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Cyclization reactions of *N*-acryloyl-2-aminobenzaldehyde derivatives: formal total synthesis of martinellic acid

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Abstract—*N*-Alkyl acryloylamides derived from *o*-aminobenzaldehyde derivatives react with *N*-alkyl glycine derivatives to provide cis-fused pyrrole[3,2-*c*]quinolones in moderate yield and high diastereoselectivity. These same substrates engage in a tandem Michael–Mannich pathway on treatment with a secondary amine, providing corresponding quinolone derivatives. The elaboration of a pyrroloquinolone derivative via addition of an in situ generated functionalized copper acetylide to an in situ generated iminium ion provided the C2-substituted derivative. Global deprotection and reduction of the alkyne afford the tricyclic triamine core (as the HCl salt) found in martinellic acid.

1. Introduction

The *Martinella* alkaloids, martinelline (**1**) and martinellic acid (**2**), were isolated from the South American medicinal plant *Martinella iquitosensis* by Witherup and co-workers at Merck Laboratories in 1995 in the course of a natural products screening program.[1,2] These alkaloids were among the first potent, naturally occurring (non-peptide) bradykinin (BK) receptor antagonists to be reported.[3] In addition to their biological activity, these alkaloids contain a partially reduced pyrrolo[3,2-*c*]quinoline ring system, which had not been observed in a natural product prior to the isolation of **1** and **2**, although the parent aromatic heterocycle was well known.[2] The novelty of the ring system found in martinelline and martinellic acid combined with the BK antagonistic behavior of these two natural products has elicited significant interest from the synthetic community,[2,4–17] which in turn has led to the development of a number of strategies for the assembly of the heterocyclic core and most recently to several total syntheses of **1** and **2**.[7,10,14,16,17] Our approach to these targets, which is illustrated below in a retrosynthetic manner (Fig. 1), involves the obvious disconnection of the guanidine groups and functional group manipulations to provide the tricyclic core **3**. Further, disconnection of the C2–C10 bond then provides the key tricyclic intermediate **4** as shown in Figure 1, which not only should function as an useful intermediate *en route* to the natural products, but also may be useful for the eventual preparation of a diverse library of analogs for application in chemical biology studies. It was envisioned that the carbonyl group in the C2-position could be utilized for the stereoselective incorporation of the three-carbon side chain found in the natural products, presumably by the Lewis

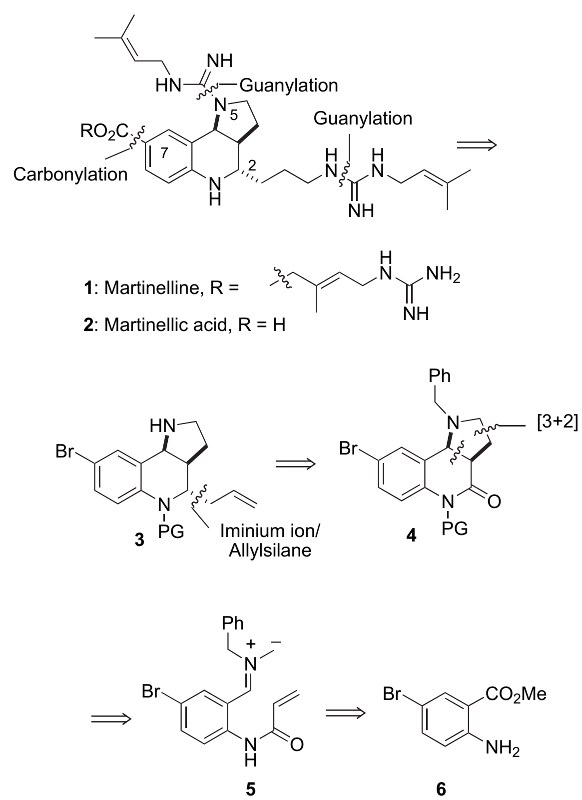

Figure 1. Retrosynthetic analysis of **1** and **2**.

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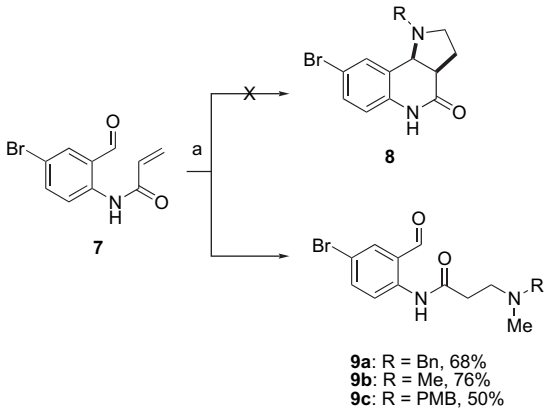
acid-mediated nucleophilic addition of an allylsilane to an iminium ion. The pyrroloquinolone core **4** would be accessed in turn via an intramolecular [3+2] cycloaddition reaction between a non-stabilized azomethine ylide and an electron deficient alkene (Fig. 1, **5**→**4**).[18,19] Related azomethine ylide-based strategies for construction of the key pyrrolo-[3,2-*c*]quinoline skeleton have not only been investigated by our group,[9] but also by Snider et al.[10] and by Nyerges et al. (intermolecular variant with stabilized ylides).[13]

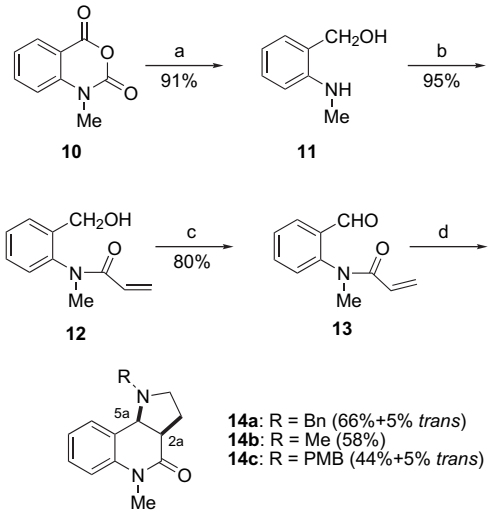
Herein, we report the full details of our investigation of the azomethine ylide cycloaddition reactions of the *N*-acryloyl-2-aminobenzaldehyde derivatives for the construction of pyrroloquinolones **4**, and subsequent conversion of one of these cycloadducts into an advanced precursor for the total synthesis of the *Martinella* alkaloids.[9] In addition to the formal total synthesis, the observation of some initially unanticipated, but nonetheless interesting, events during the course of the reactions of *N*-acryloyl-2-aminobenzaldehyde substrates with *N*-alkyl glycine derivatives, i.e., a domino Michael–Mannich reaction, are described.

Our initial approach to the construction of the key heterocyclic core of these natural products involved the reaction of acrylamide derivative **7** with various *N*-alkyl glycine derivatives.[20,21] However, the expected product **8** was not obtained, but adducts **9a–c** were obtained from a net decarboxylative Michael addition (Scheme 1).[22] Extensive control studies indicated that the requisite azomethine ylide **5** (Fig. 1) was being formed, but underwent protonation and hydrolysis, leading to formation of the amine, followed by conjugate addition to the acryloyl moiety. Our interpretation of this observation centered on low population of the reactive rotamer.[23,24] Therefore to address this possibility, we turned our attention to the use of *N*-alkyl acrylamide derivatives.[25]



Scheme 1. Reagents and conditions: (a) $RNHCH_2CO_2H$ (R=Bn, PMB as HCl salt), Et_3N, DMF, reflux.

Initially attempts were made to alkylate **7** with MeI directly, however, these experiments were unsuccessful, and therefore, *N*-methyl isatoic anhydride (**10**) was employed as the starting material. Reduction with $LiAlH_4$ provided the known amino alcohol **11**, which was then acylated chemoselectively with acryloyl chloride according to the protocol of Heaney and co-workers,[26] providing **12** in an excellent yield (Scheme 2). Subsequent MnO_2 oxidation provided the required cyclization precursor, acrylamide **13**, however, the yield of this reaction was found to be scale dependent (0.3 mmol scale, 88%; 8.0 mmol scale, 55%). PCC oxidation only afforded the product in a moderate 40% yield. Ultimately, the hypervalent IBX (*o*-iodoxybenzoic acid) reagent[27] was found to give the most satisfactory result providing **13** in an excellent yield, regardless of the reaction scale.

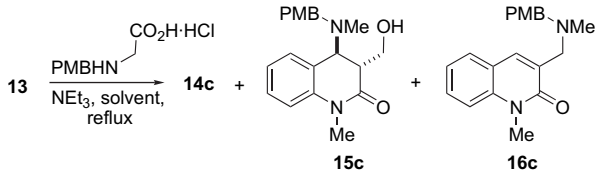


Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF; (b) acryloyl chloride, CH_2Cl_2, $NaHCO_3$; (c) IBX, DMSO; (d) $RNHCH_2CO_2H{\cdot}HCl$, Et_3N, toluene, reflux.

When **13** was subjected to reaction with *N*-benzylglycine·HCl in refluxing toluene, we were delighted to find that it had undergone the desired cycloaddition reaction to provide the cis-fused pyrroloquinolone **14a** in 66% yield. In addition to the cis-fused adduct ($J_{2a,5a}$=5.5 Hz), a small quantity of the *trans*-adduct ($J_{2a,5a}$=13.8 Hz) ca. 5% was isolated.[9c] In similar cycloaddition reactions with sarcosine and PMB-glycine·HCl, *cis*-pyrroloquinolones, **14b** and **14c** were obtained in 58 and 44% (the latter in DMF, vide infra) yields, respectively. The corresponding *trans*-isomers were also produced in these reactions, but in less than 5% yield based on the analysis of the ^1H NMR spectra of the crude reaction mixture. However, isolation of this minor adduct only proved possible with the *N*-PMB-protected derivative.

It was observed in initial experiments conducted with **13** and PMB-glycine·HCl that the expected cycloaddition product **14c** was isolated in relatively poor yield (<20%, Scheme 3). This outcome struck us as unusual as our prior experience suggested that this protected glycine derivative should behave similarly to the benzyl analog. It was determined that this was due to the formation of two byproducts **15c** and **16c**, while similar reactions with sarcosine or benzylglycine·HCl appear to afford only the cycloaddition products in reasonable yields. Analysis of the NMR data suggested that the structure of byproduct **15c** was a 1,2,3,4-tetrahydroquinolin-2-one derivative, with *trans*-substituents at C3 and C4 ($J_{3,4}$=12.4 Hz), and byproduct **16c** was established to be the 1,2-dihydroquinolin-2-one derivative. The initial cycloaddition reaction with PMB-glycine·HCl was performed in toluene at reflux for 10 h, giving **14c** (16%), **15c** (11%), and **16c** (20%) (entry 1, Table 1). It was subsequently determined that these experiments were conducted with an older sample of *N*-PMB-glycine·HCl, which presumably had picked up water from the atmosphere. Employing more

recently prepared material led to an improvement in the amount of **14c** produced, but byproducts **15c** and **16c** were still obtained in reasonable amounts (entry 2, Table 1). Interestingly, extending the reaction time to 20 h saw a reduction in the amount of **15c** formed, providing only **14c** and **16c**, whereas, adding water to the reaction increased the yield of byproduct **15c**. In contrast, when the reaction was carried out in DMF at reflux for 1 h, only byproduct **15c** was obtained, along with the expected cycloadduct **14c**.



Scheme 3.

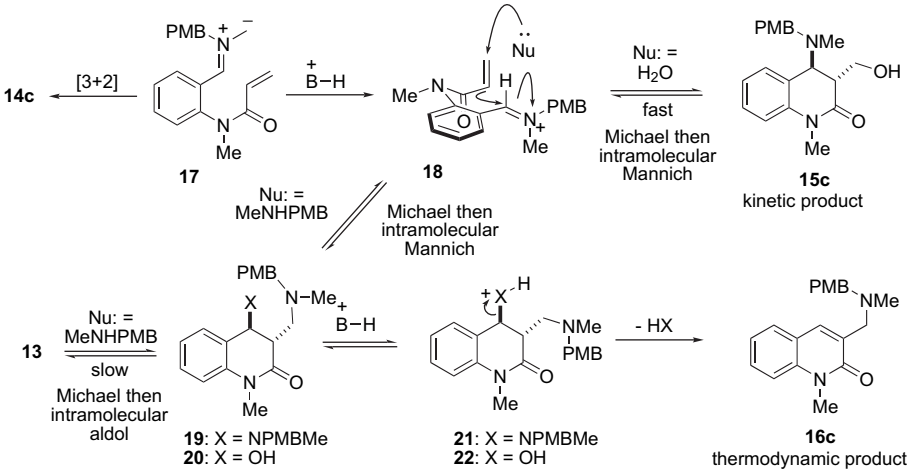
Table 1. Product distribution from reaction of PMB-glycine with aldehyde **13**

Entry	Solvent	Time (h)	**14c** (%)	**15c** (%)	**16c** (%)
1	Toluene	10	16	11	20
2	Toluene	8	38	20	18
3	Toluene	20	40	0	48
4	DMF	1	44	10	0

Our interpretation of the results obtained in these reactions involves two competing pathways, the 'normal' [3+2] pathway (**17**→**14c**) and a domino Michael–Mannich reaction sequence (**17**→**15c** and **16c**) and are illustrated in Scheme 4.[28] The studies on the decarboxylative Michael addition described previously (Scheme 9)[9c] have already shown that the azomethine ylide can be protonated under the reaction conditions to form an iminium ion **18**. In the presence of nucleophiles (H_2O or MeNHR), **18** undergoes an intermolecular Michael reaction and subsequent intramolecular Mannich reaction to furnish the cycloadduct 1,2,3,4-tetrahydroquinolin-2-one derivatives **15c** or **16c**, the latter after an elimination reaction. The cycloaddition appears to be stereoselective, providing the *trans*-substituted product, presumably as a result of the large iminium moiety occupying the sterically more favorable pseudoequatorial position in the putative transition state **18** (Scheme 4). It has also been demonstrated in the studies described above that the PMB methylamine is formed under these reaction conditions. Thus, when PMB methylamine functions as the nucleophile, **19** and/or **20** would be formed,[29] elimination then affords the more stable conjugated 1,2-dihydroquinolin-2-one **16c**.[14b,30]

The time variation in byproduct distribution suggests that **15c** is the kinetic product and **16c** is the thermodynamic product. It is assumed that the initial concentration of H_2O in the reaction mixture would be higher than NHMePMB as the formation of the latter nucleophile requires additional steps, and thus an induction period for the concentration to build up. However, once it accumulates it competes effectively with H_2O leading to the formation of **16c**, which is thermodynamically more stable due to its extended conjugation. This is consistent with the experimental observation that extending the reaction time leads to the exclusive formation of **16c**. The isolation of these byproducts in the case of reactions involving an *N*-PMB moiety and not with an *N*-Bn or *N*-Me warrants further discussion. Several factors may contribute to the competitive formation of the byproducts and the desired pyrroloquinolone. (a) The PMB moiety is electron donating; therefore, the azomethine ylide is rendered more electron rich and as a result is rapidly protonated (Scheme 4, **17**→**18**), and thus cannot participate in cycloaddition. (b) The thus produced iminium ion is more electron rich and thus is less susceptible to hydrolysis, therefore, it accumulates and will lead to an increase in intermolecular reactions (with water or amine). (c) *p*-Methoxybenzylmethylamine is more nucleophilic than methylbenzylamine and dimethylamine, leading to an increase in the rate of Michael addition processes.[31]

In order to provide support for the proposed mechanism, some additional experiments were performed. For example, aldehyde **13** was heated at reflux with NHMeBn in the presence of Et_3N under various conditions, the results of which are listed in Table 2 (Scheme 5). As can be seen, in refluxing toluene, both analogs **15a** and **16a** were obtained in 38 and 13%, respectively. Adding water to the reaction mixture led to the formation of **15a** in an excellent 85% yield plus a small amount (12%) of **16a**. In refluxing DMF and

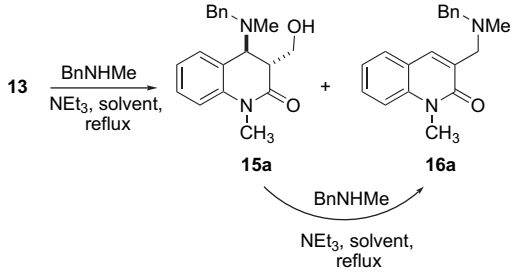


Scheme 4.

Table 2. Yields and conditions for the Michael–Mannich reaction of **13**

Entry	Solvent	Time (h)	**15a** (%)	**16a** (%)
1	Toluene	3	38	13
2	Toluene, H_2O (5 equiv)	2	85	12
3	DMF	1.5	70	28
4	DMF	2	60	38
5	DMF	8	0	90
6	DMF, H_2O	1.5	90	0

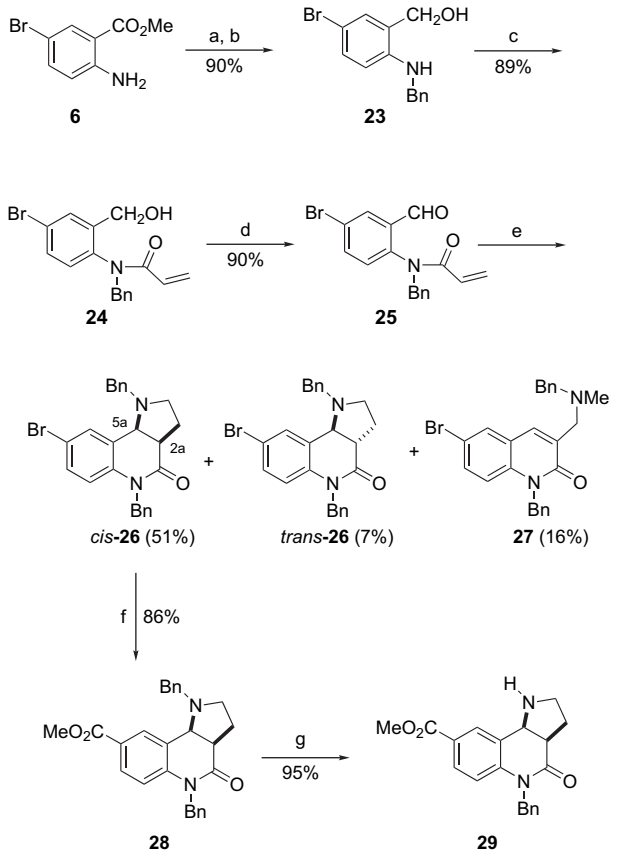
extending the reaction time led to the formation of more of the thermodynamic product **16a** and less of the kinetic product **15a**. Heating at reflux in DMF for 8 h led to the exclusive formation of **16a** in an excellent 90% yield. Not surprisingly, adding water to the reaction and heating at reflux for a short time (1.5 h) gave the **15a** exclusively. These results provide compelling evidence that compound **15a** is the kinetic product and **16a** is formed as the thermodynamic product. This was further supported by control experiments in which **15a** was heated at reflux with only Et_3N, no reaction was observed but when NHMeBn was added, **15a** converted to **16a** quantitatively after refluxing for 18 h. Thus by controlling the reaction conditions, either cycloadduct (**15a** or **16a**) can be obtained in an excellent yield. The fact that MeNHBn participates in the tandem Mannich–Michael sequence strongly suggests that the corresponding azomethine ylide undergoes cycloaddition faster than protonation.



Scheme 5.

Although the *N*-methyl derivatives were useful for assessing the influence of *N*-substituents in the azomethine ylide cycloaddition reaction, as far as the total synthesis was concerned, a more appropriate substrate had to be evaluated which contained, inter alia, a readily removable N1-protecting group and a halo moiety at C7 for introduction of the carboxyl group. Thus, the *N*-benzyl acrylamide derivative **25** was identified as being appropriate and was constructed through a largely analogous sequence of reactions to those previously employed for the synthesis of **13**. Thus, benzoylation of anthranilate derivative **6**[32] and reduction with $LiAlH_4$ gave the *N*-benzyl alcohol **23** (Scheme 6). Subsequent acroylation and IBX-oxidation afforded the cyclization substrate **25**.

Gratifyingly, when **25** was subjected to the cycloaddition reaction using *N*-benzylglycine in toluene at reflux, the desired pyrroloquinolone, *cis*-**26** was obtained in 51% yield (Scheme 6). The H_{5a} benzylic proton appeared as a doublet in the ^1H NMR spectrum at δ=3.40 ppm, with an associated coupling constant of 5.0 Hz, which suggested that the ring fusion was cis (the magnitude of the *J*-value is consistent with our previous results).[9] This assignment was subsequently confirmed through an X-ray structure determination



Scheme 6. Reagents and conditions: (a) BzCl, $NaHCO_3$, CH_2Cl_2, 0 °C→rt; (b) $LiAlH_4$, THF, −9 °C→ rt; (c) acryloyl chloride, $NaHCO_3$, CH_2Cl_2; (d) IBX, DMSO; (e) $BnNHCH_2CO_2H\cdot HCl$, PhMe, Et_3N, reflux; (f) $Pd(OAc)_2$, PPh_3, CO (60 psi), MeOH, *i*-Pr_2NEt, DMF, 100 °C; (g) 20% $Pd(OH)_2/C$, HCl, H_2, MeOH.

on this adduct (Fig. 2), which unequivocally demonstrated the cis fusion of the pyrrole/quinolone ring system. In addition to the major *cis*-adduct, a small quantity (7%) of the diastereoisomer, *trans*-**26** ($J_{2a,5a}$=13.8 Hz) was isolated.[9] This stereochemical assignment was confirmed independently

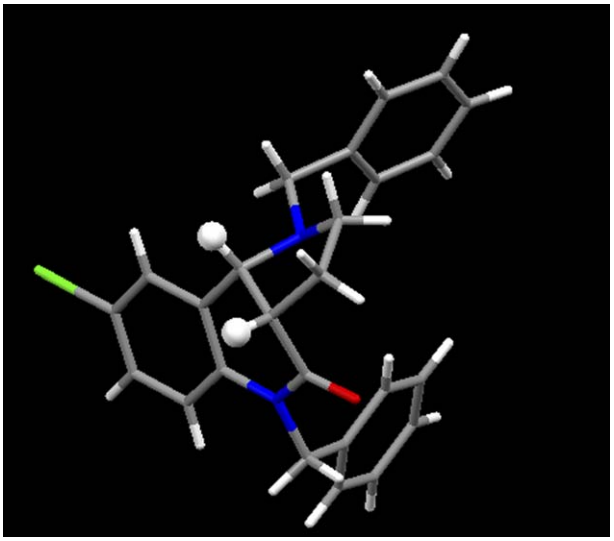


Figure 2. X-ray structure of *cis*-**26** (bridge head hydrogens picked out for emphasis).

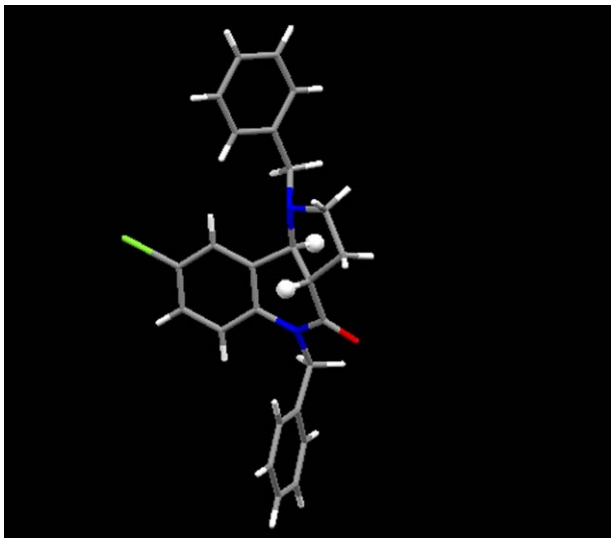


Figure 3. X-ray structure of *trans*-**26** (bridge head hydrogens picked out for emphasis).

through X-ray crystallography (Fig. 3). The formation of the *cis*/*trans*-isomers appears to be under kinetic control, since subjection of either isomer to the reaction conditions did not result in their interconversion. In addition to *cis*-**26** and *trans*-**26**, 16% of a polar byproduct was also isolated. The structure of compound was assigned as **27** and this is based on the NMR data, which is similar to **16a**, and presumably arises through a similar pathway to the formation of **16b** in the course of the cycloaddition reactions with PMB-protected glycine. Interestingly, however, the *trans*-disubstituted analog of **15a** was not observed in these reactions.

With *cis*-**26** in hand, methods for the introduction of the C7-carboxyl group were evaluated. In our earlier studies, Pd-catalyzed carbonylations were employed, and thus we gravitated toward these protocols.[9] However, unlike the carbonylation reaction (conditions=$Pd(OAc)_2$, PPh_3, CO, NaOAc) employed previously in the pyrroloquinoline series,[9a,b] it was found that the yield of the ester was substantially lower ca. 62% versus >90%. This was due to the formation of **30** (32%, Fig. 4) via a base-induced net retro Michael reaction. It was found that the ratio of the desired product and byproduct was dependent on the concentration of the base (NaOAc). Decreasing the amount of the NaOAc (0.8 equiv) led to the increased formation of **28** in 76%, however, further reduction in the amount of base (0.6 equiv) employed led to a reduction in the yield of **28** (44%). Other bases were screened and it was determined that Hunig's base (diisopropylethylamine) provided satisfactory results affording an excellent 86% yield of **28**, and a small quantity of **30** (12%). Preliminary scouting experiments were performed in an attempt to remove both of the benzyl protecting groups, interestingly with Pearlman's catalyst, the *N*5-benzyl group was removed chemoselectively to provide a polar product, **29**, in 95% (Scheme 6). At this point, no further attempts were made to remove the quinolinoyl benzyl group, or to find conditions to remove both simultaneously, rather we moved onto developing approaches for the incorporation of the C2-substitutent.

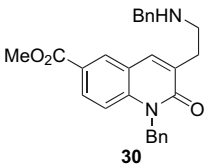


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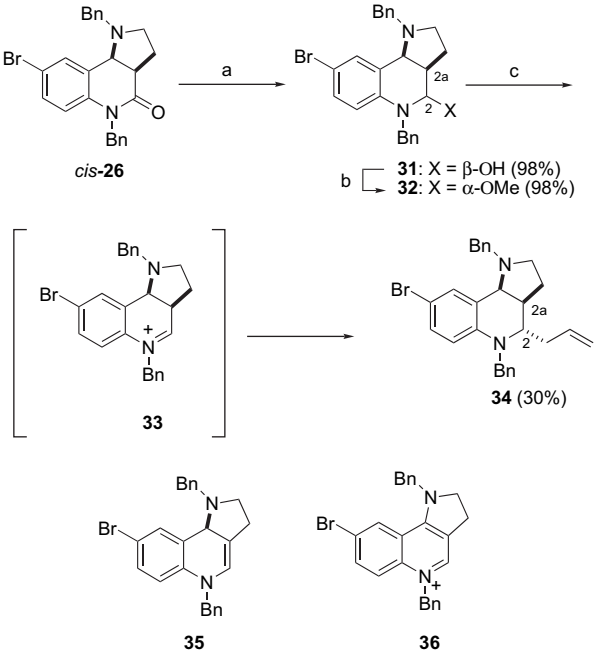
Figure 4. Byproduct from the Pd-catalyzed carbonylation.

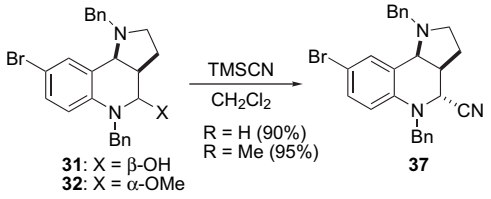
As described above, it was our intent to incorporate the C2-substituent via the formation of the iminium ion, and subsequently trap it through reaction with a nucleophilic C3-synthon. Although the formation of *N*-acyliminium (and other electron withdrawing groups on nitrogen) ions is well precedented,[33] the generation and trapping of iminium ions from simple *N*-alkyl lactams, are much less common. Overman et al. have demonstrated that reduction of an *N*-benzyl lactam to the α-hydroxybenzylamine using DIBAL as the reducing agent, followed by acid catalyzed elimination, will provide the corresponding *N*-benzyl iminium ion salt,[34] which exhibits very good diastereoselectivity in the nucleophilic addition reaction of Grignard reagents. Attempts to employ similar procedures with *cis*-**26**, involving the preparation of iminium salt and subsequent nucleophilic addition of allylmagnesium bromide were unsuccessful. Given this failure, we decided to investigate the preparation and utility of the corresponding α-methoxyamine as an iminium ion precursor. Accordingly, the *N*-benzyl aminol **31** was prepared by reduction of *cis*-**26** using DIBAL at −78 °C providing a 1:0.15 mixture of two diastereomers (for the major isomer, $J_{2,2a}$=3.2 Hz) (Scheme 7).[35] Without further purification, the mixture was converted to the corresponding α-methoxyamine **32** in 98% yield as a single diastereomer ($J_{2,2a}$=1.8 Hz) by simply refluxing in $CHCl_3$/MeOH. Compound **32** was then treated with allyltrimethylsilane in the presence of a Lewis acid, $TiCl_4$. The putative iminium ion intermediate **33**, generated in situ underwent nucleophilic addition at C2, presumably from the



Scheme 7. Reagents and conditions: (a) DIBAL-H, THF, −78 °C; (b) $CHCl_3$, MeOH, reflux; (c) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, −78 °C.

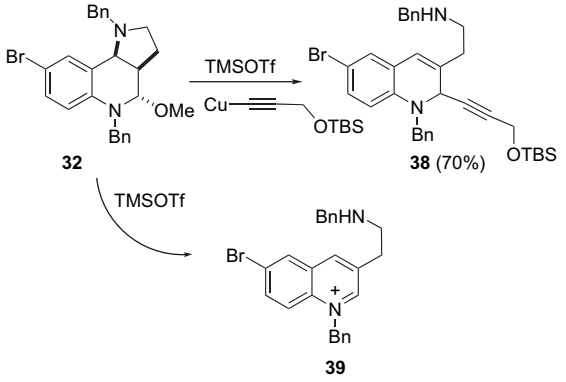
less hindered face, i.e., the opposite side to the cis-fused pyrrolidine ring, leading to the formation of major diastereoisomer **34** in 30% yield (dr=7:1 crude reaction mixture, in the major isomer, relative stereochemistry was assigned through an NOESY experiment). The low yield of the desired product was due to the formation of the β-elimination product **35** (ca. 50%), which was relatively unstable and further converted to the fully conjugated product **36**. Other Lewis acids were evaluated in this reaction, but with generally disappointing results. For example $Ti(OPr\text{-}i)_4$ was unreactive, whereas $MeAlCl_2$ gave the β-elimination product exclusively, $BF_3 \cdot Et_2O$, on the other hand, led to complete decomposition of the substrate. We attempted to elaborate **34** via hydroboration and an oxidative work-up, a product was isolated from this treatment that displayed spectroscopic properties consistent with the desired primary alcohol. However, the efficiency was very low ~30%, and the isolated material was not very pure, therefore, we sought an alternative and more efficient means to incorporate the C2-side chain.

Although the desired allylation product was not obtained from the majority of these reactions, the formation of enamine **35** was consistent with the formation of the desired reactive intermediate, iminium ion **33**. Presumably allyltrimethylsilane is insufficiently nucleophilic to trap the incipient iminium ion, which then results in alternative fates. Bearing this in mind, we wished to establish an idea of the general reactivity patterns of **33** and whether nucleophiles could be identified that would react faster than competing elimination, and so TMSCN was evaluated in this capacity. We were delighted to find that when the α-methoxyaminol **32** was treated with 4 equiv of TMSCN at room temperature, the desired cyano-substituted adduct **37** was obtained in an excellent 95% yield within couple of hours (Scheme 8). The reaction provided a single stereoisomer based on analysis of the NMR spectrum of the crude reaction mixture. It was found that reaction proceeds with essentially the same facility with the aminol **31** under similar reaction conditions, providing the same product in 90% (Scheme 8). In both cases, the stereochemistry of the adduct appears to be *exo* (based on an NOESY experiment), i.e., that required for an approach to the natural product.[36]



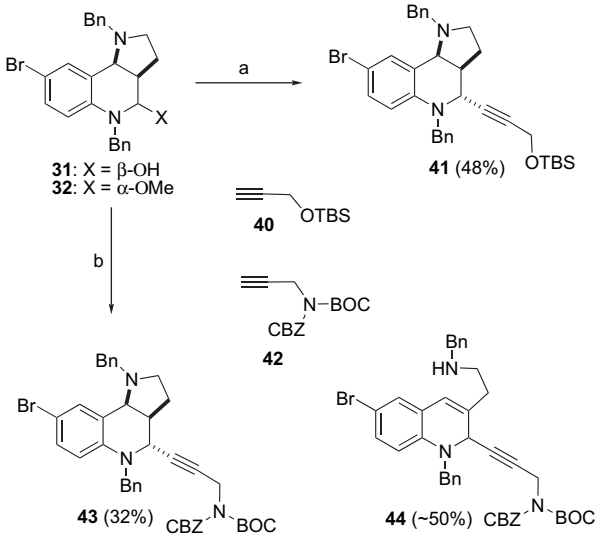
Scheme 8.

Encouraged by the fact that this silicon-based Lewis acid successfully mediated the formation of the iminium ion, which was then captured by CN^-, the use of TMSOTf in combination with a three-carbon copper acetylide (prepared from **40** and $CuCl/Et_3N$) as nucleophile was investigated.[37] As can be seen in Scheme 9, the addition took place smoothly, but was complicated by a fragmentation of the pyrrolidine ring to provide **38** in an unoptimized 70% yield (Scheme 9). Apparently the combination of relatively low electrophilicity of the iminium ion coupled with the aromatization driving force (**32**→**39**, Scheme 9) thwarted addition prior to fragmentation.[38] Indeed simply treating **32** with TMSOTf led to the efficient formation of the quinolinium ion (**39**, Scheme 9), a similar type of fragmentation has been observed previously in related systems.[8c,13a] Significant effort was expended in order to identify conditions that permitted the introduction of the side chain via acetylide chemistry using numerous modes of additions, a variety of metal acetylides (Cu, Zn, Mg) and Lewis acids, all without success. The use of **37** in the presence of $AgBF_4$, as an alternative iminium ion precursor, was evaluated with various metal acetylides, but met with no success.[39]



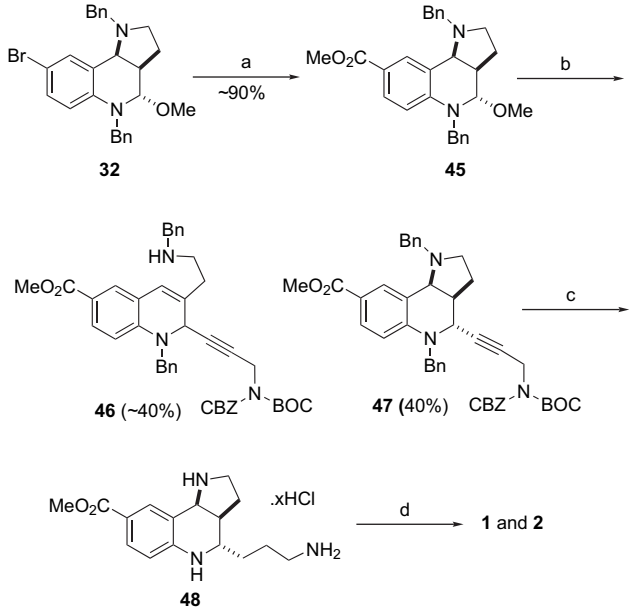
Scheme 9.

Several options were open to us at this point, none of which were particularly attractive until we became aware of Li's work, describing the in situ preparation of a copper acetylide (terminal alkyne/CuBr) under aqueous conditions with sonication in the absence of a Lewis acid (or other externally added promoter).[40] Presumably the heterogeneous conditions keep the solution concentrations of all of the reagents low thus minimizing side reactions, and the acid that is produced on reaction of the acetylene with CuBr is sufficient to ionize the α-methoxyamine **32**. Gratifyingly, when Li's protocol was applied to **32** and the silyl-protected propargyl alcohol derivative **40**, the desired adduct **41** was obtained in 48% yield, along with 40% of the fragmentation product **38** (cf. Scheme 9), it was also found that the aminol **31** would react analogously (Scheme 10).



Scheme 10. Reagents and conditions: (a) CuBr, H_2O, **40**, ultrasound; (b) CuBr, **42**, H_2O, ultrasound.

Encouraged by this result, it was decided to evaluate a propargyl amine derivative, thereby incorporating all of the remaining carbon and the nitrogen atoms in one step. When the doubly protected amine derivative **42**[41] was employed under the Li's conditions with **31**, it was found that addition took place, providing the required adduct **43** in 32% yield along with the corresponding fragmentation product **44** (~50%). We were unable to isolate and fully characterize the fragmentation product **44** as it co-eluted with unreacted **42** during column chromatography. Presumably, the two carbamate protecting groups attenuate the nucleophilicity of the acetylide and thus the fragmentation pathway becomes more dominant, thus lowering the yield of the desired adduct. Rather than spending time trying to optimize this reaction, however, it was decided to introduce the carboxymethyl group in the aryl ring and then evaluate this as a substrate. The rationale behind this approach rests on the electron withdrawing effect of the methyl ester, which should increase the electrophilicity of the iminium ion (in effect a doubly vinylogous carbamate), and additionally it should reduce the propensity of the system to fragment since it would destabilize the developing positive charge at the benzylic position. It was hoped that this modification would lead to an increase in the proportion of the simple addition product with respect to the fragmentation–addition product. Incorporation of the methyl ester was readily achieved by bromine/lithium exchange with **32**, followed by quenching of the organolithium with dimethyl carbonate, which gave the desired product (**32**→**45**, Scheme 11). Gratifyingly, when this material was treated with **42** under Li's conditions, the addition product **47** was obtained in 40%, along with the fragmentation product in a comparable amount (~40%, purification was again problematic due to co-elution of the acetylene) estimated from the integration data obtained from the ^{1}H NMR spectrum of the crude product. Reductive debenzylation, reduction of the alkyne, and acid hydrolysis of the BOC group were achieved simultaneously by treatment of **47** with $Pd(OH)_2$ and H_2 in the presence of HCl, providing the tricyclic triamine **48** in 95% (ca. 90% purity) as the hydrochloride salt, which we and others have converted into martinellic acid and martinelline.[10c,17a,b,42]



Scheme 11. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C then $CO(OMe)_2$, −78→0 °C; (b) CuBr, **42**, H_2O, ultrasound; (c) 20% $Pd(OH)_2$/C, MeOH, H_2; (d) lit.[7b,10c,17a]

In conclusion, an efficient approach for the synthesis and elaboration of the pyrrolo[3,2-*c*]quinolone, the tricyclic core of the *Martinella* alkaloids, have been developed via a stereoselective intramolecular [3+2] azomethine ylide/alkene cycloaddition approach. Conformational effects play an important role in this and related intramolecular cycloaddition processes investigated in this study. The presence of an *N*-alkyl substituent is critical to the success of this and related cycloaddition processes. In addition to the desired pyrroloquinolones, various 1,2,3,4-tetrahydroquinolin-2-one and 1,2-dihydroquinolin-2-one derivatives have also been synthesized via an interesting domino Michael–Mannich reaction of *N*-alkylated substrates, whereas the corresponding N–H substrates undergo only the Michael portion of the sequence. An advanced precursor **47** for the total synthesis of the *Martinella* alkaloids was obtained through an in situ acid mediated addition of a functionalized copper acetylide to an iminium ion, though the efficiency needs to be further improved. Global deprotection with concomitant alkyne reduction provided the tricyclic triamine **48** in good yield as the HCl salt.

2. Experimental

2.1. 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. A Pure-Solv 400 solvent purification system from Innovative Technology Inc. was also used to obtain anhydrous CH_3CN, THF, CH_2Cl_2, benzene, and toluene. NMR spectra were obtained on a JEOL Eclipse+ 500 MHz; ^{1}H NMR spectra were recorded in deuteriochloroform (unless otherwise indicated) at a spectrometer frequency of 500.16 MHz, residual protiochloroform was used as internal reference; ^{13}C NMR spectra were obtained in deuteriochloroform (unless otherwise indicated) at 125.79 MHz using $^{13}CDCl_3$ (δ=77.0 ppm) as internal reference. Infrared (IR) spectra were obtained on a Bruker Vector 22 FT-IR spectrometer, using KBr pressed pellets for solids or neat films on NaCl plate for liquids and oils, and were reported in cm^{-1}. Electron impact mass spectra (EIMS) were recorded in-house on a Bear Instruments, Kodiak 1200 spectrometer (at 70 eV) and electrospray ionization mass spectra (ESIMS) and LC/MS were recorded on an Agilent 1100 LC/MS system controlled by Chemstation version 8.3. (the ESI condition is 4.5 kV spray voltage with 10 μL min^{-1} infusion) at HT Laboratories Inc. High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) time-of-flight reflectron experiments performed on an Agilent ESI-TOF mass spectrometer at the Center for Mass Spectrometry at the Scripps Research Institute, La Jolla, California. Elemental analyses were performed in-house on a Perkin–Elmer 2400 CHN Elemental Analyzer or at Quantitative Technologies Inc. Melting points were recorded on a Thomas Hoover Scientific capillary tube

melting point apparatus and were uncorrected. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminum backed precoated plates (layer thickness=200 μm). A Fisher Scientific sonicator (Model FS20H, 3 qt., 120 V, 50/60 Hz, 1 A, 143 W, with heater) was used in this work.

2.1.1. *N*-(2-Hydroxymethylphenyl)-*N*-methylacrylamide (12). Acryloyl chloride (0.33 mL, 4.04 mmol) was added dropwise to a cooled suspension of the amino alcohol **11** (553 mg, 4.04 mmol) and sodium bicarbonate (400 mg, 4.76 mmol) in anhydrous CH_2Cl_2 (5 mL) and stirred for 1 h. The reaction mixture was then diluted with CH_2Cl_2 (5 mL) and washed with water (2×10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. The crude oil was re-dissolved in CH_2Cl_2 and hexane and concentrated again. The process was repeated until a solid product was obtained. Trituration of the solid with Et_2O several times provided pure **12** (686 mg, 89%) as a colorless solid. The combined Et_2O washings were concentrated and purification of the resulting oil by chromatography (hexane/ethyl acetate, 4:1) gave additional *N*-acylated product (46 mg, 6%). Mp: 64–66 °C. ^{1}H NMR: δ=7.60 (d, J=7.3 Hz, 1H), 7.41 (dd, J=7.6, 7.3 Hz, 1H), 7.36 (dd, J=7.8, 7.6 Hz, 1H), 7.13 (d, J=7.8 Hz, 1H), 6.34 (dd, J=16.8, 1.8 Hz, 1H), 5.90 (dd, J=16.8, 10.3 Hz, 1H), 5.48 (dd, J=10.3, 1.8 Hz, 1H), 4.60 (m, 2H), 3.28 (s, 3H), 2.30 (br s, 1H); ^{13}C NMR: δ=166.1, 140.8, 138.5, 129.1, 129.03, 128.97, 128.3, 128.2, 127.9, 60.8, 37.1; IR (KBr, cm^{-1}): 3401, 2873, 1650, 1613; EIMS (*m*/*z*): 191.1 (M^+, 18), 173.3 (19), 135.2 (40), 159.2 (100), 117.1 (84), 89.9 (34), 53.7 (32). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.36; H, 7.09; N, 7.32.

2.1.2. *N*-(2-Formylphenyl)-*N*-methylacrylamide (13). Alcohol **12** (150 mg, 0.78 mmol, 1 equiv) was dissolved in DMSO (3 mL) and then IBX (330 mg, 1.18 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with H_2O. The resulting precipitate was filtered and rinsed with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine (2×), dried (Na_2SO_4), after concentration the crude product was passed through a plug of SiO_2 (CH_2Cl_2) and concentrated to afford pure **13** as a thick oil (119 mg, 80%). ^{1}H NMR: δ=10.07 (s, 1H), 7.99 (dd, J=7.8, 1.4 Hz, 1H), 7.70 (ddd, J=7.8, 7.3, 1.4 Hz, 1H), 7.54 (dd, J=7.8, 7.3 Hz, 1H), 7.29 (d, J=7.8 Hz, 1H), 6.40 (dd, J=16.7, 1.8 Hz, 1H), 5.87 (dd, J=16.7, 10.5 Hz, 1H), 5.54 (dd, J=10.5, 1.8 Hz, 1H), 3.39 (s, 3H); ^{13}C NMR: δ=189.2, 166.0, 145.4, 135.7, 132.9, 130.0, 129.4, 129.1, 129.0, 127.7, 38.4; IR (neat, cm^{-1}): 3055, 2918, 2850, 1695, 1656, 1596, 1265; EIMS (*m*/*z*): 189.3 (M^+, 45), 159.2 (100), 133.0 (88), 105.0 (70), 75.9 (41), 53.7 (56). HRMS (*m*/*z*): calcd for MH^+ $C_{11}H_{12}NO_2$ 190.0863, found 190.0868.

2.2. General procedure for azomethine ylide cycloaddition reactions

2.2.1. (3a*R,9b*S**)-1-Benzyl-5-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one *cis*-(14a).** Compound **13** (60 mg, 0.32 mmol) and *N*-benzylglycine·HCl (116 mg, 0.57 mmol, 1.8 equiv) were mixed in anhydrous toluene (10 mL), then Et_3N (0.13 mL, 0.95 mmol, 3 equiv) was added. The resulting mixture was heated under reflux for 2 h, at which time TLC analysis indicated the completion of the reaction. The mixture was cooled to room temperature, diluted with EtOAc (10 mL), and washed with H_2O (2×15 mL) and brine (15 mL), dried (Na_2SO_4), and then concentrated. The crude product was purified by chromatography (hexane/ethyl acetate, 2:1) to give the title compound as a colorless solid (61 mg, 66%). Mp: 80–82 °C. ^{1}H NMR: δ=7.35 (m, 1H), 7.12–7.26 (m, 6H), 7.03–7.06 (m, 2H), 4.02 (d, J=13.1 Hz, 1H), 3.44 (s, 3H), 3.38 (d, J=5.5 Hz, 1H), 3.14 (d, J=13.1 Hz, 1H), 2.98 (m, 2H), 2.63 (m, 1H), 2.16 (m, 2H); ^{13}C NMR: δ=171.7, 140.3, 139.5, 130.9, 129.2, 128.3, 128.1, 126.8, 122.8, 122.2, 114.8, 64.9, 57.4, 51.3, 43.6, 29.9, 26.2; IR: 3025, 2914, 2788, 1665, 1602; EIMS (*m*/*z*): 292.4 (M^+, 4), 291.1 (M^+-1, 64), 200.0 (33), 185.0 (62), 158.9 (70). Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.43; H, 7.12; N, 9.41.

2.2.2. (3a*S,9b*S**)-1-Benzyl-5-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one *trans*-(14a).** Eluted out right after the *cis*-adduct as brown oil (5 mg, 5%). ^{1}H NMR: δ=7.49 (d, J=7.3 Hz, 2H), 7.46 (d, J=7.3 Hz, 1H), 7.37 (dd, J=7.8, 7.3 Hz, 2H), 7.28–7.32 (m, 2H), 7.11 (dd, J=7.3, 7.3 Hz, 1H), 7.07 (d, J=7.8 Hz, 2H), 4.48 (d, J=14.2 Hz, 1H), 3.65 (d, J=13.8 Hz, 1H), 3.49 (d, J=14.2 Hz, 1H), 3.39 (s, 3H), 3.36 (ddd, J=10.5, 8.3, 8.3 Hz, 1H), 2.76 (ddd, J=14.0, 10.8, 8.3 Hz, 1H), 2.67 (ddd, J=10.5, 10.1, 3.8 Hz, 1H), 2.01–2.12 (m, 2H); ^{13}C NMR: δ=171.8, 140.6, 139.2, 131.3, 128.6, 128.4, 127.4, 127.2, 123.3, 122.3, 115.4, 64.4, 61.2, 55.2, 47.4, 29.8, 26.7; IR (neat, cm^{-1}): 3062, 3030, 2926, 1683, 1648, 1604; EIMS (*m*/*z*): 290.7 (M^+-1, 74), 200.0 (76), 104.1 (30), 89.7 (100).

2.2.3. (3a*R,9b*S**)-1,5-Dimethyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one *cis*-(14b).** Compound **13** (210 mg, 1.11 mmol) and sarcosine (198 mg, 2.22 mmol, 2 equiv) were mixed in toluene (37 mL), then Et_3N (0.46 mL, 3.33 mmol, 3 equiv) was added. The mixture was then heated under reflux for 5 h. After work-up (see synthesis of **14a**), chromatography (ethyl acetate/MeOH, 4:0.2) gave the title compound as a colorless solid (140 mg, 58%). Mp: 116–117 °C. ^{1}H NMR: δ=7.35 (ddd, J=8.3, 7.3, 1.6 Hz, 1H), 7.17 (dd, J=7.3, 1.6 Hz, 1H), 7.06 (ddd, J=7.3, 7.3, 0.9 Hz, 1H), 7.02 (d, J=8.3 Hz), 3.38 (s, 3H), 3.16 (m, 1H), 3.05 (d, J=6.0 Hz, 1H), 2.98 (m, 1H), 2.66 (m, 1H), 1.98–2.27 (m, 2H), 2.24 (s, 3H); ^{13}C NMR: δ=171.6, 140.1, 130.6, 129.2, 122.2, 122.0, 114.8, 66.3, 54.5, 43.6, 40.0, 30.0, 26.5; IR (KBr, cm^{-1}): 2945, 2803, 1664, 1602; EIMS (*m*/*z*): 216.3 (M^+, 100), 199.2 (22), 186.1 (35), 173.0 (10). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 71.93; H, 7.50; N, 12.77.

2.3. Synthesis of 14c, 15c, and 16c

Compound **13** (60 mg, 0.32 mmol) and *N*-*p*-methoxybenzylglycine hydrochloride (116 mg, 0.57 mmol, 1.8 equiv) were mixed in anhydrous toluene (11 mL), then Et_3N (0.13 mL, 0.95 mmol, 3 equiv) was added. The mixture was heated under reflux for 10 h, at which time TLC analysis indicated the completion of the reaction. The mixture was cooled to room temperature, diluted with EtOAc (10 mL), and washed with

H_2O (2×15 mL) and brine (15 mL), dried (Na_2SO_4), and then concentrated. The crude oil was purified by chromatography (hexane/ethyl acetate, 2:1) to give *cis*-**14c** (16 mg, 16%), *trans*-**14c** (3 mg, 3%), byproduct **15c** (12 mg, 11%), and byproduct **16c** (20 mg, 20%) in the order of elution from the column. Following the above procedure, when anhydrous DMF (11 mL) was used instead of toluene and the reaction was refluxed for 1 h instead of 10 h, after chromatography, *cis*-**14c** (45 mg, 44%), *trans*-**14c** (5 mg, 5%), and byproduct **15c** (11 mg, 10%) were obtained.

2.3.1. (3a*R,9b*S**)-1-(4-Methoxybenzyl)-5-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one *cis*-(14c).** A colorless solid. Mp: 94–95 °C. ^{1}H NMR: δ=7.35 (ddd, *J*=7.8, 7.8, 1.4 Hz, 1H), 7.23 (dd, *J*=7.3, 1.4 Hz, 1H), 7.03–7.06 (m, 4H), 6.74 (d, *J*=8.7 Hz, 2H), 3.95 (d, *J*=12.8 Hz, 1H), 3.75 (s, 3H), 3.43 (s, 3H), 3.36 (d, *J*=5.5 Hz, 1H), 3.07 (d, *J*=12.8 Hz, 1H), 2.92–2.99 (m, 2H), 2.59–2.62 (m, 1H), 2.11–2.19 (m, 2H); ^{13}C NMR: δ=171.7, 158.5, 140.3, 131.5, 130.9, 129.4, 129.1, 122.8, 122.2, 114.8, 113.5, 64.8, 56.8, 55.3, 51.2, 43.6, 29.9, 26.2; IR (KBr, cm^{-1}): 3039, 3006, 2924, 1662, 1604; EIMS (*m*/*z*): 322.1 (M$^+$, 35), 279.1 (28), 201.2 (21), 167.1 (30), 149.1 (98), 136.3 (40), 121.2 (100). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.45; H, 6.84; N, 8.96.

2.3.2. (3a*S,9b*S**)-1-(4-Methoxybenzyl)-5-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one *trans*-(14c).** Colorless oil. ^{1}H NMR: δ=7.46 (d, *J*=7.3 Hz, 1H), 7.39 (d, *J*=8.7 Hz, 2H), 7.30 (dd, *J*=7.3, 7.3 Hz, 1H), 7.11 (dd, *J*=7.8, 7.3 Hz, 1H), 7.06 (d, *J*=7.8 Hz, 1H), 6.90 (d, *J*=8.7 Hz, 2H), 4.40 (d, *J*=14.2 Hz, 1H), 3.82 (s, 3H), 3.62 (d, *J*=13.8 Hz, 1H), 3.42 (d, *J*=14.2 Hz, 1H), 3.39 (s, 3H), 3.31 (ddd, *J*=10.5, 8.3, 8.3 Hz, 1H), 2.74 (ddd, *J*=13.8, 10.5, 8.3 Hz, 1H), 2.67 (ddd, *J*=10.5, 10.1, 4.1 Hz, 1H), 2.00–2.12 (m, 2H); ^{13}C NMR: δ=171.8, 158.9, 140.6, 131.3, 131.1, 129.6, 127.4, 123.3, 122.4, 115.4, 113.9, 64.3, 60.5, 55.4, 55.0, 47.4, 29.9, 22.6; IR (neat, cm^{-1}): 3032, 2962, 2923, 2853, 2839, 1683, 1605. EIMS (*m*/*z*): 322.0 (M$^+$, 31), 201.1 (42), 179.1 (59), 121.1 (100).

2.3.3. (3*R,4*R**)-3-Hydroxymethyl-4-[(4-methoxybenzyl)methylamino]-1-methyl-3,4-dihydro-1*H*-quinolin-2-one (15c).** Brown oil. ^{1}H NMR: δ=7.61 (d, *J*=7.8 Hz, 1H), 7.29 (dd, *J*=7.8, 7.3 Hz, 1H), 7.24 (d, *J*=8.7 Hz, 2H), 7.16 (dd, *J*=7.3, 7.3 Hz, 1H), 6.96 (d, *J*=7.3 Hz, 1H), 6.87 (d, *J*=8.7 Hz, 2H), 4.82 (d, *J*=12.4 Hz, 1H), 3.79 (s, 3H), 3.70 (d, *J*=12.8 Hz, 1H), 3.41 (d, *J*=12.8 Hz, 1H), 3.31 (s, 3H), 3.23 (dd, *J*=12.8, 3.7 Hz, 1H), 3.03 (dd, *J*=12.8, 11.9 Hz, 1H), 2.80 (ddd, *J*=12.4, 11.9, 3.7 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR: δ=169.1, 159.1, 137.7, 130.6, 129.9, 129.3, 128.0, 124.2, 123.7, 114.3, 114.0, 70.9, 62.4, 58.2, 55.3, 42.5, 42.0, 29.8; IR (neat, cm^{-1}): 2965, 2923, 2856, 1669, 1604; EIMS (*m*/*z*): 340.2 (M$^+$, 8), 219.2 (19), 201.2 (59), 172.2 (21), 150.2 (100), 121.1 (68), 84.0 (16).

2.3.4. 3-{[(4-Methoxybenzyl)methylamino]methyl}-1-methyl-1*H*-quinolin-2-one (16c). Pale yellow oil. ^{1}H NMR: δ=7.88 (s, 1H), 7.60 (d, *J*=7.8 Hz, 1H), 7.58 (dd, *J*=8.3, 7.3 Hz, 1H), 7.33 (d, *J*=8.3 Hz, 1H), 7.31 (d, *J*=8.7 Hz, 2H), 7.23 (dd, *J*=7.8, 7.3 Hz, 1H), 6.86 (d, *J*=8.7 Hz, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.59 (s, 2H), 3.58 (s, 2H), 2.28 (s, 3H); ^{13}C NMR: δ=162.3, 158.7, 139.1, 135.8, 131.3, 130.8, 130.1, 129.8, 128.6, 122.1, 120.8, 114.0, 113.7, 61.9, 55.8, 55.3, 42.7, 29.7; IR (neat, cm^{-1}): 3031, 2934, 2834, 1649, 1597; EIMS (*m*/*z*): 323.8 (M$^+$+1, 9), 201.4 (95), 174.7 (30), 149.7 (100), 130.1 (20), 79.8 (12). HRMS (*m*/*z*): calcd for MH$^+$ $C_{20}H_{23}N_2O_2$ 323.1754, found 323.1756.

2.4. Control experiments

Compound **13** (150 mg, 0.79 mmol) and HNMeBn (0.20 mL, 1.55 mmol, 2 equiv) were mixed in anhydrous DMF (27 mL), then Et_3N (0.33 mL, 2.37 mmol, 3 equiv) was added followed by addition of H_2O (71 mg, 3.95 mmol). The mixture was heated at 150 °C for 1.5 h. The solvent was completely removed by vacuum distillation and the residue was dissolved in EtOAc (30 mL) and washed with H_2O (2×15 mL) and brine (15 mL), dried (Na_2SO_4), and then concentrated. The crude product was purified by chromatography (hexane/ethyl acetate, 1:1) to give **15a** (220 mg, 90%). When the same reaction was conducted in the absence of water and heated at 150 °C for 8 h, **16a** (206 mg, 90%) was obtained after chromatography (hexane/ethyl acetate, 1:1).

2.4.1. (3*R,4*R**)-4-(Benzylmethylamino)-3-hydroxymethyl-1-methyl-3,4-dihydro-1*H*-quinolin-2-one (15a).** A colorless solid. Mp: 94–95.5 °C. ^{1}H NMR: δ=7.86 (br s, 1H), 7.62 (d, *J*=7.3 Hz, 1H), 7.26–7.36 (m, 5H), 7.16 (dd, *J*=7.8, 7.3 Hz, 1H), 6.96 (d, *J*=7.8 Hz, 1H), 4.84 (d, *J*=12.1 Hz, 1H), 3.76 (d, *J*=12.8 Hz, 1H), 3.48 (d, *J*=12.8 Hz, 1H), 3.32 (s, 3H), 3.27 (dd, *J*=13.1, 3.4 Hz, 1H), 3.04 (d, *J*=13.1, 11.9 Hz, 1H), 2.81 (ddd, *J*=12.1, 11.9, 3.4 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR: δ=169.1, 137.7, 137.3, 129.9, 129.3, 128.7, 128.1, 127.7, 124.3, 123.7, 114.3, 70.9, 63.1, 58.5, 42.5, 29.9; IR (neat, cm^{-1}): 3062, 3029, 2951, 2854, 2801, 1669, 1605; EIMS (*m*/*z*): 310.9 (M$^+$, 22), 220.0 (95), 201.5 (13), 176.8 (100), 159.6 (15), 134.4 (28), 120.3 (9), 91.9 (12). Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.51; H, 6.96, N, 9.36.

2.4.2. 3-[(Benzylmethylamino)methyl]-1-methyl-1*H*-quinolin-2-one (16a). Brown oil. ^{1}H NMR: δ=7.93 (s, 1H), 7.60 (d, *J*=7.8 Hz, 1H), 7.55 (dd, *J*=8.3, 7.3 Hz, 1H), 7.39–7.43 (m, 2H), 7.30–7.38 (m, 3H), 7.23–7.26 (m, 2H), 3.74 (s, 3H), 3.68 (s, 2H), 3.63 (s, 2H), 2.31 (s, 3H); ^{13}C NMR: δ=162.3, 139.1, 135.9, 130.5, 129.9, 129.0, 128.6, 128.4, 127.1, 122.1, 120.8, 113.9, 62.5, 56.0, 42.7, 29.7; IR (neat, cm^{-1}): 3062, 3028, 2938, 2841, 2783, 1649, 1597; EIMS (*m*/*z*): 293.8 (M$^+$+1, 21), 202.0 (100), 187.9 (10), 173.1 (50), 120.7 (50). HRMS (*m*/*z*): calcd for MH$^+$ $C_{19}H_{21}N_2O$ 293.1648, found 293.1647.

2.4.3. (2-Benzylamino-5-bromophenyl)methanol (23). Benzoyl chloride (0.28 mL, 2.39 mmol, 1.1 equiv) was added dropwise to a cooled suspension of the methyl 5-amino-2-bromobenzoate (**6**) (500 mg, 2.17 mmol, 1 equiv) and sodium bicarbonate (365 mg, 4.35 mmol, 2 equiv) in CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 5 h then diluted with CH_2Cl_2 (10 mL) and washed with water (2×15 mL) and brine (15 mL), dried (Na_2SO_4), and

evaporated to dryness. Purification of the crude product by trituration with Et_2O gave benzamide[32] (706 mg, 97%) as a colorless solid. Mp: 130–132 °C. ^{1}H NMR: δ=11.97 (br s, 1H), 8.87 (d, J=9.2 Hz, 1H), 8.02 (d, J=2.8 Hz, 2H), 7.69 (dd, J=9.2, 2.8 Hz, 1H), 7.50–7.56 (m, 3H), 3.98 (s, 3H); ^{13}C NMR: δ=168.0, 165.8, 141.0, 137.6, 134.6, 133.6, 132.3, 129.0, 127.5, 122.2, 116.8, 115.1, 52.9.

A solution of the benzamide (650 mg, 1.95 mmol) in THF (5 mL) was added dropwise at −9 °C (ice/methanol) to a suspension of $LiAlH_4$ (406 mg, 10.7 mmol) in THF (12 mL). The reaction mixture was then allowed to warm up to room temperature and continued stirring overnight. Reaction was then quenched by H_2O (1 mL), NaOH (15%, 1 mL), and Rochelle's salt (20%, 5 mL). The resulting white slurry was filtered and then the filtrate was concentrated under vacuum. The filter cake was washed thoroughly by EtOAc (4×5 mL). The extract was combined with concentrated filtrate and washed with brine. After drying (Na_2SO_4), concentrating under vacuum, the residue was purified by flash chromatography (hexane/ethyl acetate, 4:1) to provide the title compound **23** (530 mg, 93%) as colorless oil. ^{1}H NMR: δ=7.32–7.36 (m, 4H), 7.25–7.29 (m, 1H), 7.23 (dd, J=8.7, 2.3 Hz, 1H), 7.19 (d, J=2.3 Hz, 1H), 6.50 (d, J=8.7 Hz, 1H), 5.20 (br s, 1H), 4.64 (s, 2H), 4.36 (s, 2H), 1.56 (br s, 1H); ^{13}C NMR: δ=146.4, 139.0, 132.1, 131.6, 128.8, 127.4, 127.3, 126.2, 112.7, 108.3, 64.3, 47.8; IR (neat, cm^{-1}): 3555, 3407, 3062, 3029, 2870, 1598; EIMS (*m*/*z*): 293.0 (M^++1, 49), 291.1 (M^+−1, 44), 213.2 (100), 194.2 (78).

2.4.4. *N*-Benzyl-*N*-(4-bromo-2-hydroxymethylphenyl)-acrylamide (24). Following the general procedure for N-acrylation described for compound **12**, amino alcohol **23** (1.03 g, 3.53 mmol) was used, and then purification of the crude oil by chromatography (hexane/ethyl acetate, 3:2) gave the *N*-acylated product **24** (1.09 g, 89%). Mp: 76–77 °C. ^{1}H NMR: δ=7.71 (d, J=2.3 Hz, 1H), 7.40 (dd, J=8.3, 2.3 Hz, 1H), 7.26–7.28 (m, 3H), 7.21–7.18 (m, 2H), 6.78 (d, J=8.3 Hz, 1H), 6.44 (dd, J=17.0, 1.8 Hz, 1H), 5.84 (dd, J=17.0, 10.1 Hz, 1H), 5.56 (dd, J=10.1, 1.8 Hz, 1H), 4.92 (d, J=14.2 Hz, 1H), 4.85 (d, J=14.2 Hz, 1H), 4.28 (dd, J=13.8, 6.4 Hz, 1H), 4.14 (dd, J=13.8, 5.5 Hz, 1H), 1.30 (dd, J=6.4, 5.5 Hz, 1H); ^{13}C NMR: δ=165.5, 141.4, 137.6, 136.6, 132.2, 131.9, 130.8, 129.6, 129.4, 128.7, 128.0, 127.7, 123.0, 60.2, 52.8; IR (KBr, cm^{-1}): 3321, 3094, 3055, 3023, 1642, 1608; EIMS (*m*/*z*): 347.0 (M^++2, 40), 345.8 (M^+, 28), 329.2 (100), 273.1 (34), 193.1 (21), 117.1 (11), 91.0 (92), 55.0 (37). Anal. Calcd for $C_{17}H_{16}BrNO_2$: C, 58.97; H, 4.66; N, 4.05. Found: C, 59.15; H, 4.90; N, 3.96.

2.4.5. *N*-Benzyl-*N*-(4-bromo-2-formylphenyl)acrylamide (25). Following the general procedure for the IBX-oxidation described for compound **13**, alcohol **24** (4.00 g, 11.5 mmol) provided aldehyde **25** (3.57 g, 90%). Mp: 112–113 °C. ^{1}H NMR: δ=9.45 (s, 1H), 8.00 (d, J=2.3 Hz, 1H), 7.73 (dd, J=8.4, 2.3 Hz, 1H), 7.26–7.28 (m, 3H), 7.14–7.16 (m, 2H), 7.00 (d, J=8.4 Hz, 1H), 6.45 (dd, J=16.5, 1.8 Hz, 1H), 5.80 (dd, J=16.5, 10.1 Hz, 1H), 5.60 (dd, J=10.1, 1.8 Hz, 1H), 5.10 (d, J=13.8 Hz, 1H), 4.87 (d, J=13.8 Hz, 1H); ^{13}C NMR: δ=187.4, 165.3, 141.3, 138.2, 135.4, 134.5, 132.2, 131.7, 130.4, 129.6, 128.9, 128.4, 127.6, 123.3, 54.0; IR (KBr, cm^{-1}): 3083, 2871, 1938, 1690, 1653, 1616, 1582; EIMS (*m*/*z*): 345.1 (M^++2, 11), 343.0 (M^+, 11), 290.1 (100), 288.1 (92), 209.2 (27), 179.9 (28). Anal. Calcd for $C_{17}H_{14}BrNO_2$: C, 59.32; H, 4.10; N, 4.07. Found: C, 59.60; H, 4.21; N, 3.95.

2.4.6. (3a*R,9b*S**)-8-Bromo-1,5-dibenzyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one *cis*-(26).** Benzaldehyde **25** (800 mg, 2.32 mmol) and *N*-benzylglycine·HCl (844 mg, 4.18 mmol) were dissolved in anhydrous toluene (80 mL), then Et_3N (0.97 mL, 6.97 mmol) was added to the mixture. The resulting mixture was stirred under reflux for 2 h. After this period the mixture was cooled to room temperature, then diluted with EtOAc (10 mL). The organic phase was washed with H_2O (2×10 mL) and brine (10 mL), dried (Na_2SO_4), and then concentrated by rotary evaporation. The crude oil, which solidified after coevaporation with CH_2Cl_2/hexane, was triturated with Et_2O several times to provide pure solid product *cis*-**26** (363 mg, 35%). The Et_2O washings were concentrated and purified by chromatography (hexane/ethyl acetate, 5:1) to give an additional batch of *cis*-**26** as a white solid (166 mg, 16%) Total yield: 51%. Mp: 139–140 °C. ^{1}H NMR: δ=7.32 (d, J=2.3 Hz, 1H), 7.16–7.30 (m, 11H), 6.80 (d, J=8.7 Hz, 1H), 5.59 (d, J=16.5 Hz, 1H), 4.98 (d, J=16.5 Hz, 1H), 4.01 (d, J=12.8 Hz, 1H), 3.40 (d, J=5.0 Hz, 1H), 3.19 (d, J=12.8 Hz, 1H), 3.04–3.12 (m, 2H), 2.72–2.78 (m, 1H), 2.16–2.28 (m, 2H); ^{13}C NMR: δ=171.4, 139.1, 138.2, 136.5, 133.5, 131.9, 128.8, 128.3, 128.2, 127.2, 127.0, 126.6, 125.2, 117.5, 114.9, 64.8, 57.6, 51.2, 45.4, 43.7, 26.0; IR (KBr, cm^{-1}): 2802, 1669; EIMS (*m*/*z*): 448.2 (M^++2, 24), 446.1 (M^+, 28), 356.9 (14), 354.9 (13), 314.0 (16), 201.2 (12), 150.2 (14), 133.2 (28), 91.1 (100), 65.0 (15), 35.9 (17). Anal. Calcd for $C_{25}H_{23}BrN_2O$: C, 67.12; H, 5.18; N, 6.26. Found: C, 67.44; H, 5.23; N, 6.10.

2.4.7. (3a*S,9b*S**)-8-Bromo-1,5-dibenzyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one *trans*-(26).** The *trans*-diastereoisomer eluted out immediately after the *cis*-cycloadduct as a colorless solid (73 mg, 7%). Mp: 185–186 °C. ^{1}H NMR: δ=7.52 (d, J=2.3 Hz, 1H), 7.48–7.50 (m, 2H), 7.1–7.38 (m, 9H), 7.30–7.33 (m, 3H), 7.23–7.26 (m, 2H), 7.19–7.20 (m, 2H), 6.83 (d, J=8.7 Hz, 1H), 5.24 (d, J=16.3 Hz, 1H), 5.11 (d, J=16.3 Hz, 1H), 4.41 (d, J=14.0 Hz, 1H), 3.70 (d, J=13.8 Hz, 1H), 3.53 (d, J=14.0 Hz, 1H), 3.37 (ddd, J=10.5, 8.3, 8.3 Hz, 1H), 2.90 (ddd, J=14.0, 10.8, 8.0 Hz, 1H), 2.72 (ddd, J=10.5, 10.5, 3.4 Hz, 1H), 2.05–2.20 (m, 2H); ^{13}C NMR: δ=171.5, 138.8, 138.7, 136.7, 133.7, 130.2, 128.9, 128.7, 128.4, 127.4, 126.6, 125.7, 117.9, 116.5, 64.4, 61.2, 55.2, 47.4, 46.1, 22.7; IR (KBr, cm^{-1}): 3029, 2880, 1689; EIMS (*m*/*z*): 448.2 (M^++3, 25), 447.2 (M^++2, 27), 446.1 (M^++1, 26), 445.0 (M^+, 28), 357.1 (87), 354.9 (100), 329.0 (12), 326.9 (15), 277.1 (17), 91.1 (73), 65.0 (12). Anal. Calcd for $C_{25}H_{23}BrN_2O$: C, 67.12; H, 5.18; N, 6.26. Found: C, 67.34; H, 5.22; N, 6.19.

2.4.8. 1-Benzyl-3-[(benzylmethylamino)methyl]-6-bromo-1*H*-quinolin-2-one (27). Compound **27** eluted out immediately after *trans*-**26** as brown oil (166 mg, 16%). ^{1}H NMR: δ=7.91 (s, 1H), 7.74 (d, J=2.3 Hz, 1H), 7.44 (dd, J=9.2, 2.3 Hz, 1H), 7.42 (d, J=7.3 Hz, 2H), 7.33–7.36 (m, 3H), 7.23–7.31 (m, 4H), 7.17 (d, J=7.3 Hz, 2H), 7.11 (d, J=9.2 Hz, 1H), 5.53 (br s, 2H), 3.70 (s, 2H), 3.67

(s, 2H), 2.34 (s, 3H); ^{13}C NMR: δ=162.1, 139.3, 137.4, 136.2, 134.9, 132.5, 132.3, 130.8, 129.0, 128.9, 128.4, 127.5, 127.2, 126.7, 122.6, 116.6, 115.0, 62.6, 55.9, 46.3, 42.9; IR (neat, cm^{-1}): 3062, 3029, 2943, 2840, 2787, 1650, 1620, 1590; EIMS (*m*/*z*): 446.3 (M$^+$, 7), 357.1 (100), 355.0 (86), 238.0 (8), 235.9 (12), 235.9 (11), 120.1 (60), 91.0 (98). Anal. Calcd for $C_{25}H_{23}BrN_2O$: C, 67.12; H, 5.18; N, 6.26. Found: C, 67.20; H, 4.92; N, 6.10.

2.4.9. (3a*R,9b*S**)-1,5-Dibenzyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one-8-carboxylic acid methyl ester (28).** *cis*-**26** (100 mg, 0.22 mmol), $Pd(OAc)_2$ (16 mg, 0.07 mmol, 0.3 equiv), PPh_3 (19 mg, 0.07 mmol, 0.33 equiv), *N*,*N*-diisopropylethylamine (23 mg, 0.18 mmol, 0.8 equiv), anhydrous MeOH (1.5 mL), and anhydrous DMF (1.5 mL) were added to a high pressure reaction tube, which was connected to a Teflon screw cap fitted with a pressure gauge. The reaction mixture was pressurized with CO, purged 4–6 times with CO, and then heated to 100 °C with stirring for 24 h at 75 psi of CO. After cooling down to the room temperature, the mixture was diluted with CH_2Cl_2 and filtered through Celite and the Celite pad was washed several times with CH_2Cl_2. The combined filtrates were washed 3–4 times with water. The organic phase was dried and evaporated to dryness. The residue was purified by chromatography (hexane/ethyl acetate, 4:1) to give the ester **28** (81 mg, 86%) and the byproduct **30** (12 mg, 13%). Data for **28**: a colorless solid. Mp: 157–158 °C. ^{1}H NMR: δ=7.90 (d, *J*=2.0 Hz, 1H), 7.86 (dd, *J*=8.3, 2.0 Hz, 1H), 7.26–7.30 (m, 4H), 7.20–7.24 (m, 3H), 7.14–7.18 (m, 3H), 6.98 (d, *J*=8.3 Hz, 1H), 5.66 (d, *J*=16.6 Hz, 1H), 5.02 (d, *J*=16.6 Hz, 1H), 3.99 (d, *J*=12.7 Hz, 1H), 3.87 (s, 3H), 3.50 (d, *J*=4.9 Hz, 1H), 3.20 (d, *J*=12.7 Hz, 1H), 3.14 (m, 1H), 3.07 (m, 1H), 2.78 (m, 1H), 2.22 (m, 2H); ^{13}C NMR: δ=171.8, 166.5, 143.0, 139.1, 136.4, 132.3, 130.9, 128.8, 128.3, 128.2, 127.2, 126.9, 126.6, 123.9, 122.9, 115.5, 64.9, 57.5, 52.1, 51.2, 45.5, 43.8, 26.0; IR (KBr, cm^{-1}): 3029, 2951, 2804, 1717, 1678, 1612; EIMS (*m*/*z*): 426.1 (M$^+$, 100), 335.2 (25), 320.2 (25), 294.2 (20), 133.2 (58), 91.1 (49). Anal. Calcd for $C_{27}H_{26}N_2O_3$: C, 76.03; H, 6.14; N, 6.57. Found: C, 75.94; H, 6.30; N, 6.45.

2.4.10. 1-Benzyl-3-(2-benzylaminoethyl)-1*H*-quinolin-2-one-6-carboxylic acid methyl ester (30). Brown oil. ^{1}H NMR: δ=8.21 (d, *J*=1.8 Hz, 1H), 8.00 (dd, *J*=8.8, 1.8 Hz, 1H), 7.64–7.67 (m, 2H), 7.46 (m, 1H), 7.21–7.34 (m, 7H), 7.18 (d, *J*=7.3 Hz, 2H), 5.57 (br s, 2H), 3.91 (s, 3H), 3.85 (s, 2H), 3.01 (t, *J*=6.9 Hz, 2H), 2.92 (t, *J*=6.9 Hz, 2H); ^{13}C NMR: δ=166.4, 162.8, 141.7, 140.5, 136.6, 136.1, 132.8, 130.4, 130.3, 130.0, 128.5, 128.3, 127.5, 127.0, 126.7, 124.0, 120.4, 114.8, 53.9, 52.3, 47.9, 46.6, 31.8; IR (neat, cm^{-1}): 1718, 1650, 1601; EIMS (*m*/*z*): 426.1 (M$^+$, 6), 424.1 (8), 335.5 (22), 319.0 (13), 277.9 (100), 229.5 (14), 217.1 (34), 183.4 (24), 119.8 (53), 90.1 (50).

2.4.11. (3a*R,9b*S**)-5-Benzyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-4-one-8-carboxylic acid methyl ester (29).** Compound **28** (50 mg, 0.12 mmol) was dissolved in methanol (4 mL) under nitrogen. $Pd(OH)_2$/C (20%) (8 mg, 0.01 mmol, 10 mol %.) and four drops of concd HCl (ca. 0.04 mL, 0.44 mmol) were added to it. The reaction flask was purged with H_2 and then stirred under a hydrogen balloon for 24 h. The mixture was diluted with MeOH and filtered through Celite and the Celite pad was washed several times with MeOH. The combined filtrates were concentrated and the residue was dissolved in saturated $NaHCO_3$ solution (8 mL), extracted with CH_2Cl_2 three times. The organic extract was dried and evaporated. The residue was purified through a short silica gel plug (ethyl acetate/MeOH, 4:0.2) to give **29** as a colorless solid (37 mg, 95%). Mp: 127–129 °C. ^{1}H NMR: δ=8.05 (d, *J*=2.3 Hz, 1H), 7.82 (dd, *J*=8.7, 2.3 Hz, 1H), 7.17–7.31 (m, 5H), 6.90 (d, *J*=8.7 Hz, 1H), 5.33 (d, *J*=16.5 Hz, 1H), 5.15 (d, *J*=16.5 Hz, 1H), 4.27 (d, *J*=6.0 Hz, 1H), 3.86 (s, 3H), 3.14 (ddd, *J*=8.7, 6.4, 4.1 Hz, 1H), 3.05 (m, 2H), 2.56 (m, 1H), 2.35 (m, 1H), 1.90 (br s, 1H); ^{13}C NMR: δ=171.4, 166.5, 142.4, 136.4, 130.9, 130.6, 128.9, 127.3, 126.3, 124.6, 124.4, 115.5, 58.4, 52.1, 46.4, 44.3, 44.2, 29.7; IR (KBr, cm^{-1}): 2950, 1715, 1675, 1610; EIMS (*m*/*z*): 336.0, 294.2 (100) (M$^+$, 85), 216.2 (39), 128.2 (24), 91.1 (86). Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.28; H, 6.02; N, 8.26.

2.4.12. (3a*R,4*R**,9b*S**)-8-Bromo-1,5-dibenzyl-2,3,3a,4,5,9b-hexahydro-4-hydroxy-1*H*-pyrrolo[3,2-*c*]quinoline (31).** DIBAL-H (1 M in hexanes, 2.68 mL, 2.68 mmol) was added dropwise to a solution of lactam *cis*-**26** (600 mg, 1.34 mmol) in anhydrous THF (6.2 mL) at −78 °C and stirred for 4 h at −78 °C. The reaction was then quenched by dropwise addition of MeOH (2.4 mL) at the same temperature. Rochelle's salt (20%, 6 mL) and water (6 mL) were added and mixture was warmed up to room temperature. The aqueous solution was extracted with CH_2Cl_2 (3×15 mL). The organic layers were dried and evaporated to provide the pure product **26** (592 mg, 98%, a 87:13 mixture of two diastereomers) as a colorless solid after drying under vacuum overnight, which was stored at −20 °C. Data for the major *endo* isomer: mp: 133–135 °C. ^{1}H NMR: δ=7.19–7.34 (m, 12H), 6.91 (d, *J*=9.9 Hz, 1H), 6.49 (d, *J*=8.9 Hz, 1H), 4.72 (dd, *J*=9.9, 3.2 Hz, 1H), 4.71 (d, *J*=17.4 Hz, 1H), 4.66 (d, *J*=17.4 Hz, 1H), 4.43 (d, *J*=12.1 Hz, 1H), 3.39 (d, *J*=4.4 Hz, 1H), 3.07 (d, *J*=12.1 Hz, 1H), 2.90 (m, 1H), 2.69 (m, 1H), 2.18 (m, 1H), 2.02–2.09 (m, 2H); ^{13}C NMR: δ=142.3, 138.6, 138.3, 134.6, 132.4, 128.8, 128.60, 128.57, 127.3, 127.1, 126.5, 120.1, 114.9, 108.5, 84.3, 64.4, 57.8, 54.3, 51.2, 38.9, 24.2; IR (neat, cm^{-1}): 3028, 2949, 2806, 1594; EIMS (*m*/*z*): 450.0 (M$^+$+2, 7), 448.1 (M$^+$, 9), 432.0 (11), 430.0 (11), 358.8 (79), 356.9 (71), 312.9 (100), 310.9 (94).

2.4.13. (3a*R,4*S**,9b*S**)-8-Bromo-1,5-dibenzyl-2,3,3a,4,5,9b-hexahydro-4-methoxy-1*H*-pyrrolo[3,2-*c*]quinoline (32).** The diastereomeric mixture of aminals **31** (459 mg, 1.02 mmol) directly from last step was dissolved in $CHCl_3$ (4.5 mL) and MeOH (18 mL) and then heated to reflux under N_2 for 4 h. The solvents were completely removed and the crude product was further dried under high vacuum to provide the pure methoxyaminal **32** (463 mg, 98%) as a light brown semi-solid, which was stored at −20 °C and used without any further purification. ^{1}H NMR: δ=7.40–7.39 (m, 2H), 7.28–7.34 (m, 2H), 7.22–7.26 (m, 2H), 7.11 (dd, *J*=8.7, 2.3 Hz, 1H), 6.48 (d, *J*=8.7 Hz, 1H), 4.82 (d, *J*=16.3 Hz, 1H), 4.51 (d, *J*=16.3 Hz, 1H), 4.36 (d, *J*=16.3 Hz, 1H), 4.36 (d, *J*=2.1 Hz, 1H), 4.04 (d, *J*=12.8 Hz, 1H), 3.62 (d, *J*=8.5 Hz, 1H), 3.38 (d, *J*=12.8 Hz, 1H), 3.26 (s, 3H), 2.87–2.96 (m, 2H), 2.31 (ddd, *J*=9.4,

9.4, 6.9 Hz, 1H), 2.06 (m, 1H), 1.83 (m, 1H); ^{13}C NMR: δ=142.4, 140.0, 138.4, 132.52, 132.46, 130.8, 129.0, 128.8, 128.7, 128.3, 127.2, 127.0, 115.5, 110.9, 95.1, 61.7, 58.9, 55.3, 55.0, 52.0, 43.1, 28.4; IR (neat, cm^{-1}): 3027, 2928, 2806, 1592; EIMS (*m*/*z*): 464.2 (M^++2, 3), 462.2 (M^+, 24), 373.0 (100), 371.0 (99), 312.9 (78), 310.9 (59), 106.2 (45), 105.2 (33), 86.0 (32), 84.0 (50).

2.4.14. (3a*R,4*S**,9b*S**)-4-Allyl-8-bromo-1,5-dibenzyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline (34).** A solution of $TiCl_4$ (0.38 mL, 3.43 mmol) in anhydrous CH_2Cl_2 (3.4 mL) was added dropwise to a stirred solution of methoxyaminal **32** (265 mg, 0.57 mmol) and allyltrimethylsilane (1.09 mL, 6.86 mmol) in anhydrous CH_2Cl_2 (12 mL) at −78 °C. The reaction mixture was allowed to warm up to room temperature slowly and stirred overnight. An NaOH solution (1 N, 20 mL) was added carefully to the reaction mixture and the organic phase was separated. The aqueous layer was further extracted with CH_2Cl_2 (2×). The combined organic layers were dried (Na_2SO_4) and concentrated. An ^{1}H NMR spectrum of the crude reaction mixture showed the formation of **34** and **35** in a ratio of ca. 0.6:1. The residue was purified by chromatography (hexane/ethyl acetate, 8:1) to provide the major isomer **34** as pale yellow oil (80 mg, 30%). Compound **35** was not isolated from the column due to its instability. Data for **34**: ^{1}H NMR: δ=7.28–7.38 (m, 8H), 7.21–7.26 (m, 2H), 7.24 (d, *J*=2.5 Hz, 1H), 7.07 (dd, *J*=8.7, 2.5 Hz, 1H), 6.35 (d, *J*=8.7 Hz, 1H), 5.69–5.78 (m, 1H), 4.99–5.06 (m, 2H), 4.56 (d, *J*=16.0 Hz, 1H), 4.23 (d, *J*=16.0 Hz, 1H), 4.01 (d, *J*=12.8 Hz, 1H), 3.64 (d, *J*=8.5 Hz, 1H), 3.54 (d, *J*=12.8 Hz, 1H), 3.21 (ddd, *J*=8.7, 5.3, 2.3 Hz, 1H), 2.93 (ddd, *J*=9.6, 7.6, 3.7 Hz, 1H), 2.67 (ddd, *J*=17.1, 8.7, 2.3 Hz, 1H), 2.36 (ddd, *J*=9.6, 8.9, 7.1 Hz, 1H), 2.28–2.33 (m, 1H), 2.06–2.12 (m, 1H), 1.90–1.98 (m, 2H); ^{13}C NMR: δ=144.3, 140.0, 138.6, 135.4, 132.5, 130.6, 129.0, 128.7, 128.4, 128.2, 127.2, 127.1, 127.0, 117.7, 114.9, 109.4, 63.1, 60.6, 59.4, 54.5, 52.3, 41.1, 35.9, 29.6; IR (neat, cm^{-1}): 3062, 3028, 2928, 2795, 1591; EIMS (*m*/*z*): 474.1 (M^++2, 12.5), 472.0 (M^+, 12), 432.5 (100), 282.8 (22). HRMS (*m*/*z*): calcd for MH^+ $C_{28}H_{30}{}^{79}BrN_2$ 473.1587, found 473.1571; calcd for MH^+ $C_{28}H_{30}{}^{81}BrN_2$ 475.1566, found 475.1558.

2.4.15. 1,5-Dibenzyl-8-bromo-2,3,5,9b-tetrahydro-1*H*-pyrrolo[3,2-*c*]quinoline (35). Following the above representative procedure, methoxyaminal **32** (72 mg, 0.16 mmol), allyltrimethylsilane (0.25 mL, 1.56 mmol), $MeAlCl_2$ (1 M in hexanes, 0.62 mL, 0.62 mmol), and anhydrous CH_3CN (3.1 mL) were used. After work-up, **35** (~71 mg, >85% based on ^{1}H NMR) was obtained, which was not very stable and after trituration with Et_2O and exposure to air, slowly converted to **36**. Data for **35**: a brown semi-solid. ^{1}H NMR: δ=7.36–7.88 (m, 10H), 7.10 (d, *J*=2.3 Hz, 1H), 7.04 (dd, *J*=8.7, 2.3 Hz, 1H), 6.39 (d, *J*=8.7 Hz, 1H), 6.31 (s, 1H), 5.13 (s, 1H), 4.70 (m, 2H), 3.68 (m, 2H), 3.09 (m, 1H), 2.75 (m, 1H), 2.58 (m, 2H); ^{13}C NMR: δ=142.5, 139.8, 137.6, 137.5, 130.4, 129.0, 128.6, 128.5, 128.4, 128.3, 127.1, 127.0, 126.8, 125.1, 118.3, 114.4, 109.6, 80.6, 58.6, 50.4, 49.3, 29.3.

2.4.16. 1,5-Dibenzyl-8-bromo-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]quinolinium chloride (36). A brown semi-solid. ^{1}H NMR: δ=9.35 (s, 1H), 8.07 (s, 1H), 7.72 (d, *J*=9.3 Hz, 1H), 7.68 (d, *J*=9.3 Hz, 1H), 7.21–7.46 (m, 11H), 5.94 (s, 2H), 5.14 (s, 2H), 4.30 (t, *J*=8.8 Hz, 2H), 3.59 (t, *J*=8.8 Hz, 2H), 1.85 (br s, 1H); ^{13}C NMR: δ=158.4, 141.5, 139.0, 137.3, 134.2, 133.6, 129.9, 129.4, 128.9, 128.7, 127.9, 126.2, 122.1, 120.5, 119.5, 115.7, 58.7, 58.1, 54.1, 24.5; IR (neat, cm^{-1}) 3400, 3031, 2943, 1637, 1609. HRMS (*m*/*z*): calcd for M^+ $C_{25}H_{22}{}^{79}BrN_2^+$ 429.0961, found 429.0959; calcd for M^+ $C_{25}H_{22}{}^{81}BrN_2^+$ 431.0941, found 431.0944.

2.4.17. (3a*R,4*R**,9b*S**)-8-Bromo-4-cyano-1,5-dibenzyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline (37).** Methoxyaminal **32** (60 mg, 0.13 mmol) was dissolved in anhydrous CH_2Cl_2 (2.6 mL), and TMSCN (51 mg, 0.07 mL, 0.52 mmol) was added dropwise at room temperature. After stirring at room temperature for 3 h, the reaction mixture was diluted with CH_2Cl_2 and quenched with saturated $NaHCO_3$ (2 mL). The organic layer was separated, washed with H_2O and brine, dried (Na_2SO_4), and concentrated. The crude sample was purified by flash chromatography (hexane/ethyl acetate, 2:1) to provide the title product **37** (58 mg, 98%) as a colorless solid. Mp: 126–128 °C. ^{1}H NMR: δ=7.27–7.37 (m, 9H), 7.20–7.24 (m, 3H), 6.76 (d, *J*=8.8 Hz, 1H), 4.82 (d, *J*=15.2 Hz, 1H), 4.17 (d, *J*=15.2 Hz, 1H), 4.06 (d, *J*=13.0 Hz, 1H), 4.03 (d, *J*=4.6 Hz, 1H), 3.53 (d, *J*=7.8 Hz, 1H), 3.29 (d, *J*=13.0 Hz, 1H), 2.85–2.92 (m, 2H), 2.25 (dd, *J*=17.4, 8.6 Hz, 1H), 2.02–2.10 (m, 1H), 1.75–1.81 (m, 1H); ^{13}C NMR: δ=144.1, 139.2, 136.2, 133.6, 131.7, 129.0, 128.6, 128.3, 128.04, 128.00, 127.1, 126.6, 118.2, 116.2, 112.2, 61.9, 57.4, 53.9, 53.8, 51.4, 42.3, 28.1; IR (neat, cm^{-1}): 3067, 3028, 2970, 2939, 2797. HRMS (*m*/*z*): calcd for MH^+ $C_{26}H_{25}{}^{79}BrN_3$ 458.1226, found 458.1213; calcd for MH^+ $C_{26}H_{25}{}^{81}BrN_3$ 460.1206, found 460.1198.

2.4.18. 1-Benzyl-6-bromo-2-[3-(*tert*-butyldimethylsilanyloxy)-prop-1-ynyl]-3-(2-benzylaminoethyl)-1,2-dihydroquinoline (38). Methoxyaminal **32** (20 mg, 0.043 mmol) was dissolved in anhydrous CH_2Cl_2 (0.5 mL), and TMSOTf (8 μL, 0.04 mmol) was added dropwise at −78 °C. After stirring at −78 °C for 5 min, a copper acetylide solution (1.3 mL, 0.13 mmol), which was prepared in situ by stirring the TBS-protected propargyl alcohol **40** (22 mg, 0.13 mmol), CuCl (13 mg, 0.13 mmol), and NEt_3 (18 μL, 0.13 mmol) in anhydrous CH_2Cl_2 (1.3 mL) at room temperature for 20 min, was added. The reaction mixture was allowed to warm up slowly from −78 °C to room temperature. After stirring overnight, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$, H_2O, and brine, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate, 2:1) to provide **38** (17 mg, 70%) as brown oil. ^{1}H NMR: δ=7.23–7.35 (m, 10H), 7.12 (dd, *J*=8.8, 2.4 Hz, 1H), 7.06 (d, *J*=2.4 Hz, 1H), 6.49 (d, *J*=8.8 Hz, 1H), 6.18 (s, 1H), 4.61 (d, *J*=14.7 Hz, 1H), 4.45 (t, *J*=1.5 Hz, 1H), 4.22 (d, *J*=1.5 Hz, 2H), 4.19 (d, *J*=14.6 Hz, 1H), 3.76 (d, *J*=2.4 Hz, 2H), 2.69–2.79 (m, 2H), 2.35–2.42 (m, 2H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR: δ=144.8, 140.3, 136.8, 134.6, 130.6, 129.0, 128.8, 128.5, 128.2, 127.9, 127.7, 127.1, 125.4, 122.0, 114.0, 110.6, 83.5, 81.3, 54.0, 52.2, 51.8, 51.5, 46.7, 34.5, 25.8, 18.3, −5.1; IR (neat, cm^{-1}): 3375, 3031, 2957, 2928, 2856, 1651, 1590. HRMS (*m*/*z*): calcd for MH^+ $C_{34}H_{42}{}^{79}BrN_2OSi$ 601.2244, found

601.2236; calcd for MH^+ $C_{34}H_{42}{}^{81}BrN_2OSi$ 603.2224, found 603.2225.

2.4.19. 1-Benzyl-3-(2-benzylaminoethyl)-6-bromoquinolinium triflate (39). To a stirred solution of methoxyaminal **32** (20 mg, 0.044 mmol) in anhydrous CH_2Cl_2 (0.9 mL) was added dropwise a solution of TMSOTf (16 μL, 0.089 mmol) in anhydrous at −78 °C. The reaction mixture was allowed to warm to room temperature slowly and stirred for 5 h. Then it was diluted with CH_2Cl_2, washed by saturated $NaHCO_3$ and brine (2×), dried ($CaCl_2$), and concentrated to provide the title compound **38** (~18 mg, ca. 90%) as pale yellow oil. ^{1}H NMR: δ=10.29 (s, 1H), 8.85 (s, 1H), 8.25 (s, 1H), 8.14 (d, J=9.5 Hz, 1H), 7.95 (d, J=9.5 Hz, 1H), 7.39–7.42 (m, 2H), 7.20–7.38 (m, 8H), 6.35 (s, 1H), 3.93 (s, 2H), 3.48 (m, 2H), 3.25 (m, 2H); ^{13}C NMR: δ=152.5, 146.4, 138.2, 135.7, 135.0, 133.8, 132.6, 132.3, 131.1, 129.9, 129.6, 129.5, 128.8, 128.5, 127.5, 124.5, 120.6, 61.8, 52.4, 47.0, 30.5, 29.9.

2.5. General procedure for CuBr mediated reactions with sonication

2.5.1. (3a*R,4*R**,9b*S**)-8-Bromo-1,5-dibenzyl-2,3,3a,4,5,9b-hexahydro-4-[3-(*tert*-butyldimethylsilyloxy)-prop-1-ynyl]-1*H*-pyrrolo[3,2-*c*]quinoline (41).** Aminal **31** (50 mg, 0.11 mmol) and the TBS-protected propargyl alcohol **40** (57 mg, 0.33 mmol) were mixed efficiently in a test tube. Then CuBr (48 mg, 0.33 mmol) was added followed by addition of water (1 mL) and mixed by efficient magnetic stirring. Then the test tube was sonicated for 3 h under N_2 protection in a darkened hood. During the course of the reaction, the water bath was warmed up to ~40–45 °C under sonication. After cooling to room temperature, the reaction mixture was partitioned between CH_2Cl_2 and 10% aqueous NH_3 solution. The organic layer was separated and further washed with 10% NH_3 solution, H_2O, and brine, dried (Na_2SO_4), and concentrated. The crude oil was purified by column chromatography (hexanes/ethyl acetate, gradient elution, 10:1 to 1:1) to provide product **41** (32 mg, 48%) as a colorless oil and fragmentation product **38** (27 mg, 40%) as a brown oil. ^{1}H NMR: δ=7.22–7.35 (m, 10H), 7.21 (d, J=2.2 Hz, 1H), 7.14 (dd, J=8.8, 2.2 Hz, 1H), 6.54 (d, J=8.8 Hz, 1H), 4.78 (d, J=16.1 Hz, 1H), 4.42 (d, J=16.1 Hz, 1H), 4.23 (d, J=1.5 Hz, 2H), 4.16 (d, J=13.0 Hz, 1H), 4.12 (dt, J=6.6, 1.5 Hz, 1H), 3.45 (d, J=6.6 Hz, 1H), 3.29 (d, J=13.0 Hz, 1H), 2.90 (ddd, J=9.0, 8.8, 3.4 Hz), 2.62 (m, 1H), 2.24 (ddd, J=8.8, 8.8, 8.8 Hz, 1H), 2.04 (m, 1H), 1.88 (m, 1H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR: δ=144.7, 139.9, 138.3, 133.5, 131.1, 128.65, 128.61, 128.2, 127.3, 127.1, 126.9, 125.3, 115.4, 109.4, 83.7, 82.9, 62.5, 57.8, 53.6, 53.4, 51.8, 51.3, 42.7, 27.8, 25.9, 18.3, −5.1; IR (neat, cm^{-1}): 3064, 3030, 2958, 2929, 2857. HRMS (*m*/*z*): calcd for MH^+ $C_{34}H_{42}{}^{79}BrN_2OSi$ 601.2244, found 601.2227; calcd for MH^+ $C_{34}H_{42}{}^{81}BrN_2OSi$ 603.2224, found 603.2222.

2.5.2. *N*-(Benzyloxycarbonyl)-*N*-(*tert*-butyloxycarbonyl)-propargylamine (42). To a stirred solution of *N*-(benzyloxycarbonyloxy)succinimide (3.00 g, 12.0 mmol) in anhydrous CH_2Cl_2 (30 mL) was added dropwise propargylamine (0.80 mL, 12.5 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then overnight at room temperature. On completion of the reaction, the mixture was washed with 2 N HCl (10 mL), water (10 mL), and brine (10 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated. The crude product, which can be directly used in the next step without further purification, was purified by flash chromatography (hexane/ethyl acetate, 3:1) to provide the corresponding *N*-(benzyloxycarbonyl)propargylamine (1.64 g, 72%) as a colorless solid. Mp: 39–41 °C. (lit.[41] mp: 35–36 °C). ^{1}H NMR: δ=7.30–7.37 (m, 5H), 5.12 (s, 2H), 5.08 (br s, 1H), 3.98 (d, J=2.4 Hz, 2H), 2.25 (t, J=2.4 Hz, 1H); ^{13}C NMR: δ=156.0, 136.3, 128.7, 128.34, 128.30, 79.8, 71.7, 67.2, 30.9. *N*-(Benzyloxycarbonyl)propargylamine (500 mg, 2.64 mmol) and di-*tert*-butyl-dicarbonate (700 mg, 3.20 mmol) were dissolved in anhydrous CH_3CN (5 mL) at room temperature, then DMAP (20 mg, 0.16 mmol) was added. After stirring at room temperature for 4 h, the reaction mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution, H_2O, and brine, dried (Na_2SO_4), and concentrated. The crude sample was purified by chromatography (hexane/ethyl acetate, 2:1) to provide the title product **42** (688 mg, 90%) as a colorless oil. ^{1}H NMR: δ=7.38–7.41 (m, 2H), 7.30–7.37 (m, 3H), 5.25 (s, 2H), 4.41 (d, J=2.4 Hz, 2H), 2.20 (t, J=2.4 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR: δ=153.1, 151.1, 135.4, 128.6, 128.5, 128.3, 83.7, 79.3, 71.2, 68.8, 36.1, 28.0; IR (neat, cm^{-1}): 3309, 3067, 3036, 2982, 2935, 1797, 1762, 1729, 1696. ESIMS (*m*/*z*): 328 ($M+K^+$, 2), 312 ($M+Na^+$, 100), 256 (15), 212 (16).

2.5.3. (3a*R,4*R**,9b*S**)-4-[3-(Benzyloxycarbonyl-*tert*-butyloxycarbonylamino)prop-1-ynyl]-8-bromo-1,5-dibenzyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline (43).** Following the general sonication procedure, aminal **31** (50 mg, 0.11 mmol), propargylamine **42** (95 mg, 0.33 mmol) and CuBr (48 mg, 0.33 mmol) were used. ^{1}H NMR of the crude reaction mixture indicated that the required adduct and the fragmentation product were formed in the ratio of 0.6:1. Chromatographic purification (hexane/ethyl acetate, 6:1 to 1:1) of the crude product provided the title compound **43** (25 mg, 32%) as colorless oil. The pure byproduct **44** was not obtained from the column due to the contamination with unreacted **42**. ^{1}H NMR: δ=7.21–7.38 (m, 15H), 7.18 (d, J=2.4 Hz, 1H), 7.12 (dd, J=8.8, 2.4 Hz, 1H), 6.52 (d, J=8.8 Hz, 1H), 5.18 (s, 2H), 4.75 (d, J=16.1 Hz, 1H), 4.40 (d, J=16.1 Hz, 1H), 4.35 (d, J=1.7 Hz, 2H), 4.15 (d, J=13.0 Hz, 1H), 4.09 (dt, J=7.1, 1.7 Hz, 1H), 3.38 (d, J=6.3 Hz, 1H), 3.25 (d, J=13.0 Hz, 1H), 2.87 (ddd, J=9.0, 9.0, 3.7 Hz), 2.52 (m, 1H), 2.21 (ddd, J=8.8, 8.8, 8.3 Hz, 1H), 1.99 (m, 1H), 1.81 (m, 1H), 1.44 (s, 9H); ^{13}C NMR: δ=153.0, 151.0, 144.6, 139.9, 138.2, 135.5, 133.6, 131.1, 128.65, 128.62, 128.55, 128.4, 128.2, 127.3, 127.1, 126.9, 124.9, 115.4, 109.3, 83.5, 81.7, 79.9, 68.6, 62.5, 57.6, 53.3, 53.1, 51.2, 42.4, 36.4, 28.0, 27.6; IR (neat, cm^{-1}): 3089, 3065, 3032, 2982, 2934, 2885, 2850, 2801, 1796, 1757, 1725, 1697. HRMS (*m*/*z*): calcd for MH^+ $C_{41}H_{43}{}^{79}BrN_3O_4$ 720.2431, found 720.2424; calcd for MH^+ $C_{41}H_{43}{}^{81}BrN_3O_4$ 722.2411, found 720.2422.

2.5.4. Methyl (3a*R,4*S**,9b*S**)-1,5-dibenzyl-4-methoxy-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate (45).** To Methoxyaminal **32** (200 mg, 0.43 mmol) in anhydrous THF (4.5 mL) at −78 °C was added *n*-BuLi (1.6 M solution in hexane, 0.28 mL, 0.45 mmol) and stirred for 15 min at −78 °C. Dimethyl

carbonate (0.09 mL, 1.08 mmol) was added dropwise and stirred for 3 h while the reaction temperature was allowed to warm up slowly to 0 °C. The reaction was quenched by careful addition of saturated NH_4Cl solution (15 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organics were dried (Na_2SO_4) and concentrated. Ether was added to the crude oily product, removed by rotary evaporation, and then dried under high vacuum overnight to provide **45** (189 mg, greater than 90% pure by ^1H NMR analysis) as a brown semi-solid, which was directly used in the next step without further purification. ^1H NMR: δ=7.89 (d, J=2.2 Hz, 1H), 7.76 (dd, J=8.6, 2.2 Hz, 1H), 7.39–7.41 (m, 2H), 7.20–7.34 (m, 8H), 6.65 (d, J=8.6 Hz, 1H), 4.92 (d, J=16.4 Hz, 1H), 4.60 (d, J=16.4 Hz, 1H), 4.47 (d, J=2.9 Hz, 1H), 4.08 (d, J=13.0 Hz, 1H), 3.83 (s, 3H), 3.66 (d, J=8.1 Hz, 1H), 3.37 (d, J=13.0 Hz, 1H), 3.27 (s, 3H), 2.95 (m, 1H), 2.90 (ddd, J=16.1, 8.1, 2.7 Hz), 2.32 (ddd, J=9.3, 9.0, 7.6 Hz), 2.08 (m, 1H), 1.83 (ddd, J=16.1, 12.2, 8.1 Hz); ^{13}C NMR: δ=167.4, 147.9, 140.1, 138.0, 131.7, 130.4, 128.7, 128.2, 127.2, 127.0, 126.9, 125.4, 119.7, 113.0, 94.3, 62.0, 58.6, 54.9, 54.0, 51.79, 51.71, 51.67, 42.4, 28.2; IR (neat, cm^{-1}): 3062, 3028, 2963, 2930, 2850, 2824, 1711, 1609. ESIMS (m/z): 465 ($M+Na^+$, 1), 443 ($M+H^+$, 5), 411 (100), 353 (15).

2.5.5. Methyl (3a*R,4*R**,9b*S**)-4-[3-(benzyloxycarbonyl-*tert*-butyloxycarbonylamino)-prop-1-ynyl]-1,5-dibenzyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate (47).** Following the general sonication procedure, crude methyl ester **45** obtained directly from last step (100 mg, ~0.22 mmol), **42** (195 mg, 0.66 mmol) and CuBr (97 mg, 0.66 mmol) were used. Chromatography (hexanes/EtOAc, 6:1 to 1:1) of the crude oil provided product **47** (63 mg, 40% for two steps) as colorless oil. The pure fragmentation byproduct was not obtained from the column due to the contamination with unreacted **42**. ^1H NMR: δ=7.78 (d, J=2.0 Hz, 1H), 7.74 (dd, J=8.8, 2.0 Hz, 1H), 7.26–7.37 (m, 8H), 7.18–7.25 (m, 7H), 6.67 (d, J=8.8 Hz, 1H), 5.18 (s, 2H), 4.93 (d, J=16.9 Hz, 1H), 4.69 (d, J=16.9 Hz, 1H), 4.37 (d, J=1.5 Hz, 2H), 4.28 (dt, J=8.8, 1.5 Hz, 1H), 4.21 (d, J=13.0 Hz, 1H), 3.83 (s, 3H), 3.36 (d, J=5.1 Hz, 1H), 3.20 (d, J=13.0 Hz, 1H), 2.89 (ddd, J=9.0, 9.0, 3.7 Hz), 2.45 (m, 1H), 2.19 (ddd, J=9.8, 9.5, 7.1 Hz, 1H), 2.04 (m, 1H), 1.78 (m, 1H), 1.45 (s, 9H); ^{13}C NMR: δ=167.3, 153.0, 151.1, 149.0, 140.0, 137.8, 135.4, 133.6, 130.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 127.1, 127.0, 126.8, 120.4, 117.9, 112.6, 83.6, 81.6, 80.6, 68.7, 63.0, 57.0, 53.0, 52.3, 51.7, 50.8, 41.5, 36.4, 28.0, 27.1; IR (neat, cm^{-1}): 3062, 3006, 3030, 2979, 2945, 2796, 1794, 1756, 1711, 1610. HRMS (m/z): calcd for MH^+ $C_{43}H_{46}N_3O_6$ 700.3381, found 700.3380.

2.5.6. Methyl (3a*R,4*S**,9b*S**)-4-(3-aminopropyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-8-carboxylate, hydrochloride salt (48).** A slurry of 20% $Pd(OH)_2$ on carbon (51 mg, 0.073 mmol) and **46** (30 mg, 0.043 mmol) in MeOH (6 mL) and concd HCl (0.30 mL) was stirred under H_2 balloon for 28 h at room temperature. The catalyst was then removed by filtration and rinsed with MeOH (2×6 mL). The filtrate was concentrated, and then more MeOH was added and concentrated again to co-evaporate water. This procedure was repeated several times until an oily compound was obtained, which was triturated with Et_2O to provide the oily compound **48** as the hydrochloride salt (15 mg, >90% pure by ^1H NMR analysis).[43] ^1H NMR (CD_3OD): δ=7.98 (s, 1H), 7.74 (d, J=8.0 Hz, 1H), 6.83 (d, J=8.0 Hz, 1H), 4.65 (br s, 1H), 3.81 (s, 3H), 3.34–3.42 (br s, 2H), 3.10 (br s, 1H), 2.99 (br s, 2H), 2.39–2.50 (br s, 2H), 2.12–2.20 (br s, 1H), 1.80–1.95 (br s, 3H), 1.70 (br s, 1H); ^{13}C NMR (CD_3OD): δ=168.3, 151.0, 133.9, 132.6, 119.2, 115.7, 113.3, 59.3, 52.3, 50.8, 43.9, 41.1, 39.4, 30.5, 28.2, 24.0; ESIMS (m/z): 290 ($M+H^+$, 100), 273 (75), 256 (22).

2.6. X-ray data collection, solution, and refinement of the structures *cis*-26 and *trans*-26

A suitable crystal was selected and attached to a glass fiber using 5 min epoxy-glue and immediately placed in the path of the X-ray beam. Data collections for compounds *cis*-**26** and *trans*-**26** were carried out on a Siemens P4 diffractometer equipped with a LT-2A device for low-temperature work and graphite monochromated Mo Kα radiation (λ=0.710 73 Å). Data were collected at the room temperature. All the structures were solved and refined using the Bruker SHELXTL software package. Compound *cis*-**26** crystallizes in the triclinic $P\bar{1}$ space group with two chemically similar, but crystallographically different molecules in the asymmetric unit. *trans*-**26** Crystallizes in the monoclinic $P2(1)/n$ space group. Crystallographic data (cif files) for *cis*-**26** and *trans*-**26** have been deposited at the Cambridge Crystallographic Data Center, CCDS nos. 287965 and 287966. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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