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NEW ROUTES TO PERHYDROHISTRIONICOTOXIN

DAVID TANNER* and PETER SOMFAI

Department of Organic Chemistry

Chalmers University of Technology

S-412 96 Göteborg, Sweden

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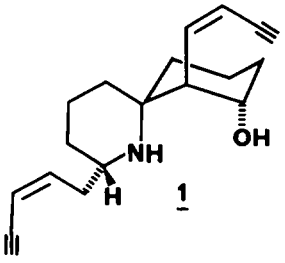
Abstract - Two stereocontrolled routes to the alkaloid depentylperhydrohistrionicotoxin, 3, are described. The key steps are alkylation, with retention of configuration, of the iodide 8 and the mesylate 12, respectively. A tricyclic aziridinium species is proposed as the reactive intermediate in the latter reaction. The synthesis of 3 represents a formal total synthesis of the title alkaloid.

Histrionicotoxin, 1, is an alkaloid of unusual structure isolated[1,2] from the Colombian "poison arrow" frog species Dendrobates histrionicus. The remarkable neurophysiological properties of 1 and congeners such as 2 and 3 have caused demand for research samples to outweigh the supply from animal sources, and the low natural abundance coupled with the intriguing molecular architecture makes the synthesis of such alkaloids a worthy challenge for the organic chemist. Very recently Kishi[3a] crowned a decade of effort with the total synthesis of racemic histrionicotoxin itself, but the major thrust has traditionally been towards the perhydro-derivative 2 since this species displays pharmacological activity very similar to that of its parent. Depentylperhydrohistrionicotoxin, 3, of interest in its own right, was the key intermediate in Corey's original synthesis[4] of 2 and a multitude of syntheses or attempted syntheses of 2 and 3 have appeared[3b,5] since 1975.



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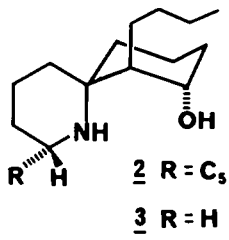
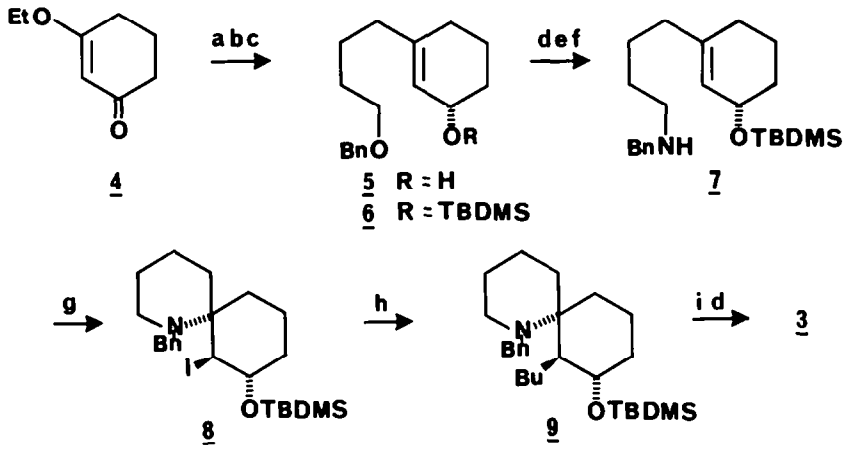


2 R = C_5H_{11}

3 R = H

We recently reported[6] two simple, efficient and stereocontrolled routes to the cis-azaspiro-[5.5]-undecan-8-ol skeleton of the histrionicotoxins, and the present paper describes the elaboration of two of our key intermediates to 3, this work

thus constituting a formal total synthesis of 2. (See Schemes 1 and 2).



Bn = $CH_2\phi$, TBDMS = Si*t*-BuMe_2

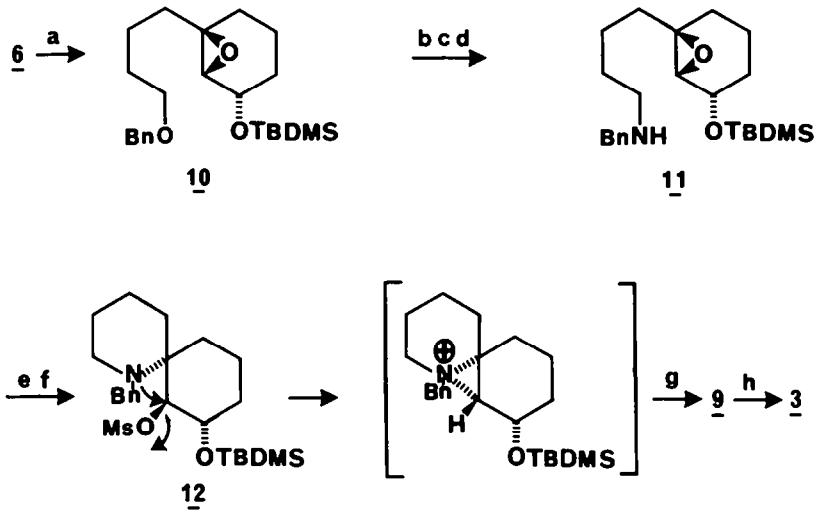
Scheme 1

(a) BnO$(CH_2)_4$MgBr,THF,then H^+/H_2O, 85% yield (b) DIBAL,toluene 97% (c) TBDMSCl,imidazole,DMF, 98% (d) H_2,$Pd(OH)_2$/C,EtOH, 100% (e) p-TsCl,pyridine, 93% (f) $BnNH_2$,cat. NaI,DMSO, 85% (g) I_2, CH_2Cl_2, 90% (h) ^{t}BuLi,Et_2O/pentane,then BuOTs/HMPA, 30-40% (i)F^-, THF, 86% (d) 90%.

The readily available[7] vinylogous ester 4 was the starting point for both routes. After a Grignard reaction and acidic work-up, the appropriate 3-substituted enone was reduced with DIBAL and the resulting allylic alcohol protected as the ^{t}butyldimethylsilyl (TBDMS) ether, 6. This protecting group was chosen as it is chemically rather robust and its steric bulk was to play a major rôle in the subsequent transformations. Compound 6 was transformed efficiently to the 2^o amine 7 by routine operations. From inspection of models, we reasoned that the iodocyclisation[8] of 7 should yield 8 predominantly or even exclusively, the intermediate iodonium species being formed with the iodine trans to the bulky silyloxy group and subsequent formation of the six-membered heterocycle being favoured entropically. Our expectation was fulfilled by the isolation of crystalline 8 as a single diastereomer in 90% yield from the reaction of 7 with excess iodine in CH_2Cl_2. In the high-field ^{1}H NMR spectrum of 8 a well-separated benzylic AB-type pattern[5g] (J 13.5Hz) at δ2.83 and 3.89 strongly implied that the desired ring-closure had indeed occurred, and the appearance of a one-proton doublet (J 10Hz) at 4.27 (-CHI) compelled the stereochemical assignment of the expected trans-diequatorial relationship between the iodo and silyloxy substituents. The total yield of 8 from 4 was thus 57% for seven steps, and having secured a rapid and efficient assembly of the spirocyclic framework our next major task was the introduction of the butyl side-chain. Not unexpectedly[5c], this proved troublesome, but after considerable experimentation with a variety of organometallic reagents we found that 8 could be lithiated at low temperature by ^{t}BuLi and the resultant organolithium species alkylated with butyl tosylate. Gratifyingly, this sequence delivered 9 as a single diastereomer, the stereochemical assignment resting on the clean triplet of doublets (-CHOSi, J 9 and 4Hz, δ4.23) observed in the ^{1}H NMR spectrum. The major drawback to this procedure was, of course, the propensity of α-alkoxyorganometallics towards Boord-type elimination and the appropriate olefin was always encountered in the product mixture. However, the desired 9 could be obtained in 30-40% yield and two deprotection steps

(fluoride-ion desilylation and hydrogenolytic debenzylation) completed the synthesis of 3, the synthetic material being chromatographically and spectroscopically identical to an authentic sample kindly provided by Dr. Arnold Brossi of the NIH. The ^{1}H NMR spectrum of the final product indicated the expected trans,trans-diaxial dispositions of the hydroxyl, butyl, and amino groups. The total yield of 3 from 4 was thus, at best, 17% for the ten steps.

An alternative procedure for the introduction of the butyl side-chain is shown in Scheme 2.



Scheme 2

(a) mCPBA,CH_2Cl_2, 87%, trans:cis 9:1 (b) H_2,$Pd(OH)_2$/C,EtOH, 100% (c) p-TsCl,pyridine, 95% (d) $BnNH_2$,cat.NaI, DMSO, 82% (e) toluene, reflux,10 days, 100% (f) MeLi then MsCl,Et_2O,ca.100% product not usually isolated (g) $LiBu_2Cu$, Et_2O, ca. 35% (h) see Scheme 1.

The TBDMS group in 6 directed[9] a trans epoxidation (mCPBA) to give the desired 10 in 78% yield after flash chromatographic removal of minor amounts of the cis-isomer. Transformation of the benzyloxy group of 10 to the corresponding benzylamino moiety proceeded as previously with no ill effects on the epoxide ring. A dilute toluene solution[10] of the ω-amino-epoxide 11 was then refluxed for several days to yield a single amino-alcohol (stereochemistry corresponding to that of 12) in essentially quantitative yield. Again, the relative stereochemistry could be assigned unequivocally on the basis of the ^{1}H NMR spectrum (-CHOH doublet, J 9Hz at δ3.55).

In our original work[6] on the "naked" histrionicotoxin ring-system we removed the extraneous hydroxyl group by hydride displacement of the extremely labile mesylate 12. Further experimentation with other nucleophiles such as I^- and CN^- showed that the mesylate reacted predominantly (cyanide) or exclusively (iodide) with net retention of configuration, the reaction with a slight excess of NaI in warm acetone or methylethyl ketone giving iodide 8 as the sole product. In contrast, iodide 8 itself reacts with cyanide in DMF with clean inversion. These observations suggested the intermediacy of an aziridinium species in the reactions of 12 (see Scheme 2) and we thus considered the possibility of alkylation of the mesylate with a "butyl anion" species such as an organocuprate. At this point we received a

welcome sign of encouragement in the form of a paper by Thottathil and Moniot in which was described[11] the reaction, with net retention of configuration, between a tosyloxy derivative of L-proline and $LiPh_2Cu$, an aziridinium species being one of two very plausible intermediates. Accordingly, we exposed our freshly prepared mesylate to excess $LiBu_2Cu$ in diethyl ether and found to our delight that the "retentive" alkylation did indeed occur, albeit in rather modest yield (ca. 35%). The product was spectroscopically indistinguishable from 9 synthesised earlier and the necessary molecular cosmetics subsequently furnished the target 3. The low yield for the alkylation step is no doubt due to a combination of thermal decomposition of the cuprate under the required reaction conditions and the lability of the mesylate (which could be handled only with difficulty, was not amenable to storage, and was usually carried on without isolation). However, the total yield of 9 from 4 via the cuprate route was still a respectable 22% for ten steps if one assumes quantitative formation of the mesylate 12 from the corresponding alcohol.

In conclusion, two novel and stereocontrolled routes to 3 (and thereby to perhydrohistrionicotoxin, 2) have been developed, employing somewhat unusual chemistry for the introduction of the butyl appendage. Further work on the alkaloids described herein is currently in progress and the results will be reported elsewhere.

EXPERIMENTAL

^1H NMR spectra were obtained at 270 MHz (Bruker WH-270) using $CDCl_3$ as solvent and TMS ($\delta = 0$) as internal standard. The following abbreviations are used: s,singlet, d,doublet,t,triplet,qt,quartet,qn,quintet,b,broad, J,coupling constant in Hz. IR spectra were run on neat samples using a Perkin-Elmer 197 spectrophotometer,and only the strongest/structurally most important peaks (ν_{max}, cm^{-1}) are listed. Routine mass spectra were run on a Finnigan 1020 GC/MS. Melting points were determined using an Olympus BH - Mettler FP52 apparatus. Flash chromatography was carried out using Merck silica gel 60 (230-400 mesh). Diethyl ether, tetrahydrofuran (THF) and toluene were dried and distilled under nitrogen from sodium-benzophenone ketyl; dimethyl sulphoxide (DMSO) dimethyl formamide (DMF) hexamethyl phosphoric triamide (HMPA) methylene chloride, pyridine and benzylamine were distilled under nitrogen from calcium hydride. Copper iodide was purified by the method of House et al.(ref. 12). Commercially available solutions of alkyllithiums and diisobutylaluminium hydride,DIBAL (Aldrich) were used as received. Unless stated otherwise, reactions were run using septum-capped, flame- or oven-dried flasks under balloon pressure of argon, liquid reagents and reactant solutions being transferred via syringes which had been oven-dried (140°C) and allowed to cool in a desiccator over P_2O_5.

Allylic alcohol 5: Flame-dried Mg turnings (273 mg,11.25mg-atom) were stirred at RT in THF(5 ml). A solution of 1-benzyloxy-4-bromobutane (1.82g,7.5mmol) in THF (5 ml) was added dropwise,and one drop of 1,2-dibromoethane was added to initiate the reaction. The resultant solution was refluxed gently for 10 min then cooled to 0°C. A solution of vinylogous ester 4 (0.70g,5mmol) in THF (2 ml) was then added and the reaction mixture refluxed for 30 min,then cooled and poured onto ice (3g) and 10% HCl (5 ml). The yellow mixture was stirred vigorously at RT for 2 h. The organic layer was separated and washed with water, $NaHCO_3$aq. and brine and then dried over Na_2SO_4. The solvent was removed and the residue flash-chromatographed (60% ether-pentane) to yield 3-(4-benzyloxybutyl)cyclohex-2-ene as a pale yellow oil which crystallised in the refrigerator. M.p. 25-27°C. Yield:1.096g, 85%. ^1H NMR: δ 7.30(5H,m,aromatic) 5.87(1H,narrow m,vinylic) 4.48(2H,s,benzylic) 3.48 (2H,t,J=6,$-CH_2O-$) 2.36(2H,t,J=7) 2.27(4H,m) 1.98(2H,qn,J=7) and 1.63(4H,complex m). IR: 1670. MS: m/z 258(M^+).

The enone (1.02g,3.95mmol) was dissolved in toluene (10 ml) and stirred at 0°C during the dropwise addition of DIBAL (5.93ml of 1M hexane solution, 5.93mmol). After addition was complete the mixture was stirred at 0°C for 2 h and the reaction quenched by addition of methanol (1 ml). The resultant solution was diluted with ether (ca. 100 ml) and the precipitated aluminates filtered onto Celite. The filter cake was washed thoroughly with warm ether and the combined filtrate and washings stripped down to yield an oil which was flash-chromatographed (60% ether-pentane). There was obtained 0.996g (97%) of allylic alcohol 5 as a clear,colourless oil. ^1H NMR: 7.35(5H,m,aromatic) 5.48(1H,m,vinylic) 4.50(2H,s,benzylic) 4.17(1H,bm, $-CHOH$) 3.47(2H,t,J=6,$-CH_2O-$) 2.0-1.4(13H,complex m,methylenes and $-OH$). IR: 3350(b)

MS: m/z 260 (M^+).

Silyl ether 6: Allylic alcohol 5 (1.86g,7.15mmol) was dissolved with stirring in DMF (10 ml). t-Butyldimethylsilyl chloride (1.296g,8.6mmol) and imidazole (1.22g, 17.9mmol) were added and the resultant mixture stirred at RT overnight. The reaction mixture was then diluted with ether (25 ml) and the resultant solution washed thoroughly with water. The organic layer was separated,dried over Na_2SO_4 and stripped down to yield the pure TBDMS ether as a colourless oil (2.62g, 98%). ^{1}H NMR: 7.41(5H,m,aromatic) 5.39(1H,m,vinylic) 4.52(2H,s,benzylic) 4.24(1H,unresolved m, -CHOSi) 3.47(2H,t,J=6, $-CH_2O-$) 2.10-1.48 (12H,complex m) 0.92(9H,s, ^{t}Bu) 0.07(6H,2s,Me_2Si). IR: 1100 (-O-Si). MS: M^+ not observed, m/z 317 (M-^{t}Bu).

Amine 7: Silyl ether 6 (1.87g,5mmol) was dissolved in abs. ethanol (10 ml). Pearlman's catalyst ($Pd(OH)_2/C$, 0.20g) was added and the resultant mixture stirred while the reaction vessel was evacuated (aspirator) and then flushed with argon via a three-way stopcock. The vessel was then alternately evacuated and flushed with H_2 several times. Finally, balloon pressure of H_2 was applied and the mixture stirred at RT until completion by TLC (ca. 2 h). The reaction vessel was then evacuated and flushed with argon, the mixture filtered through a Celite pad, and the filter-cake washed thrice with fresh ethanol. The combined filtrate and washings were stripped down to yield the primary alcohol as a clear colourless oil which could be used without further purification after azeotropic drying with several portions of benzene. Yield: 1.42g, 100%. ^{1}H NMR: 5.29(1H,narrow m, vinyl) 4.16(1H,m, -CHOSi) 3.57(2H,t,J=6, $-CH_2O-$) 1.94-1.36(12H,complex m) 0.81(9H,s, ^{t}Bu) 0.00(6H,s,Me_2Si). IR: 3400 (b) 1100(^{2}O-Si). MS: m/z 284(M+).

The primary alcohol (1.42g,5mmol) was dissolved with stirring in pyridine (5 ml) and cooled to -20°C. p-Toluenesulphonyl chloride (0.953g,5mmol) was added quickly in one portion and the resultant solution allowed to reach 0°C,and then stirred at that temperature overnight (reaction complete according to TLC). The reaction mixture was then diluted with ether (30 ml) and the resultant solution washed with several portions of $CuSO_4$.aq and finally with water. The organic phase was separated, dried over Na_2SO_4 and the solvent removed to yield the tosylate as an oil which resisted crystallisation. This material,homogeneous by TLC and NMR-spectroscopically pure, was used immediately in the next step. ^{1}H NMR: 7.79 (2H, "d",J=9,aromatic) 7.35(2H, "d",J=9,aromatic) 5.31(1H, narrow m, vinylic) 4.21(1H, m, -CHOSi) 4.03(2H,t,J=6, $-CH_2O-$) 2.44(3H,s,tosyl methyl) 1.92-1.38(12H,complex m) 0.89(9H,s, ^{t}Bu) 0.07(6H,s,Me_2Si). Yield: 2.04g, 93%.

The tosylate (2.19g,5mmol) was dissolved with stirring in DMSO (15 ml). Sodium iodide (50mg) was then added, followed by slow dropwise addition of benzylamine (1.37ml,12.5mmol). The resultant solution was stirred at RT for 24 h, poured into brine and the mixture extracted thrice with ether (30-ml portions). The combined extracts were dried over Na_2SO_4 and the solvents removed to yield a dark yellow oil which was purified by flash chromatography (ether or ethyl acetate-pentane). There was obtained 1.59g (85%) of the benzylamino compound 7 as a slightly yellow oil which darkened on standing. ^{1}H NMR: 7.26(5H,m,aromatic) 5.24(1H, narrow m, vinylic) 4.12(1H,unresolved m, -CHOSi) 3.70(2H,s,benzylic) 2.53(2H,btr,J=8, $-CH_2N$) 1.88-1.23(13H,complex m, methylenes and -NH) 0.81(9H,s, ^{t}Bu) 0.00(6H,s,Me_2Si). IR: 3350(w, -N-H) 1100(-OSi). MS: m/z 373(M^+).

Iodide 8: Amine 7 (1.12g,3mmol) was dissolved with stirring in CH_2Cl_2 (30 ml) and iodine (1.14g, 4.5mg-atom) was added in small portions. The resultant dark mixture was stirred for 9 h at RT and then washed quickly with two portions of dilute NaOH solution, to yield a near-colourless organic phase which was then washed with water and dried over Na_2SO_4. Removal of solvent yielded a viscous pale yellow oil which slowly crystallised in the refrigerator. There was obtained 1.35g (90%) of the iodide 8 as off-white crystals, m.p. 105-106°C(dec.). ^{1}H NMR: 7.47-7.07(5H,m,aromatic) 4.27(1H,d,J_{axax}=10, -CHI) 3.89(1H,d,J=13.5,benzylic) 3.82 (1H,trd, J=10 and 4, -CHOSi) 2.83(1H,d, J=13.5,benzylic) 2.46(1H,b"d",J=12.5,-CHN) 2.18-1.17(13H,complex m, -CHN and methylenes) 0.75(9H,s, ^{t}Bu) 0.25(3H,s,MeSi) and 0.00(3H,s,MeSi). MS: M^+ not observed, m/z 372(M-I). HRMS: Found: 499.176, calc. for $C_{23}H_{38}NIOSi$ 499.177.

N-benzyldepentylperhydrohistrionicotoxin: Iodide 8 (0.150g,0.30mmol) was dissolved in ether-pentane (1:1, 5 ml) and cooled with stirring under argon to -100°C. ^{t}BuLi (0.32 ml of 1.9M/pentane, 0.6mmol) was then added dropwise and the resultant mixture stirred at ca. -100°C for 30 min. A solution of butyl tosylate (0.073g, 0.31mmol) in dry HMPA (1 ml) was then added and the resultant mixture allowed to reach RT overnight. The mixture was then diluted with "wet" ether and the organics washed thrice with water. Removal of solvents yielded an oily residue consisting of compound 9 contaminated with an undesired olefinic product (the result of Boord-type elimination of LiOTBDMS). The total yield was 0.085g and integration of the NMR spectrum of the mixture showed that the yield of 9 was ca. 35%. Without further purification, this mixture was dissolved in THF (1.5 ml) and stirred at RT under argon during the addition of Bu_4NF (0.3 ml of 1M/THF). The mixture was stirred at RT overnight, diluted with ether (10 ml) and the organics washed with water. The ethereal phase was dried over Na_2SO_4 and the solvent removed to yield an oil which was purified by preparative TLC (ether). There was obtained 0.0284g (86% based on 9, 30.1% based on 8) of N-benzyldepentylperhydro-

histrionicotoxin as an oil. ^{1}H NMR: 7.8(1H, b, -OH) 7.5-7.2(5H,m,aromatic) 4.10 (1H, d,J=12.5, benzylic) 4.00(1H,unresolved m, -CHOH) 3.65(1H,d,J=12.5,benzylic) 3.15-1.10(21H,complex m,methylenes and -CHBu) 0.91(3H,distorted t,J=7,methyl). IR: 3550(b) MS: m/z 315 (M^+). The spectral data are in excellent agreement with those previously reported (refs. 5e,f,g).

Compound 9: NMR: 7.4-7.2(5H,m,aromatic) 4.23(1H,trd,J=9 and 4,-CHOSi) 4.09(1H,d, J=14,benzylic) 3.90(1H,d,J=14,benzylic) 3.10(1H,b, -CHN) 2.20-1.25(20H,complex m, -CHN, -CHBu and methylenes) 0.95(9H,s, ^{t}Bu, overlapping 3H,distorted t,J=7,Me) 0.13 (3H,s,MeSi) and 0.07(3H,s,MeSi).

Depentylperhydrohistrionicotoxin 3: N-benzyldepentylperhydrohistrionicotoxin (15mg,0.047mmol) was dissolved in absolute ethanol and $Pd(OH)_2$/C catalyst (ca.2mg) was added. Using the previously described procedure, there was obtained depentylperhydrohistrionicotoxin,3,as an oil (9.6mg, 90%). ^{1}H NMR: 3.90(1H,narrow,unresolved m, -CHOH) 2.95(1H,m, -CHN) 2.83(1H,m, -CHN) 2.0-1.0(21H,complex m, -OH, -NH, -CHBu and methylenes) 0.90(3H, tr,J=7,Me). MS: m/z 225 (M+). This material was identical with an authentic sample provided by Dr. Arnold Brossi of the NIH, and our spectral data closely match those reported in refs.5e,f,g.

Epoxide 10: The protected allylic alcohol 6 (2.24g,6mmol) was dissolved in CH_2Cl_2 (50 ml) and the solution cooled with stirring to -10°C (ice/acetone). mCPBA (1.35g, 7.8mmol) was added in small portions over 15 min. The resultant mixture was stirred rapidly at 0°C for 2-3 h and then allowed to reach RT. The precipitated m-chlorobenzoic acid was removed by filtration and the filtrate washed with dilute $NaHCO_3$ solution and water. The organics were dried over Na_2SO_4 and the solvent was removed to give a semi-solid residue which was purified by careful flash chromatography (12% ether/pentane). The desired trans-isomer 10 was eluted first (1.83g,78.3%) followed by the cis-epoxide (8.7%, i.e. trans:cis = 9:1). ^{1}H NMR: 7.36(5H,m,aromatic) 4.52(2H,s,benzylic) 3.96(1H,dd,J=6 and 7, -CHOSi) 3.48 (2H,tr,J=7, $-CH_2O-$) 2.83(1H, sharp s, epoxy) 1.90-1.14(12H,complex m) 0.91(9H,s, ^{t}Bu) 0.10(3H,s, MeSi) 0.08(3H,s,MeSi). IR: 1250(epoxy) 1100(-O-Si) 830(epoxy). MS: M$^+$ not observed, m/z 333 (M-^{t}Bu).

Amino-epoxide 11: Debenzylation of 10 was carried out by hydrogenolysis over the Pearlman catalyst exactly as described above for the corresponding operation involving the intermediates in Scheme 1. From 1.95g (5mmol) of 10 was obtained 1.50g (100%) of the corresponding primary alcohol as an oil. ^{1}H NMR: 3.99(1H,dd, J=5.5 and 7, -CHOSi) 3.68(2H,tr,J=6, $-CH_2O-$) 2.80(1H,sharp s, epoxy) 1.91-1.09 (12H,complex m) 0.90(9H,s,tBu) 0.10(3H,s,MeSi) 0.08(3H,s,MeSi). IR: 3400(b) 1250 1090, 835. MS: m/z 243 (M-tBu).

The primary alcohol was tosylated by the method described above to yield the tosylate as an oil (2.16g, 95%). ^{1}H NMR: 7.72(2H,"d",J=9,aromatic) 7.28(2H,"d", J=9,aromatic) 3.98(2H,tr,J=7, $-CH_2O-$) 3.89(1H,dd,J=6 and 7, -CHOSi) 2.73(1H,sharp s, epoxy) 2.43(3H,s,tosyl Me) 1.84-1.08(12H,complex m) 0.92(9H,s,tBu) 0.12(3H,s, MeSi) 0.10(3H,s,MeSi). IR: 1360(tosyloxy) 1250 1175(tosyloxy) 1090, 840.

The tosylate (2.043g,4.5mmol) was converted to amino-epoxide 11 in 82% yield (1.435g) by the procedure described for compound 7. Spectral data for 11: ^{1}H NMR: 7.26(5H,m,aromatic) 3.91(1H,"t",J=6, -CHOSi) 3.76(2H,s,benzylic) 2.79(1H, sharp s, epoxy) 2.63(2H,t,J=7, $-CH_2N$) 1.89-1.09(12H,complex m) 0.90(9H,s,tBu) 0.11 (3H,s,MeSi) 0.09(3H,s,MeSi). IR: 3300(w, -NH) 1250(epoxy) 1090(-O-Si) 835(epoxy) MS: m/z 389(M+).

Mesylate 12: The ω-amino-epoxide 11 (1.37g, 3.52mmol) was dissolved in toluene (750 ml) and the resultant solution refluxed under argon for ten days. The reaction was monitored by NMR spectroscopy and upon completion the solvent was removed to yield the desired spirocyclic amino-alcohol as a pale yellow oil. This material was homogeneous by TLC and was NMR-spectroscopically pure, and could be used without further purification. If desired, the alcohol can easily be flash chromatographed using 5% MeOH in CH_2Cl_2.

^{1}H NMR: 7.24(5H,m,aromatic) 4.18(1H,d,J=13,benzylic) 3.73(1H,td,J=9 and 5,-CHOSi) 3.55(1H,d,J=9, -CHOH) 2.98(1H,d,J=13,benzylic) 2.63(1H, b"d", J=12, -CHN) 2.29(1H, td, J=12 and 3.5, -CHN) 1.99-1.11(12H, complex m) 0.92(9H, s, tBuSi) 0.13(3H,s, MeSi) and 0.11(3H, s, MeSi). IR: 3450(b, -OH) 1100(-O-Si).
MS: m/z 389 (M+).
Accurate mass: Found 389.275, Calc. for $C_{23}H_{39}NO_2Si$ 389.275

The amino-alcohol (0.195g, 0.5mmol) was dissolved with stirring under argon in dry diethyl ether (2 ml) and cooled to 0°C. MeLi (0.34mL of 1.6M/diethyl ether, 0.55mmol) was then added via syringe and the resultant solution stirred for 30 min at 0°C before addition of a solution of methanesulphonyl chloride (0.060g, 0.52 mmol) in diethyl ether (0.5 ml). A precipitate formed and the mixture was stirred for a further 15 min at 0 to +10°C. The reaction was quenched by addition of ether (5 ml) and ice-water (1 ml). The organics were washed quickly with ice-water and then dried over Na_2SO_4. Removal of the solvent at 0°C yielded the mesylate as a highly sensitive colourless oil which rapidly decomposed. By working quickly, the mesylate could be isolated pure in 95-100% yield. This material was characterised by high-field ^{1}H NMR spectroscopy alone:

7.39-7.09 (5H,m,aromatic) 4.86 (1H, d, J_{axax}=9, -CHOMs) 4.22 (1H,d,J=12.5, benzylic) 3.80 (1H, m, -CHOSi) 3.19 (3H,s, mesyl Me) 3.13 (1H, d, J=12.5,

benzylic) 2.78 (1H, b"d", J=12, -CHN) 2.24-1.13(13H, complex m, -CHN and methylenes) 0.91 (9H, s, tBuSi) and 0.09 (6H, s, Me_2Si).

It proved more convenient not to isolate the mesylate but generate it in situ and use it as a diethyl ether solution. The procedure described above was followed but the reaction was not quenched and the ethereal solution could easily be withdrawn via syringe. This technique was used in the following two reactions.

Reaction of the mesylate with NaI: A solution of the mesylate was prepared as described from 0.5mmol alcohol. The mesylate solution was then syringed into a refluxing solution of NaI (0.65 mmol) in acetone (5 ml). After 1 h of reflux the reaction mixture was cooled and the solvents removed. The solid residue was triturated with ether and the solids filtered off. The filtrate was concentrated to yield a yellow oil which was purified by preparative TLC. There was obtained ca. 60% yield of the iodide 8, identical in all respects with the material synthesised earlier. (E.g. ^1H NMR: -CHI doublet, J=10Hz at δ 4.27).

Reaction of the mesylate with $LiBu_2Cu$: Purified copper iodide (0.476g, 2.5mmol) was slurried under argon in dry diethyl ether (10 ml) and cooled with stirring to -78°C. BuLi (3.23 ml of 1.55M/hexanes, 5mmol) was added dropwise, the resultant clear, near-colourless solution was stirred at -78°C for 30 min, and then allowed to reach -20°C. Meanwhile a diethyl ether solution of the mesylate was prepared as described above from the alcohol (0.195g, 0.5mmol). The mesylate solution was transferred rapidly to the cuprate and the resultant mixture allowed to reach RT overnight. The reaction was quenched by addition of NH_4Cl.aq (1 ml) and the heterogeneous mixture transferred to a separating funnel containing more NH_4Cl solution and ether. Air was then bubbled gently through the mixture until the solids had been digested and the aqueous layer had turned deep blue. The pale yellow ethereal layer was separated, washed once with water and once with brine, and dried over Na_2SO_4. Removal of solvent gave a yellow oily residue which was purified by preparative TLC (ether/pentane). There was obtained 0.071g (33% yield based on mesylate 12) of O-t-butyldimethylsilyl-N-benzyldepentylperhydrohistrionicotoxin, 9, which was identified by its PMR spectrum (vide supra).

Further confirmation of the structure was provided by desilylation (Bu_4NF, THF) and debenzylation (H_2, Pearlman catalyst, EtOH) as previously to yield depentylperhydrohistrionicotoxin, 3.

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