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An intramolecular azomethine ylide–alkene cycloaddition approach to pyrrolo[3,2-*c*]quinolines-synthesis of a C2-truncated martinelline model

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Abstract—The hexahydropyrrolo[3,2-*c*]quinoline core found in the *Martinella* alkaloids was constructed through an intramolecular [3+2] azomethine ylide–alkene cycloaddition. Some chemical manipulations of the tricycle are reported. © 2001 Elsevier Science Ltd. All rights reserved.

The pyrroloquinoline ring system is found throughout nature in various guises and, depending on the mode of ring fusion, these heterocycles may contain either one or two nitrogen atoms.[1] Although the pyrrolo[3,2-*c*]quinoline system has been known for many years, it was not until a report from the Merck Laboratories in 1995 that this ring system was observed in a natural product.[2] The *Martinella* alkaloids, martinelline **1** and martinellic acid **2**, contain a partially reduced pyrrolo[3,2-*c*]quinoline ring system, in addition to two or three guanidine groups. The novelty of the ring system combined with the antagonistic behavior of these natural products toward bradykinin receptors has aroused significant interest in the synthetic community which has led to the development of several approaches to these natural products, although the assembly of the natural products have yet to be reported.[3] Our own approach, which

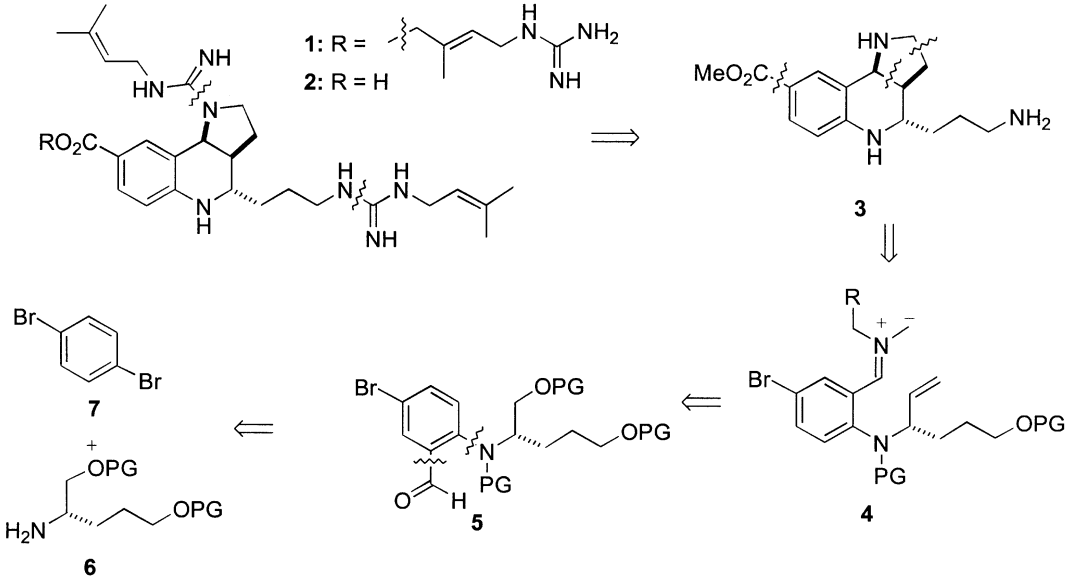

Figure 1. Retrosynthetic analysis of the *Martinella* alkaloids.

Keywords: alkaloids; cycloaddition; azomethine ylide.

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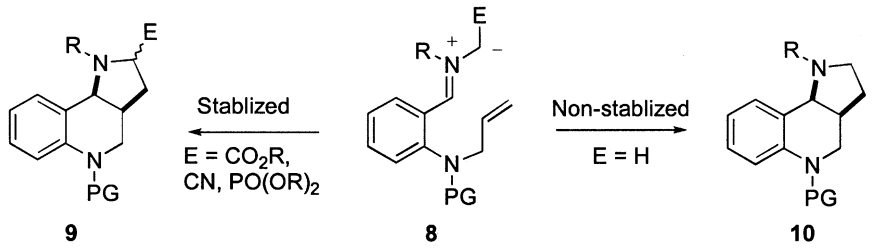
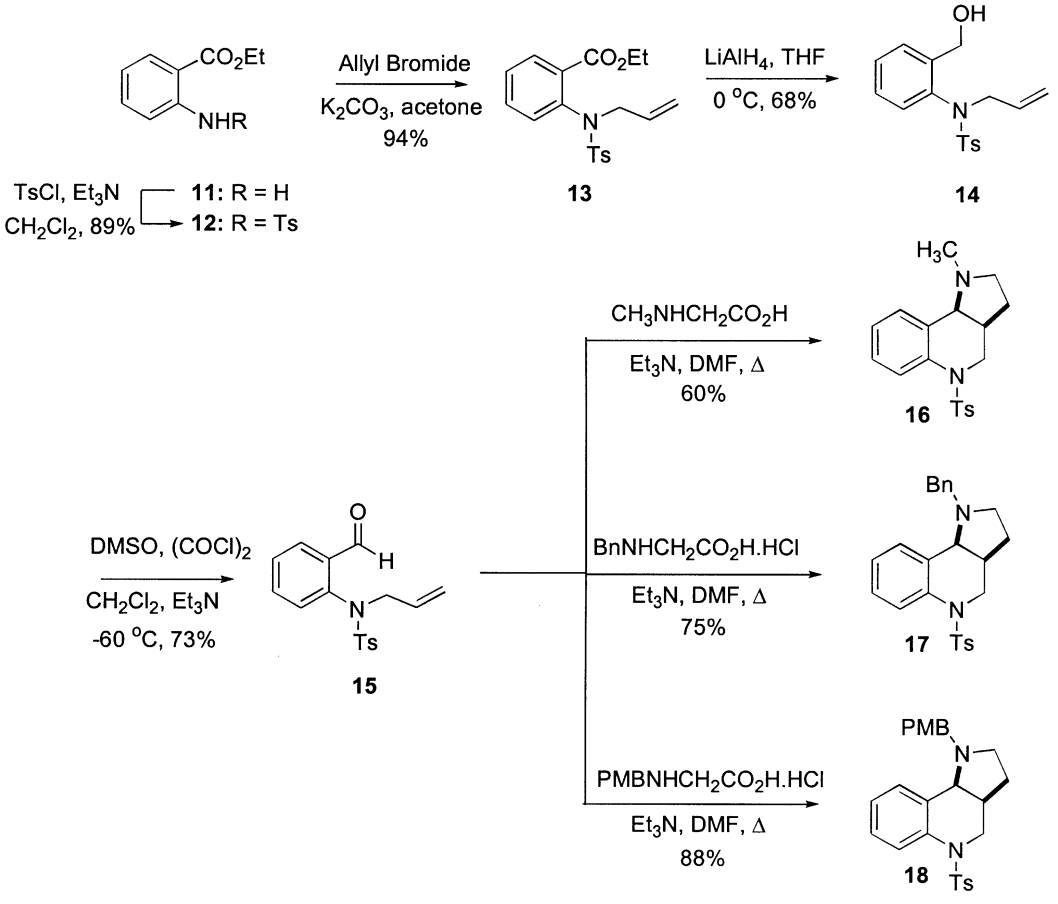


Figure 2. Stablilized and non-stabilized azomethine ylides.

is illustrated above in a retrosynthetic manner (Fig. 1), involves the obvious disconnection of the guanidine groups to afford the tricyclic triamine **3**. An intramolecular [3+2] azomethine ylide–alkene cycloaddition of **4**, which in turn would arise from the corresponding unsaturated benzaldehyde derivative, would produce the pyrrolo[3,2-*c*]quinoline. It is planned to construct the precursor to **4** through a Buchwald-Hartwig type cross coupling between **6** and **7**, which would then allow an enantiospecific synthesis of **1** and **2** since amine **6** should arise from the elaboration of glutamic acid.[4] In this paper, we describe the investigation of the use of a non-stabilized azomethine ylide for the construction of the key tricycle found in these natural products, in addition to its subsequent elaboration.

Azomethine ylides come in two distinct types (Fig. 2), stabilized (**8**, E=EWG) or non-stabilized (**8**, E=H).[5,6] The disadvantage with the former is that frequently the stabilizing group is superfluous to the target structure requiring its eventual removal, thereby introducing additional manipulations.[7] On the other hand, the generation of non-stabilized azomethine ylides requires the use of relatively harsh conditions or the preparation of precursors that necessitate additional synthetic steps. Of the two approaches to non-stabilized azomethine ylides, we chose to investigate the direct synthesis via the condensation/decarboxylation of *N*-alkyl amino acids and carbonyl compounds, pioneered by Grigg's group.[8,9] This approach offers the advantages of operational simplicity and commercial availability of the various amino acids. After surveying the literature, it became apparent that there were no previous reports of the application of this method to *o*-aminobenzaldehyde derivatives. It should be pointed out that Cheavens and Martin have evaluated the reaction of stabilized azomethine



Scheme 1.

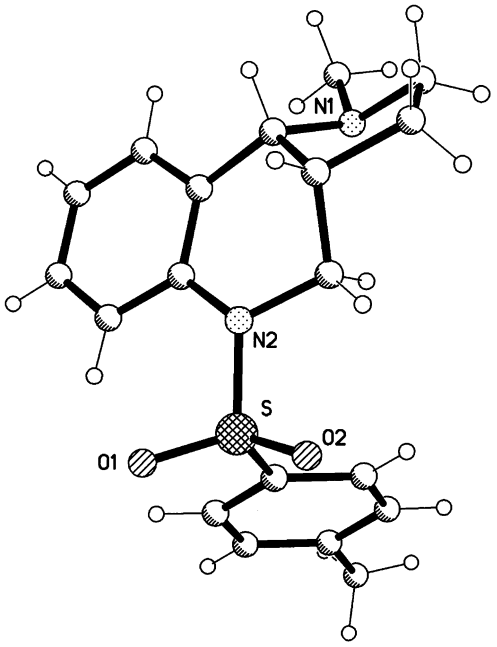


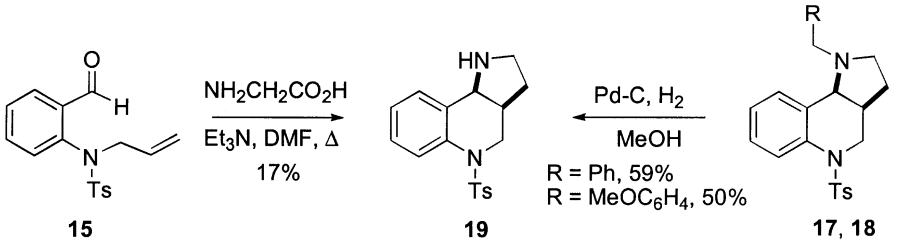
Figure 3. X-Ray crystal structure of *N*-methyl pyrroloquinoline **16**.

ylides (**8**, R=PO(OR)$_2$) with *o*-aminobenzaldehydes.[10] Therefore, we set out to investigate the application of the condensation-decarboxylation reaction of *o*-aminobenzaldehydes with *N*-alkylglycines for the construction of pyrrolo[3,2-*c*]quinolines.[3e]

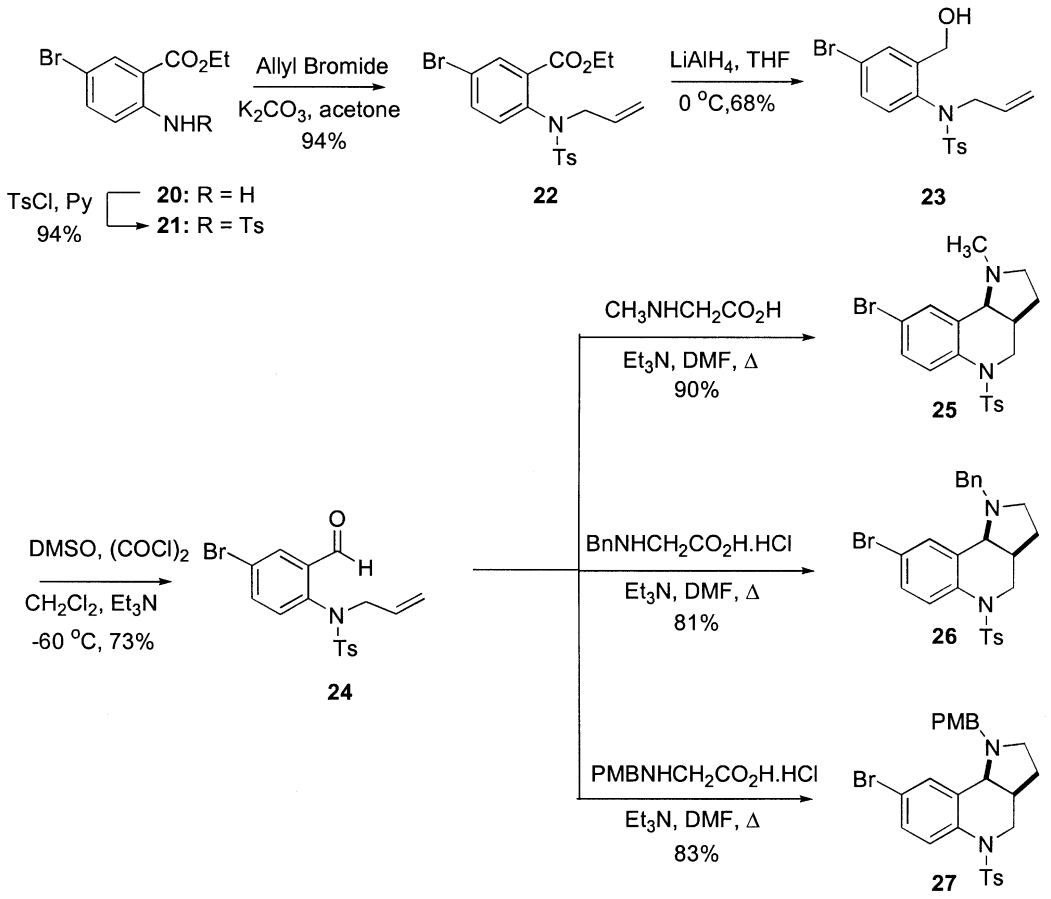
Our studies commenced with the construction of a cyclization precursor **15** (Scheme 1). This was achieved in short order from ethyl anthranilate by tosylation, followed by allylation to afford **13** in 84% yield for two steps.[11] Although the direct conversion of the ester group to the aldehyde was attempted by reduction with DIBAL-H, the major product was always the alcohol, therefore a two-step sequence involving reduction with $LiAlH_4$ and Swern oxidation was adopted, providing **15** in 50% yield. The oxidation step could also be achieved with MnO_2 in comparable efficiency.[12]

With the unsaturated benzaldehyde derivative in hand **15**, the cycloaddition reactions were evaluated. These initial experiments were carried out with sarcosine (*N*-methylglycine) in DMF at reflux. It was quickly found when one equivalent of sarcosine was reacted with **15** that a new compound was obtained in 26% yield. Both ^{1}H and ^{13}C NMR spectra suggested that the desired tricycle **16** was formed. Particularly diagnostic was the doublet due to the benzylic proton in the ^{1}H NMR spectrum which appeared at δ 2.72 (J=6.9 Hz), suggesting a *cis* fusion. This coupling constant is in good agreement with that found for the natural products (J=6.6–6.8 Hz)[2] and in other *cis* fused pyrrolo[3,2-*c*]quinolines (J=4.0–8.3 Hz).[3] The structural and stereochemical assignment was subsequently confirmed through X-ray crystallography (Fig. 3). This clearly demonstrates that the tricycle possessed the required *cis* fusion of the pyrrole to the quinoline system that is found in the natural product. With this result in hand, we proceeded to examine the cycloaddition reaction with other *N*-alkylglycines. It was found that when *N*-benzylglycine and *N*-*p*-methoxybenzylglycine were employed, they provided the corresponding pyrroloquinolines **17** and **18** in 75% and 88% yield respectively.[13] The yields of these two transformations were significantly higher than that obtained from sarcosine. There was, however, a significant experimental difference between the reactions. Since both *N*-benzyl- and *N*-*p*-methoxybenzylglycines were used as their hydrochloride salts, triethylamine was added to convert the salts into the corresponding free base. It is conceivable that in addition to serving as a base, the triethylamine or its hydrochloride salt is serving as a buffer for the multi-step process that is occurring during this reaction. As the efficiency of the reaction with sarcosine was not particularly high, the reaction was repeated with triethylamine added to the reaction mixture. Under these conditions, pyrroloquinoline **16** was obtained in 60% yield. Other *N*-substituted glycine derivatives were evaluated as possible reaction partners with aldehyde **15**. Not unexpectedly, both *N*-tritylglycine and *N*-carboxybenzyloxyglycine failed to provide the corresponding cycloadducts, presumably as a consequence of steric hindrance and attenuated nucleophilicity, respectively.[14] On the other hand, glycine itself engaged in a cycloaddition reaction providing the *NH*-pyrroloquinoline **19** in 17% yield (Scheme 2).[15] This same *NH*-pyrroloquinoline was accessible through the hydrogenolytic removal of either the *N*-benzyl or *N*-*p*-methoxybenzyl protecting groups with Pd-C/H_2 (Scheme 2).[16] Attempts to remove the *N*-methyl group were unsuccessful, as were attempts to remove the *p*-methoxybenzyl group under oxidative conditions.

With a route to the key tricycle delineated, a method for the introduction of the key 8-carboxyl group was sought.[17] Our initial analysis of the natural products suggested that this would be introduced via carbonylation of an appropriate aryl halide (Fig. 1). This particular disconnection would also permit the introduction of a variety of substituents through the utilization of cross-coupling reactions. Therefore, to explore this possibility a second benzaldehyde derivative was prepared that possessed a 5-bromo substituent. A largely analogous series of reactions to those



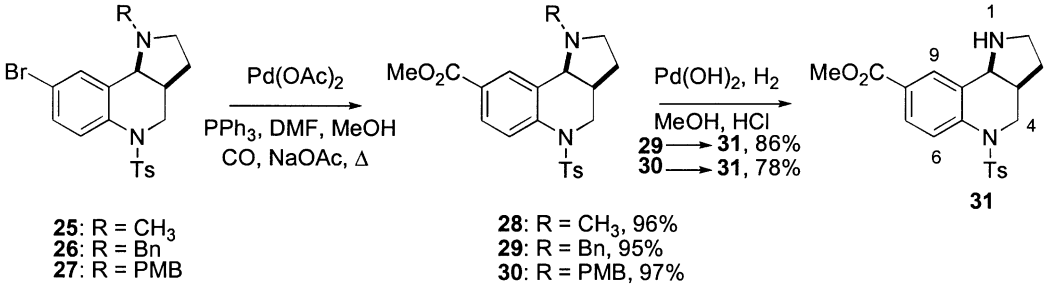
Scheme 2.



Scheme 3.

used for the preparation of **15** were employed for the construction of **24**, with the exception of the initial tosylation step. When this was performed in CH_2Cl_2, the major product from this reaction had incorporated two tosyl groups, however using pyridine as the solvent circumvented this problem.[18] The remaining synthetic steps, **21**→**24**, proceeded uneventfully (Scheme 3).

When benzaldehyde **24** was subjected to the cycloaddition chemistry, the corresponding pyrroloquinolines **25**–**27** were obtained in excellent yield and with good stereoselectivity (Scheme 3). These 8-bromopyrroloquinolines now provided the opportunity to explore the introduction of a carboxyl group. Our initial inclination was to evaluate carbonylation via bromine-metal exchange followed by reaction of the organometallic with carbon dioxide. This approach was briefly evaluated, but proved to be unsuccessful. It was anticipated that the bromine substituent ought to engage in Pd-catalyzed reactions and so these were investigated next. When **25** was treated with CO (1 atm) and MeOH in the presence of Pd(0), PPh_3 and NaOAc, the expected methyl ester **28** was obtained in 24% yield along with the reduced pyrroloquinoline **16** as the major product.[19] When the carbonylation reaction was repeated with the *N*-benzyl and *N*-*p*-methoxybenzyl derivatives the esters were formed (24% and 19% respectively) along with the reduced derivatives. Obviously, the pyrrole-protecting group exerted negligible influence on the outcome of these reactions. These results suggested that reductive elimination was taking place prior to insertion of CO and that by increasing the concentration of CO this might be circumvented. Accordingly, the carbonylation of **25** was conducted at 65 psi of CO and we were



Scheme 4.

delighted to find that under these conditions the methyl esters **28**–**30** were obtained in excellent yield, *ca*. 95%, as the only products (Scheme 4). One final task remained to be accomplished with these systems and that was removal of the *N*-protecting group on the pyrrole nitrogen. In the case of these systems, only hydrogenolysis was evaluated with the *N*-benzyl and *N*-*p*-methyoxybenzyl systems. It was found that upon treatment with hydrogen and Pearlman's catalyst both protecting groups could be removed effectively in the presence of a small quantity of concentrated HCl (Scheme 4).

In summary, a concise stereoselective approach to the pyrroloquinoline core of the *Martinella* alkaloids has been developed that relies on an intramolecular [3+2] azomethine ylide–alkene cycloaddition reaction of an *o*-aminobenzaldehyde derivative. A method for incorporating the 8-carboxyl group through a Pd-catalyzed carbonylation protocol has been defined.[17] The chemoselective hydrogenolysis of the pyrrole protecting group has been demonstrated. We are in the process of constructing more elaborate precursors for use in an enantiospecific total synthesis of martinelline and martinellic acid and we will report on these endeavors in due course.

1. Experimental

1.1. General

All chemicals and solvents were purchased from commercial vendors and were used as received unless indicated otherwise. All reactions involving air- or water-sensitive compounds were conducted in oven-dried glassware under an atmosphere of dry argon or nitrogen. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl and dichloromethane from CaH_2 under a nitrogen atmosphere. Dimethylsulfoxide and triethylamine were distilled from CaH_2 and stored over molecular sieves (4A) and NaOH pellets, respectively. NMR spectra were obtained on JEOL Eclipse+ 500 and Bruker MSL 300 spectrometers. ^{1}H NMR spectra were recorded in deuteriochloroform (unless otherwise indicated) at spectrometer frequencies of 500.16 and 300.13 MHz on JEOL Eclipse+ 500 and Bruker MSL 300 spectrometers, respectively. Residual protiochloroform was used as reference. The ^{13}C NMR spectra were measured in deuteriochloroform (unless otherwise indicated) at 125.79 and 75.47 MHz on JEOL Eclipse 500+ and Bruker MSL 300 spectrometers, respectively using $^{13}CDCl_3$ (δ=77.0) as internal reference. Infrared (IR) spectra were obtained either on a BioRad 3240-SPC or a Bruker Vector 22 FT-IR spectrometer, using KBr pressed pellets for solids or neat films between NaCl plates for liquids and oils, and reported in cm^{-1}. Mass spectra were recorded by electron impact (at 70 eV) on a Finnigan MAT TSQ-70 spectrometer. Elemental analyses were performed on a Perkin Elmer 2400 CHN Elemental Analyzer or determined by Quantitative Technologies Inc. (QTI), Whitehouse, New Jersey. Melting points were recorded on a Thomas Hoover Scientific capillary tube melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was performed on silica gel 60F_{254} aluminum backed precoated plates (0.25 mm layer).

1.1.1. Ethyl 2-(4-toluenesulfonylamino)benzoate 12. A solution of ethyl anthranilate (20.0 g, 121 mmol) and *p*-toluenesulfonyl chloride (28.6 g, 150 mmol) in CH_2Cl_2 (180 mL) was stirred at RT for 56 h. After 56 h an equal volume of H_2O (180 mL) was added to the reaction mixture, and the combined solution was diluted with EtOAc (300 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (200 mL). The combined organic phases were washed with water, dried ($MgSO_4$) and concentrated. The reddish-brown crude product was triturated with ether to remove the coloring impurities; recrystallization of the residue from EtOAc gave the pure compound **12** (30.7 g, 79% yield). mp: 111–112°C. ^{1}H NMR (500 MHz): δ=10.66 (s, 1H), 7.91 (d, *J*=8.0 Hz, 1H), 7.72 (d, *J*=8.1 Hz, 2H), 7.67 (d, *J*=8.5 Hz, 1H), 7.42 (dd, *J*=8.5, 7.7 Hz, 1H), 7.20 (d, *J*=8.1 Hz, 2H), 7.01 (dd, *J*=8.0, 7.7 Hz, 1H), 4.31 (q, *J*=7.2 Hz, 2H), 2.34 (s, 3 H), 1.33 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz): δ=167.8, 143.8, 140.5, 136.4, 134.3, 131.1, 129.5, 127.2, 122.8, 119.0, 116.2, 61.5, 21.5, 14.1. FT-IR (KBr, cm^{-1}): 3340, 3122, 3065, 2984, 1680, 1493, 1341, 1158, 703; EIMS (*m/z*): 319.2 (15, M^+), 318.4 (100, M^+-1), 272.5 (42), 208.9 (37), 180.0 (19), 154.9 (12), 119.0 (19), 91.1 (41), 65.0 (35). Anal. Calcd. For $C_{16}H_{17}NO_4S$: C, 60.13; H, 5.36; N, 4.38. Found: C, 60.11; H, 5.14; N, 4.36.

1.1.2. Ethyl 2-(2-propenyl-4-toluenesulfonylamino)benzoate 13. 12 (15.0 g, 47.0 mmol) was dissolved in acetone (75 mL) and allyl bromide (6.46 g, 53.4 mmol) and K_2CO_3 (22.5 g, 163 mmol) were added to it. The reaction mixture was stirred at RT for 34 h. After this period the mixture was diluted with an equal volume of H_2O (75 mL) and then extracted with Et_2O (3×90 mL). The ether extracts were combined, dried with anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by recrystallization from Et_2O to give **13** as a pale yellow solid (15.8 g, 93% yield). mp: 56–57°C. ^{1}H NMR (500 MHz): δ=7.85–7.84 (m, 1H), 7.50 (d, *J*=8.1 Hz, 2H), 7.39–7.34 (m, 2H), 7.22 (d, *J*=8.1 Hz, 2H), 6.88–6.85 (m, 1H), 5.94–5.86 (m, 1H), 5.04-5.00 (m, 2H), 4.27–4.24 (m, 4H), 2.40 (s, 3H), 1.37 (t, *J*=7.2 Hz, 3 H); ^{13}C NMR (125 MHz): δ=166.2, 143.1, 137.7, 136.7, 133.2, 133.0, 131.7, 131.2, 130.6, 129.3, 128.1, 127.5, 118.9, 61.3, 54.5, 21.4, 14.1; FT-IR (KBr, cm^{-1}): 3093, 3040, 2981, 1722, 1486, 1243, 1164, 661; EIMS (*m/z*): 319.2 (28, M^+), 273.0 (14), 182.2 (8), 153.0 (78), 136.0 (50), 107.0 (7), 106.0 (38), 91.0 (25), 77.1 (100); Anal. Calcd. For $C_{19}H_{21}NO_4S$: C, 63.49; H, 6.02; N, 3.89. Found: C, 63.38; H, 5.65; N, 3.79.

1.1.3. *N*-(2-Hydroxymethylphenyl)-*N*-(2-propenyl)-4-toluenesulfonamide 14. A solution of **13** (12.7 g, 35.2 mmol) in Et_2O (100 mL) was added dropwise to a well-stirred, ice-cold slurry of $LiAlH_4$ (5.96 g, 157 mmol) in Et_2O (260 mL). After 4 h, the reaction mixture was quenched by cautiously adding H_2O (6 mL), 15% NaOH (6 mL), followed by H_2O (18 mL). The aluminum salts were removed by filtration, and the solid was washed well with Et_2O. The filtrate was partitioned with H_2O (350 mL), and after separation, the ether phase was washed with saturated aqueous $NaHCO_3$ (350 mL) followed by H_2O (2x350 mL), dried (anhyd. $MgSO_4$), filtered and concentrated. Column chromatography (hexane/EtOAc: 4:1) of the crude residue gave the pure alcohol **14** (9.91 g, 89%

yield). mp: 79.5-80.5 °C. ^{1}H NMR (500 MHz): δ=7.58 (dd, J=7.7, 1.7 Hz, 1H), 7.54 (d, J=8.0 Hz, 2H), 7.33 (ddd, J= 7.7, 7.7, 1.1 Hz, 1H), 7.29 (d, J=8.0 Hz, 2H), 7.13 (ddd, J=7.9, 7.7, 1.7 Hz, 1H), 6.43 (dd, J=7.9, 1.1 Hz, 1H), 5.70 (ddt, J=17.0, 10.1, 6.9 Hz, 1H), 5.00 (dd, J=10.1, 1.2 Hz, 1H), 4.96 (dd, J=17.0, 1.2 Hz, 1H), 4.95 (brs, 1H), 4.50 (d, J=11.6 Hz, 2H), 3.72 (dd, J=13.4, 8.2 Hz, 1H), 2.85 (brs, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz): δ=144.0, 142.3, 137.0, 134.6, 131.8, 131.0, 129.6, 129.0, 128.3, 128.1, 127.5, 120.0, 61.1, 55.1, 21.6; FT-IR (KBr, cm^{-1}): 3509, 3077, 3049, 2957, 1492, 1338, 1160, 669; EIMS (*m/z*): 317.3 (3, M$^+$), 300.3 (20), 299.2 (100), 162.1 (67), 154.1 (25), 144.2 (98), 134.1 (25), 118.1 (36), 91.1 (40), 77.1 (12). Anal. Calcd. For $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.41. Found: C, 64.32; H, 5.66; N, 4.27.

1.1.4. *N*-(2-Formylphenyl)-*N*-(2-propenyl)-4-toluenesulfonamide 15. Oxalyl chloride (4.19 g, 33.0 mmol) was dissolved in CH_2Cl_2 (75 mL) and the mixture was cooled to −50 to −60°C. A solution of dimethylsulfoxide (5.1 mL, 71.9 mmol) in CH_2Cl_2 (15 mL) was then added to the stirred oxalyl chloride solution and the reaction mixture was stirred for 5 min. Alcohol **14** (9.52 g, 30.0 mmol) in CH_2Cl_2 (30 mL) was added to it; stirring was continued for an additional 15 min. Triethylamine (21 mL, 150 mmol) was added and the reaction mixture was stirred for 5 min and then allowed to warm to room temperature. Water (150 mL) was added, the aqueous phase was separated and then extracted with CH_2Cl_2 (150 mL). The organic phases were combined, washed with saturated NaCl solution (300 mL), and dried with anhydrous $MgSO_4$, filtered, and concentrated. Recrystallization of the crude product from Et_2O gave the pure aldehyde **15** as white crystals (7.10 g, 75% yield). For the MnO_2 oxidation, (5.03 g, 16.5 mmol) of the alcohol **14** was dissolved in dry CH_2Cl_2 (190 mL). MnO_2 (40.0 g, 0.46 mol) was added and the mixture was stirred at room temperature for 6 h. TLC analysis of the reaction mixture indicated that the starting materials were not completely consumed. Therefore, an additional amount (4.2 g, 0.048 mol) of MnO_2 was added to the reaction mixture and stirring was continued for a further 2 h. Then the residual solids were removed by filtration and the filtrate was concentrated by a rotary evaporation. Purification of the crude product by chromatography (hexane/EtOAc: 4/1) gave the aldehyde **15** (4.33 g, 86% yield). mp: 109-110 °C. ^{1}H NMR (500 MHz): δ=10.39 (s, 1H), 7.98 (dd, J=7.7, 1.9 Hz, 1H), 7.48 (d, J=8.3 Hz, 2H), 7.45 (dd, J= 7.5, 1.8 Hz, 1H), 7.43 (m, 1H), 7.28 (d, J=8.3 Hz, 2H), 6.71 (dd, J=7.7, 1.8 Hz, 1H), 5.74 (ddt, J=16.9, 10.1, 6.8 Hz, 1H), 5.05 (dd, J=10.1, 1.2 Hz, 1H), 5.02 (dd, J=16.9, 1.2 Hz, 1H), 4.56 (brs, 1H), 3.85 (brs, 1H), 2.44 (s, 3H). ^{13}C NMR (125 MHz): δ=190.2, 144.3, 141.4, 136.1, 134.4, 134.1, 131.6, 129.8, 128.7, 128.4, 128.0, 120.6, 54.5, 21.7. FT-IR (KBr, cm^{-1}): 3080, 3034, 2925, 2893, 1688, 1482, 1349, 1166, 668; EIMS (*m/z*): 316.5 (100, M$^+$+1), 315.0 (7, M$^+$), 160.2 (98), 132.2 (36), 91.1 (30), 77.2 (17), 65.1 (15). Anal. Calcd. For $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.75; H, 5.19; N, 4.47.

1.1.5. (3a*S,9b*S**)-2,3,3a,4,5,9b-Hexahydro-1-methyl-5-(4-toluenesulfonyl)-1*H*-pyrrolo[3,2-*c*]quinoline 16.** Benzaldehyde **15** (1.06 g, 3.4 mmol) was dissolved in DMF (13 mL) and then sarcosine (725 mg, 8.15 mmol) and Et_3N (828 mg, 8.16 mmol) were added to it. The resulting mixture was stirred under reflux for 15 h. After this period the mixture was cooled to room temperature, then diluted with H_2O (10 mL) and extracted with EtOAc (3×30 mL). The EtOAc extracts were combined and washed with H_2O (3×30 mL) to remove residual DMF. The organic phase was dried with anhydrous $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by recrystallization from Et_2O to give **16** as colorless crystals (329 mg, 60% yield). mp: 105–106°C. ^{1}H (500 MHz): δ 7.73 (dd, J=8.4, 0.8 Hz, 1H), 7.54 (d, J=8.3 Hz, 2H), 7.24 (ddd, J=9.0, 7.3, 1.7 Hz, 1H), 7.20-7.17 (m, 3H), 7.10 (ddd, J=7.3, 7.3, 1.2 Hz, 1H), 3.99 (dd, J=13.5, 5.0 Hz, 1H), 3.46 (dd, J=13.5, 9.9 Hz, 1H), 2.97 (ddd, J=8.8, 8.8, 2.4 Hz, 1H), 2.72 (d, J=6.9 Hz, 1H), 2.37 (s, 3H), 2.28 (s, 3H), 2.24-2.14 (m, 2H), 1.96 (dddd, J=17.4, 8.8, 8.8, 2.4 Hz, 1H), 1.49 (dddd, J=17.4, 8.8, 8.6, 4.3 Hz, 1H); ^{13}C NMR (125 MHz): δ 143.4, 137.4, 137.3, 130.6, 129.5, 128.9, 127.7, 127.0, 124.0, 123.3, 64.0, 55.2, 49.5, 40.4, 35.5, 27.0, 21.5; FT-IR (KBr, cm^{-1}): 3010, 2979, 2955, 2879, 2845, 2788, 1486, 1345, 1167, 660; EIMS (*m/z*): 342.3 (4, M$^+$), 188.2 (14), 187.2 (100), 156.1 (96), 130.1 (28), 97.0 (25), 57.0 (19); Anal. Calcd. For $C_{19}H_{22}N_2O_2S$: C, 66.66; H, 6.47; N, 8.18. Found: C, 66.48; H, 6.38; N, 8.19.

1.1.6. (3a*S, 9b*S**)-1-Benzyl-2,3,3a,4,5,9b-hexahydro-5-(4-toluenesulfonyl)-1*H*-pyrrolo[3,2-*c*]quinoline 17.** Benzaldehyde **15** (1.03 g, 3.3 mmol) and *N*-benzylglycine hydrochloride (960 mg, 4.76 mmol) were dissolved in DMF (15 mL). Et_3N (808 mg, 8.00 mmol) was added to it and the mixture was heated at reflux for 6 h. After work up (see synthesis of **16**), recrystallization of the crude residue from Et_2O gave the pure tricyclic compound **17** as colorless solid (1.06 g, 77% yield). mp: 119–120°C. ^{1}H NMR (300 MHz): δ=7.73 (d, J=8.3 Hz, 1H), 7.60 (d, J=8.3 Hz, 2H), 7.27-7.16 (m, 9H), 7.09 (ddd, J=7.4, 7.4, 1.0 Hz, 1H), 4.07 (d, J=12.8 Hz, 1H), 4.00 (dd, J=13.5, 5.5 Hz, 1H), 3.53 (dd, J=13.5, 9.2 Hz, 1H), 3.17 (d, J=12.8 Hz, 1H), 3.03 (d, J=7.4 Hz, 1H), 2.81 (ddd, J=10.5, 8.2, 3.0 Hz, 1H), 2.39 (s, 3H), 2.45-2.31 (m, 1H), 2.14 (ddd, J=10.5, 8.2, 8.2 Hz, 1H), 1.97 (dddd, J=12.9, 8.2, 8.2, 3.0 Hz, 1H), 1.46 (dddd, J=12.9, 8.2, 8.2, 4.9 Hz, 1H); ^{13}C NMR (75 MHz): δ=143.5, 139.6, 137.8, 137.4, 130.6, 129.9, 129.6, 128.4, 128.1, 127.7, 127.1, 126.8, 124.2, 123.1, 62.8, 58.2, 51.8, 49.7, 36.6, 27.5, 21.5; FT-IR (KBr, cm^{-1}): 3058, 3028, 2956, 2876, 2793, 1491, 1348, 1164, 773; EIMS (*m/z*): 418.2 (100, M$^+$), 419.1 (24, M$^+$+1), 263.1 (100), 218.9 (10), 144.1 (10), 91.0 (72), 77.0 (30); Anal. Calcd. For $C_{25}H_{26}N_2O_2S$: C, 71.74; H, 6.26; N, 6.69. Found: C, 71.74; H, 6.32; N, 6.89.

1.1.7. *N*-(4-Methoxybenzyl)glycine hydrochloride. Glycine (4.23 g, 56.3 mmol) was added to an alkaline solution of NaOH (2.25 g, 56.3 mmol) in H_2O (70 mL) and the mixture was stirred at RT for 10 min. *p*-anisaldehyde (7.60 g, 55.8 mmol) was then added in one portion. After being stirred for 30 min., the reaction mixture was cooled to 0°C. $NaBH_4$ (675 mg, 17.76 mmol) was added in portion over a period of 30 min. and stirring was continued for an additional 30 min. maintaining the temperature at 10–12°C. The reaction mixture was then allowed to warm to RT, and a second portion of *p*-anisaldehyde (7.60 g, 55.8 mmol) was added as before followed by $NaBH_4$ at 0 °C. The reaction

mixture was stirred at RT for 5–6 h, then washed with Et_2O (3×75 mL). The clear aqueous layer was acidified with 6M HCl to pH 4.0 and left in the hood for several days while the white precipitates of *N*-(4-methoxybenzyl)glycine hydrochloride formed. The precipitates were collected by filtration, washed with a small amount of hot water and dried to give the title compound (3.56 g, 33%).

1.1.8. (3a*S, 9b*S**)-2,3,3a,4,5,9b-Hexahydro-1-(4-methoxybenzyl)-5-(4-toluenesulfonyl)-1*H*-pyrrolo[3,2-*c*]quinoline 18.** A round bottom flask (10 mL) was charged with benzaldehyde **15** (752 mg, 2.38 mmol), *N*-p-methoxybenzylglycine hydrochloride (846 mg, 3.65 mmol) and Et_3N (481 mg, 4.76 mmol). DMF (15 mL) was added and the mixture was heated under reflux conditions for 3 h. After work-up (see preparation of **16**), the crude product was purified by flash chromatography (hexane/EtOAc: 4/1) to give **18** as colorless solid (1.0214 g, 95% yield). mp: 119.5–120.5°C. ^{1}H NMR (300 MHz): δ=7.72 (dd, *J*=7.3, 0.9 Hz, 1H), 7.60 (d, *J*=8.5 Hz, 2H), 7.28-7.23 (m, 2H), 7.20 (d, *J*=8.2 Hz, 2H), 7.09 (ddd, *J*=7.3, 7.3, 0.9 Hz, 1H), 7.08 (d, *J*=8.2 Hz, 2H), 6.78 (d, *J*=8.5 Hz, 2H), 4.00 (dd, *J*=13.5, 5.5 Hz, 1H), 3.99 (d, *J*=12.5 Hz, 1H), 3.47 (s, 3H), 3.52 (dd, *J*=13.5, 9.2 Hz, 1H), 3.11 (d, *J*=12.5 Hz, 1H), 3.01 (d, *J*=7.5 Hz, 1H), 2.78 (ddd, *J*=10.5, 8.2, 3.1 Hz, 1H), 2.39 (s, 3H), 2.42-2.32 (m, 1H), 2.13 (ddd, *J*=10.5, 8.4, 8.2 Hz, 1H), 1.94 (dddd, *J*=12.9, 8.2, 8.2, 3.1 Hz, 1H), 1.45 (dddd, *J*=12.9, 8.4, 8.2, 4.9 Hz); ^{13}C NMR (125 MHz): δ=158.5, 143.5, 137.9, 137.4, 131.6, 130.6, 130.2, 129.6, 127.6, 127.1, 124.3, 123.1, 113.5, 62.7, 57.6, 55.2, 51.6, 49.7, 36.6, 27.5, 21.5; FT-IR (KBr, cm^{-1}): 2958, 2817, 1489, 1344, 1165, 757; EIMS (*m/z*): 448.8 (100, M^+), 446.8 (27, M^+-2), 340.8 (4), 327.1 (14), 306.7 (12). Anal. Calcd. For $C_{26}H_{28}N_2O_3S$: C, 69.62; H, 6.29; N, 6.25. Found: C, 69.81; H, 6.61; N, 6.00.

1.1.9. (3a*S, 9b*S**)-2,3,3a,4,5,9b-Hexahydro-5-(4-toluenesulfonyl)-1*H*-pyrrolo[3,2-*c*]quinoline 19: cycloaddition method.** A DMF solution (3 mL) containing benzaldehyde **15** (200 mg, 0.63 mmol), glycine (475 mg, 6.33 mmol) and Et_3N (550 mg, 5.45 mmol) were heated at reflux overnight. On cooling to room temperature, the mixture was partitioned between EtOAc (5 mL) and H_2O (5 mL). The EtOAc layer was separated and washed with H_2O (2x5 mL), sat. $NaHCO_3$ (2x5 mL), dried ($NaSO_4$) and concentrated. The residue was purified by flash column chromatography ($CHCl_3$/MeOH: 92.5/7.5) to afford **19** as a colorless solid (34 mg, 17% yield).

1.2. Hydrogenolysis method

A suspension of **17** (50 mg, 0.12 mmol) in ethanol was stirred at RT for 15 min.; 5% Pd-C catalyst (62 mg) was then added to it and the reaction vessel was evacuated and refilled with hydrogen. The reaction mixture was stirred under a balloon of hydrogen for 30 h. The catalyst was removed by vacuum filtration through a Celite pad and the filtrate was evaporated to dryness. The crude residue was purified by column chromatography ($CHCl_3$/MeOH: 92.5/7.5) to obtain **19** (23 mg, 59% yield) as colorless crystals. mp: 206–208°C. ^{1}H NMR (500 MHz): δ 7.69 (d, *J*=8.2, 1H), 7.49 (d, *J*=8.3 Hz, 2H), 7.43 (d, *J*=7.3 Hz, 1H), 7.25 (dd, *J*=8.2, 7.3 Hz, 1H), 7.19 (d, *J*=8.3 Hz, 2H), 7.16 (dd, J=7.3, 7.3 Hz, 1H), 4.20 (dd, *J*=14.0, 5.6 Hz, 1H), 3.66 (d, *J*=7.6 Hz, 1H), 3.45 (brs, 1H), 3.02 (ddd, *J*=11.3, 8.2, 4.2 Hz, 1H), 2.94 (dd, *J*=14.0, 12.4 Hz, 1H), 2.79 (ddd, *J*=11.3, 8.2, 8.2 Hz, 1H), 2.38 (s, 3H), 2.18 (m, 1H), 2.05 (dddd, *J*=12.5, 8.2, 8.2, 3.9 Hz, 1H), 1.42 (dddd, *J*=12.5, 8.2, 8.2, 4.2 Hz, 1H); ^{13}C NMR (125 MHz): δ 143.7, 137.3, 136.5, 131.4, 129.9, 129.7, 127.5, 126.9, 125.7, 124.6, 57.1, 48.0, 44.9, 35.0, 30.3, 21.5; FT-IR (KBr, cm^{-1}): 3349, 3184, 3060, 2954, 2843, 1488, 1343, 1165, 883, 666; EIMS (*m/z*): 328.4 (2, M^+), 259.2 (12), 152.9 (32), 106.0 (24), 84.9 (63), 82.9 (100), 77.0 (37).

1.2.1. Methyl 5-bromo-2-(4-toluenesulfonylamino)-benzoate 21. Methyl 2-amino-5-bromobenzoate (8.00 g, 34.8 mmol) was dissolved in pyridine (56 mL) and *p*-toluenesulfonyl chloride (4.80 g, 25.2 mmol) was slowly added to it and the mixture was stirred at RT. After being stirred for 24 h, additional *p*-toluenesulfonyl chloride (4.80 g, 25.2 mmol) was added to the reaction mixture over a period of 8 h and stirring was continued for additional 16 h. After the reaction was complete (TLC analysis), the pyridine was removed by rotary evaporation, H_2O (60 mL) was added to the residue which was then extracted with EtOAc (3x100 mL). The EtOAc extracts were combined and washed successively with 20% aqueous $CuSO_4$ solution, then H_2O (2x200 mL), dried (anhyd. $MgSO_4$), filtered and concentrated. The crude product was purified by recrystallization from EtOAc to give **21** as a colorless solid (12.60 g, 94% yield). mp 121–122°C. ^{1}H NMR (300 MHz): δ=10.52 (br s, 1H), 8.03 (d, *J*=2.3 Hz, 1H), 7.72 (d, *J*=8.3, 2H), 7.61 (d, *J*=9.0 Hz, 1H), 7.53 (dd, *J*=9.0, 2.3 Hz, 1H), 7.24 (d, *J*=8.3 Hz, 2H), 3.88 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz): δ=167.1, 144.2, 139.6, 137.2, 136.1, 133.7, 129.7, 127.2, 120.6, 117.3, 115.4, 52.7, 21.5; FT-IR (KBr, cm^{-1}): 3134, 3112, 2953, 1698, 1480, 1341, 1157, 684; EIMS (*m/z*): 385.0 (92, M^++2), 383.0 (100, M^+), 227.9 (22), 197.8 (38), 155.0 (32), 152.8 (51), 106.9 (41), 91.0 (99), 77.0 (67), 64.9 (28); Anal. Calcd. for $C_{15}H_{14}NBrO_4S$: C, 46.89; H, 3.67; N, 3.65. Found: C, 47.21; H, 3.78; N, 3.29.

1.2.2. Methyl 5-bromo-2-(2-propenyl-4-toluenesulfonyl-amino)benzoate 22. Allyl bromide (0.78 g, 5.9 mmol) was added to a solution of **21** (2.01 g, 5.2 mmol) in acetone (15 mL). K_2CO_3 (2.46 g, 17.8 mmol) was added to it and the reaction mixture was stirred at RT for 24 h. After the reaction was complete, the acetone was removed by rotary evaporation, H_2O (20 mL) was added to the residue and the product was extracted with EtOAc (3x40 mL). The EtOAc extracts were combined, dried with anhydrous $MgSO_4$, filtered and evaporated to dryness. Recrystallization of the crude product from EtOAc gave the pure compound **22** as colorless crystals (2.07 g, 94% yield). mp: 96–97°C. ^{1}H NMR (500 MHz): δ=7.97 (d, *J*=2.3 Hz, 1H), 7.51-7.48 (m, 3H), 7.24 (d, *J*=8.7 Hz, 2H), 6.77 (d, *J*=8.5 Hz, 1H), 5.86 (ddt, *J*=17.0, 10.1, 6.9 Hz, 1H), 5.04 (dd, *J*=10.1, 1.3 Hz, 1H), 5.01 (dd, J=17.0, 1.3 Hz, 1H), 4.22 (d, *J*=6.9 Hz, 2H), 3.78 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (125 MHz): δ 165.1, 143.4, 136.9, 136.4, 134.9, 134.2, 132.9, 132.4, 129.5, 127.5, 122.1, 119.3, 54.4, 52.5, 21.5; FT-IR (KBr, cm^{-1}): 3090, 3037, 2949, 1741, 1484, 1347, 1163, 664; EIMS (*m/z*): 424.3 (1, M^++1), 384.7 (84), 383.0 (76), 269.7 (68), 267.7 (65), 154.9 (48), 90.9 (100), 77.0 (37), 64.9 (23).

1.2.3. *N*-(5-Bromo-2-hydroxymethylphenyl)-*N*-(2-propenyl)-4-toluenesulfonamide 23. A solution of **22** (4.70 g, 11.1 mmol) in THF (20 mL) was added dropwise to a well-stirred, ice-cold slurry of $LiAlH_4$ (2.01 g, 52.9 mmol) in Et_2O (88 mL). After 10 h the reaction mixture was cautiously quenched by adding H_2O (3 mL), 15% NaOH (3 mL), followed by H_2O (9 mL). The precipitated aluminum salts were removed by filtration, and the solid was washed well with Et_2O. The filtrate was diluted with H_2O (200 mL), and the ether phase was washed with saturated aqueous $NaHCO_3$ (200 mL), followed by H_2O (2×200 mL), dried (anhyd. $MgSO_4$), filtered and concentrated. Column chromatography (hexane/EtOAc: 4/1) of the crude residue gave the pure alcohol **23** (3.00 g, 68% yield). mp: 124–125°C. ^{1}H NMR (300 MHz): δ=7.75 (d, J=2.3 Hz, 1H), 7.54 (d, J=8.4 Hz, 2H), 7.32 (d, J=8.4 Hz, 1 H), 7.26 (dd, J=8.4, 2.3 Hz, 1H), 6.29 (d, J=8.4 Hz, 1H), 5.68 (ddt, J=16.9, 10.0, 6.9 Hz, 1H), 5.04 (dd, J=10.0, 1.2 Hz, 1H), 4.97 (brs, 1H), 4.96 (dd, J=16.9, 1.2 Hz, 1H), 4.49 (d, J=12.5 Hz, 2H), 3.67 (dd, J=12.5, 8.5 Hz, 1H), 2.94 (dd, J=6.9, 6.9 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (75 MHz): δ=144.6, 144.2, 135.9, 134.3, 133.8, 131.5, 131.3, 129.7, 129.0, 128.0, 122.9, 120.4, 60.7, 55.0, 21.6; FT-IR (KBr, cm^{-1}): 3494, 3077, 2938, 1480, 1337, 1157, 669; EIMS (*m/z*): 352.4 (3), 350.0 (3), 252.2 (18), 242.8 (100), 240.8 (100), 223.8 (63), 221.8 (58), 116.9 (100), 93.0 (46), 76.9 (42), 64.9 (23). Anal Calcd For $C_{17}H_{18}NBrO_3S$: C, 51.52, H, 4.58, N, 3.53, Found: C, 51.68, H, 4.52, N, 3.13.

1.2.4. *N*-(4-Bromo-2-formylphenyl)-*N*-(2-propenyl)-4-toluenesulfonamide 24. Oxalyl chloride (0.05 mL, 0.55 mmol) was dissolved in CH_2Cl_2 (1.25 mL) previously cooled to −50 to −60°C and the mixture was stirred up for 15 min. maintaining the same temperature. A solution of dimethylsulfoxide (0.09 mL, 1.1 mmol) in CH_2Cl_2 (0.25 mL) was then added to the stirred oxalyl chloride solution and the reaction mixture was stirred for 10 min. Alcohol **23** (200 mg, 0.51 mmol) in CH_2Cl_2 (0.5 mL) was added to it; stirring was continued for an additional 30 min. Triethylamine (0.35 mL, 2.5 mmol) was added and the mixture was stirred for 12 h allowing it to warm to room temperature. Water (5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3×3 mL). The CH_2Cl_2 extracts were combined, washed with saturated NaCl (2 x 5 mL) followed by H_2O (2×5 mL), dried with anhydrous $MgSO_4$, filtered and concentrated. The pure aldehyde **24** (145 mg, 73% yield) was obtained as colorless solid by purifying the crude product by column chromatography (hexane/EtOAc: 3/1). For the MnO_2 oxidation, 3.0 g (7.57 mmol) of the alcohol **23** was dissolved in dry CH_2Cl_2 (90 mL). MnO_2 (22.7 g, 0.32 mol) was added and the mixture was stirred at room temperature for 12 h. TLC analysis of the reaction mixture indicated that the starting materials was not completely consumed. Therefore, an additional amount (18.0 g, 0.21 mol) of MnO_2 was added to the reaction mixture and stirring was continued for a further 12 h. Then the MnO_2 was removed by filtration and the filtrate was concentrated by a rotary evaporator. Purification of the crude product by chromatography (hexane/EtOAc: 4/1) gave the aldehyde **24** (2.46 g, 82% yield). mp: 85–86°C. ^{1}H NMR (500 MHz): δ=10.30 (s, 1H), 8.08 (d, J=2.2 Hz, 1H), 7.55 (dd, J=8.5, 2.2 Hz, 1H), 7.47 (d, J=8.0 Hz, 2H), 7.29 (d, J=8.0 Hz, 2H), 6.56 (d, J=8.5 Hz, 1H), 5.72 (ddt, J=17.0, 10.0, 6.8 Hz, 1H), 5.07 (d, J=10.0 Hz, 1H), 5.02 (d, J=17.0 Hz, 1H), 4.56 (br s, 1H), 3.78 (br s, 1H), 2.44 (s, 3H); ^{13}C NMR (125 MHz): δ=188.6, 144.5, 140.1, 137.3, 136.8, 134.0, 131.4, 131.2, 129.8, 129.5, 127.9, 122.9, 120.9, 54.2, 21.6; FT-IR (KBr, cm^{-1}): 3088, 3034, 2886, 1687, 1476, 1358, 1168, 666; EIMS (*m/z*): 394.8 (55, M^+ + 2), 392.8 (57, M^+), 367.9 (100), 365.9 (64), 239.9 (100), 237.9 (92), 159.1 (28), 130.2 (100), 86.0 (22); Anal. Calcd. For $C_{17}H_{16}NBrO_3S$: C, 51.78; H, 4.09; N, 3.55. Found: C, 51.75; H, 3.78; N, 3.26.

1.2.5. (3a*S, 9b*S**)-8-Bromo-2,3,3a,4,5,9b-hexahydro-1-methyl-5-(4-toluenesulfonyl)-1*H*-pyrrolo[3,2-*c*]quinoline 25.** A round-bottom flask was charged with benzaldehyde **24** (500 mg, 1.27 mmol), sarcosine (226 mg, 2.54 mmol), Et_3N (257 mg, 2.54 mmol) and DMF (5 mL); the reaction mixture was heated at reflux for 1.5 h with constant stirring. After work up (see preparation of **16**), purification of the crude product by flash chromatography over silica gel (elution with EtOAc/hexane/NH_4OH: 3/2/0.04) gave a colorless solid **25** (481 mg, 90%). mp: 119–120°C; ^{1}H NMR (500 MHz): δ=7.62 (d, J=8.7 Hz, 1H), 7.53 (d, J=8.2 Hz, 2H), 7.34 (dd, J=8.7, 2.3 Hz, 1H), 7.30 (d, J=2.3 Hz, 1H), 7.21 (d, J=8.2 Hz, 2H), 3.98 (dd, J=13.6, 5.4 Hz, 1H), 3.38 (dd, J=13.6, 10.0 Hz, 1H), 2.96 (ddd, J=8.7, 8.7, 2.5 Hz, 1H), 2.64 (d, J=6.7 Hz, 1H), 2.38 (s, 3H), 2.27 (s, 3H), 2.21 (ddd, J=8.7, 8.7, 8.7 Hz, 1H), 2.14 (m, 1H), 1.94 (dddd, J=12.9, 8.7, 8.7, 2.5 Hz, 1H), 1.46 (dddd, J=12.9, 8.7, 8.7, 5.5 Hz, 1H); ^{13}C NMR (125 MHz): δ=143.7, 137.0, 136.5, 133.1, 131.4, 130.6, 129.6, 127.0, 125.2, 117.3, 63.7, 55.1, 49.3, 40.6, 35.7, 27.1, 21.5; FT-IR (KBr, cm^{-1}): 2950, 2772, 1479, 1345, 1167, 673; EIMS (*m/z*): 421.9 (98, M^+ + 2), 419.9 (100, M^+), 266.9 (100), 264.9 (82), 235.9 (61), 233.9 (59), 171 (76), 91.0 (43), 55.1 (64); Anal. Calcd. For $C_{19}H_{21}N_2BrO_2S$: C, 54.16; H, 5.02; N, 6.65. Found: C, 54.04; H, 4.62; N, 6.37.

1.2.6. (3a*S, 9b*S**)-1-Benzyl-8-bromo-2,3,3a,4,5,9b-hexahydro-5-(4-toluenesulfonyl)-1*H*-pyrrolo[3,2-*c*]quinoline 26.** Benzaldehyde **24** (145 mg, 0.37 mmol) and *N*-benzylglycine (111 mg, 0.55 mmol) were dissolved in DMF (1.7 mL); Et_3N (52 mg, 0.51 mol) was added and the mixture was stirred under reflux conditions for 1 h. After work up (see preparation of **16**), the reaction mixture was cooled to room temperature, H_2O (was added and it was extracted with EtOAc (3×6 mL). The combined ethyl acetate extracts were washed with H_2O (3×10 mL), dried with anhydrous $MgSO_4$, filtered and concentrated. Column chromatography (EtOAc/hexane: 1/3) of the crude product gave the tricyclic compound **26** (105 mg, 81% yield) as colorless crystals. mp: 112–113 °C. ^{1}H NMR (500 MHz): δ=7.62–7.59 (m, 3H), 7.39 (d, J=2.4 Hz, 1H), 7.33 (dd, J=8.7, 2.4 Hz, 1H), 7.27-7.17 (m, 7H), 4.01 (dd, J=13.5, 5.7 Hz, 1H), 3.99 (d, J=12.7 Hz, 1H), 3.44 (dd, J=13.5, 9.4 Hz, 1H), 3.22 (d, J=12.7 Hz, 1H), 2.96 (d, J=7.5 Hz, 1H), 2.81 (ddd, J=9.5, 8.3, 3.4), 2.40 (s, 3H), 2.43-2.33 (m, 1H), 2.19 (ddd, J=9.5, 8.3, 8.3, 1H), 1.95 (dddd, J=12.1, 8.3, 8.3, 3.4 Hz, 1H), 1.47–1.40 (m, 1H); ^{13}C NMR (125 MHz): δ=143.8, 139.2, 137.0, 136.9, 133.0, 132.6, 130.5, 129.7, 128.4, 128.2, 127.1, 126.9, 125.0, 117.6, 62.4, 58.4, 51.8, 49.4, 36.6, 27.6, 21.5; FT-IR (KBr,

cm^{-1}): 3029, 2951, 2784, 1477, 1350, 1161, 675; EIMS (*m/z*): 498.0 (13, M^++2), 496.0 (11, M^+), 498.0 (M^+ + 2), 288.9 (42), 155.0 (37), 154.0 (100), 136.3 (100), 107.0 (22), 91.0 (32), 76.9 (100); Anal. Calcd. For $C_{25}H_{25}N_2BrO_2S$: C, 60.31; H, 5.07; N, 5.63. Found: C, 60.66; H, 5.07; N, 5.25.

1.2.7. (3a*S,9b*S**)-8-Bromo-2,3,3a,4,5,9b-hexahydro-1-(4-methoxybenzyl)-5-(4-toluenesulfonyl)-1*H*-pyrrolo-[3,2-*c*]quinoline 27.** A round-bottom flask was charged with benzaldehyde **24** (148 mg, 0.38 mmol), *N*-*p*-methoxybenzylglycine hydrochloride (109 mg, 0.56 mmol), Et_3N (57 mg, 0.56 mmol) and DMF (2 mL); the reaction mixture was heated to reflux under an argon atmosphere for 1.5 h. After work-up (see preparation of **16**), the crude product was purified by flash chromatography (hexane/EtOAc: 4/1) to afford **27** as colorless powder (163 mg, 83%). mp: 146–147°C; ^{1}H NMR (500 MHz): δ=7.60 (d, *J*=8.7, 1H), 7.59 (d, *J*=8.5 Hz, 2H), 7.37 (d, *J*=2.3 Hz, 1H), 7.33 (dd, *J*=8.7, 2.3 Hz, 1H), 7.22 (d, *J*=8.2 Hz, 2H), 7.09 (d, *J*=8.2 Hz, 2H), 6.80 (d, *J*=8.5 Hz, 2H), 4.03 (dd, *J*=13.6, 5.8 Hz, 2H), 3.90 (d, *J*=12.5 Hz, 1H), 3.78 (s, 3H), 3.40 (dd, *J*=13.6, 9.4 Hz, 1H), 3.16 (d, *J*=12.5 Hz, 1H), 2.92 (d, *J*=7.6 Hz, 1H), 2.78 (ddd, *J*=10.4, 8.2, 3.4 Hz, 1H), 2.48 (m, 1H), 2.40 (s, 3H), 2.18 (ddd, *J*=8.2, 8.2, 8.2 Hz, 1H), 1.94 (dddd, *J*=12.0, 8.2, 8.2, 3.4 Hz, 1H), 1.41 (m, 1H). ^{13}C NMR (125 MHz): δ=158.6, 143.8, 137.0, 136.8, 133.0, 132.8, 131.2, 130.5, 129.7, 129.6, 127.1, 125.0, 117.7, 113.6, 62.3, 57.9, 55.2, 51.8, 49.5, 36.8, 27.7, 21.6; FT-IR (KBr, cm^{-1}): 2960, 2931, 2892, 2805, 1482, 1353, 1167, 664; EIMS (*m/z*): 527.9 (2, M^+ + 2), 525.9 (2, M^+), 404.8 (3), 372.8 (43), 251.0 (7), 155.0 (5), 120.9 (100), 91.0 (12), 77.0 (6); Anal. Calcd. For $C_{26}H_{27}N_2BrO_3S$: C, 59.20; H, 5.16; N, 5.31. Found: C, 59.29; H, 4.89; N, 5.02.

1.3. Carbonylation of bromopyrroloquinolines (28-30)—general procedure

The bromopyrroloquinoline, $Pd(OAc)_2$, Ph_3P, NaOAc, MeOH, and DMF were added to a oven-dried high pressure reaction tube which was capped with a septum. The reaction mixture was flushed with argon for several minutes. The septum was then replaced with a Teflon screw cap fitted with a pressure gauge. The reaction mixture was pressurized with carbon monoxide (CO), purged 2–3 times with CO and then heated to 110°C for 24 h at 65 psi of CO. The mixture was filtered though Celite and the Celite pad was washed several times with CH_2Cl_2. The filtrate was washed 3–4 times with water to remove DMF. The organic phase was dried with anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by flash chromatography in the indicated solvent mixture to afford the pure pyrroloquinoline esters.

1.3.1. (3a*S, 9b*S**)-Methyl 2,3,3a,4,5,9b-hexahydro-1-methyl-5-(4-toluenesulfonyl)-1*H*-pyrrolo [3,2-*c*]quinoline-8-carboxylate 28.** Carbonylation of **25** (115 mg, 0.27 mmol) with $Pd(OAc)_2$ (15 mg, 0.07 mmol), PPh_3 (20 mg, 0.08 mmol), NaOAc (28 mg, 0.34 mmol) in MeOH (1.5 mL) and DMF (1.5 mL) according to general procedure followed by flash chromatography (hexane/EtOAc: 2/2.5) provided the title compound as pale-yellow crystals (105 mg, 96%). mp: 114–115°C. ^{1}H NMR (500 MHz): δ=7.87 (dd, *J*=8.7, 2.0 Hz, 1H), 7.84 (d, *J*=2.0 Hz, 1H), 7.79 (d, *J*=8.7 Hz, 1H), 7.58 (d, *J*=8.3 Hz, 2H), 7.20 (d, *J*=8.3 Hz, 1H), 4.02 (dd, *J*=13.3, 5.0 Hz, 1H), 3.88 (s, 3H), 3.49 (dd, *J*=13.3, 9.9 Hz, 1H), 2.99 (ddd, *J*=8.9, 8.9, 2.3, 1H), 2.82 (d, *J*=6.2 Hz, 1H), 2.36 (s, 3H), 2.29 (s, 3H), 2.24 (ddd, *J*=8.9, 8.9, 8.9 Hz, 1H), 2.20-2.15 (m, 1H), 2.00 (dddd, *J*=11.2, 8.9, 8.9, 2.3 Hz, 1H), 1.52 (dddd, *J*=11.2, 8.9, 8.9, 3.8 Hz, 1H); ^{13}C NMR (125 MHz): δ=166.6, 143.8, 141.8, 136.9, 132.5, 129.7, 129.0, 127.9, 127.0, 125.0, 122.1, 64.0, 54.9, 52.1, 49.2, 40.1, 35.3, 26.7, 21.5; FT-IR (KBr, cm^{-1}): 3092, 3053, 2942, 2832, 2787, 1711, 1441, 1353, 1165; 675; EIMS (*m/z*): 399.9 (1, M^+), 245.2 (100), 214.2 (70), 154.0 (5), 115.0 (11); Anal. Calcd. For $C_{21}H_{24}N_2O_4S$: C, 62.98; H, 6.02; N, 6.99. Found: C, 63.03; H, 6.04; N, 6.84.

1.3.2. (3a*S, 9b*S**)-Methyl 1-benzyl-2,3,3a,4,5,9b-hexahydro-5-(4-toluenesulfonyl)-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate 29.** Carbonylation of **26** (700 mg, 1.41 mmol) $Pd(OAc)_2$ (90 mg, 0.40 mmol), PPh_3 (120 mg, 0.46 mmol), NaOAc (155 mg, 1.89 mmol) in MeOH (9 mL) and DMF (9 mL) according to the general procedure, followed by flash chromatography (hexane/EtOAc: 3.5/1) provided the title compound as colorless powder (638 mg, 95%). mp: 126–127°C. ^{1}H NMR (500 MHz): δ=7.88–7.82 (m, 3H), 7.64 (d, *J*=8.3 Hz, 2H), 7.25-7.12 (m, 7H), 4.06 (d, *J*=12.8 Hz, 1H), 4.00 (dd, *J*=13.1, 5.2 Hz, 1H), 3.87 (s, 3H), 3.64 (dd, *J*=13.1, 9.3 Hz, 1H), 3.19 (d, *J*=12.8 Hz, 1H), 3.14 (d, *J*=6.8 Hz, 1H), 2.83 (ddd, *J*=9.1, 9.0, 2.8 Hz, 1H), 2.39 (s, 3H), 2.42–2.26 (m, 1H), 2.16 (ddd, *J*=9.1, 9.0, 9.0 Hz, 1H), 1.99 (dddd, *J*=11.7, 9.1, 9.0, 2.8 Hz, 1H), 1.51 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=166.5, 144.0, 142.3, 139.4, 136.8, 132.7, 129.7, 129.1, 128.6, 128.4, 128.1, 127.2, 126.8, 125.0, 121.8, 62.9, 57.6, 52.0, 51.7, 49.4, 36.0, 27.0, 21.6; FT-IR (KBr, cm^{-1}): 3063, 3026, 2949, 2819, 1717, 1496, 1350, 1166, 674; EIMS (*m/z*): 475.9 (5, M^+), 385.0 (4), 320.6 (100), 277.3 (35), 263.0 (30), 155.2 (8). Anal. Calcd. For $C_{27}H_{28}N_2O_4S$: C, 68.05; H, 5.92; N, 5.48; Found: C, 68.07; H, 5.87; N, 5.79.

1.3.3. (3a*S, 9b*S**)-Methyl 2,3,3a,4,5,9b-hexahydro-1-(4-methoxybenzyl)-5-(4-toluenesulfonyl)-1*H*-pyrrolo[3,2-*c*]-quinoline-8-carboxylate 30.** Carbonylation of 27 (900 mg, 1.71 mmol) with $Pd(OAc)_2$ (145 mg, 0.65 mmol), PPh_3 (175 mg, 0.67 mmol), NaOAc (215 mg, 2.62 mmol) in MeOH (11 mL) and DMF (11 mL) according to the general procedure followed by flash chromatography (hexane/EtOAc: 2/1) afforded the title compound as colorless powder (838 mg, 97%). mp: 113–115°C. ^{1}H NMR (500 MHz): δ=7.91-7.86 (m, 2H), 7.64 (d, *J*=8.4 Hz, 2H), 7.22 (d, *J*=8.3 Hz, 2H), 7.05 (dd, *J*=8.3 Hz, 2H), 6.76 (d, *J*=8.4 Hz, 2H), 4.00-3.97 (m, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 3.62 (dd, *J*=13.3, 9.1 Hz, 1H), 3.13 (d, *J*=12.5 Hz, 1H), 3.11 (d, *J*=7.0, 1H), 2.80 (ddd, *J*=8.7, 8.7, 2.7 Hz, 1H), 2.39 (s, 3H), 2.39-2.28 (m, 1H), 2.14 (ddd, *J*=8.7, 8.7, 8.7 Hz, 1H), 1.98 (dddd, *J*=12.4, 8.7, 8.7, 2.7 Hz, 1H), 1.49 (dddd, *J*=12.4, 8.7, 8.7, 4.5 Hz, 1H); ^{13}C NMR (125 MHz): δ=166.6, 158.5, 143.9, 142.3, 136.8, 132.7, 131.4, 129.7, 129.5, 129.0, 128.8, 127.1, 125.0, 121.8, 113.5, 62.8, 57.0, 55.2, 52.0, 51.5, 49.4, 36.1, 27.0, 21.6; FT-IR (KBr, cm^{-1}): 3064, 3037, 2951, 2848, 1718, 1511, 1352, 1164, 672; EIMS (*m/z*): 506.5 (6, M^+), 350.8 (100), 293.0 (21), 278.0 (38), 182.8 (46), 155

(22). Anal. Calcd. For $C_{28}H_{30}N_2O_5S$: C, 66.38; H, 5.97; N, 5.53; Found: C, 65.96; H, 5.86; N, 5.62.

1.3.4. (3a*S, 9b*S**)-Methyl 2,3,3a,4,5,9b-hexahydro-5-(4-toluenesulfonyl)-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate 31.** Pyrroloquinoline **29** (50 mg, 0.10 mmol) was dissolved in EtOH (3 mL) and 10% $Pd(OH)_2$/C (23 mg) and one drop of conc. HCl were added to it. The reaction mixture was purged with argon followed by hydrogen and it was then stirred under a ballon of hydrogen. After 12 h, another portion of $Pd(OH)_2$/C (12 mg) was added to the reaction mixture and it was stirred for an additional 8 h. The mixture was filtered through Celite and the filter cake was washed several times with CH_2Cl_2. The filtrate, after evaporation of solvent, was purified by flash chromatography ($CHCl_3$/MeOH/NH_4OH: 282/16/1.5) to give the title compound as pale yellow powder (32 mg, 86%). mp: 228–230°C (decomp.) ^{1}H NMR (300 MHz): δ=8.08 (d, J=2.2 Hz, 1H), 7.88 (dd, J=8.7, 2.2 Hz, 1H), 7.78 (d, J=8.7 Hz, 1H), 7.53 (d, J=8.2 Hz, 2H), 7.21 (d, J=8.2 Hz, 2H), 4.24 (dd, J=13.8, 5.4 Hz, 1H), 3.88 (s, 3H), 3.63 (d, J=6.3 Hz, 1H), 3.00 (ddd, J=11.2, 8.0, 4.0 Hz, 1H), 2.90 (dd, J=13.8, 12.1 Hz, 1H), 2.80 (ddd, J=11.2, 8.0, 8.0 Hz, 1H), 2.16 (m, 1H), 2.05 (dddd, J=12.6, 8.0, 8.3, 4.0 Hz, 1H), 1.89 (brs, 1H), 1.41 (dddd, J=12.6, 8.0, 8.0, 4.0 Hz, 1H). ^{13}C NMR (125 MHz): δ=166.8, 144.0, 140.6, 137.1, 131.7, 131.0, 129.8, 128.6, 126.9, 126.7, 123.6, 57.0, 52.1, 48.0, 45.2, 35.2, 30.5, 21.6; FT-IR (KBr, cm^{-1}): 2949, 2848, 2748, 1720, 1443, 1365, 1169, 670; EIMS (*m/z*): 385.2 (3, M^+ - 1), 277.0 (100), 148.7 (50), 130.1 (87), 105.0 (51), 55.1 (58).

Hydrogenolysis of **30** (396 mg, 0.83 mmol) by the procedure described above was performed utilizing the 10% $Pd(OH)_2$/C (230 mg), conc. HCl (6 drops), MeOH (25 mL) and for 5 h. Purification of the crude product by flash chromatography afforded the *NH*-pyrroloquinoline **31** (250 mg, 78%).

1.4. X-Ray structure determination of 16

A colorless single crystal of **16** was mounted on a glass fiber using 5-minute epoxy and immediately placed in the low temperature nitrogen stream. Data collection was carried out at room temperature on a Siemens P4 diffractometer equipped with graphite monochromated MoKα radiation (λ=0.71073 Å). Cell parameters were determined using 40 reflections. Data were corrected for Lorentz and polarization effects. The structure was solved by direct methods followed by successive cycles of full-matrix least-squares refinement and difference Fourier analysis using Bruker SHELXTL 5.1 software package provided by the Bruker Analytical X-ray Instruments, Inc. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in calculated positions and refined isotropically using a riding model with 1.2 or 1.5 times the equivalent isotropic temperature factors of the atoms to which they are attached. Crystal data for **16**: $C_{19}H_{22}N_2O_2S$, Monoclinic, space group C2/c with a=16.275(4) Å, b=11.7136(14) Å, c=18.888(3) Å, β =104.285(11)°, V=3489.6(10) Å^3, Z=8, D_c=1.304 g/cm^3, T=25°C, μ (Mo Kα)=0.199 mm^{-1}, GOOF=1.042, R1 [I>2σ(I)]=0.0446, wR2=0.1134 (all data).

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11. Compound **12** is now available commercially through TimTec Inc., 1300 First State Blvd, Suite E, Wilmington, DE 19804, USA.
12. The ^{1}H NMR spectra of all of the allyl containing derivatives were somewhat unusual in that the signals for the allyl CH_2-group appeared as a pair of well separated signals instead of the expected doublet. This observation suggested that there was a conformationally slow process taking place. This suspicion was confirmed when a d4-dichlorobenzene solution of the aldehyde **24** was warmed in the probe of the NMR spectrometer and these signals became closer until they coalesced at 60°C. We speculate that this is due to hindered

rotation around the nitrogen-allyl CH_2 bond, however, confirmation of this awaits further detailed investigation.

13. In the case of pyrroloquinoline **18**, a second minor component was isolated that spectroscopically bore a resemblance to the major product and presumably is a diastereoisomer. Although a clean sample of this compound was not obtained, it is reasonably certain that it is in fact the trans fused system, with a signal for the pyrrole benzylic proton at δ 3.05 (J=13.5 Hz).
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16. Attempts to remove these protecting groups with $Pd(OH)_2$/HCl led to cleavage of the benzylic pyrrole C–N bond.
17. The numbering system used throughout this paper is that used for the parent pyrrolo[3,2-*c*]quinoline and not that for the *Martinella* alkaloids—see Ref. 1d.
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