2,4-octadienyl]-*N*-(*p*-toluenesulfonyl)-carbamate (137 mg, 0.29 mmol) and sodium dihydrogen phosphate (1.70 g, 14.2 mmol) in methanol (7 mL) was added 5% Na–Hg (3.30 g, 7.17 mmol) at 0 °C, and the reaction mixture was stirred for 0.5 h at the same temperature, quenched by the addition of H_2O, stirred for 15 min, and filtered through a pad of Celite. After evaporation of methanol, the aqueous layer was extracted with ether. The combined ether extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate–hexane (1:7)) to give **10** (85 mg, 91%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.20 (s, 9 H), 1.45 (s, 9 H), 1.60–1.87 (m, 2 H), 2.09–2.31 (m, 2 H), 3.87 (dd, J = 7.1, 7.1 Hz, 2 H), 4.07 (t, J = 6.3 Hz, 2 H), 4.50 (b s, 1 H), 5.32 (dd, J = 10.4, 7.1 Hz, 1 H), 5.72 (dt, J = 14.8, 6.9 Hz, 1 H), 6.03 (dd, J = 11.0, 10.4 Hz, 1 H), 6.34 (dd, J = 14.8, 11.0 Hz, 1 H); IR (neat) 3370, 2990, 1730, 1710, 1520, 1480, 1365, 1160 cm^{-1}; MS m/z 325 (M^+), 269 (M^+ – CH_2=CMe_2), 225 (M^+ – ^{t}BuCOOH), 209 (M^+ – NHBoc), 167 (M^+ – OPv – ^{t}Bu), 106 (b p), 57 (^{t}Bu); HRMS (M^+ – CH_2=CMe_2) calcd for $C_{14}H_{23}O_4N$ 269.1627, found 269.1652.

***tert*-Butyl *N*-[4-[(*tert*-Butyldimethylsilyl)oxy]butyl]-*N*-((*Z*)-2,4-pentadienyl)carbamate.** To a stirred suspension of KH (136 mg, 3.40 mmol) in THF (3 mL) was added **7** (500 mg, 2.73 mmol) in THF (1.5 mL) at 0 °C, and the reaction mixture was stirred for 0.5 h at room temperature. To this resulting suspension was then added 4-[(*tert*-butyldimethylsilyl)oxy]butyl iodide[4] (1.00 g, 3.18 mmol) in THF (1.5 mL) at 0 °C, and the whole reaction mixture was stirred for 12 h at room temperature, quenched by the addition of saturated aqueous NH_4Cl (0 °C), and extracted with ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (ether–hexane (1:12)) to give *tert*-butyl *N*-[4-[(*tert*-butyldimethylsilyl)oxy]butyl]-*N*-((*Z*)-2,4-pentadienyl)carbamate (826 mg, 82%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 1.45 (s, 9 H), 1.51–1.56 (m, 4 H), 3.17 (t, J = 6.8 Hz, 2 H), 3.61 (t, J = 7.1 Hz, 2 H), 4.00 (d, J = 7.1 Hz, 2 H), 5.17 (dd, J = 10.8, 1.0 Hz, 1 H), 5.24 (dd, J = 16.8, 1.0 Hz, 1 H), 5.43 (b dt, J = 10.8, 7.1 Hz, 1 H), 6.09 (dd, J = 10.8, 10.8 Hz, 1 H), 6.64 (dddd, J = 16.8, 10.8, 10.1, 1.0 Hz, 1 H); IR (neat) 3050, 2940, 2860, 1695, 1595, 1480, 1415, 1365, 1250, 1170, 1100 cm^{-1}; MS m/z 369 (M^+), 313 (M^+ – CH_2=CMe_2), 256 (M^+ – CH_2=CMe_2 – ^{t}Bu), 212, 82, 67 (b p), 57 (^{t}Bu); HRMS (M^+) calcd for $C_{20}H_{39}O_3SiN$ 369.2700, found 369.2722. Anal. Calcd for $C_{20}H_{39}O_3SiN$: C, 64.99; H, 10.63; N, 3.79. Found: C, 64.98; H, 10.57; N, 3.63.

***tert*-Butyl *N*-(4-Hydroxybutyl)-*N*-((*Z*)-2,4-pentadienyl)carbamate.** To a stirred solution of *tert*-butyl *N*-[4-[(*tert*-butyldimethylsilyl)oxy]butyl]-*N*-((*Z*)-2,4-pentadienyl)carbamate (81 mg, 0.22 mmol) in THF (1 mL) was added TBAF (1 M THF solution, 0.27 mL, 0.27 mmol) at 0 °C, and the reaction mixture was stirred for 45 min at room temperature, quenched by the addition of H_2O, and extracted with ether. The combined ether extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate–hexane (3:2)) to give *tert*-butyl *N*-(4-hydroxybutyl)-*N*-((*Z*)-2,4-pentadienyl)carbamate (56 mg, 100%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 1.51–1.64 (m, 4 H), 3.22 (t, J = 7.1 Hz, 2 H), 3.66 (t, J = 6.2 Hz, 2 H), 3.98 (dd, J = 7.0, 1.2 Hz, 2 H), 5.17 (dd, J = 10.2, 1.8 Hz, 1 H), 5.25 (dd, J = 16.8, 1.8 Hz, 1 H), 5.43 (b dt, J = 11.0, 7.0 Hz, 1 H), 6.10 (b dd, J = 11.1, 11.0 Hz, 1 H), 6.64 (dddd, J = 16.8, 11.1, 10.2, 1.0 Hz, 1 H); IR (neat) 3420, 3040, 2970, 2940, 1690, 1590, 1415, 1380, 1160 cm^{-1}; MS m/z 255 (M^+), 199 (M^+ – CH_2=CMe_2), 154 (M^+ – Boc), 96, 82, 67, 57 (b p, ^{t}Bu); HRMS (M^+) calcd for $C_{14}H_{25}O_3N$ 255.1834, found 255.1822. Anal. Calcd for $C_{14}H_{25}O_3N$: C, 65.85; H, 9.87; N, 5.49. Found: C, 65.91; H, 10.05; N, 5.47.

***tert*-Butyl *N*-(3-Formylpropyl)-*N*-((*Z*)-2,4-pentadienyl)carbamate.** A mixture of *tert*-butyl *N*-(4-hydroxybutyl)-*N*-((*Z*)-2,4-pentadienyl)carbamate (51 mg, 0.20 mmol), MS4A (387 mg) and PCC (129 mg, 0.60 mmol) in CH_2Cl_2 (3 mL) was stirred for 1 h at 0 °C, diluted with ether, and filtered through a pad of Florisil. The filtrate was concentrated to give the residue, which was purified by silica gel column chromatography (ethyl acetate–hexane (1:5)) to afford *tert*-butyl *N*-(3-formylpropyl)-*N*-((*Z*)-2,4-pentadienyl)carbamate (42 mg, 83%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 1.70–1.98 (m, 2 H), 2.46 (t, J = 7.2 Hz, 2 H), 3.22 (t, J = 7.1 Hz, 2 H), 3.97 (d, J = 7.2 Hz, 2

H), 5.20 (dd, J = 10.2, 1.8 Hz, 1 H), 5.27 (dd, J = 16.7, 1.8 Hz, 1 H), 5.43 (b dt, J = 10.5, 7.2 Hz, 1 H), 6.11 (dd, J = 11.1, 10.5 Hz, 1 H), 6.65 (dddd, J = 16.7, 11.1, 10.2, 1.0 Hz, 1 H), 9.78 (t, J = 1.4 Hz, 1 H); IR (neat) 3080, 2970, 2710, 1720, 1685, 1590, 1410, 1360, 1160 cm^{-1}; MS m/z 254 (M^+), 197 ($M^+ - CH_2{=}CMe_2$), 152 ($M^+ - {}^t$Bu), 96, 67, 57 (b p, ^{t}Bu); HRMS (M^+) calcd for $C_{14}H_{24}O_3N$ 254.1756, found 254.1761.

***tert*-Butyl *N*-[(*E*)-5-(Methoxycarbonyl)-4-pentenyl]-*N*-((*Z*)-2,4-pentadienyl)carbamate (11).** A mixture of *tert*-butyl *N*-(3-formylpropyl)-*N*-((*Z*)-2,4-pentadienyl)carbamate (50 mg, 0.20 mmol) and $Ph_3P{=}CHCOOMe$ (197 mg, 0.59 mmol) in benzene (0.4 mL) was stirred for 7 h at room temperature and filtered through a pad of silica gel. The filtrate was concentrated to give the residue, which was purified by silica gel column chromatography (ether–hexane (1:3)) to give 11 (57 mg, 93%) as a colorless oil: ^{1}H NMR (C_6D_6) δ 1.28–1.54 (m, 2 H), 1.44 (s, 9 H), 1.67–1.90 (m, 2 H), 3.01 (t, J = 6.5 Hz, 2 H), 3.42 (s, 3 H), 3.84 (b s, 2 H), 5.04 (b d, J = 10.0 Hz, 1 H), 5.08 (b d, J = 15.5 Hz, 1 H), 5.20–5.48 (m, 1 H), 5.81 (dt, J = 15.5, 1.5 Hz, 1 H), 5.97 (dd, J = 10.0, 10.0 Hz, 1 H), 6.55 (ddd, J = 15.5, 11.0, 10.0 Hz, 1 H), 6.96 (dt, J = 15.5, 6.8 Hz, 1 H); IR (neat) 3070, 2960, 1720, 1690, 1655, 1590, 1410, 1365, 1265, 1160 cm^{-1}; MS m/z 253 ($M^+ - CH_2{=}CMe_2$), 209 ($M^+ - CH_2{=}CMe_2 - CO_2$), 96, 67, 57 (b p, ^{t}Bu); HRMS ($M^+ - CH_2{=}CMe_2$) calcd for $C_{13}H_{19}O_4N$ 253.1314, found 253.1327.

Methyl *N*-[(*E*)-5-(Methoxycarbonyl)-4-pentenyl]-*N*-((*Z*)-2,4-pentadienyl)carbamate (16). To a stirred solution of 11 (31 mg, 0.10 mmol) in CH_2Cl_2 (0.25 mL) was added CF_3COOH (0.1 mL, 1.30 mmol) at 0 °C, and the reaction mixture was stirred for 20 min at room temperature. To this solution was then added diisopropylethylamine (0.5 mL, 2.87 mmol) and methyl chloroformate (15 μL, 0.19 mmol) at 0 °C, and the reaction mixture was stirred for 0.5 h at the same temperature, quenched by the addition of H_2O, and extracted with ether. The combined ether extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate–hexane (1:5)) to give 16 (23 mg, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.61–1.82 (m, 2 H), 2.10–2.32 (m, 2 H), 3.24 (t, J = 7.3 Hz, 2 H), 3.70 (s, 3 H), 3.73 (s, 3 H), 4.02 (d, J = 7.0 Hz, 2 H), 5.21 (dd, J = 10.3, 1.8 Hz, 1 H), 5.27 (dd, J = 16.6, 1.8 Hz, 1 H), 5.37–5.53 (m, 1 H), 5.84 (dt, J = 15.8, 1.5 Hz, 1 H), 6.13 (dd, J = 11.0, 10.3 Hz, 1 H), 6.64 (ddd, J = 16.6, 10.3, 10.3 Hz, 1 H), 6.95 (dt, J = 15.8, 6.7 Hz, 1 H); IR (neat) 3080, 2950, 1720, 1695, 1655, 1475, 1435, 1260 cm^{-1}; MS m/z 267 (M^+), 208 ($M^+ -$ COOMe), 160, 141, 67 (b p); HRMS (M^+) calcd for $C_{14}H_{21}O_4N$ 267.1470, found 267.1496.

General Procedure for the Isomerization. A mixture of butadiene derivatives (0.10 mmol) and (naphthalene)$Cr(CO)_3$ (0.02 mmol) in acetone (1 mL) was degassed through four freeze–pump–thaw cycles, stirred for 4 h at room temperature, and concentrated. The residue was purified by silica gel column chromatography to give dienamine derivatives.

***tert*-Butyl *N*-((1*E*,3*Z*)-1,3-Pentadienyl)carbamate (12).** Colorless solid: yield 94%; ^{1}H NMR (C_6D_6, 80 °C) δ 1.39 (s, 9 H), 1.58 (dd, J = 7.0, 1.8 Hz, 3 H, H_e), 5.20 (b dq, J = 10.7, 7.0 Hz, 1 H, H_d), 5.54 (ddd, J = 13.9, 11.0, 0.8 Hz, 1 H, H_b), 5.60 (b s, 1 H, NH), 5.85 (dddq, J = 11.0, 10.7, 1.0, 0.8 Hz, 1 H, H_c), 6.72 (b dd, J = 13.9, 11.0, Hz, 1 H, H_a); NOE $H_c \rightarrow H_a$ 2%, $H_c \rightarrow H_d$ 8%, $H_e \rightarrow H_b$ 5%, $H_e \rightarrow H_d$ 3%; ^{13}C NMR (C_6D_6) δ 13.24, 28.22, 79.94, 106.49, 121.31, 127.16, 127.76, 152.49; IR (KBr) 3310, 3020, 2980, 1690, 1620, 1510, 1400, 1370, 1290, 1170 cm^{-1}; MS m/z 183 (M^+), 127 ($M^+ - CH_2{=}CMe_2$), 82, 57 (b p, ^{t}Bu); HRMS (M^+) calcd for $C_{10}H_{17}O_2N$ 183.1260, found 183.1245; mp 72.0–75.0 °C.

***tert*-Butyl *N*-Methyl-*N*-((1*E*,3*Z*)-1,3-pentadienyl)carbamate (13).** Colorless oil: yield 89%; ^{1}H NMR (C_6D_6, 80 °C) δ 1.39 (s, 9 H), 1.65 (dd, J = 7.0, 1.8 Hz, 3 H, H_e), 2.83 (s, 3 H), 5.28 (dddq, J = 10.9, 1.0, 1.0, 7.0 Hz, 1 H, H_d), 5.66 (ddd, J = 14.2, 10.9, 1.0 Hz, 1 H, H_b), 6.03 (dddq, J = 10.9, 10.9, 0.8, 1.8 Hz, 1 H, H_c), 7.35 (b d, J = 14.2 Hz, 1 H, H_a); NOE $H_c \rightarrow H_a$ 8%, $H_c \rightarrow H_d$ 7%, $H_e \rightarrow H_b$ 6%, $H_e \rightarrow H_d$ 3%; IR (neat) 3040, 1690, 1645, 1615, 1480, 1355, 1325, 1145 cm^{-1}; MS m/z 197 (M^+), 141 ($M^+ - CH_2{=}CMe_2$), 96, 82, 57 (b p, ^{t}Bu); HRMS (M^+) calcd for $C_{11}H_{19}O_2N$ 197.1416, found 197.1420.

***tert*-Butyl *N*-[(1*E*,3*Z*)-8-(Pivaloyloxy)-1,3-octadienyl]-carbamate (14).** Colorless oil: yield 88%; ^{1}H NMR (C_6D_6, 80 °C) δ 1.22 (s, 9 H), 1.31–1.48 (m, 2 H, H_f), 1.43 (s, 9 H), 1.51–1.66 (m, 2 H), 2.07 (ddt, J = 7.2, 1.5, 7.2 Hz, 2 H, H_e), 4.07 (t, J = 6.5 Hz, 2 H), 5.15 (b dt, J = 10.6, 7.2 Hz, 1 H, H_d), 5.62 (ddd, J = 14.0, 11.0, 1.0 Hz, 1 H, H_b), 5.77 (b d, J = 11.0 Hz, 1 H, NH), 5.88 (b dd, J = 11.0, 10.6 Hz, 1 H, H_c), 6.77 (dd, J = 14.0, 11.0 Hz, 1 H, H_a); NOE $H_a \rightarrow H_c$ 6%, $H_a \rightarrow$ NH 2%, $H_e \rightarrow H_b$ 15%, $H_e \rightarrow H_d$ 5%, $H_e \rightarrow H_f$ 3%; IR (neat) 3350, 3060, 2990, 1730, 1710, 1655, 1620, 1510, 1370, 1290, 1160 cm^{-1}; MS m/z 325 (M^+), 269 ($M^+ - CH_2{=}CMe_2$), 225, 123, 82, 57 (b p, ^{t}Bu); HRMS (M^+) calcd for $C_{18}H_{31}O_4N$ 325.2253, found 325.2226.

***tert*-Butyl *N*-[(*E*)-5-(Methoxycarbonyl)-4-pentenyl]-*N*-((1*E*,3*Z*)-pentadienyl)carbamate (15).** Colorless oil: yield 97%; ^{1}H NMR (C_6D_6, 80 °C) δ 1.40 (s, 9 H), 1.54 (tt, J = 7.5, 7.5 Hz, 2 H), 1.68 (dd, J = 7.0, 2.0 Hz, 3 H, H_e), 1.87 (ddt, J = 7.5, 7.0, 2.0 Hz, 2 H), 3.38 (t, J = 7.5 Hz, 2 H), 3.46 (s, 3 H), 5.29 (dddq, J = 10.8, 1.0, 1.0, 7.0 Hz, 1 H, H_d), 5.76 (ddd, J = 14.4, 10.8, 1.0 Hz, 1 H, H_b), 5.78 (dt, J = 15.7, 2.0 Hz, 1 H), 6.02 (dddq, J = 10.8, 10.8, 0.8, 2.0 Hz, 1 H, H_c), 6.89 (dt, J = 15.7, 7.0 Hz, 1 H), 7.21 (b d, J = 14.4 Hz, 1 H, H_a); NOE $H_c \rightarrow H_a$ 4%, $H_c \rightarrow H_d$ 7%, $H_e \rightarrow H_b$ 7%, $H_e \rightarrow H_d$ 5%; IR (neat) 3090, 2990, 2950, 1725, 1705, 1645, 1615, 1385, 1365, 1265, 1155 cm^{-1}; MS m/z 309 (M^+), 222 ($M^+ - CH_2{=}CMe_2$), 209 ($M^+ - CH_2{=}CMe_2 - CO_2$), 96, 57 (b p, ^{t}Bu); HRMS (M^+) calcd for $C_{17}H_{27}O_4N$ 309.1940, found 309.1953.

Methyl *N*-[(*E*)-5-(Methoxycarbonyl)-4-pentenyl]-*N*-((1*E*,3*Z*)-pentadienyl)carbamate (17). Colorless oil: yield 89%; ^{1}H NMR (C_6D_6, 80 °C) δ 1.49 (tt, J = 7.0, 7.0 Hz, 2 H), 1.67 (dd, J = 7.0, 2.0 Hz, 3 H, H_e), 1.81 (ddt, J = 7.0, 1.6, 7.0 Hz, 2 H), 3.35 (t, J = 7.0 Hz, 2 H), 3.44 (s, 3 H), 3.45 (s, 3 H), 5.30 (dddq, J = 10.6, 1.0, 1.0, 7.0 Hz, 1 H, H_d), 5.77 (dt, J = 15.8, 1.6 Hz, 1 H), 5.77 (ddd, J = 14.3, 10.6, 1.0 Hz, 1 H, H_b), 5.99 (dddq, J = 10.6, 10.6, 0.8, 2.0 Hz, 1 H, H_c), 6.86 (dt, J = 15.8, 7.0 Hz, 1 H), 7.38 (b d, J = 14.3 Hz, 1 H, H_a); NOE $H_c \rightarrow H_a$ 3%, $H_c \rightarrow H_d$ 6%, $H_e \rightarrow H_b$ 6%, $H_e \rightarrow H_d$ 3%; IR (neat) 3080, 2960, 1720, 1710, 1645, 1615, 1440, 1380, 1360, 1260, 1195, 1170 cm^{-1}; MS m/z 267 (M^+) 236 ($M^+ -$ OMe), 180, 154, 141 (b p), 67, 59; HRMS (M^+) calcd for $C_{14}H_{21}O_4N$ 267.1470, found 267.1462.

(4a*S,5*R**,6*R**,8a*R**)-*N*,5-Bis(methoxycarbonyl)-6-methyl-1,2,3,4,4a,5,6,8a-octahydroquinoline (18).** A solution of 17 (11.1 mg, 0.04 mmol) in toluene (1.0 mL) was heated at 210 °C for 3 days and at 240 °C for 4 days in a sealed tube and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate–hexane (1:4)) to give 18 (8.8 mg, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.15 (d, J = 7.7 Hz, 3 H, Me), 1.37–1.73 (m, 4 H, H_c, H_c', H_b, H_b'), 2.18–2.26 (m, 1 H, H_d), 2.33 (dd, J = 3.0, 3.0 Hz, 1 H, H_a), 2.58–2.69 (m, 1 H, H_f), 2.75 (ddd, J = 12.9, 12.9, 3.1 Hz, 1 H, H_a), 3.70 (s, 3 H, COOMe), 3.72 (s, 3 H, COOMe), 4.00 (b d, J = 12.9 Hz, 1 H, H_a'), 4.73–4.77 (m, 1 H, H_i), 5.41 (b d, J = 10.2 Hz, 1 H, H_h), 5.68 (ddd, J = 10.2, 3.0, 3.0 Hz, 1 H, H_g); NOE $H_d \rightarrow H_i$ 5%, $H_d \rightarrow H_c$ or H_c' 2%, $H_e \rightarrow H_f$ 3%, $H_e \rightarrow H_c$ or H_c' 2%, $H_e \rightarrow$ Me 1%, $H_h \rightarrow H_g$ 3%, $H_h \rightarrow H_i$ 2%, $H_h \rightarrow H_a$ 1%; ^{13}C NMR ($CDCl_3$) δ 21.60, 25.02, 26.48, 29.70, 34.75, 39.83, 49.20, 49.89, 52.01, 52.60, 126.33, 133.19, 156.29, 175.49; IR (neat) 3010, 2950, 2850, 1730, 1695, 1645, 1440, 1260, 1185, 1160 cm^{-1}; MS m/z 267 (M^+), 252 ($M^+ -$ Me), 236 ($M^+ -$ OMe), 209 (b p), 208 ($M^+ -$ COOMe), 192, 167, 148, 141, 105, 91, 59, 41; HRMS (M^+) calcd for $C_{14}H_{21}O_4N$ 267.1470, found 267.1442.

(4a*S,5*R**,6*R**,8a*R**)-5-(Hydroxymethyl)-*N*,6-dimethyl-1,2,3,4,4a,5,6,8a-octahydroquinoline (19).** To a solution of 18 (7.0 mg, 0.03 mmol) in Et_2O (0.5 mL) was added $LiAlH_4$ (7.5 mg, 0.20 mmol) at 0 °C, and the reaction mixture was stirred for 1.5 h at room temperature, quenched by the addition of $Na_2SO_4 \cdot 10H_2O$ (0 °C), and stirred for 2 h at room temperature. The precipitate was removed by filtration and washed with ethyl acetate. The combined organic extracts were concentrated to give the residue, which was purified by silica gel column chromatography (ethyl acetate) to afford 19 (3.0 mg, 59%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.09 (d, J = 7.2 Hz, 3 H, Me), 1.37–1.53 (m, 2 H, H_b or H_b', H_c or H_c'), 1.62–1.73 (m, 1 H, H_b or H_b'), 1.78–1.88 (m, 2 H, H_d, H_e), 1.96–2.00 (m, 1 H, H_c or H_c'), 2.10–2.22 (m, 2 H, H_a or H_a', H_f), 2.29 (s, 3 H, NMe), 2.46 (b s, 1 H, H_i), 2.79 (ddd, J = 11.2, 4.0, 4.0 Hz, 1 H, H_a or H_a'), 3.75 (dd, J = 11.1, 3.0 Hz, 1 H, H_j), 3.81 (dd, J = 11.1, 3.0 Hz, 1 H, H_j), 5.66 (dd, J = 10.0, 2.5 Hz, 1 H, H_g), 5.77 (ddd, J = 10.0, 4.7, 2.5 Hz, 1 H, H_h); NOE $H_f \rightarrow H_e$ 1%, $H_f \rightarrow H_j$ 3%, $H_f \rightarrow H_g$ 2%, $H_j \leftrightarrow$ Me, $H_g \leftrightarrow$ Me; IR (neat) 3389, 3020, 2930, 2856, 2773, 1460, 1371, 1074, 1053, 1020 cm^{-1}; MS m/z 196 ($M^+ + 1$), 195 (M^+), 194 ($M^+ - 1$), 180 ($M^+ -$ Me), 178 ($M^+ -$ OH), 164 ($M^+ - CH_2OH$), 123 (b p),

111, 44; HRMS (M^+) calcd for $C_{12}H_{21}ON$ 195.1623, found 195.1601.

Supplementary Material Available: ^1H NMR spectra of 7-19 and intermediates and ^{13}C NMR spectrum of 18 (35 pages). Ordering information is given on any current masthead page.

Manzacidins A-C, Novel Tetrahydropyrimidine Alkaloids from the Okinawan Marine Sponge *Hymeniacidon* sp.

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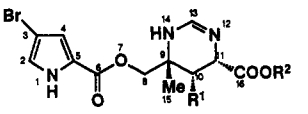
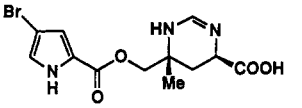
Bromopyrrole alkaloids comprise a typical class of marine natural products, frequently encountered as secondary metabolites of marine sponges of various species.[1] During our studies on bioactive substances from Okinawan marine organisms,[2] we have examined the extracts of numerous marine sponges and isolated several bromopyrrole alkaloids, which were found to be pharmacologically useful as α-adrenoceptor blockers,[3] antagonists of serotonergic receptor,[4] and actomyosin ATPase activators.[5] Recently, we investigated bioactive constituents of another Okinawan sponge *Hymeniacidon* sp. and isolated three novel compounds, named manzacidins A-C (1-3), belonging to an unprecedented class of bromopyrrole alkaloids with an unusual 3,4,5,6-tetrahydropyrimidine ring. Here, we describe the isolation and structure elucidation of 1-3.

The sponge *Hymeniacidon* sp., collected at Manza Beach, Okinawa, was extracted with methanol. The



1 R^1=R^2=H
2 R^1=OH, R^2=H
4 R^1=H, R^2=Me



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methanol extract was dissolved in a mixture of ethyl acetate and water, and then the aqueous layer was extracted with ethyl acetate and 1-butanol. The 1-butanol-soluble fraction was subjected to silica gel flash chromatography with chloroform/1-butanol/acetic acid/water (1.5:6:1:1) followed by reversed-phase HPLC on ODS (acetonitrile/water/trifluoroacetic acid (22:78:0.1)) to give manzacidins A (1; 3.5×10^{-3}% yield, wet weight), B (2; 2.1×10^{-3}%), and C (3; 1.0×10^{-3}%) as colorless oils, concurrently with previously reported bromopyrroles, dibromophakelin,[1d] and debromohymenialdisine.[1i]

Manzacidin A (1) showed a UV maximum at 272 (ϵ 5800) nm, suggestive of the presence of a substituted pyrrole chromophore.[6] A broad IR absorption band was observed at 3600-2800 cm^{-1}, which was attributable to a carboxyl group, and strong IR bands at 1710 and 1685 cm^{-1} were indicative of the presence of carbonyl (conjugated ester and carboxyl) groups. The presence of a carboxylic acid group in 1 was confirmed by the fact that a methyl ester (4) was obtained on treatment of 1 with HCl/MeOH. The positive-ion FABMS of manzacidin A (1) gave prominent quasi-molecular ions at m/z 344 and 346 $(M + H)^+$ with an intensity ratio of ca. 1:1, implying that 1 contains one bromine atom. The molecular formula was established to be $C_{12}H_{14}N_3O_4Br$ by HRFABMS (m/z 344.0251 $(M + H)^+$ for $C_{12}H_{15}N_3O_4{}^{79}Br$, Δ +0.5 mmu). The ^1H and ^{13}C NMR spectra of manzacidin A (1) showed signals characteristic corresponding to a 3-bromopyrrole-5-carboxylic acid derivative moiety (C_5H_3NOBr) (δ_H 12.32 (1 H, br s, exchangeable; NH-1), 7.25 (1 H, br t, H-2), and 6.98 (1 H, br t, H-4); δ_C 124.3 (d, C-2), 96.0 (s, C-3), 117.0 (s, C-4), 121.9 (s, C-5), and 158.6 (s, C-6)[7]). These assignments were fully corroborated by comparison of the NMR data of hymenidin,[4a] sceptrin,[1c] or ageliferin.[5a] The rest of the molecule consisting of $C_7H_{11}N_2O_3$, therefore, remains to be accounted for. Interpretation of the ^1H and ^{13}C NMR data of this part leading to the unusual structure, 3,4,5,6-tetrahydro-4-(hydroxymethyl)-4-methyl-6-pyrimidinecarboxylic acid, was achieved as follows with the aid of extensive application of one- and two-dimensional NMR techniques (DEPT,[8] difference NOE,[9] ^1H-^1H COSY,[10] INEPTNON,[11] HMQC,[12] and HMBC[13] experiments). Seven carbons of this portion of 1 were characterized as

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