Flexible Synthetic Approach to Histrionicotoxin Congeners. Formal Total Synthesis of (±)-Perhydrohistrionicotoxin

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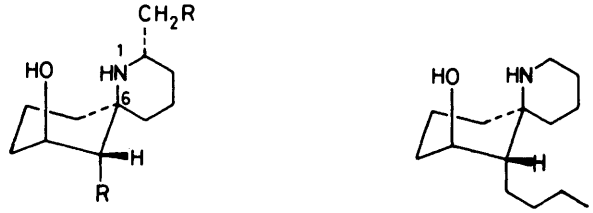
Conversion of 1-benzyl-1-azaspiro[5.5]undec-7-en-9-one (7), readily available using simple organoiron chemistry, in six steps into (±)-depentylperhydrohistrionicotoxin (3) is reported. This compound has been previously reported as an intermediate for synthesis of (±)-perhydrohistrionicotoxin.

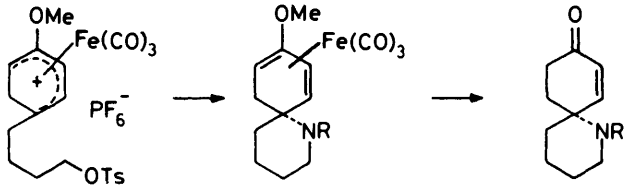
Histrionicotoxin (1), a toxic principle isolated from the skins of the Colombian frog *Dendrobates histrionicus*,[1] is a useful neurophysiological tool which reversibly blocks the acetylcholine-sensitive ion conductance system in frog neuromuscular preparations.[2] It has also been demonstrated that perhydrohistrionicotoxin (2), and more recently [3] depentylperhydrohistrionicotoxin (3), show similar activity. Since the amount of material available from natural sources is very limited (53 mg of histrionicotoxin from 400 frog skins [1]), it is of considerable interest to develop synthetic approaches to these compounds. The total syntheses of perhydrohistrionicotoxin reported by Corey,[4] and of this and octahydrohistrionicotoxin (4), by Kishi's group,[5] have been followed by a number of approaches to the same compounds.[6] None of these routes has so far proven sufficiently flexible as to allow construction of the natural product, histrionicotoxin (1).

We recently described [7] the reaction of the tosyloxybutyl substituted tricarbonylcyclohexadienyliron complex (5) with benzylamine, which gave rise to very good yields of the azaspirocyclic complex (6), by initial addition of amine at the substituted dienyl terminus followed by intramolecular displacement of tosylate. The complex (6) was readily converted into the enone (7), making this intermediate available in multigram quantities. The azaspirocyclic enone (7) presents itself as a potentially very useful intermediate for the synthesis of a wide range of compounds related to histrionicotoxin, provided the enone can be manipulated to give the required substitution pattern. We therefore set out initially to study the conversion of (7) into depentylperhydrohistrionicotoxin (3), which itself has been previously converted into perhydrohistrionicotoxin; [4] the results of our study are described in the present paper.

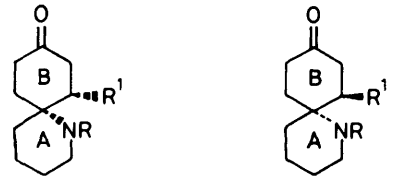


(1) R = $CH{=}^{c}CH{\cdot}C{\equiv}CH$
(2) R = Bu^n
(4) R = $CH_2CH_2CH{=}CH_2$

(3)



(5) (6) (7)



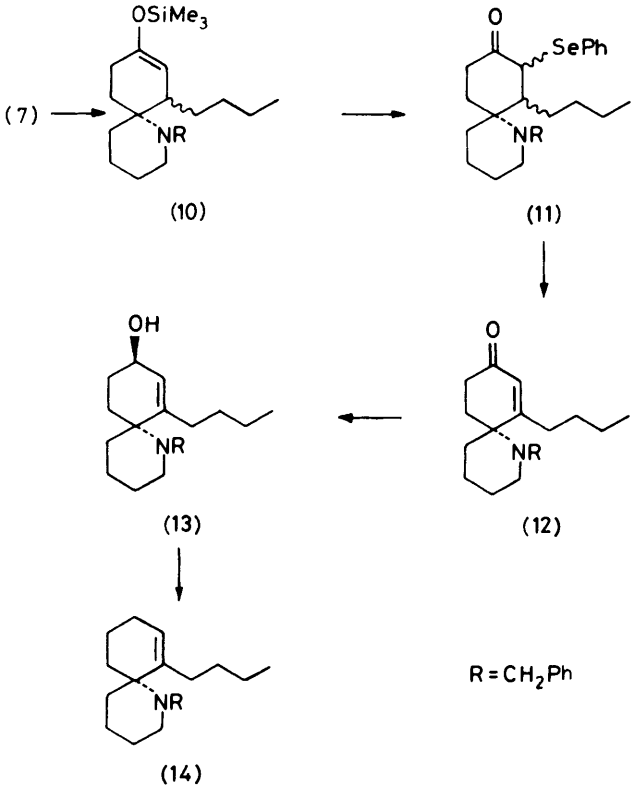
R = CH_2Ph

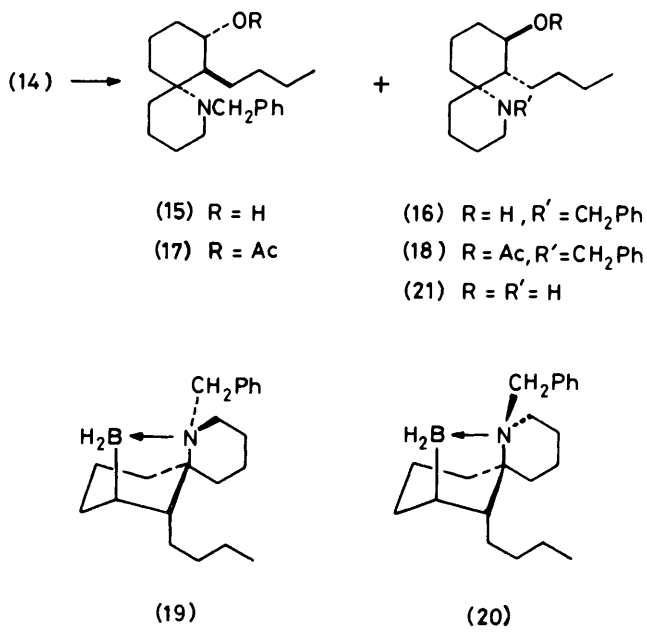
(8) (9)

a; $R^1 = Bu^n$ a; $R^1 = Bu^n$
b; R^1 = Me b; R^1 = Me

Results and Discussion

Our objective required that we introduce a butyl group at C-7, *trans* to the nitrogen atom, and the most obvious way to achieve such a transformation is by cuprate addition. However, the stereochemical outcome of conjugate addition to these particular types of azaspirocyclic enone is not known, and could not be predicted with certainty owing to the competing influences of steric and stereoelectronic factors,[8] and possible directing effects of the nitrogen atom. In the event, reaction of (7) with lithium di-n-butylcuprate resulted in the formation of two epimeric ketones in a 2 : 1 ratio. Interestingly, the two isomers showed distinctly different separation of the AB quartet in the ^{1}H n.m.r. spectrum, corresponding to the benzylic methylene protons (details in Experimental section). Whilst this observation did not allow a stereochemical assignment (nuclear Overhauser enhancement experiments also failed to give this information), it did, nevertheless, provide a useful tool for subsequent assignments. Since both butyl substituted isomers were obtained as oils, we turned our attention to reaction of (7) with lithium dimethylcuprate. Again, a 2 : 1 ratio of stereoisomeric ketones was produced, showing polarity (t.l.c.) and n.m.r. spectra analogous to the butylcuprate products. However, both products from this reaction were nicely crystalline and a single crystal *X*-ray analysis [9] showed the major isomer to have the structure (8b), with the NCH_2Ph group equatorial and a 7-methyl group axial to ring B. On this basis structure (9b) was assigned to the minor diastereoisomer from this reaction, and structures (8a) and (9a) were assigned respectively to the major and minor





products of butyl-cuprate addition. Since the major product (8a) has the incorrect relative stereochemistry for perhydrohistrionicotoxin synthesis, we decided to investigate a strategy which removed the offending centre of asymmetry in the early stages. Thus, the enolate produced during cuprate addition was treated directly with chlorotrimethylsilane to furnish the sensitive enol ethers (10), which were converted directly into α-phenylseleno ketones (11) by treatment with phenylseleninyl chloride. Oxidation of (11), followed by elimination at room temperature afforded the enone (12) in 63% overall yield from (7). The 9-keto group having served its purpose, we now turned our attention to its removal. Whilst the standard procedures we attempted (*e.g.* thioacetal treatment with Raney nickel, modified Wolff-Kishner procedures) all gave unsatisfactory results due mostly to migration of the double bond, the desired transformation was readily accomplished using a two-step procedure as follows. Sodium borohydride reduction gave the crystalline single epimeric alcohol (13), the stereochemical assignment of which was based on the assumption that the ring A nitrogen of (12) is quasi-equatorial to ring B, as shown in the *X*-ray structure determination of molecule (8b), and that addition of hydride occurs along the quasi-axial vector.[10] Reduction of the allylic alcohol (13) with $LiAlH_4/AlCl_3$ [11] furnished the desired compound (14) in *ca.* 80—85% overall yield from (12). Hydroboration/oxidation of (14) turned out to be extremely difficult and variable. Best results were obtained using freshly prepared borane in THF (from $NaBH_4/BF_3$),[12] and under these conditions the olefinic compound (14) was smoothly converted into alkylborane, as judged by t.l.c. of the reaction mixture. Oxidation of the intermediate borane at *ca.* 50 °C for *ca.* 6 h gave a mixture of alcohols, consisting of the undesired stereoisomer (16), together with variable amounts of (15) (n.m.r. of mixture). Since we were unable to separate these compounds (preparative t.l.c.) they were converted into the acetates (17) and (18), which were separated and whose structures could be assigned by ^1H n.m.r. spectroscopy. Thus, the n.m.r. spectrum of the desired acetate (17) showed for the *CH*OAc a signal corresponding to an axial proton, having two axial-axial (*J* 10.9 Hz) and one axial-equatorial (*J* 4.4 Hz) coupling. A very large non-equivalence of the benzylic methylene protons was also observed, which was expected by comparison with compounds (8) and (9), consistent with ring B-equatorial orientation of the *N*-benzyl, butyl, and acetoxy groups. The ^1H n.m.r. spectrum of the undesired acetate (18), showed a narrow pattern for the *CH*OAc proton, typical for an axial acetoxy group. A closer AB quartet was observed for the benzylic methylene group, indicating axial orientation of the butyl group whilst the *N*-benzyl group remains equatorial to ring B [as for compounds (8) and (9)]. These assignments were confirmed by conversion of (17) into the final product. Careful examination of the reaction mixture from the alkylborane oxidation revealed the presence of a non-polar compound which could be isolated and purified, and showed spectral data, including high resolution mass spectrometry, consistent with an alkylborane derivative. The ^1H n.m.r. spectrum of this product revealed the presence of apparently two isomers, but further treatment of this material with alkaline hydrogen peroxide gave rise only to the alcohol (15). Consequently, we have tentatively assigned structures (19) and (20) to these boranes, which are both cyclic aminoborane complexes, differing only in the orientation of the benzyl-N and ring-N bonds. The presence of a dative N→B bond in a five-membered ring in (19) and (20) readily explains the resistance to oxidation of the intermediate,[13] compared to the borane precursor giving the incorrect alcohol (16). These observations led us to a more efficient, if somewhat tedious, method for production of the required alcohol (15). Subsequent to hydroboration, the reaction mixture could be subjected to prolonged treatment with an excess of alkaline hydrogen peroxide, the mixture worked up and separated into alcohol and aminoborane fractions (preparative t.l.c.), and the latter material then recycled. The total recovery of alcohols and borane accounted for *ca.* 55% of the starting material, and we were able to produce an approximately equimolar mixture of alcohols in 35% yield. At this point in our investigation we became aware of similar work by Godleski *et al.*,[14] who have produced intermediate (14) using organopalladium

chemistry, and who encountered similar problems with the hydroboration step. The spectral characteristics of all our compounds produced subsequent to (14) are identical with those obtained by Godleski. Only one step, debenzylation, was now required to convert the inseparable mixture of (15) and (16) into a mixture containing (±)-dependylperhydrohistrionicotoxin which could be separated. However, since we preferred to work with single isomers, and since we wished to correlate accurately our intermediates with the final product, we acetylated the mixture as above, separated the acetates and deprotected them to produce the individual alcohols (15) and (16). Debenzylation of (15) afforded dependylperhydrohistrionicotoxin (3) showing identical spectral properties with the compound produced by Godleski *et al.*, and to those recently reported by Witkop's group.[3]

The diastereomeric alcohol (16) was also debenzylated to give a compound (21), which was different from (3) in all respects (t.l.c. and n.m.r., *etc.*), except i.r. spectrum.

Conclusions.—We have demonstrated the applicability of the azaspirocyclic enone (7), readily available using simple organoiron chemistry, to the synthesis of histrionicotoxin-like compounds. The present route suffers from the disadvantage of a difficult hydroboration step, but the presence of the enone group in (7) lends itself extremely well to modification of our strategy to overcome this problem, and to approach the synthesis of histrionicotoxin itself. These aspects will form the basis of future investigations in our laboratory. The present work has also allowed stereochemical and conformational assignments of general interest for future synthetic work in this area.

Experimental

I.r. spectra were determined with a Perkin-Elmer 577, mass spectra with an A.E.I. MS30, and ^{1}H n.m.r. spectra with Varian EM390 (90 MHz), Bruker WH250 (250 MHz), or Bruker WH400 (400 MHz) spectrometers. M.p.s are uncorrected.

1-*Benzyl*-7-*butyl*-1-*azaspiro*[5.5]*undecan*-9-*one* (8a), (9a).—Lithium di-n-butylcuprate was prepared from copper(I) iodide (0.225 g) in dry THF (5 ml) under argon at −30 °C by dropwise addition of n-butyl-lithium (1.5 ml of a 15 wt% solution in hexane) during 5 min. Stirring was continued at −30 °C for a further 5 min, when a solution of (7) (0.101 g) in dry THF (2 ml) was added dropwise. After being stirred at −25 ± 5 °C for 2 h, the mixture was poured into saturated aqueous ammonium chloride and extracted with ether and dichloromethane. The combined extracts were dried (Na_2CO_3), and solvents were removed under reduced pressure. The mixture of diastereoisomers was separated by t.l.c. (silica gel, 50% ether in hexane), yielding the less-polar isomer (9a) (0.025 g, 20%) as a colourless oil, pure according to t.l.c., $\nu_{max.}$ (CCl_4) 1 718, 1 600, and 700 cm^{-1}; δ($CDCl_3$, 400 MHz) 7.33 (2 H, d, *J* 6.4 Hz, *o*-ArH), 7.30 (2 H, t, *J* 7.5 Hz, *m*-ArH), 7.23 (1 H, t, *J* 7.1 Hz, *p*-ArH), 4.03 (1 H, d, *J* 14.2 Hz), 3.17 (1 H, d, *J* 14.2 Hz ABq, C*H*$_2$Ph), 2.67—0.99 (21 H, methylenes and C*H*Bu), and 0.83 (3 H, t, *J* 7.1 Hz, CH_3); *m*/*z* (%) 313 (*M*$^+$, 22), 201 (37), 200 (100), and 91 (95) (Found: *M*, 313.2416. Calc. for $C_{21}H_{31}NO$: 313.2406). 2,4-Dinitrophenylhydrazones (mixture of double bond isomers) (Found: C, 65.8; H, 7.3; N, 13.95%. Calc. for $C_{27}H_{35}N_5O_4$: C, 65.70; H, 7.15; N, 14.19%).

The more polar isomer (8a) (0.073 g) isolated by this procedure was contaminated with *ca.* 10% of (9a), which could be removed by repeated chromatography, yielding the ketone (8a) as a colourless oil, pure according to t.l.c., $\nu_{max.}$ (CCl_4) 1 723, 1 605, and 700 cm^{-1}; δ($CDCl_3$, 400 MHz) 7.35 (2 H, d, *J* 7.3 Hz, *o*-ArH), 7.30 (2 H, t, *J* 7.3 Hz, *m*-ArH), 7.22 (1 H, t, *J* 7.1 Hz, *p*-ArH), 3.89 (1 H, d, *J* 14.2 Hz) and 3.68 (1 H, d, *J* 14.2 Hz) (ABq, C*H*$_2$Ph), 2.68—0.92 (21 H, methylenes and CHBu), and 0.88 (3 H, t, *J* 7.3 Hz, CH_3); *m*/*z* (%) 313 (*M*$^+$, 12), 201 (36), 200 (100), and 91 (82). (Found: *M*, 313.2397. Calc. for $C_{21}H_{31}NO$: 313.2406). 2,4-Dinitrophenylhydrazones (Found: C, 56.55; H, 7.05; N, 14.3. Calc. for $C_{27}H_{35}N_5O_4$: C, 65.70; H, 7.15; N, 14.19%).

1-*Benzyl*-7-*methyl*-1-*azaspiro*[5.5]*undecan*-9-*one* (8b), (9b).—Lithium dimethylcuprate was prepared from copper(I) iodide (0.233 g) in dry ether (4 ml) under argon at 0 °C, by dropwise addition of methyl-lithium/lithium bromide solution (1.4M in ether), until the initially formed yellow precipitate just dissolved. To this was added a solution of the enone (7) (0.104 g) in ether (2 ml) at 0 °C. The solution was stirred at 0 °C for 2.5 h, poured into saturated aqueous ammonium chloride and extracted with ether and dichloromethane, followed by drying the extracts over sodium carbonate. The resultant mixture of diastereoisomers was separated by t.l.c. (silica gel, 50% ether in hexane), affording the less polar isomer (9b) (0.022 g, 20%), m.p. 73.5—74.5 °C (from trituration with pentane), $\nu_{max.}$ (CCl_4) 1 717, 1 600, and 700 cm^{-1}; δ($CDCl_3$, 400 MHz) 7.34 (2 H, d, *J* 6.8 Hz, *o*-ArH), 7.30 (2 H, t, *J* 6.7 Hz, *m*-ArH), 7.23 (1 H, t, *J* 6.8 Hz, *p*-ArH), 4.06 (1 H, d, *J* 14.6 Hz), and 3.22 (1 H, d, *J* 14.6 Hz) (ABq, C*H*$_2$Ph), 2.70—1.39 (15 H, methylenes and C*H*Me), 1.03 (3 H, d, *J* 6.8 Hz, CH_3); *m*/*z* (%) 271 (*M*$^+$, 22), 201 (42), 200 (100), 123 (83), and 91 (97) (Found: C, 79.7; H, 9.4; N, 5.1%; *M*, 271.1931. Calc. for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16% *M*, 271.1936).

The more polar isomer (0.055 g, 50%) was further purified by recrystallisation (aqueous methanol) to afford pure (8b), m.p. 77.5—79 °C, $\nu_{max.}$ (CCl_4) 1.720, 1 600, and 700 cm^{-1}; δ($CDCl_3$, 400 MHz), 7.35 (2 H, d, *J* 7 Hz, *o*-ArH), 7.29 (2 H, t, *J* 7 Hz, *m*-ArH), 7.21 (1 H, t, *J* 7 Hz, *p*-ArH), 3.86 (1 H, d, *J* 14.6 Hz) and 3.75 (1 H, d, *J* 14.6 Hz) (ABq, C*H*$_2$Ph), 2.73—1.41 (15 H, methylenes and C*H*Me), and 1.08 (3 H, d, *J* 6.8 H, CH_3); *m*/*z* (%) 271 (*M*$^+$, 23), 201 (41), 200 (100), 91 (64) (Found: C, 79.7; H, 9.1; N, 5.1%; *M*, 271.1937. Calc. for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16%, *M*, 271.1936).

1-*Benzyl*-7-*butyl*-1-*azaspiro*[5.5]*undec*-7-*en*-9-*one* (12).—To a solution of lithium di-n-butylcuprate [from copper(I) iodide (0.235 g) and n-butyl-lithium (1.58 ml) as above] in dry THF (5 ml) was added the enone (7) (0.101 g) in THF (3 ml). After reaction as above, chlorotrimethylsilane (0.169 ml, 3 equiv.) and triethylamine (0.185 ml, 3 equiv.) were added at −20 °C, and the mixture was stirred at −20 °C for 0.5 h and at 20 °C for 1 h. The resulting mixture was poured into saturated aqueous ammonium chloride/conc. ammonia solution (1 : 1) and extracted with ether and dichloromethane. The combined extracts were dried (Na_2CO_3), concentrated at reduced pressure, and immediately washed through a short column of neutral alumina (activity 1) with ether. Removal of solvent afforded the sensitive trimethylsilyl enol ether (10) (0.143 g, 93%), which was used immediately without further purification, $\nu_{max.}$ (CCl_4) 1 670, 1 605, 1 250, and 700 cm^{-1}; *M*$^+$, 385. This crude product was stirred in dry THF (4 ml) under nitrogen at −78 °C whilst phenylseleninyl chloride (0.088 g, 1.25 equiv.) was added in THF (1 ml). After 3 min at −78 °C, the solution was allowed to attain ambient temperature during 15 min. To this was then added a mixture of hydrogen peroxide solution (100 vol., 0.6 ml) and glacial acetic acid (0.15 ml) in water (0.75 ml). After a further 0.5 h at ambient temperature, the solution was poured into saturated aqueous sodium carbonate, and extracted with ether and dichloromethane as

above. Preparative t.l.c. (silica gel, 50% ether in hexane) afforded the enone (12) as a colourless oil (0.078 g, 63%), $\nu_{max.}$ (CCl_4) 1 675, 1 615, 1 600, and 700 cm^{-1}; δ($CDCl_3$) 7.31br (5 H, m, ArH), 5.95 (1 H, m, fine couplings unresolved, olefinic H), 3.58 (1 H, d, *J* 15 Hz) and 3.25 (1 H, d, *J* 15 Hz) (ABq, CH_2Ph), 2.8—1.1 (18 H, methylenes), 0.95 (3 H, t, CH_3); *m/z* (%) 311 (M^+, 8), 283 (29), 254 (43), 200 (63), and 192 (100) (Found: *M*, 311.2232. Calc. for $C_{21}H_{29}NO$: *M*, 311.2249).

1-*Benzyl*-7-*butyl*-1-*azaspiro*[5.5]*undec*-7-*en*-9-*ol* (13).—To a solution of the enone (12) (0.334 g) in dry methanol (8 ml) under nitrogen at 0 °C was added sodium borohydride (0.084 g, 2 equiv.). After being stirred at 0 °C for 0.5 h, the mixture was poured into saturated aqueous sodium carbonate and thoroughly extracted with dichloromethane; the extracts were dried (Na_2CO_3) and solvent removed under reduced pressure to yield the alcohol (13) (0.333 g, 99%), containing only trace impurities by t.l.c. This material was used without purification for subsequent reactions, but the trace impurities could be removed by preparative layer chromatography (silica gel, 60% ether in hexane), followed by recrystallisation from aqueous methanol, to give pure (13) as a white solid, m.p. 84—86 °C, $\nu_{max.}$ (CCl_4) 3 630, 1 665, 1 600, and 700 cm^{-1}; δ($CDCl_3$) 7.29 (5 H, m, ArH), 5.56 (1 H, m, fine couplings unresolved, olefinic H), 4.22br (1 H, s, C*H*OH), 3.66 (1 H, d, *J* 14.5 Hz) and 3.07 (1 H, d, *J* 14.5 Hz) (ABq, CH_2Ph), 2.7—1.1 (18 H and 1 H exch. D_2O, methylenes and OH), and 0.84 (3 H, t, CH_3); *m/e* (%) 313 (M^+, 57), 312 (51), 222 (97), 200 (67), 194 (100), and 120 (72) (Found: C, 80.45; H, 10.15; N, 4.5%; *M*, 313.2414. Calc. for $C_{21}H_{31}NO$: C, 80.46; H, 9.97; N, 4.47%; *M*, 313.2406).

1-*Benzyl*-7-*butyl*-1-*azaspiro*[5.5]*undec*-7-*ene* (14).—To a stirred mixture of aluminium chloride (1.50 g) in dry ether (15 ml) was added lithium aluminium hydride (0.300 g) at 0 °C. The mixture was stirred for 5 min after which the alcohol (13) (0.333 g) was added as a solution in dry ether (5 ml), and stirring was continued at 0 °C for 1 h. Excess of hydride was destroyed by careful addition of water, with stirring and the mixture was poured into water, separated, basified with saturated aqueous sodium carbonate, and extracted with chloroform. The combined extracts were washed with water, dried (Na_2CO_3) and solvent removed at reduced pressure, to yield the olefin (14) (0.295 g, 94%). This contained only trace impurities (t.l.c.), and was suitable for subsequent reactions without purification. Pure material was afforded by t.l.c. (silica gel, 8% ether in hexane), as a colourless oil which could not be crystallised, $\nu_{max.}$ (CCl_4) 1 605 and 700 cm^{-1}; δ($CDCl_3$, 400 MHz) 7.35 (2 H, d, *J* 7.3 Hz, *o*-ArH), 7.28 (2 H, t, *J* 7.3 Hz, *m*-ArH), 7.18 (1 H, t, *J* 7.3 Hz, *p*-ArH), 5.58br (1 H, t, *J* 3.9 Hz olefinic H), 3.76 (1 H, d, *J* 15 Hz) and 3.13 (1 H, d, *J* 15 Hz) (ABq, CH_2Ph), 2.52—1.26 (20 H, methylenes), and 0.85 (3 H, t, *J* 7.1 Hz, CH_3); *m/z* (%) 297 (M^+, 54), 254 (100), 226 (49), 200 (42), and 198 (53) (Found: *M*, 297.2451. Calc. for $C_{21}H_{31}N$: 297.2456).

O-*Acetyl*-N-*benzyldepentylperhydrohistrionicotoxin* (17) *and its* 6-*Epimer* (18).—The olefin (14) (0.028 g) and sodium borohydride (0.054 g) were stirred in dry THF (3 ml) as boron trifluoride–diethyl ether (0.24 ml, producing 20 equiv. of BH_3) was added dropwise. The mixture was stirred at ambient temperature for 0.5 h, and at 50 °C for a further 1 h, after which time excess of diborane was decomposed by addition of water, followed by dilute aqueous sodium carbonate. Extraction with dichloromethane, drying of the extract over Na_2CO_3, and the customary work-up afforded the crude borane adduct (0.031 g, quantitative). T.l.c. (silica gel, 20% ether in hexane) gave pure material, $\nu_{max.}$ (CCl_4) 2 340, 1 605, and 700 cm^{-1}; δ($CDCl_3$) 7.77 (m) and 7.36 (m) (together, 5 H, ArH), 4.37 (d, *J* 12 Hz) and 4.19 (d, *J* 12 Hz) (together, 1 H), and 3.83 (1 H, d, *J* 12 Hz) (2 × ABq, partially superimposed, CH_2Ph), 3.3—1.1 (24 H, methylenes, methines and BH_2), and 0.91 (3 H, t, *J* 6.5 Hz, CH_3) [Found: M^+ (^{11}B), 311.2789; M^+ (^{10}B), 310.2817. Calc. for $C_{21}H_{34}{}^{11}BN$: 311.2784. Calc. for $C_{21}H_{34}{}^{11}BN$: 310.2821].

To the crude borane adduct in THF (4 ml) at 35 °C was added with stirring sodium hydroxide (1 pellet), followed by aqueous hydrogen peroxide (30% solution, 4 ml) added portionwise during 4 h. The mixture was poured into aqueous sodium carbonate and extracted as above. Preparative t.l.c. (silica gel, 50% ether in hexane) then afforded the borane adduct (6.5 mg, 22%) and a mixture of the alcohols (15) and (16) (10.5 mg, 34%). Further quantities of (15) could be obtained by oxidation of recovered borane.

To the alcohols (11.5 mg) in dry pyridine (1 ml) at 0 °C was added acetyl chloride (27 μl, 10 equiv.). The mixture was warmed to ambient temperature and stirred for 17 h. After removal of solvent, the residue was dissolved in dichloromethane and the solution washed with aqueous sodium carbonate, dried (Na_2CO_3), and concentrated under reduced pressure. Preparative layer chromatography (silica gel, 50% ether in hexane) of the residue afforded the acetates (17) (4 mg, 32%) and (18) (3 mg, 24%), as colourless oils.

Acetate (17): $\nu_{max.}$ (CCl_4) 1 730, 1 605, and 700 cm^{-1}; δ($CDCl_3$) 7.3—7.15 (5 H, m, ArH), 4.91 (1 H, ddd, J_{aa} 10.9 Hz, J_{ae} 4.4 Hz, C*H*OAc), 4.13 (1 H, d, *J* 14.5 Hz) and 3.03 (1 H, d, *J* 14.5 Hz) (ABq, CH_2Ph), 2.6—1.0 (21 H, methylenes and C*H*Bu), 1.97 (3 H, s, $COCH_3$), and 0.73 (3 H, t, *J* 7.2 Hz, CH_3); *m/z* (%) 357 (M^+, 13), 298 (100), 208 (21), 200 (48), and 187 (75) (Found: *M*, 357.2652. Calc. for $C_{23}H_{35}NO_2$: 357.2668).

Acetate (18): $\nu_{max.}$ (CCl_4) 1 730, 1 605, and 700 cm^{-1}; δ($CDCl_3$) 7.35—7.15 (5 H, m, ArH), 5.13 (1 H, m, fine couplings unresolved, C*H*OAc), 3.92 (1 H, d, *J* 14.2 Hz) and 3.65 (1 H, d, *J* 14.2 Hz) (ABq, CH_2Ph), 2.7—1.1 (21 H, methylenes and C*H*Bu), 2.02 (3 H, s, $COCH_3$), and 0.90 (3 H, t, *J* 6.8 Hz, CH_3); *m/z* (%) 357 (M^+, 13), 298 (100), 200 (28), and 187 (32) (Found: *M*, 357.2662. Calc. for $C_{23}H_{35}NO_2$: *M*, 357.2668).

N-*Benzyl*-6-*epidepentylperhydrohistrionicotoxin* (16).—The acetate (18) (4 mg) was stirred with sodium hydroxide in methanol (2 ml) for 26 h, poured into aqueous sodium carbonate and extracted with dichloromethane. Work-up followed by preparative t.l.c. (silica gel, ether) afforded the alcohol (16) (3 mg, 75%) as a colourless oil, $\nu_{max.}$ (CCl_4) 3 630 and 700 cm^{-1}; δ($CDCl_3$) 7.37—7.14 (5 H, m, ArH), 4.02br (1 H, s, C*H*OH), 3.91 (1 H, d, *J* 14.5 Hz) and 3.58 (1 H, d, *J* 14.5 Hz) (ABq, CH_2Ph), 2.63—0.96 (20 H, changes on D_2O shake, methylenes, C*H*Bu and OH), and 0.92 (3 H, t, *J* 6.8 Hz, CH_3); *m/z* (%) 315 (M^+, 21), 200 (51), 187 (63), and 91 (100) (Found: *M*, 315.2573. Calc. for $C_{21}H_{33}NO$: *M*, 315.2562).

N-*Benzyldepentylperhydrohistrionocotoxin* (15).—Following the above procedure, the acetate (17) (9.5 mg) afforded the alcohol (15) (7.5 mg, 89%), as a colourless oil, $\nu_{max.}$ (CCl_4) 3 625, 1 605, and 705 cm^{-1}; δ($CDCl_3$) 7.99br (1 H, d, *J ca.* 8.5 Hz, exchanges D_2O, OH), 7.4—7.2 (5 H, m, ArH), 4.07 (1 H, d, *J* 12.5 Hz) and 3.65 (1 H, d, *J* 12.5 Hz) (ABq, CH_2-Ph), 4.00 (1 H, m, obscured, sharpens on D_2O shake), 3.15br (1 H, t, *J ca.* 14 Hz) and 2.6—1.1 (21 H, methylenes and C*H*Bu), and 0.90 (3 H, t, *J* 6.6 Hz, CH_3); *m/z* (%) 315 (M^+, 16), 200 (44), 187 (54), and 91 (100) (Found: *M*, 315.2569. Calc. for $C_{21}H_{33}NO$: *M*, 315.2562).

(±)-*Depentylperhydrohistrionicotoxin* (3).—The tertiary amine (15) (7.5 mg) was stirred with 10% palladium on charcoal (4 mg) in AnalaR ethanol (2 ml) under a hydrogen atmosphere for 7.5 h. After removal of catalyst, t.l.c. [silica gel, dichloromethane–methanol–ammonia [84 : 15 : 1)] gave depentylperhydrohistrionicotoxin (3) (4 mg, 76%); this was purified by dissolution in 10% aqueous hydrochloric acid, washing of the solution with ether followed by basification with AnalaR potassium hydroxide, and extraction with chloroform. After drying (Na_2CO_3) of the extract and removal of solvent pure material was obtained, $\nu_{max.}$ (CCl_4) 3 610 and 3 250br cm^{-1}; δ($CDCl_3$) 3.97 (1 H, m, couplings unresolved, C*H*OH), 3.02 (1 H, m) and 2.86 (1 H, m) (CH_2N), 2.1—1.0 (21 H, changes on D_2O shake, methylenes, C*H*Bu, OH and NH), 0.88 (3 H, t, *J* 6 Hz, CH_3); *m/z* (%) 225 (M^+, 33), 182 (35), 110 (100), and 97 (91) (Found: *M*, 225.2079. Calc. for $C_{14}H_{27}NO$: *M*, 225.2093).

Note added in proof: Carruthers and Cumming have recently reported conversion of (14) into (15) by hydroboration using Me_3NO as oxidant, subsequent to our communicating the difficulties encountered using alkaline hydrogen peroxide (W. Carruthers and S. A. Cumming, *J. Chem. Soc., Chem. Commun.*, 1983, 360).

References

1 J. W. Daly, I. Karle, C. W. Myers, T. Tokuyama, J. A. Waters, and B. Witkop, *Proc. Natl. Acad. Sci. U.S.A.*, 1971, **68**, 1870.
2 A. T. Elderfrawi, M. E. Elderfrawi, E. X. Albuquerque, A. C. Oliviera, N. Mansour, M. Adler, J. W. Daly, G. B. Brown, W. Burgermeister, and B. Witkop, *Proc. Natl. Acad. Sci. U.S.A.*, 1977, **74**, 2172.
3 K. Takahashi, B. Witkop, A. Brossi, M. A. Maleque, and E. X. Albuquerque, *Helv. Chim. Acta*, 1982, **65**, 252.
4 E. J. Corey and R. D. Balanson, *Heterocycles*, 1976, **5**, 445; E. J. Corey, Y. Ueda and R. A. Ruden, *Tetrahedron Lett.*, 1975, 4347; E. J. Corey, J. F. Arnett, and G. N. Widiger, *J. Am. Chem. Soc.*, 1975, **97**, 430; E. J. Corey, M. Petrzilka, and Y. Ueda, *Tetrahedron Lett.*, 1975, 4343.
5 M. M. Aratani, L. V. Dunkerton, T. Fukuyama, Y. Kishi, H. Kakoi, S. Sugiura, and S. Inoue, *J. Org. Chem.*, 1975, **40**, 2009; T. Fukuyama, L. V. Dunkerton, M. Aratani, and Y. Kishi, *ibid.*, 1975, **40**, 2011.
6 E. Gossinger, R. Imhof, and H. Werhli, *Helv. Chim. Acta*, 1975, **58**, 96; H. E. Schoemaker and W. N. Speckamp, *Tetrahedron*, 1980, **36**, 951; M. Harris, D.-S. Grierson, and H.-P. Husson, *Tetrahedron Lett.*, 1981, **22**, 1511; J. J. Venit and P. Magnus, *ibid.*, 1980, **21**, 4815; S. A. Godleski, J. D. Meinhart, D. J. Miller, and S. Van Wallendad, *ibid.*, 1981, **22**, 2247; T. Ibuka, Y. Mitsui, H. Hayashi, and Y. Inubushi, *ibid.*, 1981, **22**, 4425.
7 A. J. Pearson, P. Ham, and D. C. Rees, *Tetrahedron Lett.*, 1980, **21**, 4637; *J. Chem. Soc., Perkin Trans. 1*, 1982, 489.
8 G. H. Posner, *Org. React.*, 1972, **19**, 1.
9 Performed by Dr. J. E. Davies, University Chemical Laboratory, and Dr. C. H. McKie, Department of Earth Sciences, University of Cambridge. Full details will be published elsewhere.
10 H. O. House, ' Modern Synthetic Reactions,' W. A. Benjamin, Inc., Menlo Park, California, 1972, p. 60.
11 I. M. Cunningham and K. H. Overton, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2458.
12 H. C. Brown, K. J. Murray, L. J. Murray, J. A. Snover, and G. Sweifel, *J. Am. Chem. Soc.*, 1960, **82**, 4233.
13 N. N. Greenwood, J. H. Morris, and J. C. Wright, *J. Chem. Soc.*, 1964, 4753.
14 S. A. Godleski, University of Rochester, personal communication. We are grateful to Professor Godleski for sending spectra of his intermediates for comparison.

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