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Synthesis of the heterocyclic core of martinelline and martinellic acid

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Abstract—A Povarov reaction, between an aromatic imine derived from cinnamaldehyde and a cyclic enamide, was employed to rapidly construct the tricyclic core of the alkaloids martinelline and martinellic acid. The cycloaddition was completely regioselective though the *exo/endo* selectivity was poor. The diastereoisomers were readily separated by flash chromatography and the relative stereochemistry of the *exo*-isomer confirmed by single crystal X-ray crystallography. This intermediate was converted to the central core of the aforementioned alkaloids in five additional synthetic operations.
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1. Introduction

There is currently much interest in identifying non-peptide bradykinin inhibitors as potential therapeutic agents.[1–7] Bioassay guided fractionation of an extract from the medicinal plant *Martinella iquitosensis* led to the isolation of the first natural product bradykinin receptor inhibitors, martinellic acid and martinelline **1a**,**b**, respectively, Figure 1.[8] These alkaloids are unique in that they contain the unusual hexahydropyrroloquinoline moiety. The biological activity, coupled with the unusual heterocyclic motif, has made these alkaloids very attractive synthetic targets. This has prompted new methods for forming hexahydropyrroloquinolines,[9–26] culminating in four syntheses[27–30] and three formal syntheses of these alkaloids,[31–33] and the subject has been recently reviewed.[34]

The major challenges in this synthesis are control of the regiochemistry on the trisubstituted aromatic ring, the stereochemistry at the three contiguous chiral centres and coping with the labile heteroatom at C9b. On the last point, it is well known that heteroatoms on the 4-position of a tetrahydroquinoline are prone to eliminate, ultimately giving quinolines. Therefore, methods for producing the hexahydropyrroloquinoline must be mild and it is prudent not to do too
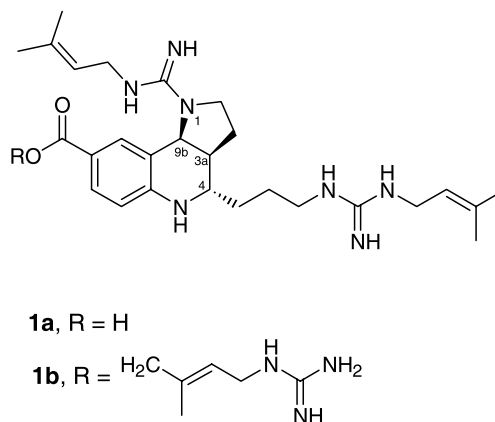

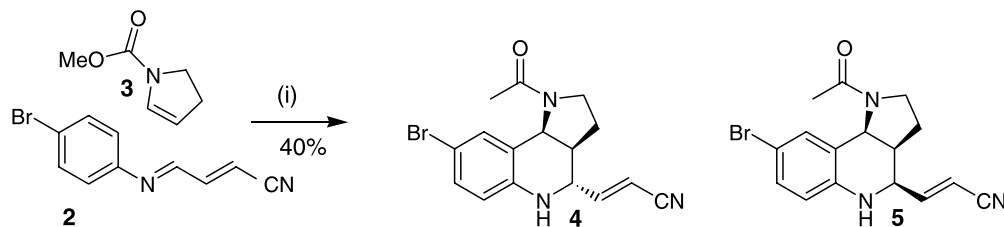**Figure 1.** Structure of martinelline and martinellic acid.

much additional chemistry once the hexahydropyrroloquinoline is in place. We previously communicated the first approach to the heterocyclic core of martinelline **17**, using a Povarov reaction of imines derived from aromatic amines with cyclic enamides as the key step and now report full details on this study. Triamine **17** was the key intermediate in all subsequent syntheses of martinellic acid.

2. Results and discussion

Our initial strategy, Scheme 1, focussed on using a Povarov reaction to construct the hexahydropyrroloquinoline with all
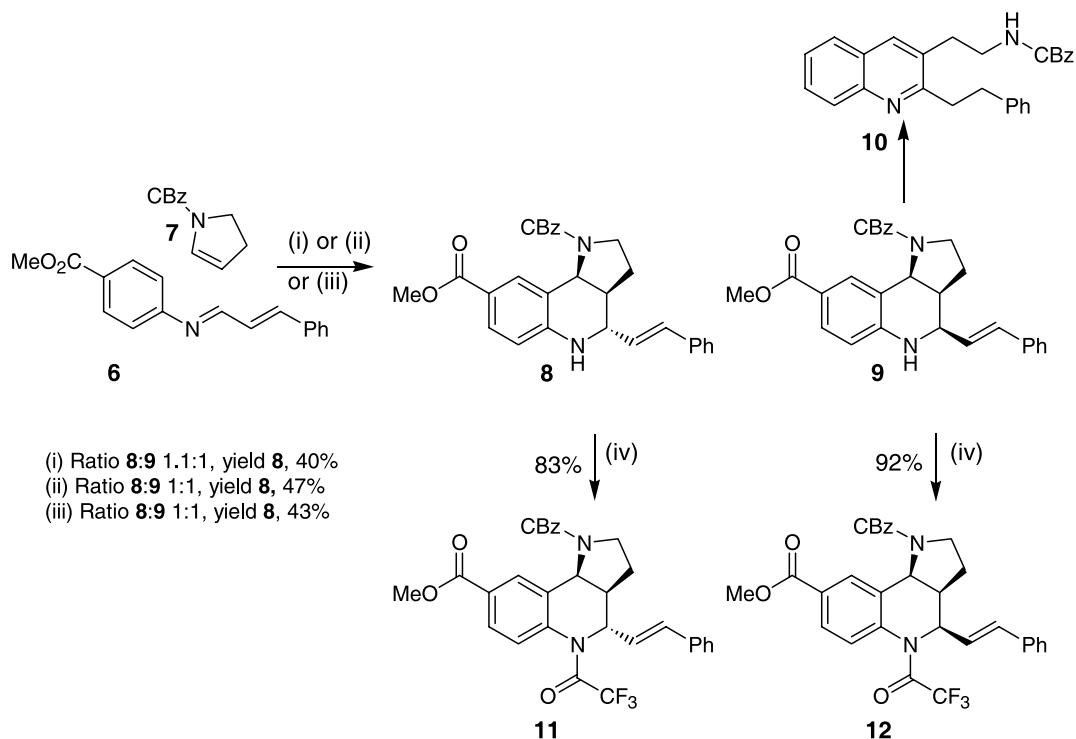
Scheme 1. Reagents and conditions: (i) indium trichloride 20%, acetonitrile 30 min 25 °C.

the carbons, bar the 8-carboxy, and nitrogens in place, though not at the correct oxidation level for martinellic acid. The main advantages of this approach were its convergence, its complete regioselectivity, and the symmetry was such that *p*-substituted benzenes ensured the correct regiochemistry of the tri-substituted aromatic ring on cycloaddition. The regioselectivity from this ionic stepwise pathway was governed by the stability of the acyliminium ion intermediate. Unfortunately, this chemistry failed with aliphatic aldehydes and with α,β-unsaturated aldehydes with hydrogens on the γ-position, making it difficult to introduce the required 4-substituent. However, this problem was overcome by using (*E*)-3-oxo-1-propenyl cyanide[35] as the aldehyde component.

We previously reported that 3-cyanoacrolein condensed with *p*-bromaniline to give an unstable imine **2**, which underwent Povarov reaction with cyclic enamide **3** to give a 1:3 mixture of *exo/endo* hexahydropyrroloquinolines **4** and **5** in 40% combined yield. Although this chemistry elegantly gave the gross structure of a key martinelline intermediate in one step, the low yield and *endo*-selectivity was unacceptable. Furthermore, attempts to reduce the alkene and nitrile using hydrogen and

palladium led to a complex mixture of products, suggesting that N5 may need protecting prior to reduction of the nitrile and that the 8-bromo substituent was also labile under these conditions. Enamide **3** was initially chosen as the NMR spectra of the cycloadducts derived from this were reasonably sharp and easy to interpret. However, with compound **4**, attempted removal of the carbomethoxy group with trimethylsilyl iodide[36] led to intractable material. It was clear from this initial study that we would have to improve the yield and *exo*-selectivity of the cycloaddition, use an enamide in which the group on N1 was more easily removed than a carbomethoxy, protect N5 before reduction of the nitrile, and have the 8-carboxy group present before the key cycloaddition. Incorporation of all these design features led to the successful synthesis of the martinelline core, **17** Scheme 2, though some convergence was inevitably lost.

Imine **6**, derived from cinnamaldehyde and methyl 4-aminobenzoate, was a yellow crystalline compound, which was stable to storage at room temperature. Enamide **7**, made by the literature procedure,[37,38] was chosen as the coupling partner because it was envisaged that in the later

(i) Ratio **8:9** 1.1:1, yield **8**, 40%
(ii) Ratio **8:9** 1:1, yield **8,** 47%
(iii) Ratio **8:9** 1:1, yield **8**, 43%

Scheme 2. Reagents and conditions: (i) 12 mol% InCl$_3$, CH$_3$CN, 25 °C, 12 h; (ii) 1 mol% Y(OTf)$_3$, CH$_3$CN 25 °C, 2 h; (iii) 100 mol% LiBF$_4$, CH$_3$CN, 12 h; (iv) trifluoroacetic anhydride, DMAP, toluene 108 °C, 24 h.

stages it could be removed simultaneously with the alkene or nitrile under reducing conditions. The main disadvantage of using enamide **7** was that the proton NMR spectra of the products were fairly broad and difficult to interpret due to hindered rotation at the carbamate.

Initially, reaction of imine **6** with enamide **7** using 12 mol% indium trichloride as catalyst gave a 1.1:1 mixture of *exo/endo* stereoisomers **8** and **9**, respectively, from which the desired *exo*-isomer **8** was easily separated in 40% yield. In our hands, indium trichloride lost its catalytic activity on storage once the bottle was opened. Yttrium triflate proved to be a much more reliable and robust catalyst. It did not deteriorate on storage, much lower loadings (1%) could be employed, and the isolated yield of the desired *exo*-hexahydropyrroloquinoline **8** rose to 46%. The relative stereochemistry of the desired *exo*-isomer **8** was established by X-ray crystallography, and this is shown in Figure 2. Interestingly, the molecule adopts a conformation, which puts the groups at C3a and C4 *trans*-diaxial in the solid state. This conformation is also the preferred one in solution and was confirmed by NOE studies. Hence, saturation of H4 led to a NOE of 5.5% onto H3a and no enhancement onto H9b indicating that H4 was indeed equatorial. Unfortunately, the peaks for H4 and H3a in the proton NMR spectrum were too broad, due to hindered rotation, to extract *J* values, but in similar compounds devoid of the CBz protecting group this coupling constant is of the order of 2 Hz for the *exo*-isomer confirming the solution conformation.
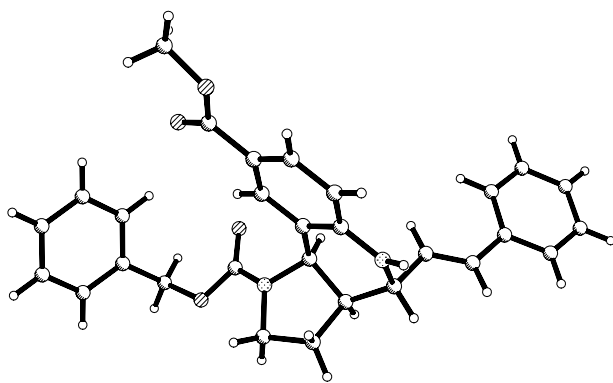

Figure 2. X-ray structure of *exo*-cycloadduct **8** depicting relative configuration and unusual conformation.

In an attempt to improve the diastereoselectivity of the cycloaddition a range of catalysts were screened. The reaction failed completely with aluminium[39] and chromium catalysts.[40] With copper chloride and triflate the reaction proceeded smoothly but with no improvement in diastereoselectivity. In order to increase the steric bulk around the metal, chiral bisoxazole complexes were employed.[41] Again, although the reaction proceeded smoothly to completion, no increase in the diastereoselectivity was observed. Unfortunately, conditions could not be found to separate the enantiomers on an analytical chiral HPLC column, but the very low optical rotation of the *exo*-isomer **8**, strongly suggested that within the error of the measurement it was racemic. High *exo*-selectivity has previously been observed in Povarov reactions of cyclic enol ethers, catalysed by lithium tetrafluoroborate[42]
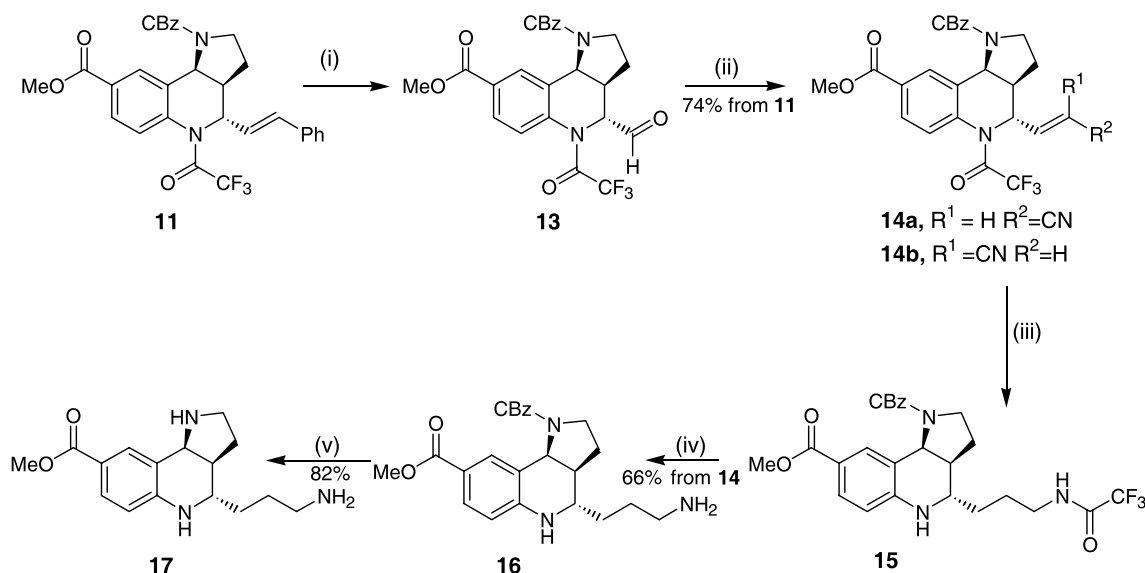
prompting an investigation of this catalyst in our system. Initial results seemed promising and only the *exo*-hexahydropyrroloquinoline **8** was formed, though the isolated yield, 43%, was disappointingly low with the mass balance comprising of quinoline **10**. When this reaction was repeated, and the solvent removed, proton NMR analysis of the crude mixture revealed it was a 1:1 mixture of *exo/endo* isomers. Clearly this reaction is not showing any *exo*-selectivity and the quinoline appears to be selectively derived from the *endo*-isomer during the aqueous work up. Presumably the mechanism for this reaction involves isomerisation of the alkene into the hexahydropyrroloquinoline six-membered ring, followed by elimination of the nitrogen from C9b to give the quinoline **10**. It is not clear why the *endo*-isomer participates in this isomerisation whilst the *exo*-isomer does not.

Finally, an attempt was made to recycle the unwanted *endo*-isomer. We have previously shown in 1-propionyl-4-phenyl substituted hexahydropyrroloquinolines, the Povarov reaction is reversible and after 20 days at room temperature in *d*-3-acetonitrile containing a crystal of yttrium triflate, the *endo*-isomer equilibrates to a 10:7 mixture of *endo/exo* isomers. As suspected the *endo*-isomer is slightly more thermodynamically stable than the *exo*-isomer. Unfortunately, the same study on the more complex tetrahydropyrroloquinoline **9** was thwarted as the initial reaction was irreversible even at 60 °C for 7 days. It is presently not clear if it is the carbamate protecting group, the 8-carbomethoxy group, or the more complex C4 substituent, which is rendering this cycloaddition irreversible.

Although it was disappointing that the *exo/endo* selectivity could not be improved further for the key reaction, the fact that the starting materials were so readily available and that the *exo/endo* isomers were easy to separate still made this an attractive synthetic procedure. With **8** at hand all that remained was elaboration of the C4 side chain.

The aromatic amine N5 was incredibly unreactive due to conjugation to the 8-carbomethoxy group. However, forcing conditions of refluxing toluene containing trifluoroacetic anhydride and a catalytic quantity of 4-dimethylaminopyridine for 24 h gave the trifluoroacetamides **11** and **12** in 83 and 92% yield, respectively. Ozonolysis of adduct **11** followed by a reductive work up gave aldehyde **13**, which was trapped at −78 °C with the nitrile stabilised ylide (triphenylphosphoranylidene)acetonitrile prior to work up, Scheme 3 Proton NMR analysis of the crude mixture showed a 2:1 mixture of *Z–E* α,β-unsaturated nitriles **14a** and **14b**, respectively. However, on flash chromatography this ratio changed to 1:5 and gave the alkenes in a combined overall yield of 74% from **11**. These alkene isomers could be separated by preparative TLC for characterisation, but for synthetic purposes the mixture was used.

At this stage, an attempt was made to incorporate the redundant *endo*-isomer into the synthesis by epimerising C4. Ma[30] has recently reported that in hexahydropyrroloquinolines with aldehyde functionality at C4 and an amide at N5, an *exo/endo* mixture isomerises to give the *exo* aldehyde. The reason for this facile isomerisation is fairly obvious. For six-membered ring cyclic amides with

Scheme 3. Reagents and conditions: (i) CH$_2$Cl$_2$, O$_3$ −78 °C then Me$_2$S; (ii) Ph$_3$P=CHCN; (iii) PtO$_2$, EtOH, CHCl$_3$, 70 °C, 45 psi, 144 h; (iv) MeOH, NH$_3$, 25 °C, 24 h; (v) Pd(OH)$_2$, CH$_3$OH, 60 °C, 45 psi, 24 h.

a 2-substituent, the thermodynamically more stable conformer is the one in which the 2-substituent is axial as this minimises pseudo allylic 1,3-strain.[43] For N5 amides derived from hexahydropyrroloquinolines then the *exo*-isomer would undoubtedly be more stable that the *endo*-isomer, as this can accommodate the adjacent axial substituent. The alkene **12** was ozonolised followed by the addition of dimethyl sulphide and then allowed to warm to room temperature. Proton NMR analysis of the crude reaction mixture revealed three aldehyde peaks at δ 10.03, 9.66 and 9.46 corresponding to benzaldehyde, *exo*-aldehyde and *endo*-aldehyde, respectively, in the ratio 1:0.53:0.47. A fresh aliquot was removed after 24 h and proton NMR analysis revealed the ratio of the three aldehydes was 1:0.72:0.15. It was clear that the amount of *exo*-aldehyde was not increasing as fast as the *endo*-aldehyde was decreasing indicating decomposition. Finally after 48 h proton NMR analysis showed no *endo*-aldehyde remaining but the amount of *exo*-isomer had dropped to 30% relative to benzaldehyde, indicating extensive decomposition. This was supported by the observation of quinoline peaks in the aromatic region of the proton NMR spectra. Due to the instability of the hexahydropyrroloquinoline aldehydes this isomerisation was not pursued further as a means of recycling the *endo*-isomer.

Catalytic reduction of the nitrile **14a,b** proved to be the most challenging reaction in the entire sequence. Initial studies focused on an Rh/C catalyst under a hydrogen pressure of 15–45 psi but this only resulted in hydrogenation of the alkene. Platinum oxide was next investigated as the catalyst. Secrist reported that in reduction of nitriles using platinum oxide as catalyst, addition of chloroform improves the efficiency of the process and minimises formation of secondary amines.[44] Using platinum oxide as the catalyst under Secrist's conditions the alkene in **14a,b** was selectively hydrogenated but the nitrile remained intact. To get reduction of both the alkene and nitrile it was necessary to increase the temperature to 70 °C for 6 days. Analysis of the proton NMR spectrum of the crude

reduction product revealed an 85:15 mixture of two compounds, from which the major product **15** could be isolated by flash chromatography. The aromatic proton in the major product H6 had changed its chemical shift from δ 7.57 in the starting material to 6.41 ppm in the product strongly indicating that the trifluoroacetyl on N5 was no longer present. However, accurate mass data and ^{19}F NMR spectra revealed that the compound still contained a trifluoroacetyl group. The most likely explanation is that the trifluoroacetyl group has migrated from the aromatic secondary amine to the aliphatic primary amine and that the minor component is the compound that was initially expected. There is good literature precedent for migrations of this type.[45] Removal of the trifluoroacetyl group on the crude mixture was accomplished with ammonia in methanol, to give **16** in 66% for the two steps. Finally, the carbobenzyloxo group was reductively removed using palladium hydroxide as catalyst to give **17** in 82% yield completing the synthesis of the tricyclic core of martinellic acid. The triamine **17** was very polar, difficult to purify by chromatography, did not give mass spectral data and decomposed on storage at 0 °C. However, the ^{13}C NMR spectrum of the crude material was clean and was in reasonable agreement with the published spectra,[28] maximum deviation 2.6 ppm average deviation 0.9 ppm, which can be attributed to these spectra being recorded in *d*-chloroform and *d*-4-methanol, respectively.

3. Conclusion

In conclusion, we have demonstrated that the Povarov reaction can be employed to give rapid entry to hexahydropyrroloquinolines with a carbomethoxy group at the 8-position and useful alkene functionality at C-4. Although the diastereoselectivity is poor, the regioselectivity and high convergence of this approach makes it very attractive. The alkene functionality can be readily converted to the required 3-aminopropyl group. The overall yield for the synthesis of

the central core of martinellic acid was 22% from methyl 4-aminobenzoate.

4. Experimental

4.1. General

Melting points were recorded using a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 983G instrument coupled to a Perkin-Elmer 3700 Data Station as potassium bromide (KBr) disks, or films (liquids). [1]H nuclear magnetic resonance (NMR) spectra were recorded at 300 MHz using Bruker DPX 300 and at 500 MHz using a Bruker DRX500 NMR spectrometers. Chemical shifts are given in parts per million (δ down field from tetramethylsilane as internal standard and coupling constants are given in Hertz). Unless otherwise stated, deuteriochloroform was used as solvent. Spectra splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were recorded using Double Focusing Triple Sector VG Auto Spec and accurate molecular masses were determined by the peak matching method using perfluorokerosene as standard reference and were accurate to within $+/-$ 0.006 amu. Analytical TLC was carried out on Merck Kielselgel 60_{254} plates and the spots visualised using a Hanovia Chromatolite UV lamp. Flash chromatography was affected using Merck Kielselgel 60 (230–400 mesh).

4.1.1. 4-(3-Phenyl-allylideneamino)-benzoic acid methyl ester 6. *trans*-Cinnamaldehyde (0.81 g, 6.13 mmol) and methyl 4-aminobenzoate (0.92 g, 59.5 mmol) were dissolved in dry methylene chloride (30 ml). Activated, 4 Å molecular sieves were then added and the reaction vessel was flushed with nitrogen for 5 min and the mixture was stirred for 6 h. The molecular sieves were removed by filtration and the methylene chloride was removed under reduced pressure and the residue was crystallised from hexane/ethyl ethanoate 9:1 to yield the titled product (1.45 g, 90%) as yellow needles. Mp 134–135 °C. HRMS (EI): $C_{17}H_{15}NO_2$ requires M^+ 265.1103, found M^+ 265.1090; ν_{max} (KBr)/cm^{-1} 1716, 1628, 1279, 735, 696; ^{1}H NMR (500.1 MHz, CDCl$_3$) δ (ppm) 3.92 (s, 3H), 7.11 (dd, $J=16.0, 8.8$ Hz, 1H), 7.18 (d, $J=8.7$ Hz, 2H), 7.21 (d, $J=16.0$ Hz, 1H), 7.38–7.44 (overlapping m, 3H), 7.55 (d, $J=8.3$ Hz, 2H), 8.06 (d, $J=8.8$ Hz, 2H), 8.25 (d, $J=8.7$ Hz, 1H); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ (ppm) 52.1, 120.8 (2C), 127.5, 127.7 (2C), 128.3, 129.0 (2C), 130.0, 130.9 (2C), 135.4, 145.4, 155.9, 163.0, 166.8; MS (EI), *m/z* (%), 265 (M^+, 38), 264 (100), 129 (3), 103 (15), 77 (26).

4.1.2. *exo*-4-Styryl-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-c]quinoline-1,8-dicarboxylic acid 1-benzyl ester 8-methyl ester 8. Imine 6 (0.45 g, 1.70 mmol) and ene–carbamate 7 (0.34 g, 1.66 mmol) were dissolved in dry acetonitrile (30 ml) and a catalytic amount of yttrium triflate (0.01 g, 1 mol%) was added and the reaction stirred for 2 h under nitrogen. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride (40 ml), washed with saturated aqueous sodium bicarbonate (20 ml), water (20 ml), dried over magnesium sulfate and concentrated under reduced pressure.

Purification by flash chromatography (eluent; hexane/diethyl ether 1:1, R_f: 0.17) afforded the titled compound (0.36 g, 46%) as a white solid. Mp 144.5–146.0 °C. HRMS (EI): $C_{29}H_{28}N_2O_4$ requires M^+ 468.2049, found M^+ 468.2049; ν_{max} (KBr)/cm^{-1} 3354, 1702, 1107, 966, 769, 695; ^{1}H NMR (500.1 MHz, CDCl$_3$) δ (ppm) (mixture of rotamers at 25 °C) 2.05 (m, 2H), 2.51 (br, 1H), 3.41 (m, 1H), 3.59 (br, 1H), 3.82 (s, 3H), 4.00 (m, 1H), 4.50 (s, 1H), 5.23 (overlapping m, 3H) 6.23 (dd, $J=15.8, 6.9$ Hz, 1H), 6.47 (d, $J=15.8$ Hz, 1H), 6.51 (d, $J=8.5$ Hz, 1H), 7.21–7.36 (m, 10H), 7.73 (dd, $J=8.5, 2.0$ Hz, 1H), 8.20 (br, 1H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ (ppm) (mixture of rotamers at 25 °C) 27.2 (br), 41.5 (br), 44.8, 51.6, 53.0, 54.0, 67.3 (br), 113.7, 119.5, 120.0 (br), 126.5 (2C), 127.9 (2C), 128.0, 128.1, 128.5 (2C), 128.6 (2C), 130.26, 130.3, 130.8, 132.5, 136.1, 136.8 (br), 145.7, 156.0 (br), 167.2; MS (EI), *m/z* (%), 468 (M^+, 23), 377 (11), 333 (14), 290 (71), 91 (47), 56 (100).

An isomeric product was also isolated (eluent; hexane/diethyl ether 1:1, R_f: 0.31) (0.36 g, 46%) as a white solid. Mp 164–165 °C. HRMS (FAB): $C_{29}H_{28}N_2O_4$ requires M^+ 468.2049, found M^+ 468.2070; ν_{max} (KBr)/cm^{-1} 3348, 1701, 1280, 1098, 772; ^{1}H NMR (500.1 MHz, CDCl$_3$) δ (ppm) (mixture of rotamers at 25 °C) 1.96–2.06 (m, 2H), 2.50 (m, 1H), 3.40 (m, 1/2H), 3.41 (m, 1/2H), 3.49 (q, $J=9.6$ Hz, 1/2H), 3.58 (q, $J=9.7$ Hz, 1/2H), 3.80 (s, 3H), 4.23 (br s, 1H), 4.27 (br, 1H), 5.29–5.34 (overlapping m, 3H), 6.19 (dd, $J=15.9, 7.6$ Hz, 1H), 6.50 (d, $J=8.5$ Hz, 1H), 6.66 (dd, $J=15.9, 4.4$ Hz, 1H), 7.26–7.39 (overlapping m, 9H), 7.50 (d, $J=7.3$ Hz, 1H), 7.72 (d, $J=8.3$ Hz, 1H), 8.19 and 8.30 (br, 1H); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ (ppm) (mixture of rotamers at 25 °C) 22.1 and 23.1, 41.8 and 42.4, 44.8 and 44.9, 52.0, 54.3, 55.7 and 55.9, 67.0 and 67.5, 113.9, 119.9, 120.2 and 120.9, 126.4 (2C), 127.7, 127.8, 128.0 and 128.1, 128.2 and 128.3, 128.4 and 128.5, 128.6 (2C) 130.0, 132.1 and 132.4, 132.3 and 132.5, 136.1, 136.5 and 136.9, 147.0, 155.5 and 156.5, 167.1; MS (FAB), *m/z* (%), 469 (M^++1, 36), 468 (M^+, 35), 437 (22), 377 (10), 333 (23), 290 (12), 154 (100), 136 (75); Anal. calcd for $C_{29}H_{28}N_2O_4$: C 74.3, H 6.0, N 5.9. Found: C 74.0, H 5.8, N 6.0.

4.1.3. 3-(2-Benzyloxycarbonylamino-ethyl)-2-phenethyl-quinoline-6-carboxylic acid methyl ester 10. Imine 6 (69 mg, 0.26 mmol) and ene–carbamate 7 (51 mg, 0.25 mmol) were dissolved in dry acetonitrile (10 ml) under a nitrogen atmosphere, lithium tetrafluoroborate (24 mg, 0.26 mmol) was then added and the mixture stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride (30 ml) and washed with aqueous saturated sodium bicarbonate (20 ml) and water (20 ml). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. Purification by preparative TLC (eluent; ethyl ethanoate/hexane 3:7, R_f: 0.30) afforded the titled product (48 mg, 41%) as a yellow oil. HRMS (FAB): $C_{29}H_{29}N_2O_4$ requires $M^+(+1)$ 469.2127, found $M^+(+1)$ 469.2106; ν_{max} (KBr)/cm^{-1} 3359, 1717, 1262, 1099, 750, 699; ^{1}H NMR (500.1 MHz, CDCl$_3$) δ (ppm) 2.93 (t, $J=6.7$ Hz, 2H), 3.20 (t, $J=8.2$ Hz, 2H), 3.30 (t, $J=8.2$ Hz, 2H), 3.43 (q, $J=6.4$ Hz, 2H), 3.98 (s, 3H), 4.82 (br, 1H), 5.08 (s, 2H), 7.17–7.33 (overlapping

m, 10H), 7.89 (s, 1H), 8.07 (d, $J=8.8$ Hz, 1H), 8.23 (dd, $J=8.8$, 1.9 Hz, 1H), 8.46 (s, 1H); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ (ppm) 32.9, 35.5, 37.8, 41.3, 52.7, 67.2, 126.5, 127.9, 128.5 (2C), 128.6, 128.83, 128.89 (2C), 128.9 (2C), 129.0 (2C), 129.1, 129.3, 130.7, 131.7, 136.8, 137.2, 142.0, 149.1, 156.7, 163.7, 167.2; MS (FAB), *m/z* (%), 469 (M^{+1}, 100), 468 (M$^+$, 15), 377 (11), 318 (10), 304 (11), 147 (41), 105 (43).

4.1.4. *exo*-4-Styryl-5-(2,2,2-trifluoro)-2,3,3a,4,5,9b-hexa-hydro-pyrrolo[3,2-*c*]quinoline-1,8-dicarboxylic acid 1-benzyl ester 8-methyl ester 11.

Anhydrous pyridine (0.17 ml, 2.10 mmol), 4-dimethylaminopyridine (8 mg, 17 mol%), and trifluoroacetic anhydride (0.11 ml, 0.79 mmol) were added sequentially to a stirred solution of amine **8** (181 mg, 0.39 mmol) in anhydrous toluene (15 ml) under a nitrogen atmosphere. The reaction was then refluxed for 24 h and the solvent was removed under reduced pressure. The residue was dissolved in methylene chloride (30 ml) and washed with 9% aqueous HCl (15 ml), saturated sodium bicarbonate (15 ml) and water (15 ml). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography (eluent; hexane/diethyl ether 35:65, R_f: 0.45) afforded the titled compound (182 mg, 83%) as a cream foam. HRMS (EI): C$_{31}$H$_{27}$F$_3$N$_2$O$_5$ requires M$^+$ 564.1872, found M$^+$ 564.1873; υ_{max} (KBr)/cm^{-1} 2954, 1708, 1699, 1409, 1277, 1196, 770, 736, 696; ^{19}F NMR (282.3 MHz, CDCl$_3$) δ (ppm) -67.6 (s, 3F); ^{1}H NMR (500.1 MHz, CDCl$_3$) δ (ppm) (mixture of rotamers at 25 °C) 1.92 (dq, $J=12.7$, 8.9 Hz, 1H), 2.23 (br, 1H), 2.89 (dtd, $J=9.6$, 7.4, 2.4 Hz, 1H), 3.46 (br, 1H), 3.62 and 3.75 (br, 1H), 3.89 (br s, 3H), 5.18 (overlapping, 3H), 5.33 (br, 1H), 5.95 (br, 1H), 6.56 (d, $J=15.9$ Hz, 1H), 7.19–7.26 (overlapping m, 5H), 7.30–7.36 (overlapping m, 5H), 7.67 (br, 1H), 7.96 (d, $J=8.4$ Hz, 1H), 8.38 and 8.64 (br, 1H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ (ppm) (mixture of rotamers at 25 °C) 27.9 (br), 42.8 (br), 45.4, 52.3, 54.7, 58.6 (br), 67.4 (br), 110.8–122.3 (q, $J=288.8$ Hz), 124.3, 124.7, 126.6 (2C), 127.9, 128.1, 128.5 (2C), 128.7 (2C), 128.9, 129.4, 130.8, 132.7, 132.9, 133.9, 135.3, 136.5 (br), 137.3 (br), 156.4, 156.8 (q, $J=36.7$ Hz), 166.1; MS (EI), *m/z* (%), 564 (M$^+$, 1.5), 533 (1), 473 (5), 429 (8), 279 (29), 149 (100), 91 (74), 57 (42).

4.1.5. *endo*-4-Styryl-5-(2,2,2-trifluoro)-2,3,3a,4,5,9b-hexa-hydro-pyrrolo[3,2-*c*]-quinoline-1,8-dicarboxylic acid 1-benzyl ester 8-methyl ester 12.

Anhydrous pyridine (0.16 ml, 1.98 mmol), dimethyl aminopyridine (7.7 mg, 17 mol%) and trifluoroacetic anhydride (0.11 ml, 0.76 mmol) were added to a stirred solution of *endo*-4-styryl-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-*c*]quinoline-1,8-dicarboxylic acid 1-benzyl ester 8-methyl ester **9** (174 mg, 0.37 mmol) in dry toluene (40 ml) and the resulting solution was refluxed for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (40 ml), washed with 9% aqueous hydrochloric acid (20 ml), saturated sodium bicarbonate solution (20 ml) and water (20 ml). The organic phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography (6:4 hexane/ethyl acetate), afforded **12** as a light brown powder (193 mg, 92%). Mp 69–70 °C. R_f: 0.66

(6:4 hexane/ethyl acetate); (C$_{31}$H$_{27}$F$_3$N$_2$O$_5$ requires M$^+$ 564.1872, found M$^+$ 564.1870); υ_{max} (KBr)/cm^{-1} 2952, 1699, 1410, 1271, 1207, 767, 737, 696; δ_H (500 MHz, CDCl$_3$) (mixture of rotamers, 25 °C) 1.52 (br m, 1H), 1.89 (dq, $J=5.7$, 15.9 Hz, 1H), 3.40 (br, 1H), 3.50 (br, 1H), 3.61 (br, 1H), 3.92 (s, 3H), 4.97 (br, 1H), 5.25 (overlapping m, 3H), 5.64 (br, 1H), 6.65 (d, $J=15.6$ Hz, 1H), 7.18–7.27 (m, 5H), 7.31–7.37 (m, 5H), 7.39 (br, 1H), 7.67 (d, $J=8.6$ Hz, 1H), 8.04–8.14 (br m, 1H); δ_C (125 MHz, CDCl$_3$) (mixture of rotamers at 25 °C) 27.1 (br), 43.6 (br), 44.6 (br), 46.4, 52.2, 55.9 (br), 67.3, 114.9, 117.2, 119.6, 122.5, 125.4 (br), 126.3 (2C), 127.8, 128.2 (br), 128.4 (2C), 128.5 (2C), 128.6–129.1 (q), 129.6, 130.7, 133.6, 134.5, 135.2, 136.2 (br), 137.4, 155.2 (q, $J=38.1$ Hz), 165.9; ^{19}F (282 MHz, CDCl$_3$) -67.5 (3F, s, C=OCF_3); MS (EI), *m/z* (%), 564 (M$^+$, 36), 489 (100), 473 (51), 466 (25), 369 (12), 152 (28), 91 (100), 57 (30).

4.1.6. *exo*-4-(2-Cyano-vinyl)-5-(2,2,2-trifluoro)2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-*c*]quinoline-1,8-dicar-boxylic acid 1-benzyl ester 8-methyl ester 14.

Alkene **11** (1.26 g, 2.23 mmol) was dissolved in anhydrous methylene chloride (60 ml) and the solution was cooled to -78 °C under a nitrogen atmosphere. Ozone was then bubbled through the system at a rate of 1 l/min for 30 min. The reaction solution changed from colourless to a deep blue hue during the course of the reaction. While maintaining the system at -78 °C, the residual ozone was removed by slowly bubbling nitrogen gas through the reaction mixture. Dimethyl sulphide (1.8 ml, 24 mmol) was added dropwise and the solution was stirred for another hour at -78 °C. (Triphenylphosphoranylidene)acetonitrile (1.90 g, 6.31 mmol) in methylene chloride (3 ml) was introduced and the solution maintained at -78 °C for a further 2 h, after which it was allowed to warm to room temperature overnight. The methylene chloride solution was washed with saturated aqueous sodium bicarbonate (15 ml), water (15 ml), dried over magnesium sulfate and concentrated under reduced pressure. The titled compound was obtained as a mixture of cis and trans isomers by flash chromatography (eluent; diethyl ether/hexane 8:2) as a white powder (0.85 g, 74%). A small sample was separated by preparative TLC R_f: 0.37 (diethyl ether/hexane 8:2) and crystallised from methanol to give the trans product **14b** as prisms. Mp 69–72 °C. HRMS (EI): C$_{26}$H$_{22}$F$_3$N$_3$O$_5$ requires M$^+$ 513.1512, found M$^+$ 513.1518; υ_{max} (KBr)/cm^{-1} 2211, 1703, 1411, 1292, 1198; ^{19}F NMR (282.3 MHz, CDCl$_3$) δ (ppm) -67.69 (s, 3F); ^{1}H NMR (500.1 MHz, CDCl$_3$) δ (ppm) (mixture of rotamers at 25 °C) 1.90 (dq, $J=12.7$, 8.2 Hz, 1H), 2.24 (td, $J=12.5$, 7.5 Hz, 1H), 2.83 (ddd, $J=16.4$, 7.2, 2.1 Hz, 1H), 3.43 (br, 1H), 3.65 (br, 1H), 3.91 (br s, 3H), 5.20 (overlapping m, 4H), 5.45 (d, $J=15.1$ Hz, 1H), 6.46 (br, 1H), 7.27–7.36 (m, 5H), 7.57 (br, 1H), 8.00 (d, $J=7.8$ Hz, 1H), 8.32 and 8.61 (br, 1H); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ (ppm) (mixture of rotamers at 25 °C) 27.3 (br), 40.9 (br), 44.3 (br), 51.4, 53.6 (br), 56.8 (br), 66.5 and 67.0 (br), 102.9, 111.7–118.6 (q, $J=288.8$ Hz), 114.4, 123.4, 126.9, 127.2 (2C overlapping), 127.5 (2C), 128.6 (br), 128.9 (2C), 129.3 (br), 132.2 (br), 135.3 (br), 147.5, 155.1 (br), 155.9 (q, $J=37.2$ Hz), 164.7; MS (EI), *m/z* (%), 513 (M$^+$, 1.1), 482 (1.6), 407 (1.4), 378 (15), 277 (30), 148 (6), 91 (100), 77 (18).

cis Product **14a**. R_f: 0.29 (diethyl ether/hexane 8:2) crystallised from methanol as prisms. Mp 66–69 °C. HRMS (EI): $C_{26}H_{22}F_3N_3O_5$ requires M^+ 513.1512, found M^+ 513.1527; ν_{max} (KBr)/cm^{-1} 2955, 2275, 2224, 1698, 1409, 1197, 770, 732, 698; ^{19}F NMR (282.3 MHz, CDCl$_3$) δ (ppm) -67.69 (s, 3F); ^{1}H NMR (500.1 MHz, CDCl$_3$) δ (ppm) (mixture of rotamers at 25 °C) 2.03 (br m, 1H), 2.33 (td, $J = 12.5$, 7.3 Hz, 1H), 2.89 (ddd, $J = 14.2$, 9.1, 2.4 Hz, 1H), 3.46 (br, 1H), 3.66 (br, 1H), 3.91 (br s, 3H), 5.13–5.25 (overlapping m, 4H), 5.48 (br, 1H), 6.26 (br, 1H), 7.30–7.36 (m, 5H), 7.64 (br, 1H), 7.99 (d, $J = 7.9$ Hz, 1H), 8.38 and 8.61 (s, 1H); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ (ppm) (mixture of rotamers at 25 °C) 27.4 (br), 42.5 and 43.4 (br), 44.3 (br), 51.4, 53.7 (br), 56.3 (br), 66.5 (br), 101.8, 111.8–118.5 (q, $J = 288.5$ Hz), 113.1, 123.9 (br), 126.9, 127.2, 127.5 (2C), 128.7 (2C), 129.7, 129.8 (br), 132.0 (br), 132.0 (br), 135.3 (br), 147.3, 155.2 (br), 155.6 (q, $J = 36.5$ Hz), 164.8 (br); MS (EI), *m/z* (%), 513 (M$^+$, 0.4), 482 (0.3), 378 (2), 277 (65), 122 (75), 105 (100).

4.1.7. *exo*-4-[3-(2,2,2-Trifluoro-acetylamino)-propyl]-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2]quinoline-1,8-dicarboxylic acid 1-benzyl ester 8-methyl ester 15.

Platinum oxide (4.5 mg, 10 mol%) was added to a solution of alkenes **14a,b** (100 mg, 0.19 mmol) in methanol (10 ml). Three drops of chloroform were then added and the reaction mixture was hydrogenated (50 psi) at the elevated temperature of 70 °C for 144 h. The mixture was filtered through Hyflo-Supercel and the solvent was removed in vacuo. The residue was dissolved in methylene chloride (30 ml) and washed with 2 M sodium hydroxide (15 ml), water (15 ml), dried over magnesium sulfate and concentrated under reduced pressure. An analytical sample was purified by flash chromatography (eluent; chloroform/methanol 95:5, R_f: 0.49) afforded the titled compound as a clear oil. HRMS (FAB): $C_{26}H_{29}F_3N_3O_5$ requires M^{+1} 520.2059, found M^{+1} 520.2068; ν_{max} (KBr)/cm^{-1} 3367, 2949, 1701, 1609, 1436, 1280, 1187, 769; ^{19}F NMR (282.3 MHz, CDCl$_3$) δ (ppm) -76.2 (s, 3F); ^{1}H NMR (500.1 MHz, CDCl$_3$) δ (ppm) (mixture of rotamers at 25 °C) 1.47 (m, 1H), 1.55 (m, 1H), 1.67 (m, 2H), 1.95 (br m, 2H), 2.32 (m, 1H), 3.31 (overlapping m, 4H), 3.51 (br, 1H), 3.80 (s, 3H), 4.75 (br, 1H), 5.12 (br, 1H), 5.29 (s, 2H), 6.41 (d, $J = 8.5$ Hz, 1H), 6.98 and 7.15 (br, 1H), 7.26–7.40 (overlapping m, 5H), 7.66 (dd, $J = 8.5$, 2.0 Hz, 1H), 8.18 (br, 1H); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ (ppm) (mixture of rotamers at 25 °C) 25.7, 26.8 and 27.7 (br), 32.9 (br), 39.6, 40.4 and 41.1 (br), 44.7, 51.0, 51.6, 52.9 (br), 67.1 and 67.7, 112.4–119.3 (q, $J = 287.8$ Hz), 113.7, 118.9, 119.6 (br), 127.7, 128.0 (2C), 128.5 (2C), 130.2, 132.4 (br), 136.8 (br), 145.4, 156.7, 157.5 (q, $J = 36.9$ Hz), 167.4; MS (FAB), *m/z* (%), 520 (M$^+$, 15), 461 (11), 341 (29), 281 (76).

4.1.8. *exo*-4-(3-Amino-propyl)-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-*c*]quinoline-1,8-dicarboxylic acid 1-benzyl ester 8-methyl ester 16.

Trifluoroacetamide **15** (103 mg, 0.20 mmol, crude from previous step) was added to a saturated solution of ammonia in methanol (6 ml) and the reaction was stirred for 3 days at room temperature. The solvent was removed under reduced pressure and the residue dissolved in methylene chloride (20 ml) and washed with 2 M sodium hydroxide (10 ml), water (10 ml), dried over magnesium sulfate and concentrated under reduced

pressure. Purification by flash chromatography (eluent; methylene chloride/methanol 95:5, R_f: 0.43) afforded the titled product (53 mg, 66% from **14**) as a clear oil. HRMS (FAB): $C_{24}H_{29}N_3O_4$ requires M^+ 423.2158, found M^+ 423.2146; ν_{max} (KBr)/cm^{-1} 3354, 2948, 1698, 770, 736, 698; ^{1}H NMR (500.1 MHz, CDCl$_3$) δ (ppm) (mixture of rotamers at 25 °C) 1.53 (overlappping m, 4H), 1.96 (br m, 2H), 2.36 (dtd, $J = 9.2$, 8.3, 2.1 Hz, 1H), 2.69 (m, 2H), 3.25 (m, 1H), 3.38 (m, 1H), 3.53 (br, 1H), 3.80 (s, 3H), 5.04 and 5.12 (br, 1H), 5.24 (s, 2H), 6.44 (d, $J = 8.5$ Hz, 1H), 7.24–7.50 (overlapping m, 5H), 7.68 (dd, $J = 8.5$, 2.0 Hz, 1H), 8.19 (br, 1H); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ (ppm) (mixture of rotamers at 25 °C) 26.9 and 27.8 (br), 30.0, 33.6 (br), 40.6 and 41.4 (br), 41.7, 44.7, 51.5, 51.6, 53.0, 67.0 and 67.5, 113.7, 118.9 (br), 127.7, 128.0 (2C), 128.5 (2C), 130.2, 132.4 (br), 137.0, 137.2, 145.6, 156.7, 167.2; MS (FAB), *m/z* (%), 424 (M^{+1}, 100), 423 (M$^+$, 26), 393 (21), 365 (46), 275 (32), 257 (18).

4.1.9. *exo*-4-(3-Amino-propyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylic acid methyl ester 17.

Tricycle **16** (11 mg, 0.02 mmol) was dissolved in methanol (5 ml) in a glass Parr hydrogenation flask. A catalytic quantity of 20% w/w palladium hydroxide on carbon (5 mg, 20 mol%) was suspended in methanol (1 ml) and then added to the hydrogenation flask. The system was hydrogenated (45 psi 60 °C) for 24 h. The reaction solution was filtered through Hyflo-Supercel and the solvent was removed under reduced pressure. The residue was dissolved in methylene chloride (20 ml) and washed with 2 M sodium hydroxide (10 ml), water (10 ml), dried over magnesium sulfate and concentrated under reduced pressure to give the titled compound (6.2 mg, 82%) as a clear oil. Due to the high polarity of **17** further purification was not attempted. ν_{max} (KBr)/cm^{-1} 1770, 1470, 1192, 866, 769, 644; ^{1}H NMR (500.1 MHz, CDCl$_3$) δ (ppm) 1.44–1.63 (5H overlap), 1.89 (m, 1H), 1.99 (m, 1H), 2.60–2.74 (overlapping m, 3H), 2.80 (m, 1H), 3.01 (m, 1H), 3.70 (s, 3H), 3.77 (d, $J = 6.5$ Hz, 1H), 6.41 (d, $J = 8.5$ Hz, 1H), 7.58 (dd, $J = 8.5$, 2.1 Hz, 1H), 7.85 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ (ppm) 29.5, 29.7, 31.0, 41.0, 42.0, 44.7, 51.5, 52.2, 57.7, 113.6, 118.6, 121.0, 129.9, 132.6, 148.8, 167.3. Mass spectral data were not secured due to the high polarity and presumably involatility of the sample. The sample also proved to be very unstable and decomposed after days on storage at 0 °C.

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