Published in final edited form as:

J Nat Prod. 2011 March 25; 74(3): 430–440. doi:10.1021/np1008637.

Xestoproxamines A–C from *Neopetrosia proxima*. Assignment of Absolute Stereostructure of *bis*-Piperidine Alkaloids by Integrated Degradation-CD Analysis†

Brandon I. Morinaka[‡] and Tadeusz F. Molinski^{*,‡,§}

Department of Chemistry and Biochemistry and Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, La Jolla, California 92093-0358

Abstract

The complete stereostructures of xestoproxamines A–C, from the Bahamian sponge *Neopetrosia proxima*, were assigned from spectroscopic analysis, including MS, 2D NMR, and integrated degradation CD-analysis. Two new CD application protocols are described for defining absolute configuration: one for allylic methyl groups in branched chains and a second for the heterocyclic core *bis*-piperidine with specific applicability to other members of this class alkaloids – known for their stereo-heterogeneity – and tertiary cyclic amines in general.

Polycyclic amines comprise a family of biologically active macrocycles reported from sponges of the genera *Haliclona*, *Xestospongia*, *Petrosia*, *Neopetrosia* and *Reniera*, among others¹. Their structures contain two or more nitrogen atoms woven into networks of fused heterocyclic and carbocyclic rings, mainly based on piperidine or cyclohexane. From the standpoint of structural characterization, polycyclic amines present difficulties in their purification due to their amphiphilic physical properties, while structure elucidation is hampered by both limited proton chemical shift dispersion presented in their ¹H NMR spectra and stereochemical heterogeneity. In fact, the structures of several alkaloids in this class have succumbed only to X-ray crystallography. We report here three new *bis*-piperidine alkaloids, xestoproxamines A–C (**1–3**) from *Neopetrosia proxima*² and assignment of their complete absolute stereostructures by an integrated approach based on NMR and circular dichroism (CD).³ A notable advancement is chiroptical analysis by CD, following double quaternization of the *bis*-piperidine, to give *N, N'*-*bis*-bromophenacyl derivatives which display characteristic split Cotton effects that reliably reflect the absolute configuration of the *bis*-piperidine core.

The molecular formula for **1** was established as C₃₀H₅₂N₂ based on HRESIMS data (*m/z* 441.4207, [M+H]⁺). The presence of two 1,2-disubstituted carbon-carbon double bonds was supported by two coupled pairs of CH=CH spin systems in the ¹H-¹H COSY spectrum (Table 1, δ 5.49 m; 5.37 m; 5.31, m, and 5.28, m) and four CH sp² carbons in the ¹³C DEPT spectrum (δ 131.74, d; 131.69, d; 130.1, d, and 129.1, d). NOESY correlations observed between allylic methylene groups (H16_b/H19_b and H26_b/H29_b) confirmed the *Z*-configuration of both double bonds. Because all sp² carbons were accounted for and no C=N

†Dedicated to Dr. Koji Nakanishi of Columbia University for his pioneering work on bioactive natural products.

*To whom correspondence should be addressed: Tel: +1 (858) 534-7115. Fax: +1 (858) 822-0386. tmolinski@ucsd.edu.

[‡]UC San Diego, Department of Chemistry and Biochemistry

[§]UC San Diego, Skaggs School of Pharmacy and Pharmaceutical Sciences

Supporting Information Available: ¹H, ¹³C NMR and 2D NMR spectra of **1–3**, ¹³C NMR spectra of **10**, **11**, **22**, and **23**, ¹H NMR spectra of **12**, **14**, **24**, **25**, and **30**, and ¹H and ¹³C NMR of all new synthetic intermediates (**15**, **18**, **19a**, **19**, and **20**). This material is available free of charge via the Internet at <http://pubs.acs.org>.

bonds were present, the remaining N atoms must be sp^3 hybridized; therefore, **1** is a di-tertiary amine related to the known alkaloids halicyclamine A (**4**),⁴ B (**5**),⁵ haliclonacyclamines A (**6**), B (**7**),⁶ arenosclerin A (**8**) and haliclonacyclamine E (**9**).⁷ The remaining four degrees of unsaturation were completed by four rings. Interpretation of ^{13}C , DEPT, and HSQC data showed six *N*-substituted CH_2 groups (δ 58.5, 56.9, 56.4, 55.3, 48.9, and 47.4) that were linked to the remaining ring and chain elements (substructures **a–c**, Figure 1), including two substituted piperidine rings, from additional 2D NMR evidence (DQF-COSY, TOCSY, gHSQC, and gHMBC), in particular, HMBC cross-peaks at of H3/C9, H4/C9, and H10/C3. Contiguous spin systems identified by TOCSY cross-peaks of H13b/H16b and H11b/H14b secured two long hydrocarbon linking chains between the CH_2 -N and CH-N groups. Substructure **c** was joined to **a** by HMBC cross-peaks from H2 to both C29 and C30. The final ring was closed by connecting substructure **b** to **c** through HMBC correlations from H22 to C24.

The relative configuration of the conjoined *bis*-piperidine rings in **1** (designated rings A and B, Figure 2) could be established from *J* coupling constants and NOESY data. The relative orientation of H2_{ax} and H3_{ax} was established by a 1D-TOCSY experiment; irradiation of H5_{eq} (δ 3.48, brd) showed H1_{ax} (dd, *J* = 12.0, 12.0 Hz) revealed two large couplings to H1_{eq} (δ 3.18, m) and to H2_{ax} (δ 2.29, m) respectively. In addition, H3_{ax} was vicinally coupled by two large scalar couplings (*J* = 11.0 Hz) to H2_{ax} and H4_{ax}. Additional large couplings (*J* = 12.0 Hz and 12.0 Hz, respectively) from H7_{ax} and H9_{ax} to H8_{ax} (δ 1.06, ddd, *J* = 12.0, 12.0, 12.0 Hz) showed the three protons to be axially disposed. The relative configuration of the remaining stereocenters in **1** was assigned by interpretation of NOESY correlations. The dihedral angle of $\sim 90^\circ$ between H3 and H9 was supported by lack of vicinal coupling ($^3J \sim 0$ Hz). Conformational constraints placed on the rings by NOE and *J* data, in particular, mutual correlations between the pairs H2_{ax} and H8_{ax} and H10_{eq} and H3_{ax}, lead to the depicted relative configuration and a conformer that places the averaged planes of ring A and B orthogonal to each other (Figure 2).

Xestoproxamine B (**2**) showed a molecular formula of $C_{30}H_{54}N_2$, which has one degree of unsaturation less than xestoproxamine A (**1**). The 1H NMR signals for **2** (Table 2) were similar to those of **1** except for the presence of two vinyl protons (δ 5.48, m and 5.33, m) indicating only one C=C double bond. 2D NMR data confirmed both **1** and **2** share the same *bis*-piperidine ring system, including relative configuration (*J*_{HH} and NOESY). The double bond was positioned between C17/C18 by COSY and TOCSY correlations to H19. Therefore xestoproxamine B (**2**) is a dihydro derivative of xestoproxamine A (**1**).

The third new *bis*-piperidine alkaloid, xestoproxamine C (**3**) $C_{31}H_{56}N_2$, showed a characteristic signal for a secondary methyl branch in the 1H NMR spectrum (Table 3, δ 0.87, d, *J* = 6.7 Hz) that was absent in **1** and **2**. 2D NMR and NOESY data indicated the configuration of **3** in the core *bis*-piperidine heterocycle differed from **1** and **2** but corresponded to the relative configuration found in haliclonacyclamine A (**6**).⁵ While ring B remained in the same conformation as **1** and **2**, ring A in **3** had undergone ring flip to the opposite chair conformation, apparently without inversion at the ring A sp^3 nitrogen (NOESY, Figure 2), a consequence of the inverted C2 configuration, yet in the new torsional arrangement a dihedral angle of $\sim 90^\circ$ for H3-C3-C9-H9 ($^3J_{H3-H9} \sim 0$ Hz) was retained.

Compound **3** failed to produce suitable X-ray quality crystals under a variety of conditions. Stereoanalysis by spectroscopic means would require separate assignments of the two stereocenters in **3**; the C23 stereocenter and the *bis*-piperidine core. We devised the following degradative approach for assignment of the lone C23 stereocenter *exo* to the heterocyclic core. Hofmann elimination of suitably quaternized nitrogen atoms in **3** would provide a terminal olefin (δ 21), which could then be subjected to cross metathesis with a

styrenyl derivative to insert a chromophore next to the secondary Me branch (first sphere of asymmetry), rendering the molecular amenable to analysis by CD. Due to the scarcity of **3**, the method was first piloted with more abundant xestoproxamine A (**1**) (Scheme 1). Catalytic hydrogenation of **1** (Pd-C, MeOH, H₂), purification, and conversion to the free base **10** by HPLC with buffered solvent (Lux-cellulose; CH₃CN/*i*-PrOH/Et₂NH), and immediate exhaustive alkylation with CH₃I cleanly provided the *bis*-methiodide salt **11**. The iodide counter ion was exchanged with hydroxide by treatment of **11** with either Ag₂O or strong anion exchange resin (Amberlite-IRA 400, HO⁻ form). Two possible major products were anticipated from cleavage of C21-N and cleavage of either C5-N or C11-N, based on the Hofmann rule that leads to the least substituted alkenes. In the event, Hofmann elimination (10 min, 300 W, 140°C) of the neat quaternary ammonium hydroxide double salt afforded only one major alkene product, **12**. The structure of **12** was confirmed by 2D NMR (COSY, TOCSY, HSQC, and HMBC), which showed piperidine ring B was intact: *exo* cleavage of the C5-N bond was supported by the multiplicity of H4 (δ 5.55, dt, J = 17.0, 10.3 Hz). In contrast, ring A had undergone *endo* cleavage of the C21-N bond, and the vinyl methine signal exhibited the more complex pattern for vinyl proton H22 associated with a terminal allyl group (δ 5.80 (dddd, J = 17.0, 10.3, 6.8, 6.8 Hz, 1H). Alkene **12** was subjected to cross metathesis with excess 2-methoxy-6-vinylnaphthalene **138** (~10 eq) in the presence of Grubbs' second generation catalyst⁹ which selectively engaged only the less hindered vinyl group derived from ring B to give the conjugated naphthalene **14**. The UV spectrum of **14** in CH₃CN showed characteristic λ_{max} (246 and 292 nm) for the conjugated naphthalene chromophore, however – as expected – this styrenyl system was CD silent due to the remoteness of the chromophore from the distal sphere of asymmetry near C2 (xestoproxamine numbering, Figure 1).

In order to assign the observed Cotton effect to the configuration of the C23 center in **3**, an appropriate methyl-branched model was required. Because the Cotton effect anticipated for the degradation/cross metathesis product of **3** would arise from asymmetric perturbation of the vinyl-conjugated 6-methoxynaphthalene, the model could consist of a chromophore adjacent to an allylic methyl branch of known configuration, appended to a short chain. Preparation of the model was achieved as depicted in Scheme 2. The α -branched propionamide **15**, obtained by diastereoselective Myers alkylation of the enolate of (*R,R*)-(-)-*N*-propionylpseudoephedrine¹⁰ (**16**) (LDA, LiCl),¹¹ with 1-iodosilyloxy ether **17** was selectively reduced (LiBH₃N(CH₂)₄, rt) to the alcohol **18**¹² (%ee >94% by modified Mosher method).¹³ Swern oxidation of **18** to the corresponding aldehyde, followed by Wittig olefination (Ph₃PC=CH₂) gave terminal olefin **19**. Finally, cross metathesis of **19** (Grubbs' II, MeO-NpV) provided model alkene (*S*)-**20**.

Xestoproxamine C (**3**) was converted to **21**, via the intermediates **22–24** (Scheme 3), by a similar sequence of reactions used to convert **1** to **14**. The CD spectra (Figure 3 and Table 4) of synthetic (*S*)-**20** [λ 256 nm ($\delta\epsilon$ +3.9)] and **21** [λ 255 nm ($\delta\epsilon$ +3.8)] were of the same sign and magnitude, therefore, **21** and xestoproxamine C (**3**) have the 23*S* configuration.

No simple spectroscopic method was available for defining the absolute configuration of the *bis*-piperidine ring system in **1–3**. Since this is an outstanding problem of configurational analysis in this class of alkaloids, we turned to refinement of a general method for assignment of cyclic tertiary amines involving derivatization and CD first published by Nakanishi and coworkers.¹⁴ Nakanishi's assignment of the absolute configuration of quinuclidinols¹⁴ – bicyclic tertiary amines – followed simultaneous quaternization of the tertiary nitrogen and esterification of the pendant secondary OH group with excess *p*-phenylbenzylchloride and interpretation of the resultant split CD spectrum arising from exciton coupling of the two arene chromophores. Although the xestoproxamines differ considerably from the quinuclidinols the same principle could be applied: quaternization of

both *N* atoms with a suitable chromophore and interpretation of exciton coupling CD (ECCD) would be informative of the absolute configuration of the heterocyclic *bis*-piperidine core. However, three possible problems were anticipated. The distance between chromophores attached to the *N* atoms in **1–3** is considerably larger than those in derivatized quinuclidinols with an expectedly weaker ECCD. This could be compensated for by substitution of the *p*-phenylbenzyl group with a more polarized chromophore: a phenacyl group. It was anticipated that possible differences in conformations of the natural products and quaternized derivatives and the introduction of two new stereocenters at *N* would complicate *non-empirical* interpretation of ECCD effects. On the other hand, the stereochemical outcome of *N*-quaternization should be predictable. The alkylating reagent should approach both *N* atoms in **1–3** along a trajectory in line with the lone pair without changing the *N*-configuration. In any case, the resultant configuration and conformation of the derivatives would be revealed by CD spectra and could be interpreted as ‘fingerprint’ spectra that relate the handedness of the heterocyclic core. This would confer an important advantage to chiroptical analysis of antipodal *bis*-piperidines by CD over comparisons using $[\alpha]_D$. Optical rotations of alkanamines are typically weak in magnitude and comparisons of specific rotation alone are notoriously unreliable due to changes in sign resulting from even slight structural variants (unsaturation). By comparing a fingerprint Cotton effect with that of a *bis*-piperidine phenacyl derivative of known absolute configuration, the configuration of any member of the series could be assigned.

To ensure a reasonably strong CD signal in the final product, an *N*-(4-bromophenacyl) chromophore (λ_{max} 265 nm, $\epsilon \sim 12,000$) was introduced by exhaustive quaternization of the alkaloids. The *bis*-TFA salt of tetrahydroxestoproxamine (**10**) was converted to the free base (KOH/MeOH) followed by alkylation with *p*-bromophenacylbromide (toluene, 90 °C) to give **25** after HPLC purification (Scheme 4). The CD spectrum (Table 4) of **25** showed a characteristic negative split Cotton effect (λ 273 nm, $\delta\epsilon -6.0$; 253 (+2.6)) arising from exciton coupling of equatorial and axial *N*-*p*-bromophenacyl chromophores disposed with a negative helicity (see Figure 4). The relative conformations of the conjoined *bis*-piperidine ring system in **25** and **1** maintain the same conformations as starting material (analysis of *J* and NOESY data), however, the exact orientation of the transition dipole vectors that align along the average axes of the *N*-*p*-Br-phenacyl groups is highly dependent upon the conjoining C3-C9 bond which is subject to subtle torsional angle changes from non-bonding effects of the side chains and not easily predictable. Instead, we chose to make *empirical* chiroptical comparisons with *p*-Br-phenacyl derivatives with a compound of known configuration.

The relative configuration of (–)-‘perhaliclonacyclamine’ (**26**),¹⁵ the hydrogenation product of (+)-tetrahydrohaliclonacyclamine A (**31**) obtained from an Indonesian sponge, *Halichondria* sp., differs from the tetrahydroxestoproxamine A (**10**) in the relative configuration at C2 and the presence of two additional CH₂ groups in the lower linking chain.¹⁶ A sample of (–)-**26**,¹⁷ was alkylated in the same manner (see above) to give derivative **27**. The CD spectrum of **27** (λ 273 nm ($\delta\epsilon -6.1$); 254, (+3.2); Figure 4, Table 4) is almost identical to that of **25**. Therefore, despite differences in relative configuration in the two piperidine rings in **25** and **27**, both conform to the same chromophore alignments (a negative N–(C=O)–(C=O)–N’ angle) – imposed largely by the constraint of the C3-C9 torsional angle – and CD reveals they share the same absolute stereostructure, with the exception of the epimeric C2 position. A sample of haliclonacyclamine E (**9**), isolated from a Brazilian sample of *Arenosclera braziliensis*,¹⁸ was hydrogenated (H₂, Pd-C) to the tetrahydro derivative (**28**), and exhaustively alkylated (*p*-bromo-phenacylbromide, 90 °C) as before to the *bis*-*p*-Br-phenacylated compound **29** that showed a CD spectrum (λ 273 nm, $\delta\epsilon -6.0$; 255 (+3.1), Table 4) almost identical with those of **25** and **27**. Finally, the CD

spectrum of the *bis-p*-bromophenylacyl derivative (**30**, λ 273 nm, $\delta\epsilon$ —7.1; 253 (+3.5)), obtained from tetrahydroxestoproxamine C (**22**) was identical to those of **25**, **27** and **30**.¹⁹ Therefore the absolute configuration of the heterocyclic cores in xestoproxamine A (**1**), haliclonaclamamine E (**9**), (–)-perhaliclonaclamamine (**26**) and xestoproxamine C (**3**) are the same, with the exception of C2 as noted above. Since the absolute configuration of (–)-**26** was established earlier by X-ray crystallography,¹⁵ the stereostructures of **1–3** and **9** are now completely assigned. *Bis*-piperidine **8** co-occurs with **97** and it is likely both of these natural products share the same heterocyclic core configuration.

A summary of the configurational analysis of **1–3** and the CIP descriptors for the core stereocenters of related *bis*-piperidine alkaloids is given in Table 5, along with a comparison of reported $[\alpha]_D$ values. No clear trend can be seen except that the compounds have high stereochemical heterogeneity that may reflect their geographic origins. The specific rotations vary in sign and magnitude with a strong dependence upon the presence and position of unsaturation in the top and bottom linking chains and possibly the chain lengths. Haliclonaclamamines A (**6**) and (**7**), from *Haliclona* sp. from the Great Barrier Reef, differ in the linking chains but the cores are antipodal to those of (–)-**26** and (+)-**31** from *Halichondria* sp. collected in Indonesia. We note that the recently reported (–)-neopetrosiamine (**32**)²⁰ from the sponge *Neopetrosia proxima*,² collected in the Caribbean sea south of the Bahamas, is very similar to **1–3**, but the configuration was not defined.

Bis-piperidine alkaloids have shown modest activity against various cancer cell lines. Compounds **1–3** were assayed in vitro against human colon tumor cells (HCT-116) and showed IC₅₀ values of 21.2, 6.3, and 5.4 μ M respectively.

In conclusion, three new *bis*-piperidine alkaloids, xestoproxamines A–C (**1–3**) are reported and their complete structures assigned by integrated MS, NMR, and chiroptical analysis. We assigned the absolute configuration of the remote methyl group in xestoproxamine C (**3**) by CD following a Hoffman degradation/cross metathesis protocol, a sensitive technique that can be extended to other natural products containing acyclic allylic methyl branches. Finally, we have shown that ECCD of *N, N'*-di-*p*-bromophenacyl *bis*-piperidine alkaloids, obtained by quaternization of the tertiary amines, reliably reflects the absolute configurations of the heterocyclic cores in **1–3**, independent of the relative configuration at C2. This observation was exploited to show the two groups of structures, **1**, **2**, **8**, **9**, and **3**, **26**, have the same absolute configuration in their core heterocyclic rings and should be applicable to other *bis*-piperidine alkaloids in this class.

Experimental Section

General Experimental Procedures

General procedures are described elsewhere.²¹ Yields were determined gravimetrically except for those of masses of less than ~100 μ g which are estimated from UV extinction coefficients or by quantitative solvent ¹³C satellite (QSCS)²² analysis of cryomicroprobe-measured ¹H NMR spectra. HPLC was carried out using either a Gilson Model 302 pump equipped with tandem detectors – UV-visible (ISCO Model UA-5, λ 254 nm) and refractive index (Waters R401) – or a Rainin HPXL dual-pump with split flow (7:1) between two detectors – a Jasco CD-2095 UV-CD and an ESA Model 301 evaporative light scattering detector (ELSD).

Animal Material—The sponge *Neopetrosia proxima*² was collected in June 2008 at Stirrup Cay, the Bahamas (25° 49.511N 77° 53.924' W) at a depth of 8.5 m and identified by Sven Zea (Universidad Nacional de Colombia, InveMar). The surface of the tissue was dark

brown and free of epiphytic zoanthids. A voucher sample of the sponge (08-13-073) is stored at UC San Diego.

Extraction and Isolation—A sample of *N. proxima* (252.6 g wet wt.) was extracted with MeOH (3 × 2.5 L, 25 °C, overnight) then CH₂Cl₂/MeOH (2 × 2.5 L, 25 °C, overnight). The resulting extract was partitioned between hexanes (3 × 500 mL) and 9:1 MeOH/H₂O (1 L). The aqueous MeOH layer was removed and the H₂O content adjusted to 1:1 MeOH/H₂O before extraction with CH₂Cl₂ (3 × 1 L). The aqueous MeOH layer was concentrated under reduced pressure and then applied directly onto a reversed-phase (C₁₈) silica column (~400 g) successively eluting with 1:9, 3:7, 1:1, 9:1 CH₃CN/H₂O + 0.2% TFA, and *i*-PrOH + 0.2% TFA to give five fractions. A portion (305 mg) of the third fraction (1.22 g) was subjected to preparative HPLC (reversed-phase, C₁₈, 10 mL·min⁻¹, gradient elution with 3:7 to 2:5 CH₃CN/H₂O + 0.3% TFA over 40 min.) to give 12 fractions. The third preparative HPLC fraction (27.2 mg) was subjected to semi-preparative HPLC (reversed-phase Synergi-HydroRP, 2.5 mL·min⁻¹, mobile phase: 2:2:6:0.05 CH₃CN/*i*-PrOH/H₂O/TFA) to give xestoproxamine A (**1**, 14.0 mg). A portion (4 mg) of the fourth preparative HPLC fraction (24.0 mg) was subjected to semi-preparative HPLC over the same column (2.5 mL·min⁻¹, 22.5:22.5:55:0.5 CH₃CN/*i*-PrOH/H₂O/TFA) to give xestoproxamine B (**2**, 2.9 mg). The entire sixth HPLC fraction was subjected to HPLC (Phenomenex Lux-cellulose, 1.5 mL·min⁻¹, mobile phase: 9:1:0.02 CH₃CN/*i*-PrOH/Et₂NH) to give xestoproxamine C (**3**, 1.5 mg).

Xestoproxamine A (1)—Colorless glass; [α]_D²⁴ +4.4 (*c* 2.0, MeOH); FTIR (ATR): ν 1676, 1437, 1203, 1133, 841, 801, 723 cm⁻¹; ¹H and ¹³C NMR, see Table 1. HRESIMS *m/z* 441.4207 [M+H]⁺ (calcd for C₃₀H₅₃N₂, 441.4203)

Xestoproxamine B (2)—Colorless glass; [α]_D²⁴ +2.7 (*c* 2.4, MeOH); FTIR (ATR): ν 2934, 2862, 1674, 1463, 1199, 1131, 833, 799, 721 cm⁻¹; ¹H and ¹³C NMR, see Table 2; HRESIMS *m/z* 443.4362 [M+H]⁺ (calcd for C₃₀H₅₅N₂, 443.4358)

Xestoproxamine C (3)—Colorless solid; [α]_D²⁴ -18.5 (*c* 0.67, CHCl₃); FTIR (ATR): ν 2933, 2862, 1673, 1470, 1199, 1128, 829, 797, 721 cm⁻¹; ¹H and ¹³C NMR, see Table 3; HRESIMS *m/z* 457.4513 [M+H]⁺ (calcd for C₃₁H₅₇N₂, 457.4516)

Tetrahydroxestoproxamine A Free Base (10)—A solution of xestoproxamine A (**1**) TFA salt (1.0 mg) and Pd/C (10%, 0.2 mg) in MeOH + 2% AcOH (0.5 mL) was vigorously stirred under 1 atmosphere of H₂ overnight. The mixture was passed through a membrane filter (0.45 μ). The solvent was removed from the filtrate under reduced pressure, and the residue subjected to HPLC (Phenomenex Lux-cellulose, 1.5 mL·min⁻¹, mobile phase: 9:1:0.02 CH₃CN/*i*-PrOH/Et₂NH) to give tetrahydroxestoproxamine A free base (**10**, 0.55 mg) which was used immediately after characterization. Colorless solid; [α]_D²³ -12.1 (*c* 0.7, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 2.90 (dt, 1H, *J* = 12.0, 5.5 Hz), 2.80 (dd, 1H, *J* = 12.5, 4.0 Hz), 2.73 (brd, 1H, *J* = 10.0 Hz), 2.70-2.61 (m, 5H), 2.54 (brp, 1H, *J* = 5.5 Hz), 2.41 (brt, 1H, *J* = 9.8 Hz), 2.24 (t, 1H, 11 Hz), 2.04 (d, 1H, *J* = 12.5 Hz), 1.87 (t, 1H, *J* = 11 Hz), 1.82 (m, 1H), 1.64-1.21 (m, 40H), 0.97 (m, 1H), 0.72 (q, 1H, *J* = 12 Hz); HRESIMS *m/z* 445.4518 [M+H]⁺ (calcd for C₃₀H₅₇N₂, 445.4516)

Tetrahydroxestoproxamine A bis-Methiodide Salt (11)—Free base **10** (0.55 mg) was dissolved in CH₂Cl₂ (0.8 mL), excess CH₃I (0.2 mL) was added, and the mixture stirred overnight in the dark. Volatiles were removed under a stream of N₂ to give the *bis*-methiodide salt (**11**, 0.9 mg) as an off-white solid. ¹H NMR (500 MHz, CD₃OD) δ 3.84 (d, *J* = 10.5 Hz, 1H), 3.54-3.49 (m, 3H), 3.41-3.15 (m, 8H) 3.17 (s, 3H), 3.12 (s, 3H), 2.20 - 1.22

(m, 44H), 1.19 (q, $J = 12.5$ Hz, 1H); ^{13}C (125 MHz, CD_3OD) δ 69.4 (CH_2), 66.5 (CH_2), 64.6 (CH_2), 63.6 (CH_2), 60.4 (CH_2), 57.9 (CH_2), 53.3 (CH_3), 47.6 (CH_3), 37.0 (CH), 35.2 (CH), 32.2 (CH), 32.1 (CH_2), 31.8 (CH_2), 31.7 (CH), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 28.6 ($2 \times \text{CH}_2$), 28.3 (CH_2), 28.2 (CH_2), 28.1 (CH_2), 27.4 (CH_2), 27.3 (CH_2), 26.8 (CH_2), 26.6 (CH_2), 25.7 (CH_2), 25.3 (CH_2), 22.3 (CH_2), 20.7 (CH_2), 20.2 (CH_2); HRESIMS m/z 237.2453 $[\text{M}]^{2+}$ (calcd for $\text{C}_{32}\text{H}_{62}\text{N}_2$, 474.4908)

Hofmann degradation of Tetrahydroxestoproxamine A *bis*-Methiodide salt—A

solution of the *bis*-methiodide (**11**, 0.9 mg) was eluted with MeOH through a short column of strong anion exchange resin (Amberlite IRA-400, HO^- form, prepared immediately before from Cl^- form by, elution with aqueous 1N NaOH, followed by washing with distilled H_2O until the eluate was neutral, then MeOH). The eluate was concentrated under reduced pressure to remove the volatiles, and solvent-free methohydroxide was irradiated (microwave, 300 W, 140 $^\circ\text{C}$, 10 min). The crude product was taken up in MeOH and passed through a reversed-phase silica (C_{18}) cartridge (200 mg) by elution with MeOH + 0.1 % TFA. The solvent was removed under a stream of N_2 , and the residue subjected to HPLC (reversed-phase, C_{18} Phenomenex Luna, 5 μ , 10 $\times$ 250 mm, gradient: 40–100% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ + 0.1 % TFA over 40 min) to give a single major elimination product **12** (0.45 mg).

12: ^1H NMR (600 MHz, CD_3OD , representative signals) δ 5.80 (dddd, $J = 17.0, 10.3, 6.8, 6.8$ Hz, 1H), 5.55 (dt, $J = 17.0, 10.3$ Hz, 1H), 5.31 (dd, $J = 10.3, 1.4$ Hz, 1H), 5.18 (dd, $J = 17.0, 1.4$ Hz), 4.98 (dq, $J = 17.0, 1.9$ Hz, 1H), 4.92 (1H, under solvent), 3.44 (brd, $J = 12.5$ Hz, 1H), 3.40 (brd, $J = 12.5$ Hz, 1H), 3.20 (td, $J = 12.5, 4.7$ Hz, 1H), 3.10 (td, $J = 12.5, 5.2$ Hz, 1H), 2.92 (s, 3H), 2.85 (s, 3H), 2.54 (t, $J = 12$ Hz, 1H), 2.53 (t, $J = 12$ Hz, 1H), 2.18 (t, $J = 10.4$ Hz, 1H), 2.05 (q, 7.3 Hz, 2H), 0.88 (q, $J = 12$ Hz, 1H); HRESIMS m/z 473.4828 $[\text{M} + \text{H}]^+$ (calcd for $\text{C}_{32}\text{H}_{61}\text{N}_2$, 473.4829)

Cross Metathesis of 12 with 2-Methoxy-6-vinylnaphthalene (13)—To a solution of alkene **12** (450 μg , 0.642 μmol) and 6-methoxy-2-vinylnaphthalene (**13**, 1.2 mg, 6.42 μmol) in CH_2Cl_2 (0.5 mL) was added Grubbs' 2nd generation catalyst9 (226 μg , 0.265 μmol) in CH_2Cl_2 (1 mL) in three portions over a period of 11 h at 80 $^\circ\text{C}$. The solvent was evaporated under a stream of N_2 . The crude reaction mixture was passed through a reversed-phase C_{18} cartridge by elution with MeOH + 0.1% TFA, then subjected to HPLC (Luna, C_{18} , 250 $\times$ 10 mm, 40–100% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ + 0.1 % TFA over 40 min) to give the 6-methoxy-2-naphthyl-ethenyl derivative **14** (240 μg). UV (CH_3CN) λ_{max} 246, 292 nm; CD: See Table 4; ^1H NMR (600 MHz, CD_3OD , representative signals) δ 7.685 (d, $J = 9.0$ Hz, 1H), 7.681 (d, $J = 8.6$ Hz, 1H), 7.60 (brs, 1H), 7.55 (dd, $J = 8.6, 2.0$ Hz, 1H), 7.18 (d, $J = 2.0$ Hz, 1H), 7.09 (dd, $J = 9.0, 2.0$ Hz, 1H), 6.51 (d, $J = 16.0$ Hz, 1H), 6.32 (dt, $J = 16.0, 7.0$ Hz, 1H), 5.55 (dt, $J = 17.0, 10.3$ Hz, 1H), 5.31 (dd, $J = 10.3, 1.4$ Hz, 1H), 5.18 (dd, $J = 17.0, 1.4$ Hz), 3.90 (s, 3H), 2.91 (s, 3H), 2.83 (s, 3H), 2.50 (t, $J = 12$ Hz, 1H), 2.49 (t, $J = 12$ Hz, 1H), 2.26 (q, $J = 7.0$ Hz, 2H), 0.86 (q, $J = 12$ Hz, 1H); HRESIMS m/z 629.5403 $[\text{M}]^+$ (calcd for $\text{C}_{43}\text{H}_{69}\text{N}_2\text{O}$, 629.5404)

Degradation of Xestoproxamine C

Dihydroxestoproxamine C TFA salt (22)—A solution of xestoproxamine C (**3**) (0.8 mg) and Pd/C (10%, 0.2 mg) in MeOH + 2% AcOH (0.5 mL) was vigorously stirred overnight under H_2 (1 atm). The solution was passed through a membrane filter (0.45 μm) and the volatiles removed under a stream of N_2 . The residue was purified by HPLC (reversed-phase, Phenomenex, Synergi-HydroRP, 4 μ , 10 $\times$ 250 mm; 3 $\text{mL} \cdot \text{min}^{-1}$; mobile phase: 25:25:50:0.5 $\text{CH}_3\text{CN}/i\text{-PrOH}/\text{H}_2\text{O}/\text{TFA}$) to give dihydroxestoproxamine C (**22**). Colorless glass; ^1H NMR (500 MHz, CD_3OD , representative signals) δ 3.68 (brd, $J = 11.2$ Hz, 1H), 3.48 (td, $J = 13.0, 4.0$ Hz, 1H), 2.91 (t, $J = 12.0$ Hz, 1H), 2.84 (t, $J = 12.0$ Hz, 1H),

2.33 (brd, $J = 12.0$ Hz, 1H), 0.95 (d, $J = 7.0$ Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 58.0 (CH_2), 57.5 (CH_2), 56.6 (CH_2), 54.9 (CH_2), 53.1 (CH_2), 43.3 (CH), 40.3 (CH), 37.1 (CH), 35.74 (CH_2), 35.67 (CH_2), 33.7 (CH_2), 33.6 (CH_2), 33.3 (CH), 32.9 (CH_2), 31.5 (CH), 28.8 (CH_2), 25.56 (CH_2), 28.53 (CH_2), 27.8 (3 x CH_2), 27.7 (CH_2), 26.8 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 25.6 (CH_2), 21.9 (CH_2), 21.0 (CH_3); HRESIMS m/z 460.4748 $[\text{M}+\text{H}]^+$ (calcd for $\text{C}_{31}\text{H}_{60}\text{N}_2$, 460.4751)

Tetrahydroxestoproxamine C bis-Methiodide Salt (23)—The TFA salt **22** was subjected to HPLC (chiral column, Lux-cellulose, $1.5\text{ mL}\cdot\text{min}^{-1}$, mobile phase: 9:1:0.02 $\text{CH}_3\text{CN}/i\text{-PrOH}/\text{DEA}$) to give the free base (0.5 mg). Immediately after removal of the volatiles, the free base (0.5 mg) was dissolved in CH_2Cl_2 (0.8 mL), treated with excess CH_3I (0.2 mL), and the mixture stirred overnight in the dark. The solvent was evaporated under a stream of N_2 to give the methiodide (**23**, 0.8 mg) as an off-white solid. ^1H NMR (500 MHz, CD_3OD , representative signals) δ 3.87 (brd, $J = 11.4$ Hz, 1H), 3.77 (td, $J = 13.8, 3.0$ Hz, 1H), 3.21 (s, 3H), 3.12 (s, 3H), 3.04 (t, $J = 12.0$ Hz, 1H), 1.03 (d, $J = 7.0$ Hz, 3H); ^{13}C (125 MHz, CD_3OD) δ 69.5 (CH_2), 69.0 (CH_2), 67.4 (CH_2), 65.3 (CH_2), 61.7 (CH_2), 57.2 (CH_2) [obscured by solvent] (CH_3), 45.9 (CH_3), 39.3 (CH), 36.4 (CH_2), 36.2 (CH), 35.2 (CH_2), 34.0 (CH_2), 33.3 (CH), 33.1 (CH), 32.6 (CH_2), 31.2 (CH), 30.2 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.7 (CH_2), 28.4 (CH_2), 28.2 (CH_2), 27.94 (CH_2), 27.86 (2 x CH_2), 27.5 (CH_2), 26.9 (CH_2), 26.1 (CH_2), 25.3 (CH_2), 25.2 (CH_2), 22.1 (CH_3), 22.0 (CH_2); HRESIMS m/z 244.2531 $[\text{M}]^{2+}$ (calcd for $\text{C}_{33}\text{H}_{64}\text{N}_2$, 488.5064).

Hofmann Degradation of Tetrahydroxestoproxamine C bis-Methiodide Salt (23)—A solution of the methiodide **23** in MeOH was passed through a short column of strong anion exchange resin (Amberlite IRA-400 (Cl^-), converted to the HO^- form with 1N NaOH). After removal of solvent under reduced pressure, the methohydroxide was transferred to a 10 mL microwave vessel, dried, and irradiated (μ wave, 300W, 140°C over 7.5 min, then an additional 4.5 min). The crude product obtained was taken up in MeOH passed through a reversed-phase silica cartridge (C_{18} , 200 mg) eluting with MeOH + 0.1 % TFA. Solvent was removed under a stream of N_2 , and the residue purified by HPLC (reversed-phase, C_{18} Phenomenex Luna, $5\text{ }\mu\text{m}$, $10 \times 250\text{ mm}$, gradient: 40–100% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ + 0.1 % TFA over 40 min) to give the double-elimination product **24** (~140 μg).

24: ^1H NMR (600 MHz, CD_3OD , representative signals) δ 5.67 (ddd, $J = 17.2, 10.2, 7.8$ Hz, 1H), 5.62 (dt, $J = 17.2, 10.0$ Hz, 1H), 5.35 (d, $J = 10.0$ Hz, 1H), 5.29 (d, $J = 17.2$ Hz, 1H), 4.94 (brd, $J = 17.2$ Hz, 1H), 2.93 (s, 3H), 2.86 (s, 3H), 2.58 (t, $J = 12.2$ Hz, 1H), 2.50 (t, $J = 12.2$ Hz, 1H), 0.98 (d, $J = 7$ Hz, 3H); HRESIMS m/z 487.4983 $[\text{M}+\text{H}]^+$ (calcd for $\text{C}_{33}\text{H}_{63}\text{N}_2$, 487.4886).

Cross Metathesis of 24 with 2-Methoxy-6-vinylnaphthalene (13)—Grubbs' 2nd generation catalyst (95 μg , 0.112 μmol) in CH_2Cl_2 (0.8 mL) was added in three portions over a period of 11 h to alkene **24** (140 μg , 0.199 μmol) and 2-methoxy-6-vinylnaphthalene (**13**, 0.8 mg, 4.20 μmol) and the mixture stirred vigorously in a sealed vial at 80°C . The solvent was removed under a stream of N_2 and the residue passed through a reversed-phase silica cartridge (C_{18} , 200 mg) eluting with MeOH + 0.1% TFA, and finally purified by HPLC (reversed-phase, C_{18} Phenomenex Luna, $5\text{ }\mu\text{m}$, $10 \times 250\text{ mm}$, gradient: 40–100% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ + 0.1 % TFA over 40 min) to give the 6-methoxy-2-naphthyl-ethenyl derivative **21** (6 μg). UV (CH_3CN) λ 246, 292 nm; CD (CH_3CN) λ 256 ($\delta\epsilon$ +3.9); ^1H NMR (600 MHz, CD_3OD , representative signals) δ 7.69 (d, $J = 8.6$ Hz, 2H), 7.62 (brs, 1H), 7.55 (dd, $J = 8.6, 2.0$ Hz, 1H), 7.19 (brs, $J = 2.0$ Hz, 1H), 7.10 (dd, $J = 9.0, 2.0$ Hz, 1H), 6.48 (d, $J = 16.2$ Hz, 1H), 6.16 (dd, $J = 16.2, 8.0$ Hz, 1H), 5.58 (dt, $J = 17.2, 10.0$ Hz, 1H), 5.32 (d, $J =$

10.0 Hz, 1H), 5.27 (d, $J = 17.2$ Hz, 1H), 3.90 (s, 3H), 2.89 (s, 3H), 2.81 (s, 3H), 1.12 (d, $J = 7$ Hz, 3H); HRESIMS m/z 643.5563 $[M]^+$, calcd 643.5561 for $C_{44}H_{71}N_2O$.

Preparation of *p*-bromophenacyl derivatives

***bis-p*-Bromophenacyl Tetrahydroxestoproxamine A (25)**—The acetate salt of tetrahydroxestoproxamine A (0.6 mg, 1.06 μ mol) was converted to the free base **10** by addition of KOH (238 μ g, 4.25 μ mol) in MeOH (0.5 mL). After a few minutes the solvent was evaporated under a stream of N_2 then on high vacuum. Toluene (0.5 mL) and *p*-bromophenacyl bromide (5.9 mg, 21.2 μ mol) were added and the mixture was stirred at 90 °C for 12 h. The solvent was evaporated under a stream of N_2 , and the mixture was subjected to HPLC (reversed-phase Phenomenex, Luna, C_{18} , 10 $\times$ 250 mm; 2 mL.min⁻¹ 40–100 % CH_3CN/H_2O + 0.1% TFA over 40 min) to give the *bis-p*-bromophenacyl TFA salt **25** (0.7 mg). UV (MeOH) λ_{max} 265 (log ϵ 4.38) nm; CD (MeOH) λ 254 ($\delta\epsilon$ +2.6), 276 ($\delta\epsilon$ -6.0) nm; ¹H NMR (500 MHz, CD_3OD , representative signals) δ 7.99 (d, $J = 8.8$ Hz, 2H), 7.94 (d, $J = 8.8$ Hz, 2H), 7.78 (d, $J = 8.8$ Hz, 2H), 7.77 (d, $J = 8.8$ Hz, 2H), 5.32 (d, $J = 18.2$ Hz, 1H), 5.17 (d, $J = 18.2$ Hz, 1H), 5.17 (d, $J = 18.2$ Hz, 1H), 5.14 (s, 2H), 4.18 (brd, $J = 11.3$ Hz, 1H), 4.11 (brd, $J = 12.7$ Hz, 1H); 3.99 (m, 1H), 3.98 (m, 1H), 3.81 (m, 2H), 3.77 (m, 1H), 3.58 (td, $J = 13.1, 3.3$ Hz, 1H), 3.56 (m, 1H), 3.54 (t, $J = 12.8$ Hz, 1H), 3.31 (under solvent), 3.24 (t, $J = 12.8$ Hz, 1H), 1.21 (q, $J = 12.6$ Hz, 1H); HRESIMS m/z 838.3632 $[M]^{2+}$ (calcd for $C_{46}H_{68}Br_2N_2O_2$, 838.3636).

***bis-p*-Bromophenacyl Perhaliclonacyclamine (27)**—(–)-perhaliclonacyclamine (**26**, 150 μ g, 0.317 μ mol) was stirred with KOH (71 μ g, 1.27 μ mol) in MeOH (0.5 mL). After a few minutes the solvent was evaporated under a stream of N_2 then on high vacuum. Toluene (0.5 mL) and *p*-bromophenacylbromide (1.8 mg, 6.34 μ mol) were added and the mixture was stirred at 90 °C for 12 h. The solvent was evaporated under a stream of N_2 , and the mixture was subjected to HPLC (reversed-phase Phenomenex, Luna, C_{18} , 10 $\times$ 250 mm; 2 mL.min⁻¹; mobile phase/gradient: 40–100 % CH_3CN/H_2O + 0.1% TFA over 40 min) to give the *bis-p*-bromophenacyl TFA salt **27** (ca 44 μ g). UV (MeOH) λ 265 nm; CD (MeOH) λ 254 ($\delta\epsilon$ +3.2), 272 ($\delta\epsilon$ -6.1) nm; HRESIMS m/z 866.3946 $[M]^{2+}$ (calcd for $C_{48}H_{72}Br_2N_2O_2$, 866.3950).

***bis-p*-Bromophenacyl Perhydrohaliclonacyclamine E (29)**—A solution of (+)-haliclonacyclamine E⁷ (**9**, TFA salt, 0.8 mg, 1.15 μ mol) in MeOH/AcOH (49:1, 0.25 mL) was stirred with Pd/C (10%, 0.1 mg) at room temperature under H_2 (1 atm) for 48 h. The mixture was filtered through a nylon syringe filter (0.45 μ m) and the solvent removed from the filtrate under a stream of N_2 . The residue was subjected to HPLC (Phenomenex, Synergi Hydro-RP, 4 μ , 10 $\times$ 250 mm; 2.5 mL.min⁻¹, 25:25:50:0.5 CH_3CN/i -PrOH/ H_2O /TFA) to give perhydrohaliclonacyclamine E TFA salt (**28**, 0.3 mg). The TFA salt was subjected to HPLC (Phenomenex Lux-cellulose, 1.5 mL.min⁻¹, 9:1:0.02 CH_3CN/i -PrOH/ Et_2NH) and the solvent removed under a stream of N_2 and further dried under high vacuum. Toluene (0.5 mL) and *p*-bromophenacylbromide (1.2 mg, 4.28 μ mol) were added and the mixture was stirred at 90 °C for 12 h. The solvent was removed under a stream of N_2 , and the mixture was subjected to HPLC (reversed-phase, Phenomenex, Luna, C_{18} , 10 $\times$ 250 mm; 2 mL.min⁻¹, 40–100 % CH_3CN/H_2O + 0.1% TFA over 40 min) to give the *bis-p*-bromophenacyl TFA salt **29** (ca 7.0 μ g). UV (MeOH) λ 265 nm (log ϵ 4.38); CD (MeOH) λ 254 ($\delta\epsilon$ +2.6), 272 ($\delta\epsilon$ -6.0); HRESIMS m/z 866.3940 $[M]^{2+}$ (calcd for $C_{48}H_{72}Br_2N_2O_2$, 866.3950).

***bis-p*-bromophenacyl dihydroxestoproxamine C (30)**—Xestoproxamine C free base (**22**, 0.4 mg, 0.876 μ mol) was stirred with Pd/C (10%, 0.1 mg) in 0.25 mL MeOH/AcOH (49:1) at room temperature under H_2 (1 atm) for 48 h. The mixture was filtered through a membrane filter (0.45 μ m) and the solvent was evaporated under a stream of N_2 then by high

vacuum. The dihydroxestoproxamine C acetate salt was subjected to HPLC (Phenomenex Lux-cellulose, 1.5 mL.min⁻¹, mobile phase: 9:1:0.02 CH₃CN/*i*-PrOH/Et₂NH) and the solvent concentrated under a stream of N₂ then dried under reduced pressure. Dihydroxestoproxamine C free base was stirred with *p*-bromophenacylbromide (3.0 mg, 10.8 mmol) in toluene at 80 °C for 2 h in a microwave reactor (300W). The solvent was removed under a stream of N₂ and the mixture subjected to RPHPLC (column: Phenomenex, Luna, C18(2), 10 × 250 mm; 2 mL.min⁻¹; 40–100 % CH₃CN/H₂O + 0.1% TFA over 40 min) to give the *bis-p*-bromophenacyl TFA salt derivative **30** (137 μg). UV (MeOH) λ_{max} 265 nm; CD (MeOH) λ 254 (δ_E +3.5), 276 (δ_E -7.1) nm; HRESIMS *m/z* 852.3792 [M]²⁺ (calcd for C₄₇H₇₀Br₂N₂O₂, 852.3799).

Synthesis of Model Compound 20

Amide (15)—*n*-BuLi (2.21 M in hexanes, 3.0 mL, 6.64 mmol) was added to a stirred solution of anhydrous lithium chloride (0.84 g, 19.8 mmol) and diisopropylamine (0.94 mL, 6.64 mmol) in THF (20 mL) at -78 °C. The mixture was kept at -78 °C for 20 min, then placed in an ice bath for 30 min, then cooled back to -78 °C. Amide **16** (0.70 g, 3.16 mmol, prepared by acylation of pseudoephedrine with propionyl chloride) was added over 10 min, and the solution slowly warmed to room temperature over 1.5 h, and stirred an additional 15 min, then cooled to -40 °C. The 1-*O*-TBS-9-iododecane **17** (1.75 g, 4.39 mmol) was added dropwise and the mixture allowed to warm to room temperature overnight with stirring. The mixture was poured into saturated NH₄Cl solution (75 mL), and the organic layer separated. The aqueous layer was extracted with EtOAc (4 × 50 mL) and the combined organic layers were dried (MgSO₄), the solvent removed under reduced pressure and the crude product purified by flash chromatography (SiO₂, 1:3 EtOAc/hexanes) to give the amide **15** (1.20 g, 77% yield) [α]_D²² -36.7 (*c* 3.1, CHCl₃); FTIR (ATR): ν 3376, 2926, 2854, 1620, 1464, 1408, 1254, 1099, 1052, 835, 775, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.38-7.23 (m, 5H), 4.61 (t, *J* = 7.2 Hz, 1H, major), 4.59 (m, 1H, minor), 4.39 (brs, 1H, major), 4.08 (p, *J* = 8.0 Hz, 1H, minor), 3.59 (t, *J* = 6.4 Hz, 2H, major), 3.58 (t, *J* = 6.4 Hz, 2H, minor), 2.91 (s, 3H, minor), 2.84 (s, 3H, major), 2.78 (t, *J* = 6.4 Hz, 1H, minor), 2.58 (sex, *J* = 7.2 Hz, 1H, major), 2.29 (brs, 1H, minor), 1.71 (brs, 1H, major), 1.60-1.46 (m), 1.31-1.19 (m), 1.14 (d, *J* = 6.8 Hz, 3H, major), 1.08 (d, *J* = 6.8 Hz, 3H, major), 1.02 (d, *J* = 6.8 Hz, 3H, minor), 0.89 (s, 9H), 0.04 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 179.3 (C), 142.6 (C), 128.3 (CH), 127.5 (CH), 126.3 (CH), 76.5 (CH), 63.3 (CH₂), 36.6 (CH), 34.0 (CH₂), 32.9 (CH₂), 29.9-29.4 (5 × CH₂), 27.4 (CH₂), 26.0 (3 × CH₃), 25.8 (CH₂), 18.4 (C), 17.3 (CH₃), 14.5 (CH₃), -5.3 (2 × CH₃); HRESIMS *m/z* 514.3685 [M+Na]⁺ (calcd for C₂₉H₅₃NO₃SiNa, 514.3687).

Alcohol (18)—BH₃•THF complex (1 M in THF, 3.0 mL, 3 mmol) was added to pyrrolidine (246 mL, 3 mmol) at 0 °C, and the solution was warmed to room temperature and stirred for 45 min. The solution was cooled back to 0 °C and treated, dropwise, with *n*-BuLi (2.21 M in hexanes, 1.36 mL, 3 mmol) with stirring for an additional 30 min. The amide **15** (500 mg, 1 mmol) in THF (10 mL) was added and stirred at room temperature overnight. 3M HCl (5 mL) was added to quench the excess hydride and the layers were separated. Ether (5 mL) was added to the aqueous layer, and the mixture cooled to 0 °C before being made basic (pH 9–10) by addition of 2 N NaOH. The aqueous mixture was extracted with ether (3 × 5 mL) and the combined organic extracts washed with 1:1 brine/1 N NaOH (2 × 10 mL), dried (Na₂SO₄), the solvent evaporated, and subjected to flash chromatography (SiO₂, 12.5% EtOAc/hexanes) to give the alcohol **18** (135 mg, 41% yield) [α]_D²³ -5.5 (*c* 2.1, CHCl₃); FTIR (ATR): ν 3340, 2926, 2855, 1464, 1254, 1102, 1041, 835, 775 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.59 (t, *J* = 6.4 Hz, 2H), 3.50 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.41 (dd, *J* = 10.0, 6.8 Hz, 1H), 1.59 (m, 1H), 1.50 (p, *J* = 6.8 Hz, 2H), 1.41-1.26 (m, 15H), 1.09 (m, 1H) 0.91 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ¹³C NMR (100

MHz, CDCl₃): δ 68.4 (CH₂), 63.3 (CH₂), 35.7 (CH), 33.2 (CH₂), 32.9 (CH₂), 29.9–29.4 (5 $\times$ CH₂), 27.0 (CH₂), 26.0 (3 $\times$ CH₃), 25.8 (CH₂), 18.4 (C), 16.6 (CH₃), –5.3 (2 $\times$ CH₃); HRESIMS m/z 353.2849 [M+Na]⁺ (calcd for C₁₉H₄₂O₂SiNa, 353.2846)

Aldehyde (19a)—DMSO (64 mL, 0.91 mmol) was added dropwise to a stirred solution of oxalyl chloride (51 mL, 0.60 mmol) in CH₂Cl₂ (3 mL) at –78 °C, and stirred for 10 min. A solution of the alcohol **18** (100 mg, 0.302 mmol) in CH₂Cl₂ was added, and the mixture stirred for 30 min at –50 °C. Et₃N (168 mL, 1.21 mmol) was added and the mixture brought to –30 °C followed by stirring an additional 30 min. Saturated NH₄Cl solution (5 mL) was added, and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 $\times$ 3 mL) and the combined organic extracts were dried (MgSO₄), concentrated and the residue purified by flash chromatography (SiO₂, 3% EtOAc/hexanes) to give the aldehyde **19a** (91 mg, 92% yield) [α]_D²⁴ +12.8 (*c* 3.4, CHCl₃); FTIR (ATR): ν 2926, 2854, 1730, 1463, 1254, 1099, 835, 774 cm^{–1}; ¹H NMR (400 MHz, CDCl₃): δ 9.61 (d, *J* = 2.4 Hz, 1H), 3.59 (t, *J* = 6.4 Hz, 2H), 2.32 (sd, *J* = 7.2, 1.6 Hz, 1H), 1.69 (m, 1H), 1.50 (p, *J* = 7.2 Hz, 2H) 1.25 (m, 15H), 1.08 (d, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 205.5 (CH), 63.3 (CH₂), 46.3 (CH), 32.9 (CH₂), 30.5 (CH₂), 29.6–29.4 (5 $\times$ CH₂), 26.9 (CH₂), 26.0 (3 $\times$ CH₃), 25.8 (CH₂), 18.4 (C), 13.3 (CH₃), –5.3 (2 $\times$ CH₃); HRESIMS m/z 351.2691 [M+Na]⁺ (calcd for C₁₉H₄₀O₂SiNa, 351.2690)

Olefin (19)—*n*-BuLi (1.2 M in hexanes, 143 μ L, 0.171 mmol) was added to a slurry of MePPh₃Br (65 mg, 0.183 mmol) in THF (0.5 mL) at 0 °C, then the mixture stirred at room temperature for 5 min. The aldehyde **19a** (40 mg, 0.122 mmol) in THF (0.5 mL) was added and stirring continued for 2 h at room temperature. Saturated NH₄Cl solution (1 mL) was added followed by ether (2 mL) and the layers were separated. The aqueous layer extracted with ether (2 $\times$ 2 mL) and the combined organic extracts dried (MgSO₄), concentrated, and the residue purified by flash chromatography (SiO₂, hexanes) to give the chiral olefin **19** (35 mg, 88% yield) [α]_D²³ +6.5 (*c* 2.8, CHCl₃) FTIR (ATR): ν 2925, 2854, 1463, 1254, 1099, 994, 909, 834, 773 cm^{–1}; ¹H NMR (400 MHz, CDCl₃): δ 5.69 (ddd, *J* = 17.2, 10.0, 7.2 Hz, 1H), 4.94 (ddd, *J* = 17.2, 2.0, 1.2 Hz, 1H), 4.89 (ddd, *J* = 10.0, 2.4, 1.2 Hz, 1H), 3.51 (t, *J* = 6.8 Hz, 2H), 2.10 (m, 1H), 1.50 (p, *J* = 7.2 Hz, 1H), 1.25 (m, 16H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 145.1 (CH), 112.2 (CH₂), 63.3 (CH₂), 37.8 (CH), 36.7 (CH₂), 32.9 (CH₂), 29.8–29.4 (5 $\times$ CH₂), 27.2 (CH₂), 26.0 (3 $\times$ CH₃), 25.8 (CH₂), 20.2 (CH₃), 18.4 (C), –5.3 (2 $\times$ CH₃); HRESIMS m/z 327.3081 [M+H]⁺ (calcd for C₂₀H₄₃O₂SiNa, 327.3078)

Alkene (20)—A mixture of alkene **19** (2 mg, 6.12 μ mol) and 2-methoxy-6-vinylnaphthalene (11.3 mg, 61.2 μ mol) was treated with Grubbs' 2nd generation catalyst (1 mg, 1.22 μ mol) in CH₂Cl₂ (3 mL) at 70 °C in a sealed vial for 12 h. Additional catalyst (1 mg, 1.22 μ mol) was added and the mixture stirred an additional 6 h at 80 °C. The solvent was removed under a stream of N₂, and the mixture passed through a reversed-phase (C₁₈) silica cartridge (CH₃CN then MeOH), followed by HPLC (reversed-phase, C₈, 85% CH₃CN/H₂O) to give alkene **20** (1.3 mg, 42%) [α]_D²² +31.1 (*c* 1.0, CHCl₃); UV (CH₃CN) 246 nm (log ϵ 4.62), 292 (4.20); CD (CH₃CN) λ 255 nm ($\delta\epsilon$ +3.8). FTIR (ATR): ν 2925, 2853, 1256, 1100, 1035, 837, 777 cm^{–1}; ¹H NMR (500 MHz, CDCl₃): δ 7.68 (d, *J* = 9.0 Hz, 1H), 7.66 (d, *J* = 9.0, 1H), 7.62 (brs, 1H), 7.55 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.11 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.10 (brs, 1H), 6.46 (d, *J* = 16 Hz, 1H), 6.16 (dd, *J* = 16.0, 8.5 Hz, 1H), 3.91 (s, 3H), 3.59 (t, *J* = 7.0 Hz, 2H), 2.32 (sep, *J* = 6.5 Hz, 1H), 1.50 (m, 2H), 1.38 (m, 2H), 1.27 (m, 14H), 1.10 (d, *J* = 6.5 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 157.4 (C), 136.6 (CH), 133.7 (C), 133.4 (C), 129.3 (CH), 129.1 (C), 128.0 (CH), 126.9 (CH), 125.1 (CH), 124.2 (CH), 118.8 (CH), 105.8 (CH), 63.3 (CH₂), 55.3 (CH₃), 37.4 (CH), 37.2 (CH₂), 32.9 (CH₂), 29.8–29.4 (5 $\times$ CH₂), 27.4 (CH₂), 26.0 (3 $\times$ CH₃), 25.8 (CH₂), 20.8

(CH₃), 18.4 (C), −5.3 (2 × CH₃); HRESIMS *m/z* 482.3573 [M]⁺ (calcd for C₃₁H₅₀O₂Si, 482.3575)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank S. Zea (INVEMAR, Universidad Nacional de Colombia) for identification of the sponge, J. R. Pawlik (University of North Carolina, Wilmington), and the captain and crew of the *RV Seward Johnson* for logistical support during collecting expeditions, D. Dalisay for assistance with biological assays. The NSF Biological Oceanography Program (OCE-0095724, 0550468 to J.R.P.) is acknowledged for ship time, and NSF (CRIF, CHE0741968) for funds to acquire the 500 MHz NMR spectrometer. This work was supported by grants from NIH (CA122256 and AI039987 to T. F. M.), and a Ruth L. Kirschstein National Research Service Award NIH/NCI (T32 CA009523 to B. I. M).

References and Notes

1. a) Andersen, R.J.; Van Soest, R.W.M.; Kong, F. *Alkaloids: Chemical and Biological Perspectives*. Pelletier, S.W., editor. Vol. 10. Pergamon; New York: 1996. p. 301-355. b) Berlin RGS. *Top Heterocycl Chem*. 2007; 10:211–238.
2. *Neopetrosia proxima* and *Xestoproxima proxima* are synonymous; the former name now replaces the latter. Campos M, Mothes B, Eckert R, Van Soest RWM. *Zootaxa*. 2005; 963:1–22. We retain the names ‘xestoproxamines’, based on the latter genus name, to comply with precedent disclosure. See Ref. 3.
3. Presented in part at the 13th International Symposium on Marine Natural Products; Phuket, Thailand. 17–22 October, 2010;
4. Jaspars M, Pasupathy V, Crews P. *J Org Chem*. 1994; 59:3253–3255.
5. Harrison B, Talapatra S, Lobkovsky E, Clardy J, Crews P. *Tetrahedron Lett*. 1996; 37:9151–9154.
6. a) Charan RD, Garson MJ, Brereton IM, Willis AC, Hooper JNA. *Tetrahedron*. 1996; 52:9111–9120. b) Clark RJ, Field KL, Charan RD, Garson MJ, Brereton IM, Willis AC. *Tetrahedron*. 1998; 54:8811–8826. c) Mudianta IW, Garson MJ, Bernhardt PV. *Aust J Chem*. 2009; 62:667–670.
7. Torres YR, Berlin RGS, Magalhães A, Schefer AB, Ferreira AG, Hajdu E, Muricy G. *J Nat Prod*. 2000; 63:1098–1105. [PubMed: 10978205]
8. 2-Methoxy-6-vinylnaphthalene was synthesized from 2-bromo-6-methoxynaphthalene. Lindh J, Savmarker J, Nilsson P, Sjöberg PJR, Larhed M. *Chem Eur J*. 2009; 15:4630–4636. [PubMed: 19274694]
9. Scholl M, Ding S, Lee CW, Grubbs RH. *Org Lett*. 1999; 1:953–956. [PubMed: 10823227]
10. Myers AG, Yang BH, Chen H, Gleason JL. *J Am Chem Soc*. 1994; 116:9361–9362.
11. Prepared from 1,10-decanediol. Tully SE, Cravatt BF. *J Am Chem Soc*. 2010; 132:3264–3265. [PubMed: 20178358]
12. Fisher GB, Fuller JC, Harrison J, Alvarez SG, Burkhardt ER, Goralski CT, Singaram B. *J Org Chem*. 1994; 59:6378–6385.
13. Ohtani I, Kusumi T, Kashman Y, Kakisawa H. *J Am Chem Soc*. 1991; 113:4092–4096.
14. Zhao N, Kumar N, Neuenschwander K, Nakanishi K, Berova N. *J Am Chem Soc*. 1995; 117:1844–1845.
15. The absolute configuration of (–)-perhaliclonacyclamine was established from X-ray single crystal structure determination of the parent compound, (+)-tetrahydro-haliclonacyclamine A, obtained with Cu-Kα radiation, and interpretation of anomalous scattering (Bijvoet method). Mudianta IW, Katavic PL, Lambert LK, Hayes PY, Banwell MG, Munro MHG, Bernhardt PV, Garson MJ. *Tetrahedron*. 2010; 66:2752–2760.
16. It’s worth recalling that it is not possible, strictly, to assign absolute configuration to chiral compounds by comparison of signs of [α]_D, alone, except for enantiomers, even those as similar as **1–3** and **26**. Two counter example are prescient and sufficient to illustrate this often ignored

tenet in stereochemistry. The paired compounds (–)-perhydrohaliclonacyclamine (**26**) and the parent (+)-tetrahydrohaliclonacyclamine A (**31**), and (–)-haliclonacyclamine A (**6**) ($[\alpha]_D = -3.4$) and (+)-haliclonacyclamine B (**7**) ($[\alpha]_D = +3.4$), differ only in position of a single double bond in the lower linking chain, yet the pairs show opposite signs of specific rotation. Also, the absolute configuration of (–)- **26** ($[\alpha]_D = -20.9$)¹⁵ was shown to be antipodal to that of (–)- **6** despite the same sign of $[\alpha]_D$. Lastly, the signs of $[\alpha]_D$ of alkaloid salts and their parent free bases may also differ.

17. We are grateful to Professor Mary Garson, University of Queensland, for the generous gift of **26**.
18. We are grateful to Professor Roberto Berlinck, University of São Paulo, for the generous gift of **9**.
19. The chair-chair conformations and *N*-configurations adopted by the bis-piperidine ring systems in the pairs **25** and **29**, and **27** and **30** are preserved with respect to their starting materials (see Supporting Information for assignment of conformation of **25** using NOESY data). Although the Br-phenacyl substituents are disposed differently – equatorial/axial on rings A and B of **25** and **29**, and axial/axial for **27** and **30** – examination of molecular models show the C-N bond vectors subtend similar angles ($\theta \sim 90^\circ$) in all four derivatives. This explains why the diastereomeric variants give the same CD spectra because helicity and the consequent exciton coupling is dictated largely by the orthogonality of the piperidine ring planes. It is likely that the *reactive conformers* of each bis-piperidine ring requires an equatorial lone pair and, consequently, a ring flip for the B ring in all four starting materials and an A ring flip in **22** than **26** (see Figure 2). Reaction of **22**, with both lone pairs on N in the axial orientation, was particularly sluggish and required more forcing conditions (microwave reactor, 140 °C) compared to **10**, **26**, and **28** (90 °C), possibly a consequence of torsional constraints imposed on **22** for the A ring flip (two less CH₂ groups in the ‘northern’ linker chain) compared to the more flexible **26**.
20. Wei X, Nieves K, Rodríguez AD. Bioorg Med Chem Lett. 2010; 20:5905–5908. [PubMed: 20727745]
21. Dalisay DS, Rogers EW, Edison A, Molinski TF. J Nat Prod. 2009; 72:732–738. [PubMed: 19254038]
22. Dalisay DS, Molinski TF. J Nat Prod. 2009; 72:739–744. [PubMed: 19399996]

xestoproxamine A, 27Z: (1)
xestoproxamine B : (2)

xestoproxamine C : (3)

halicyclamine A: (4)

halicyclamine B: (5)

(-)-haliclonacyclamine A, 25Z: (6)

(+)-haliclonacyclamine B, 29Z: (7)

arenosclerin A, 13Z,23Z,25Z, R = OH: (8)

haliclonacyclamine E, 13Z,23Z,25Z, R = H: (9)

perhydrohaliclonacyclamine E: (28)

(-)-perhydrohaliclonacyclamine: (26)

13E,15Z,23Z,25Z-(+)-: (31)

(-)-neopetrosiamine: (32)

Figure 1.
Substructures **a–c** of xestoproxamine A (**1**). Points of attachment of linking chains are indicated by •.

Figure 2. Selected NOESY correlations between the piperidine rings of (a) xestoproxamine A (**1**) and (b) xestoproxamine C (**3**). Points of attachment of linking chains are indicated by •. Note, ring 'A' has undergone ring-flip in **3** with respect to **1**.

Figure 3.
CD spectra (CH_3CN , 23°C) of (a) **20**, (b) **21**, (c) **14**.

Figure 4.
CD spectra (MeOH, 23°C) of (a) **25**, (b) **27**, (c) **29**, (d) **30**.

Scheme 1.

Hofmann degradation of xestoproxamine A (**1**) and cross metathesis with 6-MeO-2-vinylnaphthalene (**13**).

Scheme 2.
Synthesis of model compound **20**.

Scheme 3.
Hofmann degradation of xestoproxamine C (**3**) and cross metathesis with 6-MeO-2-vinylnaphthalene (**13**).

Scheme 4. Preparation of *N, N'*-*p*-Br-phenacyl derivatives of *bis*-piperidine alkaloids.

Table 1¹H (600 MHz) and ¹³C NMR (125 MHz) for **1** (CD₃OD)

No.	δ_C , mult. ^a	δ_H , mult (J in Hz, ax/eq)	DQF-COSY	HMBC ^b
1	55.3, CH ₂	3.32, dd (12.0, ax) ^e 3.18, m (eq)	2	2, 3, 11, 30 2, 3, 5, 11, 30
2	29.7, CH	2.29, m (ax)	1, 3, 30	3, 29, 30
3	36.0, CH	1.91, m (ax)	2, 4, 4	4, 5, 8, 9, 10, 30
4	25.2, CH ₂	1.80, m (eq) 1.69, m (ax)	3	3, 5, 9, 2, 3
5	47.4, CH ₂	3.48, brd (13.2, eq) 3.19, m (ax)	4	1, 3, 4, 11 1, 3, 4
6	58.5, CH ₂	3.21, brd (12.0, eq) 2.84, dd (12.0, 12.0, ax)	7	7, 8, 9, 10, 20, 21 7, 8, 9, 10
7	34.3, CH	1.90, m (ax)	6, 8, 20	6, 8, 9, 10, 20
8	27.5, CH ₂	1.84, m (eq) 1.06, ddd (12.0, 12.0, 12.0, ax)	7, 9	3, 6, 7 6, 7, 20
9	42.1, CH	1.74, m (ax)	8, 10	2, 3, 4, 7, 8
10	56.9, CH ₂	3.69, m (eq) 2.84, dd (12.0, 12.0 ax)	9	3, 6, 8, 9, 21 6, 8, 9
11	48.9 ^c , CH ₂	3.32, m 3.02, ddd (12.8, 12.8, 3.7)	12	1, 5, 12, 13 5, 12, 13
12	25.2, CH ₂	1.79, m 1.66, m	11, 13	11, 13, 14 11, 14
13	21.7, CH ₂	1.79, m 1.65, m	12, 14	11, 12, 14, 15 11, 12, 14
14	27.3, CH ₂	1.52, m 1.44, m	13, 15	12, 13, 15, 16 12, 13, 15, 16
15	29.0, CH ₂	1.43, m 1.25, m	14, 16	14, 16, 17 14, 16, 17
16	29.4, CH ₂	2.25, m 2.00, m	15, 17	15, 17, 18 14, 17, 18
17	131.69 ^d , CH	5.49, m	16, 18	15, 16, 18, 19
18	129.1, CH	5.31, m	17, 19	16, 19, 20,
19	23.4, CH ₂	2.50, m 2.12, brd (15.4)	18, 20	7, 17, 18, 20
20	31.5, CH ₂	1.74, m 1.27, m	7	6, 7, 8, 18, 19 6, 7, 8
21	56.4, CH ₂	3.20, m	22	6, 22, 23
22	22.6, CH ₂	1.81, m	21, 23	21, 23, 24, 25
23	28.1, CH ₂	1.62, m	22, 24	21, 22, 24, 25

No.	δ_C , mult. ^a	δ_H , mult (<i>J</i> in Hz, ax/eq)	DQF-COSY	HMBC ^b
		1.42, m		21, 22, 24
24	27.0, CH ₂	1.42, m	23, 25	22, 23, 25, 26
25	29.0, CH ₂	1.53, m	24, 26	23, 24, 26, 27
		1.45, m		23, 24, 26, 27
26	27.1, CH ₂	2.35, m	25, 27	28
		1.91, m		24, 25, 27, 28
27	131.74 ^d , CH	5.37, m	26, 28	25, 26, 28, 29
28	130.1, CH	5.28, m	27, 29	26, 27, 29, 30
29	21.5, CH ₂	2.24, m	28, 30	28, 30
		1.82, m		27, 28, 30
30	31.9, CH ₂	1.72, m	29	1, 3, 28, 29
		1.57, m		1, 3, 28, 29

^a Determined from DEPT and HSQC.

^b HMBC correlations, optimized for 8 Hz, are from proton(s) stated to the indicated carbon.

^c Observed by HSQC.

^d May be interchanged.

^e Coupling constant assigned by 1-D TOCSY (irradiation of H5_{eq}).

Table 2¹H (600 MHz) and ¹³C NMR (125 MHz) for xestoproxamine B (**2**) (CD₃OD)

No.	δ _C , mult. ^a	δ _H , mult (<i>J</i> in Hz, ax/eq)	COSY	HMBC ^b
1	55.7, CH ₂	3.23, dd (12.0, 12.0, ax) 3.16, m (eq)	3	2, 3, 5, 11, 30 2, 3, 5, 11, 30
2	29.9, CH	2.24, m (ax)	1, 3, 30	1, 3, 29, 30
3	36.1, CH	1.87, m (ax)	2, 4	1, 2, 4, 5, 8, 10, 29, 30
4	25.3, CH ₂	1.81, m (eq) 1.68, m (ax)	3, 5	2, 3, 9, 11 2, 3, 9
5	47.5, CH ₂	3.45, brd (13.7, eq) 3.17, m (ax)	4	1, 3, 4 1, 3, 4
6	57.4, CH ₂	3.23, brd (12.0, eq) 2.85, dd (12.0, 12.0, ax)	7	7, 8, 10, 20, 21 7, 8, 10, 21
7	34.5, CH	1.91, m (ax)	6, 8, 20	6, 8, 19, 20
8	27.9, CH ₂	1.87, m (eq) 1.08, ddd (12.0, 12.0, 12.0, ax)	7, 9	3, 6, 7, 9, 10, 20 3, 6, 7, 9, 10, 20
9	42.1, CH	1.78, m (ax)	8, 10	4, 7,
10	56.7, CH ₂	3.53, m (eq) 2.98, dd (12.0, 12.0, ax)	9	6, 8, 9, 21 6, 8, 9
11	49.3, CH ₂	3.30, m 3.02, m	12	1, 5, 12, 13 1, 5, 12, 13
12	21.7, CH ₂	1.77, m 1.65, m	11, 13	11, 13, 14 11, 13
13	25.4, CH ₂	1.68, m 1.60, m	12, 14	11, 12, 14, 15 11, 12, 15
14	27.5, CH ₂	1.44, m	13, 15	12, 13, 15
15	28.9, CH ₂	1.44, m 1.26, m	14, 16	13, 16, 17 13, 16, 17
16	29.5, CH ₂	2.22, m 2.00, m	15, 17	14, 15, 17, 18 14, 15, 17, 18
17	131.7, CH	5.48, m	16, 18	16, 18, 19
18	129.2, CH	5.33, m	17, 19	17, 18, 19
19	23.5, CH ₂	2.45, m 2.15, m	18, 20	17, 20
20	31.7, CH ₂	1.75, m 1.28, m	19, 7	6, 7, 18, 6, 7, 8, 18, 19
21	56.1, CH ₂	3.30, m 3.07, m	22	6, 10, 22, 23 6, 10, 22, 23
22	20.0, CH ₂	1.77, m	21, 23	21, 23
23	26.2, CH ₂	1.50, m	22, 24	22

No.	δ_C , mult. ^a	δ_H , mult (<i>J</i> in Hz, ax/eq)	COSY	HMBC ^b
		1.37, m		21, 22
24–28	29.0–26.4, CH ₂	1.53–1.25, m		
29	21.8, CH ₂	1.25, m	30	
		1.21, m		
30	32.1, CH ₂	1.69, m	2, 29	1, 2, 3
		1.44, m		1, 2, 3

^a Determined from DEPT and HSQC.

^b HMBC correlations, optimized for 8 Hz, are from proton(s) stated to the indicated carbon.

^c Observed by HSQC.

^d May be interchanged.

Table 3¹H (600 MHz) and ¹³C NMR (125 MHz) NMR Data for xestoproxamine C (**3**) (CDCl₃)

No.	δ _C , mult. ^a	δ _H , mult (<i>J</i> in Hz, ax/eq)	DQF-COSY	HMBC ^b
1	53.1, CH ₂	2.93, dd (12.0, 12.0, ax) 2.55, brd (12.0, eq)	2	2, 5
2	40.1, CH	2.03, m (ax)	1, 3, 30	
3	34.0, CH	1.96, m (eq)	2, 4	1, 2, 4, 8, 9, 10
4	34.7, CH ₂	2.12, m (ax) 1.80, m (eq)	3, 5	2
5	46.7, CH ₂	3.14, dd (12.0, 12.0, ax) 2.80, m (eq)	4	
6	60.0, CH ₂	2.76, m (eq) 1.84, dd (12.0, 12.0, ax)	7	
7	37.4, CH	1.60, m (ax)	6, 8, 20	
8	37.9, CH ₂	2.43, m (eq) 1.00, ddd (12.0, 12.0, 12.0, ax)	7, 9	6, 7, 9, 10, 20
9	44.9, CH	1.98, m (ax)	8, 10	8
10	59.9, CH ₂	2.98, brd (9.8, eq) 2.17, m (ax)	9	6, 8
11	56.5, CH ₂	2.91, m	12	1, 5, 12, 13
12	22.0, CH ₂	1.65, m 1.56, m	11, 13	11, 13 11, 13
13	26.8, CH ₂	1.40, m	12	11, 12
14	26.8–27.7	1.50–1.20, m		
15	27.3, CH ₂	1.37, m		
16	26.6, CH ₂	2.03, m 1.96, m	15, 17	15, 17, 18 15, 17, 18
17	129.5, CH	5.44, m	16, 18	16
18	129.5, CH	5.41, m	17, 19	16
19	24.8, CH ₂	2.37, m 1.81, m	18, 20	17, 18, 20 7, 17, 18, 20
20	34.1, CH ₂	1.51, m 0.93, m	7, 19	8, 18, 19 6, 7, 8, 18, 19
21	55.0, CH ₂	2.70, m 2.48, m	22	10 6, 10
22	27.9, CH ₂	1.58, m 1.48, m	21, 23	21, 23, 24 21, 24, 31
23	30.5, CH	1.51, m	22, 24, 31	
24	35.9, CH ₂	1.39, m 1.09, m	23, 25	22, 23, 31

No.	δ_{C} , mult. ^a	δ_{H} , mult (<i>J</i> in Hz, ax/eq)	DQF-COSY	HMBC ^b
25–30	26.8–27.7	1.50–1.20, m		
31	21.2, CH ₃	0.87, d (6.7)	23	22, 23, 24

^a Assigned from HSQC/HMBC.

^b HMBC correlations, optimized for 8 Hz, are from proton(s) stated to the indicated carbon.

Table 4

CD Data (23 °C) for Vinyl-naphthalene and *bis-p*-Bromophenacyl Derivatives.

No.	Solvent	λ_{nm}	$\Delta\epsilon^b$	λ_{nm}	$\Delta\epsilon^b$
14^c	CH ₃ CN			–	<i>a</i>
20^d	CH ₃ CN			255	+3.8
21^e	CH ₃ CN			256	+3.9
25^f	CH ₃ OH	276	–6.2	253	+2.6
27^f	CH ₃ OH	272	–6.9	254	+3.2
29^f	CH ₃ OH	272	–6.0	254	+2.6
30^f	CH ₃ OH	276	–7.1	254	+3.5

^a only noise.

^b mol^{–1} dm³ cm^{–1}.

^c Scheme 1.

^d Scheme 2.

^e Scheme 3.

^f Scheme 4.

Table 5

Specific rotations and Configurational Assignment of *bis*-Piperidine Alkaloids.^a

cnmpd.	[α] _D	conc. g/100 mL, solvent	linker chain C _n		absolute config. ^a	
			top	bottom		
1^b	+4.4	<i>c</i> 2.0,	CH ₃ OH	C ₁₀	C ₁₀	2 <i>R</i> ,3 <i>S</i> ,7 <i>S</i> ,9 <i>S</i>
2^b	+2.7	<i>c</i> 2.4,	CH ₃ OH	C ₁₀	C ₁₀	2 <i>R</i> ,3 <i>S</i> ,7 <i>S</i> ,9 <i>S</i>
3^b	-18.5	<i>c</i> 0.67,	CHCl ₃	C ₁₀	C ₁₀	2 <i>S</i> ,3 <i>S</i> ,7 <i>S</i> ,9 <i>S</i> ,23 <i>S</i>
4^c	-7.3	<i>c</i> , 0.73,	CH ₂ Cl ₂	C ₈	C ₁₂	2 <i>R</i> *,3 <i>S</i> *,9 <i>R</i> * ^{<i>h</i>}
5^d	-143.5	<i>c</i> , 0.65,	?	C ₁₀	C ₈	2 <i>R</i> *,3 <i>S</i> *,7 <i>S</i> * ^{<i>h</i>}
6^e	-3.4	<i>c</i> 1.21,	CH ₂ Cl ₂	C ₁₀	C ₁₂	2 <i>R</i> ,3 <i>R</i> ,7 <i>R</i> ,9 <i>R</i>
7^e	+3.4	<i>c</i> 0.55,	CH ₂ Cl ₂	C ₁₀	C ₁₂	2 <i>R</i> ,3 <i>R</i> ,7 <i>R</i> ,9 <i>R</i>
8^f	-3	<i>c</i> 0.015,	MeOH	C ₁₀	C ₁₂	2 <i>R</i> ,3 <i>S</i> ,7 <i>S</i> ,9 <i>S</i> ^{<i>b</i>}
9^f	+14	<i>c</i> 0.02,	MeOH	C ₁₀	C ₁₂	2 <i>R</i> ,3 <i>S</i> ,7 <i>S</i> ,9 <i>S</i> ^{<i>b</i>}
26^g	-20.9	<i>c</i> 0.205,	CHCl ₃	C ₁₀	C ₁₂	2 <i>S</i> ,3 <i>S</i> ,7 <i>S</i> ,9 <i>S</i>
31^g	+19.4	<i>c</i> 0.515,	CHCl ₃	C ₁₀	C ₁₂	2 <i>S</i> ,3 <i>S</i> ,7 <i>S</i> ,9 <i>S</i>
32ⁱ	-10	<i>c</i> 1.0,	CHCl ₃	C ₁₀	C ₁₀	2 <i>R</i> *,3 <i>R</i> *,7 <i>R</i> *,9 <i>R</i> * ^{<i>h</i>}

^aCore locants follow the numbering used for **1–3**. Unless indicated by *, depicted CIP assignments are absolute. Configuration of the N atoms not given.

^bthis work.

^cref. 4.

^dX-ray, ref. 5.

^eX-ray, ref. 6a.

^fref. 7.

^gX-ray, ref. 15.

^hrelative configuration only.

ⁱref. 20.