Pergamon

Tetrahedron 54 (1998) 7907–7918

TETRAHEDRON

A Convergent Enantioselective Total Synthesis of (-)-Perhydrohistrionicotoxin with an Intramolecular Imino Ene-type Reaction as a Key Step

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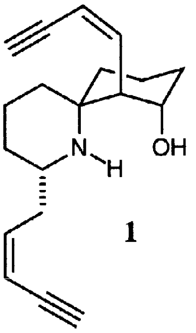
Received 3 April 1998; accepted 30 April 1998

Abstract

A convergent enantioselective total synthesis of the neurotoxic spirocyclic alkaloid (-)-perhydrohistrionicotoxin (**2**) is described. A Lewis acid-mediated intramolecular imine ene-type reaction was used for the key spirocyclisation step (**14** to **3**, with **3** being obtained as a single diastereoisomer). Spirocyclisation precursor **14** was prepared from enantiomerically pure ketone **13**, itself available *via* an efficient one-pot, three-component, coupling reaction involving chiral electrophiles **9** and **10**. The stereogenic centres of **9** and **10** derive in turn from Sharpless kinetic resolution, which allowed access to both chiral electrophiles from a common racemic precursor, **8**. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Alkaloids; Spiro compounds; Asymmetric synthesis; Imines

The spirocyclic alkaloid (-)-histrionicotoxin (**1**) was isolated [1] in 1971 from skin extracts of the "poison dart" frog *Dendrobates Histrionicus* found in Colombia. This unusual spirocycle exhibits important neurotoxic properties which are retained [2f] in the non-natural derivative perhydrohistrionicotoxin (**2**).



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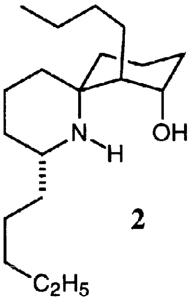

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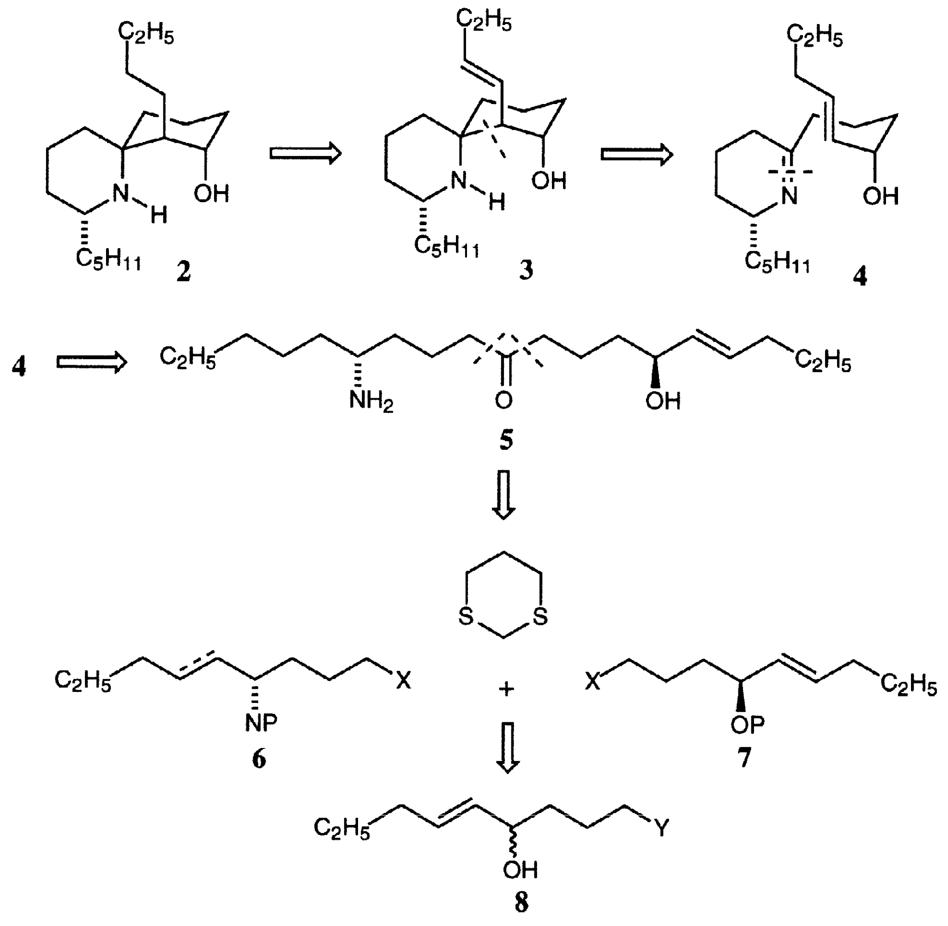
Both these structures have been popular targets for synthesis [2], with the first total synthesis of (±)-histrionicotoxin being accomplished [3] in 1985, and the first enantioselective route to the naturally occurring form of the alkaloid being reported [4] as recently as 1990. The total synthesis of the racemic form of the perhydro derivative, a

PII: S0040-4020(98)00425-6

simpler synthetic target, was first reported [5] by two groups in 1975, and since then much synthetic effort [6] has been devoted to total or formal total syntheses of **2**, with the first route not involving resolution of intermediates being recorded [7] in 1989. Herein, we report an efficient, convergent, and enantioselective total synthesis of (-)-perhydrohistrionicotoxin which relies on an intramolecular, Lewis acid-mediated, imino ene-type reaction [8] as the key spirocyclisation step. Our retrosynthetic analysis is shown in Scheme 1.

Retrosynthetic introduction of unsaturation to the C_4H_9 side-chain of the target defines **3** which can be disconnected at one of the bonds to the spiro centre, thus generating the key unsaturated imine intermediate **4**. This material was envisioned to deliver **3** *via* an intramolecular imino ene-type reaction [8c] mediated by some Lewis acid, proceeding *via* the proposed transition state assembly [8c] shown in Fig. 1.



Scheme 1. Retrosynthetic analysis for convergent enantioselective total synthesis of (-)-perhydrohistrionicotoxin (**2**). (NP = protected or potential primary amine; OP = protected alcohol; X = leaving group; Y = potential leaving group.)

In the structure shown in Fig. 1, the imine ring is in a half-chair conformation, with an equatorial pentyl group; coordination of the imine nitrogen and the oxygen of the protected alcohol to the metal centre would then allow a chair-like transition state for spirocyclisation, carbon-carbon bond formation taking place on the diastereoface of the imine opposite to the pentyl group.

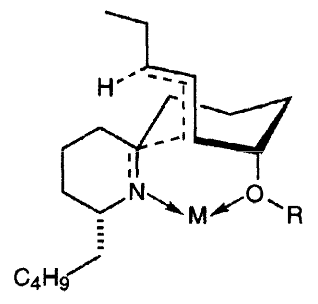
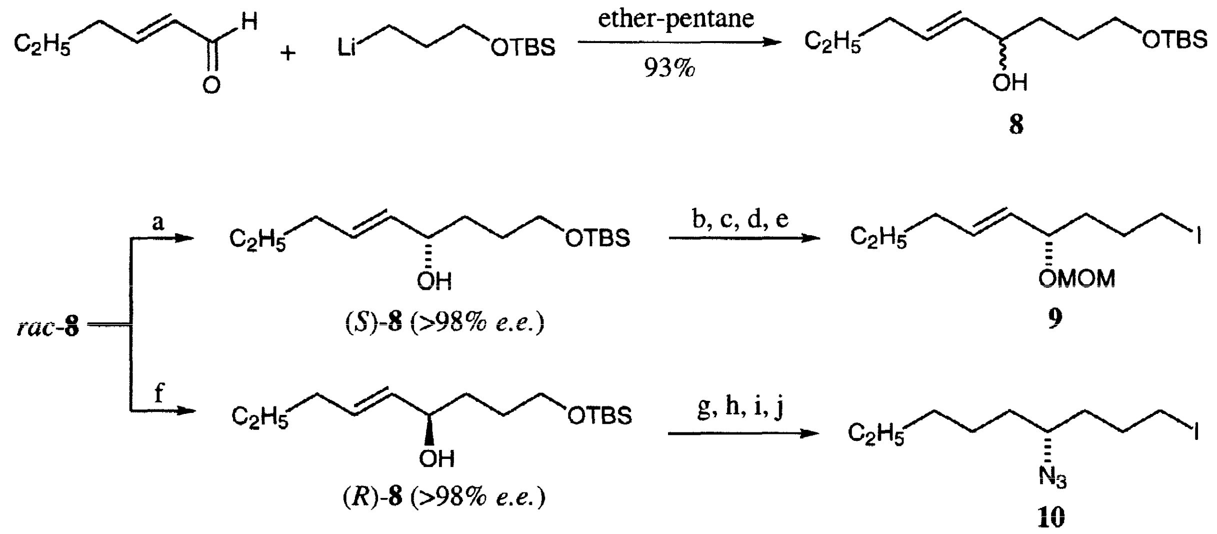


Fig. 1. Proposed transition state for diastereoselective spirocyclisation (M = Lewis acid).

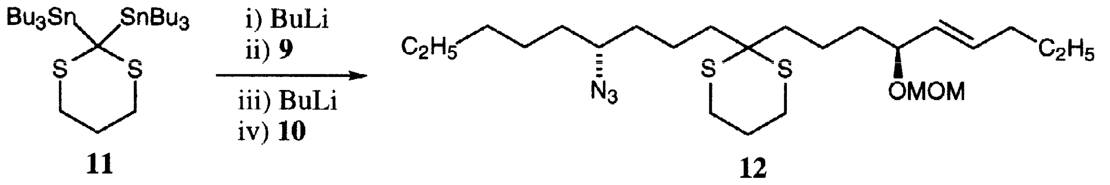
Continuing the retrosynthetic analysis of Scheme 1, disconnection at the imine site in **4** reveals ketonic precursor **5**. The synthetic equivalence of 1,3-dithiane to the keto group then allows the double disconnection shown in structure **5** and defines a convergent route involving two very similar chiral building blocks **6** and **7**, both of which should be available in high enantiomeric purity *via* Sharpless kinetic resolution [9] of their common precursor, racemic allylic alcohol **8**. Scheme 2 shows the preparation of **8** (Y = OTBS) from simple starting materials, and its subsequent conversion to chiral key intermediates **9** and **10**.



Scheme 2. (a) Ti(O^{i}Pr)$_4$, (-)-DIPT, TBHP, 3Å MS, CH_2Cl_2, -20°C, 40%. (b) MOMCl, (^{i}Pr)$_2$NEt, CH_2Cl_2, 98%. (c) TBAF, cat. HOAc, THF, 99%. (d) TsCl, DMAP, NEt_3, CH_2Cl_2, 98%. (e) NaI, acetone, 98%. (f) as for (a) but with (+)-DIPT, 40%. (g) H_2, PtO_2, hexane 100%. (h) HN_3, P(Ph)$_3$, DEAD, THF, then TBAF, cat. HOAc, 98%. (i) as for (d) 93%. (j) as for (e), 99%.

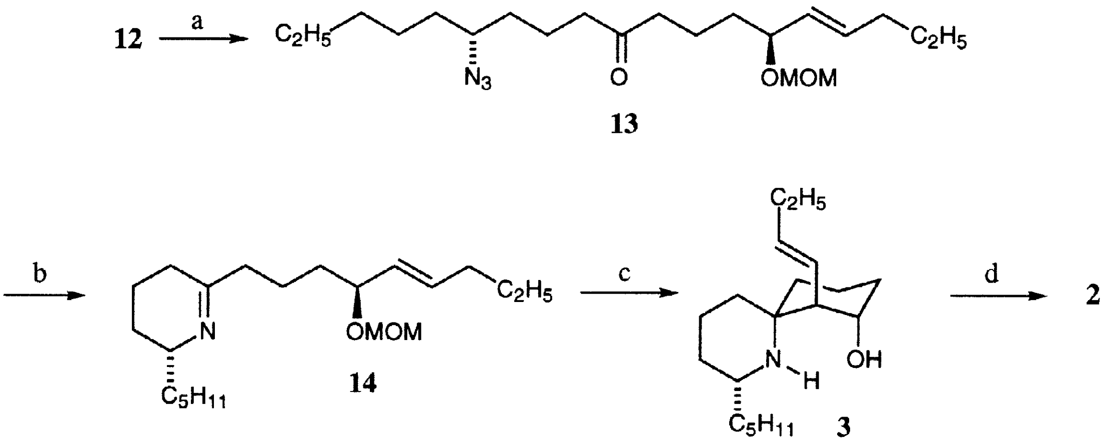
The organolithium reagent shown in Scheme 2 (see Experimental) was reacted with *trans*-2-hexenal to give **8** in near-quantitative yield and this racemic allylic alcohol was subjected to two Sharpless kinetic resolutions involving (-)- and (+)-DIPT, respectively. Chiral alcohol (*S*)-**8** was obtained in 40% yield and > 98% *e.e* [9c]. This material was taken on to iodide **9** *via* a standard sequence involving protection of the secondary alcohol as the methoxymethyl (MOM) ether, removal of the silyl protective group by fluoride, tosylation, and Finkelstein reaction. The overall yield of **9** from (*S*)-**8** was 94% (four steps).

The (*R*)-enantiomer of allylic alcohol **8** was also available in >98% *e.e* [9c]. This was converted to chiral electrophile **10** by catalytic hydrogenation to reduce the double bond, Mitsunobu reaction [10] to introduce the azide group with inversion of configuration, *in situ* removal of the silyl protective group, and transformation of the primary alcohol to the iodide in the same way as for **9**. The overall yield of **10** from (*R*)-**8** was 90% (four operations, five steps). With the two chiral electrophiles in hand, the synthesis proceeded *via* the one-pot, three-component, coupling shown in Scheme 3.



Scheme 3. Conditions: lithiation in THF (5 min at -78°C) then add **9**, stir for10 min. at -78°C, lithiation as before, then add **10** and warm to RT, 81%.

Thus, the bis(tributylstannyl) derivative [11] of 1,3-dithiane (**11**) was treated sequentially with butyllithium, electrophile **9**, butyllithium, and finally electrophile **10** to give the "open-chain" skeleton of the target (**12**) in a very satisfactory 81% isolated yield. Completion of the total synthesis involved intermediates **13** and **14** shown in Scheme 4.



Scheme 4. (a) NCS, $AgNO_3$, H_2O-CH_3CN, 86%. (b) $P(Ph)_3$, benzene, 60°C, 97%. (c) $TiCl_2(O^iPr)_2$, toluene-ether, RT, 45% based on **14**. (d) H_2, PtO_2, EtOH, 100%.

Hydrolysis [12] of the thioketal moiety by treatment with *N*-chlorosuccinimide and silver nitrate gave azido ketone **13** (86%) which was treated with triphenylphosphine [13] to yield imine intermediate **14** in near-quantitative yield. After a brief screening [14] of Lewis acids and solvents for the key spirocyclisation step, dichlorotitanium diisopropoxide was selected and, to our delight, when unsaturated imine **14** was exposed to this reagent in a toluene/ether mixture, spirocycle **3** was obtained in 45% isolated yield and *as a single diastereoisomer* with a *trans* double bond in the C4 side-chain. An added bonus was the removal of the MOM protective group during the course of the reaction and/or upon work-up. Apart from the olefinic signals, the high-field ^1H and ^{13}C NMR spectra of compound **3** were quite reminiscent of those of perhydrohistrionicotoxin itself [7], and final proof of structure was provided by catalytic hydrogenation of the double bond in **3** to yield (-)-

perhydrohistrionicotoxin in quantitative yield and with spectral and physical data in agreement with those published [7].

In conclusion, we have developed an efficient, convergent, and enantioselective route to the neurotoxic spirocyclic alkaloid (-)-perhydrohistrionicotoxin. Apart from generally high yields in the individual steps, salient features of the synthesis are (i) use of the Sharpless kinetic resolution procedure to set up two of the stereogenic centres of the target molecule from a common racemic precursor, (ii) a very efficient one-pot, three-component, coupling procedure to assemble the "open-chain" skeleton of the alkaloid, and (iii) excellent diastereoselection in the intramolecular imine ene-type reaction used for the spirocyclisation step.

Acknowledgements. We thank the *Danish Natural Science Research Council* and the *Nordisk Forskerutdanningsakademi (NorFA)* for financial support.

EXPERIMENTAL

General Remarks. ^1H (250, 300 or 500 MHz) and ^{13}C (63, 75 or 126 MHz) NMR spectra were recorded on either a Bruker AC-250, Varian XL 300 or Bruker AC-500 spectrometer ($CDCl_3$) and shifts are quoted in ppm with residual $CHCl_3$ as internal standard, unless otherwise stated. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR instrument and only the strongest/structurally most important peaks are listed. Specific rotation values were measured on a Perkin-Elmer 241 polarimeter and concentrations are quoted in g/100 mL. Elemental analyses were performed either at the Analytical Department, Research Institute for Pharmacy and Biochemistry, Prague, Czech Republic, at Analytische Laboratorien, Lindlar, Germany, or at the Microanalysis Laboratory, Institute of Physical Chemistry, University of Vienna, Austria. Ether and tetrahydrofuran (THF) were distilled under nitrogen from Na/benzophenone. Dichloromethane, triethylamine and pentane were dried over calcium hydride and distilled under nitrogen. Hexamethylphosphoramide (HMPA) was dried over calcium hydride, distilled under nitrogen and stored over activated molecular sieves (3 Å). Dry dimethylformamide (DMF) was purchased from Aldrich. Silica gel for flash chromatography was purchased from Grace-Amicon. Reactions requiring exclusion of moisture were performed under argon in glassware that had been flame-dried under vacuum. "Aqueous work up" refers to extraction of the aqueous phase 3 times with ether followed by washing the combined organic phases with brine, drying over $MgSO_4$ and subsequent concentration under reduced pressure. The pH 7 buffer was prepared from 20.5 g KH_2PO_4 and 3.5 g of NaOH and 100 ml water. Alkyllithiums were titrated against *N*-pivaloyl-*o*-toluidine [15].

Racemic allylic alcohol **8**.

(i) *tert*-Butyldimethylsilyl chloride (29.1 g, 0.193 mol) was added in one portion to a solution of 3-bromopropanol (24.36 g, 0,175 mol) and imidazole (29.7 g, 0.436 mol) in DMF (200 mL) and the reaction mixture was stirred overnight under argon at room temperature. Pentane (200 mL) was added to the reaction mixture which was washed extensively with water, then brine, and dried over $MgSO_4$ and concentrated. The residue (41.4 g) was ^1H-NMR spectroscopically pure [16] and was used directly in the following step.

(ii) A mixture of the bromide from above, NaI (39.4 g, 0.263 mol) and acetone (200 mL) was stirred under argon at room temp. for 3 days. The precipitated NaBr was filtered off, the acetone was removed *in vacuo* and the residue was distilled (92 - 94°C/5.4 mm Hg) to yield the iodide (51.20 g, 97 % over two steps) as a colourless liquid [17].

(iii) *t*-Butyllithium [18] (53.5 mL, 1.50 M in pentane, 80.3 mmol) was added to a solution of the iodide (12.05 g, 40.13 mmol) in pentane:ether (3:2, 400 mL) under argon at -78°C. The mixture was stirred for 5 min. and transferred via cannula to a solution of *trans*-2-hexenal (4.70 mL, 40.5 mmol) in pentane:ether (3:2, 50 mL) which had been precooled under argon to -78°C. The reaction mixture was allowed to reach room temp. and quenched with water. After aqueous work up and flash chromatographic purification (EtOAc:hexane/1:9) the racemic allylic alcohol **8** (10.20 g, 93 %) was obtained as a colourless oil. ^1H-NMR: ∂ 5.65 (1 H, dt J^1=15.5 Hz J^2=6.5 Hz, =C$\underline{\underline{H}}$-$CH_2$), 5.45 (1 H, ddt J^1=15.5 Hz J^2=6.5 Hz J^3=1.5 Hz, CH-C$\underline{\underline{H}}$=), 4.06 (1 H, m, CHO), 3.65 (2 H, m, OCH_2), 2.40 (1 H, bs, OH), 2.0 (2 H, dt, J^1=J^2=7 Hz, =CH-C$\underline{\underline{H_2}}$), 1.6 (4 H, m, C$\underline{\underline{H_2}}C\underline{\underline{H_2}}$CH), 1.4 (2 H, tq J^1=J^2=7 Hz, C$\underline{\underline{H_2}}$$CH_3$), 0.9 (12 H, s+t, CH_3+*t*Bu), 0.06 (6 H, s, $Si(CH_3)_2$). ^{13}C-NMR: 133.03, 131.60, 72.70, 63.39, 34.66, 34.29, 28.93, 25.93, 22.31, 18.33, 13.69. IR: 3356 2954 1472 1255 cm^{-1}. Anal. Calcd. for $C_{15}H_{32}O_2Si$: C, 66.11; H, 11.84. Found: C, 66.37; H, 12.00.

(R)-(+)- and *(S)-*(-)-**8** *via Sharpless kinetic resolution.*

(i) *(R)-*(+)-**8**. A mixture of (±)-**8** (9.969 g, 36.58 mmol), (+)-diisopropyl tartrate (1.20 mL, 5.65 mmol), n-hexadecane (1.5 mL), activated 3Å molecular sieves (3 g) and CH_2Cl_2 (150 ml) was cooled to -20°C under argon. Ti(O*i*Pr)$_4$ (1.10 mL, 3.73 mmol) was added dropwise and the reaction mixture was stirred for 30 min. at -20°C, during which time a T_0-sample was taken for GC-analysis. *tert*-Butylhydroperoxide (6.9 mL, 3.7 M in toluene, 25 mmol) was added dropwise and the reaction progress was followed by GC with n-hexadecane as internal standard. The reaction was stopped after 9.5 hours (58 % conversion at -20°C) by addition of acetone containing a small amount of water. The resultant slurry was allowed to reach room temp. and filtered through a pad of celite to yield a clear colourless solution. After concentration, the residue was purified by flash chromatography (EtOAc:hexane/1:9) to give the product (3.968 g, 40 %). Alternatively, the crude residue was dissolved in dry ether and reacted with $LiAlH_4$, followed by aqueous work up, to facilitate the chromatographic purification. $[a]^{25}_{D}$ +4.37 (*c* 1.08, CH_2Cl_2). The *e.e.* of the residual allylic alcohol was estimated [9c] to be > 98% and the spectral data were identical with those for the racemic material.

(ii) *(S)-*(-)-**8**. The above procedure was repeated with the following mixture: (±)-**8** (16.88 g, 61.96 mmol), (-)-diisopropyl tartrate (2.00 mL, 9.42 mmol), n- hexadecane (2.5 mL), 3Å molecular sieves (5 g), Ti(O*i*Pr)$_4$ (1.85 mL, 6.28 mmol), *tert*-butylhydroperoxide (11.7 mL, 3.7 M in toluene, 43 mmol) in CH_2Cl_2 (250 mL). At -20°C this gave 56 % conversion after

7.5 hours, and yielded 6.891 g (41 %) of resolved allylic alcohol, $[a]^{25}_{D}$ -4.37 (*c* 0.94, CH_2Cl_2). The *e.e.* was estimated in the same way as for the enantiomer.

(S)-Iodide **9**.

(i) Chloromethyl methyl ether (2.34 mL, 30.8 mmol) was added to a solution of *(S)*-**8** (2.795 g, 10.26 mmol) and *i*Pr_2NEt (5.36 mL, 30.8 mmol) in CH_2Cl_2 (40 mL) under argon at 0°C. The reaction mixture was allowed to reach room temp. and stirred for 3 hours. After quenching with water and aqueous work up, the residue was purified by flash chromatography (EtOAc:hexane/1:9) to yield the allylic MOM ether (3.182 g, 98 %) as a colourless oil. $[a]^{25}_{D}$ -80.9 (*c* 1.28, CH_2Cl_2). ^{1}H-NMR (C_6D_6): 5.55 (1 H, dt J^1=15.5 Hz J^2=6.5 Hz, =$C\underline{H}CH_2$), 5.32 (1 H, ddt J^1=15.5 Hz J^2=8 Hz J^3=1.5 Hz, $CHC\underline{H}$=), 4.67 (2 H, AB J=6.5 Hz, OCH_2O), 4.1 (1 H, m, $C\underline{H}OMOM$), 3.6 (2 H, t unresolved, OCH_2), 3.25 (3 H, s, OCH_3), 1.92-1.63 (6 H, m), 1.26 (2 H, tq J^1=J^2=7.5 Hz, $C\underline{H_2}CH_3$), 0.99 (9 H, s, *t*Bu), 0.81 (3 H, t J=7.5 Hz, CH_3), 0.07 (6 H, s, $Si(CH_3)_2$). ^{13}C-NMR (C_6D_6): 134.23, 131.04, 93.35, 76.61, 63.22, 55.07, 34.53, 32.65, 29.33, 26.14, 22.60, 18.50, 13.73. IR: 2955, 1098, 1037, 836; Anal. Calcd. for $C_{17}H_{36}O_3Si$: C, 64.50; H, 11.46. Found: C, 64.64; H, 11.18.

(ii) A mixture of the allylic MOM ether from above (2.159 g, 6.82 mmol), tetrabutylammonium fluoride trihydrate (10.0 g, 31.7 mmol), acetic acid (cat.) and THF (30 mL) was stirred at room temp. for 1 hour and after addition of water, aqueous work up and chromatographic purification (EtOAc:hexane/1:9) the primary alcohol product (1.365 g, 99 %) was obtained as a colourless oil, $[a]^{24}_{D}$ -114.4 (*c* 0.72, CH_2Cl_2). ^{1}H-NMR: 5.62 (1 H, dt J^1=15.5 Hz J^2=6.7 Hz, =$C\underline{H}CH_2$), 5.25 (1 H, ddt J^1=15.4 Hz J^2=8.3 Hz J^3=1.4 Hz $CHC\underline{H}$=), 4.61 (2 H, AB J=6.7 Hz, OCH_2O), 4.0 (1 H, m, $C\underline{H}OMOM$), 3.65 (2 H, bs , CH_2O), 3.36 (3 H, s, OCH_3), 2.00 (2 H, m, =$CHC\underline{H_2}$), 1.80 -1.50 (5 H, bs+m, $\underline{H}OCH_2C\underline{H_2}C\underline{H_2}$), 1.4 (2 H, tq J^1=J^2=7.4 Hz , $C\underline{H_2}CH_3$), 0.9 (3 H, t J=7.4 Hz, CH_3). ^{13}C-NMR (C_6D_6) 134.25, 130.79, 93.36, 76.72, 62.59, 55.12, 34.50, 32.71, 29.21, 22.57, 13.71. IR: 3416, 2931, 1668, 1457, 1151; Anal. Calcd. for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.15; H, 10.85.

(iii) A solution of the primary alcohol from above (1.266 g, 6.26 g), triethylamine (1.75 mL, 12.6 mmol) and 4-*N,N*-dimethylaminopyridine (cat.) in CH_2Cl_2 (20 mL) was cooled to -10°C under argon. Tosyl chloride (1.29 g, 6.75 mmol) was added in one portion and the reaction mixture was stirred under argon at 5°C overnight. After addition of water and aqueous work up, flash chromatographic purification (EtOAc:hexane/5;95 to 1:9) furnished the desired primary tosylate (2.187 g, 98 %) as a colourless oil, $[a]^{25}_{D}$ -63.43 (*c* 0.910, CH_2Cl_2). ^{1}H-NMR: 7.56 (4 H, AA′BB′ J=8.5 Hz, aromatic), 5.56 (1 H, dt J^1=15.5 Hz J^2=6.5 Hz, =$C\underline{H}CH_2$), 5.17 (1 H, ddt J^1=15.5 Hz J^2=8.5 Hz 6.5 Hz J^3=1.5 Hz, $CHC\underline{H}$=), 4.54 (2 H, AB J=6.5 Hz, OCH_2O), 4.03 (2 H, m, $TsOCH_2$), 3.86 (1 H, m, $C\underline{H}OMOM$), 3.29 (3 H, s, OCH_3), 2.43 (3 H, s, tosyl Me), 1.98 (2 H, m, =$CHC\underline{H_2}$), 1.85-1.44 (4 H, m, $C\underline{H_2}C\underline{H_2}CH$), 1.36 (2 H, tq J^1=J^2=7.5 Hz, $C\underline{H_2}CH_3$), 0.87 (3 H, t J=7.5 Hz, CH_3). ^{13}C-NMR: 144.65, 135.11, 133.11, 129.80, 129.28, 127.88, 93.11, 75.90, 70.50, 55.38, 34.22, 31.47, 25.10, 22.22, 21.63, 13.62. IR: 2957, 2930, 1362, 1178, 1035. Anal. Calc. for $C_{18}H_{28}O_5S$: C, 60.65; H, 7.92. Found: C, 60.73; H, 7.97.

(iv) A mixture of the tosylate from above (4.60 g, 12.9 mmol), NaI (5.81 g, 38.7 mmol) and acetone (50 mL) was heated to 55°C under argon for 3 hours. The mixture was concentrated and the residue purified by flash chromatography (ether:hexane/5:95) to give the *(S)*-**9** (3.95 g, 98 %) as a colourless liquid, $[a]^{25}_D$ -86.0 (*c* 1.06, CH_2Cl_2). ^{1}H-NMR: 5.61 (1 H, dt J^1=15.5 Hz J^2=7 Hz, $=C\underline{H}CH_2$), 5.24 (1 H, ddt J^1=15.5 Hz J^2=8.0 Hz J^3=1.5 Hz, $CHC\underline{H}=$), 4.61 (2 H, AB, J=6.5 Hz, OCH_2O), 3.96 (2 H, m, $C\underline{H}OMOM$), 3.35 (3 H, s, OCH_3), 3.20 (2 H, t J=7.5 Hz, ICH_2), 2.07-1.80 (4 H, m), 1.80-1.53 (2 H, m), 1.40 (2 H, tq J^1=J^2=7.5 Hz, $C\underline{H_2}CH_3$), 0.89 (3 H, t J=7.5 Hz, CH_3). ^{13}C-NMR: 135.00, 129.47, 93.15, 75.63, 55.41, 36.54, 34.25, 29.66, 22.25, 13.62, 6.71; IR 2953, 2360, 1667, 1452. Anal. Calcd. for $C_{11}H_{21}IO_2$: C, 42.32; H, 6.78. Found: C, 42.48; H, 6.83.

(R)-iodide **10**.

(i) PtO_2 (0.150 g) was added to a solution of *(R)*-**8** (4.01 g, 14.7 mmol) in hexane (20 mL) and the mixture was stirred under 1 atm. of H_2 for 15 min. at room temp. Filtration through a short column of silica gel and celite, followed by concentration, furnished 4.02 g (100 %) of the corresponding saturated secondary alcohol as a colourless oil, $[a]^{24}_D$ +2.22 (*c* 1.23, CH_2Cl_2). ^{1}H-NMR: 3.70-3.55 (3 H, m+t J=6 Hz, CHO + OCH_2), 2.5 (1 H, bs, OH), 1.69-1.56 (3 H, m), 1.48-1.22 (9 H, m), 0.89 (12 H, s+t, CH_3 and *t*Bu), 0.06 (6 H, s, $Si(CH_3)_2$). ^{13}C-NMR: 71.51, 63.56, 37.40, 34.65, 31.93, 29.14, 25.91, 25.44, 22.65, 18.30, 14.06. IR: 3734, 2930, 1471, 1255, 1098. Anal. Calcd for $C_{15}H_{34}O_2Si$: C, 65.63; H, 12.48. Found: C, 65.46; H, 12.50.

(ii) Diethylazodicarboxylate (0.170 mL, 1.05 mmol) was added dropwise over 15 min. to a solution of the alcohol from above (0.271 g, 0987 mmol), PPh_3 (0.290 g, 1.11 mmol) and HN_3 (2.15 mL, 0.7 M in benzene, 1.5 mmol) in CH_2Cl_2 (15 mL) under argon at room temp. After 6 hours, tetrabutylammonium fluoride (5.0 mL, 1.0 M in THF, 5.0 mmol) and a few drops of acetic acid were added. The reaction was quenched after 12 hours by addition of water and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave a crude product which was purified by flash chromatography (EtOAc:hexane/1:9) to give the desired product (2^o azide, 1^o alcohol, 0.183 g, 100 %) as a colourless oil, $[a]^{25}_D$ -3.48 (*c* 1.17, CH_2Cl_2). ^{1}H-NMR: 3.67 (2 H, t unresolved, OCH_2), 3.29 (1 H, m, CHN), 1.8-1.22 (12 H, m, $6xCH_2$), 0.9 (3 H, t unresolved, CH_3). ^{13}C-NMR: 62.89, 62.52, 34.39, 31.58, 30.73, 29.23, 25.73, 22.52, 13.98. IR: 3318 (b), 2933, 2099, 1456. Anal. Calcd. for $C_9H_{19}N_3O$: C, 58.35; H, 10.34; N, 22.68. Found: C, 58.46; H, 10.46; N, 23.05.

(iii) A solution of the azido alcohol from above (1.398 g, 7.55 mmol), triethylamine (2.10 mL, 15.1 mmol) and 4-*N,N*-dimethylaminopyridine (cat.) in CH_2Cl_2 (25 mL) was cooled to 0°C under argon. Tosyl chloride (1.564 g, 8.20 mmol) was added in one portion and the reaction mixture was stirred under argon overnight at 5°C and then quenched with water. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$. Purification of the crude product by flash chromatography (EtOAc:hexane/1:9) furnished 2.372 g (93 %) of the desired primary tosylate as a colourless oil, $[a]^{25}_{D}$ -6.63 (*c* 1.40, CH_2Cl_2). ^{1}H-NMR: 7.57 (4 H, AA′BB′ J=8.5 Hz, aromatic) 4.05 (2 H, m, OCH_2), 3.18 (1 H, m, CHN), 2.42 (3 H, s, tosyl Me), 1.80-1.20 (12 H, m), 0.89 (3 H, t unresolved, CH_3). ^{13}C-NMR: 144.85, 132.93, 129.86, 127.87, 70.01, 62.26, 34.29, 31.53, 30.31, 25.65, 25.57, 22.49, 21.65, 13.98. IR: 2931, 2100, 1361, 1189, 1177. Anal. Calcd. for $C_{16}H_{25}N_3O_3S$: C, 56.61; H, 7.42; N, 12.38. Found: C, 56.75; H, 7.48; N, 12.51.

(iv) A solution of the tosylate from above (0.387 g, 1.14 mmol) and NaI (0.51 g, 3.4 mmol) in acetone (5 mL) was heated at 55°C under argon for 3 hours. After filtration and concentration, the residue was purified by flash chromatography (ether:pentane/5:95) to give *(R)*-**10** (0.334 g, 99 %) as a colourless oil, $[a]^{25}_{D}$ -12.1 (*c* 1.22 CH_2Cl_2). ^{1}H-NMR: 3.31-3.15 (3 H, m+t J=6.5 Hz, CHN+ICH_2), 2.08-1.20 (10 H, m), 0.9 (3 H, t unresolved, CH_3). ^{13}C-NMR: 61.95, 35.09, 34.28, 31.52, 29.84, 25.67, 22.48, 13.96 6.16. IR: 2933, 2098, 1727. Anal. Calcd. for $C_9H_{18}IN_3$: C, 36.62; H, 6.15; N, 14.24. Found: C, 36.86; H, 5.91; N, 14.22.

Dithiane **12**.

n-Butyllithium (0.285 mL, 1.58 M in hexane, 0.450 mmol) was added dropwise to a solution of **11** (0.314 g, 0.450 mmol) in THF:HMPA (1.5 mL, 9:1) at -78°C under argon and the reaction mixture was stirred for 10 min. A solution of **9** (0.141 g, 0.452 mmol) in THF:HMPA (1.5 mL, 9:1) which had been precooled to -78°C was transferred to the reaction flask via a cannula and after an additional 10 min. of stirring, *n*-butyllithium (0.285 mL, 1.58 M in hexane, 0.450 mmol) was added dropwise. After 10 min., a solution of **10** (0.137 g, 0.464 mmol) in THF:HMPA (1.5 mL, 9:1) which had been precooled to -78°C was transferred to the mixture via a cannula and the resultant solution was allowed to reach room temp. before the reaction was quenched by addition of water. Aqueous work up and flash chromatography (EtOAc:hexane/1:9) yielded **12** (0.172 g, 81 %) as a colourless oil, $[a]^{24}_{D}$ -54.0 (*c* 0.90, CH_2Cl_2). ^{1}H-NMR: 5.62 (1 H, dt J^1=15.5 Hz J^2=7.0 Hz, $=C\underline{H}CH_2$), 5.24 (1 H, ddt J^1=15.5 Hz J^2=8.5 Hz J^3=1.5 Hz, $CHC\underline{H}=$), 4.60 (2 H, AB J=6.5 Hz, OCH_2O), 3.95 (1 H, m, CHO), 3.36 (3 H, s, OCH_3), 3.25(1 H, m, CHN), 2.8 (4 H, m, $SC\underline{H_2}CH_2C\underline{H_2}S$), 2.07-1.75 (8 H, m), 1.7-1.2 (18 H, m), 0.89 (6 H, m, 2xCH_3). ^{13}C-NMR: 134.77, 129.86, 93.18, 76.59, 62.76, 55.39, 53.04, 38.24, 37.98, 35.75, 34.44, 34.36, 34.27, 31.58, 26.00, 25.74, 25.39, 22.52, 22.27, 20.86, 20.22, 13.98, 13.63. IR: 2932, 2100, 1458, 1035. Anal. Calcd. for $C_{24}H_{45}N_3O_3S_2$: C, 61.10; H, 9.61; N, 8.91. Found: C, 61.20; H, 9.70; N, 8.56.

Ketone **13**.

A solution of dithiane **12** (2.06 g, 4.37 mmol) in CH_3CN (10 mL) was added to a mixture of *N*-chlorosuccinimide (2.33 g, 17.5 mmol), silver nitrate (3.34 g, 19.7 mmol), 2,6-lutidine (1 mL) and acetonitrile:water (60 mL, 5:1), at 0°C. After 5 min. stirring, dimethylsulfoxide (9.5 mL) was added and the reaction mixture was filtered though a pad of celite which was then rinsed with EtOAc. The aqueous phase was extracted 3 times with EtOAc and the combined organic phases were dried over $MgSO_4$ and concentrated. Flash chromatographic purification (EtOAc:hexane/5:95) gave the product (1.44 g, 86 %) as a colourless oil, $[a]^{25}_{D}$ -71.4 (*c* 0.82, CH_2Cl_2). ^{1}H-NMR: 5.61 (1 H, dt J^1=15.5 Hz J^2=6.5 Hz, =C$\underline{H}$CH$_2$), 5.23 (1 H, ddt J^1=15.5 Hz J^2=8.5 Hz J^3=1.5 Hz, CHC$\underline{H}$=), 4.59 (2 H, AB J=6.5 Hz, OCH_2O), 3.92 (1 H, m, CHO), 3.35 (3 H, s, OCH_3), 3.22 (1 H, m, CHN), 2.41 (4 H, t J=7 Hz, CH_2COCH_2), 2.01 (2 H, m, =CH$\underline{H_2}$), 1.75-1.20 (18 H, m), 0.88 (6 H, m, 2xCH_3). ^{13}C-NMR: 210.11, 134.62, 129.65, 93.13, 76.38, 62.76, 55.23, 42.46, 42.09, 35.04, 34.13, 33.66, 31.46, 25.59, 22.38, 22.15, 20.20, 19.77, 13.82, 13.47. IR: 2932, 2099, 1715, 1459, 1036. Anal. Calcd. for $C_{21}H_{39}N_3O_3$: C, 66.11; H, 10.30; N, 11.01. Found: C, 66.31; H, 10.22; N, 10.93.

Imine **14**.

A solution of **13** (0.1514 g, 3.97 mmol) and triphenylphosphine (0.1040 g, 3.97 mmol) in benzene (5 mL) was heated at 60°C under argon for 4 hours. The mixture was evaporated onto silica gel and purified by flash chromatography (EtOAc:hexane:triethylamine, 10:85:5) to give the product (0.1294 g, 97 %) as a yellow oil, $[a]^{25}_{D}$ -74.6 (*c* 0.68, CH_2Cl_2). ^{1}H-NMR: 5.60 (1 H, dt J^1=15.5 Hz J^2=6.5 Hz, =C$\underline{H}$CH$_2$), 5.22 (1 H, ddt J^1=15.5 Hz J^2=8.5 Hz J^3=1.5 Hz, CHC$\underline{H}$=), 4.59 (2 H, AB J=6.5 Hz, OCH_2O), 3.92 (1 H, m, CHO), 3.36-3.16 (4 H, s+m, OCH_3 + CHN), 2.20-1.91 (6 H, m), 1.79-1.00 (18 H, m), 0.87 (6 H, t J=7 Hz, 2xCH_3). ^{13}C-NMR: 168.93, 134.60, 129.90, 93.10, 76.57, 57.49, 55.27, 40.89, 37.62, 35.30, 34.27, 28.80, 26.99, 25.84, 22.79, 22.66, 22.26, 18.71, 14.09, 13.61. IR: 2933, 1661, 1458, 1149, 1097, 1036, 970, 920. This material was used as soon as possible in the next step.

Spirocycle **3**.

The imine from above (0.0309 g, 0.093 mmol) was dissolved with stirring under argon in toluene:ether (1 mL, 1:1) and $TiCl_2(O\textit{i}Pr)_2$ (0.0641 g, 0.270 mmol) was added. After an additional 24 hours stirring at room temp., the reaction was quenched by addition of pH 7 buffer solution (1 mL). The mixture was partitioned between ether and water, the aqueous phase was extracted with ether, and the combined organic phases were dried over $MgSO_4$. Purification by flash chromatography (EtOAc:methanol:triethylamine/8:1:1) provided the product (0.0129 g, 45 % based on **3**) as a colourless oil, $[a]^{25}_{D}$ -3.7 (*c* 0.25, CH_2Cl_2). ^{1}H-NMR: 5.64 (1 H, dt J^1=16 Hz J^2=6.5 Hz, CH$_2$C$\underline{H}$=), 5.47 (1 H, ddt J^1=16 Hz J^2=6 Hz J^3=1.5 Hz, =C$\underline{H}$CH), 3.79 (1 H, m, CHO), 2.70 (1 H, m, CHN), 2.30-0.95 (25 H,m), 0.88 (6 H, t unresolved, 2xCH_3). ^{13}C-NMR (C_6D_6): 133.23, 129.96, 68.70, 55.10, 48.98, 38.53, 37.67, 36.21, 34.82, 33.13, 32.54, 32.23, 26.00, 23.19, 23.05, 22.77, 19.42, 14.34, 13.84.

(-)-Perhydrohistrionicotoxin, **2**.

PtO_2 (0.020 mg) was added to a solution of **3** (0.0129 g, 0.0440 mmol) in ethanol (1 mL) and the mixture was stirred under 1 atm. of H_2 overnight at room temp. Filtration through a short column of silica gel and celite followed by concentration furnished 0.0130 g (100%) of **2** as a colourless oil. This material showed physical ($[a]^{25}_{D}$) and spectral (^{1}H- and ^{13}C-NMR) data in agreement with those published [7].

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