an E map showing an 18-atom fragment of the molecule. Several successive Fourier syntheses[13] served to locate the remaining nonhydrogen atoms. Hydrogens were located on difference maps after partial refinement of the nonhydrogen atoms. The latter were refined anisotropically and hydrogens were refined isotropically by using blocked least-squares methods and minimizing the quantity $w(|F_o| - |F_c|)^2$, wherre $w = (1.0 + ((|F_o| - 16.0)/12.0)^2)^{-1}$. Some of the thermal parameters for C(6A) were more than twice as large as those for other atoms in the molecule, but no more than one discrete position for this methyl could be found on difference maps, so a disordered model was not used. The hydrogens attached to C(6A) did not refine to reasonable positions, and so they were fixed in ideal positions with isotropic temperature factors slightly higher than the isotropic temperature factor of C(6A). Refinement was terminated at $R = 0.043$ and $R_w = 0.056$ when the average ratio of parameter shift to error was 0.11 and the maximum ratio was 0.74. A final difference map showed no peaks greater than 0.14 e Å^{-3}.

Registry No. **4**, 83710-13-8; **5**, 60050-12-6; **7**, 561-07-9; **8**, 60450-64-8; **9**, 83705-17-3; **10**, 83705-18-4; **14**, 83705-19-5; **15**, 83705-20-8; **16**, 83705-21-9.

Stereocontrolled Synthesis of Exocyclic Trisubstituted Double Bonds by Stereospecific Iminium Ion–Vinylsilane Cyclizations. A Short Synthetic Route to Indoloquinolizidine Alkaloids[1]

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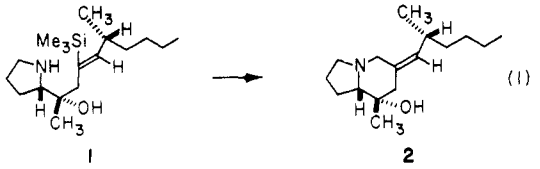
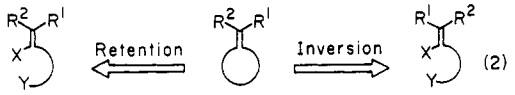
The reaction of (*Z*)- and (*E*)-trisubstituted vinylsilanes **9** and **10** with paraformaldehyde and acid proceeded with >98% retention of configuration to give indoloquinolizidines **13** and **3** in excellent yield. This is the first demonstration that iminium ion–vinylsilane cyclizations occur with complete retention of configuration with either vinylsilane stereoisomer. The simple indole alkaloid *dl*-deplancheine (**3**) was prepared in a stereocontrolled fashion in 26% overall yield from commercially available 1-(trimethylsilyl)propyne.

Significant advances have been made in recent years in stereoselective synthesis of alkenes.[2] In spite of this progress, stereocontrol in the preparation of alkenes which are exocyclic to a ring remains an unsolved problem.[3] We recently reported[1] the stereospecific[4] cyclization of (*Z*)-vinylsilane **1** upon treatment with formaldehyde and acid to form the (*Z*)-alkylideneindolizidine ring of *Dendrobatid* toxin 251D (**2**, eq 1). This is an example of a potentially

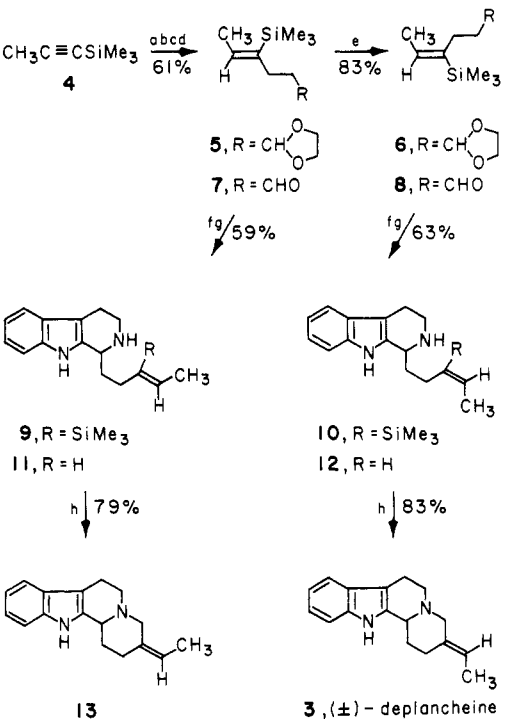


general stereocontrolled approach to exocyclic alkenes (eq 2) in which stereochemistry is established in an acyclic



synthon and then transferred to the desired cyclic product via a stereospecific cyclization reaction which proceeds with either inversion or retention of alkene stereochemistry. Since a variety of methods are available for the stereoselective synthesis of vinylsilanes,[5] iminum ion–vinylsilane

Scheme I[a]



[a] (a) Bu_2AlH, EtO_2, 40 °C; (b) Br_2, pyridine, −78 °C to room temperature; (c) *sec*-BuLi, THF, −78 °C; (d) $ICH_2CH(OCH_2CH_2O)$, −78 °C to room temperature; (e) NBS (catalytic amount), $h\nu$, 0 °C; (f) 0.5 N HCl, THF-H_2O, 25 °C; (g) tryptamine hydrochloride, methanol-H_2O, 85 °C; (h) $(CH_2O)_n$, $CamSO_3H$, CH_3CN, 80 °C.

(1) Applications of Iminium Ion–Vinylsilane Cyclizations in Organic Synthesis. 2. For paper 1 in this series see: Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851–1853.

(2) For reviews of stereoselective olefin synthesis, see: Faulkner, D. J. *Synthesis* **1971**, *175*–189. Reucroft, J.; Sammes, P. G. *Q. R., Chem. Soc.* **1971**, *25*, 135–169. Arora, A. S.; Ugi, I. K. In "Methoden der Organischen Chemie (Houben-Weyl)", 4th ed.; Muller, E.; Ed.; Georg Thieme Verlag: Stuttgart, 1972; Vol. V. Part 1B, pp 728–945. Gosney, I.; Rowley, A. G. In "Organophosphorus Reagents in Organic Synthesis"; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979. For references to some newer methods, see: Marfat, A.; McQuick, P. R.; Kramer, R.; Helquist, P. *J. Am. Chem. Soc.* **1977**, *99*, 253–255. For a summary of methods compiled for computer-assisted synthetic analysis, see: Corey, E. J.; Long, A. K. *J. Org. Chem.* **1978**, *43*, 2208–2216.

(3) Examples of the inability of existing methods to control this type of alkene stereochemistry may be found in several recent total syntheses. Cf.: (a) Ashcroft, W. R.; Joule, J. A. *Tetrahedron Lett.* **1980**, 2341–2344. (b) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E. *J. Am. Chem. Soc.* **1980**, *102*, 6611–6612.

(4) We use stereospecific and stereoselective in the sense discussed by Zimmerman and House: House, H. O. "Modern Synthetic Reactions", 2nd. ed.; W. A. Benjamin: Menlo Park, CA 1972; pp 307–308 and ref 40a,b therein.

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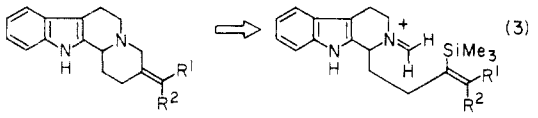
cyclizations potentially provide a general stereocontrolled route to 3-alkylidene azacyclics.

In this paper we report the preparation of 20-alkylideneindoloquinolizidines via iminium ion–vinylsilane cyclizations (eq 3). In particular, we demonstrate that



(3)

both (*E*)- and (*Z*)-trisubstituted vinylsilanes can be cyclized with *>98% retention of configuration* to give (*E*)- and (*Z*)-alkylidene products, respectively. The 20(*E*)-ethylideneindoloquinolizidine ring system is found in a variety of indole alkaloids,[6] and we report the efficient stereocontrolled total synthesis of the simplest of these, *dl*-deplancheine (**3**),[7,8] by this procedure.

Results and Discussion

The required (*Z*)- and (*E*)-tetrahydro-β-carbolines **9** and **10** were prepared from 1-(trimethylsilyl)propyne (**4**) as outlined in Scheme I. Hydroalumination of **4** and subsequent bromination by the procedure of Zweifel[9] afforded (*E*)-(1-bromo-1-propenyl)trimethylsilane,[10] which yielded the (*Z*)-silyl acetal **5** when treated sequentially at −78 °C in tetrahydrofuran (THF) with *sec*-butyllithium[11] and 2-(2-iodoethyl)-1,3-dioxolane.[12] Capillary gas chromatography (GC) analysis[13] showed that the isomeric purity of **5** was >99%. The more stable (*E*)-silyl acetal **6** was readily secured by bromine atom catalyzed isomerization of **5**,[14] which gave **6** and **5** in a 94:6 ratio. Hydrolysis of **5**, and Pictet–Spengler condensation[15] of the resulting aldehyde with tryptamine hydrochloride afforded tetrahydro-β-carboline **9** in 36% overall yield from silylalkyne **4**. In a similar fashion, silyl acetal **6** was converted to the (*E*)-tetrahydro-β-carboline **10** (32% overall yield from **4**). Tetrahydro-β-carboline **9** was >99% isomerically pure[13] and showed vinylic hydrogen absorption at δ 6.11 in the 250-MHz ^{1}H NMR spectrum, characteristic[11] of a (*Z*)-trisubstituted vinylsilane. The vinylic hydrogen absorption for the (*E*)-vinylsilane **10** was observed at δ 5.90, and this sample was contaminated[13] with 4% of the corresponding *Z* isomer.

Initial optimization of the conditions for the iminium ion vinylsilane cyclization was carried out with **9**. When **9** was heated for 15 h in refluxing ethanol with paraformaldehyde (3 equiv) and 0.95 equiv of a sulfonic acid catalyst,[1] the desired (*Z*)-indoloquinolizidine **13** was indeed formed. However, a major amount of **9** remained, and **13** was contaminated with ~30% of the (*Z*)-alkene **11** and traces of what is believed to be the N_a-ethoxymethyl derivative of **13**. The known[16] alkene **11**, which arises from protodesilylation of **9**, had been previously observed as a byproduct of the Pictet–Spengler cyclization. Protodesilylation under the essentially neutral conditions (<1 equiv of acid) of the iminium ion–vinylsilane cyclization is surprising, and further investigations of the details of this conversion are clearly warranted.[17] Protodesilyation could be completely surpressed by conducting the cyclization with a large excess of paraformaldehyde. The reaction is best accomplished at 80 °C with 30 equiv of paraformaldehyde, in which case clean cyclization occurred within 2 h in ethanol and in <1 h in acetonitrile. Preparative-scale cyclization of **9** under optimum conditions afforded crystalline **13**[3a] in 79% yield. Capillary GC analysis[13] of the crude cyclization product showed that **13** was produced with an isomeric purity of >98%. Preparative-scale cyclization of the *E* isomer **10** (which was contaminated with 4% of **9**) under identical conditions gave crystalline *dl*-deplancheine **3**: 95% isomeric purity;[13] 83% yield. Synthetic **3** (mp 143 °C) was identical by capillary GC[13] and TLC analysis with an authentic sample of racemic deplancheine kindly provided by Professor Joule[3a] and showed 250-MHz ^{1}H NMR and 63-MHz ^{13}C NMR spectra consistent[3a,7,8] with those reported.

Conclusion

The simple indole alkaloid *dl*-deplancheine was prepared via iminium ion–vinylsilane cyclization in a short stereocontrolled fashion. The overall yield from commercially available 1-(trimethylsilyl)propyne was 26%. Importantly, this study demonstrates that iminium ion–vinylsilane cyclizations of both (*E*)- and (*Z*)-trisubstituted vinylsilanes occur with virtually *complete* (*>98%*) *retention of configuration*, and, thus, this reaction provides a convenient route to either exocyclic trisubstituted alkene isomer. In principle, the use of cyclization initiators other than iminium ions should allow the similar stereocontrolled synthesis of alkenes which are exocyclic to carbocylic as well as other heterocyclic rings. Reactions of this type, as well as applications of iminium ion–vinylsilane cyclizations for the total synthesis of complex indole alkaloids[6] are being actively pursued in these laboratories.

(5) For recent reviews, see: Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761–786. Fleming, I. In "Comprehensive Organic Chemistry"; Barton, D., Ollis, W. D., Eds.; Pergamon Press: New York, 1979; Vol. 3, Chapter 13. Pawlenko, S. In "Methoden der Organischen Chemie (Houben-Weyl)"; Müller, E., Bayer, O., Eds.; Georg Thieme Verlag: Stuttgart, 1980; Vol. 13, Part 5, pp 30–78.

(6) Cf.: Kutney, J. P. In "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley-Interscience: New York, 1977; Vol. III, Chapter 2. Phillipson, J. D.; Zenk, M. H., Eds. "Indole and Biogenetically Related Alkaloids"; Academic Press: New York, 1980.

(7) Isolation and synthesis: Besselievre, R.; Cosson, J.-P.; Das, B. C.; Husson, H.-P. *Tetrahedron Lett.* **1980**, *21*, 63–66.

(8) Synthesis: (a) Thielke, D.; Wegener, J.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 602–603. (b) Reference 3a. (c) Hämeilä, M.; Lounasmaa, M. *Acta Chem. Scand. Ser. B* **1981**, *35*, 217–218. (d) Calabi, L.; Danieli, B.; Lesma, G.; Palmisano, G. *Tetrahedron Lett.* **1982**, 2139–2142.

(9) Zweifel, G.; Lewis, W. *J. Org. Chem.* **1978**, *43*, 2739–2744.

(10) (a) A nonstereoselective synthesis of this bromide has been reported: Seyferth, D.; Lefferts, J. L.; Lambert, R. L., Jr. *J. Organomet. Chem.* **1977**, *142*, 39–53. (b) The stereoisomer assignments for the (1-bromo-1-propenyl)trimethylsilanes are incorrect in the paper referenced above. Our structural assignments for the (*E*)-bromide and derived compounds **5**–**10** follow unequivocally from (a) the established[9] suprafacial stereochemistry of silylalkyne hydroalumination–bromination, (b) the characteristic[11] downfield signals observed in the ^{1}H NMR spectrum for the vinylic hydrogens of *Z* isomers **5**, **7**, and **9** (ca. 0.2 ppm downfield of the same signals for *E* isomers **6**, **8**, and **10**), and (c) the nearly complete isomerization[14] of **5** to *E* isomer **6**.

(11) Cf.: Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1979**, *44*, 4623–4633.

(12) Prepared from the bromo analogue, which is readily available form acrolein: Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122–1123.

(13) A 25-m SE-30 glass capillary column was used for this analysis. Base line separation of **9** and **10**, and **3** and **13** was obtained.

(14) Zweifel, G.; On, H. P. *Synthesis* **1980**, 803–805.

(15) For a recent study of this reaction and leading references see, Ungemach, F.; DiPierro, M.; Weber, R.; Cook, J. M. *J. Org. Chem.* **1981**, *46*, 164–168.

(16) Winterfeldt, E.; Ahmad, V.; Feuerherd, K. *Chem. Ber.* **1977**, *110*, 3624–3635.

(17) Intramolecular assistance from N_a and N_b is presumably involved. Protodesilylation of vinylsilanes is typically accomplished with strong acids which have nucleophilic conjugate bases. Cf.: Büchi, G.; Wüest, H. *Tetrahedron Lett.* **1977**, 4305–4306.

Experimental Section[18]

(*Z*)-[1-[3-(Ethylenedioxy)-1-propyl]-1-propenyl]trimethylsilane (5). (*E*)-(1-Bromo-1-propenyl)trimethylsilane[10] was prepared in 70% yield from 1-(trimethylsilyl)propyne by the general procedure of Zweifel:[9] a colorless liquid after bulb-to-bulb distillation (100 °C, 15 mm); IR (neat) 2980, 1610, 1312, 1250, 1095 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.82 (q, J = 7.4 Hz, C=CH), 1.73 (d, J = 7.4 Hz, C=CCH_3), 0.27 (s, $SiMe_3$); ^{13}C NMR (23 MHz, $CDCl_3$) δ 144.2, 129.8, 19.8, 2.1; mass spectrum (CI, isobutane), m/z (relative intensity, 5% cutoff) 194 (MH^+, 8), 193 (7), 192 (9), 139 (13), 137 (12), 113 (37), 83 (6), 73 (100).

According to the general method of Miller,[11] a stirred solution of (*E*)-(1-bromo-1-propenyl)trimethylsilane (8.60, 44.0 mmol) and 45 mL of THF was cooled to −78 °C, and *sec*-butyllithium (45.0 mL of a 1.1 M solution in cyclohexane) was added dropwise over 1 h. After the mixture was stirred for 30 min at −78 °C, a solution of 2-(2-iodoethyl)-1,3-dioxolane[12] (9.64 g, 42.3 mmol, freshly filtered through neutral alumina) and 3 mL of THF was added dropwise over 40 min. After being stirred for 30 min at −78 °C, the reaction mixture was warmed to room temperature. An aqueous workup (ether, $MgSO_4$) gave 7.94 g (88%) of **5**, which was >97% pure by GC analysis[13] and contained no detectable *E* isomer **6**. An analytical sample was obtained by preparative GC:[20] IR ($CDCl_3$) 2960, 2890, 1619, 1405, 1250, 1130, 1030, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.09 (broadened q, J = 7.0 Hz, C=CH), 4.83 (t, J = 4.9 Hz, ROCHOR), 3.8–4.0 (m, CH_2OR), 2.1–2.25 (m, CH_2), 1.74 (d, J = 7.0 Hz, C=CCH_3), 1.6–1.8 (m, C=CCH_2), 0.15 (s, $SiMe_3$); ^{13}C NMR (63 MHz, $CDCl_3$) 139.3, 136.7, 104.3, 64.9, 35.0, 32.4, 17.6, 0.0; mass spectrum (CI, isobutane), m/z (relative intensity, 20% cutoff) 215 (MH^+, 52), 171 (23), 81 (21), 73 (61).

(*E*)-[1-[3-(Ethylenedioxy)-1-propyl]-1-propenyl]trimethylsilane (6). According to the general procedure of Zweifel,[14] a stirred solution of **5** (5.00 g, 23.4 mmol), pyridine (1.9 mL, 23 mmol), and 105 mL of ether was placed in an ice–water bath, and 0.20 g (1.12 mmol) of *N*-bromosuccinimide was added. The reaction mixture was irradiated with a 275-W sunlamp, and additional *N*-bromosuccinimide (0.20 g, 1.12 mmol) was added at 45-min intervals. Equilibration was complete[13] in 2 h, and the ethereal solution was decanted from a gummy residue and washed with 1 N HCl (50 mL), 20% aqueous $CdCl_2$ (50 mL), H_2O (50 mL), 1 N NaOH (50 mL), and brine (50 mL). After the solution was dried ($CaSO_4$), concentration gave 4.15 g (83%) of crude **6**, which capillary GC analysis[13] showed was contaminated only with 6% of the *Z* isomer **5**. An analytical sample of **6** was obtained by preparative GC:[20] IR (neat) 2960, 2880, 1619, 1410, 1250, 1140, 1040, 835 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.87 (q, J = 6.6 Hz, C=CH), 4.85 (t, J = 4.8 Hz, ROCHOR), 3.8–4.05 (m, CH_2OR), 2.2–2.3 (m, CH_2), 1.70 (d, J = 6.6 Hz, C=CCH_3), 1.55–1.75 (m, C=CCH_2), 0.06 (s, $SiMe_3$); mass spectrum (CI isobutane), m/z (relative intensity, 20% cutoff) 215 (MH^+, 58), 171 (28), 117 (100), 99 (30), 81 (68), 73 (78).

(*E*)-2,3,4,9-Tetrahydro-1-[3-(trimethylsilyl)-3-pentenyl]-1*H*-pyrido[3,4-*b*]indole (10). A solution of acetal **6** (1.90 g, 8.88 mmol; contaminated with 6% of **5**), 100 mL of 1 N HCl, and 100 mL of the THF was stirred at room temperature for 24 h. A basic workup (pentane, Na_2SO_4) gave 1.6 g of crude **8**, which was contaminated with ~20% of THF. This material was used directly in the Piclet–Spengler reaction, since distillation resulted in some decomposition. A pure specimen of **8** was obtained by preparative GC:[20] IR ($CHCl_3$) 2720, 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.78 (br s, CHO), 5.91 (unsymmetrical q, J = 6.6 Hz, C=CH), 1.69 (d, J = 6.6 Hz, C=CCH_3); mass spectrum (CI, isobutane), m/z (relative intensity, 25% cutoff) 171 (MH^+, 51), 81 (100), 73 (24).

By use of a modification of the procedure of Cook,[15] a solution of the crude aldehyde sample described above, tryptamine hydrochloride (2.21 g, 11.2 mmol; twice recrystallized from ethanol–ethyl acetate), methanol (25 mL), and H_2O (12 mL) was heated at 85 °C for 30 h. A basic workup (CH_2Cl_2, Na_2SO_4) and purification of the residue by flash chromatography (silica gel, 15:1.0:0.1 $CHCl_3$/ethanol/NH_4OH) gave 1.75 g (63%) of **10** as a light brown solid. GC analysis[13] showed that this sample was contaminated with 4% of **9**. Molecular distillation (120 °C, 0.3 mm) gave an analytical sample of **10**: mp 108–109 °C; IR ($CHCl_3$) 3480, 2980, 2930, 1610, 1450, 1250, 835 cm^{-1}; UV (MeOH) 233, 272, 282, 289 nm; ^1H NMR (250 MHz, $CDCl_3$) δ 7.75 (br s, indole NH), 7.5–7.05 (m, indole H), 5.90 (q, J = 6.6 Hz, C=CH), 4.0–4.1 (m, 1 H), 3.4–3.3 (m, 1 H), 3.0–3.1 (m, 1 H), 2.7–2.8 (m, 2 H), 2.2–2.5 (m, 2 H), 1.71 (d, J = 6.6 Hz, C=CCH_3), 1.6–1.9 (m, 3 H), 0.08 (s, $SiMe_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 141.6, 136.4, 135.9, 135.0, 127.8, 121.6, 119.5, 118.2, 110.9, 109.2, 53.2, 42.5, 35.0, 25.8, 23.0, 14.5, −0.95; mass spectrum (CI, isobutane), m/z (relative intensity, 25% cutoff) 313 (MH^+, 90), 184, (43), 171 (100); high-resolution mass spectrum (EI), m/z 312.2013 (calcd for $C_{19}H_{28}N_2Si$, 312.2022).

A later chromatography fraction gave 80 mg (4%) of the known[16] (*Z*)-tetrahydro-β-carboline **12**: IR ($CHCl_3$) 3480, 2930, 1450 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.99 (br s, 1 H, indole NH), 7.5–7.0 (m, indole H), 5.3–5.6 (m, CH=CH), 1.62 (d, J = 6.0 Hz, C=CCH_3); mass spectrum (CI, isobutane), m/z (relative intensity, 10% cutoff) 241 (MH^+, 100), 171 (15).

(*Z*)-2,3,4,9-Tetrahydro-1-[3-(trimethylsilyl)-3-pentenyl]-1*H*-pyrido[3,4-*b*]indole (9). Acetal **5** (2.18 g, 10.2 mmol) was hydrolyzed by following exactly the procedure described for the preparation of **10**, and the resulting aldehyde **7** (IR 1725 cm^{-1}, $CHCl_3$) was condensed with 2.58 g (13.1 mmol) of tryptamine hydrochloride to afford, after chromatographic purification, 1.88 g (59%) of chromatographically pure **9** as a light brown oil. An analytical sample was prepared by molecular distillation (120 °C, 0.3 mm): IR ($CHCl_3$) 3480, 2920, 1630, 1450, 1250, 835 cm^{-1}; UV (MeOH) 236, 275, 283, 290 nm; ^1H NMR (250 MHz, $CDCl_3$) δ 7.84 (br s, indole NH), 7.5–7.0 (m, indole H), 6.11 (q, J = 7.0 Hz, C=CH), 3.95–4.05 (m, 1 H), 3.4–3.3 (m, 1 H), 3.05–2.95 (m, 1 H), 2.65–2.8 (m, 2 H), 2.35–2.15 (m, 2 H), 1.75 (d, J = 7.0 Hz, C=CCH_3), 1.85–1.65 (m, 3 H), 0.18 (s, $SiMe_3$); ^{13}C NMR (23 MHz, $CDCl_3$) δ 140.2, 137.5, 136.5, 136.0, 127.9, 122.6, 119.5, 118.2, 110.9, 109.2, 52.9, 42.4, 36.5, 34.9, 23.0, 17.8, 0.40; mass spectrum (CI, isobutane), m/z (relative intensity, 30% cutoff) 313 (MH^+, 91), 184 (55), 171 (100); high-resolution mass spectrum (EI), m/z 312.2009 (calcd for $C_{19}H_{28}SiN_2$, 312.2022).

A later chromatography fraction gave 100 mg (5%) of the known[16] (*E*)-tetrahydro-β-carboline **11**: IR ($CHCl_3$) 3480, 2930, 1450, 965 cm^{-1} (*trans*-CH=CH); ^1H NMR (250 MHz, $CDCl_3$) δ 7.87 (br s, indole NH), 7.5–7.05 (m, indole H), 5.5–5.3 (m, HC=CH), 1.66 (d, J = 4.0 Hz, C=CCH_3); mass spectrum (CI, isobutane, m/z (relative intensity, 20% cutoff) 241 (MH^+, 100), 171 (58).

(*E*)-3-Ethylidene-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizidine. *dl*-Deplancheine (3). A solution of **10** (390 mg, 1.24 mmol), *d*-camphor-10-sulfonic acid (290 mg, 1.16 mmol), paraformaldehyde (1.08 g, 36.0 mmol), and CH_3CN (25 mL) was stirred for 2 h at 82 °C. Excess paraformaldehyde was removed by filtration through a plug of glass wool. A basic workup (CH_2Cl_2, Na_2SO_4), followed by purification of the residue by flash chromatography (silica gel, 20:1.0:0.1 $CHCl_3$/2-propanol/NH_4OH) and sublimation (140 °C, 0.3 mm), gave 260 mg (83%) of crystalline *dl*-deplanchine. GC analysis[13] showed that this sample was contaminated with 5% of **13** and contained no other detectable impurities. An analytical sample of **3** was prepared by one additional sublimation (140 °C, 0.3 mm): mp 143 °C (lit.[3a] mp

(18) General experimental details have been described recently, see: Overman, L. E.; Freerks, R. L.; Petty, C. B.; Clizbe, L. A.; Ono, R. K.; Taylor, G. F.; Jessup, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 2816–2822. 1-(Trimethylsilyl)propyne (commercially available from Farchan) was prepard from 1-lithiopropyne (propyne and MeLi) and chlorotrimethylsilane in THF at −78 to +25 °C.[19] 2-(2-Iodoethyl)-1,3-dioxolane was prepared from the corresponding bromide[12] in 85% yield by reaction with NaI (in 2-butanone containing 1% pyridine, 25 °C, 24 h). Ultraviolet spectra were determined with a Beckman Model 25 spectrophotometer. Electron-impact high-resolution mass spectra were determined at 70 eV with a Kratos MS-50 at the Midwest Center for Mass Spectroscopy, University of Nebraska. Chemical-ionization mass spectra were determined at 100 eV on a Finnigan 4000 GC/MS/DS. In cases where synthetic intermediates or products were isolated by "aqueous workup (organic solvent, drying agent)", the procedure was to quench the reaction mixture with H_2O, dilute with the indicated organic solvent, separate the organic layer, extract the aqueous layer several times, with the organic solvent, dry the combined organic layers with the indicated drying agent, and remove the solvent by using a rotary evaporator at reduced pressure. When "basic workup (organic solvent, drying agent)" is indicated the procedure is similar to aqueous workup, except 1 N NaOH was used instead of H_2O.

(19) Corey, E. J.; Kirst, H. A *Tetrahedron Lett.* **1968**, 5041–5043.

(20) A 0.25 in. × 10 ft glass column packed with 3% SP-2100 on 100/120 Supelcoport was used for this purification.

140–143 °C); IR ($CHCl_3$) 3440, 2840–2700 (*trans*-quinolizidine Bohlmann bands) 1435, 1300 cm^{-1}; UV (MeOH) 235, 273, 283, 290 nm; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70 (br s, indole NH), 7.48–7.04 (m, indole H), 5.43 (broadened q, J = 6.8 Hz, C=CH), 3.45–3.3 (m, 2 H), 3.1–2.95 (m, 3 H), 2.85–2.6 (m, 3 H), 2.2–2.1 (m, 1 H), 2.05–1.93 (br t, 1 H), 1.63 (d, J = 6.8 Hz, $C=CCH_3$), 1.65–1.5 (m, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 136.3, 134.9, 134.3, 127.7, 121.5, 119.6, 119.5, 118.4, 110.9, 108.6, 63.7, 60.4, 53.1, 30.5, 26.1, 21.8, 12.9; mass spectrum (CI, isobutane), m/z (relative intensity, 30% cutoff) 253 (MH^+, 100). Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 80.89; H, 8.09; N, 11.08.

(*Z*)-3-Ethylidene-1,2,3,4,6,7,12,12b-octahydrolindolo[2,3-*a*]quinolizidine (13). By use of a procedure identical with that described for the preparation of **3**, tetrahydro-β-carboline **9** (542 mg, 1.73 mmol) was cyclized, and the resulting product purified by chromatography and sublimation (140 °C, 0.3 mm) to give 346 mg (79%) of crystalline **13**. Analysis of capillary GC[13] showed that this sample was contaminated with 1.7% of **3** and contained no other detectable impurities. An analytical sample of **13** was prepared by one additional sublimation (140 °C, 0.3 mm): mp 163 °C (lit.[3a] 148–153 °C); IR ($CHCl_3$) 3480, 2930, 2850–2745 (*trans*-quinolizidine Bohlmann bands), 1450, 1320 cm^{-1}; UV (MeOH) 235, 274, 282, 289 nm; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70 (br s, indole NH), 7.5–7.05 (m, indole H), 5.33 (broadened q, J = 6.8 Hz, C=CH), 3.81 (br d, J = 12.3 Hz, C_{21} H) 3.43, (br dd, J = 1.7, 11.2 Hz, 1 H), 3.2–2.95 (m, 2 H), 2.8–2.65, (m, 3 H), 2.45–2.3 (m, 2 H), 2.2–2.05 (m, 1 H), 1.7–1.6 (m, 1 H), 1.66 (d, J = 6.9 Hz, $C=CCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 136.2, 135,0, 134.0, 127.5, 121.3, 119.3, 118.8, 118.2, 110.9, 108.1, 60.0, 55.1, 53.1, 34.1, 30.9, 21.7, 12.9; mass spectrum (CI, isobutane), m/z (relative intensity, 35% cutoff) 253 (MH^+, 100), 252 (42). Anal. Calcd for $C_{21}H_{24}N_2O_4$ (maleate salt): C, 68.46; H, 6.57; N, 7.60. Found: C, 68.25; H, 6.70; N, 7.46.

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Registry No. (±)-**3**, 56491-03-3; **4**, 6224-91-5; **5**, 83665-51-4; **6**, 83665-52-5; **7**, 83665-56-9; **8**, 83681-25-8; (±)-**9**, 83665-53-6; (±)-**10**, 83665-54-7; (±)-**11**, 65601-17-4; (±)-**12**, 65601-15-2; (±)-**13**, 76549-66-1; (±)-**13** maleate, 83665-57-0; 2-(2-iodoethyl)-1,3-dioxolane, 83665-55-8.

Enzymatic Synthesis of Dynorphin (1–8)

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Conventional syntheses of arginyl peptides are often accompanied by undesired side reactions. An alternative approach is proposed to overcome these difficulties which exploits the proteosynthetic potential of trypsin. The enzyme's specificity ensures regio- and stereocontrolled synthesis of peptide bonds whose carbonyl moiety is associated with a basic amino acid residue. To demonstrate the feasibility of the enzymatic method all the peptide bonds of a biologically active dynorphin (1–8) (primary structure H-Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-OH) were prepared by protease catalysis as follows: the protected octapeptide **31** was obtained via α-chymotrypsin-mediated condensation of Boc-Tyr(Bzl)-Gly-Gly-Phe-OEt (**13**) and H-Leu-Arg-Arg-Ile-N_2H_2Ph. The preparation of **13** has already been described.[15] Boc-Leu-Arg-Arg-Ile-N_2H_2Ph (**30**) was synthesized from Boc-Leu-Arg-OMe (**28**) and H-Arg-Ile-N_2H_2Ph in the presence of trypsin. Boc-Leu-Arg-N_2H_2Ph (**27**) the precursor of **28**, was prepared by α-chymotrypsin-catalyzed coupling of Boc-Leu-OEt and H-Arg-N_2H_2Ph. Boc-Arg-Ile-N_2H_2Ph (**29**) was obtained by tryptic condensation of Boc-Arg-OMe and H-Ile-N_2H_2Ph.

Although the recent development of new methods for the chemical coupling of appropriate protected amino acid or peptide derivatives has improved significantly the prospects of peptide synthesis, the preparation of arginine peptides still represents an intricate procedure.[1-3] Despite the strongly basic character of the δ-guanidine group of arginine (pK_a = 12.5), which is generally protonated under conditions prevailing in peptide synthesis, the low solubility in organic solvents of charged arginine derivatives and their tendency to form lactams during the activation of the carboxyl group often necessitates N^G protection. However, the nucleophilicity of the δ-guanidine group, even in the protected form, is high enough for an intramolecular reaction of the carbonyl with the vicinal guanidine nitrogen, resulting in cyclization to piperidinones.[2] According to Bodanszky and Martinek,[2] complete protection to fully suppress the basicity of the δ-guanidine group requires N^δ, N^ω-diacylation by bulky protecting groups. On the other hand, as stated by Barany and Merrifield,[4] the advantages of this kind of protection are counterbalanced by considerations of ease of synthesis, potential steric hindrances during coupling, and selective removal of N^α-protecting groups. Therefore, biologically active oligopeptides containing arginine residues or even Arg-Arg subsequences are difficult to prepare. In this paper I propose an alternative approach to the synthesis of arginyl peptides which relies on the capacity of trypsin to catalyze peptide bond formation when the amino acid which contributes the carbonyl portion of the bond to be formed is an arginine or a lysine residue. The regio- and stereospecificity of tryptic action prevents the occurrence of undesired side reactions

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