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Tetrahedron 63 (2007) 1544–1552
Tetrahedron

Stereoselective synthesis of (–)-4-epiaxinyssamine

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Received 5 October 2006; revised 1 December 2006; accepted 11 December 2006

Abstract—The synthetic studies towards axinyssamine, a cytotoxic and coral-lethal compound isolated from the Caribbean sponge *Axinyssa ambrosia* were performed. The Ritter reaction on the key intermediate with chloroacetonitrile, resulted in the introduction of the amino group at C-4 generating the configuration of this stereocentre opposite to that of the natural product. As a result, the first total synthesis of the unnatural (–)-4-epiaxinyssamine was achieved.

1. Introduction

The isolation of a new sesquiterpene amine having an eudesmane framework, named axinyssamine (**1a**), from the methanolic extract of the Caribbean sponge *Axinyssa ambrosia* was recently reported.[1] This compound showed cytotoxic and lethal activities against tumour cell lines and polyps of the coral *Madracis mirabilis*, respectively. In the course of our continuing search for biologically active secondary metabolites and the elucidation of the possible role that these compounds play in the chemical defence of marine sponges, we focused our attention on the synthesis of axinyssamine (**1a**) and its analogues in order to explore the structure–activity relationships for this type of compounds.

The structure of (–)-axinyssamine (**1a**) is characterized by the presence of a *trans*-decaline core having four chiral centres at C-4, C-5, C-7 and C-10, and an amino group at the tertiary carbon C-4. A few methods have been reported in the literature for the introduction of an amino functionality at a tertiary carbon atom. One of the most widely used is the Ritter reaction, where nitriles react with carbocations generated in situ to give *N-tert*-alkylamides.[2] For this reason, in our synthetic plan for the synthesis of **1a**, we wanted to explore the Ritter reaction on a key olefinic intermediate **2** with three of the four chiral centres, to introduce amino group at C-4 (Fig. 1). The synthesis of the *trans*-decaline core with the desired configuration at C-7 and C-10 of the key olefinic intermediate **2** was build from (+)-dihydrocarvone, whereas the diastereoselective Birch reduction of the double bond of an α,β-unsaturated ketone provided the

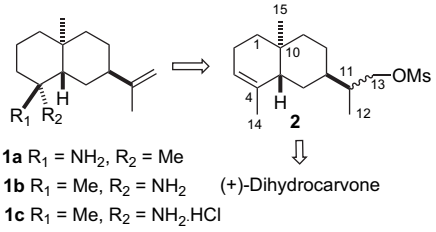

Figure 1.

desired configuration at C-5. For the introduction of the amino group in the molecule by the Ritter reaction, it is reasonable to assume that the nitrile capture by the carbocation should occur predominantly from the opposite face to the methyl group at C-10 due to its steric effect. However, based on the existing information from literature, the stereochemical outcome of the Ritter reaction was difficult to predict and it could provide axinyssamine and/or its epimer. In fact, the Ritter reaction on the key olefinic intermediate **2** provided the product with the configuration at C-4 opposite to that of natural product **1a**. As a result the first total synthesis of (–)-4-epiaxinyssamine (**1b**) starting from commercially available (+)-dihydrocarvone was achieved.

2. Results and discussion

The synthesis was started with the condensation of (+)-dihydrocarvone with ethyl vinyl ketone followed by water elimination to give the resulting α,β-unsaturated ketone **4** (Scheme 1).[3] Birch reduction of **4**, using *t*-BuOH as the proton donor, gave alcohol **6** in 87% yield along with the ketone **5** in a 10:1 ratio. Subsequent conversion of **5** into **6** was achieved in 92% yield using a Birch reduction under the

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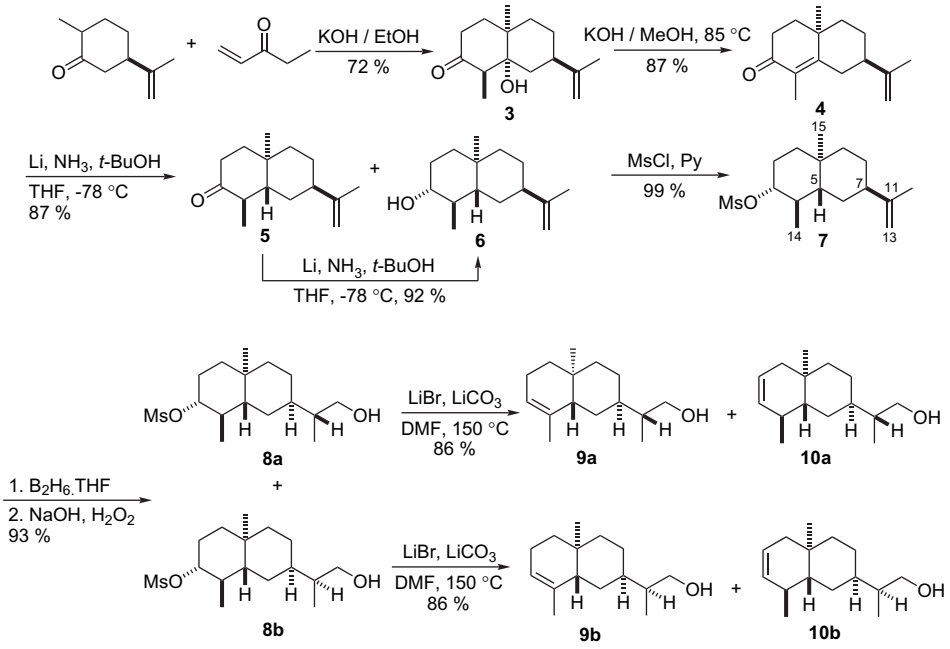
doi:10.1016/j.tet.2006.12.019



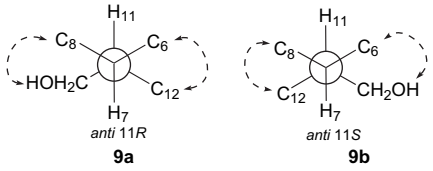
Scheme 1.

same conditions. Mesylation of **6** under standard conditions afforded the desired derivative **7** in quantitative yield.[3b] The carbon chemical shift of the C-15 methyl group at 16.52 ppm in the ^{13}C NMR of **7** was in good agreement with that of the *trans*-eudesmane derivatives, which appears upfield shifted (around δ_C 18 ppm) in relation to that of the *cis*-eudesmane derivatives where the C-15 signal is downfield shifted (around 28–31 ppm).[4] This was confirmed by a NOESY experiment, where NOE correlations of H-3 to H-5, and this in turn to H-13 in the NOESY of **7** indicated the β disposition of these protons, while the NOE correlation between H-4 and H-15 confirmed their α disposition.

In order to avoid the involvement of the terminal Δ^{11} double bond in the Ritter reaction, compound **7** was hydroxylated.[3] Hydroboration of **7** followed by the treatment with H_2O_2 in a basic medium gave a mixture of epimeric primary alcohols **8a** and **8b** (6:4) in very good yield. After chromatographic separation, both epimers were heated with LiBr and $LiCO_3$ to give the alkenes **9a** and **9b** as the major compounds along with a small amount of alkenes **10a** and **10b**. These isomers were separated by reverse phase HPLC to give pure compounds.

Compounds **9a** and **9b** could be distinguished by conformational analysis around the C-7/C-11 bond.[5] The large $^3J_{HH}$ found between H-7 and H-11 (10.0 Hz) indicated an *anti* relationship for these protons. Furthermore, NOE correlations found in the NOESY spectra allowed us to determine the absolute configuration of this fragment in each compound (see Fig. 2).

With the intermediate olefinic compounds **9a** and **9b** in hand, we used the Ritter reaction to introduce the amino group. In our case, we employed a recent and efficient procedure in which treatment with chloroacetonitrile was followed by cleavage of the resulting chloroacetyl group with thiourea.[6] Since primary alcohols did not react under Ritter conditions,



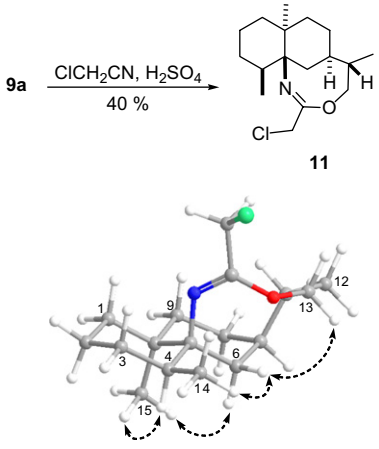
9a **9b**

Figure 2. NOE correlations around the C7–C11 bond found in **9a** and **9b**.

we considered performing the initial trial on **9a** with an unprotected hydroxyl group.

Reaction of **9a** in sulfuric acid with chloroacetonitrile gave compound **11** in 40% yield (Fig. 3). The structure of this 1,3-oxazocine was established by 1D, 2D NMR, MS data and MMX analysis.

The *trans*-fused decaline skeleton in **11** was initially suggested by the carbon chemical shift of C-15 at 19.29 ppm



11

Figure 3. Ritter reaction of **9a** and selected NOE correlations on a MMX minimized model of **11**.

and by the downfield shift of H-1 axial at 2.27 ppm (ddd, J=13.3, 13.3, 4.6 Hz), probably due to the anisotropic effect of the double bond N=C, indicating a β disposition. NOESY correlations from H-4 to H_3-15, and this in turn to H-6 axial at 1.45 ppm suggested a α disposition for these protons. In addition, NOESY correlations between H_3-14 and H-6 equatorial at δ_H 2.74 (br d, J=13.8 Hz), and this in turn to H-13′ at 3.75 ppm (dd, J=10.8 and 12.4 Hz) indicated a β disposition for these protons. These results established the stereochemistry of **11** as shown in Figure 3. The formation of **11** can be explained in terms of a carbocation rearrangement from C-4 to C-5, and subsequent attack of the chloroacetonitrile followed by nucleophilic addition of the hydroxyl group to nitrilium ion.

For this reason, we decided to protect the hydroxyl group in a way that the double bond could be regenerated at the end of the synthesis (see Scheme 2). Thus, mesylation of **9a** and **9b** afforded **2a** and **2b**, respectively, in quantitative yields.

Our attention was next directed to the amination of the key olefinic intermediates **2a** and **2b** (Table 1). Treatment of **2b** with triflic acid in chloroacetonitrile at low temperature furnished **12b** and **13b** in low yield in a ratio of 7:2.5. Under different acidic conditions (H_2SO_4) we were able to improve the yield and also invert the ratio of **12b** and **13b** to 1.5:10. Treatment with a weaker acid (HCOOH) did not improve the yield and the same ratio of these isomers was formed. The best results were obtained using a 11:1 mixture of formic and sulfuric acids as the proton source at low temperature to give the chloroacetamides **13a** and **13b** in 60% and 58% yield, respectively, along with chloroacetamides **12a** and **12b**. Unfortunately, the stereochemistry of the chloroacetamide group at C-4 in **13a** and **13b** was found to be opposite to that expected, bearing in mind the steric influence of the methyl group at C-10. The stereochemistry at C-4 in **13a** and **13b** was deduced from the significant NOESY correlation observed between the NH amide proton and H_3-15 spectra along with the chemical shift of C-14 at δ_C 26.09. The *trans*-fused decaline skeleton in these compounds was supported by the chemical shift of the C-15 methyl group at 18.96 ppm.

Table 1. Ritter reaction conditions for compounds **2a** and **2b**

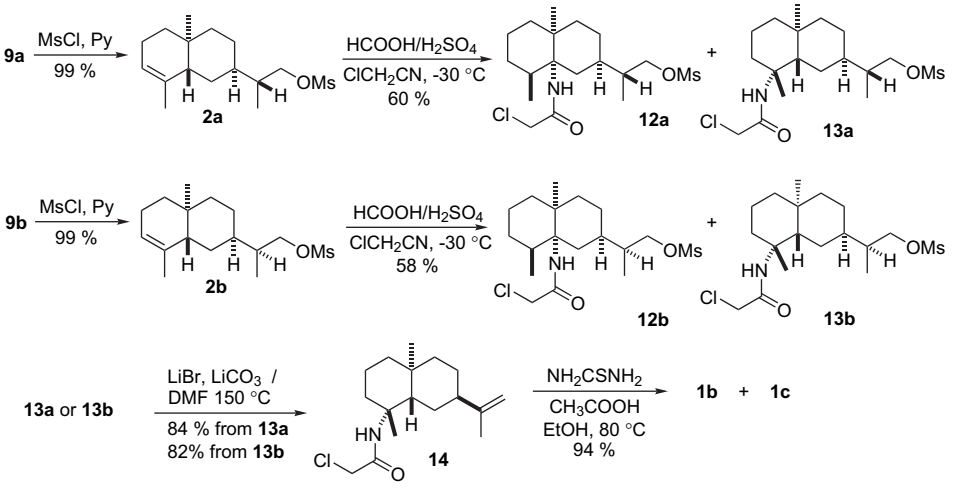
Compd	Acid	Temp (°C)	Products (yield, %)	
2b	CF_3SO_3H	−78	**12b** (17)	**13b** (6)
2b	H_2SO_4, 96%	0	**12b** (9)	**13b** (49)
2b	HCOOH	0	**12b** (9)	**13b** (30)
2a	HCOOH	40	**12a** (8)	**13a** (35)
2a	$HCOOH/H_2SO_4$	−30	**12a** (13)	**13a** (60)
2b	$HCOOH/H_2SO_4$	−30	**12b** (8)	**13b** (58)

In addition, NOE correlations of H-4 with H_3-15, and this in turn with NH amide proton of **12a** and **12b** indicated the α disposition of these protons. These results allowed us to establish the stereochemistry at C-4 and the *cis*-fused decaline framework in these compounds. The carbon chemical shift of the C-15 methyl at 22.98 ppm is also in agreement with these structures.

Noteworthy, the use of $Hg(NO_3)_2$ and $Hg(AcO)_2$ as catalysts[7] or TBDPS instead of the mesylate group on the hydroxyl group in **9** did neither improve reaction yields nor provide access to the stereochemistry at C-4 as the natural product.

Although there is little information in the literature about the stereochemistry of the Ritter reaction, the formation of the product **13** can be explained, as suggested by Ichikawa, in terms of the *trans*-antiparallel electrophilic addition of H^+ and $ClCH_2CN$ to the olefinic bond and the preference for axial nucleophilic attack.[8] A similar case was also found in the synthesis of 3-amino-3-methylbicyclo[3.3.1]nonanes[9] and it seems to confirm, as postulated by Dobrev and Bon,[10] the weak influence of steric effects in the nucleophilic attack on the carbocation. The formation of the minor chloroacetamides **12a** and **12b** may be explained by rearrangement of the resulting carbocation from C-4 to C-5 and subsequent nucleophilic addition of chloroacetonitrile.

Treatment of chloroacetamides **13a** and **13b** with a mixture of LiBr and $LiCO_3$ in DMF at 150 °C afforded the same alkene **14** as the sole product in 84% and 82% yield, respectively. Finally, cleavage of the chloroacetyl group with



Scheme 2.

thiourea gave the corresponding free amine **1b** along with its chlorohydrate amine **1c** in 94% yield. The structure of **1b** and **1c** was confirmed by their 1D and 2D NMR and MS data. NOE correlation between the NH_2 protons and H_3-15 in the NOESY spectrum of **1c** and the carbon chemical shift of C-14 methyl group (29.45 ppm in **1b** and 25.96 in **1c**) confirmed the stereochemistry at C-4.[11] Furthermore, the values of C-15 methyl group (18.90 ppm in **1b** and 19.04 ppm in **1c**) are in perfect agreement with a *trans*-decaline skeleton.

A moderate cytotoxic activity (IC_{50}=5 μg/mL) was found for compound **11** against A549 (human lung carcinoma), H116 (human colon carcinoma) and PSN1 (human pancreatic adrenocarcinoma) cells and weak (IC_{50}=10 μg/mL) against T98G (human caucasian glioblastoma). The hydrochloride of 4-epiaxinyssamine (**1c**) showed a weak cytotoxic activity (IC_{50}=10 μg/mL) against H116, PSN1 and T98G tumour cells, and it was devoid of activity against A549. This result is in contrast with the cytotoxic activity (IC_{50}=2 μg/mL) of axinyssamine (**1a**) against A549, suggesting the crucial role of the stereochemistry at C-4 for the presence of activity. The studies of coral-lethal activity of **1c** are underway.

In conclusion, the total synthesis of (–)-4-epiaxinyssamine has been achieved for the first time and gave 21% overall yield in 10 steps from (+)-dihydrocarvone. The development of an alternative synthesis providing natural axinyssamine (**1a**) is currently underway.

3. Experimental section

3.1. General experimental procedures

The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer at 500 and 125 MHz, respectively, using $CDCl_3$ as solvent unless otherwise stated. The assignments of ^1H and ^{13}C NMR spectra were determined by H–H COSY, HSQC, HMBC and the stereochemistry by NOESY experiments. The carbon and proton numbering is based on the eudesmane skeleton. LREIMS were recorded on a VG-Quattro instrument while (+)-HRESIMS were measured on QSTAR Elite of Applied Biosystem and Bruker spectrometers. Optical rotations were determined on a JASCO DIP-1000 polarimeter. All reactions were run under an atmosphere of argon. THF and Et_2O were distilled from sodium benzophenone ketyl. DMF was stored in a bottle with 4 Å molecular sieves. CH_2Cl_2 was distilled from CaH_2. Pyridine was distilled from KOH. MeOH, EtOH and *t*-BuOH were distilled from $Mg(OMe)_2$, $Mg(OEt)_2$ and NaO*t*-Bu, respectively.

3.2. (1*R*,4a*R*,7*R*,8a*R*)-8a-Hydroxy-1,4a-dimethyl-7-(prop-1-en-2-yl)-octahydronaphthalen-2(1*H*)-one (3)

Compound **3** was prepared by the method reported in the literature[3] as a colourless oil in 72% yield.

Compound **3**: $[\alpha]_D^{20}$ +46.4 (*c* 0.095, $CHCl_3$). EIMS, *m*/*z* (relative intensity), $C_{15}H_{24}O_2$: 236 $[M]^+$ (15), 218 $[M-H_2O]^+$ (5), 152 (76), 137 (40), 123 (32), 109 (84), 95 (27), 83 (100). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.69 (H-13, br s, 1H), 4.66 (H-13′, br s, 1H), 2.87 (H-4, q, *J*=6.6 Hz, 1H), 2.58 (H-2α, ddd, *J*=14.1, 14.1, 7.1 Hz, 1H), 2.33 (H-2β, m, 1H), 2.25 (H-7, m, 1H), 2.10 (H-1β, ddd, *J*=14.1, 14.1, 4.6 Hz, 1H), 1.89 (H-9α, ddd, *J*=14.0, 14.0, 5.0 Hz, 1H), 1.68 (H-12, s, 3H), 1.59 (H-8α, m, 1H), 1.56 (H-6α, m, 1H), 1.43 (H-1α, m, 1H), 1.42 (H-6β, m, 1H), 1.40 (H-9β, m, 1H), 1.24 (H-15, s, 3H), 1.06 (H-8β, m, 1H), 1.04 (H-14, dd, *J*=6.6, 1.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 210.88 (C-3, s), 149.32 (C-11, s), 109.03 (C-13, t), 77.96 (C-5, s), 51.77 (C-4, d), 39.68 (C-7, d), 37.67 (C-2, t), 37.56 (C-10, s), 35.38 (C-9, t), 33.39 (C-8, t), 31.58 (C-1, t), 25.78 (C-6, t), 21.72 (C-15, q), 20.83 (C-12, q), 6.57 (C-14, q). ^1H NMR (500 MHz, $(CD_3)_2SO$) δ (ppm): 4.64 (H-13, br s, 1H), 4.62 (H-13′, br s, 1H), 4.58 (OH, s, 1H), 2.83 (H-4, q, *J*=6.7 Hz, 1H), 2.62 (H-2α, ddd, *J*=14.0, 14.0, 7.2 Hz, 1H), 2.25 (H-7, m, 1H), 2.10 (H-2β, dd, *J*=14.0, 4.0 Hz, 1H), 1.96 (H-1β, ddd, *J*=14.0, 14.0, 4.0 Hz, 1H), 1.82 (H-9β, ddd, *J*=13.0, 13.0, 5.0 Hz, 1H), 1.64 (H-12, s, 3H), 1.45 (H-8, m, 1H), 1.42 (H-6, m, 1H), 1.32 (H-1 and H-6, m, 2H), 1.14 (H-15, s, 3H), 0.87 (H-14, d, *J*=6.7 Hz, 3H), 0.81 (H-8, t, *J*=13.0 Hz, 1H). ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ (ppm): 211.19 (C-3, s), 150.23 (C-11, s), 109.09 (C-13, t), 76.91 (C-5, s), 51.55 (C-4, d), 39.29 (C-7, d), 37.81 (C-2, t), 37.69 (C-10, s), 35.48 (C-9, t), 33.40 (C-8, t), 31.41 (C-1, t), 25.90 (C-6, t), 21.16 (C-15, q), 21.23 (C-12, q), 7.21 (C-14, q).

3.3. (4a*R*,7*R*)-1,4a-Dimethyl-7-(prop-1-en-2-yl)-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (4)

Compound **4** was prepared by the method reported in the literature[3] as colourless oil in 87% yield.

Compound **4**: $[\alpha]_D^{20}$ −180.2 (*c* 0.15, $CHCl_3$). EIMS, *m*/*z* (relative intensity), $C_{15}H_{22}O$: 218 $[M]^+$ (32), 203 $[M-CH_3]^+$ (33), 190 $[C_{14}H_{22}]^+$ (76), 175 $[C_{13}H_{19}]$ (33), 161 (58), 147 (70), 132 (64), 119 (69), 105 (78), 91 (100). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.81 (H-13, br s, 1H), 4.62 (H-13′, br s, 1H), 2.90 (H-6β, br d, *J*=16.5 Hz, 1H), 2.58 (H-7, m, 1H), 2.55 (H-2α, m, 1H), 2.42 (H-2β, ddd, *J*=17.0, 5.0, 2.3 Hz, 1H), 2.37 (H-6α, dd, *J*=16.5, 5.0 Hz, 1H), 1.92 (H-8, dddd, *J*=13.6, 13.6, 5.0, 5.0 Hz, 1H), 1.86 (H-1, m, 1H), 1.82 (H-14, s, 3H), 1.72 (H-12, s, 3H), 1.68 (H-8′, m, 1H), 1.66 (H-1′, m, 1H), 1.52 (H-9α, ddd, *J*=13.6, 13.6, 3.6 Hz, 1H), 1.34 (H-9β, ddd, *J*=13.6, 3.6, 3.6 Hz, 1H), 1.24 (H-15, s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 198.78 (C-3, s), 163.02 (C-5, s), 147.40 (C-11, s), 129.14 (C-4, s), 111.04 (C-13, t), 40.94 (C-7, d), 37.55 (C-1, t), 35.88 (C-9, t), 35.85 (C-10, s), 33.98 (C-2, t), 31.12 (C-6, t), 23.11 (C-8, t), 23.09 (C-15, q), 22.61 (C-12, q), 10.98 (C-14, q).

3.4. (1*R*,2*R*,4a*R*,7*R*,8a*R*)-1,4a-Dimethyl-7-(prop-1-en-2-yl)-decahydronaphthalen-2-ol (6)

Lithium wire (4 cm, 0.225 g, 32.6 mmol) was washed with Et_2O, cut into 0.5 cm lengths and placed in 10 mL of Et_2O in a flask under an atmosphere of argon. The flask was cooled to −78 °C and 30 mL of ammonia was trapped in the flask with stirring. After the lithium had dissolved, the cooling bath was removed and excess ammonia was removed under a stream of argon. The lithium–bronze was

recooled to −78 °C. A solution of enone **4** (0.501 g, 2.29 mmol) and *tert*-butyl alcohol (0.44 mL, 4.6 mmol) in THF (14 mL) was added dropwise over 20 min. The reaction mixture was stirred for 30 min after the addition was complete and then EtOH (2.0 mL) was added slowly. The reaction mixture was allowed to warm up to −30 °C and the excess lithium was decomposed with a solution of MeOH/acetone (1:1). The reaction mixture was allowed to stand at room temperature, poured into saturated aqueous NaCl (50 mL) and extracted with Et_2O (4×50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was chromatographed (hexane/EtOAc 9:1) to give **5** (42 mg, 0.2 mmol) and **6** (0.434 g, 2.0 mmol, 87%). Birch reduction of **5** under the previously described conditions gave **6** (92%) as colourless plates.

Compound **5**: $[\alpha]_D^{20}$ −19.5 (*c* 1.12, $CHCl_3$). EIMS, *m/z* (relative intensity), $C_{15}H_{24}O$: 220 $[M]^+$ (21), 205 $[M-CH_3]^+$ (11), 202 (6), 177 $[C_{13}H_{17}]^+$ (73), 159 (15), 149 (27), 138 (55), 109 (53), 93 (59), 82 (100). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.90 (H-13, br s, 1H), 4.78 (H-13′, br s, 1H), 2.51 (H-2α, ddd, *J*=14.6, 14.2, 6.7 Hz, 1H), 2.38 (H-7, m, 1H), 2.32 (H-2β, ddd, *J*=14.6, 4.8, 2.2 Hz, 1H), 2.18 (H-4, dddd, *J*=13.0, 6.6, 6.6, 6.6 Hz, 1H), 1.96 (H-6β, dddd, *J*=13.5, 2.2, 2.2, 2.2 Hz, 1H), 1.88 (H-8, m, 1H), 1.81 (H-8′, m, 1H), 1.72 (H-12, s, 3H), 1.68 (H-1α, ddd, *J*=13.6, 6.7, 2.2 Hz, 1H), 1.48 (H-1β, ddd, *J*=14.2, 13.6, 4.8 Hz, 1H), 1.41 (H-6α, dd, *J*=13.5, 5.2 Hz, 1H), 1.34 (H-5, dd, *J*=13.0, 2.2 Hz, 1H), 1.30 (H-9, m, 2H), 1.14 (H-15, s, 3H), 1.05 (H-14, d, *J*=6.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 213.25 (C-3, s), 146.28 (C-11, s), 111.06 (C-13, t), 45.66 (C-5, d), 45.24 (C-4, d), 41.74 (C-1, t), 38.32 (C-7, d), 38.20 (C-2, t), 36.32 (C-9, t), 33.99 (C-10, s), 27.54 (C-6, t), 23.02 (C-8, t), 22.71 (C-12, q), 16.10 (C-15, q), 11.18 (C-14, q).

Compound **6**: $[\alpha]_D^{20}$ −11.6 (*c* 1.02, $CHCl_3$). EIMS, *m/z* (relative intensity), $C_{15}H_{26}O$: 222 $[M]^+$ (15), 207 $[M-CH_3]^+$ (9), 204 $[M-H_2O]^+$ (20), 189 $[M-H_2O-CH_3]^+$ (18), 179 (18), 161 (63), 147 (18), 133 (26), 122 (76), 107 (76), 93 (60), 81 (86), 67 (100). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.92 (H-13, br s, 1H), 4.82 (H-13′, br s, 1H), 3.12 (H-3, m, $W_{h/2}$=26.2 Hz, 1H), 2.37 (H-7, m, 1H), 1.95 (H-6β, dd, *J*=14.0, 2.3 Hz, 1H), 1.80 (H-8, m, 1H), 1.80 (H-2β, m, 1H), 1.75 (H-12, s, 3H), 1.74 (H-8′, m, 1H), 1.57 (H-2α, m, 1H), 1.48 (OH, br s, 1H), 1.38 (H-1α, ddd, *J*=13.2, 3.7, 3.7 Hz, 1H), 1.27 (H-6α, m, 1H), 1.26 (H-9, m, 1H), 1.23 (H-4, m, 1H), 1.19 (H-1β, m, 1H), 1.19 (H-9′, m, 1H), 1.00 (H-14, d, *J*=6.5 Hz, 3H), 0.92 (H-15, s, 3H), 0.91 (H-5, m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 147.11 (C-11, s), 110.67 (C-13, t), 76.86 (C-3, d), 43.22 (C-5, d), 39.93 (C-1, t), 39.19 (C-7, d), 38.88 (C-4, d), 37.10 (C-9, t), 33.78 (C-10, s), 30.92 (C-2, t), 26.05 (C-6, t), 23.08 (C-8, t), 22.82 (C-12, q), 16.68 (C-15, q), 14.87 (C-14, q).

3.5. (1*R*,2*R*,4a*R*,7*R*,8a*R*)-1,4a-Dimethyl-7-(prop-1-en-2-yl)-decahydronaphthalen-2-yl methanesulfonate (7)

A solution of **6** (0.508 g, 2.28 mmol) in pyridine (8 mL) was cooled to 0 °C and methanesulfonyl chloride (300 μL, 0.92 mmol) was added dropwise for 30 min. The mixture was stirred for 1 h and then allowed to reach room temperature and left to stand for 12 h. The reaction mixture was worked up in the usual way to give 0.685 g of **7** (2.28 mmol, 99%) as a viscous oil.

Compound **7**: $[\alpha]_D^{23}$ −18.1 (*c* 1.00, $CHCl_3$). EIMS, *m/z* (relative intensity), $C_{16}H_{28}O_3S$: 300 $[M]^+$ (1), 270 $[M-2CH_3]^+$ (1), 255 $[M-3CH_3]^+$ (1), 204 $[M-CH_3SO_3H]^+$ (35), 189 $[M-CH_3SO_3H-CH_3]^+$ (27), 161 (84), 147 (20), 133 (23), 122 (74), 107 (68), 93 (64), 79 (100). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.93 (H-13, br s, 1H), 4.81 (H-13′, br s, 1H), 4.25 (H-3, ddd, *J*=10.8, 10.8, 5.2 Hz, 1H), 3.03 (CH_3SO_2O–, s, 3H), 2.38 (H-7, m, 1H), 2.09 (H-2β, dddd, *J*=12.6, 5.2, 4.8, 3.7 Hz, 1H), 1.97 (H-6β, br d, *J*=13.8 Hz, 1H), 1.87 (H-8, m, 1H), 1.77 (H-8′, m, 1H), 1.74 (H-12, s, 3H), 1.83 (H-2α, m, 1H), 1.54 (H-4, m, 1H), 1.44 (H-1α, ddd, *J*=13.5, 3.7, 3.7 Hz, 1H), 1.28 (H-6α, m, 1H), 1.25 (H-9, m, 2H), 1.20 (H-1β, m, 1H), 1.03 (H-5, m, 1H), 1.01 (H-14, d, *J*=6.5 Hz, 3H), 0.94 (H-15, s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 146.58 (C-11, s), 110.97 (C-13, t), 88.43 (C-3, d), 43.42 (C-5, d), 39.48 (C-1, t), 38.84 (CH_3SO_3, q), 38.67 (C-7, d), 36.65 (C-9, t), 36.57 (C-4, d), 33.52 (C-10, s), 28.67 (C-2, t), 26.09 (C-6, t), 22.98 (C-8, t), 22.76 (C-12, q), 16.52 (C-15, q), 15.08 (C-14, q).

3.6. (1*R*,2*S*,4a*R*,7*R*,8a*R*)-7-(-1-Hydroxypropan-2-yl)-1,4a-dimethyl-decahydronaphthalen-2-yl methanesulfonate (8a and 8b)

A solution of borane tetrahydrofuran complex solution (1.0 M, 9.0 mL) was added to a solution of alkene **7** (1.217 g, 4.06 mmol) in dry THF (20 mL) under argon. The reaction mixture was allowed to stand for 10 h, and water (2.5 mL), 3 N NaOH (5.0 mL) and 30% H_2O_2 (5.0 mL) were added. The mixture was stirred for 2 h and NaCl was added until the solution was saturated. The mixture was extracted with EtOAc (5×25 mL) and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Silica gel flash chromatography (hexane/EtOAc, 3:1) afforded alcohols **8a** and **8b** (1.202 g, 3.78 mmol, 93%) as a colourless gum. The mixture of alcohols (50 mg) was separated by normal phase HPLC [SiO_2 Scharlau Science 300×8 mm, hexane/EtOAc (3:1), 3 mL/min] to give **8a** (t_R 22 min, 28 mg) as a white solid and **8b** (t_R 27 min, 22 mg) as a colourless viscous oil.

3.6.1. (1*R*,2*S*,4a*R*,7*R*,8a*R*)-7-[(*R*)-1-Hydroxypropan-2-yl]-1,4a-dimethyldecahydronaphthalen-2-yl methanesulfonate (8a). $[\alpha]_D^{24}$ −16.9 (*c* 0.40, $CHCl_3$). EIMS, *m/z* (relative intensity), $C_{16}H_{30}O_4S$: 300 $[M-H_2O]^+$ (1), 222 $[M-CH_3SO_3H]^+$ (13), 207 $[M-CH_3SO_3H-CH_3]$ (62), 193 (81), 189 $[M-CH_3SO_3H-CH_3-H_2O]^+$ (44), 163 $[M-CH_3SO_3H-CH_3CHCH_2OH]^+$ (82), 121 (62), 107 (97), 95 (87), 81 (100). (+)-HRESIMS: *m/z* 341.1720 $[M+Na]^+$ (calcd for $C_{16}H_{30}O_4NaS$, 341.1757). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.25 (H-3, ddd, *J*=10.9, 10.9, 5.2 Hz, 1H), 3.71 (H-13, dd, *J*=10.7, 3.3 Hz, 1H), 3.46 (H-13′, dd, *J*=10.7, 6.4 Hz, 1H), 3.03 (CH_3SO_2O–, s, 3H), 2.10 (H-2β, dddd, *J*=12.6, 4.8, 4.8, 3.4 Hz, 1H), 1.90 (H-2α, m, 1H), 1.80 (H-11, m, 1H), 1.76 (H-6β, br d, *J*=14.0 Hz, 1H), 1.60 (H-8, m, 2H), 1.55 (H-4 and H-7, m, 2H), 1.46 (H-1α, ddd, *J*=13.5, 3.4, 3.4 Hz, 1H), 1.25 (H-1β, m, 1H),

1.23 (H-9, m, 2H), 1.19 (H-6α, m, 1H), 0.98 (H-14, d, J=6.6 Hz, 3H), 0.97 (H-12, d, J=6.6 Hz, 3H), 0.95 (H-5, m, 1H), 0.93 (H-15, s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 88.47 (C-3, d), 66.82 (C-13, t), 43.37 (C-5, d), 39.61 (C-1, t), 38.96 (CH_3SO_3, q), 36.66 (C-4, d), 36.44 (C-9, t), 34.72 (C-7, d), 33.54 (C-11, d), 33.45 (C-10, s), 28.74 (C-2, t), 25.78 (C-6, t), 23.00 (C-8, t), 16.67 (C-15, q), 15.38 (C-12, q), 15.22 (C-14, q).

3.6.2. (1*R*,2*S*,4a*R*,7*R*,8a*R*)-7-[(*S*)-1-Hydroxypropan-2-yl]-1,4a-dimethyldecahydronaphthalen-2-yl methanesulfonate (8b). $[\alpha]_D^{24}$ −10.1 (*c* 0.42, $CHCl_3$). EIMS, *m/z* (relative intensity), $C_{16}H_{30}O_4S$: 300 $[M-H_2O]^+$ (1), 222 $[M-CH_3SO_3H]^+$ (17), 207 $[M-CH_3SO_3H-CH_3]^+$ (56), 193 (36), 189 $[M-CH_3SO_3H-CH_3-H_2O]^+$ (44), 163 $[M-CH_3SO_3H-CH_3CHCH_2OH]^+$ (51), 121 (51), 107 (83), 93 (74), 81 (100). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.24 (H-3, ddd, J=10.9, 10.9, 5.2 Hz, 1H), 3.68 (H-13, dd, J=10.6, 3.4 Hz, 1H), 3.46 (H-13′, dd, J=10.6, 6.4 Hz, 1H), 3.02 (CH_3SO_2O–, s, 3H), 2.11 (H-2β, dddd, J=12.6, 4.8, 4.8, 3.6 Hz, 1H), 1.90 (H-2α, m, 1H), 1.81 (H-11, m, H-1), 1.76 (H-6β, br d, J=14.6 Hz, 1H), 1.60 (H-8, m, 2H), 1.55 (H-4 and H-7, m, 2H), 1.46 (H-1α, ddd, J=13.6, 3.6, 3.6 Hz, 1H), 1.25 (H-1β, m, 1H), 1.23 (H-9, m, 2H), 1.19 (H-6α, m, 1H), 1.02 (H-5, dd, J=11.0, 2.5 Hz, 1H), 0.99 (H-12, d, J=6.6 Hz, 3H), 0.97 (H-14, d, J=6.4 Hz, 3H), 0.93 (H-15, s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 88.36 (C-3, d), 66.22 (C-13, t), 43.45 (C-5, d), 39.50 (C-1, t), 38.85 (CH_3SO_3, q), 36.59 (C-4, d), 36.18 (C-9, t), 35.17 (C-7, d), 33.40 (C-10, s), 33.21 (C-11, d), 28.68 (C-2, t), 25.90 (C-6, t), 22.65 (C-8, t), 16.59 (C-15, q), 15.86 (C-12, q), 15.12 (C-14, q).

3.7. 2-[(2*R*,4a*S*,8a*S*)-4a,8-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-2-yl]propan-1-ol (9a and 9b)

A solution of **8a** (0.125 g, 0.39 mmol), LiBr (0.189 g, 2.82 mmol) and Li_2CO_3 (0.236 g, 2.73 mmol) in DMF (5 mL) was stirred at 150 °C (bath temperature) for 75 min. The mixture was allowed to cool and was filtered under reduced pressure. The filtrate was poured into saturated aqueous NaCl (20 mL) and extracted with Et_2O (4×25 mL). The combined extracts were worked up in the usual way to give a pale yellow oil, which was purified by flash column chromatography (hexane/EtOAc, 10:1) to give 82 mg of a 10:1 mixture of **9a** (86%) and **10a** (8%). The mixture of alkenes (28 mg) was separated by reverse phase HPLC [C-18, Scharlau Science 300×8 mm, H_2O/MeOH (75:25), 3 mL/min] to give **10b** (t_R 28 min, 2.5 mg) and **9b** (t_R 30 min, 25.5 mg). The ratio of 10:1 was determined by integration of the chromatogram. A similar procedure was performed with **8b** to give a 10:1 mixture of **9b** and **10b** as a viscous oil, which was separated by HPLC as before.

3.7.1. (*R*)-2-[(2*R*,4a*S*,8a*S*)-4a,8-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-2-yl]propan-1-ol (9a). $[\alpha]_D^{24}$ +3.6 (*c* 0.83, $CHCl_3$). EIMS, *m/z* (relative intensity), $C_{15}H_{26}O$: 222 $[M]^+$ (29), 207 $[M-CH_3]^+$ (71), 189 $[M-CH_3-H_2O]^+$ (72), 163 $[M-CH_3CHCH_2OH]^+$ (45), 133 (48), 107 (82), 93 (79), 81 (100). (+)-HRESIMS: *m/z* 223.2084 $[M+H]^+$ (calcd for $C_{15}H_{27}O$, 223.2056). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.34 (H-3, br s, 1H), 3.75 (H-13, dd, J=10.6, 3.4 Hz, 1H), 3.49 (H-13′, dd, J=10.6, 6.7 Hz, 1H), 2.12 (H-2, m, 1H), 2.05 (H-5, m, 1H), 1.98 (H-2′, m, 1H), 1.89 (H-11, dddddd, J=10.0, 6.7, 6.6, 6.6, 6.6, 3.4 Hz, 1H), 1.83 (H-6β, ddd, J=14.0, 2.3, 2.3 Hz, 1H), 1.76 (H-8, dddd, J=14.0, 14.0, 5.0, 5.0 Hz, 1H), 1.63 (H-14, br s, 3H), 1.63 (H-8′, H-7, m, 2H), 1.47 (OH, br s, 1H), 1.35 (H-1, m, 2H), 1.32 (H-6α, m, 1H), 1.25 (H-9, m, 1H), 1.21 (H-9′, ddd, J=13.1, 3.6, 3.6 Hz, 1H), 1.02 (H-12, d, J=6.6 Hz, 3H), 0.86 (H-15, s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 135.26 (C-4, s), 121.20 (C-3, d), 67.10 (C-13, t), 40.87 (C-5, d), 38.34 (C-1, t), 35.79 (C-9, t), 35.22 (C-7, d), 33.62 (C-11, d), 32.70 (C-10, s), 24.88 (C-6, t), 23.30 (C-8, t), 22.94 (C-2, t), 21.09 (C-14, q), 15.50 (C-15, q), 15.35 (C-12, q).

3.7.2. (*S*)-2-[(2*R*,4a*S*,8a*S*)-4a,8-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-2-yl]propan-1-ol (9b). $[\alpha]_D^{16}$ +14.3 (*c* 0.77, $CHCl_3$). EIMS, *m/z* (relative intensity), $C_{15}H_{26}O$: 222 $[M]^+$ (9), 207 $[M-CH_3]^+$ (22), 189 $[M-CH_3-H_2O]^+$ (20), 163 $[M-CH_3CHCH_2OH]^+$ (14), 133 (17), 107 (29), 93 (22), 83 (100). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.34 (H-3, br s, 1H), 3.74 (H-13, dd, J=10.6, 3.4 Hz, 1H), 3.53 (H-13′, dd, J=10.6, 6.6 Hz, 1H), 2.12 (H-2α, m, 1H), 2.05 (H-5, m, 1H), 1.98 (H-2β, m, 1H), 1.91 (H-11, dddddd, J=10.0, 6.6, 6.6, 6.6, 6.6, 3.4 Hz, 1H), 1.82 (H-6β, ddd, J=13.9, 2.5, 2.5 Hz, 1H), 1.76 (H-8α, dddd, J=13.6, 13.6, 5.3, 4.4 Hz, 1H), 1.62 (H-14, br s, 3H), 1.61 (H-8β, m, 1H), 1.59 (H-7α, m, 1H), 1.35 (H-1, m, 2H), 1.31 (H-6α, m, 1H), 1.26 (H-9β, m, 1H), 1.22 (H-9α, ddd, J=13.6, 4.4, 3.7 Hz, 1H), 1.02 (H-12, d, J=6.6 Hz, 3H), 0.86 (H-15, s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 135.19 (C-4, s), 121.23 (C-3, d), 66.55 (C-13, t), 41.08 (C-5, d), 38.35 (C-1, t), 35.95 (C-7, d), 35.66 (C-9, d), 33.30 (C-11, d), 32.73 (C-10, s), 25.21 (C-6, t), 22.98 (C-8, t), 22.97 (C-2, t), 21.14 (C-14, q), 15.96 (C-12, q), 15.48 (C-15, q).

3.8. Compound 11

A solution of alkene **9b** (46.5 mg, 0.21 mmol) in $ClCH_2CN$ (0.5 mL) was cooled to −15 °C and 96% H_2SO_4 (30 μL, 0.56 mmol) was added for 10 min. The mixture was stirred for 1 h and then allowed to reach 0 °C. After stirring at that temperature for 2 h, the mixture was poured into ice and saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted with diethyl ether (5×15 mL) and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. After solvent evaporation, the chromatography (hexane/EtOAc, 10:1) afforded 25 mg of oxazocine **11** (0.08 mmol, 40%).

3.8.1. (1*R*,6*S*,7*R*,10*S*,14*S*)-6,10,14-Trimethyl-4-oxa-2-azatricyclo[8,4,1^{1,7}]tridec-2-ene (11). $[\alpha]_D^{24}$ +102.2 (*c* 0.09, $CHCl_3$). EIMS, *m/z* (relative intensity), $C_{17}H_{28}ClNO$: 299/297 $[M]^+$ (3/9), 282 $[M-CH_3]^+$ (3), 262 $[M-Cl]^+$ (67), 254 (19), 248 $[M-CH_2Cl]^+$ (15), 220 (17), 204 (24), 189 (32), 172 (61), 161 (79), 147 (50), 107 (71), 105 (73), 84 (100). (+)-HRESIMS: *m/z* 300.1900/298.1943 $[M+H]^+$ (calcd for $C_{17}H_{29}NOCl$, 300.1908/298.1932). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.08 (CH_2Cl, s, 2H), 4.06 (H-13, dd, J=10.8, 3.4 Hz, 1H), 3.75 (H-13′, dd, J=12.4, 10.8 Hz, 1H), 2.74 (H-6β, br d, J=13.8 Hz, 1H), 2.27 (H-1β, ddd, J=13.3, 13.3, 4.6 Hz, 1H), 1.85 (H-8α, m, H-1), 1.84 (H-11, m, 1H), 1.77 (H-4, m, 1H), 1.72 (H-2β, m, 1H), 1.50 (H-2α, H-9β, H-7, m, 3H), 1.45 (H-6α, m,

H-1), 1.41 (H-3α, m, 1H), 1.34 (H-8β, m, 1H), 1.25 (H-3β, m, 1H), 1.12 (H-15, s, 3H), 0.93 (H-9α, m, 1H), 0.85 (H-1α, m, 1H), 0.82 (H-12, d, J=6.4 Hz, 3H), 0.63 (H-14, d, J=6.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 149.20 (C=N, s), 74.45 (C-13, t), 65.19 (C-5, s), 45.98 (CH_2Cl, t), 39.57 (C-7, d), 38.83 (C-10, s), 36.19 (C-4, d), 34.78 (C-1, t), 34.03 (C-11, d), 33.08 (C-9, t), 30.60 (C-3, t), 29.23 (C-6, t), 24.11 (C-8, t), 21.52 (C-2, t), 19.29 (C-15, q), 17.03 (C-12, q), 15.83 (C-14, q).

3.9. 2-[(2*R*,4a*S*,8a*S*)-4a,8-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-2-yl]propyl methanesulfonate (2a/2b)

A solution of **9a** (0.106 g, 0.477 mmol) in pyridine (5 mL) was cooled to 0 °C and methanesulfonyl chloride (180 μL, 0.55 mmol) was added dropwise for 10 min. The mixture was stirred for 1 h, allowed to reach room temperature and then allowed to stand for 12 h. The reaction mixture was worked up as usual to give 0.141 g of **2a** (0.476 mmol, 99%) as a viscous oil.

Compound **9b** was treated in a similar way to give **2b** in 99% yield as a colourless oil.

3.9.1. (*R*)-2-[(2*R*,4a*S*,8a*S*)-4a,8-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-2-yl]propyl methanesulfonate (2a). $[\alpha]_D^{24}$ +7.0 (*c* 0.40, $CHCl_3$). EIMS, *m/z* (relative intensity), $C_{16}H_{28}O_3S$: 300 $[M]^+$ (9), 285 $[M-CH_3]^+$ (38), 204 $[M-MsOH]^+$ (18), 189 $[M-MsOH-CH_3]^+$ (75), 161 (48), 133 (56), 107 (84), 84 (100). (+)-HRESIMS: *m/z* 205.1960 $[M-MsOH+H]^+$ (calcd for $C_{15}H_{25}$, 205.1950). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.36 (H-3, br s, 1H), 4.31 (H-13, dd, J=9.5, 3.3 Hz, 1H), 4.11 (H-13′, dd, J=9.5, 6.5 Hz, 1H), 3.03 (s, CH_3SO_2O, 3H), 2.15 (H-11, dddddd, J=10.0, 6.7, 6.7, 6.7, 6.5, 3.3 Hz, 1H), 2.12 (H-2, m, 1H), 2.09 (H-5, m, 1H), 2.02 (H-2′, m, 1H), 1.83 (H-6β, m, 1H), 1.78 (H-8, m, 1H), 1.70 (H-7, m, 1H), 1.63 (H-8′, m, 1H), 1.62 (H-14, br s, 3H), 1.37 (H-6α, m, 1H), 1.30 (H-1, m, 2H), 1.20 (H-9, m, 2H), 1.07 (H-12, d, J=6.7 Hz, 3H), 0.87 (H-15, s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 134.75 (C-4, s), 121.48 (C-3, d), 74.04 (C-13, t), 40.80 (C-5, d), 38.23 (C-1, t), 37.25 (CH_3SO_2O, q), 35.58 (C-9, t), 35.15 (C-7, d), 32.71 (C-10, s), 31.36 (C-11, d), 24.66 (C-6, t), 23.15 (C-2, t), 22.89 (C-8, t), 21.03 (C-14, q), 15.44 (C-12, q), 15.44 (C-15, q).

3.9.2. (*S*)-2-[(2*R*,4a*S*,8a*S*)-4a,8-Dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalen-2-yl]propyl methanesulfonate (2b). $[\alpha]_D^{24}$ +20.6 (*c* 0.35, $CHCl_3$). EIMS, *m/z* (relative intensity), $C_{16}H_{28}O_3S$: 300 $[M]^+$ (7), 385 $[M-CH_3]^+$ (28), 204 $[M-MsOH]^+$ (9), 189 $[M-MsOH-CH_3]^+$ (51), 161 (35), 133 (37), 107 (48), 84 (100). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.35 (H-3, br s, 1H), 4.29 (H-13, dd, J=9.5, 3.4 Hz, 1H), 4.12 (H-13′, dd, J=9.5, 6.3 Hz, 1H), 3.03 (s, CH_3SO_2O, 3H), 2.15 (H-11, dddddd, J=10.0, 6.7, 6.7, 6.7, 6.3, 3.4 Hz, 1H), 2.11 (H-2, m, 1H), 2.10 (H-5, m, 1H), 2.02 (H-2′, m, 1H), 1.83 (H-6β, m, 1H), 1.75 (H-8, m, 1H), 1.68 (H-7, m, 1H), 1.63 (H-14, br s, 3H), 1.62 (H-8′, m, 1H), 1.37 (H-6α, m, 1H), 1.30 (H-1, m, 2H), 1.21 (H-9, m, 2H), 1.08 (H-12, d, J=6.7 Hz, 3H), 0.87 (H-15, s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 134.67 (C-4, s), 121.20 (C-3, d), 73.65 (C-13, t), 41.06 (C-5, d), 38.25 (C-1, t), 37.24 (CH_3SO_2O, q), 35.76 (C-9, t), 35.49 (C-7, d), 32.73 (C-10, s), 31.26 (C-11, d), 25.16 (C-6, t), 22.91 (C-2, t), 22.72 (C-8, t), 21.10 (C-14, q), 16.06 (C-12, q), 15.44 (C-15, q).

3.10. 2-[(2*R*,4a*S*,8*R*,8a*S*)-8-(2-Chloroacetamido)-4a,8-dimethyldecahydronaphthalen-2-yl]propyl methanesulfonate (13a/13b)

A solution of alkene **2a** (288 mg, 0.96 mmol) in $ClCH_2CN$ (3 mL) was cooled to −30 °C. A mixture of formic acid (330 μL, 8.4 mmol), H_2SO_4 (30 μL) and $ClCH_2CN$ (5 mL) was added for 20 min. The reaction mixture was allowed to reach room temperature, stirred for 12 h and poured into ice/saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted with EtOAc (5×25 mL) and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and chromatography (hexane/EtOAc, 3:1) afforded the amides **12a** (50 mg, 0.13 mmol, 13.5%) and **13a** (227 mg, 0.58 mmol, 60.4%) as a colourless gum.

Compound **2b** was treated in a similar way to give **12b** (8% yield) and **13b** (58% yield) as a colourless oil.

3.10.1. (*R*)-2-[(2*R*,4a*S*,8*S*,8a*R*)-8a-(2-Chloroacetamido)-4a,8-dimethyldecahydronaphthalen-2-yl]propyl methanesulfonate (12a). $[\alpha]_D^{24}$ +7.6 (*c* 0.97, $CHCl_3$). EIMS, *m/z* (relative intensity), $C_{18}H_{32}ClNO_4S$: 358 $[M-Cl]^+$ (16), 316 $[M-COCH_2Cl]^+$ (2), 300 $[M-NH_2COCH_2Cl]^+$ (24), 285 $[M-NH_2COCH_2Cl-CH_3]^+$ (44), 256 $[M-CH_3CHCH_2OMs]^+$ (15), 204 $[M-NH_2COCH_2Cl-MsOH]^+$ (100), 189 $[204-CH_3]^+$ (45), 163 (54). (+)-HRESIMS: *m/z* 396.1781/394.1806 $[M+H]^+$ (calcd for $C_{18}H_{33}ClNO_4S$, 396.1789/394.1813). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.52 (NH, br s, 1H), 4.24 (H-13, dd, J=9.7, 5.6 Hz, 1H), 4.11 (H-13′, dd, J=9.7, 7.0 Hz, 1H), 4.02 (CH_2Cl, d, J=1.1 Hz, 2H), 3.05 (CH_3SO_3, s, 3H), 2.47 (H-6β, ddd, J=13.3, 2.2, 2.2 Hz, 1H), 2.31 (H-4, m, 1H), 1.95 (H-1β, ddd, J=13.3, 13.3, 4.7 Hz, 1H), 1.86 (H-11, m, 1H), 1.61 (H-9, m, 1H), 1.55 (H-2α, H-2β, H-3β, H-7, m, 4H), 1.44 (H-6α, m, 1H), 1.42 (H-8, m, 2H), 1.27 (H-3α and H-9′, m, 2H), 1.10 (H-15, s, 3H), 1.04 (H-1α, m, 1H), 1.03 (H-12, d, J=7.0 Hz, 3H), 0.90 (H-14, d, J=7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 164.71 (C=O, s), 73.36 (C-13, t), 63.79 (C-5, s), 43.85 (CH_2Cl, t), 38.47 (C-10, s), 37.91 (C-11, d), 37.18 (CH_3SO_3, q), 37.11 (C-9, t), 36.98 (C-4, d), 34.74 (C-7, d), 33.33 (C-1, t), 31.29 (C-3, t), 24.55 (C-8, t), 23.55 (C-6, t), 22.98 (C-15, q), 21.26 (C-2, t), 16.43 (C-14, q), 13.07 (C-12, q).

3.10.2. (*S*)-2-[(2*R*,4a*S*,8*S*,8a*R*)-8a-(2-Chloroacetamido)-4a,8-dimethyldecahydronaphthalen-2-yl]propyl methanesulfonate (12b). $[\alpha]_D^{25}$ +6.4 (*c* 0.51, $CHCl_3$). EIMS, *m/z* (relative intensity), $C_{18}H_{32}ClNO_4S$: 393 $[M]^+$ (1), 358 $[M-Cl]^+$ (16), 316 $[M-COCH_2Cl]^+$ (2), 300 $[M-NH_2COCH_2Cl]^+$ (31), 285 $[M-NH_2COCH_2Cl-CH_3]^+$ (56), 262 $[M-MsOH-Cl]^+$ (5), 256 $[M-CH_3CHCH_2OMs]^+$ (23), 204 $[M-NH_2COCH_2Cl-MsOH]^+$ (100), 189 $[204-CH_3]^+$ (51), 163 (71). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.52 (NH, br s, 1H), 4.28 (H-13, dd, J=9.8, 5.5 Hz, 1H), 4.11 (H-13′, dd, J=9.4, 6.6 Hz, 1H), 4.02 (CH_2Cl, br s, 2H), 3.05 (CH_3SO_3, s, 3H), 2.49 (H-6β, br d, J=8.6 Hz, 1H), 2.34 (H-4, m, 1H), 1.95 (H-1β, ddd, J=13.3, 13.3,

4.5 Hz, 1H), 1.81 (H-11, m, 1H), 1.63 (H-9, m, 1H), 1.56 (H-2α, H-2β, H-3β, m, 3H), 1.48 (H-6α, m, 1H), 1.45 (H-7, H-8, m, 2H), 1.35 (H-8′, m, 1H), 1.30 (H-3α, H-9′, m, 2H), 1.11 (H-15, s, 3H), 1.05 (H-1α, m, 1H), 1.02 (H-12, d, J=7.0 Hz, 3H), 0.90 (H-14, d, J=6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 164.71 (C═O, s), 73.31 (C-13, t), 63.92 (C-5, s), 43.85 (CH_2Cl, t), 38.44 (C-10, s), 37.86 (C-11, d), 37.35 (CH_3SO_3, q), 37.01 (C-9, t), 36.71 (C-4, d), 34.84 (C-7, d), 33.32 (C-1, t), 31.25 (C-3, t), 25.95 (C-6, t), 23.00 (C-15, q), 22.89 (C-8, t), 21.26 (C-2, t), 16.39 (C-14, q), 13.51 (C-12, q).

3.10.3. (*R*)-2-[(2*R*,4a*S*,8*R*,8a*S*)-8-(2-Chloroacetamido)-4a,8-dimethyldecahydronaphthalen-2-yl]propyl methanesulfonate (13a). $[\alpha]_D^{24}$ +7.2 (*c* 0.97, $CHCl_3$). EIMS, *m/z* (relative intensity), $C_{18}H_{32}ClNO_4S$: 393 $[M]^+$ (1), 378 $[M-CH_3]^+$ (4), 358 $[M-Cl]^+$ (11), 316 $[M-COCH_2Cl]^+$ (4), 300 $[M-NH_2COCH_2Cl]^+$ (16), 285 $[M-NH_2COCH_2Cl-CH_3]^+$ (45), 204 $[M-NH_2COCH_2Cl-MsOH]^+$ (81), 189 $[204-CH_3]^+$ (92), 161 (76), 79 (100). (+)-HRESIMS: *m/z* 396.1773/394.1802 $[M+H]^+$ (calcd for $C_{18}H_{33}ClNO_4S$, 396.1789/394.1813), *m/z* 418.1585/416.1616 $[M+Na]^+$ (calcd for $C_{18}H_{32}ClNNaO_4S$, 418.1609/416.1632). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.51 (NH, br s, 1H), 4.28 (H-13, dd, J=9.6, 3.2 Hz, 1H), 3.75 (H-13′, dd, J=9.6, 6.4 Hz 1H), 3.98 (CH_2Cl, d, J=2.8 Hz, 2H), 3.02 (CH_3SO_3, s, 3H), 2.77 (H-3α, ddd, J=14.5, 5.0, 3.0 Hz, 1H), 2.11 (H-11, dddd, J=10.3, 6.8, 6.4, 3.2 Hz, 1H), 1.90 (H-6β, br d, J=14.0 Hz, 1H), 1.75 (H-8 and H-7, m, 2H), 1.58 (H-2 and H-8′, m, 2H), 1.49 (H-6α, ddd, J=14.0, 4.2, 4.2 Hz, 1H), 1.47 (H-1α and H-2′, m, 2H), 1.42 (H-14, s, 3H), 1.29 (H-9α, ddd, J=14.1, 14.1, 4.1 Hz, 1H), 1.24 (H-5, m, 1H), 1.17 (H-1β, H-3β and H-9β, m, 3H), 1.13 (H-15, s, 3H), 1.06 (H-12, d, J=6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 164.44 (C═O, s), 73.61 (C-13, t), 56.19 (C-4, s), 47.77 (C-5, d), 43.33 (CH_2Cl, t), 41.38 (C-1, t), 39.85 (C-9, t), 37.27 (CH_3SO_3, q), 36.09 (C-3, t), 35.47 (C-7, d), 34.29 (C10, s), 31.29 (C-11, d), 26.09 (C-14, q), 23.02 (C-8, t), 22.47 (C-6, t), 18.96 (C-15, q), 18.06 (C-2, t), 15.50 (C-12, q). ^{1}H NMR (500 MHz, C_6D_6) δ (ppm): 6.40 (NH, br s, 1H), 4.06 (H-13, dd, J=9.8, 3.3 Hz, 1H), 3.86 (H-13′, dd, J=9.8, 6.1 Hz, 1H), 3.68 (CH_2Cl, s, 2H), 3.13 (H-3α, ddd, J=14.0, 5.0, 3.2 Hz, 1H), 2.32 (CH_3SO_3, s, 3H), 1.74 (H-11, dddd, J=9.5, 6.4, 6.1, 3.3 Hz, 1H), 1.66 (H-6β, br d, J=13.8 Hz, 1H), 1.65 (H-2, m, 2H), 1.50 (H-3β and H-8, m, 2H), 1.48 (H-14, s, 3H), 1.42 (H-2′ and H-8′, m, 2H), 1.32 (H-1α, m, 1H), 1.30 (H-6α, ddd, J=13.8, 4.8, 4.8 Hz, 1H), 1.07 (H-15, s, 3H), 1.05 (H-7 and H-9, m, 1H), 0.98 (H-1β and H-9′, m, 2H), 0.90 (H-12, d, J=6.4 Hz, 3H), 0.88 (H-5, dd, J=13.0, 2.2 Hz, 1H). ^{13}C NMR (125 MHz, C_6D_6) δ (ppm): 163.69 (C═O, s), 73.05 (C-13, t), 56.03 (C-4, s), 47.66 (C-5, d), 43.45 (CH_2Cl, t), 41.55 (C-1, t), 40.00 (C-9, t), 36.64 (CH_3SO_3, q), 36.08 (C-3, t), 35.58 (C-7, d), 34.34 (C-10, s), 31.36 (C-11, d), 26.21 (C-14, q), 23.10 (C-8, t), 22.55 (C-6, t), 19.00 (C-15, q), 18.40 (C-2, t), 15.56 (C-12, q).

3.10.4. (*S*)-2-[(2*R*,4a*S*,8*R*,8a*S*)-8-(2-Chloroacetamido)-4a,8-dimethyl-decahydronaphthalen-2-yl]propyl methanesulfonate (13b). $[\alpha]_D^{25}$ +11.1 (*c* 0.37, $CHCl_3$). EIMS, *m/z* (relative intensity), $C_{18}H_{32}ClNO_4S$: 395/393 $[M]^+$ (1/3), 378 $[M-CH_3]^+$ (2), 358 $[M-Cl]^+$ (5), 316 $[M-COCH_2Cl]^+$ (2), 300 $[M-NH_2COCH_2Cl]^+$ (7), 285 $[M-NH_2COCH_2Cl-CH_3]^+$ (15), 262 $[M-MsOH-Cl]^+$ (4), 204 $[M-NH_2COCH_2Cl-MsOH]^+$ (46), 189 $[204-CH_3]^+$ (43), 161 (37), 146 (28), 84 (100). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.52 (NH, br s, 1H), 4.31 (H-13, dd, J=9.6, 3.2 Hz, 1H), 4.10 (H-13′, dd, J=9.6, 6.4 Hz, 1H), 3.99 (CH_2Cl, d, J=2.2 Hz, 2H), 3.03 (CH_3SO_3, s, 3H), 2.78 (H-3α, ddd, J=14.0, 5.0, 3.2 Hz, 1H), 2.12 (H-11, dddd, J=10.0, 6.7, 6.4, 3.2 Hz, 1H), 1.84 (H-6β, br d, J=13.9 Hz, 1H), 1.75 (H-7, m, 1H), 1.71 (H-8, ddd, J=14.2, 4.5, 4.5 Hz, 1H), 1.62 (H-2 and H-8′, m, 2H), 1.53 (H-6α, ddd, J=13.9, 4.4, 4.4 Hz, 1H), 1.48 (H-2′, m, 1H), 1.46 (H-1α, m, 1H), 1.45 (H-14, s, 3H), 1.25 (H-5 and H-9α, m, 2H), 1.20 (H-3β, m, 1H), 1.16 (H-1β and H-9β, m, 2H), 1.15 (H-15, s, 3H), 1.09 (H-12, d, J=6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 164.42 (C═O, s), 73.30 (C-13, t), 56.20 (C-4, s), 48.09 (C-5, d), 43.33 (CH_2Cl, t), 41.41 (C-1, t), 39.73 (C-9, t), 37.32 (CH_3SO_3, q), 36.15 (C-3, t), 35.57 (C-7, d), 34.32 (C10, s), 31.33 (C-11, d), 26.06 (C-14, q), 22.80 (C-6, t), 22.63 (C-8, t), 18.99 (C-15, q), 18.09 (C-2, t), 15.91 (C-12, q).

3.11. 2-Chloro-*N*-[(1*R*,4a*S*,7*R*,8a*S*)-1,4a-dimethyl-7-(prop-1-en-2-yl)-decahydronaphthalen-1-yl]acetamide (14)

A mixture of **13a** (197 mg, 0.50 mmol), LiBr (250 mg, 2.88 mmol) and Li_2CO_3 (0.380 g, 5.7 mmol) in DMF (5 mL) was stirred at 150 °C (bath temperature) for 105 min. The mixture was allowed to cool and was filtered. The filtrate was poured into saturated aqueous NaCl (10 mL) and extracted with ethyl acetate (4×15 mL) and CH_2Cl_2 (4×15 mL). The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the pale yellow oil was purified by column chromatography (hexane/EtOAc, 10:1) to give 123 mg of **14** (0.42 mmol, 84%).

Methanesulfonate **13b** was treated in a similar way to give **14** (82%) as a colourless oil.

Compound **14**: $[\alpha]_D^{25}$ −13.1 (*c* 0.22, $CHCl_3$). EIMS, *m/z* (relative intensity), $C_{17}H_{28}ClNO$: 297/299 $[M]^+$ (15/6), 262 $[M-Cl]^+$ (5), 203 $[M-NH_2COCH_2Cl]^+$ (60), 121 (100). (+)-HRESIMS: *m/z* 300.1886/298.1904 $[M+H]^+$ (calcd for $C_{17}H_{29}ClNO$, 300.1908/298.1932). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.57 (NH, br s, 1H), 4.97 (H-13, br s, 1H), 4.86 (H-13′, br s, 1H), 4.00 (CH_2Cl, d, J=3.8 Hz, 2H), 2.81 (H-3α, ddd, J=14.0, 5.0, 3.2 Hz, 1H), 2.51 (H-7, m, 1H), 2.07 (H-6β, ddd, J=13.8, 2.3, 2.1 Hz, 1H), 1.81 (H-8, m, 1H), 1.77 (H-12, br s, 3H), 1.56 (H-6α, m, 1H), 1.44 (H-14, s, 3H), 1.42 (H-1α, H-1β, H-2α, H-2β, m, 4H), 1.40 (H-9, m, 1H), 1.27 (H-5, dd, J=13.2, 2.3 Hz, 1H), 1.15 (H-3β, m, 1H), 1.14 (H-15, s, 3H), 1.13 (H-9′, m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 164.45 (C═O, s), 146.34 (C-11, s), 111.16 (C-13, t), 56.32 (C-4, s), 47.80 (C-5, d), 43.37 (CH_2Cl, t), 41.44 (C-1, t), 40.39 (C-9, t), 39.41 (C-7, d), 35.84 (C-3, t), 34.41 (C-10, s), 25.88 (C-14, q), 23.24 (C-8, t), 22.93 (C-6, t), 22.77 (C-12, q), 19.06 (C-15, q), 18.09 (C-2, t).

3.12. (–)-4-Epiaxinyssamine (1b) and (–)-4-epiaxinyssamine hydrochloride (1c)

A solution of amide **14** (88 mg, 0.30 mmol) and thiourea (33 mg, 0.43 mmol) in a mixture of EtOH (2.5 mL) and

AcOH (170 μL) was heated at 80 °C for 10 h. The reaction mixture was poured into saturated aqueous NaCl (10 mL) and a solution of saturated aqueous $NaHCO_3$ (20 mL) was added until a basic pH was obtained. The mixture was extracted with EtOAc (5×25 mL) and CH_2Cl_2 (2×10 mL). The organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and chromatography (hexane/EtOAc, 1:1 and EtOAc) afforded the amine chlorohydrate **1c** (50 mg, 0.23 mmol, 75%) and its free amine **1b** (15 mg, 0.058 mmol, 19%).

3.13. (–)-4-Epiaxinyssamine free amine (1b)

$[\alpha]_D^{25}$ −15.7 (*c* 0.16, $CHCl_3$), EIMS, *m/z* (relative intensity) $C_{15}H_{27}N$: 221 $[M]^+$ (3), $[M-CH_3]^+$ (15), 204 $[M-NH_3]^+$ (2), 189 $[M-NH_3-CH_3]^+$ (2), 178 (12), 84 (57), 70 (100). (+)-HRESIMS: *m/z* 222.2226 $[M+H]^+$ (calcd for $C_{15}H_{28}N$, 222.2216). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.94 (H-13, br s, 1H), 4.83 (H-13′, br s, 1H), 2.51 (H-7, m, 1H), 1.98 (H-6β, br d, *J*=13.8 Hz, 1H), 1.90 (H-2, m, 1H), 1.88 (H-3, m, 1H), 1.81 (H-8, m, 2H), 1.72 (H-6α, m, 1H), 1.76 (H-12, s, 3H), 1.52 (H-2′, m, 1H), 1.45 (H-1 and H-3′, m, 2H), 1.35 (H-9, m, 1H), 1.11 (H-9′, m, 1H), 1.09 (H-1′, m, 1H), 1.28 (H-14, br s, 3H), 1.27 (H-5, m, 1H), 1.17 (H-15, s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 146.94 (C-11, s), 110.96 (C-13, t), 54.10 (C-4, s), 46.52 (C-5, d), 41.35 (C-1, t), 40.72 (C-9, t), 40.45 (C-3, t), 39.45 (C-7, d), 34.43 (C-10, s), 23.04 (C-6, t), 23.44 (C-8, t), 22.90 (C-12, q), 29.45 (C-14, q), 18.90 (C-15, q), 17.94 (C-2, t).

3.14. (–)-4-Epiaxinyssamine hydrochloride (1c)

$[\alpha]_D^{25}$ −20.5 (*c* 0.23, $CHCl_3$). EIMS, *m/z* (relative intensity), $C_{15}H_{28}NCl$: 204 $[M-NH_2-HCl]^+$ (16), $[M-NH_3-HCl-CH_3]^+$ (8), 161 (14), 149 (6), 122 (9), 83 (100). (+)-HRESIMS: *m/z* 260.1972/258.1997 $[M+H]^+$ (calcd for $C_{15}H_{29}ClN$, 260.1958/258.1983); *m/z* 222.2229 $[M-HCl+H]^+$ (calcd for $C_{15}H_{28}N$, 222.2216); *m/z* 205.1958 $[M-NH_2-HCl+H]^+$ (calcd for $C_{15}H_{25}$, 205.1950). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.11 (NH, br s, 1H), 4.95 (H-13, br s, 1H), 4.85 (H-13′, br s, 1H), 2.77 (H-3α, ddd, *J*=14.0, 4.8, 3.0 Hz, 1H), 2.50 (H-7, m, 1H), 2.08 (H-6β, ddd, *J*=13.3, 3.9, 1.7 Hz, 1H), 1.84 (H-8, m, 1H), 1.75 (H-12, br s, 3H), 1.73 (H-8′, m, 1H), 1.60 (H-2, m, 1H), 1.55 (H-6α, m, 1H), 1.44 (H-2′, m, 1H), 1.43 (H-14, s, 3H), 1.41 (H-1, m, 1H), 1.36 (H-9, m, 1H), 1.27 (H-5, br d, *J*=13.7 Hz, 1H), 1.16 (H-3β, m, 1H), 1.13 (H-1′ and H-9′, m, 2H), 1.12 (H-15, s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 146.25 (C-11, s), 111.18 (C-13, t), 56.55 (C-4, s), 47.69 (C-5, d), 41.46 (C-1, t), 40.39 (C-9, t), 39.42 (C-7, d), 35.99 (C-3, t), 34.49 (C-10, s), 25.96 (C-14, q), 23.28 (C-8, t), 23.03 (C-6, t), 22.70 (C-12, q), 19.04 (C-15, q), 18.14 (C-2, t).

A solution of (–)-4-epiaxinyssamine hydrochloride **1c** (20 mg) in $CHCl_3$ (10 mL) was washed twice with saturated $NaHCO_3$. The separated $CHCl_3$ layer was dried over Na_2SO_4 and then concentrated to give the free amine **1b** in quantitative yield.

Acknowledgements

This work was financially supported by Grants from Xunta de Galicia (PGIDIT05RMA10302PR), Ministerio de Educación y Ciencia (CQT2005-00793) and COLCIENCIAS from Colombia (grant 1101-09-13544). L.C. thanks to Programme Alβan, the European Union Programme of High Level Scholarships for Latin America, for a scholarship (E04D033392CO) and Universidad Nacional de Colombia for the leave of absence to perform doctoral studies. We are grateful for BIOMAR S.A. for the pharmacological assays.

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