C), 147.0 and 146.8 (CH), 144.5, 144.4 and 144.1 (CH), 138.8 and 138.6 (C), 136.5 (C), 132.8 (C), 128.7 (2CH), 128.1 (CH), 128.0 and 127.9 (CH), 127.5 (CH), 127.4 and 127.3 (CH), 126.0 and 125.9 (CH), 125.8 (C), 122.4 and 122.3 (CH), 115.0 and 114.3 (C), 109.0, 108.4, 108.3 and 108.0 (CH), 102.9, 102.8 and 102.6 (CH), 98.0, 97.9, 97.8 and 97.5 (CH), 80.6 and 80.1 (C), 70.3 (CH_2), 61.7, 61.6, 61.0 and 60.7 (CH_2), 47.1, 42.9 and 42.3 (CH_2), 29.6 and 29.2 (CH_2), 28.5 and 28.3 ($3CH_3$), 25.0, 24.9 and 24.7 (CH_2), 18.6, 18.5, 18.0, 17.8 and 17.6 (CH_2); IR (neat) ν_{max} 3066, 3034, 2944, 2873, 1703, 1699, 1694, 1674, 1620, 1593 cm^{-1}; FABHRMS (NBA-CsI) m/e 700.0699 ($M + Cs^+$, $C_{30}H_{34}BrNO_5$ requires 700.0675).

5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-[(tetrahydropyranyloxy)methyl]-1,2-dihydro-3*H*-benz[*e*]indole (10). A solution of **9** (385 mg, 0.678 mmol) and 2,2′-azobis(2-methylpropionitrile) (AIBN, 22.3 mg, 0.136 mmol, 0.2 equiv) in 30 mL of C_6H_6 at 24 °C under Ar was treated with Bu_3SnH (0.38 mL, 1.36 mmol, 2.0 equiv), and the reaction mixture was warmed at reflux for 1 h. The reaction mixture was cooled, and the solvent was removed in vacuo. After azeotropic drying with anhydrous THF (10 mL × 2), chromatography (1.5 × 20-cm Florisil, 200 mesh, 20–40% EtOAc–hexane containing several drops of Et_3N, gradient elution) afforded **10** (324 mg, 332 mg theoretical, 97%) as a pale yellow oil: ^1H NMR ($CDCl_3$, 400 MHz, ppm) 8.31 (d, 1 *H*, *J* = 8 Hz, C6-H), 7.92 (br s, 1 H, C4-H), 7.77 (d, 1 H, *J* = 6 Hz, C9-H), 7.56–7.31 (m, 7 H, C7-H, C8-H, $OCH_2C_6H_5$), 5.29 (br s, 2 H, $OCH_2C_6H_5$), 4.67 and 4.58 (two br m, 1 H, $OCHCH_2$), 4.27–3.37 (m, 7 H, C1-H, C2-H_2, CH_2OTHP, OCH_2CH_2), 1.87–1.53 (m, 15 H, $OC(CH_3)_3$, $OCH_2CH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) 155.5 (C), 152.8 (C), 141.4 (C), 137.0 (C), 130.7 (C), 128.6 (2CH), 127.9 (CH), 127.6 (CH), 127.2 (CH), 127.1 (CH), 123.2 (CH), 122.9 (CH), 122.8 (CH), 122.3 (C), 115.6 (C), 99.9 (CH), 98.5 and 96.5 (CH), 80.6 (C), 70.2 (CH_2), 69.2 (CH_2), 62.6 (CH_2), 52.9 (CH_2), 39.5 and 39.0 (CH), 30.6 (CH_2), 28.5 ($3CH_3$), 25.4 (CH_2), 19.7 (CH_2); IR (neat) ν_{max} 2941, 1699, 1627, 1582, 1517 cm^{-1}; FABHRMS (NBA-CsI) m/e 622.1576 ($M + Cs^+$, $C_{30}H_{34}BrNO_5$ requires 622.1570).

Anal. Calcd for $C_{30}H_{35}NO_5$: C, 73.64; H, 7.21; N, 2.86. Found: C, 73.40; H, 7.23; N, 3.03.

5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-(hydroxymethyl)-1,2-dihydro-3*H*-benz[*e*]indole (11). A solution of **10** (131 mg, 0.267 mmol) in 4 mL of CH_3OH was treated with Amberlyst 15[16] (8.0 mg, 1 mequiv). The reaction mixture was warmed at 45 °C for 6 h. The resin was removed by filtration, and the solvent was concentrated in vacuo. Chromatography (SiO_2, 40–60% EtOAc–hexane gradient elution) afforded **11** (103 mg, 108 mg theoretical, 95%) as a colorless foam identical in all respects to authentic material.[6]

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA 41986 and 55276).

Registry No. 1, 69866-21-3; **2**, 132-86-5; **3**, 90923-79-8; **4**, 139975-98-7; **5**, 122745-36-2; **6**, 122745-37-3; **7**, 129918-05-4; **8**, 129918-06-5; (*E*)-**9**, 139975-99-8; (*Z*)-**9**, 139976-00-4; **10**, 139976-01-5; **11**, 122745-39-5; $BrCH_2CH{=}CMe_2$, 870-63-3; $Ph_3P{=}$CHOTHP, 62209-77-2.

Supplementary Material Available: ^1H NMR spectra of **4** and **7–10** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Enantiogenic Total Syntheses of (−)-Indolizidines (Bicyclic Gephyrotoxins) 205A, 207A, 209B, and 235B via the Intramolecular Diels–Alder Reaction of a Chiral *N*-Acylnitroso Compound

Yuji Shishido and Chihiro Kibayashi*

Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

Received August 12, 1991

A general protocol for the enantiogenic total syntheses of a series of the 5-substituted 8-methylindolizidine class of alkaloids from the arrow poison frog, i.e., (−)-indolizidines **205A** (**1**), **207A** (**2**), **209B** (**3**), and **235B** (**4**), is described, in which a key step is the asymmetric intramolecular Diels–Alder reaction of the chiral *N*-acylnitroso compound **8** leading to the bicyclic oxazinolactam **7** which was utilized as a versatile common chiral intermediate for the preparation of these alkaloids. Subsequent introduction of the C-5 (in future) side chain was elaborated by means of a completely stereocontrolled process involving a Grignard reaction followed by reduction with $NaBH_4$ in acidic media. The bicyclic oxazines **20a**, **24**, and **26** thus obtained were then subjected to reductive N–O bond cleavage followed by cyclodehydration using $PPh_3/CBr_4/Et_3N$, which provided the (−)-enantiomers of the title alkaloids.

Introduction

A number of simple congeneric indolizidine alkaloids, the 5-substituted 8-methylindolizidines, whose mass spectra all show a base peak at m/z = 138, have been detected in extracts of the skins of members of the Dendrobatidae family of neotropical arrow-poison frogs.[1] The base peak arises as the result of the loss of the C-5 side chain from the molecular ion. So far, 18 5-substituted 8-methylindolizidines, which together constitute a new subclass of dendrobatis indolizidine alkaloids, have been found,[1,2] mainly by gas chromatographic–mass spectrometric analysis, to be present in certain dendrobatid frogs. Of these, only four, indolizidines (formerly called bicyclic gephyrotoxins) **205A**[3] (**1**),[4] **207A** (**2**),[2] **235B** (**4**),[4] and **235B′**

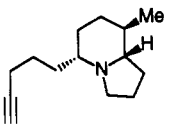
(1) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1, pp 1–274.

(2) Edwards, M. W.; Daly, J. W.; Myers, C. W. *J. Nat. Prod.* **1988**, *51*, 1188.

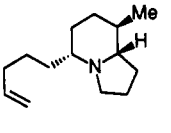
(3) The convention whereby numerical designations are given to dendrobatid alkaloids was originated in 1978 by J. W. Daly's group at the National Institutes of Health. Thus, the identity of an alkaloid is denoted by a series of boldface Arabic numerals (the compound's molecular weight) and a boldface capital letter(s) (a symbol which indicates that the compound is one of two or more isomers). See: Daly, J. W.; Brown, G. B.; Mensah-Dwumah, M.; Myers, C. W. *Toxicon* **1978**, *16*, 163. Daly, J. W. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: Vienna, 1982; Vol. 41, pp 205–340.

0022-3263/92/1957-2876$03.00/0

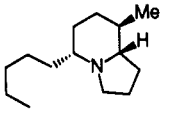
(5),[2] have been isolated in quantities sufficient to permit their further characterization. ^1H and ^{13}C NMR analysis[5] showed that each possesses an equatorial 8-methyl group and an equatorial 5-substituent. That the structures proposed for the four were correct was confirmed when Holms and co-workers[6,7] synthesized the racemates of all four compounds. The absolute configuration of the natural products, however, remained unknown.[8]



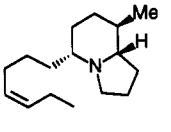
205A (1)



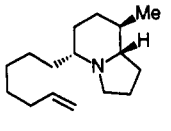
207A (2)



209B (3)



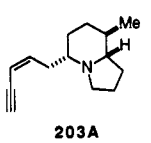
235B (4)



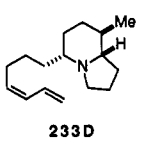
235B' (5)

Holmes et al.[6] also synthesized indolizidine (-)-**209B** (3). Because another group recently described[9] the synthesis of the dextrorotatory enantiomer, the structure of **209B** has been unequivocally established. However, which enantiomer corresponds to the natural product is not known because natural **209B** has not been isolated in quantities sufficient to permit measurement of its optical rotation.

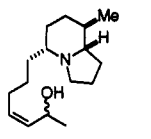
As a result of our work of recent years directed toward the synthesis of optically active dendrobatid alkaloids,[10] we have developed a general method for preparing 5-substituted 8-methylindolizidines. Here we describe in detail enantiogenic synthesis of (-)-indolizidines **205A** (1), **207A** (2), **209B** (3), and **235B** (4).[11,12]



203A



233D



251B

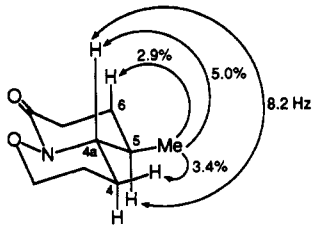


Figure 1. ^1H NMR analysis of 17: the results of NOE experiments (% signal enhancement) and coupling constant (Hz).

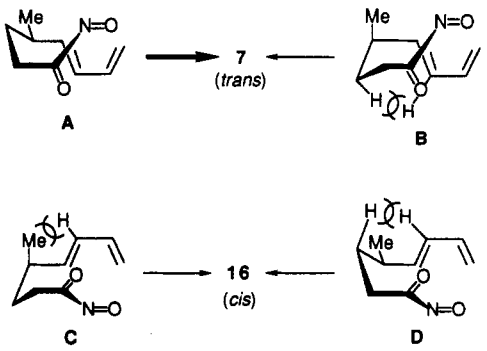
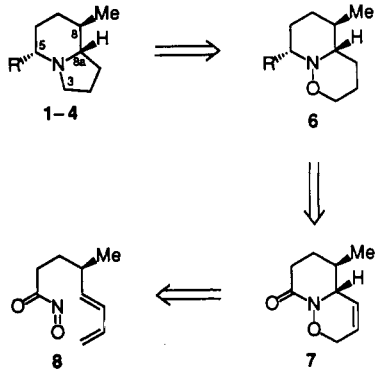


Figure 2.

Scheme I



Our strategy for constructing the molecular framework of the 5-substituted 8-methylindolizidine alkaloids 1–4, one which exploits both the knowledge gained in the course of our earlier work[13] and the results of a retrosynthetic analysis (Scheme I), utilizes, as a key step, the stereoselective intramolecular [4 + 2] cycloaddition of a chiral *N*-acylnitroso compound[14] 8 to form a common precursor,

(4) Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M. W.; Daly J. W. *Tetrahedron* **1987**, *43*, 643.

(5) Very recently, three other 5-substituted 8-methylindolizidines, **203A**, **233D**, and **251B**, were isolated. Their FTIR and ^1H and ^{13}C NMR spectra are consistent with the structures shown below. See: Tokuyama, T.; Tsujita, T.; Shimada, A.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Tetrahedron* **1991**, *47*, 5401.

(6) (a) Smith, A. L.; Williams, S. F.; Holmes, A. B.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Am. Chem. Soc.* **1988**, *110*, 8696. (b) Holmes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393.

(7) Collins, I.; Fox, M. E.; Holmes, A. B.; Williams, S. F. *J. Chem. Soc., Perkin Trans. 1* **1991**, 175.

(8) Subsequent to the submission of this MS for publication, a description of the total synthesis of (-)-**205A** and (-)-**235B**, each of which possesses the absolute configuration of the corresponding natural product, was published. See: Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1991**, *56*, 4868.

(9) Gnecco, D.; Marazano, C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1991**, 625.

(10) (a) Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396. (b) Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1990**, *31*, 3637. (c) Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1991**, *56*, 1386. (d) Machinaga, N.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1991**, 405.

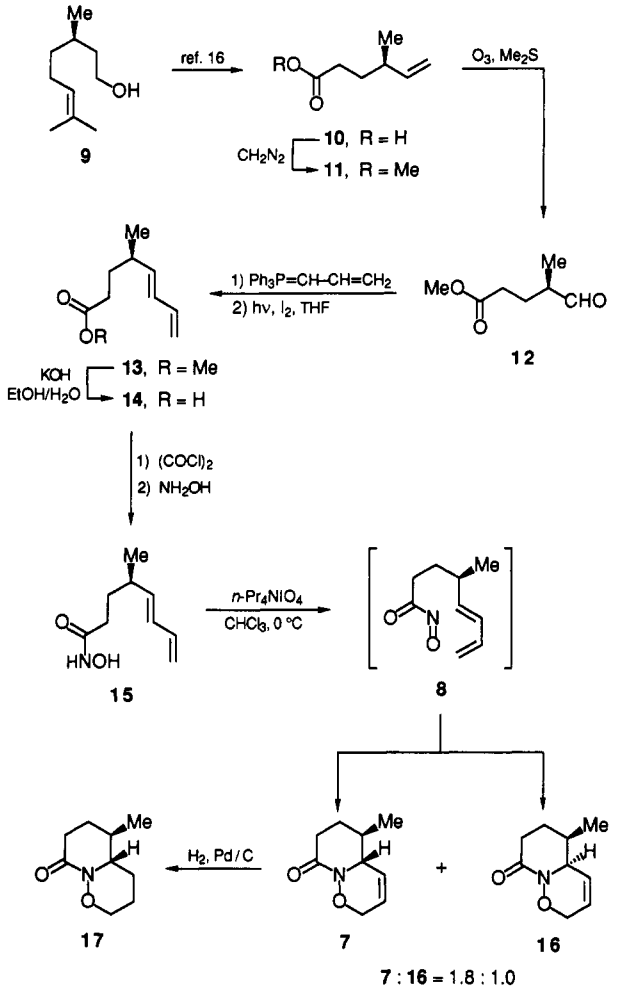
(11) This work was presented at the 109th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1989 (See: *Abstracts of Papers, Part 2*, p 25) and at the 15th Symposium on Progress in Organic Reactions and Syntheses, Kobe, Dec 1989 (See: *Abstracts of Papers*, p 79).

(12) A preliminary report of part of this work has appeared. See: Shishido, Y.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1991**, 1237.

(13) (a) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534. (b) Iida, H.; Watanabe, Y.; Kibayashi, C. *Tetrahedron Lett.* **1986**, *27*, 5513. (c) Watanabe, Y.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, *54*, 4088.

(14) For recent examples of the use of the Diels–Alder reaction of *N*-acylnitroso compounds in the total synthesis of natural products, see: (a) Keck, G. E.; Nickell, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632. (b) Jung, M.; Offenbächer, G.; Retey, J. *Helv. Chim. Acta* **1983**, *66*, 1915. (c) Baldwin, J. E.; Bailey, P. D.; Gallacher, G.; Singleton, K. A.; Wallace, P. M. *J. Chem. Soc., Chem. Commun.* **1983**, 1049. Baldwin, J. E.; Otsuka, M.; Wallace, P. M. *Ibid.* **1985**, 1549. Baldwin, J. E.; Bailey, P. D.; Gallacher, G.; Otsuka, M.; Singleton, K. A.; Wallace, P. M. *Tetrahedron* **1984**, *40*, 3696. Baldwin, J. E.; Otsuka, M.; Wallace, P. M. *Ibid.* **1986**, *42*, 3097. (d) Defoin, A.; Fritz, H.; Geffroy, G.; Streith, J. *Tetrahedron Lett.* **1986**, *27*, 4727. (e) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1988**, *110*, 2341. (f) Aoyagi, S.; Shishido, Y.; Kibayashi, C. *Tetrahedron Lett.* **1991**, *32*, 4325.

Scheme II

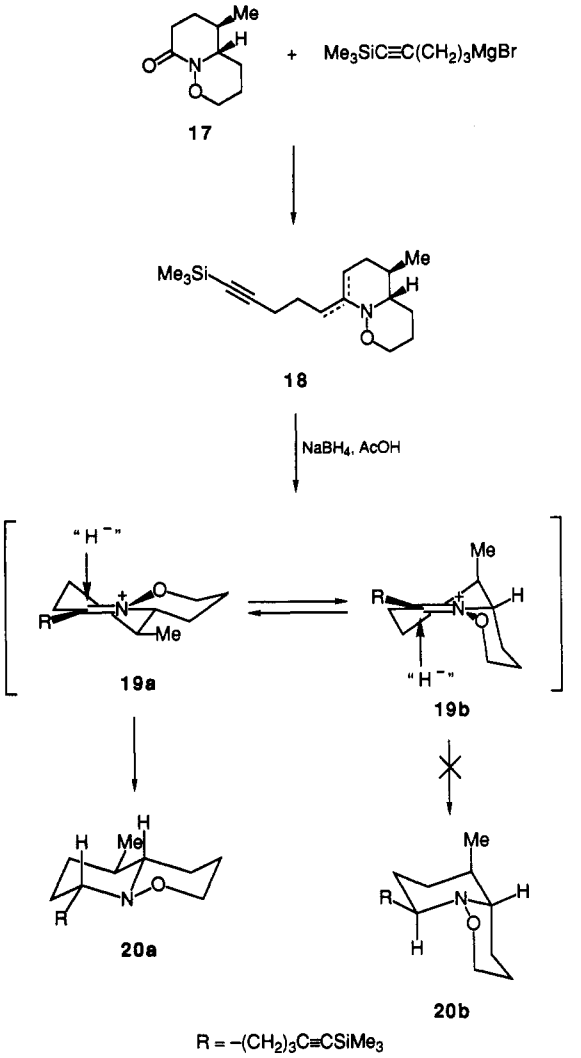


the chiral *trans*-oxazinolactam **7**.

Results and Discussion

The starting point for the synthesis of **7** (Scheme II) was (*R*)-4-methyl-5-hexenoic acid (**10**), which can be prepared from (*R*)-citronellol (**9**)[15] by known procedures.[16] Esterification of **10** by treatment with ethereal diazomethane gave the ester **11**, ozonolysis of which gave the aldehyde **12** in 67% yield overall (two steps). The Wittig reaction of **12** and the ylide generated from allyltriphenylphosphonium bromide gave a mixture of methyl (5*E*)- and (5*Z*)-4-methylocta-5,7-dienoates. The mixture, to which iodine was added, was irradiated with UV light in order to induce isomerization of the (5*Z*)-isomer to the desired (5*E*)-isomer. Workup and chromatographic purification provided **13** in 41% yield. Alkaline hydrolysis of **13** gave the corresponding acid **14** in 92% yield. Treatment of **14** with, successively, oxalyl chloride and hydroxylamine gave the hydroxamic acid **15** in 78% yield overall (two steps). Oxidation of **15** by treatment with tetrapropylammonium periodate at 0 °C generated the *N*-acylnitroso compound **8**, which spontaneously underwent intramolecular [4 + 2] cycloaddition to afford a 1.8:1.0 mixture of *trans*- and *cis*-bicyclic oxazinolactams (**7** and **16**, respectively) in 88% yield.[17] The desired product, **7**, was isolated in a pure state by column chromatography of the mixture on silica gel and subsequent recrystallization.[18]

Scheme III



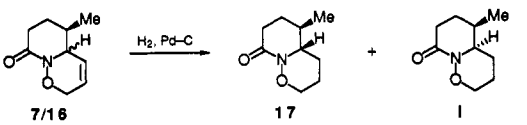
The stereochemistry of **7** was inferred from the 500-MHz ^{1}H NMR spectrum of the dihydro derivative **17** obtained by the catalytic hydrogenation (10% Pd/C) of **7**. The 2D NOESY spectrum of **17** and the results of difference NOE experiments (Figure 1) established that the 5-methyl group is cis to the angular proton at C-4a. Furthermore, the magnitude of the coupling constant (J = 8.2 Hz) of the signals due to the protons at C-4a and C-5 showed that the

(15) A sample of **9** was kindly provided by Takasago International Co. It can be prepared from commercially available (*R*)-pulegone in three steps. See: Plesek, *J. Chem. Listy.* **1956**, *50*, 1854. Lukes, R.; Zabacova, A.; Plesek, J. *Croat. Chem. Acta* **1957**, *29*, 201.

(16) Cernigliaro, G. J.; Kocienski, P. J. *J. Org. Chem.* **1977**, *42*, 3622. Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. P. *J. Am. Chem. Soc.* **1982**, *104*, 4708.

(17) The ratio of **7** to **16** in the product mixture was calculated from the integrals of the ^{1}H NMR signals due to the respective C-5 methyl protons, which resonated at δ 1.12 (d, J = 6.4 Hz) in the case of **7** and δ 1.00 (d, J = 7.1 Hz) in the case of **16**.

(18) Hydrogenation (10% Pd/C) of the mixture of cycloadducts **7** and **16** gave a mixture of *trans*- and *cis*-oxazinolactams (**17** and **i**, respectively) which could be separated by silica gel chromatography (*i*-Pr_2O/acetone (2:1)). **i**: Colorless prisms; mp 85–86 °C (*i*-Pr_2O/hexane); $[\alpha]^{26}_D$ −88.3° (*c* 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.00 (3 H, d, J = 7.0 Hz), 1.50 (1 H, dq, J = 12.6, 4.5 Hz), 1.59–1.67 (2 H, m), 1.69–1.77 (1 H, m), 1.80–1.88 (1 H, m), 2.01 (1 H, dtt, J = 13.7, 12.6, 4.7 Hz), 2.16–2.35 (1 H, m), 2.42 (1 H, dd, J = 6.4, 1.6 Hz), 2.45 (1 H, d, J = 6.4 Hz), 3.78 (1 H, ddd, J = 12.0, 5.7, 2.7 Hz), 3.89 (1 H, ddd, J = 12.6, 11.5, 2.5 Hz), 4.10 (1 H, ddt, J = 11.5, 5.0, 1.3 Hz). Compound **i** is less polar than **17** (for data, see Experimental Section).



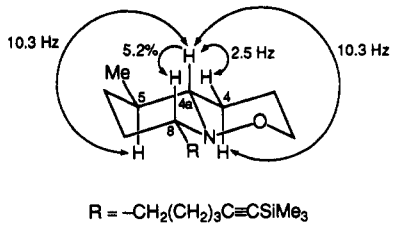


Figure 3. ^{1}H NMR analysis of **20a**: the results of NOE experiments (% signal enhancement) and coupling constants (Hz).

two are trans to each other, which is in accord with structure **17**.

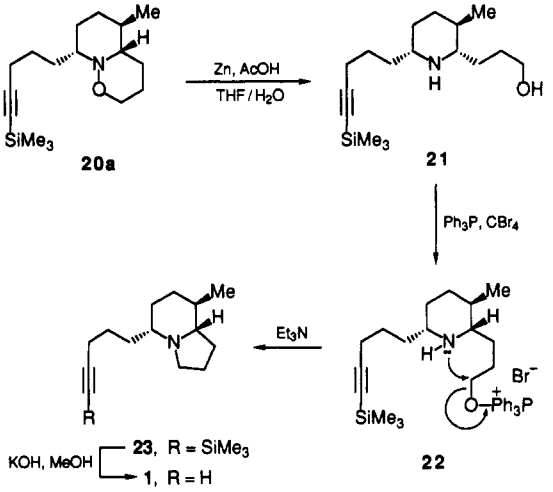
That the *trans*-oxazinolactam **7** is the major product of intramolecular [4 + 2] cycloaddition can be rationalized as being the result of preferential reaction by way of one of four possible transition states (Figure 2),[19] each of which permits secondary interactions between the orbitals of the carbonyl group and those of the diene system and leads to a product of endo addition. There exist two possible boatlike transition states (A and C) and two possible chairlike transition states (B and D). In the latter two, B and D, which would lead to the trans adduct **7** and the cis adduct **16**, respectively, unfavorable nonbonded interactions occur. Of the two boatlike transition states, A and C, the latter, which would lead to the cis adduct **16**, is disfavored due to the occurrence of allylic strain ($A^{(1,3)}$ strain).[20] Thus, reaction by way of the former, which leads to the trans adduct **7**, should be preferred.

Next, an alkynyl side chain was stereospecifically introduced at C-8 of the oxazinolactam **17** (the future C-5 of indolizidine **205A**) (Scheme III). Thus, the Grignard reaction of **17** with 5-(trimethylsilyl)-4-pentynylmagnesium bromide in diethyl ether afforded the unstable enamine **18** as a ca. 1:1 equilibrium mixture of geometric isomers. No attempt was made to separate the two. The mixture was immediatedly treated with $NaBH_4$ under acidic conditions (AcOH). A single product, **20a** (65% yield overall from **17**), was isolated. The results (summarized in Figure 3) of its analysis by 500-MHz ^{1}H NMR spectroscopy and 2D NOESY showed that **20a** possessed the desired structural feature, i.e., an equatorial alkynyl group at C-8.

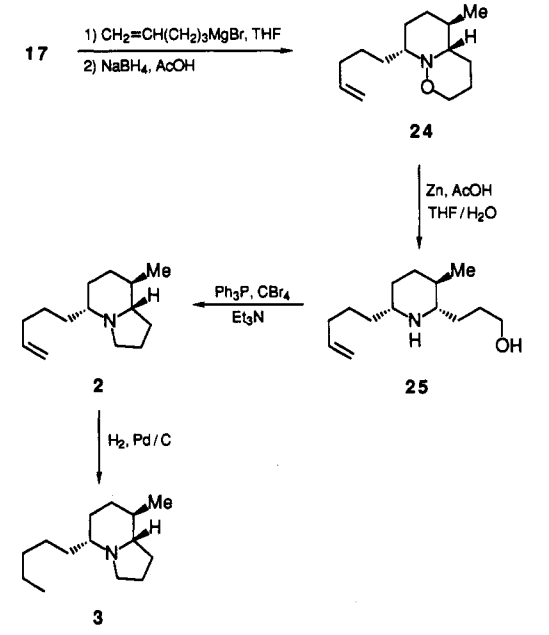
The exclusive formation of **20a** can be rationalized as being the result of a stereoelectronically controlled addition of hydride ion to the transient iminium ion **19**, which is generated from **18** under acidic conditions (Scheme III). There are two possible kinetically preferred chairlike transition states, **19a** and **19b** (which would lead to **20a** and **20b**, respectively), in which maximum orbital overlap with respect to the hydride ion and the developing lone pair on nitrogen would be maintained.[21] Reaction by way of **19a**, in which "topside" attack (β-attack) by hydride ion on **19a** occurs, would be favored because the nucleophile would encounter less steric hindrance. Reaction by way of **19a** would yield **20a**, which is, in fact, the product of reduction. A similar argument can be used to rationalize the formation of **24** and **26** (see below).

Compound **20a** was then converted to (−)-indolizidine **205A** (**1**) (Scheme IV). Cleavage of the N–O bond of **20a**, by treatment with zinc in aqueous acetic acid, gave **21** in 90% yield (Scheme IV). Upon exposure, at 0 °C, to Ph_3P/CBr_4 and then to triethylamine, **21** smoothly underwent intramolecular cyclodehydration via the alkoxyphosphonium salt **22**.[22] The reaction was complete within 40 min and afforded the cyclic product **23** in 73% yield. Removal of the trimethylsilyl group from **23** by treatment with alkali provided the desired product, **1**. The spectra (^{1}H and ^{13}C NMR, MS) of the synthetic material were identical to those of natural **205A**[4] and also to those reported for synthetic racemic **205A**.[7] Also, the specific rotation of **1**, $[\alpha]^{20}_D$ −74.2° (MeOH), was of the same sign as that reported for natural **205A** [lit.[4] $[\alpha]_D$ −35° (MeOH)].[23] The results indicated that natural **205A** is (5*R*,8*R*,8a*S*)-(−)-**1**.

Scheme IV



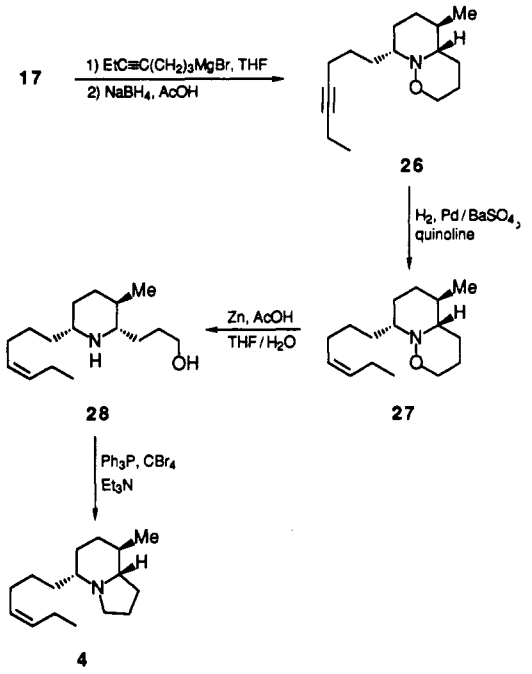
Scheme V



From these results, we concluded that the oxazinolactam **17** could also serve as the key precursor in syntheses of both (−)-**207A** (**2**) and (−)-**209B** (**3**) (Scheme V). Thus, treatment of **17** with, successively, 1-pent-4-enylmagnesium bromide in THF and $NaBH_4$/AcOH, in the same pot, yielded a single product, **24** (71% yield overall from **17**). Reductive cleavage of the N–O bond of **24** (Zn/aq AcOH) yield the amino alcohol **25**, intramolecular cyclodehydration of which, upon treatment with $PPh_3/CBr_4/Et_3N$, gave (−)-indolizidine **207A** (**2**) (73% yield overall

(19) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187.
(20) Johnson, F., *Chem. Rev.* **1968**, *68*, 375. Hoffman, R. W. *Ibid.* **1989**, *89*, 1841.
(21) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032. Stevens, R. V. In *Strategies and Tactics in Organic Synthesis*; Lindberg T.; Academic Press: Orlando, FL, 1984; Chapter 10, pp 275–298.
(22) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801.
(23) Subsequent to the submission of this paper for publication, a specific rotation of $[\alpha]_D$ −83.5° (*c* 0.30, MeOH) was reported for (−)-**205A**.[8]

Scheme VI



from **24**). Conversion of the 1-pent-4-enyl side chain of **2** to a propyl group by catalytic hydrogenation (10% Pd/C) provided, in 93% yield, (−)-indolizidine **209B** (**3**). The spectra (^{1}H and ^{13}C, MS) and specific rotation of **3** were in good agreement with those of (−)-**209B** prepared by Holms et al.[7]

We then applied the methodology outlined above to the synthesis of (−)-indolizidine **235B** (**4**) (Scheme VI). A 1-hept-4-ynyl side chain was introduced at C-8 of **17** by adding 1-hept-4-ynylmagnesium bromide to the C-8 carbonyl group. Reduction ($NaBH_4$/AcOH) of the mixture of enamines so formed produced **26** (70% yield overall from **17**). Catalytic hydrogenation (Lindlar catalyst) of **26** gave **27**, which bears the required (4*Z*)-1-hept-4-enyl side chain at C-8. Reductive cleavage of the N–O bond of **27** afforded **28** (87% yield overall from **26**). Intramolecular cyclodehydration of **28** (PPh_3/CBr_4/Et_3N) gave (−)-indolizidine **235B** (**4**) in 70% yield.

The ^{1}H and ^{13}C NMR spectra of **4** were identical to those of the natural alkaloid[4] and also to those of synthetic racemic **235B**.[7] However, somewhat surprisingly, the specific rotation, $[\alpha]^{28}_D$ −85.4° (MeOH),[24] of **4** was different, both in magnitude and sign, from that [$[\alpha]_D$ + 11.3° (MeOH)] reported[4] for natural **235B**. The synthetic (−)-indolizidines **205A** (**1**), **207A** (**2**), and **209B** (**3**) described above are all (5*R*,8*R*,8a*S*)-isomers and are levorotatory. Natural **235B′** (**5**) and the recently isolated[5] **203A** and **233D** are also levorotatory[25] as is natural **205A**. These facts suggest that naturally occurring 8-methylindolizidines whose C-5 side chain does not incorporate an asymmetric carbon are all (5*R*,8*R*,8a*S*)-isomers and are all levororatatory. Thus, natural **235B** *should* be levorotatory.[26] The discrepancy between the optical rotation of the synthetic **235B** described here and that of natural **235B** may be the result of contamination of the sample of natural material by a dextrorotatory impurity.

(24) Subsequent to the submission of this paper for publication, a specific rotation of $[\alpha]_D$ −73.4° (*c* 1, MeOH) was reported for (−)-**235B**.[8]

(25) The following specific rotations have been reported: **235B′**, $[\alpha]^{25}_D$ −61° (MeOH);[2] **203A**, $[\alpha]_D$ −23.3° (*c* 0.30, $CHCl_3$);[5] **233D**·HCl, $[\alpha]_D$ −3.4° (*c* 0.16, MeOH).[5]

(26) Polniaszck et al.[8] have also asserted that the absolute configuration of natural **235B** should be 5*R*,8*R*,8a*S*.

Enantiogenic syntheses of the (−)-indolizidines **205A**, **207A**, **209B**, and **235B** have thus been achieved. The pharmacological activity of each as a noncompetitive blocker of nicotinic receptor channels has been determined.[27] The syntheses described here, which use the intramolecular Diels–Alder reaction of a chiral *N*-acylnitroso compound to construct the key precursor, demonstrate the versatility of our methodology, which should prove applicable to the synthesis of other members of that subclass of dendrobatid alkaloids known as the 5-substituted 8-methylindolizidines.

Experimental Section

General Procedures. Optical rotations were measured with a digital polarimeter (a 1-dm cell was used in all cases). IR spectra were recorded with an FTIR instrument. ^{1}H NMR spectra were recorded at either 400 or 500 MHz. ^{13}C NMR spectra were recorded at either 100 or 125 MHz. $CHCl_3$ (δ 7.26) and $CDCl_3$ (δ 77.1) served as the respective internal standards. Mass spectra were recorded at an ionization voltage of 70 eV. Merck silica gel 60 (230–400 mesh) was used for column chromatography. Microanalyses were performed by the Microanalytical Laboratory of the Tokyo College of Pharmacy.

Methyl (4*R*)-4-Methyl-5-hexenoate (11). To a cold (0 °C) stirred solution of (*R*)-4-methyl-5-hexenoic acid (**10**) (5.20 g, 40.6 mmol) in Et_2O (20 mL) was added excess ethereal CH_2N_2. After 20 min, the excess CH_2N_2 was destroyed by adding AcOH. The solution was then washed (saturated aqueous $NaHCO_3$, water) and dried ($MgSO_4$). Evaporation of the solvent and distillation of the residue afforded **11** (5.11 g, 88%): a colorless oil; bp 60–61 °C/18 mmHg; $[\alpha]^{27}_D$ −14.4 (*c* 2.11, $CHCl_3$); IR (neat) 2956, 1742, 1640, 1437, 1376, 1325, 1259, 1175, 997, 915 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.01 (3 H, d, *J* = 6.7 Hz), 1.54–1.71 (2 H, m), 2.08–2.18 (1 H, m), 2.29 (2 H, ddd, *J* = 8.7, 6.9, 5.1 Hz), 3.65 (3 H, s), 4.95 (1 H, ddd, *J* = 10.2, 1.7, 0.8 Hz), 4.97 (1 H, ddd, *J* = 17.3, 1.7, 1.2 Hz), 5.63 (1 H, ddd, *J* = 17.3, 10.2, 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 20.2, 31.5, 32.0, 37.6, 51.5, 113.7, 143.5, 174.3; MS *m*/*z* (rel intensity) 142 (M^+, 5), 127 (6), 110 (43), 82 (58), 74 (86), 55 (100); HRMS calcd for $C_8H_{14}O_2$ (M^+) 142.0993, found 142.0990.

Methyl (4*R*)-4-Methyl-5-oxopentanoate (12). Ozone was bubbled through a cold (−65 °C) stirred mixture of **11** (15.0 g, 105 mmol), MeOH (220 mL), and $NaHCO_3$ (500 mg) for 22 h. Ar was then bubbled through the mixture to expel unreacted O_3. Dimethyl sulfide (19.7 g, 317 mmol) was added. The mixture was stirred at rt for 15 h, and then it was filtered. The filtrate was concentrated. Water (50 mL) was added to the residue, and the whole was extracted with Et_2O. The extract was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc (30:1)) to give **12** (11.5 g, 76%): a colorless oil; $[\alpha]^{24}_D$ +3.03° (*c* 4.43, $CHCl_3$); IR (neat) 2956, 2720, 2361, 1737, 1438, 1376, 1258, 1176 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13 (3 H, d, *J* = 7.4 Hz), 1.69 (1 H, dt, *J* = 14.3, 7.5 Hz), 2.06 (1 H, dt, *J* = 14.3, 7.5 Hz), 2.37 (2 H, t, *J* = 7.5 Hz), 2.40 (1 H, dtt, *J* = 14.0, 7.0, 1.6 Hz), 3.67 (3 H, s), 9.62 (1 H, d, *J* = 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 13.3, 25.5, 31.3, 45.6, 51.7, 173.6, 204.1.

Methyl (4*R*,5*E*)-4-Methyl-5,7-octadienoate (13). To a cold (0–5 °C) stirred suspension of allyltriphenylphosphonium bromide (21.7 g, 56.6 mmol) in Et_2O (370 mL) under Ar was slowly added *n*-BuLi (36 mL of a 1.6 M solution in hexane, 58 mmol). The mixture was allowed to warm to rt. To the resulting orange-red solution was added, drop-by-drop, a solution of **12** (6.80 g, 47.2 mmol) in Et_2O (90 mL). Two h later, water (15 mL) was added. The two liquid layers were separated. The organic layer was dried ($MgSO_4$) and concentrated. The semisolid residue was suspended in 2:1 pentane/Et_2O (400 mL). The suspension was filtered through a pad of silica gel to remove a small quantity of solid Ph_3PO. The filtrate was concentrated. The residue was dissolved in THF (150 mL). To the solution was added I_2 (5 mg). The

(27) Daly, J. W.; Nishizawa, Y.; Padgett, W. L.; Tokuyama, T.; Smith, A. L.; Holmes, A. B.; Kibayashi, C.; Aronstam, R. S. *Neurochem. Res.* **1991**, *16*, 1213.

solution was then irradiated through a Pyrex filter with the UV light from a 100-W high-pressure Hg lamp for 1 h. Concentration of the solution gave an oil, which was purified by column chromatography on silica gel (hexane/EtOAc (150:1) then (80:1)) to give **13** (3.24 g, 41%): a colorless oil; $[\alpha]^{26}_D$ -22.2° (*c* 2.33, $CHCl_3$); IR (neat) 2956, 1741, 1651, 1605, 1437, 1325, 1176, 1006, 900, 855 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (3 H, d, *J* = 6.8 Hz), 1.56–1.73 (2 H, m), 2.13–2.23 (1 H, unresolved), 2.29 (2 H, ddd, *J* = 8.7, 6.9, 4.2 Hz), 3.65 (3 H, s), 4.98 (1 H, dd, *J* = 10.3, 1.2 Hz), 5.11 (1 H, dd, *J* = 17.1, 1.2 Hz), 5.52 (1 H, dd, *J* = 15.2, 8.0 Hz), 6.02 (1 H, ddd, *J* = 15.2, 10.3, 0.7 Hz), 6.29 (1 H, dt, *J* = 17.1, 10.3 Hz); ^{13}C NMR ($CDCl_3$) δ 20.4, 31.8, 32.1, 36.5, 51.5, 115.4, 130.3, 137.2, 139.7, 174.3; MS *m*/*z* (rel intensity) 168 (M^+, 5), 108 (13), 93 (28), 81 (54), 79 (100), 78 (42), 67 (36); HRMS calcd for $C_{10}H_{16}O_2$ (M^+) 168.1150, found 168.1180.

(4*R*,5*E*)-4-Methyl-5,7-octadienoic Acid (14). A mixture of **13** (5.15 g, 30.6 mmol), KOH (4 g), and 95:5 EtOH/water (12(mL) was refluxed for 1h. The mixture was cooled and concen trated in vacuo. The residue was dissolved in water (100 mL). The solution was washed with Et_2O (30 mL), and then it was neutralized by adding 5 N aqueous HCl. The neutral solution was extracted with Et_2O (4 × 50 mL). The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc (20:1)) to give **14** (4.36 g, 92%): a colorless oil; $[\alpha]^{25}_D$ -27.0° (*c* 1.97, $CHCl_3$); IR (neat) 2956, 1713, 1651, 1605, 1456, 1416, 1280, 1216, 1086, 1005, 953, 901 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (3 H, d, *J* = 6.7 Hz), 1.57–1.75 (2 H, m), 2.16–2.27 (1 H, unresolved), 2.34 (2 H, ddd, *J* = 8.7, 6.7, 5.1 Hz), 4.99 (1 H, dd, *J* = 10.4, 1.2 Hz), 5.12 (1 H, dd, *J* = 17.2, 1.2 Hz), 5.52 (1 H, dd, *J* = 15.2, 8.2 Hz), 6.04 (1 H, dd, *J* = 15.2, 10.4 Hz), 6.29 (1 H, dt, *J* = 17.2, 10.4 Hz); ^{13}C NMR ($CDCl_3$) δ 20.4, 31.6, 32.0, 36.4, 115.6, 130.5, 137.1, 139.4, 179.8; MS *m*/*z* (rel intensity) 155 (M^+ + 1, 4), 154 (M^+, 38), 109 (6), 94 (61), 81 (92), 79 (100), 67 (21); HRMS calcd for $C_9H_{14}O_2$ (M^+) 154.0993, found 154.1011. Anal. Calcd for $C_9H_{14}O_2$: C, 70.08; H, 9.16. Found: C, 69.93; H, 9.35.

(4*R*,5*E*)-*N*-Hydroxy-4-methyl-5,7-octadienamide (15). To a cold (0 °C) stirred solution of **14** (2.50 g, 16.2 mmol) in CH_2Cl_2 (60 mL) was added oxalyl chloride (8.00 g, 63.0 mmol). The mixture was allowed to warm to rt and was kept there for 1.5 h, and then it was concentrated in vacuo to give the crude acid chloride. In the meantime, hydroxylamine hydrochloride (1.47 g, 21.1 mmol) was dissolved in a mixture of $CHCl_3$ (30 mL) and an aqueous solution (30 mL) of Na_2CO_3 (3.02 g, 28.5 mmol). The mixture was cooled (0 °C), and with stirring, a solution of the crude acid chloride in $CHCl_3$ (40 mL) was added drop-by-drop. The mixture was allowed to warm to rt and was kept there for 2.5 h, and then it was neutralized by adding 10% aqueous HCl. The two liquid phases that formed were separated. The aqueous phase was extracted with $CHCl_3$ (4 × 50 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The residual oil was purified by column chromatography on silica gel (hexane/EtOAc (40:1)) to give **15** (2.12 g, 85%): a pale yellow oil; $[\alpha]^{24}_D$ -18.5° (*c* 0.67, $CHCl_3$); IR (neat) 3219, 2966, 1738, 1646, 1435, 1375, 1240, 1006, 976, 900, 757, 617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02, (3 H, d, *J* = 6.6 Hz), 1.43–1.64 (1 H, br m), 1.66–1.84 (1 H, br m), 1.99–2.27 (3 H, br m), 5.00 (1 H, d, *J* = 10.2 Hz), 5.12 (1 H, dd, *J* = 17.0, 0.9 Hz), 5.50 (1 H, dd, *J* = 15.2, 8.1 Hz), 6.02 (1 H, dd, *J* = 15.2, 10.2 Hz), 6.28 (1 H, dt, *J* = 17.0, 10.2 Hz), 8.57 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 20.5, 30.9, 32.1, 36.5, 115.7, 130.6, 137.1, 139.4, 171.6; MS *m*/*z* (rel intensity) 169 (M^+, 10), 152 (14), 134 (16), 109 (27), 95 (74), 81 (74), 79 (100), 75 (88), 67 (82); HRMS calcd for $C_8H_{12}NO_2$ (M^+ - CH_3) 154.0867, found 154.0901.

(4a*R*)-5-Methyl-2,4a,6,7-tetrahydropyrido[1,2-*b*][1,2]oxazin-8(2*H*)-one (7). To a cold (0 °C) stirred solution of tetrapropylammonium periodate (7.18 g, 19.0 mmol) in $CHCl_3$ (380 mL) was slowly added a solution of **15** (2.83 g, 16.7 mmol) in $CHCl_3$ (220 mL). The mixture was stirred for 1 h at 0 °C, and then it was washed, successively, with 5% aqueous $Na_2S_2O_3$, 5% aqueous KOH, and brine. The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$) to give a 1.8:1.0 mixture of **7** and **16** (2.47 g, 88%) as a colorless semisolid. Compound **7** was separated from the oily cis adduct **16** by column chromatography on silica gel ($CHCl_3$). Recrystallization (*i*-Pr_2O) gave pure **7** (1.40 g, 50%): mp 93–94 °C; $[\alpha]^{20}_D$ +259° (*c* 0.93, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.12 (3 H, d, *J* = 6.4 Hz), 1.53 (1 H, ddt, *J* = 13.0, 12.3, 5.2 Hz), 1.62–1.70 (1 H, m), 1.75 (1 H, ddt, *J* = 13.0, 5.9, 2.2 Hz), 2.40 (1 H, ddd, *J* = 17.4, 12.3, 5.9 Hz), 2.53 (1 H, ddd, *J* = 17.4, 5.2, 2.4 Hz), 3.96 (1 H, unresolved), 4.33 and 4.64 (each 1 H, dtt, *J* = 15.7, 2.6, 1.3 Hz), 5.87 (1 H, unresolved), 5.94 (1 H, ddt, *J* = 10.3, 3.5, 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 17.5, 28.0, 32.2, 35.1, 62.5, 69.2, 124.9 (two carbons), 165.4; MS *m*/*z* (rel intensity) 167 (M^+, 30), 166 (3), 138 (12), 125 (8), 95 (23), 84 (100), 67 (46); HRMS calcd for $C_9H_{13}NO_2$ (M^+) 167.0946, found 167.0977. Anal. Calcd for $C_9H_{13}NO_2$: C, 64.63; H, 7.84; N, 8.38. Found: C, 64.51; H, 7.89; N, 8.46.

(4a*S*,5*R*)-5-Methyl-2,3,4,4a,6,7-hexahydropyrido[1,2-*b*][1,2]oxazin-8(2*H*)-one (17). A solution of **7** (401 mg, 2.40 mmol) in MeOH (35 mL) was hydrogenated over 10% Pd/C (400 mg) at 1 atm for 2.5 h. Filtration of the mixture and concentration of the filtrate provided an oily residue. This was purified by column chromatography on silica gel ($CHCl_3$) to give **17** (389 mg, 96%): colorless needles; mp 74–75 °C (*i*-Pr_2O/hexane); $[\alpha]^{20}_D$ + 90.8° (*c* 0.89, $CHCl_3$); IR (neat) 2928, 2871, 2361, 1664, 1460, 1402, 1360, 1312, 1266, 1233, 1212, 1150, 1069, 1044, 952, 929 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (3 H, d, *J* = 6.6 Hz), 1.40 (1 H, ddt, *J* = 12.9, 11.5, 4.4 Hz), 1.50 (1 H, ddt, *J* = 11.5, 10.0, 4.8 Hz), 1.65–1.77 (3 H, m), 1.91 (1 H, dtt, *J* = 13.2, 12.8, 4.6 Hz), 2.01–2.07 (1 H, m), 2.41 (1 H, ddd, *J* = 17.0, 11.7, 5.3 Hz), 2.49 (1 H, ddd, *J* = 17.0, 4.9, 3.7 Hz), 3.30 (1 H, ddt, *J* = 11.5, 8.3, 2.8 Hz), 3.82 (1 H, ddd, *J* = 12.4, 11.5, 2.3 Hz), 4.19 (1 H, ddt, *J* = 11.5, 4.8, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 18.1, 24.8, 27.8, 29.7, 32.2, 36.5, 65.2, 72.0, 165.7; MS *m*/*z* (rel intensity) 169 (M^+, 16), 127 (4), 12 (6), 99 (15), 86 (100), 68 (28); HRMS calcd for $C_9H_{15}NO_2$ (M^+) 169.1102, found 169.1090. Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.49; H, 9.02; N, 8.11.

(4a*S*,5*R*,8*R*)-5-Methyl-8-[5-(trimethylsilyl)-4-pentynyl]-2,3,4,4a,5,6,7,8-octahydropyrido[1,2-*b*][1,2]oxazine (20a). To a cold (0 °C) stirred solution of 5-(trimethylsilyl)-4-pentynylmagnesium bromide (prepared from 5-bromo-1-(trimethylsilyl)pentyne (1.53 g, 7.00 mmol), Mg (160 mg, 6.58 mmol), and Et_2O (6 (mL)) in Et_2O under Ar was added, by syringe, a solution of **17** (370 mg, 2.19 mmol) in Et_2O (4 mL). The mixture was allowed to warm to rt and was kept there for 4 h, and then the reaction was quenched by adding 5% aqueous NaOH (8 mL). The mixture was filtered through a pad of silica gel. The two liquid phases of the filtrate were separated. The aqueous phase was extracted with Et_2O. The combined extracts were washed with brine and dried ($MgSO_4$). Concentration of the extract afforded the crude enamine **18**, which immediately dissolved in AcOH (3 mL). To the stirred solution was added $NaBH_4$ (42 mg, 1.1 mmol) in small portions at rt. After 30 min at rt, the mixture was neutralized by adding 20% aqueous NaOH and was then extracted with $CHCl_3$. The extract was washed with brine and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by chromatography on silica gel (hexane/EtOAc (100:1) then (80:1)) furnished **20a** (417 mg, 65%): a colorless oil; $[\alpha]^{20}_D$ -62.7° (*c* 0.98, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.13 (9 H, s), 0.87 (3 H, d, *J* = 6.4 Hz), 1.04 (1 H, ddt, *J* = 13.2, 12.2, 3.9 Hz), 1.28–1.41 (3 H, m), 1.42–1.54 (2 H, m), 1.54–1.69 (4 H, m), 1.75 (1 H, ddd, *J* = 13.5, 6.6, 3.2 Hz), 1.87–1.97 (2 H, m), 2.09 (1 H, dt, *J* = 10.4, 2.5 Hz), 2.19–2.23 (2 H, m), 2.35–2.41 (1 H, m), 3.79 (1 H, dt, *J* = 11.6, 3.2 Hz), 3.91–3.95 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 0.3 (three carbons), 17.9, 20.5, 25.3, 26.0, 28.1, 30.3, 32.9, 33.0, 36.7, 64.7, 69.4, 70.9, 84.3, 108.0; MS *m*/*z* (rel intensity) 293 (M^+, 0.5), 292 (0.3), 264 (1.6), 250 (2), 220 (1.7), 180 (49), 154 (100), 96 (18); HRMS. Calcd for $C_{17}H_{31}NOSi$ (M^+) 293.2174, found 293.2184. Anal. Calcd for $C_{17}H_{31}NOSi$: C, 69.57; H, 10.66; N, 4.78. Found: C, 69.76; H, 10.57; N, 4.86.

(2*S*,3*R*,6*R*)-2-(3-Hydroxypropyl)-3-methyl-6-[5-(trimethylsilyl)-4-pentynyl]piperidine (21). To a stirred solution of **20a** (108 mg, 0.483 mmol) in 3:1:1 AcOH/THF/H_2O (7 mL) at rt was added Zn dust (375 mg, 5.90 mmol) in small portions. The stirred mixture was then heated at 60 °C for 4 h. The cooled mixture was filtered through a pad of silica gel. The filtrate was concentrated in vacuo. The residue was neutralized by adding 15% aqueous Na_2CO_3, and the whole was extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/10% methanolic NH_3 (40:1)) to give **21** (116 mg, 90%): a pale yellow oil; $[\alpha]^{20}_D$ -7.7° (*c* 0.53, $CHCl_3$); ^1H NMR

($CDCl_3$) δ 0.13 (9 H, d, J = 0.5 Hz), 0.85 (3 H, d, J = 6.5 Hz), 1.01–1.16 (2 H, m), 1.28–1.82 (12 H, m), 2.15–2.27 (3 H, m), 2.48–2.58 (1 H, m), 3.47–3.63 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 0.3 (three carbons), 18.6, 20.1, 25.2, 29.5, 33.0, 33.3, 34.1, 35.0, 36.4, 56.4, 62.4, 63.1, 84.8, 107.3; MS m/z (rel intensity) 295 (M^+, 4), 294 (3), 280 (10), 236 (64), 182 (70), 156 (100), 138 (46); HRMS calcd for $C_{17}H_{33}NOSi$ (M^+) 295.2331, found 295.2330.

(5*R*,8*R*,8a*S*)-8-Methyl-5-[5-(trimethylsilyl)-4-pentynyl]octahydroindolidine (23). To a cold (0 °C) stirred mixture of **21** (103 mg, 0.349 mmol), CBr_4 (145 mg, 0.437 mmol), and CH_2Cl_2 (1 mL) was added Ph_3P (137 mg, 0.522 mmol). The mixture was stirred at 0 °C for 30 min, and then Et_3N (0.8 mL) was added. Ten min later the mixture was concentrated in vacuo to give a semisolid residue. This was extracted with petroleum ether (4 × 30 mL). The extract was concentrated, and the residue was purified by column chromatography on silica gel ($CHCl_3$/10% methanolic NH_3 (200:1)) to give **23** (71 mg, 73%): a pale yellow oil; $[\alpha]^{20}_D$ −58.1° (*c* 0.78, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.13 (9 H, *s*), 0.86 (3 H, d, J = 6.5 Hz), 0.94 (1 H, dq, J = 12.5, 3.6 Hz), 1.18–1.54 (6 H, m), 1.55–1.81 (6 H, m), 1.82–2.02 (3 H, m), 2.21 (2 H, dt, J = 6.8, 2.4 Hz), 3.26 (1 H, br t, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 0.3 (three carbons), 18.9, 20.3, 20.5, 25.0, 29.2, 31.4, 33.9 (two carbons), 36.6, 51.9, 63.2, 71.6, 84.7, 107.5; MS m/z (rel intensity) 277 (M^+, 8), 276 (8), 262 (34), 204 (12), 164 (99), 139 (63), 138 (100); HRMS calcd for $C_{17}H_{31}NSi$ (M^+) 277.2225, found 277.2229.

(5*R*,8*R*,8a*S*)-8-Methyl-5-(4-pentynyl)octahydroindolidine [(−)-Indolizidine 205A] (1). A mixture of **22** (56 mg, 0.20 mmol) and a 10% methanolic KOH (0.5 mL) was stirred at rt for 2.5 h. The mixture was concentrated. The residue was dissolved in CH_2Cl_2. The solution was washed with brine and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by column chromatography on silica gel ($CHCl_3$/10% methanolic NH_3 (150:1)) gave **1** (32 mg, 77%): a pale yellow oil; $[\alpha]^{20}_D$ −74.2° (*c* 0.82, MeOH) [lit.[4] $[\alpha]^{20}_D$ −35° (*c* 0.24, MeOH)]; ^1H NMR ($CDCl_3$) δ 0.84 (3 H, d, J = 6.5 Hz), 0.93 (1 H, ddt, J = 13.2, 11.9, 4.1 Hz), 1.17–1.54 (6 H, m), 1.56–1.78 (6 H, m), 1.86–1.93 (2 H, m), 1.96 (1 H, q, J = 9.0 Hz), 2.16 (2 H, dt, J = 6.9, 2.6 Hz), 3.25 (2 H, dt, J = 8.7, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 18.7, 18.8, 20.3, 24.7, 29.0, 31.1, 33.6 (two carbons), 36.4, 51.8, 63.0, 68.3, 71.4, 84.3; MS m/z (rel intensity) 205 (M^+, 2), 204 (2), 139 (10), 138 (100), 96 (14), 70 (12).

(4a*S*,5*R*,8*R*)-5-Methyl-8-(4-pentenyl)-2,3,4,4a,5,6,7,8-octahydropyrido[1,2-*b*][1,2]oxazine (24). In a manner similar to that described for the preparation of **20a**, a solution of **17** (117 mg, 0.691 mmol) in THF (1 mL) was allowed to react with the Grignard reagent prepared from 5-bromo-1-heptene (360 mg, 2.03 mmol), Mg (45 mg, 1.85 mmol), and THF (2 mL). The crude product was then treated with $NaBH_4$ (13 mg, 0.34 mmol) in AcOH (1 mL). Workup and purification of the crude product by column chromatography on silica gel (hexane/EtOAc (100:1)) provided **24** (109 mg, 71%): a colorless oil; $[\alpha]^{20}_D$ −113.7° (*c* 1.04, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.87 (3 H, d, J = 6.6 Hz), 1.04 (1 H, ddt, J = 13.0, 12.2, 3.8 Hz), 1.24–1.52 (6 H, m), 1.53–1.73 (3 H, m), 1.77 (1 H, ddd, J = 11.5, 6.6, 3.2 Hz), 1.85–2.13 (5 H, m), 2.33–2.39 (1 H, m), 3.80 (1 H, dt, J = 11.7, 3.1 Hz), 3.90–3.99 (1 H, unresolved), 4.92 (1 H, unresolved), 4.99 (1 H, ddd, J = 17.1, 3.5, 1.7 Hz), 5.82 (1 H, ddt, J = 17.1, 10.3, 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 18.0, 25.2, 26.0, 28.1, 30.2, 33.0, (two carbons), 34.3, 36.7, 65.1, 69.4, 70.9, 114.2, 139.3; MS m/z (rel intensity) 223 (M^+, 3), 222 (1), 180 (6), 167 (4), 154 (100); HRMS calcd for $C_{14}H_{25}NO$ (M^+) 223.1936, found 223.1965.

(2*S*,3*R*,6*R*)-2-(3-Hydroxypropyl)-3-methyl-6-(4-pentenyl)piperidine (25). In a manner similar to that described for the preparation of **21**, a solution of **24** (108 mg, 0.484 mmol) in 3:1:1 AcOH/THF/H_2O (7 mL) was treated with Zn dust (375 mg, 5.74 mmol). Workup and purification of the crude product by column chromatography on silica gel ($CHCl_3$/10% methanolic NH_3 (60:1)) gave **25** (106 mg, 97%): a pale yellow oil; $[\alpha]^{25}_D$ −16.5° (*c* 0.85, $CHCl_3$); IR (neat) 3273, 3077, 2926, 2850, 1641, 1457, 1377, 1339, 1286, 1209, 1118, 1060, 993, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (3 H, dd, J = 6.5, 1.1 Hz), 1.04–1.13 (2 H, m), 1.29–1.49 (7 H, m), 1.50–1.84 (6 H, m), 1.99–2.09 (2 H, m), 2.16–2.28 (1 H, m), 2.44–2.59 (1 H, m), 3.48–3.61 (2 H, m), 4.94 (1 H, ddd, J = 10.2, 2.0, 1.1 Hz), 4.9–5.03 (1 H, m), 5.79 (1 H, ddt, J = 17.0, 10.2, 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 18.6, 25.3, 29.4, 32.8, 33.3, 33.9, 34.0, 34.8, 36.5, 56.8, 62.4, 63.0, 114.7, 138.7; MS m/z (rel intensity) 225 (M^+, 6), 224 (3), 182 (6), 166 (91), 156 (100), 138 (20), 83 (36); HRMS calcd for $C_{14}H_{27}NO$ (M^+) 225.2092, found 225.2121.

(5*R*,8*R*,8a*S*)-8-Methyl-5-(4-pentenyl)octahydroindolidine [(−)-Indolizidine 207A] (2). In a manner similar to that described for the preparation of **23**, a mixture of **25** (100 mg, 0.444 mmol), CBr_4 (184 mg, 0.555 mmol), and CH_2Cl_2 (2 mL) was treated, successively, with PPh_3 (175 mg, 0.667 mmol) and Et_3N (8 mL). Workup and purification of the crude product by column chromatography on silica gel gave **2** (69 mg, 75%): a pale yellow oil; $[\alpha]^{28}_D$ −86.5° (*c* 0.95, $CHCl_3$); IR (neat) 3076, 2931, 2872, 2777, 2701, 2456, 1641, 1457, 1417, 1376, 1333, 1321, 1293, 1243, 1221, 1164, 1134, 1109, 1088, 991, 910, 807 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (3 H, d, J = 6.6 Hz), 0.95 (1 H, ddt, J = 13.3, 11.6, 4.4 Hz), 1.16–1.55 (7 H, m), 1.57–1.81 (5 H, m), 1.81–2.12 (5 H, m), 3.26 (1 H, dt, J = 8.7, 2.0 Hz), 4.93 (1 H, ddt, J = 10.2, 2.2, 1.2 Hz), 4.99 (1 H, ddt, J = 17.1, 2.2, 1.6 Hz), 5.80 (1 H, ddt, J = 17.1, 10.2, 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 18.9, 20.5, 25.2, 29.2, 31.3, 33.8, 34.2, (two carbons), 36.6, 51.9, 63.5, 71.5, 114.5, 138.9; MS m/z (rel intensity) 207 (M^+, 2.6), 206 (1.3), 205 (0.7), 138 (100), 96 (9), 70 (8); HRMS calcd for $C_{14}H_{25}N$ (M^+) 207.1986, found 207.1972.

(5*R*,8*R*,8a*S*)-8-Methyl-5-(4-pentyl)octahydroindolidine [(−)-Indolizidine 209B] (3). A solution of **2** (64 mg, 0.309 mmol) in THF (8 mL) was hydrogenated over 10% Pd/C (85 mg) at 1 atm for 5 h. The mixture was filtered. Concentration of the filtrate and purification of the residue by column chromatography on silica gel ($CHCl_3$/10% methanolic NH_3 (80:1)) gave **3** (60 mg, 93%): a pale yellow oil; $[\alpha]^{28}_D$−91.3° (*c* 0.58, MeOH) [lit.[6] $[\alpha]^{22}_D$ −94.3° (*c* 1.85, MeOH)]; IR (neat) 2956, 2929, 2860, 2777, 2701, 2444, 2361, 2341, 1458, 1377, 1332, 1243, 1220, 1166, 1133, 1113, 1087, 1034, 921, 892 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (3 H, d, J = 6.5 Hz), 0.88 (3 H, t, J = 7.0 Hz), 0.95 (1 H, ddt, J = 13.5, 11.7, 4.4 Hz), 1.14–1.55 (11 H, m), 1.57–1.79 (5 H, m), 1.80–2.02 (3 H, m), 3.27 (1 H, dt, J = 8.7, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.0, 20.5, 22.7, 25.6, 29.2, 31.3, 32.4, 33.8, 34.7, 36.6, 51.9, 63.7, 71.5; MS m/z (rel intensity) 209 (M^+, 3), 208 (4), 138 (100), 96 (10), 70 (8); HRMS calcd for $C_{14}H_{27}N$ (M^+) 209.2143, found 209.2143.

(4a*S*,5*R*,8*R*)-5-Methyl-8-(4-heptynyl)-2,3,4,4a,5,6,7,8-octahydropyrido[1,2-*b*][1,2]oxazine (26). A solution of **17** (228 mg, 1.35 mmol) in THF (3 mL) was treated with the Grignard reagent prepared from 7-bromo-3-heptyne (819 mg, 4.68 mmol), Mg (104 mg, 4.28 mmol) and THF (4 mL). The crude product was then treated with $NaBH_4$ (26 mg, 0.69 mmol) and AcOH (2 mL) in a manner similar to that described for the preparation of **20a**. Workup and purification of the crude product by column chromatography on silica gel (hexane/EtOAc (40:1)) gave **26** (234 mg, 70%): a pale yellow oil; $[\alpha]^{20}_D$ −99.8° (*c* 1.15, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.87 (3 H, d, J = 6.6 Hz), 0.98–1.13 (1 H, unresolved, containing 3 H, t, J = 7.4 Hz, at δ 1.10), 1.26–1.40 (3 H, m), 1.41–1.50 (2 H, m), 1.51–1.69 (4 H, m), 1.75 (1 H, ddd, J = 13.5, 6.6, 3.2 Hz), 1.85–1.97 (2 H, m), 2.06–2.17 (5 H, m), 2.34–2.41 (1 H, m), 3.79 (1 H, dt, J = 11.6, 3.2 Hz), 3.90–3.96 (1 H, unresolved); ^{13}C NMR ($CDCl_3$) δ 12.5, 14.5, 17.9, 19.3, 25.7, 26.0, 28.1, 30.2, 32.9, 33.0, 36.7, 64.8, 69.4, 70.9, 79.7, 81.7; MS m/z (rel intensity) 249 (M^+, 2), 248 (2), 180 (74), 154 (100); HRMS calcd for $C_{16}H_{27}NO$ (M^+) 249.2092, found 249.2075.

(4a*S*,5*R*,8*S*)-5-Methyl-8-[4(*Z*)-heptenyl]-2,3,4,4a,5,6,7,8-octahydropyrido[1,2-*b*][1,2]oxazine (27). To a solution of **26** (200 mg, 0.802 mmol) in MeOH (25 mL) was added quinoline (10 mg) and Lindlar catalyst (75 mg). The mixture was hydrogenated at 1 atm for 8 min. Then it was filtered. Concentration of the filtrate and purification of the residue by column chromatography on silica gel (hexane/EtOAc (80:1)) gave **27** (186 mg, 92%): a colorless oil; $[\alpha]^{20}_D$ −90.2° (*c* 1.57, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.87 (3 H, d, J = 6.6 Hz), 0.94 (3 H, t, J = 7.5 Hz), 1.04 (1 H, ddt, J = 13.1, 12.2, 3.9 Hz), 1.23–1.45 (6 H, m), 1.55–1.72 (3 H, m), 1.77 (1 H, ddd, J = 13.5, 6.6, 3.1 Hz), 1.87–2.14 (7 H, m), 2.32–2.38 (1 H, m), 3.80 (1 H, dt, J = 11.7, 3.1 Hz), 3.90–3.91 (1 H, unresolved), 5.29–5.38 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 14.4, 18.0, 20.6, 26.0, 26.1, 27.7, 28.1, 30.2, 33.0, 33.1, 36.7, 65.2, 69.4, 70.9, 129.4, 131.7; MS m/z (rel intensity) 251 (M^+, 3), 180 (18), 167 (12), 154 (100); HRMS calcd for $C_{16}H_{29}NO$ (M^+) 251.2249, found 251.2268. Anal. Calcd for $C_{16}H_{29}NO$: C, 76.43; H, 11.63; N, 5.57. Found: C, 76.30; H, 11.63; N, 5.71.

(2*S*,3*R*,6*R*)-(6*E*)-2-(3-Hydroxypropyl)-3-methyl-6-(4-heptenyl)piperidine (28). In a manner similar to that described

for the preparation of **21**, a solution of **27** (119 mg, 0.473 mmol) in 3:1:1 AcOH/THF/H_2O (8 mL) was treated with Zn dust (420 mg, 6.42 mmol) at 60 °C for 2.5 h. Workup and purification of the crude product by column chromatography on silica gel ($CHCl_3$/10% methanolic NH_3 (40:1)) gave **27** (113 mg, 94%): a pale yellow oil; $[\alpha]^{20}_D$ -14.5° (*C* 1.13, $CHCl_3$); IR (neat) 3263, 3005, 2927, 1652, 1456, 1377, 1338, 1286, 1118, 1061, 933, 888, 824, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (3 H, d, J = 6.5 Hz), 0.94 (3 H, t, J = 7.5 Hz), 1.08 (2 H, dt, J = 8.5, 2.7 Hz), 1.28–1.46 (6 H, m), 1.50–1.82 (7 H, m), 1.95–2.04 (4 H, m), 2.23 (1 H, ddd, J = 9.9, 6.5, 2.4 Hz), 2.45–2.55 (1 H, m), 3.50–3.62 (2 H, m), 5.26–5.39 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 14.4, 18.6, 20.6, 26.1, 27.2, 29.4, 32.7, 33.2, 34.0, 34.8, 36.6, 56.9, 62.4, 63.0, 128.9, 132.1; MS *m/z* (rel intensity) 253 (M^+, 5), 252 (3), 194 (74), 182 (26), 169 (9), 156 (100), 138 (28); HRMS calcd for $C_{16}H_{31}NO$ (M^+) 253.2405, found 253.2398.

(5*R*,8*R*,8a*S*)-8-Methyl-5-[4(*Z*)-heptenyl]octahydroindolidine [(-)-Indolizidine 235B] (4). In a manner similar to that described for the cyclization of **21**, a mixture of **28** (110 mg, 0.434 mmol), CBr_4 (180 mg, 0.543 mmol), and CH_2Cl_2 (2 mL) was treated, successively, with PPh_3 (170 mg, 0.648 mmol) and Et_3N (0.8 mL). Workup and purification of the crude product by column chromatography on silica gel ($CHCl_3$/10% methanolic NH_3 (200:1)) gave **4** (72 mg, 71%): a pale yellow oil; $[\alpha]^{28}_D$-85.4° (*c* 0.79, MeOH); IR (neat) 3005, 2962, 2932, 2873, 2777, 2701, 1457, 1375, 1332, 1243, 1221, 1163, 1134, 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (3 H, d, J = 6.5 Hz), 0.95 (3 H, t, J = 7.5 Hz), 1.17–1.52 (8 H, m), 1.56–1.79 (5 H, m), 1.79–2.09 (7 H, m), 3.25 (1 H, dt, J = 8.7, 1.8 Hz), 5.27–5.39 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 14.5, 19.0, 20.5, 20.6, 26.1, 27.5, 29.2, 31.4, 33.9, 34.4, 36.7, 52.0, 63.6, 71.5, 129.1, 131.9; MS *m/z* (rel intensity) 235 (M^+, 3), 234 (2), 164 (10), 151 (8), 138 (100), 96 (10), 70 (8); HRMS calcd for $C_{16}H_{29}N$ (M^+) 235.2299, found 235.2311.

Acknowledgment. We are grateful to Dr. J. W. Daly (National Institutes of Health) for supplying invaluable information on 5-substituted 8-methylindolizidine dendrobatid alkaloids and the manuscript cited.[5] We are also indebted to Dr. A. B. Holmes (Cambridge University) for providing the spectra of synthetic (±)-indolizidine **207A** and (-)-indolizidine **209B**. We thank Takasago International Co. for a gift of (*R*)-citronellol. This work was supported in part by a Grant-in-Aid for Science Research (No. 01571167) from the Ministry of Education, Science and Culture, Japan (to C.K.).

Supplementary Material Available: ^1H and ^{13}C NMR spectra of compounds 1–4, 11–13, 15, 21, 23–26, and 28 (28 pages). Ordering information is given on any current masthead page.

Synthesis of 2-Arylbenzoxazoles via the Palladium-Catalyzed Carbonylation and Condensation of Aromatic Halides and *o*-Aminophenols

Robert J. Perry,* B. David Wilson, and Richard J. Miller

Corporate Research Laboratories, Eastman Kodak Company, Rochester, New York 14650-2110

Received December 10, 1991

A new synthetic method is reported in which 2-arylbenzoxazoles can be prepared by the palladium-catalyzed condensation of aryl halides with *o*-aminophenols followed by dehydrative cyclization. This method is tolerant of a wide variety of functional groups on either aromatic ring and gives good to excellent yields of products. An aliphatic vicinal amino alcohol gave a bis-acylated product as well as a chlorine-containing product with only a small amount of the desired 2-aryloxazole being formed. Methyl iodide and benzyl bromide gave only alkylated products.

Introduction

As part of an effort to explore the synthetic utility of aromatic halides, we initiated a study of the palladium-catalyzed carbonylation of aryl iodides and bromides and their reactions with various nucleophiles. These "Heck" carbonylation reactions have been well documented for the formation of amides[1] and esters,[2] as well as α-keto amides,[3] α-keto esters,[3e,4] α-keto acids,[5] α-hydroxy acids,[6] anhydrides,[7] acid fluorides,[8] acids,[9] lactams,[10] lactones,[11] aldehydes,[12] and imides.[13] During the course of our investigation, we became aware that the use of *o*-aminophenols could lead to *N*-(2-hydroxyphenyl)amides **1**, which are precursors to the benzoxazole ring system **2** (eq 1).

Arylbenzoxazoles are commonly made by the condensation of an aromatic carboxylic acid (derivative) with an *o*-aminophenol (eq 1, path b). Initial reaction between these two compounds results in the formation of a 2-hydroxy amide intermediate **1**, which is the same as that obtained through carbonylation reaction (eq 1, path a).

(1) (a) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327. (b) Nicholas, P. P. *J. Org. Chem.* **1987**, *52*, 5266. (c) Bumagin, N. A.; Gulevich, Y. V.; Beletskaya, I. P. *Izv. Akad. Nauk. SSSR, Ser. Khim. (Eng. Transl.)* **1986**, 1498.

(2) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Hidai, M.; Hikita, T.; Wada, Y.; Fujikura, Y.; Uchida, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2075. (c) Inamasa, K.; Kudo, K.; Sugita, N. *Bull. Inst. Chem. Res., Kyoto Univ.* **1983**, *61*, 282. (d) Moser, W. R.; Wang, A. W.; Kildahl, N. K. *J. Am. Chem. Soc.* **1988**, *110*, 2816. (e) Milstein, D. *J. Chem. Soc., Chem. Commun.* **1986**, 817. (f) Ito, T.; Mori, K.; Mellzoroki, T.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2091. (g) Stille, J. K.; Wong, P. K. *J. Org. Chem.* **1975**, *40*, 532. (h) Mutin, R.; Lucas, C.; Thivolle-Cazat, J.; Dufaud, V.; Dany, F.; Basset, J. M. *J. Chem. Soc., Chem. Commun.* **1988**, 896.

(3) (a) Ozawa, F.; Soyama, H.; Yanagihara, H.; Aoyama, I.; Takino, H.; Izawa, K.; Yamamoto, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1985**, *107*, 3235. (b) Ozawa, F.; Sugimoto, T.; Yuasa, Y.; Santra, M.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1984**, *3*, 683. (c) Ozawa, F.; Sugimoto, T.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1984**, *3*, 692. (d) Ozawa, F.; Yamamoto, A. *J. Organomet. Chem.* **1987**, *334*, C9. (e) Feng, Z.; Chen, B.; Liu, H. *J. Macromol. Sci.-Chem.* **1987**, *A23*, 289. (f) Kobayashi, T.; Tanaka, M. *J. Organomet. Chem.* **1982**, *233*, C64. (g) Ozawa, F.; Soyama, H.; Yamamoto, T.; Yamamoto, A. *Tetrahedron Lett.* **1982**, *23*, 3383. (h) Ozawa, F.; Yamamoto, A. *Chem. Lett.* **1982**, 865.

(4) (a) Tanaka, M.; Kobayashi, T. A.; Skakura, F.; Itatani, N.; Danno, S.; Zushi, K. *J. Mol. Catal.* **1985**, *32*, 115. (b) Ozawa, F.; Kawasaki, N.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1985**, 567. (c) Morin, B.; Hirschauer, A.; Hugues, F.; Commereuc, D.; Chauvin, Y. *J. Mol. Catal.* **1986**, *34*, 317.

(5) Tanaka, M.; Kobayashi, T. A.; Skakura, F. *J. Chem. Soc., Chem. Commun.* **1985**, 837.

(6) Kobayashi, T.; Sakakura, T.; Tanaka, M. *Tetrahedron Lett.* **1987**, *28*, 2721.

(7) Pri-Bar, I.; Alper, H. *J. Org. Chem.* **1989**, *54*, 36.

(8) Sakakura, T.; Chaisupakitsin, M.; Hayashi, T.; Tanaka, M. *J. Organomet. Chem.* **1987**, *334*, 205.

(9) (a) Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1988**, *53*, 624. (b) Cassar, L.; Foa, M.; Gardano, A. *J. Organomet. Chem.* **1976**, *121*, C55.

(10) Mori, Y.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1978**, *43*, 1684.

(11) Martin, L. D.; Stille, J. K. *J. Org. Chem.* **1982**, *47*, 3630.

(12) (a) Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 7761. (b) Pri-Bar, I.; Buckman, O. *J. Org. Chem.* **1984**, *49*, 4009.

(13) Perry, R. J.; Turner, S. R. *J. Org. Chem.* **1991**, *56*, 6573.

0022-3263/92/1957-2883$03.00/0