85662-51-7; **16**, 3643-16-1; (±)-**17** (isomer 1), 85662-52-8; (±)-**17** (isomer 2), 85662-53-9; (±)-**18**, 85662-54-0; (±)-**19**, 85662-55-1; (±)-**20**, 51704-29-1; methyl phenyl selenide, 4346-64-9; ethyl phenyl selenide, 17774-38-8; isopropyl phenyl selenide, 22233-89-2.

Formal Total Synthesis of Perhydrohistrionicotoxin. An Organopalladium Route

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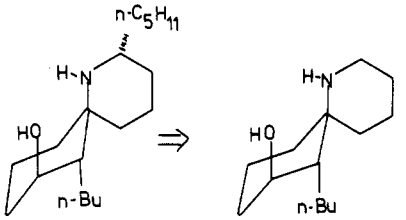
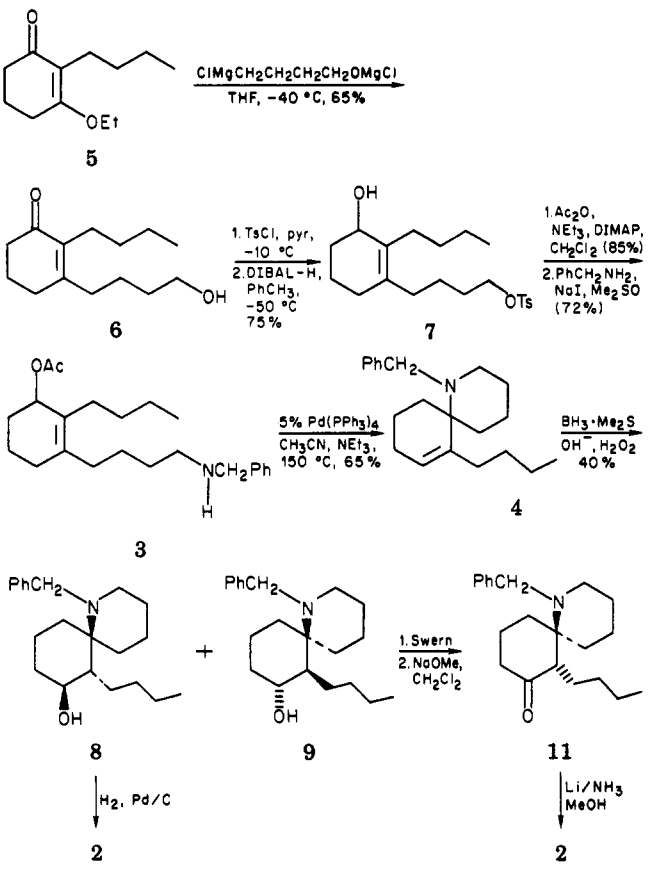
Members of the histrionicotoxin family of alkaloids have attracted considerable interest among synthetic chemists because of their unique structural features and their important properties as cholinolytics and modifiers of specific ion channels in nerves.[1,2] Syntheses of perhydrohistrionicotoxin (**1**,[3-6] PHTx), a nonnaturally occurring congener of histrionicotoxin with comparable activity, and accounts describing approaches to **1**[7-9] have appeared in the literature. A resurgence of interest in these alkaloids has recently occurred on the basis of reports that a variety of structurally simpler analogues of **1** also possess significant neurological activity.[10,11]



1 **2**

Having recently developed a general methodology for the preparation of spirocycles based on (π-allyl)palladium chemistry,[12-14] we sought to further demonstrate its utility by applying it in a synthesis of **1**. We selected deamylperhydrohistrionicotoxin (**2**) as our primary synthetic target because it had been efficiently carried on by Corey[3a] to PHTx (**1**) and had recently been found to possess equal bioactivity to **1**.[10] Model studies[12] had indicated that the key spirocyclization could be readily achieved by a palladium-catalyzed reaction of the amino allylic acetate **3**. Transformation of the product of this cyclization (**4**) to **2** via a hydroboration–oxidation seemed likely.

Scheme I



The (π-allyl)palladium precursor **3** was assembled as indicated in Scheme I. The sequence was initiated by treatment of the known vinylogous ester **5**[15] with the Normant Grignard[16] reagent derived from 4-chlorobutanol which provided on acidic workup the enone alcohol **6** in 65% yield. Tosylation of **6** (TsCl, pyr, -10 °C, 8 h) and reduction[17] (DIBAL-H, $PhCH_3$, -50 °C, 5 h) yielded the allylic alcohol–tosylate **7** (75% yield for two steps). Conversion of **7** to **3** was accomplished by acetylation of the alcohol (Ac_2O, 1 equiv of NEt_3, catalytic amount of DIMAP, CH_2Cl_2, 0 °C, 2 h; 85%) and amination of the tosylate ($PhCH_2NH_2$, catalytic amount of NaI, Me_2SO, room temperature, 18 h;[17] 72%).

Reaction of the amino allylic acetate **3** with 5–7% Pd(PPh_3)$_4$ (1 equiv of NEt_3, CH_3CN, 150 °C, sealed tube) gave the spirocyclic olefin **4** in 65% isolated yield. Conversion of **4** to *N*-benzyldeamylperhydrohistrionicotoxin proved, however, to be other than routine. The optimal conditions that were developed for this transformation included the use of 1.1 equiv[18] of BH_3·Me_2S in THF at room temperature for 18 h, followed by oxidation with a large excess of basic hydrogen peroxide in diglyme at 85 °C (10 h),[19] which provided the isomeric alcohols **8** and **9**

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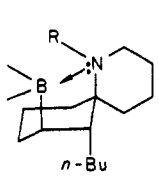
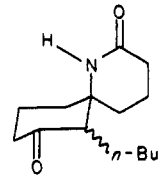
0022-3263/83/1948-2101$01.50/0

in a 2:1 ratio, favoring the desired isomer 8 in 40% overall yield.[20] The forcing conditions required for the oxidation of the cyclic aminoborane complex 10 and the production of some tertiary alcohol accounts, in part, for the low yield in this process. Attempts to increase regio- and stereoselectivity in this reaction by the use of other hydroborating agents or directing groups on the amine, e.g., *N*-allyl,[21] proved inferior to the BH_3·Me_2S conditions. The desired alcohol 8 could be chromatographically separated and debenzylated (60 psi, H_2, Pd/C, EtOH, 48 h; 85%) to provide deamyl PHTx (2) identical in all respects with an authentic sample given to us by A. Brossi.

Alternatively, the crude mixture of alcohols from the hydroboration–oxidation could be oxidized by employing Swern conditions[22] to provide the isomeric ketones 11 and 12 in a 2:1 ratio in 44% yield from the olefin. Epimerization of ketones ($NaOMe/CH_2Cl_2$, room temperature, 24 h) produced a 13:1 ratio of 11 to 12. It is noteworthy that the comparable epimerization of the Kishi lactam 13 reportedly gave only a 4:1 ratio of desired to undesired material. Li/NH_3 reduction of 11 (2 equiv of MeOH) neatly effected both completely stereoselective reduction of the ketone and debenzylation to give the deamyl PHTx (2, 65%).[23]



10



13

This work provides a facile route to deamyl PHTx (2) and demonstrates the synthetic utility of the palladium-based methodology.

Experimental Section

General Methods. Infrared spectra were determined on a Perkin-Elmer PE 467 and are reported in reciprocal centimeters. ^1H NMR spectra were recorded on a JEOLCO MH-100 (100 MHz), a Varian EM-390 (90 MHz), or a Bruker WH-400 (400 MHz). Chemical shifts are reported in δ units and coupling constants in hertz. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were recorded on a Du Pont 21-490B at an ionizing voltage of 70 eV. Precise mass were obtained on a VG 7035. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Medium-pressure liquid chromatography (MPLC) was run with Woelm silica gel (32–63 μm) in the indicated solvent. Et_2O, DME, and THF were distilled immediately before use from benzophenone ketyl. Pyridine, hexane, CH_2Cl_2, and NEt_3 were distilled from CaH_2.

2-Butyl-3-(4-hydroxybutyl)-2-cyclohexen-1-one (6). 4-Chlorobutanol (Fluka; 1.8 g, 16 mmol) dissolved in 25 mL of THF was cooled to −20 °C under a N_2 atmosphere. Methylmagnesium chloride (2.9 M in THF, 18 mmol; Aldrich) was then added dropwise. After the addition was complete, magnesium turnings (0.37 g, 16 mmol) were added, and the solution was heated at reflux for 12 h.[16] The reaction mixture was then cooled to −50 °C, and 2-butyl-3-ethoxy-2-cyclohexen-1-one (1; 2.1 g, 11 mmol)[15] which was dissolved in a minimum amount of THF was added. The solution was allowed to warm to −20 °C and was stirred at this temperature for 3.5 h. The reaction mixture was then partitioned between 50 mL of ethyl acetate and 25 mL of cold 3 N HCl. The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 25 mL). The ethyl acetate fractions were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated at reduced pressure. This compound was typically carried on without purification. Purification of the product can be effected by flash chromatography on alumina with hexane/ether (1:1) as the eluant, yielding 1.6 g (65%) of 6 as a light yellow oil: ^1H NMR (100 MHz, $CDCl_3$) 4.6(br s, 1 H), 3.6 (t, J = 5 Hz, 2 H), 2.8–1.1 (m, 18 H), 0.9 (t, J = 5 Hz, 3 H); IR (CCl_4) 3630, 3400, 1670 cm^{-1}; mass spectrum, m/e 224 (m^+).

2-Butyl-3-[4-(*p*-tolylsulfonoxy)butyl]cyclohex-2-en-1-one. The alcohol 6 (1.6 g, 7.1 mmol) was dissolved in 5 mL of dry pyridine and cooled to −10 °C under a N_2 atmosphere. Tosyl chloride (1.49 g, 7.8 mmol) was added, and the mixture was stirred at −10 °C for 18 h. The solution was then partitioned between 50 mL of ethyl acetate and 25 mL of cold 3 N HCl. The organic phase was separated, washed with 10 mL of cold 3 N HCl and 10 mL of brine, dried over anhydrous Na_2SO_4, and concentrated at reduced pressure to yield a yellow oil (2.55 g, 95%) which was utilized without further purification. An analytical sample was prepared by MPLC on silica gel with ether/hexane (3:2) as the eluant: ^1H NMR(100 MHz) 7.76, 7.32 (AB q, J = 8Hz, 4 H, 4.04 (t, J = 5 Hz, 2 H), 2.5 (s, 3 H), 2.50–1.0 (m, 8 H), 0.9 (t, J = 5 Hz, 3 H); IR (CCl_4) 2970, 1670, 1370, 1195, 1180, 730 cm^{-1}; mass spectrum, m/e 378 (m^+). Anal. Calcd for $C_{21}H_{30}O_4S$: C, 66.63, H, 7.99. Found: C, 66.51; H, 7.98.

2-Butyl-3-[4-(*p*-tolylsulfonoxy)butyl]cyclohex-2-en-1-ol (7). The enone tosylate (3.8 g, 10.0 mmol) was dissolved in 10 mL of toluene and cooled to −50 °C under a N_2 atmosphere. DIBAL-H (25% solution in toluene, 11.0 mmol) was added, and the solution was stirred at −50 °C for 5 h. Methanol (1 mL) was then added to quench excess hydride, followed by water (0.07 g, 40.0 mmol) and 5 g of Celite. The reaction mixture was allowed to warm slowly to room temperature, and vigorous stirring was maintained. The solution was filtered, and the solid residue was washed with ethyl acetate (5 × 10 mL). The washings were combined with the original filtrate, extracted with 10 mL of saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The allylic alcohol tosylate was purified by MPLC on silica gel with ether/hexane (1:1) as the eluant, providing 3.0 g (79%) of 7. This material was immediately carried on to the next reaction: ^1H NMR (100 MHz, $CDCl_3$) 7.92, 7.44 (AB q, J = 9 Hz, 4 H), 4.08 (br s, 1 H), 4.04 (t, J = 6 Hz, 2 H), 2.46 (s, 3 H), 2.40–1.0 (m, 18 H), 0.84 (br t, J = 6 Hz, 3 H); IR (CCl_4) 3610, 3550, 2950, 1660, 1600, 1450, 1365, 1175, 960, 930 cm^{-1}; mass spectrum, m/e 378 (m^+).

1-Acetoxy-2-butyl-3-[4-(*p*-tolylsulfonoxy)butyl]cyclohex-2-ene. The allylic alcohol 7 (3.0 g, 7.9 mmol), triethylamine (0.7 g, 7.9 mmol), and dimethylaminopyridine (catalyst, ~10 mg) were dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C under a N_2 atmosphere. Acetic anhydride (0.8 g, 7.9 mmol) was added, and the solution was stirred at 0 °C for 2 h. The reaction mixture was then partitioned between 50 mL of CH_2Cl_2 and 50 mL of dilute aqueous $NaHCO_3$. The organic phase was separated, washed with brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated at reduced pressure to yield 2.8 g (85%) of the allylic acetate which was used without purification: ^1H NMR (90 MHz, $CDCl_3$) 7.92, 7.44 (AB q, J = 9 Hz, 4 H), 5.25 (br s, 1 H), 4.0 (t, J = Hz, 2 H), 2.40 (s, 3 H), 2.05 (s, 3 H), 2.3–1.0 (m, 18 H), 0.8 (br t, J = 6 Hz, 3 H); IR (CCl_4) 2950, 1735, 1375, 1240, 1180, 940

(19) These conditions for oxidation were provided to us by Professor A. J. Pearson.

(20) The alcohols 8 and 9 were converted to their acetates to simplify their stereochemical assignments in the 400-MHz ^1H NMR. The acetate derived from 8 clearly showed the required axial methine for CHOAc. Alcohols 8 and 9 could be separated by MPLC and independently oxidized to 11 or 12, respectively, thereby establishing stereochemical assignments for these ketones.

(21) We reasoned that the *N*-allyl derivative would be rapidly hydroborated on the terminal olefin. The RBH_2 reagent thus provided would then hydroborate the trisubstituted olefin intramolecularly, providing the correct regio- and stereoisomeric alcohol on the spiro ring. Subsequent specific oxidation of the primary alcohol to an aldehyde and β elimination of acrolein would give 2. Unfortunately, the second, intramolecular hydroboration is extremely sluggish, presumably due to formation of a cyclic amine complex.

(22) The direct oxidation of the hydroboration product to the ketones by using dichromate was not successful. The Swern oxidation on the alcohol was run as described in: Mancuso, A. J.; Huang, S.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(23) Anhydrous Li/NH_3 reduction gave only 8. Use of >2 equiv of a proton source caused significant amounts of Birch reduction in the benzyl group, competitive with debenzylation.

cm^{-1}; mass spectrum, m/e 422 (m^+).

1-Acetoxy-2-butyl-3-[4-(benzylamino)butyl]cyclohex-2-ene (3). The acetoxy tosylate (2.8 g, 6.6 mmol) was dissolved in 4 mL of Me_2SO under a N_2 atmosphere. Sodium iodide (catalytic amount, ~50 mg), triethylamine (0.67 g, 6.6 mmol), and benzylamine (1.06 g, 9.9 mmol) were then added. The solution was allowed to stir at room temperature for 12 h, and then it was partitioned between 50 mL of ethyl acetate and 25 mL of brine which had been basified with 10% NaOH (pH ~10). The organic layer was separated, washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated at reduced pressure. The resulting oil was purified by MPLC on silica gel with ethyl acetate/methanol (15:1) as the eluant to give 1.7 g (72%) of **3** which was immediately carried on to the next reaction: ^1H NMR (100 MHz, $CDCl_3$) 7.3 (s, 5 H), 5.3 (br s, 1 H), 3.76 (s, 2 H), 2.64 (br s, 2 H), 2.0 (s, 3 H), 2.2–1.1 (m, 19 H), 0.9 (t, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 170.9, 137.9, 128.8, 128.2, (2 C), 128.1, 126.9, 70.1, 54.0, 49.3, 33.1, 31.2, 30.1, 29.5, 29.4, 29.1, 26.0, 22.9, 21.4, 18.4, 14.0; IR (CCl_4) 2940, 1735, 1455, 1370, 1240, 1005, 905 cm^{-1}; mass spectrum, m/e 357 (m^+).

7-Butyl-*N*-benzyl-1-azaspiro[5.5]undec-7-ene (4). The amino allylic acetate **3** (0.25 g, 0.68 mmol), triethylamine (0.068 g, 0.68 mmol), and $Pd(PPh_3)_4$ (0.08 g, 0.068 mmol) were dissolved in 5 mL of CH_3CN, cooled to −78 °C, and sealed in a thick-walled glass tube under a vacuum. The sealed tube was heated at 150 °C for 24 h, cooled, and opened, and the contents were partitioned between ether (20 mL) and 2 N HCl (25 mL). The aqueous acid phase was separated, basified with concentrated aqueous NH_4OH, and extracted with ethyl acetate (3 × 20 mL). The organic extracts were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated. The resulting oil was purified by MPLC on silica gel with hexane/ether (4:1) as the eluant. The yield of **4** was 0.13 g (65%): ^1H NMR (100 MHz, $CDCl_3$) 7.2 (m, 5 H), 5.64 (br s, 1 H), 3.84, 3.16 (AB q, J = 10 Hz), 2.8–1.2 (m, 20 H), 0.88 (t, J = 5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 144.2, 141.2, 127.9, 127.8, 126.0, 123.9, 59.8, 55.0, 45.4, 33.1, 31.7, 28.2, 26.3, 25.7, 23.0, 21.8, 20.3; IR (CCl_4) 2950, 1500, 1450, 700 cm^{-1}; mass spectrum, m/e 313 (m^+); high-resolution mass spectrum, calcd for $C_{12}H_{31}N$ m/e 297.2456, found 297.2451.

(6*RS*,7*SR*,8*SR*)-7-*n*-Butyl-*N*-benzyl-1-azaspiro[5.5]undecan-8-ol (8) and (6*RS*,7*RS*,8*RS*)-7-*n*-Butyl-*N*-benzyl-1-azaspiro[5.5]undecan-8-ol (9). The olefin **4** (0.5 g, 1.7 mmol) was dissolved in 5 mL of THF under a N_2 atmosphere at room temperature. BH_3·Me_2S (2 M in hexane, 1.85 mmol) was added dropwise, and the reaction mixture was then heated at 40 °C for 24 h. The solution was cooled and the THF removed under reduced pressure. To the resulting oil was added 10 mL of diglyme, 2.5 mL of 10% NaOH (6.0 mmol), and 0.7 mL of 30% H_2O_2 (6.0 mmol). The mixture was heated at 80 °C for 18 h, cooled, and partitioned between 30 mL of ethyl acetate and 10 mL of brine. The organic phase was separated, dried over anhydrous Na_2SO_4, and concentrated at reduced pressure. MPLC on silica gel using ether/hexane (1:1) as the eluant yielded 0.14 g (27%) of **8** (R_f 0.5) and 0.07 g (13%) of **9** (R_f 0.4).

For **8**: ^1H NMR (400 HMz, $CDCl_3$) 7.25 (5 H), 4.0, 3.6 (AB q, J = 9 Hz, 2 H), 3.85 (m, 1 H), 3.1 (pseudo t, J = 10 Hz, 1 H), 2.6 2.43 (AB q, J = 11 Hz, 2 H), 1.9 (m, 1 H), 1.68–1.06 (m, 18 H), 0.86 (t, J = 5 Hz, 3 H); IR (CCl_4) 2970, 1550, 1250, 1215, 1000, 975 cm^{-1}; mass spectrum, m/e 315 (m^+).

For **9**: ^1H NMR (400 MHZ, $CDCl_3$) 7.25 (5 H), 4.0 (br s, 1 H), 3.8, 3.55 (AB q, J = 10 Hz, 2 H), 2.55 (br d, 1 H), 2.4–1.0 (m, 21 H); mass spectrum, m/e 315 (m^+).

Deamylperhydrohistrionicotoxin (2), H_2–Pd/C Reduction. The *N*-benzyl alcohol **8** (0.048 g, 0.15 mmol) was dissolved in 2 mL of absolute ethanol and added to a Parr pressure bottle along with ca. 100 mg of 10% Pd/C. The reduction was performed on a Parr apparatus at 60 psi under H_2 for 36 h. The solution was filtered through Celite to remove the catalyst, and the filtrate was concentrated at reduced pressure. MPLC with silica gel and CH_2Cl_2/MeOH/NH_4OH (84:15:1) yielded 0.29 g (85%) of **2**. This material was found to be identical in all respects with an authentic sample produced by Brossi.[24]

(24) Takahashi, K.; Witkop, B.; Brossi, A.; Maleque, M.; Albuquerque, E. Y. *Helv. Chim. Acta* **1982**, *65*, 252.

Compounds 11 and 12 by Swern Oxidation of 8 and 9. The crude product of the BH_3·Me_2S hydroboration–oxidation of **4** (0.15 g, 0.5 mmol) was subjected to Swern oxidation under the following conditions. Freshly distilled oxalyl chloride (0.13 g, 1.0 mmol) was added to 1 mL of CH_2Cl_2 and cooled to −78 °C under a N_2 atmosphere. Me_2SO (0.15 g, 2.0 mmol) was added to the CH_2Cl_2 solution, and the mixture was stirred for 15 min. The alcohols were dissolved in 0.5 mL of CH_2Cl_2 and added to the reaction mixture. The solution was stirred for 0.5 h at −78 °C, triethylamine (0.5 g, 5.0 mmol) was added, and the mixture was allowed to warm slowly to room temperature. The workup consisted of partitioning the reaction mixture between 25 mL of CH_2Cl_2 and 10 mL of brine. The organic phase was washed with 10 mL of brine, dried over anhydrous Na_2SO_4, and concentrated at reduced pressure. MPLC on silica gel with ether/hexane (1:1) as eluant provided **11** and **12** in a 2:1 ratio (0.07 g, 44%). Epimerization in CH_2Cl_2–NaOMe at room temperature for 25 h yielded 13:1 **11**/**12**.

For **11**: ^1H NMR (400 MHz, $CDCl_3$) 7.3–7.1 (m, 5 H), 4.0, 3.15 (AB q, J = 10 Hz, 2 H), 2.6, 2.51 (AB q, J = 8 Hz, 2 H), 2.36–2.1 (m, 4 H), 2.0–1.08 (m, 14 H), 0.85 (m, 1 H), 0.75 (t, J = 5 Hz, 3 H); IR (CCl_4) 2970, 1720, 1500, 1085, 1030 cm^{-1}; mass spectrum, m/e 313 (m^+). Anal. Calcd for $C_{21}H_{31}NO$: C, 80.45; H, 9.96; N, 4.47. Found: C, 80.25; H, 9.83; N, 4.38.

For **12**: ^1H NMR (400 MHz, $CDCl_3$) 7.3–7.1 (m, 5 H), 3.65, 3.5 (AB q, J = 10 Hz, 2 H), 2.5 (m, 2 H), 2.3 (m, 2 H), 2.15 (br d, 1 H), 1.9–1.0 (m, 16 H), 1.75 (t, J = 5 Hz, 3 H); mass spectrum, m/e 313 (m^+).

Deamylperhydrohistrionicotoxin (2), Li/NH_3 Reduction. Distilled NH_3 (25 mL) was condensed into a 100-mL flask fitted with a dry ice condenser and immersed in a −78 °C bath. The spirocyclic ketone **11** (0.7 g, 2.2 mmol) was dissolved in 2 mL of THF and added to the NH_3, followed by methanol (0.14 g, 4.4 mmol). Lithium metal (0.76 g, 110 mmol) was then added and the cooling bath removed. After 5 h, 5 mL of THF was added, and the NH_3 was allowed to evaporate. The lithium was destroyed with methanol, and the residue was taken up in 25 mL of ethyl acetate. The ethyl acetate solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The resulting colorless oil was purified by MPLC on silica gel with CH_2Cl_2/MeOH/NH_4OH (84:15:1) as the eluant, providing 0.33 g (65%) of **2**.

Acknowledgment. We gratefully acknowledge the agencies that supported this work, including the NIH, the Merck Foundation, and the CIBA-GIEGY Corp. We are especially indebted to Professor A. J. Pearson for sharing results from his laboratories prior to publication and to A. Brossi and E. Albuquerque for providng a sample of **2**.

Registry No. (±)-**1**, 55254-30-3; (±)-**2**, 55228-77-8; (±)-**3**, 85612-37-9; (±)-**4**, 83562-28-1; **5**, 56459-18-8; **6**, 83562-29-2; **6** tosylate, 85612-39-1; **7**, 85612-88-0; **7** acetate, 85612-40-4; (±)-**8**, 83562-31-6; (±)-**9**, 83602-28-2; (±)-**11**, 83562-26-9; (±)-**12**, 83562-34-9; 4-chlorobutanol, 928-51-8; benzylamine, 100-46-9; $Pd(PPh_3)_4$, 14221-01-3.

Electroorganic Chemistry. 59. Electroreductive Synthesis of Oximes from Nitro Olefins

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The elongation of aldehydes and the elongating transformation of aldehydes to ketones have been desirable tools in organic synthesis, though most of the hitherto known methods are not necessarily satisfactory due to trouble-

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