Enanantioselective Synthesis of the Dendrobatid Alkaloid (−)-Indolizidine 207A

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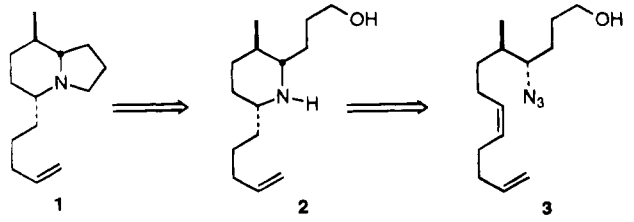
An enantioselective synthesis of the *Dendrobates* alkaloid (−)-indolizidine 207A (**1**) is reported. The key intermediate in this synthesis is alcohol **6** (Scheme 1), prepared in four steps from geraniol with control of both relative and absolute configuration.

The Dendrobatid poison frogs of Central America have been a rich source of pharmacologically potent and structurally novel alkaloids. Recently, an intriguing new class of these alkaloids, the 5-substituted 8-methylindolizidines, exemplified by indolizidine 207A (**1**), was reported.[2] Although syntheses of **1** and related alkaloids have been described,[3–6] none of these approaches allows the direct establishment of both the relative and the absolute configuration of this class of alkaloids. We report a straightforward solution to this problem, based on a retro-Mitsunobu cyclization[8] to **2**, followed by a retro-azide cycloaddition[9–11] to **3**. The key to this approach is the ready availablity of the acyclic azide.

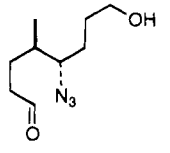


1 **2** **3**

We recently developed11 a procedure for reduction[12] of the Sharpless-derived epoxide[14] of geraniol (**4**) (Scheme 1), to give 2-hydroxycitronellol (**5**). Exposure of **5** to *p*-toluenesulfonyl chloride in the presence of aqueous sodium hydroxide led to a mixture of the tosylate and the volatile oxirane. The mixture was converted to **6** with allylmagnesium bromide in THF. This reaction may in any case be proceeding *via* the oxirane intermediate. The symchiral[7] product **6**, readily prepared in gram quantities, was diastereomerically homogeneous (^{13}C NMR).

Mesylation of **6** followed by addition of the crude mesylate to NaN_3 in HMPA gave azide **7**. Both azide **7** and the derived epoxide are prone to cyclize,[9–11] even at room temperature. Nevertheless, by working quickly it was possible to isolate reasonable yields of triol **8**.

Exposure of triol **8** to periodate gave the very unstable aldehyde **9**. This decomposed on attempted purification. Fortunately, we found that the recently developed alternative[15] of $NaIO_4$ on silica gel gave a CH_2Cl_2 solution of the aldehyde that was dry enough to carry on directly to the Wittig reaction.



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As expected,[9–11] thermolysis of azide **3** proceeded via dipolar azide cycloaddition and subsequent fragmentation to give the cyclic imine. Selective reduction[16] then led smoothly to the all-equatorial trisubstituted piperidine **2**. Direct cyclization of the amino alcohol with Ph_3P/

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(2) (a) For a detailed account of the isolation and structure of the *Dendrobates* alkaloids, including indolizidine 223AB, see 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) For the structure of **1**, see Edwards, M. D.; Daly, J. W.; Myers, C. W. *J. Nat. Prod.* **1988**, *51*, 1188.

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(9) (a) For the first report of cyclic imine construction by intramolecular azide cycloaddition, see Logothetis, A. L. *J. Am. Chem. Soc.* **1965**, *85*, 749. For applications to natural product synthesis, see (b) Taber, D. F.; Deker, P. B.; Fales, H. M.; Jones, T. H.; Lloyd, H. A. *J. Org. Chem.* **1988**, *53*, 2968. (c) Bennett, R. B., III; Choi, J. R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2581. (d) Hudlicky, T.; Seoane, G.; Lovelace, T. C. *J. Org. Chem.* **1988**, *53*, 2094. (e) Pearson, W. H. *Tetrahedron Lett.* **1985**, *26*, 3527.

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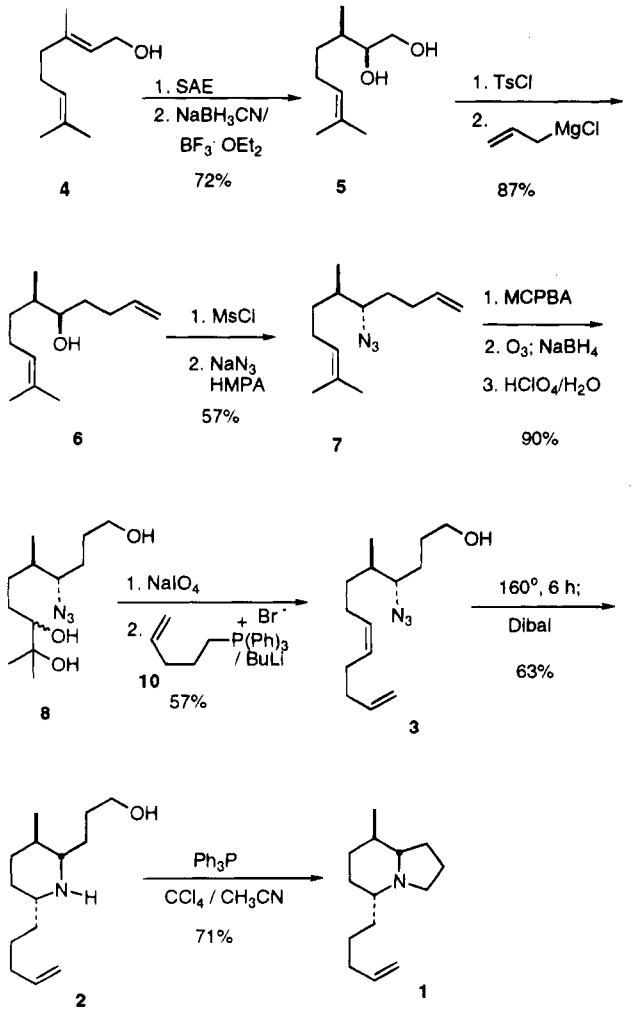
0022-3263/95/1960-0529$09.00/0

Scheme 1



CCl_4[8] gave indolizidine 207A (**1**), $[\alpha]_D = -85$ ($c = 0.174$, ethanol), identical ($[\alpha]_D$, ^1H and ^{13}C NMR, MS) with those reported.[3a]

As one could start the synthesis with nerol[12] rather than geraniol, it should be possible to use this approach to specifically prepare each of the diastereomers of the 8-methyl 5-alkylindolizidines, with control of both relative and absolute configuration. A key to this is the observation[16] that the intermediate cyclic imine can be reduced to give *either* relative configuration at C-5 (indolizidine numbering).

Experimental Section

A general experimental procedure was recently published.[12]

(5*R*,6*R*)-6,10-Dimethylundeca-1,9-dien-5-ol (6). The diol[12] (1.24 g, 7.2 mmol), 15 mL CH_2Cl_2, and 10 mL of 50% aqueous NaOH solution were stirred together for 15 min. The mixture was chilled in an ice–water bath, then *p*-toluenesulfonyl chloride (1.37 g, 7.2 mmol) in 8 mL of CH_2Cl_2 was added slowly. The reaction was stirred and allowed to come to rt overnight. Water (50 mL) was added. After an additional 15 min of stirring, the reaction mixture was partitioned between CH_2Cl_2 and water. The organic phase was dried (Na_2SO_4) and evaporated to one-quarter of the original volume. THF was added, and evaporation to one-quarter of the original volume was repeated.

The product (a mixture of tosylate and epoxide) was diluted to a total volume of 36 mL with THF and stirred in an ice–water bath. Allylmagnesium chloride (2.0 M, 18 mL, 36 mmol) was added slowly. The reaction was stirred and allowed to come to rt overnight and then partioned between ether and, sequentially, 5% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the secondary alcohol **6** as a colorless oil (1.17 g, 87% from diol). ^1H NMR: 5.8 (m, 1H), 5.0 (m, 2H), 3.53 (m, 1H), 1.2–2.3 (m, 9H), 1.68 (s, 3H), 1.60 (s, 3H), 0.88 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR: up 131.4, 114.6, 33.5, 33.3, 30.6, 25.7; down 138.6, 124.5, 74.5, 37.8, 25.6, 17.8, 13.5. IR (cm^{-1}): 3381 (broad), 3078, 2973, 2924, 2868, 1644, 1447, 1377, 1117, 1082. MS (*m/z*): 196 (17), 163 (7); 153 (5), 125 (100), 113 (53). $[\alpha]_D = +12.75$ ($c = 0.298$, ethanol).

(5*S*,6*R*)-5-Azido-6,10-dimethylundeca-1,9-diene (7). Dry Et_3N (3.4 mL, 24.3 mmol) in Et_2O (5 mL) was added dropwise at 0 °C to alcohol **6** (1.59 g, 8.11 mmol) and methanesulfonyl chloride (1.26 mL, 16.2 mmol, 2 equiv) in Et_2O (20 mL). After stiring for 3 h, the mixture was partioned between saturated aqueous NaCl solution and Et_2O. The combined organic extracts were dried (Na_2SO_4) and evaporated.

The residual oil was taken up in HMPA (8 mL) and NaN_3 (2.6 g, 40 mmol, 5 eq) was added. After 4.5 h at 40 °C, the mixture was partioned between saturated aqueous NaCl and Et_2O. The combined organic extacts were dried (Na_2SO_4) and concentrated. The residual oil was chromatographed to yield **7** as a colorless oil (868 mg, 55% yield from **6**). TLC R_f (3% EtOAc/petroleum ether) = 0.74. ^1H NMR: 5.8 (m, 1H), 5.1 (m, 2H), 3.22 (m, 1H), 1.4–2.3 (m, 8H), 1.70 (s, 3H), 1.60 (s, 3H), 1.20 (m, 1H), 0.93 (d, $J = 8.3$ Hz, 3H). ^{13}C NMR: up 131.6, 115.4, 32.5, 30.7, 29.8, 25.5 down 137.5, 124.1, 67.3, 36.7, 25.6, 17.5, 15.6. IR(cm^{-1}): 3077, 2101, 1643.

(3*RS*,6*R*,7*S*)-7-Azido-2,6-dimethyldecane-2,3,10-triol (8). Azide **7** (382 mg, 1.73 mmol) was added to *m*-chloroperoxybenzoic acid (324 mg, 1.88 mmol) in CH_2Cl_2 (10 mL) at −10 °C. After 50 min, the mixture was filtered, and the volume was brought back to 10 mL with CH_2Cl_2. The solution was transferred to a gas bubbler, MeOH (10 mL) and Sudan III indicator (5 mg) were added, and the mixture was chilled to −78 °C. Ozone-containing oxygen was bubbled through the solution until the red indicator color was discharged (2.3 min). The solution was purged with N_2, $NaBH_4$ (132 mg, 3.48 mmol) was added, and the mixture was allowed to come to room temperature.

The solution was filtered, the solvent was evaporated, and the residue was taken up in THF (24 mL) containing 5% aqueous $HClO_4$ (20 mL). After 20 min, the pH of the reaction mixture was adjusted to 10 with 5% aqueous NaOH. The mixture was then diluted with half-saturated aqueous NaCl and extracted with ethyl acetate. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed on 60–200 mesh silica gel with 40/60 acetone/CH_2Cl_2 to give **8** as a thick oil (406 mg, 90% from **7**). TLC R_f (30% acetone/CH_2Cl_2)= 0.23, as a 1:1 mixture of diastereomers. ^1H NMR (δ): 3.64 (bs, 2H), 3.34 (m, 2H), 2.4–2.9 (broad, 3H), 1.3–1.9 (m, 9H), 1.20 (s, 3H), 1.17 (s, 3H), 0.97 (d, $J = 8.2$ Hz, 1H); 0.95 (d, $J = 7.9$ Hz, 2H). ^{13}C NMR (δ): 79.1, 78.2, 73.1, 68.2, 67.6, 62.3, 62.1, 37.4, 36.9, 29.8, 29.5, 29.3, 28.9, 27.2, 26.7, 26.5, 23.3, 15.9, 15.7. IR (cm^{-1}): 3416 (broad), 2973, 2875, 2530, 2361, 2101, 1728, 1461, 1384, 1250. MS (*m/z*): 198 (6), 181 (11), 154 (22), 142 (18), 128 (36), 114 (100).

[1-(4-Pentenyl)]triphenylphosphonium Bromide (10). A mixture of 1-bromo-4-pentene (1.0 g, 6.66 mmol) and triphenylphosphine (1.8 g, 8.66 mmol) was heated to melting and then maintained at that temperature (≈110 °C) for 10 min. The resulting cloudy oil was poured into petroleum ether in a mortar and ground under petroleum ether to a white powder. This powder was washed three times with petroleum ether, sucked dry, and further dried in a desiccator to give a free-flowing white powder (1.45 g, 53% from bromide), mp = 191–192 °C. ^1H NMR (δ): 7.7–7.9 (m, 15H), 5.7 (m, 1H), 5.05 (d, $J = 16.2$ Hz, 1H), 5.00 (d, $J = 9.0$ Hz, 1H), 3.8 (m, 2H), 2.44 (dd, $J = 6.9, 7.0$ Hz, 2H), 2.44 (m, 2H), 1.74 (m, 2H). ^{13}C NMR (δ): 136.4, 135.0, 133.8, 133.6, 130.5, 130.4, 119.1, 118.2, 116.8, 33.9, 33.6, 22.5, 22.0, 21.7.

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(4S,5R)-4-Azido-5-methyltrideca-8,12-dien-1-ol (3). Following the procedure of Vo-Quang,[15] 1.85 mL of a 0.65 M aqueous solution of $NaIO_4$ was added dropwise to a slurry of 60−200 mesh silica gel (1.8 g) in CH_2Cl_2 (12 mL). Triol **8** (135 mg, 0.52 mmol) in EtOAc (2 mL) and CH_2Cl_2 (6.5 mL) was then added dropwise. After 1 h, the mixture was filtered, and the solid was washed with 40 mL of 25% EtOAc/petroleum ether. One half of the combined filtrates was concentrated to 3 mL and then added to a solution prepared by adding BuLi (0.60 mL, 2.26 M in hexane) to phosphonium salt **10** (448 mg, 1.09 mmol) in THF (5.5 mL) at -78 °C. After 5 min, the cooling bath was removed. After the mixture had reached rt, it was partioned between saturated aqueous NH_4Cl and Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residual oil was taken up in CH_3OH (5 mL) containing K_2CO_3 (100 mg). After 20 min, the mixture was concentrated and directly chromatographed to give alcohol **3** (37 mg, 0.15 mmol, 57% yield from **8**) as a colorless oil, TLC R_f (40% EtOAc/petroleum ether) = 0.56. ^1H NMR: 5.85 (m, 1H), 5.38 (m, 2H), 5.05 (d, J = 17.9 Hz, 1H), 4.96 (d, J = 11.9 Hz, 1H), 3.69 (t, J = 9.5 Hz, 2H), 3.23 (m, 1H), 2.10 (bs, 4H), 1.4−1.8 (m, 6H), 1.2 (m, 1H), 0.95 (d, J = 8.9 Hz, 3H). ^{13}C NMR: up 114.8, 62.2, 33.1, 31.0, 27.9, 25.7, 24.9, 23.2; down 138.1, 129.8, 129.7, 67.1, 36.7, 15.0. IR (cm^{-1}): 3386 (broad), 2954, 2876, 2096, 1717. MS (m/z): 205 (26), 192 (10), 178 (19), 169 (100), 164 (66), 151 (73), 136 (34), 125 (13).

(2S,3R,6R)-3-Methyl-6-(1-pent-4-enyl)-2-piperidinepropanol (2). Diene **3** (90.5 mg, 0.36 mmol) in *o*-dichlorobenzene (3 mL) in a 5 mL reactivial was stirred at 160 °C for 6 h. After the mixture was allowed to cool, the solvent was removed by bulb-to-bulb distillation. The residue was taken up in CH_2Cl_2 (6 mL) and cooled to −65 °C, then DIBAL (2.3 mL, 1.0 M in CH_2Cl_2) was added. The mixture was held sequentially at −65 °C (30 min), −45 °C (1 h), −20 °C (1 h), and 0 °C (1 h). Et_2O (20 mL) was added, followed by solid NaF (400 mg). Water (132 μL) was added, and stirring was continued for 25 min. The mixture was filtered with ether containing 5% triethylamine, dried (Na_2SO_4), and chromatographed to yield **2** as a colorless oil (51.5 mg, 63% from **3**). TLC R_f (10% diethylamine/petroleum ether) = 0.27. ^1H NMR (δ): 5.76 (m, 1H), 4.97 (d, J = 17.7 Hz, 1H), 4.92 (d, J = 11.0 Hz, 1H), 3.55 (m, 2H), 2.51 (bs, 1H), 2.2 (bs, 1H), 2.05 (bs, 2H), 1.05−1.8 (m, 13H), 0.85 (d, J = 8.5 Hz, 3H). ^{13}C NMR (δ): up 114.6, 62.7, 36.2, 33.8, 33.7, 32.9, 32.5, 29.3, 25.1; down 138.5, 62.3, 56.6, 34.6, 18.5. IR (cm^{-1}): 3388, 3275, 3078, 2924, 2846, 1637, 1454. MS (m/z): 225 (3), 182 (9), 166 (93), 156 (100), 138 (24), 124 (5).

Alkaloid 207A (1). Piperidine **2** (26.8 mg, 0.119 mmol), triphenylphosphine (48.3 mg, 0.184 mmol), triethylamine (25.9 μL, 0.184 mmol), CCl_4 (17.7 μL, 0.184 mmol), and CH_3CN (126 μL) were combined in a 1 mL reactivial. After 32 h at room temperature, the mixture was concentrated and then chromatographed directly. The crude chromatographed oil was distilled bulb-to-bulb (0.5 mm, bath ≈ 110 °C) to give indolizidine **1** as a colorless oil (17.4 mg, 71%). TLC R_f (10% diethylamine/petroleum ether) = 0.68. ^1H NMR: 5.8 (m, 1H), 5.00 (d, J = 17.0 Hz, 1H), 4.94 (d, J = 9.9 Hz, 1H), 3.26 (bt, J = 8.6 Hz, 1H), 1.2−2.1 (m, 18H), 0.86 (d, J = 6.4 Hz, 3H). ^{13}C NMR (δ): up 114.4, 51.8, 34.1, 33.7, 31.3, 29.1, 25.1, 20.4; down 138.8, 71.4, 63.4, 36.5, 18.8. MS: 207 (22), 164 (10.8), 151 (50.3), 138 (100). $[\alpha]_D$ = −85.25° (c = 0.174, ethanol).

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Supplementary Material Available: Copies of ^1H and ^{13}C spectra for compounds **1-3** and **6-8** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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