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Graphical Abstract

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Catalytic asymmetric total syntheses of (*R*)-bgugaine and (*R*)-irnidine

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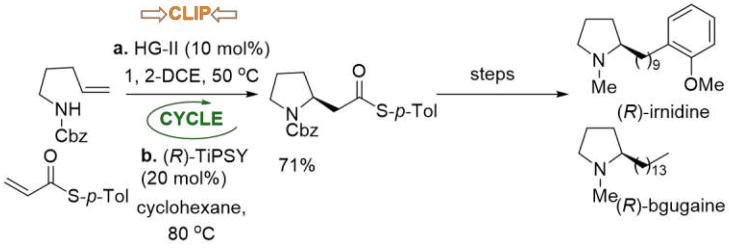

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Catalytic asymmetric total syntheses of (*R*)-bgugaine and (*R*)-irnidine

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This paper is dedicated to Professor Richard J. K. Taylor on the occasion of his 70th birthday and in recognition of his many contributions to *Tetrahedron* as an editor and author.

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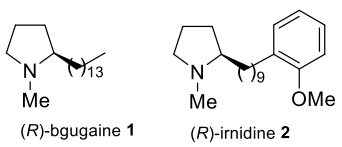
ABSTRACT

An enantioselective total synthesis of (*R*)-bgugaine and the first enantioselective total synthesis of (*R*)-irnidine are reported. The key steps are the asymmetric 'clip-cycle' formation of the pyrrolidine ring in 94:6 e.r., which is common to both natural products, followed by Liebeskind–Srogl coupling and Wolf-Kishner reduction. The route yields (*R*)-bgugaine and (*R*)-irnidine in 6 steps and in overall yields of 33% and 18% respectively.

1. Introduction

(*R*)-Bgugaine **1** and (*R*)-irnidine **2** (Figure 1) are pyrrolidine alkaloids isolated from tubers of *Arisarum vulgare*, a species which has been used in traditional medicine, and is found on the Mediterranean coasts of Morocco and Spain. (*R*)-Bgugaine was first isolated in 1993, and was shown to have antimicrobial activity against Gram +ve bacteria and inhibited the yeast *C. tropicalis*.[1] (*R*)-Bgugaine was also shown to interact strongly with DNA.[2] It was shown to be a potent hepatotoxin in both rats and humans, and induced significant DNA damage in human hepatoblastoma (HepG^2) cell line. Interestingly, (*R*)-bgugaine was shown to have IC_{50} values of 10 μL^{-1} and 5 μL^{-1} against mastocytoma P815 and carcinoma Hep respectively,[3] implying that it may have some anticancer properties. (*R*)-Irnidine was isolated and characterized in 1998, and along with (*R*)-bgugaine was shown to be toxic in the brine shrimp bioassay.[4]



(*R*)-bgugaine **1** (*R*)-irnidine **2**

Fig. 1. Structures of (*R*)-Bgugaine and (*R*)-Irnidine

Bgugaine has succumbed to total syntheses on several occasions, although we can find no reports of the asymmetric synthesis of irnidine. Three racemic syntheses of bgugaine have been reported,[5-7] and there have been five syntheses of single enantiomers of bgugaine.[8-12] The key steps in the racemic syntheses were the reductive alkylation of a *N*-methyl pyrrolidinone,[5] a radical reaction of an oxime with an alkyl iodide,[6] and the intramolecular hydroamination of a conjugated enyne.[7] The syntheses of (*R*)-bgugaine start either with *L*-proline,[8] or they use chiral auxiliary chemistry as the key step to set the absolute stereochemistry. Chiral auxiliaries used include the Ellman auxiliary,[9] a phenylglycinol auxillary[10] and the SAMP hydrazone.[11] There has been one catalytic asymmetric synthesis of (*R*)-bgugaine where the stereochemistry was installed using the Sharpless asymmetric dihydroxylation protocol.[12]

We recently developed the asymmetric 'Clip-Cycle' reaction for the synthesis of substituted pyrrolidines (Scheme 1).[13] In this process a *N*-Cbz *bis*-homoallylic amine is activated by 'clipping' it to a thioacrylate *via* an alkene metathesis reaction. The resulting α,β-unsaturated thioester can then undergo a Brønsted acid catalyzed intramolecular aza-Michael reaction to generate a chiral pyrrolidine in high yields with good to excellent levels of enantioselectivity. As a chiral pyrrolidine forms the core of both bgugaine and irnidine we rationalized that our 'clip-cycle' reaction

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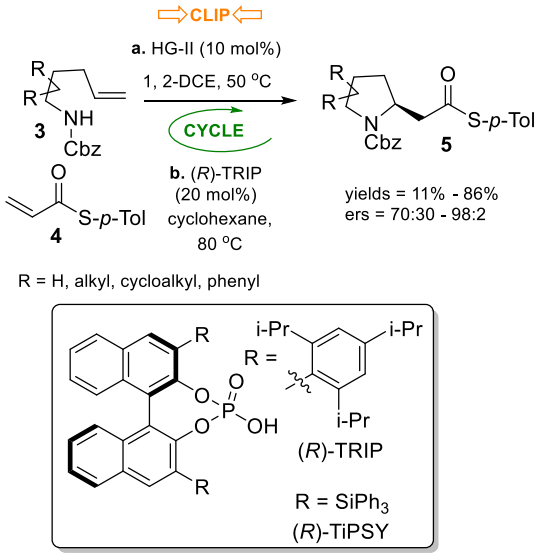
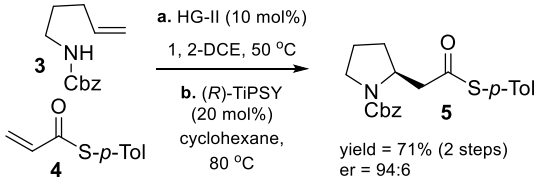
could lead to the efficient synthesis of both natural products from a common intermediate.



Scheme 1. Asymmetric 'Clip-Cycle' Synthesis of Chiral Pyrrolidines.

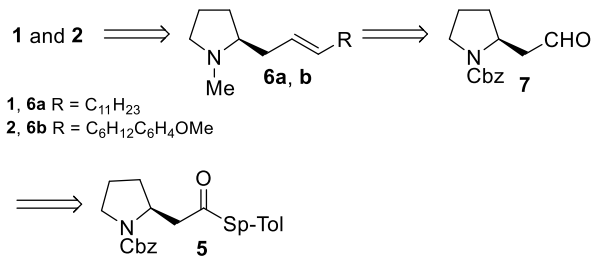
2. Results and Discussion

The priority for a successful synthesis of (*R*)-bgugaine and (*R*)-irnidine was the asymmetric synthesis of pyrrolidine **5**, where R=H. Application of our optimal 'clip-cycle' conditions using chiral phosphoric acid (*R*)-TRIP as a catalyst resulted in the formation of β-homoproline derivative **5** (R=H) with an enantiomeric ratio of 90:10 (80% e.e.) in favour of the (*R*)-enantiomer. The enantiomeric ratio was determined by chiral HPLC analysis and compared to the racemate.[13,14] Screening of alternative chiral phosphoric acid catalysts led to products with lower enantiomeric purity, the exception being (*R*)-TiPSY, which delivered **5** in an enantiomeric ratio of 94:6 (88% e.e.) in favour of the (*R*)-enantiomer (Scheme 2).



Scheme 2. Asymmetric 'Clip-Cycle' Synthesis of β-Homoproline thioester Derivative **5**

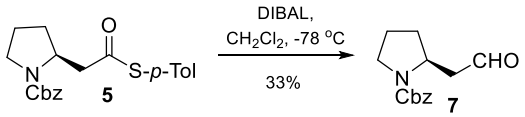
With **5** in hand investigations were undertaken to convert this common precursor into both (*R*)-bgugaine **1** and (*R*)-irnidine **2**. Retrosynthetic analysis of **1** and **2**, back to **5** is shown in Scheme 3, and involved the retrosynthetic conversion of the *N*-methyl group to a *N*-Cbz group and installation of an alkene one methylene group removed from the pyrrolidine ring **6**.



Disconnection of the alkene *via* a Wittig reaction revealed aldehyde **7**, which would come from the reduction of thioester **5**.

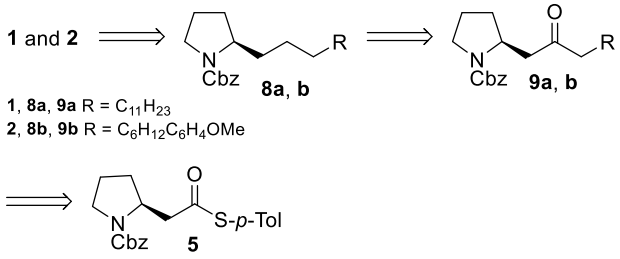
Scheme 3. Initial Retrosynthetic Analysis of **1** and **2**.

Thioesters have been reported to be smoothly reduced to aldehydes using Et_3SiH and Pd/C (5 mol%).[15] However, attempts to utilize this method for the reduction of **5** to **7** met with failure. An alternative procedure based on a protocol involving Bu_3SnH, $(Ph_3P)_4Pd$ (1 mol%) in benzene[16] was also unsuccessful. The reduction of **5** to **7** was achieved in a mediocre yield of 33%, by the action of DIBAL in CH_2Cl_2 at -78 °C. Attempts at optimization or scaling up of the reaction did not lead to any improvement in yield, and so this strategy was not pursued further.



Scheme 4. Formation of Aldehyde **7** *via* DIBAL Reduction of Thioester **5**.

The next retrosynthetic plan developed (Scheme 5) focused on the retrosynthetic installation of a ketone carbonyl group one methylene removed from the pyrrolidine ring **9a**, **b**, which would allow for a Liebeskind–Srogl disconnection directly to thioester **5**. Removal of the ketone to reveal **8a**, **b** was envisaged as being achieved via one of several possible transformations including reduction to a secondary alcohol and either elimination, hydride displacement or Barton-McCombie deoxygenation. Removal of the ketone carbonyl could also prove possible *via* reduction of a dithiolane or Wolff-Kishner reduction.

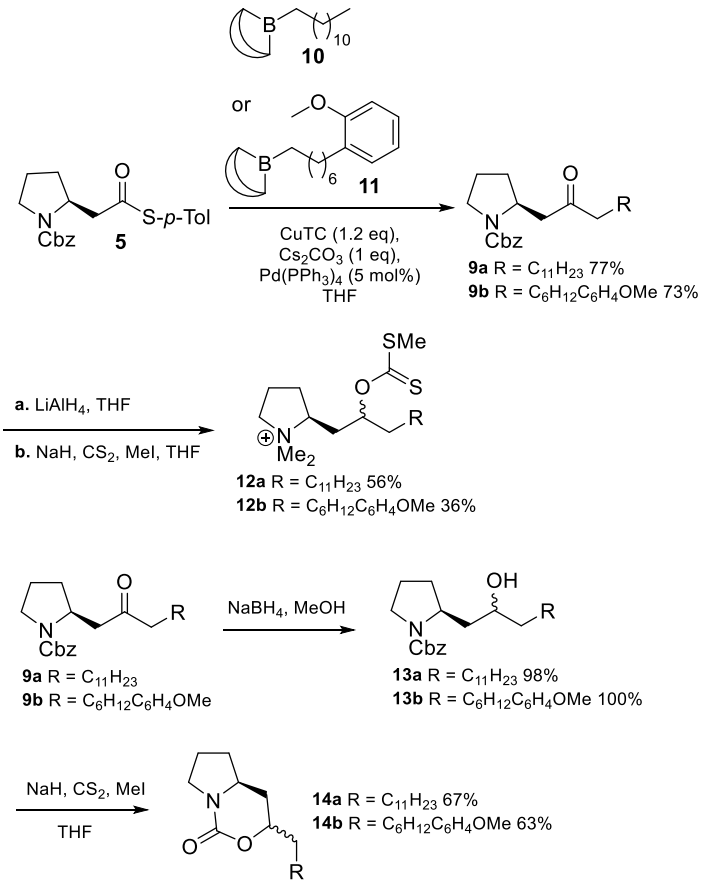


Scheme 5. Alternative Retrosynthetic Analysis of **1** and **2**.

Ketones **9a**, **b** were formed by the smooth Liebeskind–Srogl coupling of the appropriate alkyl boranes **10** or **11** with thioester[17] **5**, yielding **9a** in 77% and **9b** in 73% (Scheme 6). Reduction of **9a** and **9b** with $LiAlH_4$, reduced the *N*-Cbz groups of **9a** and **9b** to the *N*-Me groups present in both **1** and **2**, and also reduced the ketone to the secondary alcohol. It was anticipated that a Barton-McCombie deoxygentation[18] of the subsequent alcohols would complete the syntheses of **1** and **2**. However, treatment with NaH, CS_2 and MeI, instead led to the formation of quaternary ammonium salts **12a** and **12b** in 56% and 36% yields respectively. With few options available for the conversion of **12a** and **12b** into **1** and **2**, alternative methods of reduction were investigated.

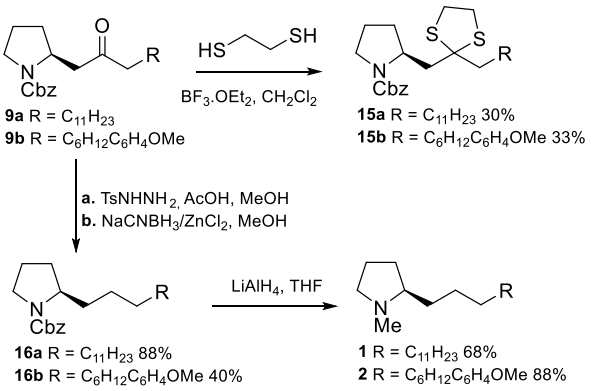
Selective reduction of the ketone carbonyls of **9a** and **9b** over the *N*-Cbz groups was achieved with $NaBH_4$ and gave alcohols **13a** and **13b** in 77% and 73% yields respectively (Scheme 6). However, Barton-McCombie conditions led to the formation of cyclic carbamates **14a** and **14b** in 67% and 63% yields

respectively. Cyclic carbamates **14a** and **14b** are formed by attack of the alkoxide (formed from NaH deprotonation of the alcohol) onto the *N*-Cbz group with expulsion of benzyl alcohol. Attempts to tosylate the hydroxyls of **13a** and **13b** in order to affect a hydride displacement failed at the tosylation step, and so alternative methods to remove the ketone carbonyl group were sought.

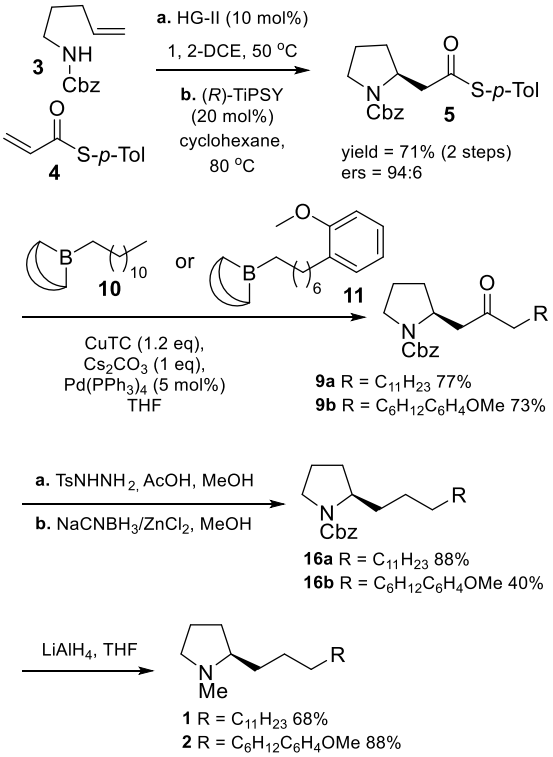


Scheme 6. Attempted Synthesis of **1** and **2** via Liebeskind–Srogl Coupling and Hydride-Mediated Carbonyl Reduction.

The next route to be investigated was the direct removal of the ketone carbonyl via either reduction of a dithiolane or Wolff-Kishner reduction (Scheme 7). The group has had success previously in the removal of unwanted ketones via formation of a dithiolane followed by reduction with Raney nickel,[19] and so this was investigated first. Treatment of **9a** and **9b** with 1,2-ethane dithiol and $BF_3{\cdot}Et_2O$ in CH_2Cl_2, converted the ketone carbonyl into the corresponding dithiolanes **15a** and **15b**, but in low yields of 30% and 33% respectively. Despite attempts at optimization, the yields did not improve sufficiently to enable continuation of this route. Instead attention was turned Wolff-Kishner carbonyl removal.[20] To this end **9a** and **9b** were converted to the tosyl hydrazones by treatment with tosyl hydrazine in AcOH, MeOH. Direct reduction of the tosyl hydrazone with $LiAlH_4$ led to an intractable mess, while attempted reduction with $NaBH_4$, hardly proceeded at all. Interestingly, when $NaCNBH_3/ZnCl_2$ was used as the reducing agent in MeOH,[21] the tosyl hydrazones were converted into alkanes **16a** and **16b** in 88% and 40% isolated yields respectively. With **16a** and **16b** to hand, the natural products **1** and **2** could be formed by $LiAlH_4$ mediated reduction. This generated (*R*)-bgugaine **1** and (*R*)-irnidine **2** in 68% and 88% yields.



Scheme 7. Conversion of **9a** and **9b** into (*R*)-Bgugaine **1** and (*R*)-Irnidine **2**.



Scheme 8. Total synthesis of (*R*)-bgugaine **1** and (*R*)-irnidine **2**.

In conclusion the total synthesis of (*R*)-bgugaine **1** and (*R*)-irnidine **2** have been achieved in 6 steps (Scheme 8). Asymmetric 'Clip-Cycle' formation of chiral pyrrolidine **5** in 94:6 e.r, gave a common intermediate which was elaborated into both natural products. Liebeskind–Srogl coupling of alkyl boranes **10** or **11** with **5** gave **9a** and **9b**, precursors for (*R*)-bgugaine **1** and (*R*)-irnidine **2** respectively. Formation of the tosyl hydrazones and subsequent Wolff-Kishner reduction with $NaCNBH_3/ZnCl_2$ in MeOH gave the immediate precursors **16a** and **16b** to the natural products. Both (*R*)-bgugaine **1** and (*R*)-irnidine **2** where then revealed via $LiAlH_4$ reduction of the *N*-Cbz group. (*R*)-Bgugaine **1** was synthesized in a 33% overall yield, which compares very favorably to previous syntheses,[5-12] while (*R*)-irnidine **2** has been synthesized for the first time in an overall yield of 18%. The stereochemistry of the synthesized alkaloids was determined as (*R*) by comparision of their optical rotations with the literature values. For (*R*)-bgugaine $[\alpha]_D^{20}$ -35.9° (c 0.22, MeOH), lit $[\alpha]_D^{22}$ -48° (c

0.5, MeOH)[1], and for (*R*)-irnidine $[\alpha]_D^{20}$ -18.2° (c 0.165, $CHCl_3$) lit. $[\alpha]_D^{25}$ -20° (c 0.3, $CHCl_3$).[4]

3. Experimental section

Unless otherwise noted all compounds were bought from commercial suppliers and used without further purification. Where a solvent is described as "dry" it was purified by PureSolv alumina columns from Innovative Technologies. Melting points were determined using a Stuart SMP3 apparatus. Infra-red spectra were acquired on a ThermoNicolet Avatar 370 FT-IR spectrometer. Nuclear magnetic resonance spectra were recorded on a Jeol ECS-400 at ambient temperature and are referenced to $CHCl_3$ (^{1}H δ = 7.25 ppm and ^{13}C 77.0 ppm). Assignments of ^{1}H and ^{13}C resonances were made by 2D NMR techniques. Mass spectrometry was performed by the University of York mass spectrometry service using electrospray ionisation (ESI) technique or APCI, and is given as m/z. Thin layer chromatography was performed on glass-backed plates coated with Merck Silica gel 60 F_{254}. The plates were developed using ultraviolet light, acidic aqueous ceric ammonium molybdate or basic aqueous potassium permanganate. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by Fluorochem or silica gel Merck TLC grade 11695 supplied by Sigma-Aldrich.

*3.1. N-Cbz-(S)-2-p-Tolylsulfanylcarbonylmethyl-pyrrolidine (**5**)*

A solution of thioacrylic acid S-p-tolyl ester (235 mg, 1.32 mmol) in 1,2-DCE (7.5 mL) was added under N_2 to a dry flask containing Hoveyda-Grubbs Catalyst™ 2nd generation (27.6 mg, 0.0441 mmol) and copper iodide (83.8 mg, 0.441 mmol) while stirring. A solution of *N*-Cbz-4-penten-1-amine (96.6 mg, 0.441 mmol) in 1,2-DCE (7.5 mL) was added under N_2 and the reaction heated to 50 °C for 16 hours. The reaction was then cooled to room temperature, exposed to air and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20% EtOAc/hexane) to afford 6-benzyloxycarbonylamino-hex-2-enethioic acid S-p-tolyl ester as a colourless solid (137 mg, 0.371 mmol, 84% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 - 7.42 (m, 5 H, Ar-H), 7.32 (d, *J* = 7.6 Hz, 2 H, H-14), 7.23 (d, *J* = 7.6 Hz, 2 H, H-15), 6.95 (dt, *J* = 16.0, 6.6 Hz, 1 H, H-10), 6.20 (d, *J* = 16.0 Hz, 1 H, H-11), 5.11 (s, 2 H, H-5), 4.80 (br. s., 1 H, NH), 3.25 (q, *J* = 7.1 Hz, 2 H, H-7), 2.39 (s, 3 H, H-17), 2.28 (td, *J* = 7.1, 6.6 Hz, 2 H, H-9), 1.72 (quin, *J* = 7.1 Hz, 2 H, H-8) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.4 (C-12), 156.4 (C-6), 144.9 (C-10), 139.7 (C-16), 136.4 (C-4), 134.6 (C-14), 130.0 (C-15), 128.5 (Ar-CH), 128.5 (Ar-CH), 128.3 (Ar-CH), 128.2 (C-11), 123.9 (C-13), 66.7 (C-5), 40.5 (C-7), 29.4 (C-9), 28.4 (C-8), 21.3 (C-17) ppm; IR (ATR): ν_{max} 3345, 3032, 2980, 2884, 1720, 1691, 1631, 1597, 1524, 1494, 1454, 1399, 1378 1336, 1248, 1140, 1104, 1091, 1026, 1017, 992, 808, 776, 752, 737, 697, 635, 649, 615, 476 cm^{-1}; HRMS (ESI) 392.1292 (M + Na^+. $C_{21}H_{23}NNaO_3S^+$ requires 392.1291); mp. 71.5-72.5 °C.

A solution of 6-benzyloxycarbonylamino-hex-2-enethioic acid S-p-tolyl ester (98.8 mg, 0.267 mmol) in cyclohexane (0.02M) was added to (*R*)-TRIP (40.3 mg, 0.0535 mmol) under N_2 and the reaction heated to 80 °C for 24 hours. The reaction was then cooled to room temperature, quenched with Et_3N (2 mL) and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc/hexane) to afford **5** as a yellow oil (86.3 mg, 0.233 mmol, 87% yield, 90:10 er). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 - 7.44 (m, 5 H, Ar-H), 7.25 - 7.30 (m, 2 H, H-14), 7.16 - 7.24 (m, 2 H, H-15), 5.08 - 5.26 (m, 2 H, H-5), 4.21 - 4.35 (m, 1 H, H-10), 3.38 - 3.51 (m, 2 H, H-7), 3.33 (dd, *J* = 14.9, 3.4 Hz, 0.5 H, *rotamer 1*, H-11), 3.10 (dd, *J* = 14.9, 3.4 Hz, 0.5 H, *rotamer 2*, H-11), 2.75 (dd, *J* = 15.3, 9.9 Hz, 0.5 H, *rotamer 1*, H-11), 2.68 (dd, *J* = 15.3, 9.9 Hz, 0.5 H, *rotamer 2*, H-11), 2.38 (s, 3 H, H-17), 1.99 - 2.15 (m, 1 H, H-9), 1.78 - 1.98 (m, 3 H, H-9, H-8) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 195.8(195.7) (C-12), 154.6(154.5) (C-6), 139.8(139.4) (C-16), 136.8(136.6) (C-4), 134.4(134.3) (C-14), 130.0(130.0) (C-15), 128.5 (Ar-CH), 128.4 (Ar-CH), 127.9(127.8) (Ar-CH), 124.1(123.9) (C-13), 66.9(66.7) (C-5), 55.0(54.4) (C-10), 47.7(46.7) (C-11), 46.7(46.4) (C-7), 30.9(30.2) (C-9), 23.6(22.8) (C-8), 21.3(C-17) ppm; IR (ATR): ν_{max} 3031, 2955, 2923, 1697, 1597, 1494, 1449, 1409, 1356, 1336, 1306, 1281, 1211, 1181, 1160, 1060, 1009, 985, 916, 879, 807, 768, 751, 697, 603, 551, 533, 474 cm^{-1}; HRMS (ESI) 370.1467 (M + H^+. $C_{21}H_{24}NO_3S$ requires 370.1471); 392.1289 (M + Na^+. $C_{21}H_{23}NNaO_3S^+$ requires 392.1291); $[\alpha]_D^{25}$ -21.6° (c 1.035, $CHCl_3$).

With (R)-TiPSY catalyst

A solution of 6-benzyloxycarbonylamino-hex-2-enethioic acid S-p-tolyl ester (194 mg, 0.526 mmol) in cyclohexane (0.02M) was added to (*R*)-TiPSY (91 mg, 0.105 mmol) under N_2 and the reaction heated to 80 °C for 24 hours. The reaction was then cooled to room temperature, quenched with Et_3N (2 mL) and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc/hexane) to afford **5** as a yellow oil (156 mg, 0.422 mmol, 80% yield, 94:6 er). Spectroscopic data was identical to that reported above. $[\alpha]_D^{20}$ -23.8° (c 0.358, $CHCl_3$).

*3.2. N-Cbz-(S)-2-(2-oxoethyl)pyrrolidine (**7**)*

A solution of pyrrolidine **5** (72.9 mg, 0.197 mmol) in CH_2Cl_2 (0.4 M) was cooled to -78 °C and a solution of DIBAL-H (1 M in hexanes, 0.60 mL) was added dropwise with and stirred for 1 h. The reaction was quenched with MeOH (1 mL) at -78 °C and allowed to warm to room temperature. The reaction was partitioned with an aqueous solution of Rochelle's salt (2 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fraction was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (15% EtOAc/hexane) to afford **7** as a colourless oil (15.9 mg, 0.0643 mmol, 33% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.78 (s, 0.6H, H-12, *rotamer 1*), 9.66 (s, 0.4H, H-12, *rotamer 2*), 7.43 – 7.26 (m, 5H, Ar-H), 5.16 – 5.04 (m, 2H, H-5), 4.33 – 4.28 (m, 1H, H-10), 3.54 – 3.35 (m, 2H, H-7), 2.98 (dd, *J* = 16.5, 3.7 Hz, 0.6H, H-11, *rotamer 1*), 2.81 (dd, *J* = 16.5, 3.7 Hz, 0.4H, H-11, *rotamer 2*), 2.49 (dd, *J* = 16.5, 7.6 Hz, 1H, H-11'), 2.19 – 2.06 (m, 1H, H-9), 1.91 – 1.80 (m, 2H, H-8), 1.70 – 1.62 (m, 1H, H-9') ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 200.9(200.7) (C-12), 155.0 (C-6), 136.9(136.6) (C-4), 128.6 (Ar-CH), 128.2(128.1) (Ar-CH), 128.0 (Ar-CH), 67.1(66.9) (C-5), 53.1(52.3) (C-10), 49.4(48.7) (C-11), 46.9(46.5) (C-7), 32.1(31.3) (C-9), 23.8(23.1) (C-8) ppm; IR (ATR): ν_{max} 2955, 1722, 1697, 1414, 1357, 1337, 1187, 1104, 729, 698 cm^{-1}; HRMS (ESI) 248.1278 (M + H^+. $C_{14}H_{18}NO_3^+$ requires 248.1281); 270.1100 (M + Na^+. $C_{14}H_{17}NNaO_3^+$ requires 270.1101); 286.0838 (M + K^+. $C_{14}H_{17}KNO_3^+$ requires 286.0840); $[\alpha]_D^{20}$ -31.3° (c 0.35, $CHCl_3$).

*3.2. N-Cbz-2-(2-Oxo-tetradecyl)-pyrrolidine (**9a**)*

1-Dodecene (0.22 mL, 1.00 mmol) was cooled to 0 °C under N_2 and a solution of 9-BBN (0.5 M in THF, 1.00 mmol) was added dropwise. The solution stirred for 1 hour at 0 °C and 2 hours at room temperature to afford the dodecyl-borane 10 solution (0.5 M, 1.00 mmol). A degassed solution of pyrrolidine 5 (38.2 mg, 0.103 mmol, 94:6 er) in dry THF (0.1 M) was added to CuTC (23.7 mg,

0.124 mmol), $Pd(PPh_3)_4$ (5.97 mg, 0.00517 mmol), and Cs_2CO_3 (36.5 mg, 0.103 mmol) under N_2 followed by 10 (0.5 M, 0.248 ml, 0.124 mmol). The solution was then degassed and backfilled with N_2 3 times and heated to 45 °C for 20 hours. The reaction was cooled to room temperature, diluted with Et_2O (20 ml) and partitioned with 2M HCl (10 mL). The organic fraction was washed with 2M NH_3 (3 x 10 mL) and saturated brine solution (10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc/hexane) to give **9a** as a colourless oil (32.9 mg, 0.0792 mmol, 77 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.26 (m, 5H, Ar-H), 5.19 – 5.04 (m, 2H, H-5), 4.23 – 4.15 (m, 1H, H-10), 3.50 – 3.34 (m, 2H, H-7), 3.14 (dd, *J* = 16.2, 3.3 Hz, 0.6H, *rotamer 1*, H-11), 2.86 (dd, *J* = 16.2, 3.3 Hz, 0.4H, *rotamer 2*, H-11), 2.49 – 2.31 (m, 2H, H-11', H-13), 2.30 – 2.20 (m, 1H, H-13'), 2.15 – 2.01 (m, 1H, H-9), 1.92 – 1.74 (m, 2H, H-8), 1.72 – 1.56 (m, 1H, H-9'), 1.55 – 1.36 (m, 3H, CH_2), 1.34 – 1.10 (m, 17H, CH_2), 0.86 (t, *J* = 6.8 Hz, 3H, H-24) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.9(209.7) (C-12), 154.7 (C-6), 137.0 (C-4), 128.6 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 66.9(66.7) (C-5), 54.2(53.4) (C-10), 47.6(46.8) (C-11), 46.6(46.5) (C-7), 43.5(43.3) (C-13), 32.1(32.0) (C-9), 31.7(31.0) (C-22), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.3 (CH_2), 23.8(22.9) (C-14), 23.7(22.8) (C-8), 22.1(C-23), 14.2 (C-24) ppm; IR (ATR): ν_{max} 3406, 2923, 2853, 1701, 1498, 1452, 1410, 1357, 1338, 1300, 1211, 1183, 1103, 1029, 977, 916, 875, 769, 734, 697, 600, 552, 460 cm^{-1}; HRMS (ESI) 416.3156 (M + H$^+$. $C_{26}H_{42}NO_3^+$ requires 416.3159); 438.2976 (M + Na$^+$. $C_{26}H_{41}NNaO_3^+$ requires 438.2979); 454.2705 (M + K$^+$. $C_{26}H_{41}NKO_3^+$ requires 454.2718); $[\alpha]_D^{20}$ -20.2° (c 1.00, $CHCl_3$).

*3.3. N-Cbz-2-[9-(2-Methoxy-phenyl)-2-oxo-nonyl]-pyrrolidine (**9b**)*

Olefin **S3** (43.1 mg, 0.211 mmol) was cooled to 0 °C under N_2 and a solution of 9-BBN (0.5 M in THF, 0.211 mmol) was added dropwise. The solution stirred for 1 hour at 0 °C and 2 hours at room temperature to afford the borane **11** solution (0.5 M, 0.211 mmol). A degassed solution of pyrrolidine **5** (64.8 mg, 0.176 mmol, 94:6 er) in dry THF (0.1 M) was added to CuTC (40.2 mg, 0.211 mmol), $Pd(PPh_3)_4$ (10.2 mg, 0.00880 mmol), and Cs_2CO_3 (62.1 mg, 0.176 mmol) under N_2 followed by **11** (0.5 M, 0.422 mL, 0.211 mmol). The solution was then degassed and backfilled with N_2 3 times and heated to 45 °C for 20 hours. The reaction was cooled to room temperature, diluted with Et_2O (20 mL) and partitioned with 2M HCl (10 mL). The organic fraction was washed with 2M NH_3 (3 x 10 mL) and saturated brine solution (10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (15% EtOAc/hexane) to give **9b** as a colourless oil (58.1 mg, 0.129 mmol, 73 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.26 (m, 5H, Ar-H), 7.16 (dd, *J* = 8.2, 7.6 Hz, 1H, H-23), 7.12 (d, *J* = 7.4 Hz, 1H, H-21), 6.87 (dd, *J* = 7.6, 7.4 Hz, 1H, H-22), 6.83 (d, *J* = 8.2 Hz, 1H, H-24), 5.22 – 5.05 (m, 2H, H-5), 4.25 – 4.16 (m, 1H, H-10), 3.80 (s, 3H, H-26), 3.44 – 3.36 (m, 2H, H-7),3.15 (dd, *J* = 16.7, 3.4 Hz, 0.6H, *rotamer 1*, H-11), 2.86 (dd, *J* = 16.7, 3.4 Hz, 0.4H *rotamer 2*, H-11), 2.59 (t, *J* = 7.6 Hz, 2H, H-19), 2.44 – 2.34 (m, 2H, H-11', H-13), 2.29 – 2.21 (m, 1H, H-13'), 2.16 – 2.02 (m, 1H, H-9), 1.87 – 1.79 (m, 2H, H-8), 1.71 – 1.62 (m, 1H, H-9'), 1.58 – 1.42 (m, 3H, H-18, H-14), 1.40 – 1.13 (m, 7H, H-14', H-15, H-16, H-17) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.8(209.6) (C-12), 157.5 (C-25), 154.7 (C-6), 137.0(136.8) (C-4), 131.3 (C-20), 129.8 (C-21), 128.6 (Ar-CH), 128.1 (Ar-CH), 128.0(127.9) (Ar-CH), 126.9 (C-23), 120.4 (C-22), 110.3 (C-24), 66.9(66.7) (C-5), 55.3 (C-26), 54.2(53.4) (C-10), 47.6(46.8) (C-11), 46.6(46.5) (C-7), 43.4(43.3) (C-13), 31.8(31.0) (C-9), 30.2 (C-19), 29.9 (C-18), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 23.8 (C-14), 23.7(22.9) (C-8) ppm; IR (ATR): ν_{max} 2928, 2855, 1698, 1600, 1493, 1455, 1411, 1356, 1336, 1241, 1178, 1103, 1049, 1029, 752, 698 cm^{-1}; HRMS (ESI) 452.2795 (M + H$^+$. $C_{28}H_{38}NO_4$ requires 452.2795); 474.2616 (M + Na$^+$. $C_{28}H_{37}NNaO_4$ requires 474.2615); 490.2356 (M + K$^+$. $C_{28}H_{37}NKO_4$ requires 490.2354); $[\alpha]_D^{20}$ -22.6° (c 1.00, $CHCl_3$).

*3.4. 1,1-Dimethyl-(S)-2-(2-methylsulfanylthiocarboxyoxy-tetradecyl)-pyrrolidinium iodide (mixture of diastereomers) (**12a**)*

A solution of pyrrolidine ketone **9a** (39.0 mg, 0.0938 mmol) in dry THF (0.5 mL) was added dropwise to a stirred solution of $LiAlH_4$ (17.8 mg, 0.469 mmol) in dry THF (0.5 mL) at 0 °C under N_2. The reaction was stirred at 0 °C for 1 hour then allowed to warm to room temperature and stirred overnight. The reaction was cooled to 0 °C and diluted with diethyl ether (2 mL) quenched with H_2O (0.1 mL), followed by NaOH solution (15% w/w aq, 0.1 mL), followed by H_2O (0.3 mL) and the reaction warmed to rt. $MgSO_4$ was added and the suspension was filtered through Celite®, followed by washings with diethyl ether (10 mL). The filtrate was concentrated *in vacuo* and the crude residue was further purified by silica plug filtration (1:10:90 NH_3/MeOH/DCM) to give crude the hydroxy pyrrolidine (22.7 mg, 0.763 mmol). The hydroxy pyrrolidine was dissolved in dry THF (1 mL) and added to NaH (60% in mineral oil, 6.1 mg, 0.153 mmol) and imidazole (0.1 mg, 0.00153 mmol) in a dry flask under N_2 at room temperature and the reaction was stirred for 30 mins. Carbon disulfide (0.023 mL, 0.0381 mmol) was added dropwise and the reaction stirred for 30 mins, followed by dropwise addition of methyl iodide (0.024 mL, 0.381 mmol). The reaction was stirred for 16 hours, then quenched with H_2O (1 mL) and partitioned with diethyl ether (20 mL). The organic fraction was washed with H_2O (20 mL) and saturated brine solution (20 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified using sodium iodide coated silica gel, eluting with 5% MeOH/CH_2Cl_2.[1] The isolated salt was then washed on a charcoal column with water, followed by MeOH to remove excess sodium iodide, then isolated by washing with 1:1 MeOH/CH_2Cl_2 to give the quaternary ammonium **12a** as a pale-orange oil (27.8 mg, 0.0525 mmol, 56% yield over two steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.83 – 5.70 (m, 1H, H-7), 4.33 (dt, *J* = 11.4, 5.4 Hz, 0.7H, H-2, *diastereomer 1*), 4.24 (ddd, *J* = 11.1, 8.1, 2.5 Hz, 0.3H, H-2, *diastereomer 2*), 3.90 – 3.54 (m, 2H, H-2', H-5), 3.53 (s, 0.9H, H-1, *diastereomer 1*), 3.47 (s, 2.1H, H-1, *diastereomer 2*), 3.20 (s, 2.1H, H-1', *diastereomer 1*), 3.11 (s, 0.9H, H-1', *diastereomer 2*), 2.56 (s, 2.1H, H-21, *diastereomer 1*), 2.55 (s, 0.9H, H-21, *diastereomer 2*), 2.47 – 2.36 (m, 1H, H-6), 2.28 – 2.10 (m, 2H, H-3), 2.10 – 1.64 (m, 4H, H-6, H-8, CH_2), 1.37 – 1.09 (m, 19H, CH_2), 0.84 (t, *J* = 6.7 Hz, 3H, H-19) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 216.7(215.9) (C-20), 81.1(80.2) (C-7), 73.9(73.4) (C-5), 67.1(66.6) (C-2), 51.7(51.5) (C-1), 45.7(45.3) (C-1'), 34.5(34.2) (C-8), 33.0(32.9) (C-6), 32.0 (C-17), 29.7 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.2(28.0) (C-4), 25.2(25.1) (C-9), 22.8 (C-18), 19.8(19.6) (C-3), 19.5(19.3) (C-21), 14.2 (C-19) ppm; IR (ATR): ν_{max} 3454, 2923, 2853, 1467, 1221, 1206, 1128, 1051, 965, 722 cm^{-1}; HRMS (ESI) 402.2858 (M$^+$. $C_{22}H_{44}NOS_2$ requires 402.2859).

*3.5. (S)-2-[9-(2-Methoxy-phenyl)-2-methylsulfanylthiocarboxyoxy-nonyl]-1,1-dimethyl-pyrrolidinium iodide (mixture of diastereomers) (**12b**)*

A solution of pyrrolidine ketone **9b** (50.7 mg, 0.112 mmol) in dry THF (0.5 mL) was added dropwise to a stirred solution of $LiAlH_4$ (21.3 mg, 0.561 mmol) in dry THF (0.5 mL) at 0 °C under N_2. The reaction was stirred at 0 °C for 1 hour then allowed to warm to room temperature and stirred overnight. The reaction was cooled to 0 °C and diluted with diethyl ether (2 mL) quenched with

H_2O (0.1 mL), followed by NaOH solution (15% w/w aq, 0.1 mL), followed by H_2O (0.3 mL) and the reaction warmed to rt. $MgSO_4$ was added and the suspension was filtered through Celite®, followed by washings with diethyl ether (10 mL). The filtrate was concentrated *in vacuo* and the crude residue was further purified by silica plug filtration (1:10:90 NH_3/MeOH/DCM) to give crude the hydroxy pyrrolidine (33.6 mg, 0.0101 mmol). The hydroxy pyrroldine was dissolved in dry THF (1 mL) and added to NaH (60% in mineral oil, 8.1 mg, 0.201 mmol) and imidazole (0.2 mg, 0.002 mmol) in a dry flask under N_2 at room temperature and the reaction was stirred for 30 mins. Carbon disulfide (0.030 mL, 0.504 mmol) was added dropwise and the reaction stirred for 30 mins, followed by dropwise addition of methyl iodide (0.030 mL, 0.504 mmol). The reaction was stirred for 16 hours, then quenched with H_2O (1 mL) and partitioned with diethyl ether (20 mL). The organic fraction was washed with H_2O (20 mL) and saturated brine solution (20 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified using sodium iodide coated silica gel, eluting with 5% MeOH/CH_2Cl_2.[1] The isolated salt was then washed on a charcoal column with water, followed by MeOH to remove excess sodium iodide, then isolated by washing with 1:1 MeOH/CH_2Cl_2 to give the quaternary ammonium **12b** as a yellow oil (22.6 mg, 0.0400 mmol, 36% yield over two steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.13 (ddd, *J* = 8.2, 7.6, 1.8 Hz, 1H, H-18), 7.09 (dd, *J* = 7.3, 1.8 Hz, 1H, H-16), 6.84 (dd, *J* = 7.6, 7.3 Hz, 1H, H-17), 6.81 (d, *J* = 8.2 Hz, 1H, H-19)5.81 – 5.73 (m, 1H, H-7), 4.36 – 4.27 (m, 0.7H, H-2, *diastereomer 1*), 4.27 – 4.18 (m, 0.3H, H-2, *diastereomer 2*),3.89 – 3.80 (m, 0.3H, H-5, *diastereomer 1*), 3.78 (s, 3H, H-21), 3.76 – 3.64 (m, 1H, H-2), 3.62 – 3.53 (m, 0.7H, H-5 *diastereomer 2*), 3.51 (s, 0.9H, H-1, *diastereomer 1*), 3.46 (s, 2.1H, H-1, *diastereomer 2*), 3.19 (s, 2.1H, H-1', *diastereomer 1*), 3.10 (s, 0.9H, H-1', *diastereomer 2*), 2.56 (s, 3H, H-23), 2.55 (t, *J* = 7.8 Hz, 2H, H-14),2.46 – 2.36 (m, 1H, H-6),2.28 – 2.10 (m, 2H, H-3), 2.07 – 2.00 (m, 1H, H-6'), 2.00 – 1.79 (m, 3H, H-8, CH_2), 1.79 – 1.67 (m, 1H, H-8'), 1.56 – 1.48 (m, 2H, H-13), 1.42 – 1.24 (m, 8H, CH_2) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 216.7(216.0) (C-22), 157.5 (C-20), 131.3 (C-15), 129.8 (C-16), 126.9 (C-18), 120.4 (C-17), 110.3 (C-19), 81.1(80.2) (C-7), 73.4 (C-5), 67.1 (C-2), 55.4 (C-21), 51.7 (C-1), 45.7 (C-1'), 34.5(34.2) (C-8), 33.0(32.8) (C-6), 30.2 (C-14), 29.8 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.2 (C-4), 25.2(25.1) (C-9), 19.8 (C-3), 19.6 (C-23) ppm; IR (ATR): ν_{max} 3452, 2926, 2854, 1706, 1599, 1492, 1464, 1289, 1241, 1223, 1125, 1052, 965, 754 cm^{-1}; HRMS (ESI) 438.2496 (M^+. $C_{24}H_{40}NO_2S_2$ requires 438.2495).

*3.6. N-Cbz-(S)-2-(2-Hydroxy-tetradecyl)-pyrrolidine (mixture of diastereomers) (**13a**)*

A solution of pyrrolidine ketone **9a** (47.8 mg, 0.115 mmol) in dry MeOH (5 mL) was cooled to 0 °C and $NaBH_4$ (8.70 mg, 0.230 mmol) was added portion wise. The reaction was stirred for 1 hour, then quenched with 2M HCl (5 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ solution (2 x 20 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo* without further purification to give **13a** as a colourless oil (47.3 mg, 0.113 mmol, 98% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.26 (m, 5H, Ar-H), 5.19 – 5.05 (m, 2H, H-5), 4.71–4.14 (m, 0.4H, OH), 4.14–3.14 (m, 4H, H-7, H-10, H-12), 2.07 – 1.55 (m, 5H, CH_2), 1.57 –1.02 (m, 23H, CH_2), 0.91 – 0.77 (m, 3H, H-24) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.0(155.6) (C-6), 137.0(136.8) (C-4), 128.6(128.6) (Ar-CH), 128.1(128.0) (Ar-CH), 128.0(127.9) (Ar-CH), 70.8(70.3)(67.7) (C-12), 67.2(66.9) (C-5), 56.2(54.7) (C-10), 46.4(46.3) (C-7), 43.9(43.5) (CH_2), 38.2(37.1) (CH_2), 32.1(32.0) (CH_2), 31.3 (CH_2), 29.9(29.8) (CH_2), 29.7(CH_2), 29.7(CH_2), 29.5(CH_2), 27.5(26.9) (CH_2), 26.3(26.2) (CH_2), 25.8 (CH_2), 23.9 (CH_2), 22.8 (CH_2), 22.1 (CH_2), 14.2 (C-24) ppm; IR (ATR): ν_{max} 3418, 2922, 2852, 1681, 1498, 1453, 1411, 1357, 1337, 1300, 1260, 1211, 1187, 1164, 1101, 1029, 979, 912, 870, 803, 768, 732, 696, 675, 602 cm^{-1}; HRMS (ESI) 418.3319 ($M + H^+$. $C_{26}H_{44}NO_3$ requires 418.3316); 440.3135 ($M + Na^+$. $C_{26}H_{43}NNaO_3$ requires 440.3135).

*3.7. N-Cbz-(S)-2-[2-Hydroxy-9-(2-methoxy-phenyl)-nonyl]-pyrrolidine (mixture of diastereomers) (**13b**)*

A solution of pyrrolidine ketone **9b** (90.0 mg, 0.199 mmol) in dry MeOH (5 mL) was cooled to 0 °C and $NaBH_4$ (15.1 mg, 0.399 mmol) was added portion wise. The reaction was stirred for 1 hour, then quenched with 2M HCl (5 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ solution (2 x 20 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo* without further purification to give **13b** as a colourless oil (90.3 mg, 0.199 mmol, 100% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.25 (m, 5H, Ar-H), 7.16 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H, H-23), 7.12 (dd, *J* = 7.5, 1.8 Hz, 1H, H-21), 6.88 (ddd, *J* = 7.8, 7.5, 1.1 Hz, 1H, H-22), 6.84 (dd, *J* = 7.8, 1.1 Hz, 1H, H-24), 5.23 – 5.01 (m, 2H, H-5), 4.69 (s, 0.3H, O-H), 4.32 – 3.98 (m, 1H, H-10), 3.81 (s, 3H, H-26), 3.69 – 3.47 (m, 1H, H-12), 3.47 – 3.29 (m, 2H, H-7), 2.60 (t, *J* = 7.5 Hz, 2H, H-19), 2.10 – 1.24 (m, 18H, CH_2) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.5(157.0) (C-25), 155.6(155.0) (C-6), 137.0(136.8) (C-4), 131.4 (C-20), 129.8 (C-21), 128.6(128.6) (Ar-CH), 128.1(128.1) (Ar-CH), 128.0(127.9) (Ar-CH), 126.9 (C-23), 120.4 (C-22), 110.3 (C-24), 70.8(70.3) (C-12 *diastereomer 1*), 69.8(67.7) (C-12 *diastereomer 2*),67.2(66.9) (C-5), 56.2(54.7) (C-10), 55.3 (C-26), 46.5(46.3) (C-7), 43.9(43.5) (CH_2), 38.2(37.1) (CH_2), 32.1(31.3) (CH_2), 30.2(30.0) (CH_2), 30.0(29.9) (CH_2), 29.8(29.8) (CH_2), 29.7(29.6) (CH_2), 26.2(25.8) (CH_2), 23.9(23.7) (CH_2),22.4(22.1) (CH_2) ppm; IR (ATR): ν_{max} 3424, 2924, 2853 , 1678, 1600, 1587, 1493, 1454, 1411, 1356, 1336, 1290, 1240, 1212, 1187, 1162, 1101, 1049, 1029, 978, 913, 871, 808, 768, 751, 697, 675, 603, 542, 464 cm^{-1}; HRMS (ESI) 454.2954 ($M + H^+$. $C_{28}H_{40}NO_4$ requires 454.2952); 476.2773 ($M + Na^+$. $C_{28}H_{39}NNaO_4$ requires 476.2771).

*3.8. 3-Dodecyl-hexahydro-pyrrolo[1,2-c][1,3]oxazin-1-one (mixture of diastereomers) (**14a**)*

A solution of hydroxy pyrrolidine **13a** (47.3 mg, 0.113 mmol) in dry THF (2 mL) was added to NaH (60% in mineral oil, 9.1 mg, 0.227 mmol) and imidazole (0.2 mg, 0.00227 mmol) in a dry flask under N_2 at room temperature and the reaction was stirred for 30 mins. Carbon disulfide (0.040 mL, 0.566 mmol) was added dropwise and the reaction stirred for 30 mins, followed by dropwise addition of methyl iodide (0.040 mL, 0.566 mmol). The reaction was stirred for 16 hours, then quenched with H_2O (2 mL) and partitioned with CH_2Cl_2 (20 mL). The organic fraction was washed with 1M HCl (20 mL), saturated aqueous $NaHCO_3$ solution (20 mL), and H_2O (20 mL) dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified with flash column chromatography (25-75% EtOAC/hexane) to give **14a** as a white solid (23.4 mg, 0.0756 mmol, 67% yield, 5:1 dr). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.44 – 4.35 (m, 0.1H, H-7 *diastereomer 1*), 4.24 – 4.13 (m, 0.9H, H-7 *diastereomer 2*), 3.62 – 3.40 (m, 3H, H-2, H-5), 2.19 – 1.90 (m, 3H, CH_2), 1.84 – 1.61 (m, 2H, CH_2), 1.61 – 1.13 (m, 23H, CH_2), 0.86 (t, *J* = 6.7 Hz, 3H, H-19) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 153.5 (C-1), 77.5 (C-7), 56.6 (C-5), 46.5 (C-2), 35.3 (CH_2), 33.8 (CH_2), 33.3 (CH_2), 32.0 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 24.9 (CH_2), 23.1 (CH_2), 22.8 (CH_2), 14.2 (C-19) ppm; IR (ATR): ν_{max} 2954, 2917, 2849, 1688, 1519, 1463, 1437, 1378, 1324, 1306, 1243, 1200, 1155, 1127, 1050, 1015, 971, 905, 887, 802, , 754, 729, 670, 655,

631, 588, 523, 483, 458 cm^{-1}; HRMS (ESI) 310.2740 (M + H^+. $C_{19}H_{36}NO_2$ requires 310.2741); 332.2555 (M + Na^+. $C_{19}H_{35}NNaO_2$ requires 332.2560); mp. 63-66 °C.

*3.9. 3-[7-(2-Methoxy-phenyl)-heptyl]-hexahydro-pyrrolo[1,2-c][1,3]oxazin-1-one (mixture of diastereomers) (**14b**)*

A solution of hydroxy pyrrolidine **13b** (90.3 mg, 0.199 mmol) in dry THF (2 mL) was added to NaH (60% in mineral oil, 15.9 mg, 0.398 mmol) and imidazole (0.3 mg, 0.00398 mmol) in a dry flask under N_2 at room temperature and the reaction was stirred for 30 mins. Carbon disulfide (0.060 mL, 0.995 mmol) was added dropwise and the reaction stirred for 30 mins, followed by dropwise addition of methyl iodide (0.060 mL, 0.995 mmol). The reaction was stirred for 16 hours, then quenched with H_2O (2 mL) and partitioned with CH_2Cl_2 (20 mL). The organic fraction was washed with 1M HCl (20 mL), saturated aqueous $NaHCO_3$ solution (20 mL), and H_2O (20 mL) dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified with flash column chromatography (25-75% EtOAC/hexane) to give **14b** as a pale yellow oil (43.0 mg, 0.124 mmol, 63% yield, 7:1 dr). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.14 (ddd, *J* = 7.8, 7.4, 1.8 Hz, 1H, H-16), 7.10 (dd, *J* = 7.4, 1.8 Hz, 1H, H-18), 6.86 (dd, *J* = 7.4, 7.4 Hz, 1H, H-17), 6.82 (d, *J* = 7.8 Hz, 1H, H-19), 4.50 – 4.30 (m, 0.1H, H-7 *diastereomer 1*), 4.27 – 4.11 (m, 0.9H, H-7 *diastereomer 2*), 3.80 (s, 3H, H-21), 3.66 – 3.35 (m, 3H, H-2, H-5), 2.58 (t, *J* = 7.8 Hz, 2H, H-14), 2.17 – 2.05 (m, 2H, CH_2), 2.03 – 1.91 (m, 1H, CH_2), 1.86 –1.43 (m, 7H, CH_2), 1.43 – 1.17 (m, 8H, CH_2) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.5 (C-20), 153.5 (C-1), 131.3 (C-15), 129.8 (C-16), 126.9 (C-18), 120.4 (C17), 110.3(C19), 77.5 (C-7), 56.6(55.3) (C-5), 55.4 (C-21), 46.5 (C-2), 35.3 (CH_2), 33.8 (CH_2), 33.3 (C-4), 30.2 (C-14), 29.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 24.9 (CH_2), 23.1 (C-3) ppm; IR (ATR): ν_{max} 2925, 2854, 1689, 1600, 1587, 1493, 1462, 1423, 1370, 1342, 1312, 1289, 1240, 1201, 1176, 1117, 1049, 1029, 924, 887, 753, 653, 568, 477 cm^{-1}; HRMS (ESI) 346.2375 (M + H^+. $C_{21}H_{32}NO_3$ requires 346.2377); 368.2194 (M + Na^+. $C_{21}H_{31}NNaO_3$ requires 368.2196).

*3.10. N-Cbz-(S)-2-(2-Dodecyl-[1,3]dithiolan-2-ylmethyl)-pyrrolidine (**15a**)*

Pyrrolidine ketone **9a** (42.4 mg, 0.102 mmol) and 1,2-ethanedithiol (0.17 mL, 2.04 mmol) was dissolved in dry CH_2Cl_2 (0.7 mL, 0.16M) under N_2. $BF_3.Et_2O$ (0.15 mL, 1.22 mmol) was added dropwise and the reaction stirred for 4 hours. The reaction was quenched with acetone (0.6 mL), diluted with saturated aqueous $NaHCO_3$ solution (10 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic fractions were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc/hexane) to give **15a** as a colourless oil (14.9 mg, 0.0303 mmol, 30% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.23 (m, 5H, Ar-H), 5.18 – 5.05 (m, 2H, H-5), 4.20 – 4.01 (m, 1H, H-10), 3.43 – 3.30 (m, 2H, H-7), 3.32 – 3.00 (m, 4H, H-25, H-26), 2.52 (d, *J* = 14.2 Hz, 0.5H, H-11), 2.31 (d, *J* = 14.2 Hz, 0.5H, H-11), 2.11 – 2.07 (m, 1H, H-9), 2.01 – 1.76 (m, 6H, CH_2), 1.55 – 1.00 (m, 20H, CH_2), 0.86 (t, *J* = 6.7 Hz, 3H, H-24) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.8 (C-6), 134.9 (C-4), 128.5 (Ar-CH), 127.9 (Ar-CH), 127.8 (Ar-CH), 69.8 (C-12), 66.9 (66.6) (C-5), 56.4 (55.8) (C-10), 46.0 (C-7), 45.4 (C-11), 44.6 (CH_2), 39.6 (C-25), 39.1 (C-26), 32.1(31.6) (C-9), 32.0 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 26.8 (CH_2), 24.0(23.2) (C-8), 22.8 (C-23), 14.2 (24) ppm; IR (ATR): ν_{max} 2923, 2852, 1700, 1497, 1455, 1408, 1356, 1337, 1186, 1029, 768, 750, 697, 602 cm^{-1}; HRMS (ESI) 492.2950 (M + H^+. $C_{28}H_{46}NO_2S_2$ requires 492.2964); 514.2778 (M + Na^+. $C_{28}H_{45}NNaO_2S_2$ requires 514.2784); 530.2717 (M + K^+. $C_{28}H_{45}KNO_2S_2$ requires 530.2733); $[\alpha]_D^{25}$ -23.6° (c 0.71, $CHCl_3$).

*3.11. N-Cbz-(S)-2-{2-[7-(2-Methoxy-phenyl)-heptyl]-[1,3]dithiolan-2-ylmethyl}-pyrrolidine (**15b**)*

Pyrrolidine ketone **9b** (55.9 mg, 0.124 mmol) and 1,2-ethanedithiol (0.210 mL, 2.48 mmol) was dissolved in dry CH_2Cl_2 (0.8 mL, 0.16M) under N_2. $BF_3.Et_2O$ (0.180 mL, 1.49 mmol) was added dropwise and the reaction stirred for 4 hours. The reaction was quenched with acetone (0.6 mL), diluted with saturated aqueous $NaHCO_3$ solution (10 mL), and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic fractions were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (15% EtOAc/hexane) to give **15b** as a colourless oil (21.3 mg, 0.0404 mmol, 33% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.25 (m, 5H, Ar-H), 7.15 (ddd, *J* = 8.1, 7.4, 1.8 Hz, 1H, H-23), 7.11 (dd, *J* = 7.3, 1.8 Hz, 1H, H-21), 6.87 (dd, *J* = 7.4, 7.3 Hz, 1H, H-22), 6.83 (d, *J* = 8.1 Hz, 1H, H-24), 5.19 – 5.02 (m, 2H, H-5), 4.21 – 4.03 (m, 1H, H-10), 3.80 (s, 3H, H-26), 3.47 – 3.31 (m, 2H, H-7), 3.32 – 3.01 (m, 4H, H-27, H-28), 2.58 (t, *J* = 7.5 Hz, 2H, H-19), 2.52 (d, *J* = 14.2 Hz, 0.5H, H-11, *rotamer 1*), 2.31 (d, *J* = 14.6 Hz, 0.5H, H-11, *rotamer 2*), 2.11 – 2.07 (m, 1H, H-9), 2.03 – 1.75 (m, 6H, CH_2), 1.59 – 1.12 (m, 10H, CH_2) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.5 (C-25), 154.8 (C-6), 131.4 (C-20), 129.8 (C-21),128.5 (Ar-CH), 128.1 (Ar-CH), 127.9 (Ar-CH), 126.8 (C-23), 120.4 (C-22), 110.3 (C-24), 69.8 (C-12), 67.0(66.5) (C-5), 56.4(55.7) (C-10), 55.3 (C-26), 46.0 (45.3) (C-11), 44.6 (CH_2), 39.6 (C-27), 39.0 (C-28), 32.1 (31.6) (C-9), 30.2 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 26.8 (CH_2), 24.0(23.2) (C-8) ppm; IR (ATR): ν_{max} 2927, 2854, 1698, 1493, 1455, 1409, 1356, 1336, 1288, 1241, 1185, 1101, 1050, 1030, 752, 697, 602 cm^{-1}; HRMS (ESI) 528.2609 (M + H^+. $C_{30}H_{42}NO_3S_2$ requires 528.2601); 550.2426 (M + Na^+. $C_{30}H_{41}NNaO_3S_2$ requires 550.2420); $[\alpha]_D^{20}$ -20.8° (c 0.915, $CHCl_3$).

*3.12. N-Cbz-2-Tetradecyl-pyrrolidine (**16a**)*

Ketone **9a** (48.4 mg, 0.116 mmol) was dissolved in MeOH (5 mL) and added to p-toluenesulfonyl hydrazide (32.5 mg, 0.175 mmol) followed by AcOH (cat. ~0.1 mL). The reaction was stirred at room temperature for 24 hours, then concentrated in vacuo. The crude material was filtered through a pad of silica (25% EtOAc/hexane) to give the tosylhydrazone as a brown residue (59.4 mg, 0.102 mmol, 88 % yield). A portion of the tosylhydrazone (16.5 mg, 0.0283 mmol) in anhydrous MeOH (1 mL) was added to $NaBH_3CN$ (8.86 mg, 0.141 mmol) and $ZnCl_2$ (9.63 mg, 0.0707 mmol) under N_2 and the reaction heated to reflux for 16 hours. The reaction was quenched with 5% NaOH (aq) (5 mL) extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with water (10 mL) and saturated brine solution (10 mL), dried with $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by column chromatography (10% Et_2O/hexane) to give **16a** as a yellow oil (9.2 mg, 0.0229 mmol, 81 % yield). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.46 – 7.25 (m, 5H, Ar-H), 5.20 – 5.05 (m, 2H, H-5), 3.89 – 3.74 (m, 1H, H-10), 3.50 – 3.31 (m, 2H, H-7), 2.01 – 1.61 (m, 5H, CH_2), 1.38 – 1.00 (m, 25H, CH_2), 0.87 (t, J = 7.4 Hz, 3H, H-24) ppm; ^{13}C NMR (101 MHz, Chloroform-d) δ 154.1 (C-6), 128.5 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 66.7(66.5) (C-5), 58.2(57.4) (C-10), 46.7(46.3) (C-7), 34.6(34.0) (CH_2), 32.0 (CH_2), 30.6(30.4) (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 23.9 (CH_2), 23.1 (CH_2), 22.8 (C-23), 14.2 (C-24) ppm; IR (ATR): ν_{max} 2923, 2853, 1703, 1618, 1456, 1410, 1357, 1334, 1185, 1100, 768, 696 cm^{-1}; HRMS (ESI) 402.3372 (M + H^+. $C_{26}H_{44}NO_2$ requires 402.3367); 424.3185 (M + Na^+. $C_{26}H_{43}NNaO_2$ requires 424.3186); $[\alpha]_D^{20}$ -22.8° (c 0.285, $CHCl_3$), lit. $[\alpha]_D^{26}$ -23.07° (c 0.89, $CHCl_3$)[12].

*3.13. N-Cbz-2-[9-(2-Methoxy-phenyl)-nonyl]-pyrrolidine (**16b**)*

Ketone **9b** (55.0 mg, 0.122 mmol) was dissolved in MeOH (5 mL) and added to *p*-toluenesulfonyl hydrazide (34.0 mg, 0.183 mmol) followed by AcOH (cat. ~0.1 mL). The reaction was stirred at room temperature for 24 hours, then concentrated *in vacuo*. The crude material was filtered through a pad of silica (30% EtOAc/hexane) to give the tosylhydrazone as a brown residue (66.8 mg, 0.108 mmol, 88 % yield). A portion of the tosylhydrazone (5.7 mg, 0.00920 mmol) in anhydrous MeOH (1 mL) was added to $NaBH_3CN$ (2.89 mg, 0.0460 mmol) and $ZnCl_2$ (3.13 mg, 0.0230 mmol) under N_2 and the reaction heated to reflux for 16 hours. The reaction was quenched with 5% NaOH (aq) (5 mL) extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with water (10 mL) and saturated brine solution (10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (15% Et_2O/hexane) to give **16b** as a yellow oil (1.6 mg, 0.00366 mmol, 40 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.25 (m, 5H, Ar-H), 7.15 (dd, *J* = 8.4, 7.8 Hz, 1H, H-23), 7.12 (d, *J* = 7.6 Hz, 1H, H-21), 6.87 (t, *J* = 7.8, 7.6 Hz, 1H, H-22), 6.83 (d, *J* = 8.4 Hz, 1H, H-24), 5.20 – 5.05 (m, 2H, H-5), 3.89 – 3.77 (m, 1H, H-10), 3.81 (s, 3H, H-26), 3.52 – 3.31 (m, 2H, H-7), 2.58 (t, *J* = 7.8 Hz, 2H, H-19), 1.98 – 1.61 (m, 5H, CH_2), 1.59 – 1.51 (m, 2H, CH_2), 1.42 – 1.13 (m, 13H, CH_2) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.5 (C-25), 154.9 (C-6), 131.4 (C-20), 129.8 (C-21), 128.5 (Ar-CH), 127.9 (Ar-CH), 127.9 (Ar-CH), 126.8 (C-23), 120.4 (C-22), 110.3 (C-24), 66.5 (C-5), 58.2 (C-10), 55.3 (C-26), 46.7 (C-7), 34.0(C-11), 30.7 (C-9), 30.2(C-19), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 26.4 (C-12), 23.9 (CH_2), 23.1 (C-8) ppm; IR (ATR): ν_{max} 2924, 2853, 1701, 1601, 1587, 1493, 1455, 1410, 1356, 1334, 1288, 1259, 1241, 1178, 1097, 1050 1029, 913, 864, 802, 763, 751, 697, 600 cm^{-1}; HRMS (ESI) 460.2819 (M + Na$^+$. $C_{28}H_{39}NNaO_3$ requires 460.2822); $[\alpha]_D^{20}$ -24.4° (c 0.20, $CHCl_3$).

*3.14. (R)-Bgugaine (**1**)*

A solution of pyrrolidine **16a** (9.2 mg, 0.0229 mmol) in dry THF (0.25 mL) was added to a solution of $LiAlH_4$ (8.69 mg, 0.229 mmol) in dry THF (0.25 mL) at 0 °C under N_2. The reaction was allowed to warm to room temperature with stirring for 15 hours. The reaction was cooled to 0 °C, diluted with Et_2O (5 mL), quenched with 5% NaOH solution (0.1 mL) and dried with $MgSO_4$. The mixture wa filtered through celite and concentrated *in vacuo*. The crude material was purified by column chromatography (1:10:90 NH_3/MeOH/DCM) to give **1** as a yellow oil (4.4 mg, 0.0156 mmol, 68% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.05 (ddd, *J* = 9.1, 7.8, 2.2 Hz, 1H, H-5), 2.29 (s, 3H, N-Me), 2.10 (ddd, *J* = 9.1, 9.1, 8.7 Hz, 1H, H-5), 1.99 – 1.84 (m, 2H, H-2, CH_2), 1.80 – 1.69 (m, 1H, CH_2), 1.69 – 1.58 (m, 2H, CH_2), 1.48 – 1.34 (m, 1H, CH_2), 1.34 – 1.06 (m, 25H, CH_2), 0.84 (t, *J* = 7.1 Hz, 3H, H-14') ppm;^{13}C NMR (101 MHz, Chloroform-*d*) δ 66.5 (C-2), 57.3 (C-5), 40.4 (N-Me), 33.8 (C-1'), 31.9 (C-12'), 30.8 (C-3), 30.0 (C-3'), 29.7-29.6 (C-4'-C-10'), 29.4 (C-11'), 26.7 (C-2'), 22.7 (C-13'), 21.8 (C-4), 14.1 (C-14') ppm; IR (ATR): ν_{max} 2922, 2852, 2772, 1457, 1376, 1350, 1215, 1163, 1114, 1042, 896, 721, 573 cm^{-1}; HRMS (ESI) 282.3159 (M + H$^+$. $C_{19}H_{40}N$ requires 282.3155); $[\alpha]_D^{20}$ -35.9° (c 0.22, MeOH), lit $[\alpha]_D^{22}$ -48° (c 0.5, MeOH)[1]. Spectra was identical to that reported in the literature.[1]

*3.15. (R)-Irnidine (**2**)*

A solution of pyrrolidine **16b** (10.8 mg, 0.0247 mmol) in dry THF (0.25 mL) was added to a solution of $LiAlH_4$ (9.34 mg, 0.247 mmol) in dry THF (0.25 mL) at 0 °C under N_2. The reaction was allowed to warm to room temperature with stirring for 15 hours. The reaction was cooled to 0 °C, diluted with Et_2O (5 mL), quenched with 5% NaOH solution (0.1 mL) and dried with $MgSO_4$. The mixture was filtered through celite and concentrated *in vacuo*. The crude material was purified by column chromatography (1:10:90 NH_3/MeOH/DCM) to give **2** as a yellow oil (6.9 mg, 0.0217 mmol, 88% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.15 (td, *J* = 8.2, 7.4, 1.8 Hz, 1H, H-4"), 7.11 (dd, *J* = 7.3, 1.8 Hz, 1H, H-6"), 6.86 (ddd, *J* = 7.4, 7.3, 1.2 Hz, 1H, H-5"), 6.83 (dd, *J* = 8.2, 1.2 Hz, 1H, H-3"), 3.81 (s, 3H, O-CH_3), 3.05 (ddd, *J* = 9.5, 7.8, 2.1 Hz, 1H, H-5), 2.58 (t, *J* = 7.8 Hz, 2H, H-14), 2.29 (s, 3H, H-1), 2.18 – 2.05 (m, 1H, H-5), 2.04 – 1.84 (m, 2H, H-2, CH_2), 1.84 – 1.60 (m, 3H, CH_2), 1.60 – 1.50 (m, 2H, CH_2), 1.49 – 1.11 (m, 14H, CH_2) ppm; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.4 (C-2"), 131.3 (C-1"), 129.7 (C-6"), 126.7 (C-4"), 120.2 (C-5"), 110.1 (C-3"), 66.6 (C-2), 57.2 (C-5), 55.2 (O-CH_3), 40.2 (N-Me), 33.5 (C-1'), 30.6 (C-3), 30.1 (C-9'), 30.0 (C-8'), 29.8 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 26.7 (C-2'), 21.7 (C-4) ppm; IR (ATR): ν_{max} 2925, 2853, 2775, 1672, 1601, 1493, 1463, 1289, 1241, 1176, 1127, 1050, 1031, 751 cm^{-1}; HRMS (ESI) 318.2790 (M + H$^+$. $C_{21}H_{36}NO$ requires 318.2791); $[\alpha]_D^{20}$ -18.2° (c 0.165, $CHCl_3$) lit. $[\alpha]_D^{25}$ -20° (c 0.3, $CHCl_3$).[4]

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Supplementary Material

Supplementary material contains ^{1}H NMR and ^{13}C NMR spectra of compounds in the manuscript. Additional reference spectroscopic and reaction data can be found at DOI: 10.15124/ea517ae1-da80-4922-adbb-1e00f7e151ec