BH_3·Me_2S complex in THF (0.37 mL, 0.74 mmol). The mixture was allowed to warm to room temperature and refluxed for 1 h. The reaction mixture was cooled in an ice bath, and 6 N HCl (5 mL) was added with stirring. After being stirred for 2 h at room temperature, the mixture was basified with 20% KOH, extracted with $CHCl_3$ (2 × 30 mL), and dried (Na_2CO_3). Evaporation of the solvent and chromatography on silica gel with $CHCl_3$–MeOH (50:1) as eluent afforded **29** (13 mg, 62%) as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 0.85 (6 H, t, J = 6.4 Hz), 1.03–1.28 (12 H, m), 1.43–1.59 (4 H, m), 1.84–1.88 (2 H, m), 2.83 (2 H, br s), 3.64 and 3.81 (total 2 H, AB q, J = 13.9 Hz), 7.18–7.37 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 14.11, 14.19, 22.75, 23.11, 25.73, 26.21, 28.50 (2 C), 28.79, 30.47, 30.73, 32.30, 51.47, 60.49 (2 C), 126.40, 128.09 (2 C), 128.53 (2 C), 141.24; MS m/z (relative intensity) 287 (M^+, 0.8), 286 (M^+ – 1, 0.6), 230 (57), 216 (67), 91 (100); HRMS calcd for $C_{20}H_{33}N$ (M^+) 287.2611, found 287.2586.

Acknowledgment. We are indebted to Drs. J. W. Daly and T. F. Spande (the National Institutes of Health) for generously providing a sample of natural pyrrolidine 197B.

Stereoselective Synthesis of (±)-Indolizidines 167B, 205A, and 207A. Enantioselective Synthesis of (–)-Indolizidine 209B[1]

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The first syntheses of the dendrobatid indolizidine alkaloids 167B (**3**), 205A (**4**), and 207A (**5**) are described using as a key step the highly stereoselective intramolecular nitrone cycloaddition of the (*Z*)-*N*-alkenylnitrone **10** to prepare the isoxazolidine **11**. Mesylate-promoted cyclization of the alcohol **12**, followed by reductive cleavage of the resulting mesylate salt, afforded the key axial hydroxymethyl compound **13**, which was epimerized via the aldehyde to the equatorial alcohol, and was subsequently reduced to the required 8-methyl-substituted indolizidine. The feasibility of extending this strategy to the enantioselective synthesis of such alkaloids was demonstrated in the first synthesis of (–)-indolizidine 209B (**6**), whose nitrone precursor **10d** was obtained from the (*S*)-glutamate-derived amine **40**.

A large number of alkaloids have been isolated in minute quantity from the skin extracts of neotropical poison-dart frogs family (Dendrobatidae).[2] The lack of availability of natural material and the fascinating biological activity of the compounds which have been studied[2] make these alkaloids ideal targets for total synthesis.[3,4] In recent years we have been interested in examining the intramolecular nitrone cycloaddition reaction[5] and its application to alkaloid synthesis. These studies have included a stereoselective synthesis of (±)-carpamic acid (**1**)[6] and a stereoselective approach to gephyrotoxin (**2**).[7] This report details these synthetic studies within the context of the previously unsynthesized dendrobatid alkaloids 167B (**3**), 205A (**4**), and 207A (**5**).[1] This intramolecular nitrone cycloaddition approach represents a new, highly efficient, and stereoselective strategy for the synthesis of 5,8-disubstituted indolizidines.[8] The method was further extended

(1) For a preliminary account of this work, see: Smith, A. L.; Williams, S. F.; Holmes, A. B.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Am. Chem. Soc.* **1988**, *110*, 8696–8698. For indolizidines 235B and 235B1, see: Collins, I.; Fox, M. E.; Holmes, A. B.; Williams, S. F.; Baker, R.; Forbes, I. T.; Thompson, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, in press.

(2) 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. (b) Daly, J. W.; Myers, C. W.; Whittaker, N. *Toxicon* **1987**, *25*, 1023–1095. (c) Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1987**, *43*, 643–652.

(3) Indolizidine 223AB has been synthesized by more than one strategy, and its structure and stereochemistry have been defined as (3*R*,5*R*,8a*R*)-3-butyl-5-propylindolizidine: (a) MacDonald, T. L. *J. Org. Chem.* **1980**, *45*, 193–194. (b) Hart, D. J.; Tsai, Y.-M. *J. Org. Chem.* **1982**, *47*, 4403–4409. (c) Broka, C. A.; Eng, K. K. *J. Org. Chem.* **1986**, *51*, 5043–5045. (d) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534–5535. (e) Watanabe, Y.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, *54*, 4088–4097. (f) Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1985**, *26*, 1515–1518. (g) Edwards, O. E.; Greaves, A. M.; Sy, W. W. *Can. J. Chem.* **1988**, *66*, 1163–1172. (h) Brandi, A.; Cordero, F.; Querci, C. *J. Org. Chem.* **1989**, *54*, 1748–1750. (i) Cordero, F. M.; Brandi, A.; Querci, C.; Goti, A.; De Sarlo, F.; Guarna, A. *J. Org. Chem.* **1990**, *55*, 1762–1767.

(4) (a) Both enantiomers of indolizidine 195B have been synthesized by Kibayashi, establishing its structure as (3*S*,5*S*,8a*S*)-3-butyl-5-methylindolizidine. See: Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396–1408. (b) For recent syntheses of the racemate: Jefford, C.; Tang, Q.; Zaslona, A. *Helv. Chim. Acta* **1989**, *72*, 1749–1752. Nagasaka, T.; Kato, H.; Hayashi, H.; Shioda, M.; Hikasa, H.; Hamaguchi, F. *Heterocycles* **1990**, *30*, 561–566. Vavrecka, M.; Hesse, H. *Helv. Chim. Acta* **1989**, *72*, 847–855.

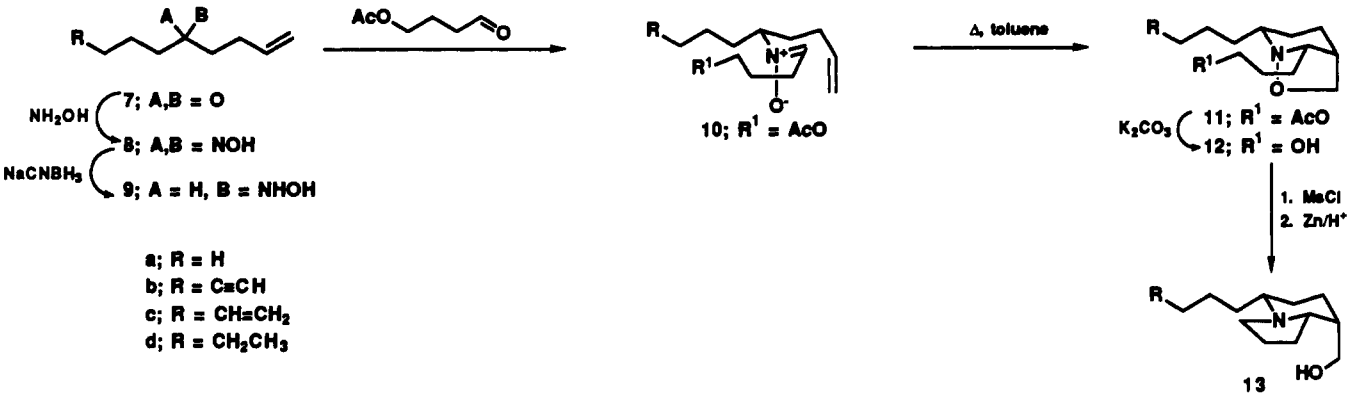
(5) (a) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, Chapter 12, pp 277–406. (b) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1–173.

(6) Holmes, A. B.; Swithenbank, C.; Williams, S. F. *J. Chem. Soc., Chem. Commun.* **1986**, 265–266.

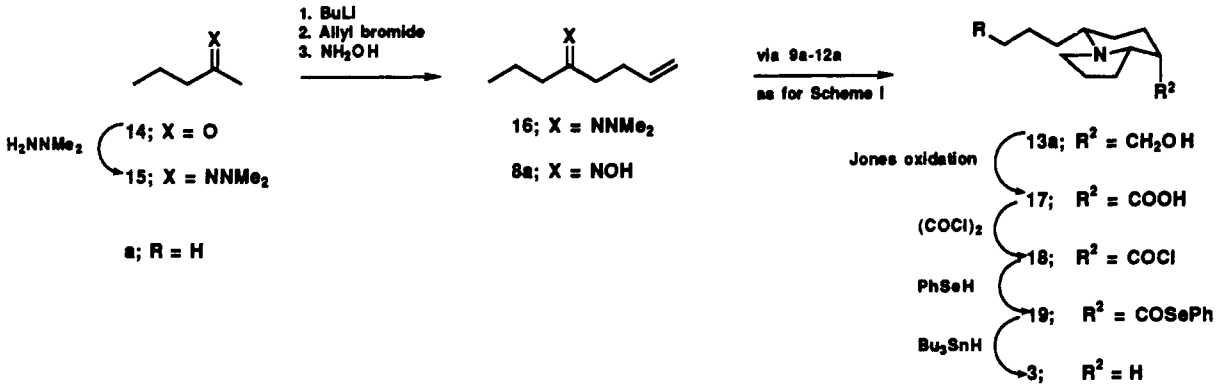
(7) Holmes, A. B.; Hughes, A. B.; Smith, A. L., unpublished experiments.

0022-3263/91/1956-1393$02.50/0

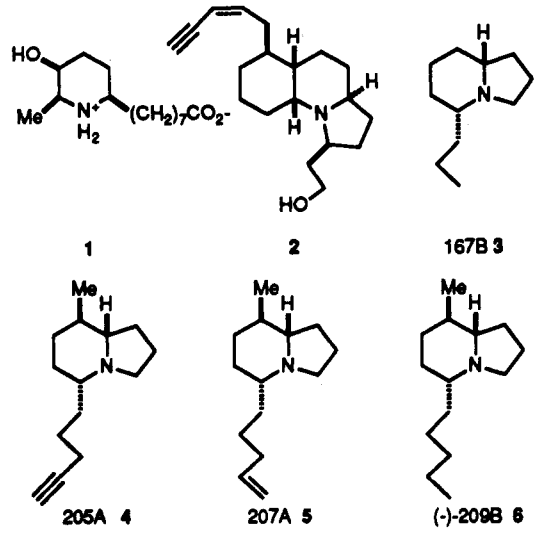
Scheme I



Scheme II



to the enantioselective synthesis of (−)-indolizidine 209B (6).



The key feature of our approach to the 5,8-disubstituted indolizidine alkaloids is the intramolecular dipolar cycloaddition of the (*Z*)-*N*-alkenylnitrone **10** to give the isoxazolidine **11** as the only isolated product (Scheme I). Related cycloadditions have been studied by other workers,[5] with particularly noteworthy contributions having been made by Oppolzer,[9a,b] and by LeBel in his pioneering synthesis of pumiliotoxin C.[9c] Subsequent conversion of **11** into the corresponding mesylate **11** (R^1 = OMs) results in a spontaneous intramolecular cyclization to generate the five-membered ring. Reductive cleavage of the N–O bond provides a rapid construction of the indolizidine skeleton from relatively simple molecules with complete stereocontrol at C-5, C-8, and C-8a.

Scheme III

In order to test our strategy, we initially chose the relatively simple alkaloid 167B (**3**) as a target for total synthesis. This alkaloid has recently been identified as a trace component in the skin secretions of a dendrobatid species from Panama, and its structure was tentatively assigned as a 5-propylindolizidine based upon its mass spectral fragmentation pattern.[10] The *N*,*N*-dimethylhydrazone of 2-pentanone **15** was regioselectively alkylated using the Corey–Enders procedure[11] to give a 78% overall yield of the alkylated product **16** (Scheme II). It was then found

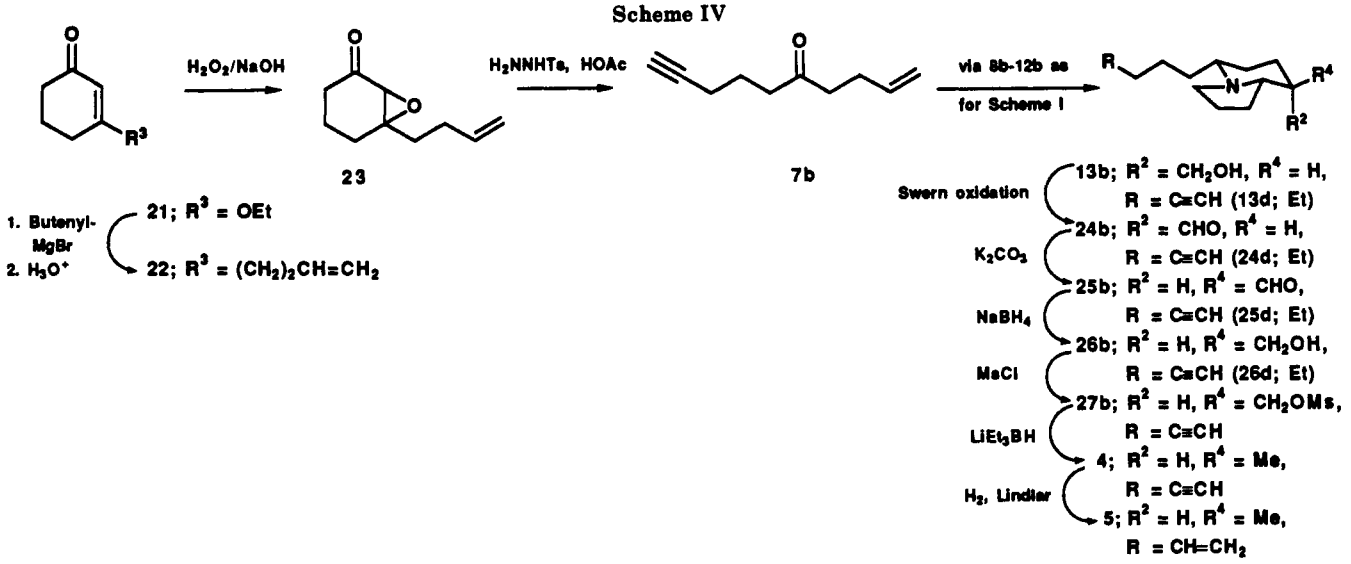
(8) For previous approaches to 5,8-disubstituted indolizidines, see: (a) LaLonde, R. T.; Muhammad, N.; Wong, C. F.; Sturiale, E. R. *J. Org. Chem.* **1980**, *45*, 3664–3671. (b) Tufariello, J. J.; Dyszlewski, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1138–1140. (c) Ohnuma, T.; Tabe, M.; Shiiya, K.; Ban, Y.; Date, T. *Tetrahedron Lett.* **1983**, *24*, 4249–4252.

(9) For related intramolecular nitrone cycloadditions, see: (a) Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron Lett.* **1979**, *20*, 4391–4394. (b) Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron* **1985**, *41*, 3497–3509. (c) LeBel, N. A.; Balasubramanian, N. 186th National Meeting of the American Chemical Society: Washington, D.C., August 28–September 2, 1983; ORGN 0123. Balasubramanian, N. *Diss. Abstr. Int. B* **1983**, *44*, 799. Balasubramanian, N. *Chem. Abstr.* **1983**, *99*, 212302u. Balasubramanian, N. *Org. Prep. Proced. Int.* **1985**, *17*, 23–47. LeBel, N. A.; Balasubramanian, N. *J. Am. Chem. Soc.* **1989**, *111*, 3363–3368.

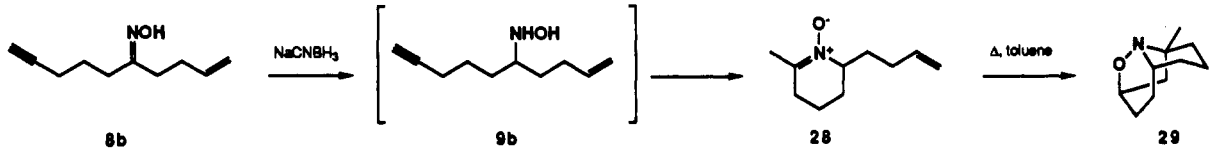
(10) Daly, J. W. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 205–340.

(11) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3–6.

Scheme IV



Scheme V



possible to convert the *N,N*-dimethylhydrazone **16** directly into the oxime **8a** in 97% yield by treatment with hydroxylamine, without recourse to the intermediacy of the corresponding ketone.

Chemoselective reduction of the oxime **8a** with sodium cyanoborohydride under mildly acidic conditions (HCl, MeOH, methyl orange indicator) rapidly gave the hydrochloride salt of the hydroxylamine **9a**, which was subsequently liberated under basic conditions. It is well known that *N*-(4-alkenyl)hydroxylamines such as **9a** are moderately unstable and will cyclize upon brief warming to give *N*-hydroxypyrrolidines **20** (Scheme III) via an intermediate nitroxide in a radical chain mechanism promoted by molecular oxygen.[9a,b,12]

However, this was not a major problem for the hydroxylamine **9a** provided that it was freshly prepared prior to use. Condensation of the hydroxylamine **9a** with 4-acetoxybutanal[13] gave the (*Z*)-nitrone **10a**, which smoothly cyclized in refluxing toluene to give isoxazolidine **11a** as a single adduct in 40% yield over three steps. It was subsequently found that the use of a Dean–Stark head helped prevent decomposition during the cyclization by the azeotropic removal of water. The high degree of stereoselectivity observed in the cycloaddition reaction is ascribed to the preference for a chairlike transition state in which the substituents adopt a pseudoequatorial orientation.[9]

Alkaline hydrolysis of the acetate **11a** (K_2CO_3, MeOH), mesylation (accompanied by spontaneous cyclization), and reductive N–O bond cleavage (Zn, HOAc) of the intermediate mesylate salt gave the 5,8-disubstituted indolizidine **13a** in 80% yield. The synthesis of indolizidine 167B was completed by removal of the C-8 hydroxymethyl substituent. This was achieved by oxidation[14] to the carboxylic acid **17** and subsequent decarboxylation[15] via the selenoester **19** to give racemic indolizidine 167B (**3**) in 32% yield from **13a**.[16a,b]

We next turned our attention to the synthesis of the 5,8-disubstituted alkaloid 205A (**4**) (Scheme IV), isolated from the frog *D. pumilio*.[2c] It was hoped that the equatorial C-8 methyl group of 205A (**4**) could be obtained from the axial C-8 (hydroxymethyl)indolizidine **13b** via base-catalyzed epimerization of the corresponding aldehyde **24b**. This should then be readily accessible from the nitrone adduct **11b**.

Such a strategy required the synthesis of the acetylenic ketone **7b**, which was readily achieved by means of an Eschenmoser fragmentation reaction.[17] Using a standard procedure for synthesizing 3-substituted 2-cyclohexenones,[18] 3-ethoxy-2-cyclohexenone **21** was treated with the Grignard reagent derived from 4-bromo-1-butene in THF, and the intermediate enol ether underwent acid-catalyzed hydrolysis with allylic rearrangement of the tertiary alcohol during the acidic work-up to give the 3-alkyl-2-cyclohexenone **22** (93–96% yield). Epoxidation[17]

(12) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855–863.

(13) 4-Acetoxybutanal[43b] was readily prepared from 1,4-butanediol by monoacetylation[43a] [NaH (1 equiv), THF; Ac_2O (54%)] followed by pyridinium dichromate or Swern oxidation (77%).

(14) Jones oxidation using a modified workup procedure was used to overcome the problem of complexation of the indolizidine nitrogen atom to the chromium. See: Müller, R. H.; DiPardo, R. M. *J. Org. Chem.* **1977**, *42*, 3210–3212.

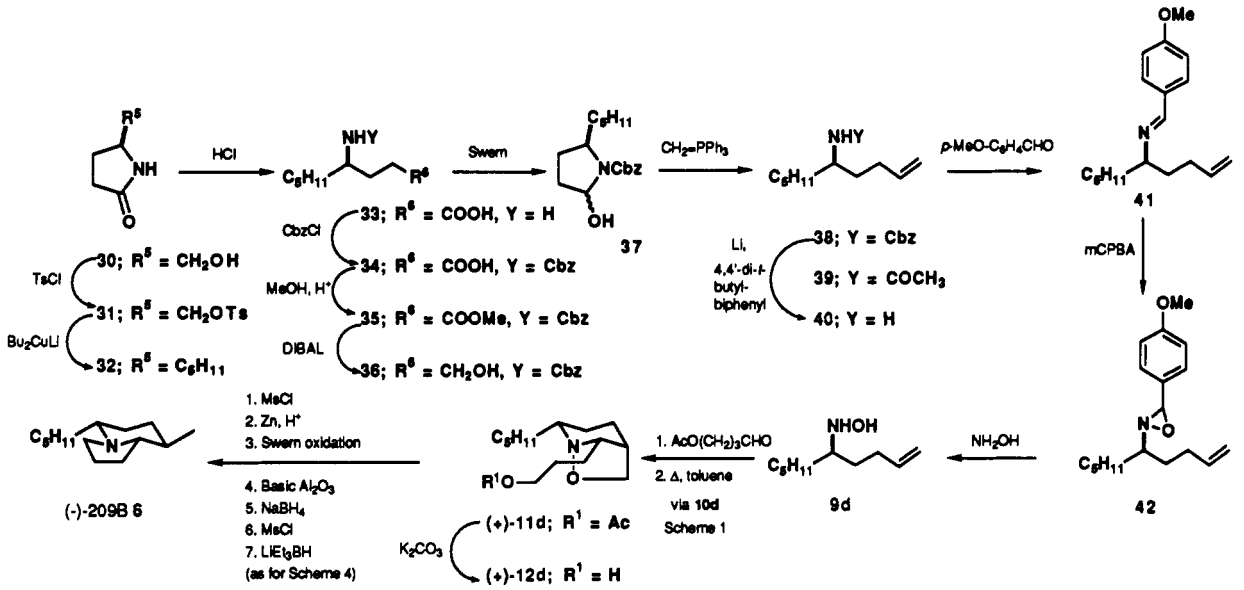
(15) Pfenninger, J.; Heuberger, C.; Graf, W. *Helv. Chim. Acta* **1980**, *63*, 2328–2337.

(16) (a) Comparison of the synthetic material with an authentic sample (GC/MS) by Dr. T. Spande (NIH) showed the two to be identical and hence confirmed the assigned structure. (b) Indolizidine 167B has also been prepared by alternative routes: Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688–4693. Jefford, C. W.; Tang, Q.; Zaslona, A. (from D-norvaline, manuscript in press; personal communication). Das, B. C. (personal communication). (c) The synthetic sample was found to be identical with the natural material by NMR, IR, MS, and GC (Dr. J. W., Daly, personal communication). (d) Indolizidines 205A, 207A, 209B, and 235B have been prepared in enantiomerically pure form: Shishido, Y.; Kibayashi, C. 15th Symposium on Progress in Organic Reactions and Syntheses; Kobe, Japan, November 7–8, 1989, pp 79–83.

(17) Felix, D.; Schreiber, J.; Ohloff, G.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 2896–2912.

(18) Woods, G. F.; Tucker, I. W. *J. Am. Chem. Soc.* **1948**, *70*, 2174–2177.

Scheme VI

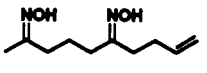


of the α,β-unsaturated ketone **22** was achieved in quantitative yield using alkaline hydrogen peroxide to give the α,β-epoxy ketone **23**, which readily fragmented under the Eschenmoser conditions[17] to give the acetylenic ketone **7b** (60–73% yield). Brief treatment[19] of **7b** with hydroxylamine gave the oxime **8b** (92% yield), which was subjected to the standard nitrone-forming conditions (cyanoborohydride reduction under mildly acidic conditions, extraction of the *N*-alkenylhydroxylamine into dichloromethane, and evaporation to dryness, followed by addition of a suitable aldehyde component). However, initial efforts (Scheme V) led to the surprising isolation of the cyclic nitrone **28** (79% yield), with only trace amounts of the required nitrone **10b**. This suggests that the acetylenic hydroxylamine **9b** cyclizes onto the terminal triple bond in preference to the terminal double bond as illustrated for the analogous *N*-alkenylhydroxylamines **9** (cf. Scheme III).[20] This reaction may well follow a pericyclic reaction pathway, and has some analogy with the cycloreversion process of nitrones to alkenes and oximes observed by Boyd et al.[21a] Related cyclizations of oximes have recently been reported by Bishop[21b] and Grigg and co-workers.[21c] The nitrone **28** is, itself, an *N*-alkenylnitrone, and when heated in refluxing toluene gave a single adduct **29** (74% yield). This novel pathway to cyclic nitrones with subsequent intramolecular trapping is currently under investigation.

A modified, more rapid workup procedure in the cyanoborohydride reduction/nitrone formation completely overcame the formation of **28** giving good yields of nitrone **10b**. The thermal cyclization of nitrone **10b** proceeded selectively for the double bond at 80 °C to give isoxazolidine **11b** as the sole adduct (63% from oxime **8b**).

By analogy with the synthesis of 167B (**3**), the adduct **11b** was readily converted into the axial C-8 (hydroxymethyl)indolizidine **13b** (Scheme IV) in 94% yield. In order to complete the synthesis of indolizidine 205A (**4**), it then remained to epimerize the C-8 substituent of **13b** and convert the side chain into a methyl group. Oxidation of **13b** to the corresponding aldehyde **24b** was not possible using chromium-based reagents owing to complexation of the indolizidine to the metal. The transformation was, however, achieved using Swern conditions.[22] The axial aldehyde **24b** thus obtained was readily epimerized to the corresponding equatorial aldehyde **25b** under basic conditions (either K_2CO_3 in MeOH or grade III basic alumina, EtOAc), with an equilibrium ratio of **25b**/**24b** = 17:1.[23,24] Preliminary investigations into the deoxygenation of aldehyde **25b** via modifications of the Wolff–Kishner reduction, in which the corresponding tosylhydrazone is reduced with sodium borohydride[25] or sodium cyanoborohydride,[26] resulted in low yields of the alkaloid 205A (**4**). A far superior deoxygenation procedure proved to be hydride reduction of the mesylate **27b** of the hydroxymethyl compound **26b** (obtained by $NaBH_4$/EtOH reduction of **25b**; 57% from **13b**). Thus Super-Hydride (Aldrich) reduction[27] completed the synthesis of indol-

(19) Prolonged exposure to excess hydroxylamine, or elevated temperatures, gave considerable amounts of the dioxime i.



i

(20) This was a rather surprising result, since alkyl-substituted 1-alkynes are reported not to react with hydroxylamines, even at elevated temperatures. See: Padwa, A.; Wong, G. S. K. *J. Org. Chem.* **1986**, *51*, 3125–3133. A referee has pointed out that addition of an *N*-alkylhydroxylamine to dimethyl acetylenedicarboxylate to form a nitrone which can be intermolecularly trapped is well precedented. See: Winterfeldt, E; Krohn, W.; Stracke, H.-U. *Chem. Ber.* **1969**, *102*, 2346–2361. This is of course an entirely different pathway from that observed for **28**.

(21) (a) Boyd, D. R.; Neill, D. C. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1308–1313. (b) Bishop, R.; Brooks, P. R.; Hawkins, S. C. *Synthesis* **1988**, 997. (c) Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron Lett.* **1990**, *31*, 559–562. (c) For the silver-catalyzed addition of oximes to allenes, see: Grimaldi, J.; Cormons, A. *Tetrahedron Lett.* **1985**, *26*, 825–828. Lathbury, D.; Gallagher, T. *Tetrahedron Lett* **1985**, *26*, 6249–6252. Lathbury, D.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1017–1018.

(22) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

(23) The two epimeric aldehydes were readily distinguished in the ^1H NMR spectrum by the characteristic aldehyde signals [δ_{ax} *CHO* 10.0 (d, J = 2.0 Hz), δ_{eq} *CHO* 0.65 (d, J = 2.0 Hz)]. Integration of the ^1H NMR spectrum of the equilibrium mixture indicated the ratio of **25b**/**24b** = 17:1. The aldehydes were not easily separated, but the corresponding 8-hydroxymethyl compounds were readily separated by flash chromatography on silica eluting with EtOAc/NH_3 mixtures.

(24) The epimerization of related aldehydes has been independently studied by LeBel. See ref 9c.

(25) Caglioti, L.; Grasselli, P. *Chem. Ind. (London)* **1964**, 153.

(26) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662–3668.

(27) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1973**, *95*, 1669–1671.

izidine 205A (4) in an overall yield of 16% from 21.[16c,d,28] Partial catalytic hydrogenation of the triple bond (Lindlar catalyst) of 205A (4) afforded the alkaloid 207A (5), which has been identified in the skin secretions of the frog *D. speciosus*.[16c,d]

Following the successful syntheses of racemic indolizidines 167B (3), 205A (4), and 207A (5), the enantioselective synthesis of (−)-indolizidine 209B was initiated. Consideration of the general strategy (Scheme I) shows that all three stereogenic centers in indolizidine 13 are controlled by a single stereogenic center α to the nitrogen in nitrone 10. An enantioselective synthesis therefore requires methodology for the asymmetric synthesis of the *N*-alkenylnitrone 10.[29] This requires the synthesis of the previously unknown enantiomerically pure α-chiral *N*-alkenylhydroxylamine 9.[30] An enantioselective synthesis of the amine 40, coupled with methodology for the oxidation of amines to hydroxylamines,[31] should produce the required hydroxylamine 9, provided that the pendant alkenyl side chain survives the oxidation procedure. In order to avoid similar complications with the potentially sensitive acetylenic side chain needed for a synthesis of indolizidine 205A (4), the perhydro version, indolizidine 209B (6), was chosen for enantioselective synthesis. This alkaloid had been identified as a trace component in the skin secretions of the frog *D. pumilio*. The synthesis of (−)-209B (6) is outlined in Scheme VI.

The required alkenylamine 40 was obtained in 53% overall yield from (*S*)-5-(hydroxymethyl)-2-pyrrolidinone (30)[32] by a chain-extension sequence. The alcohol 30 was tosylated (92%), and the tosylate 31 was coupled[33] with excess *n*-Bu_2CuLi (derived from *n*-butyllithium and copper(I) bromide–dimethyl sulfide complex) to introduce the pentyl side chain of 32 (88% yield). Hydrolysis of 32 in refluxing dilute hydrochloric acid gave a quantitative yield of the γ-amino acid 33, which was N-protected as the (benzyloxy)carbamate 34, and then converted into the methyl ester 35. Attempts to reduce the methyl ester 35 selectively to the corresponding aldehyde with diisobutylaluminum hydride were unsuccessful, giving significant quantities of the overreduced product 36. Therefore reduction was taken to completion (99% yield), and the resulting alcohol 36 was oxidized[22] to the corresponding closed hemiaminal 37 (86% yield). Treatment of 37 with the Wittig reagent derived from methyltriphenylphosphonium bromide and *n*-butyllithium in THF failed, but the ylide generated with dimsyl sodium[34] as base in DMSO reacted virtually instantaneously to give a 91% yield of the alkene 38. Care was needed in this Wittig reaction, since a second, slower reaction with the (benzyloxy)carbamate group was found to occur in the presence of excess ylide to give the acetamide 39. This could arise by further methylenation of the carbamate carbonyl group, to give a ketene aminal which would hydrolyze to the acetamide on workup. This second (slower) process in fact proved an efficient procedure (86%) for the preparation of 39. To our knowledge this has not previously been observed, although the methylenation of esters in dimethyl sulfoxide is well precedented.[35]

Removal of the (benzyloxy)carbamate protecting group from 38 proved to be somewhat difficult using a wide range of standard procedures.[36] However, application of a debenzylation procedure recently popularized by Ireland,[37] using the lithium radical anion of 4,4′-di-*tert*-butylbiphenyl (LiDBB), was found to be very effective at cleanly removing the benzyloxycarbamate protecting group. The reaction itself is little more than a titration of the dark green radical anion solution, and the workup/purification of the resulting primary amine is very straightforward, giving a near-quantitative yield of the enantiomerically pure amine 40.

The key series of reactions for converting the alkenylamine 40 into the *N*-alkenylhydroxylamine 9d involved formation of the imine 41 and chemoselective oxidation to the oxaziridine 42 (1 equiv of mCPBA, −78 °C → 20 °C; 88%).[38] Treatment with hydroxyammonium *p*-toluenesulfonate in methanol resulted in cleavage of the oxaziridine 42 to give the salt of the unstable[9a,b,12] enantiomerically pure *N*-alkenylhydroxylamine 9d, which was liberated under basic conditions and condensed with 4-acetoxybutanal to give the *N*-alkenylnitrone 10d in rather variable yield (25–45%). The thermal cyclization of the nitrone 10d proceeded smoothly in refluxing toluene to give a single, enantiomerically pure adduct (+)-11d[39] in 89% yield. Subsequent elaboration using the strategy developed for the synthesis of racemic 205A (4) resulted in the synthesis of (−)-indolizidine 209B (6)[40,16d] (42% yield from 11d).

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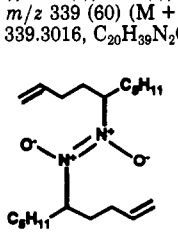
(38) No epoxidation of the alkene was observed, and in the presence of excess mCPBA, further oxidation occurred to give the nitroso dimer, 5(*R*),5′(*R*)-azobis(1-decene) *N*,*N*-dioxide ii: IR 3040, 1640, 1450, 1385, 1180, and 910 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.80–5.67 (2 H, m, 2 C*H*=CH_2), 5.45–5.38 (2 H, m, 2 C*H*N^+), 5.04–4.94 (4 H, m, 2 CH=CH_2), 2.04–1.86 (4 H, br s, 2 CH_2CH=CH_2), 1.70–1.40 (20 H, m, CH_2's), 0.84 (6 H, t, J = 6.6 Hz, 2 Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.0 (d), 137.0 (d), 115.7 (t), 115.6 (t), 66.2 (d), 66.2 (d), 31.9 (t), 31.9 (t), 31.4 (t), 31.3 (t), 31.3 (t), 31.2 (t), 30.1 (t), 30.1 (t), 25.6 (t), 25.5 (t), 22.4 (t), 22.4 (t), 13.9 (q), 13.9 (q); MS (CI) m/z 339 (60) $(M + H)^+$, 292 (52), 170 (100), 154 (20); found $(M + H)^+$ 339.3016, $C_{20}H_{39}N_2O_2$ requires 339.3022.



ii

(39) The enantiomeric excess was judged to be >95% by ^1H NMR chiral shift studies on (+)-11d and its racemate using (+)-Eu(hfc)$_3$.

(40) $[\alpha]^{22}_D$ −94.3° (*c* 1.85, MeOH). The optical rotation of natural 209B is not available at present owing to the lack of natural material.

In summary, the *N*-alkenylnitrones **10** have been shown to serve as extremely efficient precursors for the stereocontrolled construction of enantiomerically pure 5,8-disubstituted indolizidine alkaloids by a general strategy which should make these compounds readily available for biological evaluation.[28]

Experimental Section

General experimental and analytical techniques have been reported in a previous publication.[41] Optical rotations were measured using concentration expressed in g/100 mL. Small separations were carried out using a Harrison 7924 chromatotron on plates coated to a thickness of 1 mm with Merck 7749 silica. Gas chromatography was carried out on S.G.E. BP5 (5% phenylmethylsiloxane as stationary phase) 25-m column, diameter 0.3 mm, carrier gas flow rate 2.0 cm^3/min^{-1}. Hydrochloride salts of amines were prepared by passing dry HCl gas through a solution of the amine in dry dichloromethane for 10 min. Evaporation in vacuo gave the hydrochloride salt as a white solid. Hydrogen oxalate salts of isoxazolidine adducts were prepared by precipitation from an ethereal solution of the isoxazolidine upon treatment with a saturated solution of oxalic acid. Reagents were purified and dried where necessary by standard techniques.[42]

4-Acetoxybutanal. 4-Acetoxybutanol[43a] (8 g, 60.61 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise to a stirred suspension of pyridinium chlorochromate (19.6 g, 90.9 mmol) in dry CH_2Cl_2 (140 mL) containing powdered molecular sieves (3 Å, 30 g), at 0 °C. The suspension was allowed to warm to room temperature, stirred for 5 h, and evaporated under reduced pressure. Ether (300 mL) was added, and the suspension was filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with Et_2O–hexane (1:1) to give the 4-acetoxybutanal (5.78 g, 73%) as a colorless liquid, bp 41–42 °C (0.4 mmHg) (lit.[43b] bp 85–89 °C (14 mmHg); IR (liquid film) 2950, 2900, 2840, 2720, and 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 9.78 (1 H, t, J = 1.3 Hz, C*H*O), 4.10 (2 H, t, J = 6.2 Hz, CH_2OAc), 2.54–2.41 (2 H, m, CH_2CHO), 2.03 (3 H, s, Me), and 2.01–1.93 (2 H, m, CH_2CH_2OAc). Anal. Found: C, 54.3; H, 9.0. $C_6H_{12}O_3$ requires: C, 54.5; H, 9.2. Alternatively, oxidation of 4-acetoxybutanol (10 g, 75.8 mmol) in dry dichloromethane (150 mL) by the Swern[22] procedure using oxalyl chloride (7.9 mL, 91 mmol) in dry dichloromethane (200 mL) with dimethyl sulfoxide (DMSO, 12.9 mL, 182 mmol) in dry dichloromethane (50 mL) and dry triethylamine (63 mL, 452 mmol) gave, after flash chromatography on silica eluting with hexane/ethyl acetate (4:1 → 1:1), 4-acetoxybutanal (7.63 g, 77%).

Pentan-2-one *N*,*N*-Dimethylhydrazone (15). Pentan-2-one (21.5 g, 0.25 mol) and *N*,*N*-dimethylhydrazine (30 g, 0.5 mol) were refluxed for 6 h. The mixture was then cooled, NaOH pellets (4 g) were added, and the solution was allowed to stand for 12 h. The aqueous phase was removed, and the organic layer was distilled from NaOH pellets to give the hydrazone **15** (27.44 g, 86%) as a colorless liquid (mixture of geometrical isomers): bp 134 °C (lit.[9c] bp 133 °C); IR (liquid film) 2960, 2860, 2770, and 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 2.35 and 2.38 (6 H, 2 s, $NNMe_2$), 2.22–2.32 (2 H, m, $CH_2C{=}N$), 1.86 and 1.89 (3 H, 2 s, $CH_3C{=}N$), 1.35–1.64 (2 H, m, CH_3CH_2), and 0.76–0.99 (3 H, m, CH_3CH_2); MS m/z 129 (12) M^+ + 1, 128 (100) M^+, 113 (12), 100 (20), 99 (12), 85 (16), 84 (16), 72 (22), 71 (26), 70 (43), 68 (10), 59 (13), 58 (65), 57 (14), 56 (67), and 55 (12); found M^+ 128.1316, $C_7H_{16}N_2$ requires 128.1314.

Oct-7-en-4-one *N*,*N*-Dimethylhydrazone (16). *n*-Butyllithium (215 mL of a 1.6 M solution in hexane, 0.344 mol) was added to a stirred solution of pentan-2-one *N*,*N*-dimethylhydrazone **15** (38.5 g, 0.301 mol) in dry THF (200 mL) at −78 °C. Allyl bromide (36.42 g, 0.301 mol) was added, and the mixture was allowed to warm to room temperature over 2 h. Saturated NH_4Cl solution (1 L) was added, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 500 mL). The organic phases were washed with saturated NaCl solution (500 mL), combined, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was distilled to give the stereoisomeric mixture of hydrazones **16** (30.29 g, 60%) as a colorless liquid: bp 74–76 °C (15 mmHg); IR (liquid film) 3060, 2940, 2850, 2760, 1630, 990, and 900 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 5.66–5.78 (1 H, m, C*H*=CH_2), 4.88–5.15 (2 H, 3 m, CH=CH_2), 2.08–2.68 (6 H, m, $CH_2C{=}N$ and $CH_2CH_2C{=}N$), 2.37 and 2.38 (6 H, 2 s, $NNMe_2$), 1.36–1.69 (2 H, m, CH_3CH_2), and 0.91 and 0.94 (3 H, 2 t, J = 7.0 and 7.1 Hz, CH_3CH_2); MS m/z 168 (5) M^+, 127 (15), 126 (66), 125 (26), 124 (18), 110 (20), 98 (13), 97 (73), 94 (14), 84 (25), 83 (23), 82 (45), 81 (10), 80 (12), 72 (10), 71 (23), 70 (30), 69 (22), 68 (14), 67 (13), 60 (30), 59 (25), 58 (33), 57 (30), 56 (48), and 55 (100). (The yield of **16** when prepared on a 10-mmol scale was 91%.)

Oct-7-en-4-one Oxime (8a). Oct-7-en-4-one *N*,*N*-dimethylhydrazone (**16**; 210 mg, 1.25 mmol), hydroxylamine hydrochloride (248 mg, 3.57 mmol), and sodium acetate trihydrate (486 mg, 3.57 mmol) in absolute EtOH (30 mL) were refluxed for 20 h; the mixture was then evaporated under reduced pressure. Saturated NaCl solution (50 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with Et_2O–hexane (1:4) to give the stereoisomeric mixture of oximes **8a** (170 mg, 97%) as a colorless liquid: bp 110–112 °C (15 mmHg); IR (liquid film) 3250, 3080, 2960, 2920, 2870, 1640, 990, and 910 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 5.60–6.01 (1 H, m, C*H*=CH_2), 4.90–5.18 (2 H, 3 m, CH=CH_2), 2.06–2.52 [6 H, m, $CH_2{=}CHCH_2$ and $(CH_2)_2C{=}N$], 1.31–1.78 (2 H, m, CH_3CH_2), and 0.92 and 0.95 (3 H, 2 t, J = 6.5 and 6.6 Hz, CH_3); MS m/z 142 (3) M^+ + 1, 141 (5) M^+, 140 (8), M^+-1, 126 (35), 124 (15), 122 (16), 121 (10), 113 (76), 112 (25), 98 (45), 96 (20), 94 (13), 93 (10), 84 (10), 83 (11), 82 (43), 81 (42), 80 (19), 79 (28), 73 (26), 70 (33), 69 (20), 68 (14), 67 (35), 66 (10), 57 (16), 56 (17), and 55 (100). Anal. Found: C, 68.0; H, 10.9; N, 9.7. $C_8H_{15}NO$ requires: C, 68.0; H, 10.7; N, 9.9.

(2*R,5*S**,8*S**)-8-(3-Acetoxypropyl)-2-propyl-7-oxa-1-azabicyclo[3.2.1]octane (11a).** A mixture of 6 M HCl–MeOH (1:1) was added dropwise to a stirred solution of oct-7-en-4-one oxime (**8a**, 3.9 g, 27.66 mmol) and sodium cyanoborohydride (3.5 g, 55.73 mmol) in MeOH (100 mL) at 0 °C containing methyl orange (3 mg) so as to keep the mixture at pH 3. After 30 min the solution was basified with 6 M KOH, and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The organic phases were washed with saturated NaCl solution (100 mL), combined, dried ($MgSO_4$), and evaporated under reduced pressure, all at 0 °C. 4-Acetoxybutanal (3.6 g, 27.69 mmol) in dry toluene (10 mL) was added to a stirred mixture of the hydroxylamine in dry toluene (30 mL), containing Na_2SO_4 (6 g) at 0 °C. After 24 h the mixture was filtered and evaporated under reduced pressure. The residue was dissolved in dry toluene (150 mL), refluxed for 24 h, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with Et_2O–hexane (1:2) to give the isoxazolidine **11a** (2.85 g, 40%) as a colorless oil: IR (liquid film) 2940, 2860, 1740, and 1440 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 4.07 (2 H, dt, J = 6.6 and 2.8 Hz, CH_2OAc), 3.74–3.82 (2 H, m, CH_2ON), 2.86 (1 H, dd, J = 8.4 and 5.6 Hz, CHC*H*N), 2.55–2.58 (1 H, m, $(CH_2)_2CHN$), 2.39–2.42 (1 H, m, bridgehead H), 2.03 (3 H, s, $OCOCH_3$), 1.23–1.85 (12 H, m, $CH_2CH_2CH_2OAc$ and $(CH_2CH_2)_2CH$), and 0.87 (3 H, t, J = 7.0 Hz, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 171.0, 71.6, 71.0, 65.6, 64.4, 41.7, 37.3, 29.5, 28.5, 25.8, 24.8, 20.8, 19.3, and 14.0; MS m/z 255 (50) M^+, 196 (100), 182 (25), 154 (34), 152 (58), 141 (25), 124 (17), 96 (25), 82 (16), 71 (16), 69 (16), 67 (15), and 55 (42). Anal. Found for hydrogen oxalate (mp 152–4 °C): C, 55.6; H, 7.7; N, 4.4. $C_{16}H_{27}NO_7$ requires: C, 55.6; H, 7.9; N, 4.1.

(2*R,5*S**,8*S**)-8-(3-Hydroxypropyl)-2-propyl-7-oxa-1-azabicyclo[3.2.1]octane (12a).** (2*R**,5*S**,8*S**)-8-(3-Acetoxypropyl)-2-propyl-7-oxa-1-azabicyclo[3.2.1]octane (**11a**; 600 mg, 2.35 mmol) and KOH (4 g) in 95% EtOH (100 mL) were refluxed for 1 h. The mixture was then evaporated under reduced pressure and neutralized with dilute HCl solution, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic phases were washed with saturated NaCl solution (50 mL), combined, dried

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(Na_2SO_4), and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc–hexane (2:1) to give the isoxazolidine **12a** (420 mg, 84%) as a colorless liquid: IR (liquid film) 3400, 2930, 2860, and 1440 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.83 (2 H, d, J = 2.4 Hz, $CHCH_2O$), 3.65 (1 H, ddd, J = 11.3, 5.5, 3.9 Hz, $CHHOH$), 3.55 (1 H, ddd, J = 11.3, 7.9, 3.5 Hz, $CHHOH$), 2.89 (2 H, t, J = 6.5 Hz, $CHCH_2NCH_2$), 2.62–2.71 (1 H, m, $(CH_2)_2CHN$), 2.39–2.41 (1 H, m, bridgehead H), 1.19–1.87 (12 H, m, $(CH_2CH_2)_2CH$ and $CH_2CH_2CH_2OH$), and 0.87 (3 H, t, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 72.1, 71.8, 65.4, 62.5, 42.5, 37.2, 30.9, 30.3, 29.4, 24.5, 19.2, and 14.1; MS m/z 214 (17) $M^+ + 1$, 213 (56) M^+, 196 (12), 183 (14), 182 (38), 171 (12), 170 (88), 168 (38), 158 (22), 155 (14), 154 (100), 152 (18), 142 (28), 141 (20), 140 (48), 139 (13), 138 (14), 128 (10), 127 (10), 126 (52), 125 (12), 124 (27), 122 (17), 113 (11), 112 (28), 111 (22), 110 (32), 100 (18), 99 (11), 98 (23), 97 (33), 96 (41), 95 (17), 94 (11), 88 (17), 86 (12), 84 (18), 83 (17), 82 (35), 81 (57), 80 (11), 79 (12), 72 (50), 71 (82), 70 (23), 69 (41), 68 (25), 67 (28), 57 (13), 56 (17), and 55 (52); found M^+ 213.1746, $C_{12}H_{23}NO_2$ requires 213.1728. Anal. Found: C, 67.6; H, 11.1; N, 6.7. $C_{12}H_{23}NO_2$ requires: C, 67.6; H, 10.9; N, 6.6.

(5*R,8*S**,8a*S**)-8-(Hydroxymethyl)-5-propyloctahydroindolizine (13a).** Triethylamine (9.42 g, 93.09 mmol) was added dropwise to a stirred solution of (2*R**,5*S**,8*S**)-8-(3-hydroxypropyl)-2-propyl-7-oxa-1-azabicyclo[3.2.1]octane (**12a**; 2.2 g, 10.3 mmol) and methanesulfonyl chloride (5.86 g, 51.16 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C. After 2 h the mixture was evaporated under reduced pressure, dissolved in 50% AcOH (20 mL), and heated to 55 °C. Activated zinc dust (3.5 g) was added. After 2 h the mixture was filtered, evaporated under reduced pressure, and basified with saturated Na_2CO_3 solution, and the aqueous phase was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with CH_2Cl_2–MeOH–ammonia solution (98:1.5:0.5) to give the indolizidine **13a** (1.93 g, 95%) as a colorless oil: IR (liquid film) 3350, 2940, 2870, and 2790 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 4.20 (1 H, ddd, J = 10.8, 4.0, 1.4 Hz, $CHHOH$), 3.72 (1 H, d, J = 10.8 Hz, $CHHOH$), 3.16–3.24 (1 H, m, $NCHH$ or $(CH_2)_2CHN$), 2.32–2.39 (1 H, $NCHH$ or $(CH_2)_2CHN$), 1.22–2.08 (15 H, m, $(CH_2CH_2)_2CHN$, $CHCHCH_2CH_2$, and $NCHH$ or $(CH_2)_2CHN$), and 0.88 (3 H, t, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 67.2, 65.6, 63.8, 51.7, 36.9, 34.8, 31.3, 28.2, 26.2, 20.6, 17.9, and 14.5; MS m/z 197 (3) M^+, 196 (5), 155 (12), 154 (100), 96 (9), 84 (10), 71 (9), and 70 (15); found M^+ 197.1777, $C_{12}H_{23}NO$ requires 197.1779.

(5*R,8*S**,8a*S**)-8-Carboxy-5-propyloctahydroindolizine (17).** Jones reagent (2.60 mL of a 2.67 M solution, 6.94 mmol) was added dropwise to a stirred solution of 8-(hydroxymethyl)-5-propyloctahydroindolizine (**11a**; 670 mg, 3.40 mmol) in acetone (50 mL) at room temperature. After 10 min the reaction was quenched with 2-propanol; H_2O (15 mL) and trisodium citrate (4.5 g) were added. Then the flask was flushed with argon, and a catalytic amount of mossy zinc was added. After 10 min the aqueous phase was extracted with Et_2O (3 × 50 mL), and the ether extracts were evaporated under reduced pressure. The residue was purified by ion-exchange column chromatography on Amberlite IR-120 resin eluting with 2% ammonia solution to give the carboxylic acid **17** (480 mg, 67%) as a crystalline solid: mp 85–87 °C; IR ($CHCl_3$) 2960, 2860, 2500, and 1580 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.42–3.51 (1 H, m, $NCHH$ or $(CH_2)_2CHN$), 2.86 (1 H, br s, $CHCHN$), 2.32–2.49 and 2.55–2.62 (3 H, 2 m, $CHCHN$, $NCHH$, and $(CH_2)_2CHN$, or $NCHH$), 1.22–2.22 (12 H, m, $(CH_2CH_2)_2CHN$ and $CH_2CH_2CH_2N$), and 0.93 (3 H, t, J = 7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 175.8, 66.4, 63.0, 50.2, 42.9, 35.7, 27.5, 27.3, 26.0, 20.3, 17.8, and 14.0; MS m/z 212 (0.5) $M^+ + 1$, 211 (0.5) M^+ 210 (2), $M^+ - 1$, 169 (10), 168 (100), 124 (22), 122 (10), 96 (15), 70 (17); found M^+ 211.1568, $C_{12}H_{21}NO_2$ requires 211.1573. Anal. Found: C, 68.3; H, 9.8; N, 6.7. $C_{12}H_{21}NO_2$ requires: C, 68.2; H, 10.0; N, 6.6.

(5*R,8*R*,*S*,8a*S**)-8-(Phenylselenocarbonyl)-5-propyloctahydroindolizine (19).** Oxalyl chloride (84 mg, 0.661 mmol) was added to a stirred solution of (5*R**,8*S**,8a*S**)-8-carboxy-5-propyloctahydroindolizine (**17**; 70 mg, 0.332 mmol) in dry CH_2Cl_2 (5 mL) containing DMF (catalytic amount) at room temperature. After 15 min, the solution was evaporated under reduced pressure and dissolved in dry THF (5 mL), and pyridine (100 mg, 1.26 mmol) was added, followed by phenylselenol (261 mg, 1.66 mmol) in dry benzene (5 mL). The mixture was stirred at room temperature for 45 min and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–ammonia solution (100:0:0 to 97.5:2:0.5) to give the selenoester **19** (91 mg, 78%) as a mixture of isomers in a ratio of 5:2 and as a pale yellow oil: IR ($CHCl_3$) 2900, 2840, 2780, and 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.29–3.35 (1 H, m, H-3, H-5, or H-9), 3.01–3.06 (1 H, m, H-8), 7.23–7.63 (5 H, 4 m, Ph), 1.23–2.17 (15 H, m, H-3, H-5, or H-9, ring and side chain CH_2's), and 0.90 and 0.91 (3 H, 2 t, J = 7.2 and 7.1 Hz, CH_3).

(5*R,8a*R**)-5-Propyloctahydroindolizine Hydrochloride (Indolizidine 167B Hydrochloride, 3·HCl Salt).** Tri-*n*-butyltin hydride (12.25 mg, 0.042 mmol) and AIBN (catalytic amount) were added to (5*R**,8*R*,*S*,8a*S**)-8-((phenylseleno)carbonyl)-5-propyloctahydroindolizine (**19**; 9.85 mg, 0.028 mmol) in refluxing dry benzene (25 mL). After 10 min, the reaction mixture was cooled, dilute HCl solution (20 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The aqueous phase was made basic and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic basic extract was dried (Na_2SO_4), acidified with HCl gas, and evaporated under reduced pressure, saturated $NaHCO_3$ solution was added, and the aqueous phase was extracted with CH_2Cl_2 (2 × 1 mL). The extract was purified by column chromatography on alumina (neutral, grade III), eluting with CH_2Cl_2–hexane (2:8 to 6:4) to give, after acidification with HCl gas and evaporation under reduced pressure, the indolizidine 167B hydrochloride (**3·HCl** salt) (3.5 mg, 62%) as a crystalline solid: mp 167–169 °C; IR ($CHCl_3$) 2920, 2860, and 2400 cm^{-1}; ^1H NMR (CF_3CO_2D, 250 MHz) δ 3.83–3.91 (1 H, m, $H\text{-}3_{eq}$), 2.56–2.81 (3 H, m, $H\text{-}3_{ax}$, H-5, and H-9), 1.24–2.33 (14 H, ring and side chain CH_2's), and 0.93 (3 H, t, J = 7.2 Hz, CH_3); ^{13}C NMR (CF_3CO_2D, 100 MHz) δ 72.07, 69.02, 54.06, 36.43, 31.10, 30.64, 30.34, 24.39, 20.87, 20.11, and 14.27; MS m/z (free base) 167 (6) M^+, 166 (10), 125 (14), 124 (100), 96 (13), 70 (7); found M^+ 167.1674. $C_{11}H_{21}N$ requires 167.1674; GC retention time (free base) 4.8 min (96%). The sample was identical with an authentic sample.[10,16a]

3-(3-Butenyl)-2-cyclohexen-1-one (22). 1,2-Dibromoethane (0.10 mL) was added to a suspension of magnesium turnings (7.35 g, 275 mmol) in dry THF (15 mL) under N_2. When the reaction was initiated, a solution of 4-bromo-1-butene (31.41 g, 233 mmol) in dry THF (400 mL) was added dropwise at 20 °C without cooling. Stirring was continued for 1 h. The Grignard solution was cooled to 0 °C (upon which a white suspension of the Grignard reagent appeared) and 3-ethoxy-2-cyclohexen-1-one (**21**) (25.0 g, 179 mmol) in dry THF (100 mL) was added dropwise. The solution immediately turned yellow, and the white suspension dissolved. After 12 h the reaction was quenched with 15% aqueous acetic acid (250 mL) and stirred for 2 h. The organic layer was separated from the aqueous layer, which was extracted with dichloromethane (2 × 150 mL). The combined organic layers were evaporated in vacuo to remove most of the solvent. Saturated sodium bicarbonate solution (500 mL) was added, followed by solid sodium bicarbonate until effervescence ceased. The aqueous layer was removed and extracted with dichloromethane (2 × 150 mL), and the combined organic layers were washed with distilled water (150 mL) and dried ($MgSO_4$). Evaporation in vacuo gave the crude product **22** as an orange oil. Purification by flash chromatography on silica eluting with petroleum ether/ether (8:1) gave pure cyclohexenone **22** (25.04 g, 93%) as a pale yellow liquid: bp 129–130 °C (19 mmHg); IR (neat) 3080, 1665, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.86 (1 H, s, C=C*H*C=O), 5.81–5.68 (1 H, m, $CH{=}CH_2$) 5.06, 5.00, 4.96 (2 H, 3 signals, $CH{=}CH_2$), 2.36–2.21 (8 H, m), 2.01–1.91 (2 H, m); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 199.4, 165.1, 136.8, 125.8, 115.4, 37.2, 37.0, 30.8, 29.6, 22.5; MS m/z 150 (31) M^+, 132 (20), 121 (15), 107 (14), 104 (12), 94 (32), 93 (19), 91 (13), 81 (11), 80 (34), 79 (100), 77 (15), 66 (10), 53 (18); found M^+ 150.1038, $C_{10}H_{14}O$ requires 150.1045. Anal. Found: C, 80.1; H, 9.4. $C_{10}H_{14}O$ requires: C, 80.0; H, 9.4.

3-(3-Butenyl)-2,3-epoxycyclohexanone (23). Hydrogen peroxide solution (30%, 100 mL) and aqueous sodium hydroxide solution (20%, 0.5 mL) were added to a solution of the cyclohexenone (**22**; 21.43 g, 143 mmol) in methanol (150 mL). The temperature of the solution rapidly rose to 35 °C before dropping

back to room temperature. After 2 h, additional 30% hydrogen peroxide (100 mL) and 20% aqueous sodium hydroxide (0.5 mL) were added. After a further 8 h, the reaction mixture was saturated with solid sodium chloride, ice was added, and the resulting white suspension was extracted with dichloromethane (4 × 150 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to give the pure epoxide **23** (23.73 g, 100%) as a clear pale yellow liquid: bp 121–122 °C (41 mmHg); IR (CCl_4) 3080, 1710, and 1640 cm^{-1}; ^1H NMR δ 5.86–5.70 (1 H, m, C*H*=CH_2), 5.06, 5.00, 4.97 (2 H, 3 signals, CH=CH_2), 3.08 (1 H, s, OC*H*C=O), 2.55–2.43 (2 H, m, CH_2C=O), 2.23–1.57 (8 H, m); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 206.2, 137.0, 115.2, 64.7, 60.8, 35.7, 35.0, 28.6, 26.3, and 17.2; MS *m/z* 137 (9) M^+, 125 (45), 112 (64), 110 (11), 97 (98), 95 (14), 93 (32), 91 (25), 84 (30), 83 (18), 81 (31), 80 (15), 79 (100), 77 (27), 69 (26), 67 (76), 65 (13), 56 (11), 55 (84), 54 (17), 53 (43), and 51 (16). Anal. Found: C, 72.5; H, 8.4. $C_{10}H_{14}O_{25}$ requires: C, 72.3; H, 8.5.

1-Decen-9-yn-5-one (7b). 3-(3-Butenyl)-2,3-epoxycyclohexanone (**23**; 21.82 g, 131.4 mmol) in glacial acetic acid/dichloromethane (1:1 by volume, 350 mL) was cooled to −25 °C under N_2, and *p*-toluenesulphonyl hydrazide (24.48, g, 131.4 mmol) was added in one portion. The solution was stirred for 36 h at −15 °C, during which time the solution slowly turned yellow. The solution was warmed to 0 °C for 2 h and then to 20 °C for 6 h, during which time copious quantities of gaseous nitrogen were evolved. The reaction mixture was slowly poured into saturated sodium bicarbonate solution (1 L) containing ice, solid sodium bicarbonate was added, and the mixture was stirred until effervescence ceased. The supernatant aqueous layer was decanted off and extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with distilled water (1 L), and the aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to give the crude odoriforous acetylenic ketone **7b** as a red liquid. Distillation under reduced pressure afforded the pure acetylenic ketone (11.85 g, 60%) as a clear, colorless liquid: bp 56–58 °C (0.3 mmHg); IR (CCl_4) 3300, 3080, 2120, 1715, and 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.87–5.71 (1 H, m, C*H*=CH_2), 5.05, 4.98, 4.95 (2 H, 3 multiplets, CH=CH_2), 2.58–2.48 (4 H, m, CH_2COCH_2), 2.36–2.27 (2 H, m, CH_2C=C), 2.22 (2 H, dt, *J* = 6.9, 2.6 Hz, CH_2C≡C), 1.95 (1 H, t, *J* = 2.6 Hz, C≡C*H*), 1.78 (2 H, quintet, *J* = 6.9 Hz, $CH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 209.0, 136.9, 115.0, 83.4, 68.9, 41.7, 40.9, 27.6, 22.1, and 17.6; MS *m/z* 150 (1) M^+, 149 (4), 135 (5), 122 (11), 121 (12), 98 (15), 95 (55), 83 (47), 67 (35), 65 (14), 55 (100), 53 (11); found M^+ 150.1043, $C_{10}H_{14}O$ requires 150.1044. Anal. Found: C, 80.2; H, 9.6. $C_{10}H_{14}O$ requires C, 80.0; H, 9.4.

1-Decen-9-yn-5-one Oxime (8b). 1-Decen-9-yn-5-one (**7b**; 1.97 g, 13.1 mmol) was dissolved in pyridine/ethanol (1:1 by volume, 20 mL), hydroxylamine hydrochloride (2.73 g, 39 mmol) was added, and the solution was stirred at 20 °C for 15 min. The reaction mixture was poured into 2 N hydrochloric acid (50 mL) and was extracted with dichloromethane (4 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to give the crude oxime **8b** as a pale yellow liquid. Purification by flash chromatography on silica eluting with petroleum ether/ether (1:1) gave the pure oxime as a 1:1 mixture of geometrical isomers (2.00 g, 92%) as a pale yellow liquid: IR (CCl_4) 3600, 3500–3000, 3300, 3080, 2120, and 1635 cm^{-1}; ^1H NMR δ ($CDCl_3$, 250 MHz) 5.87–5.74 (1 H, m, C*H*=CH_2), 5.08, 5.00, 4.96 (2 H, 3 signals, CH=CH_2), 2.46–2.40 (2 H, m, CH_2C=C), 2.33–2.20 (6 H, m), 1.96 (1 H, m, C≡C*H*), 1.81–1.68 (2 H, m, $CH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 160.11 and 160.08; 137.40 and 137.19, 115.25 and 115.09, 83.65 and 83.58, 68.87 and 68.85, 33.54 and 32.98, 30.14 and 29.46, 24.82 and 24.41, 18.56 and 17.94; MS *m/z* 165 (2) M^+, 164 (7), 148 (37), 136 (69), 131 (17), 120 (46), 113 (63), 112 (27), 109 (18), 108 (16), 107 (16), 106 (18), 98 (51), 96 (21), 94 (31), 93 (27), 92 (26), 91 (54), 82 (23), 81 (63), 80 (31), 79 (53), 77 (33), 73 (30), 67 (74), 65 (29), 55 (100), 54 (54), and 53 (51); found M^+ 165.1149, $C_{10}H_{15}NO$ requires 165.1153. Anal. Found: C, 72.5; H, 9.4; N, 8.3. $C_{10}H_{15}NO$ requires: C, 72.7; H, 9.2; N, 8.5.

(2*R,5*S**,8*S**)-8-(3-Acetoxypropyl)-2-(4-pentynyl)-7-oxa-1-azabicyclo[3.2.1]octane (11b).** 1-Decen-9-yn-5-one oxime (**8b**, 1.59 g, 9.64 mmol) was dissolved in methanol (40 mL), and methyl orange indicator (5 drops) was added. The solution was stirred at −10 °C under N_2. Sodium cyanoborohydride (0.91 g, 14.5 mmol) was added, and a 6 M solution of hydrochloric acid in methanol was added dropwise to just keep the solution red. After 45 min, the solution was made strongly alkaline with 20% aqueous sodium hydroxide solution, poured into saturated brine containing ice (50 mL), and extracted with dichloromethane (4 × 50 mL). The organic extracts were added directly to a solution of 4-acetoxybutanal (2.1 g, 16 mmol) in dry dichloromethane (20 mL, containing anhydrous $MgSO_4$) at 0 °C. The suspension was stirred for 1 h, filtered, and evaporated in vacuo to give crude (±)-(*Z*)-4-{[1-(3-butenyl)-5-hexynyl]imino}-1-butyl acetate *N*-oxide **10b** as a pale yellow oil: ^1H NMR δ ($CDCl_3$, 250 MHz) 6.67 (1 H, t, *J* = 5.8 Hz, C*H*=N^+), 5.86–5.68 (1 H, m, C*H*=CH_2), 5.02, 5.00, 4.96 (2 H, 3 signals, CH=CH_2), 4.09 (2 H, t, *J* = 6.4 Hz, CH_2OAc), 3.64–3.58 (1 H, m, C*H*N^+), 2.60–2.47 (2 H, m, CH_2C=N^+), 2.08 ((3 H, s, CH_3), 1.97 (1 H, t, C≡C*H*), 2.3–1.2 (12 H, m); The crude nitrone **10b** was dissolved in dry toluene (250 mL, containing anhydrous $MgSO_4$) and stirred under N_2 at 76 °C for 15 h. Filtration and evaporation in vacuo gave the crude isoxazolidine **11b**, which was purified by flash chromatography on silica eluting with petroleum ether/ether (5:1 → 3:1) to give the pure isoxazolidine (1.70 g, 63%) as a pale yellow oil: IR (CCl_4) 3300, 2110, and 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 4.09–4.02 (2 H, m, CH_2OAc), 3.81–3.76 (2 H, m, CHCH_2O), 2.85 (1 H, dd, *J* = 5.6, 8.5 Hz, CHC*H*N), 2.64–2.50 (1 H, m, NC*H*CH_2), 2.40 (1 H, br s, bridgehead H), 2.19–2.13 (2 H, m, CH_2C≡C), 2.02 (3 H, s, CH_3), 1.91 (1 H, t, *J* = 2.6 Hz, C≡C*H*), 1.90–1.28 (12 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.05, 84.57, 71.58, 70.81, 68.09, 65.28, 64.31, 41.50, 33.96, 29.33, 28.31, 25.72, 25.12, 24.75, 20.90, 18.33.

Hydrogen oxalate salt: mp 127–128 °C; MS *m/z* 279 (10) M^+, 250 (7), 236 (9), 220 (48), 206 (16), 190 (9), 178 (14), 162 (13), 152 (15), 148 (11), 134 (13), 126 (26), 122 (23), 120 (19), 96 (100), 81 (73), 79 (50), 67 (60), and 55 (37); found M^+ 279.1828, $C_{16}H_{25}NO_3$ requires 279.1834. Anal. Found: C, 58.4; H, 7.3; N, 4.0. $C_{16}H_{25}NO_3 \cdot C_2H_2O_4$ requires: C, 58.5; H, 7.4; N, 3.8.

2-(3-Butenyl)-6-methyl-2,3,4,5-tetrahydropyridine 1-Oxide (28). A solution of the oxime (**8b**; 675 mg, 4.09 mmol) in MeOH (30 mL) containing methyl orange indicator (few drops) was treated with sodium cyanoborohydride (0.42 g, 8.2 mmol) and 0 °C under argon. The solution was treated with 6 M HCl in MeOH/water dropwise so as to keep the solution pink. After 30 min, the solution was poured into ice/brine (50 mL), made strongly basic (20% NaOH), and extracted with dichloromethane (4 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and stirred in the presence of Na_2SO_4 for 16 h. The solution was filtered, evaporated in vacuo, and purified by flash chromatography on silica, eluting with 10% methanol/ethyl acetate to give pure nitrone **28** (540 mg, 79%) as a colorless liquid which polymerized upon standing at 25 °C for 5 days: IR (CCl_4) 3080 and 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.85–5.69 (1 H, m, C*H*=CH_2), 4.98–4.89 (2 H, m, CH=CH_2), 3.71–3.66 (1 H, m, C*H*N^+), 2.42–2.34 (2 H, m, CH_2C=N^+), 2.15–2.06 (2 H, m, CH_2CH=CH_2), 2.03 (3 H, d, *J* = 1.1 Hz, Me), 1.94–1.22 (6 H, m); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 145.4 (s), 137.4 (d), 115.2 (t),66.1 (d), 31.3 (t), 30.7 (t), 30.4 (t), 26.5 (t), 18.9 (q), 15.5 (t); MS *m/z* 167 (6) M^+ 150 (10), 136 (12), 113 (26), 96 (100), 55 (56); found M^+ 167.1301, $C_{10}H_{17}NO$ requires 167.1310. Anal. Found: C, 71.8; H, 10.2; N, 8.4. $C_{10}H_{17}NO$ requires: C, 71.8; H, 10.2; N, 8.4.

(3*R,6*R**,10*S**)-10-Methyl-2-oxa-1-azatricyclo-[4.4.1^{3,10}.0]undecane (29).** A solution of the nitrone (**28**; 213 mg, 1.275 mmol) in dry toluene (25 mL) was refluxed using a Dean–Stark head for 20 h and evaporated in vacuo, and the residue was purified by flash chromatography on silica eluting with ethyl acetate to give the adduct **29** (157 mg, 74%) as an off-white crystalline solid: mp 59–60 °C; IR (CCl_4) 2940 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 4.34 (1 H, br s, C*H*O), 3.59–3.52 (1 H, m, C*H*N), 2.09–1.24 (12 H, m), 1.13 (3 H, s, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 74.9 (d), 64.0 (s), 54.3 (d), 41.4 (t), 34.0 (t), 32.4 (q), 29.0 (t), 19.6 (t), 14.9 (t); MS *m/z* 167 (55) M^+, 150 (18), 113 (97), 110 (45), 96 (100), 82 (30), 67 (23), 55 (69); found M^+ 167.1296, $C_{10}H_{17}NO$ requires 167.1310.

(2*R,5*S**,8*S**)-8-(3-Hydroxypropyl)-2-(4-pentynyl)-7-oxa-1-azabicyclo[3.2.1]octane (12b).** The acetate (**11b**; 1.69 g, 6.06 mmol) was dissolved in methanol (100 mL), anhydrous potassium carbonate (100 mg, catalytic) was added, and the solution was stirred at 20 °C under N_2 for 8 h. The methanol was evap-

orated in vacuo, and the residue was dissolved in ether and filtered through a short column of silica to give the pure alcohol **12b** (1.359 g, 95%) as a pale yellow liquid: IR (CCl_4) 3630, 3600–3100, 3300, and 2120 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.85 and 3.84 (2 H, 2 s, $CHCH_2O$), 3.71–3.52 (2 H, m, CH_2OH), 2.89 (1 H, t, J = 6.5 Hz, $CHCHN$), 2.74–2.63 (1 H, m, $NCHCH_2$), 2.42–2.39 (1 H, m, bridgehead H), 2.22–2.14 (2 H, m, $CH_2C{\equiv}C$), 1.92 (1 H, t, J = 2.7 Hz, $C{\equiv}CH$), 1.84–1.45 (12 H, m); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 84.38, 72.20, 71.77, 68.36, 65.17, 62.56, 42.33, 33.86, 30.85, 30.30, 29.24, 24.90, 24.51 and 18.39; MS m/z 237 (13) M^+, 220 (16), 208 (25), 206 (20), 192 (12), 184 (19), 178 (30), 170 (15), 162 (28), 154 (60), 152 (15), 148 (54), 135 (36), 126 (31), 122 (24), 120 (22), 112 (49), 110 (31), 97 (39), 96 (100), 91 (36), 81 (77), 79 (75), 77 (44), 71 (79), 67 (62), and 55 (75); found M^+ 237.1711, $C_{14}H_{23}NO_2$ requires 237.1729.

Hydrogen chloride salt: mp 103–105 °C.

(5*R,8*S**,8a*S**)-8-(Hydroxymethyl)-5-(4-pentynyl)octahydroindolizine (13b).** Triethylamine (6.04 mL, 43 mmol) was added dropwise to a stirred solution of the isoxazolidine (**12b**; 1.129 g, 4.764 mmol) and methanesulfonyl chloride (1.86 mL, 24 mmol) in dry dichloromethane at −10 °C. After 1 h, the solvent and excess reagents were evaporated in vacuo to give the crude mesylate salt. The residue was taken up in 50% aqueous acetic acid (30 mL) and treated with activated zinc dust (3 g, 46 mg·atom) at 55 °C for 2 h. The mixture was filtered with the aid of Celite, basified with aqueous 20% sodium hydroxide, and extracted with dichloromethane (1 × 50 mL, 3 × 25 mL). The combined organic layers were dried ($MgSO_4$), evaporated in vacuo, and purified by flash chromatography on silica eluting with dichloromethane/methanol/ammonia (98:1.5:0.5) to give the pure indolizidine alcohol **13b** (1.047 g, 99%) as a pale yellow liquid: IR (CCl_4) 3500–3000, 3300, 2780, 2700, and 2110 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 4.20 and 3.72 (2 H, 2 m, CH_2OH), 3.28–3.16 (1 H, m, H-3, H-5, or H-9), 2.42–2.30 (1 H, m, H-3, H-5 or H-9), 2.22–2.12 (2 H, m, $CH_2C{\equiv}C$), 2.12–2.00 (1 H, m, H-3, H-5, or H-9), 1.94 (1 H, t, J = 2.6 Hz, $C{\equiv}CH$), 2.00–1.44 (14 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 84.04, 68.34, 67.04, 65.11, 63.21, 51.55, 34.65, 33.29, 30.79, 27.85, 26.00, 23.30, 20.39, 18.53; MS m/z 221 (4) M^+, 190 (3), 180 (7), 155 (11), 154 (100), 122 (6), 96 (7), and 70 (9); found M^+ 221.1766, $C_{14}H_{23}NO$ requires 221.1779.

(5*R,8*R**,8a*S**)-8-Formyl-5-(4-pentynyl)octahydroindolizine (25b).** A solution of oxalyl chloride in dry dichloromethane was prepared (0.359 mL in 5 mL of solution). 0.50 mL (0.452 mmol) of the oxalyl chloride solution was cooled to −78 °C under N_2. A solution of DMSO in dry dichloromethane was prepared (0.642 mL in 5 mL of solution); 0.50 mL (0.904 mmol) of the DMSO solution was added dropwise over 5 min to the stirred oxalyl chloride solution at −78 °C under N_2. Stirring was continued for a further 20 min. The alcohol (**13b**; 50 mg, 0.226 mmol) in dry dichloromethane (0.50 mL) was added dropwise over 5 min to the cooled solution, and stirring was continued for a further 30 min. Triethylamine (0.315 mL, 2.26 mmol) was slowly added dropwise over 5 min, and stirring was continued at −78 °C for a further 10 min. The solution was then stirred at 0 °C for 30 min. Water (3 mL) was added, and the solution was stirred at 0 °C for 5 min, saturated sodium bicarbonate solution (2 mL) was then added, and stirring was continued for a further 5 min. Water (25 mL) was added, and the mixture was extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to give an orange oil; ^1H NMR showed a single aldehyde signal [($CDCl_3$, 90 MHz) δ 10.0 (d)] due to the aldehyde **24b**. The crude axial aldehyde **24b** was stirred in methanol (5 mL) with potassium carbonate (cat.), followed by purification on alumina eluting with ethyl acetate to give the epimerized aldehyde **25b** (43 mg, 87%) as a pale yellow liquid: IR (CCl_4) 3300, 2710, 2780, 2120, and 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 9.67 (1 H, d, J = 2.0 Hz, CHO), 3.26 (1 H, dt, J = 8.3, 2.4 Hz, H-5), 1.94 (1 H, t, J = 2.6 Hz, $C{\equiv}CH$), 2.27–1.25 (18 H, m); MS m/z 219 (3) M^+, 190 (4), 178 (4), 162 (3), 153 (10), 152 (100), 148 (5), 96 (12), 91 (16), and 70 (21); found M^+ 219.1643, $C_{14}H_{21}NO$ requires 219.1623.

(5*R,8*R**,8a*S**)-8-(Hydroxymethyl)-5-(4-pentynyl)octahydroindolizine (26b).** A solution of dry DMSO (2.36 mL, 33.3 mmol) in dry dichloromethane (7.5 mL) was added dropwise to a solution of oxalyl chloride (1.45 mL, 16.6 mmol) in dry dichloromethane (30 mL) cooled to −78 °C under N_2. The cooled solution was stirred for 20 min, and then a solution of the alcohol (**13b**; 2.45 g, 11.1 mmol) in dry dichloromethane (15 mL) was added dropwise. The cooled solution was stirred for an additional 30 min. Triethylamine (10.81 mL, 83 mmol) was added dropwise, and stirring was continued at −78 °C for 5 min. The solution was then allowed to warm to 0 °C and was stirred for a further 30 min. The solution was poured into saturated aqueous sodium bicarbonate solution (100 mL) and extracted with dichloromethane (4 × 50 mL). The organic layers were washed with a further 50 mL of sodium bicarbonate solution, combined, dried ($MgSO_4$), and evaporated in vacuo to give the crude aldehyde **24b** as an orange oil. The crude aldehyde **24b** was dissolved in methanol (100 mL), and potassium carbonate (ca. 100 mg, cat.) was added. The solution was stirred under N_2 for 48 h, after which time epimerization was complete (as judged by ^1H NMR analysis of the crude reaction mixture). Evaporation in vacuo gave the crude epimerized aldehyde **25b** as a brown oil, which was dissolved in dichloromethane (100 mL). The precipitated inorganic material was filtered off, and evaporation in vacuo gave the crude epimerized aldehyde **25b** as a brown oil (80%), which was used without further purification. The crude aldehyde **25b** was dissolved in dry ethanol (100 mL) at 0 °C under nitrogen, and sodium borohydride (840 mg, 22.2 mmol) was added to the stirred solution. After 15 min, the reaction mixture was poured into distilled water (150 mL), and the aqueous layer was extracted with dichloromethane (4 × 50 mL). The organic extracts were washed with distilled water (50 mL), dried ($MgSO_4$), and evaporated in vacuo to give the crude epimerized alcohol **26b** as a brown oil. Purification by flash chromatography on silica eluting with ethyl acetate/NH_3 (99:1) yielded the pure epimerized alcohol **26B** (1.40 g, 57% over three steps) as a pale yellow oil: IR (CCl_4) 3630, 3300, 2780, 2700, and 2100 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.65 (1 H, dd, J = 4.5, 10.7 Hz, $CHOH$), 3.47 (1 H, dd, J = 6.5, 10.7 Hz, $CHOH$), 3.27 (1 H, m, H-5), 2.19 (2 H, m, $CH_2C{\equiv}C$), 1.94 (1 H, t, J = 2.7 Hz, $C{\equiv}CH$), 2.0–1.0 (16 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 88.20, 68.35, 66.74, 65.12, 62.77, 51.31, 44.05, 33.39, 30.41, 28.85, 27.77, 24.61, 20.44, 18.59; MS m/z 221 (5) M^+, 220 (2), 190 (10), 180 (18), 154 (100); found M^+ 221.1777, $C_{14}H_{23}NO$ requires 221.1780.

Hydrogen chloride salt: mp 179–180 °C.

(5*R,8*R**,8a*S**)-8-Methyl-5-(4-pentynyl)octahydroindolizine [(±)-Indolizidine 205A, 4].** The alcohol (**26b**; 1.40 g, 6.33 mmol) in dry dichloromethane (50 mL) at 0 °C under N_2 was treated dropwise with methanesulfonyl chloride (0.99 mL, 12.7 mmol) followed by dry triethylamine (3.30 mL, 25 mmol). The solution was stirred for 1 h at 0 °C. The reaction mixture was poured into saturated sodium bicarbonate solution (100 mL) and extracted with dichloromethane (4 × 50 mL). The organic extracts were washed with a further 50 mL of sodium bicarbonate solution, combined, dried ($MgSO_4$), and evaporated in vacuo to give the crude mesylate **27b** as an orange oil. The crude mesylate was dissolved in dry THF (50 mL) and cooled to 0 °C under N_2, and lithium triethylborohydride (25 mL of a 1 M solution in THF, 25 mmol) was added dropwise. Reduction to indolizidine 205A (**4**) was virtually instantaneous. The reaction mixture was poured into distilled water (100 mL) and extracted with dichloromethane (4 × 50 mL). The organic layers were washed with saturated sodium bicarbonate solution (50 mL), dried ($MgSO_4$), and evaporated in vacuo to give crude indolizidine 205A (**4**) as a pale brown oil. Purification by flash chromatography on silica, eluting with ethyl acetate/NH_3 (99:1), yielded the pure (±)-indolizidine **4** as a mobile pale yellow oil (1.17 g, 90%): IR (CCl_4) 3300, 2770, 2700, and 2120 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.34–3.20 (1 H, m, H-5), 1.94 (1 H, t, J = 2.6 Hz, $C{\equiv}CH$), 0.86 (3 H, d, J = 6.5 Hz, CH_3), 2.19–1.17 (18 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 88.41, 71.31, 68.35, 62.94, 51.84, 36.55, 33.72, 33.62, 31.20, 29.07, 24.79, 20.36, 18.88, 18.77; MS m/z 205 (2) M^+, 204 (1), and 138 (100); Found M^+ 205.1841, $C_{14}H_{23}N$ requires 205.1830.

Hydrogen chloride salt: mp 168–169 °C.

(5*R,8*R**,8a*S**)-8-Methyl-5-(4-pentenyl)octahydroindolizine [(±)-Indolizidine 207A Hydrochloride, 5·HCl Salt].** Indolizidine 205A (**4**; 45 mg) and Lindlar catalyst (Hoffmann-La Roche "Katalysator type C", 20 mg) were stirred in ethyl acetate under H_2 at 20 °C, and the reaction was monitored by GC. When reduction of the acetylene was just complete, the reaction mixture was filtered and evaporated in vacuo to give the product (±)-

indolizidines 207A (5) and 209B (6) (45 mg, 100%) in a ratio of 20:1. Conversion into the hydrochloride salt gave an off-white crystalline solid: mp 144–145 °C; IR (CCl_4) 3080, 2800–2100, and 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 10.7 (1 H, br s, N*H*$^+$), 5.75 (1 H, m, C=C*H*), 5.00 (2 H, m, C*H*$_2$=C), 3.87 (1 H, m, H-5), 2.6–1.1 (18 H, m), 0.97 (3 H, J = 6.3 Hz, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.5, 115.4, 73.2, 65.0, 50.7, 33.1, 33.0, 32.0, 30.7, 28.1, 27.1, 24.7, 19.2, 18.3; MS m/z 207 (3) M^+, 138 (100), 96 (27); found M^+ 207.1970, $C_{14}H_{25}N$ requires 207.1986.

(5*R,8*R**,8a*S**)-8-Methyl-5-(4-pentyl)octahydroindolizine [(±)-Indolizidine 209B Hydrochloride, 6·HCl Salt].** Indolizidine 205A hydrochloride (4·HCl salt; 27.4 mg) was treated with dilute sodium bicarbonate solution (5 mL) and extracted with dichloromethane (4 × 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to give the free base. The free base was dissolved in ethyl acetate (2 mL) and 10% Pd/C (10 mg) was added. The resulting suspension was stirred vigorously under H_2 for 30 min, after which time reduction to indolizidine 209B was complete. Filtration and conversion into the hydrochloride salt gave indolizidine 209B hydrochloride (6·HCl salt) (27.6 mg, 100%) as an off-white solid: mp 150–152 °C; IR ($CHCl_3$) 2800–2000 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 11.7 (1 H, br s, N*H*$^+$), 3.87 (1 H, m, H-5), 2.68–1.02 (20 H, m), 0.96 (3 H, d, J = 6.2 Hz, Me), 0.86 (3 H, J = 6.7 Hz, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 73.0, 65.2, 50.6, 33.1, 31.9, 31.3, 31.2, 28.0, 27.0, 25.2, 22.3, 19.2, 18.2, 13.7; MS m/z 209 (1) M^+, 138 (100), 96 (10); found M^+ 209.2164, $C_{14}H_{27}N$ requires 209.2144.

(*S*)-5-(((*p*-Tolylsulfonyl)oxy)methyl)-2-pyrrolidinone (31). A solution of the alcohol (**30**;[30] 17.60 g, 153 mmol) in dry dichloromethane (1 L) was treated with dry Et_3N (200 mL, 1.44 mol), DMAP (2.0 g, 15.3 mmol), and *p*-toluenesulfonyl chloride (40 g, 214 mmol). The resulting solution was stirred at 20 °C under N_2 for 16 h, poured into distilled water (1 L), acidified (concentrated HCl), and extracted. The upper aqueous layer was extracted with dichloromethane (2 × 200 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to give the crude tosylate as a pale yellow solid. Recrystallization from ethyl acetate/hexane gave the pure tosylate **31** (37.92 g, 92%) as off-white plates: mp 125–126 °C; $[\alpha]^{20}_D$ + 10.8° (*c* 1.88, CH_2Cl_2); IR ($CHCl_3$) 3430, 1700, 1600, 1360, and 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.78 (2 H, d, J = 8.4 Hz, Ar), 7.36 (2 H, d, J = 8.4 Hz, Ar), 5.81 (1 H, br, N*H*), 4.05 (1 H, dd, J = 3.1, 9.2 Hz, CH*H*OTs), 3.84 (1 H, dd, J = 7.3, 9.2 Hz, C*H*HOTs), 3.90 (1 H, m, C*H*N), 2.45 (3 H, s, Me), 2.34–2.19 (3 H, m, C*H*C*H*$_2$C=O), 1.80–1.68 (1 H, m, C*H*CH$_2$C=O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.9, 145.2, 132.2, 130.0, 127.8, 52.5, 29.2, 22.7, 21.6; MS m/z 269 (0.9) M^+, 239 (3), 84 (100); found M^+ 269.0699, $C_{12}H_{15}NSO_4$ requires 269.0722. Anal. Found: C, 53.3; H, 5.3; N, 5.2; S, 12.3. $C_{12}H_{15}NSO_4$ requires: C, 53.5; H, 5.1; N, 5.2; S, 11.9.

(*R*)-5-Pentyl-2-pyrrolidinone (32). Freshly recrystallized CuBr·DMS complex (15.3 g, 74.4 mmol) suspended in dry ether (300 mL) was mechanically stirred under argon at −40 °C, and *n*-butyllithium (93 mL of a 1.60 M solution in hexane, 148.8 mmol) was added dropwise over 1 h. A solution of the tosylate (**31**; 4.00 g, 14.9 mmol) in dry DME (100 mL) was added dropwise through a cannula to the cuprate at −40 °C, and the resulting solution was maintained at −40 °C for 4 h, and then overnight at −20 °C. Saturated ammonium chloride solution (1 L) was added, and the mixed solution was separated. The upper organic layer was washed with a further 200 mL of a saturated ammonium chloride solution, and the aqueous washings were extracted with dichloromethane (2 × 200 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to give a pale yellow oil. Purification by flash chromatography on silica, eluting with ethyl acetate/methanol (1:0 → 9:1), gave the pure alkylated product **32** (2.022 g, 88%) as a pale yellow oil: $[\alpha]^{20}_D$ +8.51° (*c* 1.14, CH_2Cl_2); IR (CH_2Cl_2) 3430 and 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.11 (1 H, br s, N*H*), 3.66–3.55 (1 H, m, C*H*N), 2.35–2.16 (3 H, m, C*H*C*H*$_2$C=O), 1.81–1.31 (4 H, m), 1.28 (5 H, br s), 0.87 (3 H, t, J = 6.7 Hz, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.6, 54.7, 36.6, 31.6, 30.4, 27.2, 25.4, 22.4, 13.9; MS m/z 155 (5) M^+ 84 (100), 69 (3), 56 (6); found M^+ 155.1314, $C_9H_{17}NO$ requires 155.1310.

(*R*)-4-Aminononanoic Acid (33). Lactam (**32**; 2.34 g, 15.1 mmol) was heated to reflux under N_2 in 2 M aqueous HCl (50 mL) for 16 h, evaporated in vacuo, and purified by ion-exchange chromatography on DOWEX 50X8-400 ion exchange resin, eluting first with distilled water and then aqueous ammonia (H_2O/0.88 NH_3, 10:1). Evaporation in vacuo of the fractions containing the amino acid gave the pure amino acid **33** (2.62 g, 100%) as a white solid: mp 131–132 °C; $[\alpha]^{20}_D$ +11.2° (*c* 2.82, H_2O); IR (KBr disk) 2500, 2100, 1560, and 1400 cm^{-1}; ^1H NMR (CD_3OD, 250 MHz) δ 3.11 (1 H, m, C*H*N), 2.46–2.24 (2 H, m, C*H*$_2$CO$_2$), 1.87–1.56 (4 H, m), 1.48–1.34 (6 H, br s), 0.93 (3 H, t, J = 6.7 Hz, Me); ^{13}C NMR (CD_3OD, 100 MHz) δ 180.6, 53.5, 35.1, 34.3, 32.7, 29.9, 26.1, 23.5, 14.4; MS m/z 174 (5) $(M + H)^+$, 155 (6), 102 (51), 100 (23), 84 (100), 56 (10); found $(M + H)^+$ 174.1502, $C_9H_{19}NO_2$ requires 174.1494.

(*R*)-4-((Benzyloxycarbonyl)amino)nonanoic Acid (34). A solution of the amino acid (**33**; 2.62 g, 15.1 mmol) in 2 M NaOH (50 mL) was cooled under N_2 in an ice bath and treated with benzyl chloroformate (4.32 mL, 30.2 mmol). The solution was stirred at 20 °C overnight, the THF was evaporated in vacuo, ether (50 mL) was added, and the organic layer was separated. The ether layer was extracted with a further quantity of 2 M NaOH (3 × 50 mL), and the combined aqueous extracts were acidified (concentrated HCl) and extracted with dichloromethane (4 × 50 mL). The combined dichloromethane extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo to give the crude carbamate as a pale yellow oil. Recrystallization from ethyl acetate/hexane gave the pure carbamate **34** as a white solid, and purification of the residue by flash chromatography on silica, eluting with ethyl acetate/hexane (1:5 → 1:1), gave further carbamate (total yield 4.10 g, 88%): mp 74–75 °C; $[\alpha]^{20}_D$ +2.23° (*c* 8.37, CH_2Cl_2); IR ($CHCl_3$) 3430, 3500–2400, and 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.35 (5 H, m, Ph), 5.08 (2 H, s, C*H*$_2$O), 4.55 (1 H, br d, J = 9.3 Hz, N*H*), 3.70–3.59 (1 H, br s, C*H*N), 2.41 (2 H, t, J = 7.4 Hz, C*H*$_2$CO$_2$H), 1.94–1.81 (1 H, m), 1.71–1.55 (1 H, m), 1.52–1.18 (8 H, br m), 0.86 (3 H, t, J = 6.4 Hz, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.9, 156.4, 136.5, 128.5, 128.1, 128.0, 66.7, 51.0, 35.5, 31.6, 30.8, 30.3, 25.5, 22.5, 14.0; MS m/z 307 (2) M^+, 236 (8), 192 (18), 190 (10), 172 (10), 108 (18), 91 (100), 84 (10); found M^+ 307.1799, $C_{17}H_{25}NO_4$ requires 307.1784.

Methyl (*R*)-4-((Benzyloxycarbonyl)amino)nonanoate (35). A solution of the acid (**34**; 3.92 g, 12.8 mmol) in dry MeOH (40 mL) was treated with a saturated solution of HCl in dry MeOH (10 mL) and stirred at 20 °C for 1 h. The solution was evaporated in vacuo to give the pure ester **35** (4.10 g, 100%) as a white crystalline solid: mp 64–65 °C; $[\alpha]^{20}_D$ +3.36° (*c* 3.27, CH_2Cl_2); IR (CCl_4) 3430 and 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.36–7.29 (5 H, m, Ph), 5.07 (2 H, s, C*H*$_2$O), 4.49 (1 H, br d, J = 9.2 Hz, N*H*), 3.63 (3 H, s, OMe), 3.72–3.54 (1 H, br s, C*H*N), 2.37 (2 H, t, J = 7.6 Hz, C*H*$_2$CO$_2$Me), 1.94–1.81 (1 H, m), 1.71–1.55 (1 H, m), 1.49–1.26 (8 H, br m), 0.86 (3 H, t, J = 6.6 Hz, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.1, 156.2, 136.6, 128.5, 128.0, 66.6, 51.6, 51.1, 35.6, 31.6, 30.8, 30.4, 25.4, 22.5, 14.0; MS m/z 321 (2) M^+, 250 (7), 206 (11), 166 (13), 107 (23), 91 (100), 84 (70); found M^+ 321.1928, $C_{18}H_{27}NO_4$ requires 321.1940. Anal. Found: C, 67.4; H, 8.6; N, 4.5. $C_{18}H_{27}NO_4$ requires: C, 67.3; H, 8.5; N, 4.4.

(*R*)-4-((Benzyloxycarbonyl)amino)-1-nonanol (36). A solution of the ester (**35**; 4.10 g, 12.8 mmol) in dry THF (40 mL) at −78 °C under N_2 was treated with DIBAL (40 mL of a 1.0 M solution in toluene, 40 mmol), and stirring was continued for 30 min. The reaction was quenched at −78 °C by the careful addition of 2 M HCl (100 mL), allowed to warm up to 20 °C, and extracted into ethyl acetate (3 × 100 mL). The organic layers were washed with water (100 mL), combined, dried ($MgSO_4$), and evaporated in vacuo to give a white solid. Purification by flash chromatography on silica eluting with ethyl acetate/hexane (1:1) gave the pure alcohol **36** (3.69 g, 99%) as a white crystalline solid: mp 63–63.5 °C; R_f = 0.24, EtOAc/hexane (1:1); $[\alpha]^{20}_D$ +3.06° (*c* 2.29, CH_2Cl_2); IR (CCl_4) 3600, 3600–3200, 3430, and 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.36–7.29 (5 H, m, Ph), 5.08 (2 H, s, PhC*H*$_2$O), 4.53 (1 H, br s, N*H*), 3.65 (2 H, t, J = 5.7 Hz, C*H*$_2$OH), 3.74–3.54 (1 H, br s, C*H*N), 1.62–1.26 (12 H, m), 0.86 (3 H, t, J = 6.5 Hz, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.3 (s), 136.6 (s), 128.5 (d), 128.0 (d), 66.5(t), 62.5 (t), 51.1 (d), 35.5 (t), 31.9 (t), 31.7 (t), 28.8 (t), 25.5 (t), 22.5 (t), 14.0 (q); MS m/z 293 (1) M^+, 236 (1), 222 (4), 190 (4), 178 (13), 141 (10), 108 (10), 91 (100), 71 (27); found M^+ 293.2001, $C_{17}H_{27}NO_3$ requires 293.1991. Anal. Found: C, 69.3; H, 9.2; N, 4.7. $C_{17}H_{27}NO_3$ requires: C, 69.6; H, 9.3; N, 4.8.

N-(Benzyloxycarbonyl)-2-hydroxy-5(R)-pentylpyrrolidine (37). DMSO (3.58 mL, 50.4 mmol) in dry dichloromethane (20 mL) was added dropwise to a solution of oxalyl chloride (2.20 mL, 25.2 mmol) in dry dichloromethane (50 mL) at −78 °C under N_2. The resulting solution was stirred for 30 min, and then a solution of the alcohol (**36**; 3.69 g, 12.6 mmol) in dry dichloromethane (20 mL) was added dropwise. The resulting white suspension was stirred at −78 °C for 30 min, and then dry triethylamine (35 mL) was added. The solution was stirred at −78 °C for 10 min and then allowed to warm up to 0 °C for 30 min. The white suspension was poured into saturated sodium bicarbonate solution (100 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to give a pale yellow oil. Purification by flash chromatography on silica eluting with ethyl acetate/hexane (1:5) gave the pure hemiaminal **37** (3.05 g, 83%) as a pale yellow oil, consisting of two diastereomers: $[\alpha]^{20}_D$ −32.7° (*c* 9.32, CH_2Cl_2); IR (CCl_4) 3600 and 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.36–7.30 (5 H, m, Ph), 5.57–5.40 (1 H, m, OC*H*N), 5.11 and 5.19 (2 H, AB quartet, *J* = 12.3 Hz, PhCH_2O), 3.95–3.72 (1 H, m, C*H*N), 2.26–1.22 (12 H, m), 0.86 (3 H, br s, Me); MS *m/z* 291 (0.3) M^+, 273 (1), 220 (1), 176 (18), 158 (35), 91 (100), 65 (10); found M^+ 291.1836, $C_{17}H_{25}NO_3$ requires 291.1834.

(R)-N-(Benzyloxycarbonyl)-1-decen-5-amine (38). Sodium hydride (553 mg of a 50% dispersion in oil, 11.5 mmol) was washed with hexane and then treated with dry DMSO (5 mL) under N_2. The suspension was heated to 80 °C for 1 h, and then methyl(triphenyl)phosphonium bromide (4.49 g, 12.8 mmol) in dry DMSO (10 mL) was added dropwise to the cooled solution of dimsyl sodium. The ylide solution (1.2 mL, 12.56 mmol) was added dropwise to a stirred solution of the hemiaminal (**37**; 3.047 g, 10.47 mmol) in dry DMSO (10 mL) at 20 °C under N_2. After 20 min the reaction was quenched by the addition of 10 mL of saturated ammonium chloride solution, and the product was poured into distilled water (200 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to give the crude alkene as a pale yellow oil. Purification by flash chromatography on silica eluting with ethyl acetate/hexane (1:6 → 1:1) gave the pure alkene carbamate **38** (2.74 g, 91%) as a white crystalline solid, together with the alkene acetamide **39** (77.3 mg, 4%) as a white crystalline solid. The carbamate **38** was recrystallized from aqueous methanol to yield colorless crystals: mp 55–56 °C; $[\alpha]^{20}_D$ +1.29° (*c* 7.43, CH_2Cl_2); IR (CCl_4) 3430, 1720, and 1635 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.36–7.28 (5 H, m, Ph), 5.85–5.75 (1 H, m, C*H*CH_2), 5.08 (2 H, s, CH_2O), 5.03, 4.97, 4.93 (2 H, 3 signals, C=CH_2), 4.46 (1 H, br d, *J* = 8.9 Hz, N*H*), 3.72–3.55 (1 H, br s, C*H*N), 2.13–2.04 (2 H, m, CH_2CH=CH_2), 1.66–1.25 (10 H, m), 0.86 (3 H, t, *J* = 6.3 Hz, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.0, 138.1, 136.7, 128.5, 128.0, 114.8, 66.5, 51.0, 35.3, 34.6, 31.7, 30.1, 25.4, 22.5, 14.0; MS *m/z* 289 (1) M^+, 236 (3), 218 (4), 190 (7), 176 (39), 108 (11), 91 (100); found M^+ 289.2038, $C_{18}H_{27}NO_2$ requires 289.2041.

(R)-1-Decen-5-acetamide (39). Recrystallization from aqueous methanol afforded colorless crystals: mp 69–70 °C; $[\alpha]^{20}_D$ +6.4° (*c* 1.15, CH_2Cl_2); IR (CCl_4) 3430, 3300, 3080, 1670, and 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.88–5.72 (1 H, m, C*H*=CH_2), 5.15 (1 H, br d, *J* = 8.6 Hz, N*H*), 5.04, 4.97, 4.93 (2 H, 3 signals, CH=CH_2), 3.97–3.88 (1 H, m, C*H*N), 2.13–2.00 (2 H, m, CH_2C=C), 1.97 (3 H, s, COCH_3), 1.74–1.20 (10 H, m), 0.86 (3 H, t, *J* = 6.8 Hz, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.5 (s), 138.2 (d), 114.7 (t), 49.0 (d), 35.1 (t), 34.4 (t), 31.7 (t) 30.1 (t), 25.5 (t), 23.5 (q), 22.5 (t), 14.0 (q); MS *m/z* 197 (3) M^+ 142 (57), 126 (61), 100 (100), 84 (99), 60 (32); found M^+ 197.1773; $C_{12}H_{23}NO$ requires 197.1780.

(R)-1-Decen-5-amine (40). Lithium shot (ca. 300 mg, an excess) was washed with hexane, dry methanol, dry ether, and dry THF under argon and added to a solution of 4,4′-di-*tert*-butylbiphenyl (6.72 g, 25.3 mmol) in dry THF (50 mL) under argon. The solution was vigorously stirred at 25 °C until the surface of the lithium was coated in the green radical anion and then cooled to 0 °C. After 30 min the solution turned dark green, and stirring was continued for a further 2 h. The green radical anion solution was added dropwise to a solution of the (benzyloxy)carbamate (**38**; 2.18 g, 7.54 mmol) in dry THF (50 mL) under argon at −78 °C until the green color persisted in the reaction mixture. Stirring was continued for 30 min at −78 °C, and then the reaction was quenched at −78 °C by the addition of water (40 mL). The solution was allowed to warm up to 25 °C, and the THF was removed by evaporation in vacuo. The residue was poured into 2 M HCl (50 mL) and ether (50 mL) and extracted. The ether layer was extracted with further 2 M HCl (3 × 50 mL), and the combined aqueous layers were basified with 20% NaOH and extracted with ether (4 × 150 mL). The ether layers were washed with distilled water (50 mL), dried (Na_2SO_4), and evaporated in vacuo to give pure amine **40** (1.11 g, 95%) as a colorless liquid: $[\alpha]^{20}_D$ +2.30° (*c* 3.95, CH_2Cl_2); IR (CCl_4) 3080 and 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.87–5.71 (1 H, m, C*H*=CH_2), 5.04–4.89 (2 H, m, CH=CH_2), 2.69–2.64 (1 H, m, C*H*N), 2.16–1.99 (2 H, m, CH_2C=C), 1.55–1.10 (12 H, m), 0.86 (3 H, t, *J* = 6.7 Hz, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5 (d), 114.2 (t), 50.5 (d), 37.8 (t), 36.9 (t), 31.8 (t), 30.3 (t), 25.6 (t), 22.4 (t), 13.8 (q); MS *m/z* 156 (7) $(M + H)^+$, 155 (1) M^+, 154 (10), 126 (10), 112 (23), 100 (83), 84 (100), 67 (18), 55 (12); found M^+ 155.1671, $C_{10}H_{21}N$ requires 155.1674.

(E)-N-(4-Methoxybenzylidene)-1-decen-5(R)-amine (41). The amine (**40**; 1.07 g, 6.90 mmol) and anisaldehyde (0.94 g, 6.90 mmol) in dry dichloromethane (20 mL) were treated with anhydrous Na_2SO_4 (ca. 3 g) and stirred under argon for 16 h. The solution was filtered and evaporated in vacuo to give the imine **41** (1.88 g, 100%) as a yellow oil: $[\alpha]^{20}_D$ −10.3° (*c* 2.47, CH_2Cl_2); IR (CCl_4) 3080, 1640, 1600, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.12 (1 H, s, C*H*=N), 7.67 (2 H, d, *J* = 8.8 Hz, Ar), 6.91 (2 H, d, *J* = 8.8 Hz, Ar), 5.87–5.71 (1 H, m, C*H*=CH_2), 5.00–4.89 (2 H, m, CH=CH_2), 3.83 (3 H, s, OMe), 3.11–3.01 (1 H, C*H*N), 2.09–1.85 (2 H, m, CH_2C=C), 1.80–1.54 (4 H, m, CH_2C(N)CH_2), 1.26–1.14 (6 H, br s, C*H*'s), 0.84 (3 H, t, *J* = 6.6 Hz, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.4 (s), 158.7 (d), 138.7 (d), 129.6 (d), 129.3 (s), 114.3 (t), 113.9 (d), 71.0 (d), 55.3 (q), 36.3 (t), 35.4 (t), 31.8 (t), 30.7 (t), 26.1 (t), 22.6 (t), 14.0 (q); MS *m/z* 273 (30) M^+, 272 (100), 218 (20), 202 (30), 162 (25), 134 (30), 121 (38); found $(M - H)^+$ 272.2008, $C_{19}H_{26}NO$ requires 272.2014.

N-[1(R)-(3-Butenyl)hexyl]-3-(4-methoxyphenyl)oxaziridine (42). A solution of the imine (**41**; 1.80 g, 6.59 mmol) in dry dichloromethane (50 mL) was treated at −78 °C under argon with a solution of mCPBA (1.508 g of a 75.4% sample, 6.59 mmol) in dry dichloromethane (50 mL). The solution was allowed to warm up to 25 °C over 3 h and then was poured into saturated sodium bicarbonate solution (100 mL). The aqueous solution was extracted with dichloromethane (3 × 50 mL). The combined dichloromethane layers were dried (Na_2SO_4), filtered, evaporated in vacuo, and purified by flash chromatography on silica, eluting with ethyl acetate/hexane (1:15) to give the pure oxaziridine **42** (1.67 g, 88%) as a colorless liquid and a mixture of four diastereomers partially separable by flash chromatography into two pairs of diastereomers; $[\alpha]^{20}_D$ +2.1° (*c* 2.5, CH_2Cl_2); IR (CCl_4) 3080, 1640, and 1610 cm^{-1}; MS *m/z* 289 (15) M^+, 272 (28), 251 (8), 234 (10), 218 (30), 202 (10), 151 (12), 136 (60), 135 (100), 107 (11), 100 (16), 84 (21), 77 (22), 55 (39); found M^+ 289.2032, $C_{18}H_{27}NO_2$ requires 289.2041.

Diastereomer pair 1: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.35 (2 H, d, *J* = 8.8 Hz, Ar), 6.90 (2 H, d, *J* = 8.8 Hz, Ar), 5.94–5.67 (1 H, m, C*H*=CH_2), 5.11–4.95 (2 H, m, CH=CH_2), 4.47 and 4.46 (1 H, 2 singlets, NC*H*O), 3.79 (3 H, s, OMe), 2.30–2.18 (1 H, m, C*H*N), 2.16–2.02 (2 H, m, CH_2C=C), 1.92–1.21 (10 H, m), 0.91 and 0.85 (3 H, t, *J* = 6.8 Hz, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.0 (s), 160.9 (s), 138.6 (d), 138.0 (d), 128.9 (d), 128.8 (d), 127.1 (s), 127.0 (s), 115.1 (t), 114.5 (t), 113.9 (d), 80.2 (d), 80.1 (d), 70.3 (d), 70.1 (d), 55.3 (q), 34.2 (t), 33.5 (t), 32.1 (t), 32.0 (t), 31.9 (t), 31.1 (t), 30.3 (t), 29.9 (t), 26.1 (t), 25.3 (t), 22.6 (t), 22.4 (t), 14.0 (q), 13.9 (q).

Diastereomer pair 2: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.34 (2 H, d, *J* = 8.5 Hz, Ar), 6.92 (2 H, d, *J* = 8.8 Hz, Ar), 5.92–5.76 and 5.45–5.25 (1 H, m, C*H*=CH_2), 5.19 (1 H, s, OC*H*N), 5.10–4.94 and 4.79–4.73 (2 H, m, CH=CH_2), 3.82 (3 H, s, OMe), 2.28–2.19 (3 H, m, C=CCH_2 and C*H*N), 1.83–0.80 (10 H, m), 0.73 and 0.90 (3 H, t, *J* = 7.1 Hz Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.5 (s), 138.7 (d), 137.8 (d), 129.6 (d), 129.6 (d), 123.7 (s), 114.4 (t), 114.3 (t), 113.4 (d), 113.4 (d), 79.2 (d), 79.1 (d), 58.6 (d), 58.5 (d), 55.2 (q), 55.2 (q), 33.4 (t), 33.0 (t), 32.1 (t), 31.4 (t), 30.9 (t), 30.3 (t), 29.9 (t), 29.5 (t), 25.1 (t), 24.9 (t), 22.5 (t), 22.1 (t), 14.0 (q), 13.8 (q).

(*Z*)-4-[[1(*R*)-(3-Butenyl)hexyl]imino]-1-butyl Acetate *N*-Oxide (10d). A solution of the oxaziridine (**42**; 573 mg, 1.98 mmol) in dry MeOH (1 mL) was treated with a solution of hydroxyammonium *p*-toluenesulfonate (1.22 g, 5.94 mmol) in dry MeOH (6 mL) under argon. The solution was stirred for 1 h, poured into saturated sodium bicarbonate solution (25 mL), made strongly basic with 2 M NaOH, and extracted with dichloromethane (4 × 25 mL). The organic extracts were added directly to 4-acetoxybutanal (772 mg, 5.94 mmol), while being dried with Na_2SO_4. The solution was filtered, evaporated in vacuo, and purified by flash chromatography on silica, eluting with ethyl acetate to give the enantiomerically pure nitrone **10d** (199 mg, 36%) as a colorless liquid: $[\alpha]^{20}_D$ +6.6° (*c* 1.25, CH_2Cl_2); IR (CCl_4) 3080, 1740, and 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.62 (1 H, t, *J* = 5.8 Hz, C*H*=CN$^+$), 5.77–5.61 (1 H, m, C*H*=CH_2), 4.98–4.90 (2 H, m, CH=CH_2), 4.04 (2 H, t, *J* = 6.4 Hz, CH_2OAc), 3.56–3.49 (1 H, m, C*H*N$^+$), 2.55–2.47 (2 H, m, CH_2C=N$^+$), 2.12–1.76 (8 H, m), 1.52–1.33 (2 H, m), 1.23–1.11 (6 H, m), 0.80 (3 H, t, *J* = 6.6 Hz, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9 (s), 137.3 (d), 137.2 (d), 115.4 (t), 74.8 (d), 63.7 (t), 32.4 (t), 31.3 (t), 31.1 (t), 30.1 (t), 25.7 (t), 24.6 (t), 23.0 (t), 22.4 (t), 20.8 (q), 13.9 (q); MS *m/z* 283 (2) M$^+$, 268 (3), 254 (2), 240 (10), 228 (10), 224 (18), 212 (22), 196 (11), 182 (70), 168 (42), 152 (65), 123 (20), 110 (22), 100 (15), 81 (32), 71 (40), 55 (100); found M$^+$ 283.2157, $C_{16}H_{29}NO_3$ requires 282.2148.

(2*R*,5*S*,8*S*)-8-(3-Acetoxypropyl)-2-pentyl-7-oxa-1-azabicyclo[3.2.1]octane (11d). A solution of the nitrone (**10d**; 199 mg, 0.703 mmol) in dry toluene (25 mL) was refluxed under argon using a Dean–Stark head for 16 h. The solution was evaporated in vacuo and purified by flash chromatography on silica eluting with ethyl acetate/hexane (1:2) to give the pure homochiral isoxazolidine **11d** (178 mg, 89%) as a pale yellow oil: $[\alpha]^{20}_D$ +47.1° (*c* 1.42, CH_2Cl_2); IR (CCl_4) 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 4.11–4.04 (2 H, m, CH_2OAc), 3.82–3.77 (2 H, m, CHCH_2O), 2.86 (1 H, dd, *J* = 5.7, 8.4 Hz, CHC*H*N), 2.64–2.50 (1 H, m, NC*H*CH$_2$), 2.41 (1 H, br s, bridgehead H), 2.03 (3 H, s, COCH_3), 1.90–1.25 (16 H, m), 0.86 (3 H, t, *J* = 6.8 Hz, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1 (s), 71.6 (t), 70.9 (d), 65.9 (d), 64.4 (t), 41.6 (d), 35.1 (t), 31.9 (t), 29.4 (t), 28.4 (t), 25.9 (t), 25.8 (t), 24.7 (t), 20.9 (q), 14.0 (q); MS *mz* 284 (8) (M + H)$^+$, 283 (9) M$^+$, 254 (15), 240 (42), 224 (63), 212 (40), 210 (40), 197 (17), 196 (16), 184 (20), 182 (71), 166 (35) 152 (82), 135 (25), 126 (38), 111 (23), 96 (38), 81 (75), 55 (100); found M$^+$ 283.2136, $C_{16}H_{29}NO_3$ requires 283.2147.

(2*R*,5*S*,8*S*)-8-(3-Hydroxypropyl)-2-pentyl-7-oxa-1-azabicyclo[3.2.1]octane (12d). A solution of the acetate (**11d**; 291 mg, 1.03 mmol) in dry MeOH (5 mL) was treated with K_2CO_3 (anhydrous, cat.) and stirred under argon for 24 h. The solution was poured into ether (50 mL), filtered, evaporated in vacuo, and purified by flash chromatography on silica eluting with ether to give the pure alcohol **12d** (207mg., 84%) as a colorless liquid: $[\alpha]^{20}_D$ +71.7° (*c* 1.23, CH_2Cl_2); IR (CCl_4) 3250 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz), δ 3.82 and 3.81 (2 H, 2 s, CHCH_2O), 3.69–3.50 (2 H, m, CH_2OH), 2.86 (1 H, t, *J* = 6.5 Hz, CHC*H*N), 2.66–2.60 (1 H, m, NC*H*CH$_2$), 2.40–2.37 (1 H, m, bridgehead H), 1.78–1.19 (17 H, m), 0.83 (3 H, t, *J* = 6.9 Hz, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 72.1 (t), 71.8 (d), 65.6 (d), 62.6 (t), 42.4 (d), 35.0 (t), 31.9 (t), 30.9 (t), 30.5 (t), 29.3 (t), 25.7 (t), 24.4 (t), 22.5 (t), 14.0 (q); MS *m/z* 241 (4) M$^+$, 224 (5), 212 (11), 210 (20), 196 (13), 170 (42), 154 (49), 140 (42), 126 (64), 111 (42), 100 (68), 81 (77), 71 (95), 55 (100); found M$^+$ 241.2048, $C_{14}H_{27}NO_2$ requires 241.2042.

(5*R*,8*S*,8a*S*)-8-(Hydroxymethyl)-5-pentyloctahydroindolizine (13d). The isoxazolidine (**12d**; 132 mg, 0.548 mmol) in dry dichloromethane (10 mL) was treated with methanesulfonyl chloride (0.22 mL, 2.74 mmol) and triethylamine (0.69 mL, 5.0 mmol) at −10 °C for 2 h. The solution was evaporated to dryness, dissolved in 50% aqueous acetic acid (5 mL), treated with activated zinc dust (0.345 g, 5.3 mgatom), and heated to 60 °C for 2 h. The resulting solution was filtered, basified with 20% aqueous NaOH, and extracted with dichloromethane (4 × 50 mL). The combined organic layers were dried (Na_2SO_4), evaporated in vacuo, and purified by flash chromatography on silica, eluting with CH_2Cl_2/MeOH/0.88 NH_3 (98:1.5:0.5) to give the pure indolizidine **13d** (106 mg, 86%) as a colorless liquid: $[\alpha]^{20}_D$ −56.3° (*c* 0.62, MeOH); IR (CCl_4) 3250, 2780, and 2700 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 4.17 (1 H, ddd, *J* = 10.8, 4.1, 1.3 Hz, C*H*OH), 3.70 (1 H, dt, *J* = 10.7, 1.1 Hz, CH*H*OH), 3.21–3.14 (1 H, m, H-3, H-5, or H-8a), 2.04–1.17 (20 H, m), 0.84 (3 H, t, *J* = 7.0 Hz, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 67.2 (d), 65.5 (t), 63.9 (d), 51.7 (t), 34.8 (d), 34.4 (t), 32.2 (t), 31.2 (t), 28.1 (t), 26.2 (t), 24.2 (t), 22.5 (t), 20.6 (t), 14.0 (q); MS *m/z* 225 (3) M$^+$, 224 (5), 154 (100); found M$^+$ 225.2102, $C_{14}H_{27}NO$ requires 225.2093.

(5*R*,8*R*,8a*S*)-8-(Hydroxymethyl)-5-pentyloctahydroindolizine (26d). Oxalyl chloride (0.10 mL, 1.18 mmol) in dry dichloromethane (10 mL) at −78 °C under argon was treated dropwise with a solution of DMSO (0.17 mL, 2.36 mmol) in dry dichloromethane (2 mL). The solution was stirred at −78 °C for 20 min, followed by the addition of the alcohol (**12d**; 133 mg, 0.590 mmol) in dry dichloromethane (2 mL). After a further 30 min at −78 °C, triethylamine (0.82 mL, 5.90 mmol) was added, and stirring was continued for a further 30 min at −78 °C. The solution was allowed to warm up to 25 °C for 30 min, poured into saturated sodium bicarbonate solution (25 mL), and extracted with dichloromethane (4 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated in vacuo to give the crude aldehyde **24d**. The crude aldehyde was adsorbed onto a column of basic grade 3 alumina, left for 15 min, and eluted with ethyl acetate/hexane (1:1) to give the crude aldehyde (136 mg) which had been equilibrated largely to the epimer **25d**: IR (CCl_4) 2710 and 2780, and 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 9.65 (1 H, d, *J* = 2.0 Hz, C*H*O), 3.27 (1 H, dt, *J* = 8.3, 2.4 Hz, H-5), 1.40–0.96 (20 H, m), 0.86 (3 H, t, *J* = 6.8 Hz, Me); MS *m/z* 223 (8) M$^+$, 168 (26), 152 (100); found M$^+$ 223.1957, $C_{14}H_{25}NO$ requires 223.1936. The aldehyde **25d** was dissolved in dry EtOH (5 mL) and treated with $NaBH_4$ (46 mg, 1.18 mmol) under argon for 15 min. The solution was poured into saturated sodium bicarbonate solution (25 mL), and the aqueous layer was extracted with dichloromethane (4 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to give an orange oil, which was purified by flash chromatography on silica eluting with ethyl acetate/NH_3 (99:1) to give the epimerized alcohol **26d** (85.6 mg, 65%) as a colorless liquid; $[\alpha]^{20}_D$ −93.3° (*c* 0.58, MeOH); IR (CCl_4) 3640, 3300, 2780, and 2700 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.59 (1 H, dd, *J* = 10.7, 4.5 Hz, C*H*OH), 3.38 (1 H, dd, *J* = 10.7, 6.7 Hz, CH*H*OH), 3.22 (1 H, dt, *J* = 8.3, 2.0 Hz, H-3, H-5, or H-8a), 2.40 (1 H, br s, OH), 1.97–1.00 (20 H, m), 0.84 (3 H, t, *J* = 6.7 Hz, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 66.9 (d), 65.3 (t), 63.5 (d), 51.4 (t), 44.1 (d), 34.3 (t), 32.2 (t), 30.5 (t), 28.9 (t), 27.9 (t), 25.5 (t), 22.6 (t), 20.5 (t), 14.0 (q); MS *m/z* 225 (5) M$^+$, 224 (5), 154 (100); found M$^+$ 225.2088, $C_{14}H_{27}NO$ requires 225.2092.

(5*R*,8*R*,8a*S*)-8-Methyl-5-pentyloctahydroindolizine [(−)-Indolizidine 209B, 6]. A solution of the alcohol (**26d**; 85.6 mg, 0.380 mmol) in dry dichloromethane (5 mL) at 0 °C under argon was treated with methanesulfonyl chloride (0.06 mL, 0.72 mmol) and triethylamine (0.20 mL, 1.44 mmol). Stirring was continued at 0 °C for 30 min. The solution was poured into saturated sodium bicarbonate solution (25 mL), and the aqueous layer was extracted with dichloromethane (4 × 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated in vacuo to give the crude mesylate as an orange oil. The crude mesylate was dissolved in dry THF (5 mL) at 0 °C under argon and treated with Super-Hydride (1.5 mL of a 1.0 M solution in THF, 1.5 mmol). The solution was stirred at 0 °C for 30 min, poured into saturated sodium bicarbonate solution (25 mL), and extracted with dichloromethane (4 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo, and the residue was purified by flash chromatography on silica, eluting with ethyl acetate/ammonia (99.5:0.5) to give pure (−)-indolizidine 209B (**6**) (69.3 mg, 87%) as a colorless oil: $[\alpha]^{20}_D$ −94.3° (*c* 1.85, MeOH); IR (CCl_4) 2780 and 2700 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.24 (1 H, dt, *J* = 8.5, 2.1 Hz, H-5), 2.00–0.88 (20 H, m), 0.83 (3 H, t, *J* = 7.9 Hz, CH_2CH_3), 0.83 (3 H, d, *J* = 6.5 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 71.4 (d), 63.6 (d), 5.17 (t), 36.3 (d), 34.4 (t), 33.6 (t), 32.1 (t), 31.0 (t), 28.9 (t), 25.5 (t), 22.6 (t), 20.3 (t), 18.8 (q), 14.0 (q); MS *m/z* 209 (5) M$^+$, 208 (5), 152 (8), 138 (100); found M$^+$ 209.2157, $C_{14}H_{27}N$ requires 209.2144.

Hydrochloride salt: mp 184–185 °C.

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Registry No. (±)-**3**·HCl, 130884-95-6; (±)-**4**, 118015-96-6; (±)-**4**·HCl, 130979-70-3; (±)-**5**, 117982-91-9; (±)-**5**·HCl, 130979-71-4; (−)-**6**, 117959-79-2; (−)-**6**·HCl, 131319-70-5; (±)-**6**·HCl, 130979-72-5; **7b**, 117959-91-8; (*E*)-**8a**, 87830-32-8; (*Z*)-**8a**, 87830-48-6; (*E*)-**8b**, 130884-96-7; (*Z*)-**8b**, 130885-07-3; (±)-**10b**, 117959-94-1; **10d**, 117960-10-8; (±)-**11a**, 117959-84-9; (±)-**11a**·$C_2H_2O_4$, 130884-97-8; (±)-**11b**, 117959-95-2; (±)-**11b**·$C_2H_2O_4$, 130884-99-0; (+)-**11d**, 117960-11-9; (±)-**12a**, 117959-85-0; (±)-**12b**, 130885-01-7; (+)-**12d**, 117960-12-0; (±)-**13a**, 117959-86-1; (±)-**13b**, 117959-97-4; **13d**, 117960-13-1; **14**, 107-87-9; (*E*)-**15**, 65457-34-3; (*Z*)-**15**, 65457-31-0; (*E*)-**16**, 130885-00-6; (*Z*)-**16**, 130885-06-2; (±)-**17**, 117959-87-2; (±)-**19**, 117959-89-4; (±)-8-epi-**19**, 130979-79-2; **21**, 5323-87-5; **22**, 22627-45-8; (±)-**23**, 117959-90-7; (±)-**24b**, 117959-98-5; **24d**, 117960-14-2; (±)-**25b**, 118015-97-7; **25d**, 118016-00-5; (±)-**26b**, 118015-98-8; **26d**, 118016-01-6; (±)-**27b**, 117959-99-6; **27d**, 117960-15-3; (±)-**28**, 130885-02-8; (±)-**29**, 130885-03-9; **30**, 17342-08-4; **31**, 51693-17-5; **32**, 118015-99-9; **33**, 117960-00-6; **34**, 117960-01-7; **35**, 117960-02-8; **36**, 117960-03-9; *cis*-**37**, 130885-04-0; *trans*-**37**, 130979-76-9; **38**, 117960-05-1; **39**, 130885-05-1; **40**, 117960-06-2; **41**, 130979-73-6; **42** (isomer 1), 130979-74-7; **42** (isomer 2), 130979-75-8; **42** (isomer 3), 130979-77-0; **42** (isomer 4), 130979-78-1; $AcO(CH_2)_4OH$, 35435-68-8; $AcO(CH_2)_3CHO$, 6564-95-0; $Br(CH_2)_2CH{=}CH_2$, 5162-44-7.

Supplementary Material Available: NMR spectra for compounds **15**, **16**, **13a**, **19**, **3**·HCl salt, **29**, **12b**, **13b**, **25b**, **26b**, **4**, **5**·HCl salt, **6**·HCl salt, **33**, **34**, **37**, **38**, **39**, **40**, **41**, **42**, **10d**, **11d**, **12d**, **13d**, **24d**, and **6** (51 pages). Ordering information is given on any current masthead page.

Photochemically Induced Radical Cation Diels–Alder Reaction of Indole and Electron-Rich Dienes[1]

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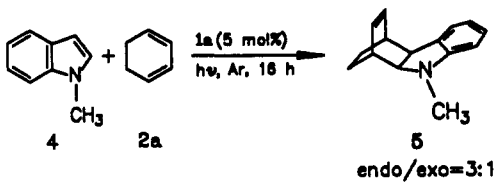
Diels–Alder reactions between indole (**3**) and substituted cyclohexa-1,3-dienes (**2**) can be effected by a photoinduced catalyzed electron transfer reaction using catalytic amounts of triarylpyrylium tetrafluoroborates (**1**) as sensitizers and an acid chloride as a trapping agent. Irradiation generates *N*-acyl-1,4,4a,9a-tetrahydro-1,4-ethanocarbazoles in one step. The products are formed with nearly total regioselectivity, such that a substituent in the 1-position of the cyclohexa-1,3-diene is always found in the 1-position of the tetrahydrocarbazole, and a substituent in the 2-position of the diene always appears in the 3-position of the product.

Introduction

Complex indole compounds often show broad and rich physiological activity. The indole nucleus of such compounds usually must be *constructed* in the course of a synthesis. Because it would be economically attractive to develop a synthesis of indole compounds starting from an *existing* indole nucleus, attempts[2] have been made to use the 2,3-double bond of indole (**3**) in stereoselective cycloaddition reactions of the Diels–Alder type. However, electron-rich indole shows only a low tendency to act as a dienophile. Its use mainly has been limited to reactions with electron-poor heterodienes such as tetrazine derivatives or tetrachlorothiophene 1,1-dioxide, in so-called Diels–Alder reactions with inverse electron demand.[3] The indole 2,3-double bond can act as a dienophile in "normal" Diels–Alder reactions, if electron-withdrawing groups are present in the 2- and 3-positions.[4] However, high temperatures (195–200 °C) and long reaction times are necessary. On the other hand, indole acrylates have been employed in Diels–Alder reactions as *electron-poor dienes*.[5,6] The indole nucleus has also been used as a link joining diene and a dienophile in intramolecular Diels–Alder reactions.[7]

We report here a Diels–Alder reaction in which indole, as the electron-rich dienophile, undergoes cycloaddition with electron-rich dienes by a photochemically induced catalyzed electron transfer reaction. As we reported earlier,[8] photoexcited triphenylpyrylium tetrafluoroborate (**1a**) can be used as the catalyst.

Scheme I



Results and Discussion

Irradiation of salt **1a**, cyclohexa-1,3-diene (**2a**), and either indole (**3**) or *N*-methylindole (**4**) in dichloromethane

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