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Natural Product Synthesis

A Straightforward Synthesis of 5-Methylaaptamine from Eugenol, Employing a 6π-Electrocyclization Reaction of a 1-Azatriene

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Abstract: Aaptamine, isolated from tropical marine sponges of the Demospongiae class, is the most prominent member of a growing family of natural products. Many aaptaminoids have been shown to have interesting biological activity. The efficient access to 5-methylaaptamine, an unnatural analogue of aaptamine, was achieved by using economic and naturally-occurring eugenol as the starting material. The synthesis involved the preparation of a 5-aminoeugenol derivative through successive nitration, *O*-methylation, and nitro group reduction reactions. An Elderfield–Johnson sequence was employed to synthesize the *N*-tosyl-5-allyl-7,8-dimethoxydihydro-1*H*-quinolin-4-one ring system. A catalytic double-bond isomerization followed by a carbonyl methoximation and 6-π electrocyclization of the 1-azatriene motif afforded the 2,3-dihydro-1*H*-benzo[*de*]-[1,6]naphthyridine tricyclic intermediate, which underwent a reductive desulfonylation and catalytic dehydrogenation to afford the target product.

Introduction

Tropical marine sponges of the Demospongiae class, especially those of the genus *Aaptos* (family Suberitidae, order Hadromerida) as well as those belonging to the genera *Xestospongia*, *Hymeniacidon*/*Suberites*, *Suberea*, and *Luffariella*, are a rich source of alkaloids collectively known as aaptaminoids, which are characterized by their unusual 1*H*-benzo[*de*][1,6]naphthyridine framework. From a biosynthetic viewpoint, these compounds appear to be derivatives of aaptamine (**1**), the most widespread and representative member of this class, and are formed by diversified substitution,[1a] dimerization,[1] and rearrangement reactions.[2]

These natural products exhibit an ample array of prominent biological activities, including α-adrenoreceptor blocking, antineoplastic, antiviral, and antimicrobial properties.[3] We previously performed a formal total synthesis of aaptamine[4a] and, in 2009, reviewed the isolation, syntheses, and biological activities of the aaptaminoid alkaloids.[4b]

Since then, the continued interest in these heterocycles has resulted in dramatic growth in the number of members of this family of compounds. In fact, 3-*N*-substituted 9-demethyl-(oxy)aaptamine derivatives **2a**–**2h** have recently been isolated from *Aaptos* marine sponges collected from the waters of Vietnam, Indonesia, South China, and eastern Peninsular Malaysia (Figure 1).[1a,5] Oxidized aaptaminoids such as **3a**–**3c**,[5b,5d] morpholino derivative **4**,[5d] and the zwitterionic aaptanone **5a** have also been reported. For structural elucidation purposes, compound **5a** was *N*-methylated to give **5b**.[6] Aaptaminoids that contain piperidine (i.e., **6**), imidazole (i.e., **7** and **8**),[5b,7] and piperazine (i.e., **9a**–**9d**)[8] rings fused to the original tricyclic skeleton along with 5-substituted ketone **10**[8a] have also been discovered. In addition to hybrid aaptamine-type/bromoindole alkaloids that have taurine- or histidine-derived residues (e.g., nakijinamines A–I), which were isolated from the Okinawan marine sponge *Suberites* species,[9] dimeric compounds **12a**, **12b**, **13a**, and **13b** (suberitines A–D)[1b] reminiscent of lihouidine and 4,4′-binecatorone[10] have been reported as well.

In recent years, new biological properties of these natural compounds have been found, which include their abilities to produce pleiotropic effects,[11] act as proteasome inhibitors,[12] nicotinic acetylcholine receptor ligands,[13] and antiproliferative and cancer-preventing agents,[14] inhibit liver cancer progression,[15] and protect kidney cells against cisplatin-induced cytotoxicity.[16] New insights have also been made about the mode of action of aaptamine and its congeners on cancer cells[17] as well as the structural features involved in the inhibition of sortase A.[18] Related tetracyclic compound **11** has been shown to strongly bind DNA and behave as a cytotoxic and intercalating agent.[19]

However, most of these biological activity and molecular biology studies regarding the search for molecular targets of aaptamine and its congeners have been performed by employing compounds extracted from natural sources, which are often scarce and difficult to access. The syntheses of unnatural oxygenated aaptaminoids have been carried out,[20] and despite that some naturally-occurring methylated aaptamines are known, methyl analogues of natural products have also been

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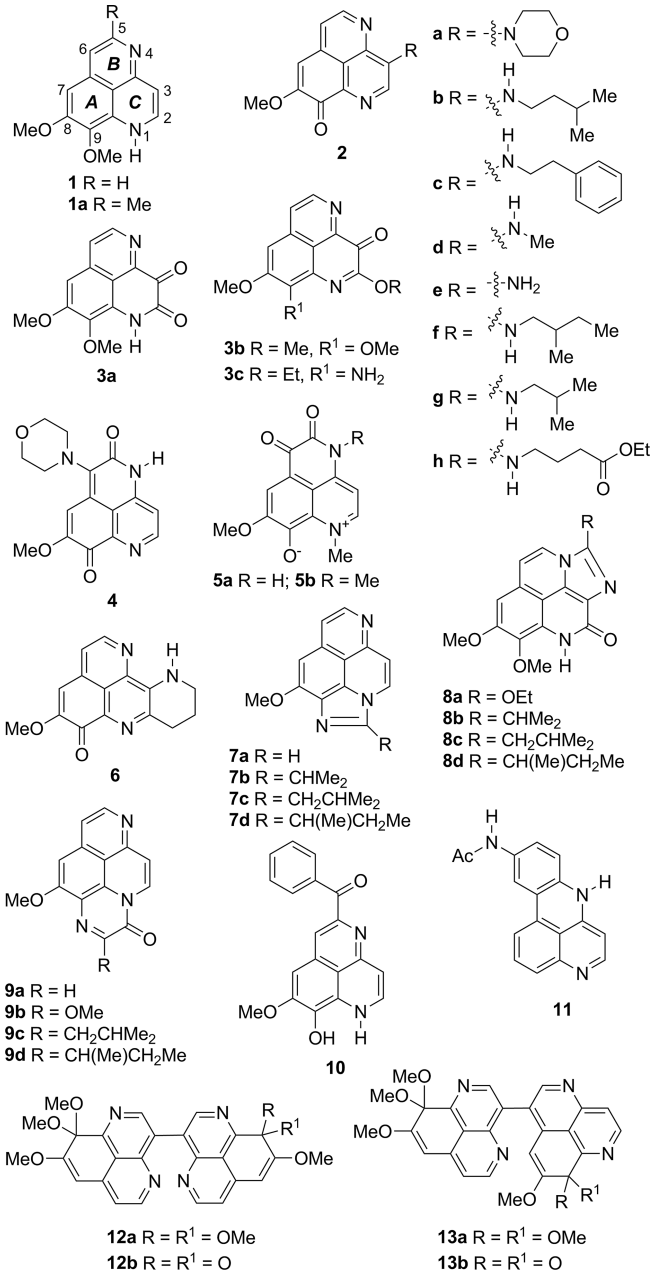


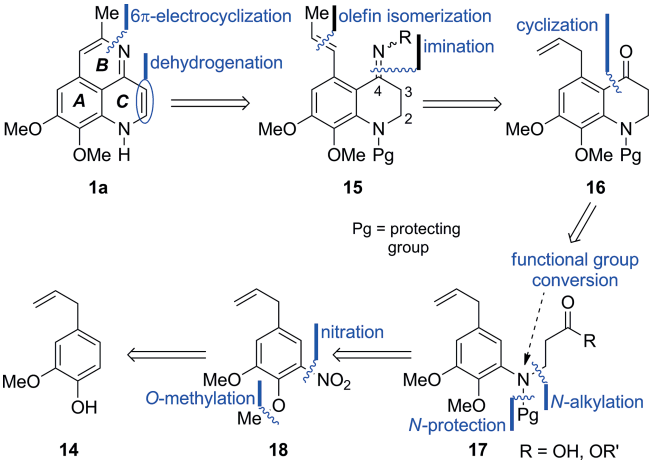
Figure 1. New members of the aaptamine family.

prepared.[21] Recently, isolated ketone **10**, a 5-substituted aaptamine derivative, and the 2-alkyl-substituted 7*H*-pyrido[4,3,2-*kl*]acridines (which contain a 1*H*-benzo[*de*][1,6]naphthyridine motif) have been synthesized as potential antitumor agents.[22]

In view of these precedents, the recent importance of aaptamine and its congeners, and the drawbacks of previous syntheses of the natural product, we sought to devise a short and efficient alternative pathway to a simple aaptamine analogue by starting from inexpensive and easily available starting materials. Herein, we report the synthesis of 5-methylaaptamine (**1a**) from eugenol (**14**), a natural product and a versatile commodity chemical that has been widely employed in synthetic organic chemistry.[23]

Results and Discussion

The retrosynthetic analysis shows the synthetic approach towards **1a** (Scheme 1). Relying on our previous experience,[24] we propose that the **B** ring of the tricycle could be formed by a 6π-electrocyclization reaction of a 1-azatriene, and, therefore, the corresponding C–N bond disconnection was planned. The chosen mode of assembly of the **B** ring imposes logistical demands, different from those of previous syntheses of aaptaminoids, but has the compensatory advantage that, in principle, it could lead to a new series of heterotricyclic compounds.



Scheme 1. Retrosynthetic analysis of 5-methylaaptamine (**1a**).

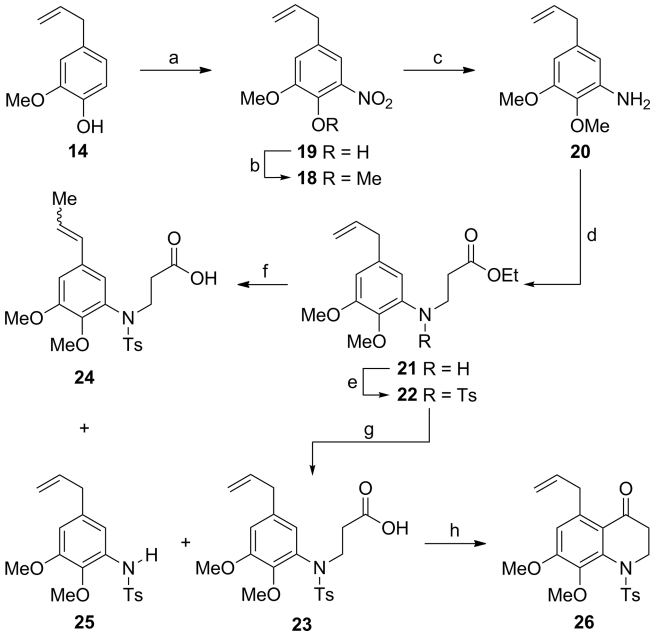
This building strategy mandates a late introduction of the C-2–C-3 double bond as a means to improve the electrophilicity of the C-4 carbonyl[25a] moiety and avoid some of the pitfalls of previous syntheses of aaptamine.[21f,25b] This approach revealed imino derivative **15** as a suitable advanced intermediate of **1a**. Structural simplification, achieved by replacing parts of the 1-azatriene components of **15** with a ketone and allylarene moiety, uncovered dihydroquinolin-4-one **16** as a primary synthetic subtarget.

Deepening the retrosynthetic analysis by disconnecting the C-4–C-4a bond, we unveiled β-amino acid derivative **17** as a suitable intermediate, which, in turn, should result from nitro derivative **18**. In the synthetic sense, this transformation should involve the reduction of the nitro moiety and alkylation of the resulting amine with a three-carbon chain.

The need of protecting groups as synthetic aids was also taken into account. Therefore, a nitrogen-protecting step was planned at an early stage, and deprotection was considered at a late phase to enable access to **16**[4a] and ease the handling of the synthetic intermediates. The final disconnections that involve the nitro moiety and the *ortho* ether motif exposed eugenol (**14**) as the recommended starting material.

According to the retrosynthetic analysis, we initiated the synthesis with the selective *ortho*-nitration of eugenol (Scheme 2). Of the various alternatives considered,[26] the most efficient one involved the treatment of natural product **14** with solid $NaNO_3$ and $KHSO_4$ in CH_2Cl_2 and the presence of wet (50 % w/w) silica,[26b] which efficiently provided **19** in 91 % yield after a quick filtration of the reaction mixture through a short pad of silica

gel. Long reaction times severely diminished the yields, presumably as a result of the polymerization of the product. A Williamson-type *O*-methylation of **19** by treatment with MeI and K_2CO_3 as the base in refluxing EtOH completed this phase and cleanly and quantitatively afforded the expected nitro derivative **18**.



Scheme 2. Reagents and conditions: (a) $NaNO_3$, $KHSO_4$, SiO_2/H_2O (50 % w/w), CH_2Cl_2, room temp., 5 h (91 %); (b) MeI, K_2CO_3, EtOH, reflux, overnight (100 %); (c) Fe^0, $CaCl_2$, EtOH/H_2O (10:1), reflux, 24 h (98 %); (d) $H_2C{=}CHCO_2Et$, AcOH (cat.), reflux, 24 h (65 %); (e) TsCl, EtN(*i*Pr)$_2$, DMAP (cat.), $CHCl_3$, reflux, 24 h (100 %); (f) (1) LiOH (1.3 M), EtOH/H_2O, reflux, overnight; (2) HCl, pH = 5 [**23** (37 %), **24** (23 %), **25** (up to 30 %)]; (g) (1) LiOH (0.64 M), EtOH/H_2O, room temp., 3 h; (2) HCl, pH = 5 (88 %); (h) polyphosphate ester (PPE), PhMe, room temp., 3 h (80 %).

To build heterocyclic ring **C** according to the Elderfield–Johnson sequence,[27] compound **18** was subjected to a selective reduction with iron powder in EtOH/H_2O (10:1) in the presence of $CaCl_2$,[28] which smoothly furnished amine **20** in 98 % yield. This was then heated in refluxing ethyl acrylate in the presence of a catalytic amount of AcOH to provide aza-Michael adduct **21** in 65 % yield. Unfortunately, despite the exploration of different alternatives, including the use of graphene oxide as a promoter as well as K_2CO_3 and β-cyclodextrins in aqueous media, no significant improvement to the yield could be achieved.[29]

The cyclization of **21** proved to be unsatisfactory, as it afforded several products,[30] which were probably the result of the insufficient activation of the carbonyl moiety. Therefore, in an effort to ease the manipulation of the polar synthetic intermediate and minimize the appearance of side products, secondary aniline **21** was protected, as planned, by treatment with TsCl (Ts = *p*-tolylsulfonyl) in chloroform and the employment of *N*,*N*-diisopropylethylamine (DIPEA) as a base. Under these conditions, the reaction to give the expected tosylamide was rather slow. However, the addition of 4-(*N*,*N*-dimethylamino)-pyridine (DMAP) as a catalyst strongly improved the performance of the sulfonamidation to furnish quantitative yields of **22** after 24 h.

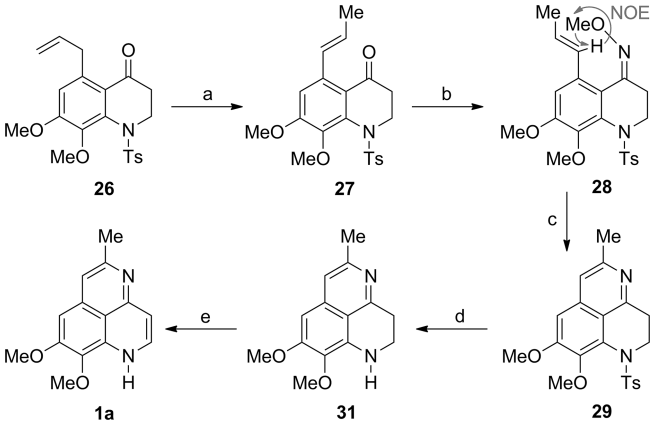
The basic hydrolysis of the ester moiety was next explored by using LiOH in an EtOH/H_2O solvent mixture. Employing previously optimized conditions (1.3 M LiOH in EtOH/H_2O, reflux overnight)[4a] afforded an inseparable mixture of carboxylic acids in combined 60 % yield. The ^{1}H NMR spectrum of the mixture revealed the presence of envisaged acid **23**, which accounted for 61 % of the acid product, accompanied by β-methylstyrene derivatives **24** (39 %), which resulted from the base-catalyzed isomerization of the allyl moiety, as a mixture of geometric isomers (*E*/*Z*, 4.8:1). In addition, considerable amounts of **25** (up to 30 %) were observed. Compound **25** corresponded to the retro-Michael product and exhibited chromatographic behavior similar to that of starting ester **22**, which complicated the assessment of the time of completion of the reaction.

Despite that compound **24** could be cyclized into the useful intermediate **27** and the presence of side products **24** and **25** could be decreased by lowering the amount of base and reducing the reaction temperature and time, the transformation was carried out with LiOH in EtOH/H_2O at a final concentration of 0.64 M at room temperature for 3 h. Under these conditions, the yield of the allyl derivative **23** improved to 88 % without the formation of β-methylstyrene **24**. Interestingly, a further decrease of the reaction temperature to 0 °C did not result in additional improvements (83 % yield). This efficient access to **23** set the stage for the projected cyclization.

It was anticipated that a Friedel–Crafts-type cyclization of the carboxylic acid onto the electron-rich arene moiety should take place with relative ease, despite steric hindrance from the allyl moiety attached at the *ortho* position to the ring-closing site. However, the likelihood of this substituent to engage in isomerization and polymerization reactions under acidic conditions imposed some limitations on the choice of the suitable cyclizing agent. Fortunately, treatment of **23** with PPE cleanly afforded cyclized product **26**. However, the use of freshly prepared reagent[31a,31b] was critical to achieve the best reaction performance and reach yields as high as 80 %.

Having secured an efficient route toward key intermediate **26**, we focused on the next task, working towards the construction of the 1-azatriene moiety, which was required to construct the remaining **B** ring. To that end, quinolin-4-one derivative **26** was exposed to freshly prepared $PdCl_2(MeCN)_2$[31c] in anhydrous 1,2-dichloroethane at reflux to uneventfully give the expected β-methylstyrene **27** in 91 % yield (Scheme 3), the (*E*) configuration of which was assigned by ^{1}H NMR analysis of the coupling constant between the vinylic protons (J = 15.7 Hz).

The submission of **26** to a reaction with methoxyamine hydrochloride in refluxing EtOH, to which NaOAc was added, afforded oxime **28**. Interestingly, model reactions revealed that the addition of catalytic amounts of $CeCl_3{\cdot}7H_2O$ greatly improved the performance of this transformation.[32] Therefore, it was not surprising that the addition of 10 % of the promoter afforded 76 % of methoxime **28** as a single isomer, to which the *syn* configuration was assigned by the reciprocal NOE enhancements for the signals of the methoxime methyl protons and the neighboring α-proton of the β-methylstyrene motif. Interestingly, H-2 and H-3, which appear as triplets at δ = 3.97 and 2.75 ppm (J = 6.4 Hz), respectively, for compound **27**, were

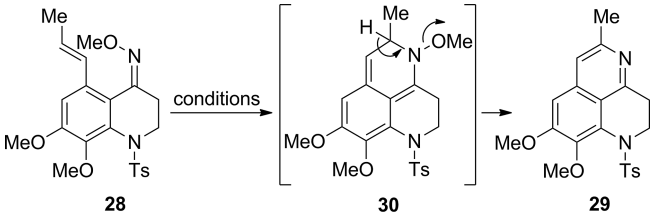


Scheme 3. Reagents and conditions: (a) $PdCl_2(MeCN)_2$, $ClCH_2CH_2Cl$, reflux, 18 h (91 %); (b) $H_2NOMe{\cdot}HCl$, NaOAc, $CeCl_3{\cdot}7H_2O$ (cat.), EtOH, reflux, overnight (76 %); (c) dimethylacetamide (DMA), microwave (MW) irradiation (140 °C), 20 min. (77 %); (d) sodium naphthalenide, 1,2-dimethoxyethane (DME), –78 °C (81 %); (e) 10 % Pd/C, *n*BuOH-PhMe, 160 °C, 48 h (85 %).

observed as broad signals at δ = 3.67 and 2.74 ppm, respectively, for compound **28**. Their mutual interactions were assessed by a total correlation spectroscopy (TOCSY) experiment, whereas the signal broadening was attributed to the vicinity of the nitrogen functionalities.

Access to the β-methylstyrene-methoxime **28** set the stage for the second cyclization, to complete the **B** ring of the target. As planned, this was performed by a 6π-electrocyclization reaction under microwaves irradiation, which presumably proceeds through intermediate **30**. However, the successful outcome required some optimization studies (Table 1). Initially, the reaction was carried out in 1,2-dichlorobenzene. Unexpectedly, a disappointing 15 % yield of **29** was obtained when the transformation was performed at 180 °C for 30 min (Table 1, Entry 1). Lowering the temperature to 160 °C for 20 min improved the yield to 50 % (Table 1, Entry 2). A further increase was observed when the reaction was performed at 140 °C (Table 1, Entry 3), but at 120 °C, the transformation required a longer time and a better yield was not obtained (Table 1, Entry 4).

Table 1. Optimization of the 6π-electrocyclization of **28** to **29**.



Entry	Solvent	Temp. [°C]	Time [min]	% Yield of **29**
1	$1,2\text{-}Cl_2C_6H_4$	180	30	15
2	$1,2\text{-}Cl_2C_6H_4$	160	20	50
3	$1,2\text{-}Cl_2C_6H_4$	140	20	62
4	$1,2\text{-}Cl_2C_6H_4$	120	45	20
5	$MeCONMe_2$	140	30	55
6	$MeCONMe_2$	140	20	77

Although the yield of the reaction at 140 °C in 1,2-dichlorobenzene could be considered satisfactory, further experiments were carried out with DMA as the solvent. Microwave irradiation of this reaction at 140 °C for 30 min afforded 55 % of **29** (Table 1, Entry 5), whereas heating for 20 min at the same temperature provided the sought-after tricycle **29** in 77 % yield (Table 1, Entry 6).

The acquisition of **29** prompted a study of the remaining transformations for ring **C**, which included a desulfonylation and the installation of the C-2–C-3 double bond. Initial attempts to effect both reactions in a single step by an oxidative desulfonylation and subsequent double-bond isomerization with KF/Al_2O_3 under microwave irradiation and solvent-free conditions (180 °C, 90 min.)[33a] were unsuccessful, and only unreacted starting material was recovered. The same outcome was observed when **29** was subjected to thermal heating in the presence of KF/Al_2O_3 (240 °C, 24 h). These results were attributed to the low acidity of the H-2 atom.[33b]

Therefore, a reductive detosylation approach was explored. Model detosylation reactions with low-valence titanium,[33c] activated magnesium powder in anhydrous MeOH,[33d] and sodium naphthalenide[33e] in ethereal solvents revealed the better suitability of the latter two reagents. However, when **29** was exposed to a 20-fold excess amount of activated Mg powder in anhydrous MeOH, no product could be isolated from the reaction mixture, despite the complete consumption of the starting material was indicated by TLC analysis after 20 h. Thus, the reaction of **29** with sodium naphthalenide in anhydrous DME at –78 °C was explored. As anticipated, these conditions cleanly furnished dihydroaaptamine analogue **31** in 81 % yield. Carrying out the reaction at low temperature, slowly adding the reducing agent, and using stoichiometric amounts of the latter ensured the best yields.

The final step, the dehydrogenation of **31**, was performed with 10 % Pd/C in toluene at reflux. To improve the solubility of the substrate, *n*-butanol was added as a co-solvent. Under these conditions, 5-methylaaptamine (**1a**) was obtained after 48 h in 85 % yield.

Conclusions

In summary, we have developed a practical and convenient approach towards the synthesis of 5-methylaaptamine (**1a**), an unnatural analogue of the 1*H*-benzo[*de*][1,6]naphthyridine alkaloid aaptamine (**1**). The synthesis was achieved in 12 steps and 14.9 % overall yield from naturally occurring eugenol (**14**) through the formation of 5-allyl-7,8-dimethoxyquinolin-2-one **26**. The sequence also featured the double-bond isomerization and methoximation of this key intermediate as well as an efficient microwave-assisted 6π-electrocyclization reaction of the 1-azatriene motif. A final reductive desulfonylation and Pd/C-mediated dehydrogenation reaction completed the synthesis. The double bond of the advanced intermediate is a useful starting point for the diversification of the C-5 side chain, which would enable the elaboration of the structure to give more complex compounds. Work in this direction is in progress, and the results will be disclosed in due course.

Experimental Section

General Methods: All the reactions were executed under anhydrous argon and employed oven-dried glassware and freshly distilled anhydrous solvents. Chlorinated solvents (1,2-$Cl_2C_6H_4$, 1,2-dichloroethane, and $CHCl_3$) were dried at reflux over P_2O_5 (4 h) followed by distillation at atmospheric pressure. Anhydrous CH_2Cl_2 was obtained by using an MBraun solvent purification and dispenser system. Anhydrous DMA was prepared by distillation from dry BaO. Toluene and DME were distilled from Na^0/benzophenone ketyl. Absolute EtOH was prepared by treatment with clean magnesium turnings and iodine and subsequent distillation from the resulting magnesium ethoxide. Anhydrous solvents were transferred by cannula and stored in dry Young ampoules that contained molecular sieves. All other reagents were used as received. The progress of the reactions was monitored by TLC analysis (silica gel 60 GF_{254}; various mixtures of hexane/EtOAc and EtOAc/EtOH). The chromatographic spots were visualized by exposure to UV light (254 nm) and spraying with 1 % methanolic $FeCl_3$, Dragendorff reagent (Munier and Macheboeuf modification),[34] ethanolic *p*-anisaldehyde/sulfuric acid reagent, or 1 % ethanolic ninhydrin followed by careful heating to improve selectivity. For the conventional workup procedure, the reaction mixture was diluted with brine, and the products were extracted with EtOAc. The combined organic extracts were then washed with brine (1×), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 60 H, particle size: 63–200 μm; polarity gradient with hexane/EtOAc and EtOAc/EtOH mixtures) under the positive pressure of N_2. Melting points were measured on an Ernst Leitz Wetzlar model 350 hot-stage microscope. FTIR spectra were recorded on a Shimadzu Prestige 21 spectrophotometer as solid dispersions in KBr disks for solid samples or as thin films held between NaCl cells for oily samples. The NMR spectroscopic data were recorded in $CDCl_3$, unless otherwise noted, with an FT-NMR Bruker Avance 300 spectrometer at 300.13 MHz (for ^1H NMR) and 75.48 MHz (^{13}C NMR). Chemical shifts are reported in parts per million on the δ scale, and TMS was used as the internal standard (for ^1H NMR, $CHCl_3$: δ = 7.26 ppm and for ^{13}C NMR $CDCl_3$: δ = 77.0 ppm). The magnitude of the coupling constants (*J*) and half-width ($w_{1/2}$) values are given in Hertz. In special cases, NOE and 2D NMR experiments [COSY, heteronuclear single quantum correlation (HSQC) spectroscopy, TOCSY, and HMBC spectroscopy) were also employed. Pairs of signals marked with an asterisk (*) indicate that the assignments may be exchanged. GC–MS experiments were performed with a Shimadzu QP2010 Plus instrument equipped with an AOC-20i autosampler, and high resolution mass spectra were obtained with a Bruker MicroTOF-Q II instrument (Bruker Daltonics, Billerica, MA). Detection of the ions was performed by electrospray ionization in the positive ion mode. Microwave-assisted reactions were carried out in a CEM Discover microwave oven.

4-Allyl-2-methoxy-6-nitrophenol (6-Nitroeugenol, 19):[26a] Eugenol (2.5 mL, 16.25 mmol) was added dropwise to a vigorously stirred mixture of potassium bisulfate (7.95 g, 58.5 mmol), sodium nitrate (5.33 g, 62.7 mmol), and wet silica gel (50 % w/w, 6.174 g) suspended in CH_2Cl_2 (50 mL). The reaction mixture was stirred at room temperature until TLC analysis (hexanes/EtOAc, 80:20) confirmed the complete consumption of the starting material (approximately 1.5 h). Then, the slurry that contained the crude reaction mixture was poured onto the top of a silica gel column (hexanes/EtOAc mixtures) to afford **19** (3.09 g, 91 %) as a yellow oil. IR (film): $\tilde{\nu}$ = 764, 920, 1063, 1136, 1263, 1331, 1393, 1547, 2853, 2924, 3050–3670 cm^{-1}. ^1H NMR: δ = 10.67 (s, 1 H, Ar-O*H*), 7.52 (s, 1 H, 5-H), 6.96 (s, 1 H, 3-H), 5.92 (ddt, *J* = 16.9, 10.5, and 6.7 Hz, 1 H, CH_2=C*H*CH_2Ar), 5.26–4.96 (m, 2 H, CH_2=CHCH_2Ar), 3.94 (s, 3 H, OCH_3-2), 3.36 (d, *J* = 6.7 Hz, 2 H, CH_2=CHCH_2Ar) ppm. ^{13}C NMR: δ = 149.9 (C-2), 144.9 (C-1), 135.9 (CH_2=*C*HCH_2Ar), 133.6 (C-6), 131.2 (C-4), 118.6 (C-3), 117.2 (*C*H_2=CHCH_2Ar), 115.1 (C-5), 56.7 (OCH_3-2), 39.4 (CH_2=C*H*CH_2Ar) ppm.

5-Allyl-1,2-dimethoxy-3-nitrobenzene (18):[26d] A mixture of 6-nitroeugenol (3.00 g, 14.34 mmol) and K_2CO_3 (7.93 g, 57.4 mmol) in absolute EtOH (150 mL) was stirred for 5 min under argon. MeI (3.57 mL, 57.4 mmol) was then added, and the resulting suspension was heated at reflux overnight. The solids were removed by filtration, and the filter cake was washed with EtOH (2 × 10 mL). The combined filtrates were evaporated under reduced pressure, and the residue was dissolved in EtOAc (50 mL). The resulting solution was washed sequentially with a NaOH (2 M solution, 5 mL) and brine (2 × 10 mL). Finally, the organic layer was dried with Na_2SO_4, and the solvent was removed in vacuo to afford **18** (3.20 g, 100 %) as an orange oil. IR (film): $\tilde{\nu}$ = 775, 920, 997, 1065, 1144, 1279, 1362, 1462, 1537, 2849, 2939 cm^{-1}. ^1H NMR: δ = 7.14 (d, *J* = 1.9 Hz, 1 H, 4-H), 6.92 (d, *J* = 1.9 Hz, 1 H, 6-H), 5.91 (ddt, *J* = 17.1, 10.5, and 6.7 Hz, 1 H, CH_2=C*H*CH_2Ar), 5.19–5.03 (m, 2 H, CH_2=CHCH_2Ar), 3.94 (s, 3 H, OCH_3-2), 3.90 (s, 3 H, OCH_3-1), 3.37 (d, *J* = 6.7 Hz, 2 H, CH_2=CHCH_2Ar) ppm. ^{13}C NMR: δ = 153.9 (C-1), 144.7 (C-3), 141.1 (C-2), 136.3 (C-5), 135.7 (CH_2=*C*HCH_2Ar), 117.2 (*C*H_2=CHCH_2Ar), 116.4 (C-6), 115.6 (C-4), 61.9 (OCH_3-2), 56.4 (OCH_3-1), 39.6 (CH_2=C*H*CH_2Ar) ppm.

5-Allyl-2,3-dimethoxyphenylamine (20): $CaCl_2$ (2.22 g, 20 mmol), clean iron powder (3.35 g, 60 mmol), and H_2O (2 mL) were successively added to a solution of **18** (850 mg, 3.81 mmol) in EtOH (20 mL), and the reaction mixture was stirred at reflux for 24 h. The suspension was then filtered through Celite, and the filter cake was washed with EtOH (20 mL). After the concentration of the combined filtrates, the residue was redissolved in EtOAc (50 mL), and the resulting solution was successively washed with a NaOH (2 M solution, 10 mL) and brine (10 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered, and the solvent was removed under vacuum. The residue was purified by silica gel column chromatography to afford **20** (722 mg, 98 %) as a reddish brown oil. IR (film): $\tilde{\nu}$ = 3464, 3371, 2931, 1614, 1593, 1504, 1454, 1352, 1230, 1134, 1072, 1002 cm^{-1}. ^1H NMR: δ = 6.23 (d, *J* = 1.9 Hz, 1 H, 6-H), 6.17 (d, *J* = 1.9 Hz, 1 H, 4-H), 5.94 (ddt, *J* = 16.9, 10.0, 6.8 Hz, 1 H, CH_2=C*H*CH_2Ar), 5.18–4.99 (m, 2 H, CH_2=CHCH_2Ar), 3.82 (br. s, 2 H, NH_2), 3.83 (s, 3 H, OCH_3-3), 3.80 (s, 3 H, OCH_3-2), 3.25 (d, *J* = 6.8 Hz, 2 H, CH_2=CHCH_2Ar) ppm. ^{13}C NMR: δ = 152.7 (C-3), 140.9 (C-1), 137.4 (CH_2=*C*HCH_2Ar), 136.2 (C-5), 134.1 (C-2), 115.6 (*C*H_2=CHCH_2Ar), 108.7 (C-6), 102.6 (C-4), 59.8 (OCH_3-2), 55.6 (OCH_3-3), 40.2 (CH_2=CH*C*H_2Ar) ppm. HRMS: calcd. for $C_{11}H_{16}NO_2$ $[M + H]^+$ 194.1181; found 194.1176.

Ethyl 3-(5-Allyl-2,3-dimethoxyphenylamino)propionate (21): Glacial AcOH (0.11 mL) was added to a stirred and degassed solution of **20** (260 mg, 1.35 mmol) in excess amount of neat ethyl acrylate (4.3 mL), and the mixture was heated at reflux for 24 h. The volatiles were then carefully evaporated, and the residue was purified by flash column chromatography to give β-amino ester **21** (258 mg, 65 %) as a yellowish oil. IR (film): $\tilde{\nu}$ = 3400, 2960, 2929, 1732, 1593, 1454, 1371, 1249, 1139 cm^{-1}. ^1H NMR: δ = 6.16 (s, 2 H, 4-H and 6-H), 5.96 (ddt, *J* = 16.8, 10.0 and 6.7 Hz, 1 H, CH_2=C*H*CH_2Ar), 5.15–5.01 (m, 2 H, CH_2=CHCH_2Ar), 4.56 (br. s, $w_{1/2}$ = 9.6 Hz, 1 H, NH), 4.15 (q, *J* = 7.1 Hz, 2 H, O*C*$H_2$$CH_3$), 3.82 (s, 3 H, OCH_3-3), 3.75 (s, 3 H, OCH_3-2), 3.46 (t, *J* = 6.5 Hz, 2 H, C$H_2$$CH_2CO_2Et$), 3.29 (d, *J* = 6.7 Hz, 2 H, CH_2=CHCH_2Ar), 2.60 (t, *J* = 6.5 Hz, 2 H, CH_2CH_2CO_2Et), 1.26 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR: δ = 172.2 (C=O), 152.3 (C-3), 141.4 (C-1), 137.6 (CH_2=CHCH_2Ar), 136.4 (C-5), 133.9 (C-2), 115.6 (*C*H_2=CHCH_2Ar), 104.3 (C-6), 101.7 (C-4), 60.6

(OCH_2CH_3), 59.8 (OCH_3-2), 55.7 (OCH_3-3), 40.7 (CH_2=$CHCH_2Ar$), 39.3 ($CH_2CH_2CO_2Et$), 34.3 ($CH_2CH_2CO_2Et$), 14.2 (OCH_2CH_3) ppm. HRMS: calcd. for $C_{16}H_{23}NNaO_4$ $[M + Na]^+$ 316.1519; found 316.1519.

Ethyl 3-[(5-Allyl-2,3-dimethoxyphenyl)-(4-tolylsulfonyl)amino]-propionate (22): DIPEA (0.22 mL, 1.28 mmol), tosyl chloride (218 mg, 1.11 mmol), and DMAP (2 mg) were successively added to a stirred solution of **21** (258 mg, 0.88 mmol) in anhydrous $CHCl_3$ (4 mL), and the mixture was kept at 0 °C in an ice water bath. The cooling bath was removed, and when the reaction reached room temperature, it was heated at reflux for 24 h. The solvent was then removed under reduced pressure, and the oily residue was purified by chromatography to give **22** (393 mg, 100 %) as an oil. IR (film): $\tilde{\nu}$ = 2978, 2943, 1732, 1581, 1494, 1348, 1161 cm^{-1}. ^1H NMR: δ = 7.68 (d, J = 8.2 Hz, 2 H, 2-ArH and 6-ArH of Ts), 7.27 (d, J = 8.2 Hz, 2 H, 3-ArH and 5-ArH of Ts), 6.70 (d, J = 1.9 Hz, 1 H, 4-H), 6.38 (d, J = 1.9 Hz, 1 H, 6-H), 5.86 (ddt, J = 17.0, 10.5, and 6.7 Hz, 1 H, CH_2=$CHCH_2Ar$), 5.16–4.93 (m, 2 H, CH_2=$CHCH_2Ar$), 4.01 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 3.82 (t, J = 7.6 Hz, 2 H, $CH_2CH_2CO_2Et$), 3.83 (s, 3 H, OCH_3-3), 3.71 (s, 3 H, OCH_3-2), 3.24 (d, J = 6.7 Hz, 2 H, CH_2=$CHCH_2Ar$), 2.54 (t, J = 7.6 Hz, 2 H, CH_2CH_2COOEt), 2.42 (s, 3 H, $ArCH_3$ of Ts), 1.17 (t, J = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR: δ = 171.2 (C=O), 153.2 (C-3), 145.7 (C-2), 143.2 (TsC-4), 137.3 (TsC-1), 136.7 (CH_2=$CHCH_2Ar$), 135.0 (C-5), 131.6 (C-1), 129.4 (2 C, TsC-3 and TsC-5), 127.7 (2 C, TsC-2 and TsC-6), 122.4 (C-6), 116.2 (CH_2=$CHCH_2Ar$), 113.2 (C-4), 60.6 (OCH_3-2), 60.4 (OCH_2CH_3), 55.9 (OCH_3-3), 46.8 (CH_2CH_2COOEt), 39.7 (CH_2=$CHCH_2Ar$), 33.9 (CH_2CH_2COOEt), 21.5 ($ArCH_3$ of Ts), 14.1 (OCH_2CH_3) ppm. HRMS: calcd. for $C_{23}H_{29}NNaSO_6$ $[M + Na]^+$ 470.1608; found 470.1606.

3-[(5-Allyl-2,3-dimethoxyphenyl)-(4-tolylsulfonyl)amino]propionic Acid (23): LiOH (10 % solution, 2 mL) was added to a stirred suspension of ester **22** (230 mg, 0.51 mmol) in EtOH/H_2O (3:1, 11 mL). The reaction mixture was stirred at room temperature for 3 h, and then it was acidified to pH = 5 to 6 by the addition of HCl (1 M). The EtOH was evaporated, and the remaining aqueous suspension was extracted with EtOAc (4 × 10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to give 5-allyl-2,3-dimethoxy-(4-tolylsulfonyl)phenylamine (**25**, 18 mg, 10 %) as a white solid, and a further increase in the solvent polarity afforded carboxylic acid **23** (190 mg, 88 %) as a pale yellow oil. Data for **25**: M.p. 134–135 °C (hexanes/EtOAc). IR (KBr): $\tilde{\nu}$ = 704, 995, 1088, 1169, 1337, 1385, 1429, 1504, 1591, 2837, 2926, 3240 cm^{-1}. ^1H NMR: δ = 7.68 (d, J = 8.2 Hz, 2 H, 2-ArH and 6-ArH of Ts), 7.20 (d, J = 8.2 Hz, 2 H, 3-ArH and 5-ArH of Ts), 7.12 (s, 1 H, NH), 7.05 (d, J = 1.6 Hz, 1 H, 6-H), 6.43 (d, J = 1.6 Hz, 1 H, 4-H), 5.90 (ddt, J = 16.8, 10.2, and 6.6 Hz, 1 H, CH_2=$CHCH_2Ar$), 5.18–4.90 (m, 2 H, CH_2=$CHCH_2Ar$), 3.77 (s, 3 H, OCH_3-3), 3.53 (s, 3 H, OCH_3-2), 3.29 (d, J = 6.6 Hz, 2 H, CH_2=$CHCH_2Ar$), 2.35 (s, 3 H, $ArCH_3$ of Ts) ppm. ^{13}C NMR: δ = 151.9 (C-3), 143.8 (TsC-4), 136.9 (CH_2=$CHCH_2Ar$), 136.5 (OCH_3-2), 136.3 (TsC-1),* 136.1 (C-5),* 130.4 (C-1), 129.5 (2 C, TsC-3 and TsC-5), 127.2 (2 C, TsC-2 and TsC-6), 116.1 (CH_2=$CHCH_2Ar$), 112.0 (C-6), 108.5 (C-4), 60.7 (OCH_3-2), 55.7 (OCH_3-3), 40.2 (CH_2=$CHCH_2Ar$), 21.5 ($ArCH_3$ of Ts) ppm. HRMS: calcd. for $C_{18}H_{21}NNaSO_4$ $[M + Na]^+$ 370.1084; found 370.1080. Data for **23**: IR (film): $\tilde{\nu}$ = 3700–2300, 2945, 1713, 1495, 1346, 1240, 1161, 1128 cm^{-1}. ^1H NMR: δ = 7.67 (d, J = 8.2 Hz, 2 H, 2-ArH and 6-ArH of Ts), 7.27 (d, J = 8.2 Hz, 2 H, 3-ArH and 5-ArH of Ts), 6.71 (d, J = 1.7 Hz, 1 H, 4-H), 6.36 (d, J = 1.7 Hz, 1 H, 6-H), 5.85 (ddt, J = 16.9, 10.4, and 6.7 Hz, 1 H, CH_2=$CHCH_2Ar$), 5.15–4.89 (m, 2 H, CH_2=$CHCH_2Ar$), 3.83 (s, 3 H, OCH_3-3), 3.80 (t, J = 7.5 Hz, 2 H, CH_2CH_2COOH), 3.72 (s, 3 H, OCH_3-2), 3.24 (d, J = 6.7 Hz, 2 H, CH_2=$CHCH_2Ar$), 2.59 (t, J = 7.5 Hz, 2 H, CH_2CH_2COOH), 2.42 (s, 3 H, $ArCH_3$ of Ts) ppm. ^{13}C NMR: δ = 176.5 (C=O), 153.2 (C-3), 145.7 (C-2), 143.3 (TsC-4), 137.0 (TsC-1), 136.6 (CH_2=$CHCH_2Ar$), 135.2 (C-5), 131.5 (C-1), 129.4 (2 C, TsC-3 and TsC-5), 127.8 (2 C, TsC-2 and TsC-6), 122.2 (C-6), 116.3 (CH_2=$CHCH_2Ar$), 113.3 (C-4), 60.8 (OCH_3-2), 55.9 (OCH_3-3), 46.6 (CH_2CH_2COOH), 39.6 (CH_2=$CHCH_2Ar$), 33.6 (CH_2CH_2COOH), 21.5 ($ArCH_3$ of Ts) ppm. HRMS: calcd. for $C_{21}H_{25}NNaSO_6$ $[M + Na]^+$ 442.1295; found 442.1285.

Preparation of Polyphosphate Ester (PPE):[31b] P_2O_5 (15 g) was added in one portion to a 2:1 mixture of anhydrous Et_2O (30 mL) and anhydrous ethanol-free $CHCl_3$ (15 mL), and the suspension was vigorously stirred at reflux for 4 d. The resulting mixture was then concentrated by using a rotary evaporator, and the polyphosphate ester was separated from the remaining volatiles under vacuum for 24 h. The residue was used without further treatment.

5-Allyl-7,8-dimethoxy-1-(4-tolylsulfonyl)-2,3-dihydro-1*H*-quinolin-4-one (26): PPE (750 mg) was added to a stirred solution of acid **23** (73 mg, 0.17 mmol) in toluene (4.5 mL), and the reaction mixture was stirred at room temperature for 3 h. Then, crushed ice was added, and the mixture was extracted with EtOAc (4 × 20 mL). The combined organic phases were dried with Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to afford quinolone **26** (56 mg, 80 %), as a white solid; m.p. 158–160 °C (hexanes/EtOAc). IR (KBr): $\tilde{\nu}$ 2916, 1678, 1589, 1558, 1333, 1263, 1151, 764 cm^{-1}. ^1H NMR: δ = 7.82 (d, J = 8.2 Hz, 2 H, 2-ArH and 6-ArH of Ts), 7.30 (d, J = 8.2 Hz, 2 H, 3-ArH and 5-ArH of Ts), 6.72 (s, 1 H, 6-H), 5.98 (ddt, J = 16.3, 13.2, and 6.5 Hz, 1 H, CH_2=$CHCH_2Ar$), 5.14–4.99 (m, 2 H, CH_2=$CHCH_2Ar$), 3.98 (t, J = 6.3 Hz, 2 H, 2-H), 3.92 (s, 3 H, OCH_3-7), 3.77 (d, J = 6.5 Hz, 2 H, CH_2=$CHCH_2Ar$), 3.51 (s, 3 H, OCH_3-8), 2.76 (t, J = 6.3 Hz, 2 H, 3-H), 2.44 (s, 3 H, $ArCH_3$ of Ts) ppm. ^{13}C NMR: δ = 193.8 (C-4), 156.7 (C-7), 143.6 (TsC-4), 142.3 (C-8), 139.9 (C-4a), 138.1 (TsC-1), 137.2 (C-8a), 137.0 (CH_2=$CHCH_2Ar$), 129.5 (2 C, TsC-3 and TsC-5), 127.4 (2 C, TsC-2 and TsC-6), 121.3 (C-5), 115.9 (CH_2=$CHCH_2Ar$), 113.0 (C-6), 60.2 (OCH_3-8), 55.9 (OCH_3-7), 46.5 (C-2), 40.1 (C-3), 39.0 (CH_2=$CHCH_2Ar$), 21.6 ($ArCH_3$ of Ts) ppm. HRMS: calcd. for $C_{21}H_{23}NNaSO_5$ $[M + Na]^+$ 424.1189; found 424.1180.

Preparation of $PdCl_2(MeCN)_2$:[31c] A suspension of $PdCl_2$ (100 mg, 0.56 mmol) in MeCN (5 mL) was stirred at room temperature for 2 d. The resulting solid was removed by filtered, washed with Et_2O, and dried under vacuum. Recrystallization (MeCN/CH_2Cl_2/hexane, 2:3:1 v/v/v) furnished the catalyst as a yellow-orange solid.

7,8-Dimethoxy-5-propenyl-1-(4-tolylsulfonyl)-2,3-dihydro-1*H*-quinolin-4-one (27): A stirred solution of 2,3-dihydro-1*H*-quinolone **26** (265 mg, 0.66 mmol) in anhydrous 1,2-dichloroethane (20 mL) was treated with freshly prepared $PdCl_2(MeCN)_2$ (18 mg, 0.07 mmol). The resulting solution was heated at reflux for 18 h, the time for complete consumption of the starting material as confirmed by ^1H NMR analysis of an aliquot of the reaction mixture. Then, crushed ice was added, and the mixture was extracted with EtOAc (4 × 20 mL). The combined organic phases were dried with Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to provide **27** (241 mg, 91 %) as a white solid; m.p. 178–180 °C (hexanes/EtOAc). IR (KBr): $\tilde{\nu}$ 2918, 2851, 1670, 1585, 1545, 1458, 1364, 1340, 1257, 1153, 1007, 758 cm^{-1}. ^1H NMR: δ = 7.83 (d, J = 8.2 Hz, 2 H, 2-ArH and 6-ArH of Ts), 7.30 (d, J = 8.2 Hz, 2 H, 3-ArH and 5-ArH of Ts), 7.22 (d, J = 15.7 Hz, 1 H, CH_3CH=$CHAr$), 6.88 (s, 1 H, 6-H), 6.05 (dq, J = 15.7 and 6.7 Hz, 1 H, CH_3CH=$CHAr$), 3.97 (t, J = 6.4 Hz, 2 H, 2-H), 3.93 (s, 3 H, OCH_3-7), 3.51 (s, 3 H, OCH_3-8), 2.75 (t, J = 6.4 Hz, 2 H, 3-H), 2.43 (s, 3 H, $ArCH_3$ of Ts), 1.91 (dd, J = 6.7 and 1.4 Hz, 3 H, CH_3CH=$CHAr$) ppm. ^{13}C NMR: δ = 194.1 (C-4), 156.7 (C-7), 143.6 (TsC-4), 142.8 (C-8), 138.1 (TsC-1), 137.7 (C-4a), 136.6 (C-8a), 130.9 (CH_3CH=$CHAr$), 129.5 (2 C, TsC-3 and TsC-5), 128.7 (CH_3CH=$CHAr$), 127.3 (2 C, TsC-2 and TsC-6), 120.2 (C-5), 109.8 (C-6), 60.2 (OCH_3-8),

55.9 (OCH_3-7), 46.4 (C-2), 40.0 (C-3), 21.6 (ArCH_3 of Ts), 18.7 (CH_3CH=CHAr) ppm. HRMS: calcd. for $C_{21}H_{23}NNaO_5S$ [M + Na]$^+$ 424.1189; found 424.1183.

7,8-Dimethoxy-5-propenyl-1-(4-tolylsulfonyl)-2,3-dihydro-1*H*-quinolin-4-one *O*-Methyloxime (28): *O*-Methylhydroxylamine hydrochloride (346 mg, 4.15 mmol), NaOAc (340 mg, 4.15 mmol), and $CeCl_3 \cdot 7H_2O$ (23 mg, 0.062 mmol) were successively added to a stirred solution of **27** (250 mg, 0.62 mmol) in EtOH (5 mL), and the mixture was heated at reflux overnight. Then, the solvent was evaporated, and the remaining solid was purified by chromatography to yield **28** (204 mg, 76 %) as a white solid; m.p. 142–144 °C (hexanes/EtOAc). IR (KBr): $\tilde{\nu}$ 2934, 1595, 1493, 1340, 1157, 1047, 758 cm^{-1}. ^{1}H NMR: δ = 7.77 (d, J = 8.1 Hz, 2 H, 2-ArH and 6-ArH of Ts), 7.25 (d, J = 8.1 Hz, 2 H, 3-ArH and 5-ArH of Ts), 6.98 (d, J = 15.7 Hz, 1 H, CH_3CH=C*H*Ar), 6.97 (s, 1 H, 6-H), 6.04 (dq, J = 15.7 and 6.7 Hz, 1 H, CH_3*CH*=CHAr), 3.91 (s, 3 H, OCH_3-7), 3.87 (s, 3 H, ArNOC*H*$_3$), 3.68 (s, 3 H, OCH_3-8), 3.67 (br. s, $w_{1/2}$ = 41.1, 2 H, 2-H), 2.74 (br. s, $w_{1/2}$ = 22.7 Hz, 2 H, 3-H), 2.42 (s, 3 H, ArCH_3 of Ts), 1.87 (dd, J = 6.7 and 1.4 Hz, 3 H, C*H*$_3$CH=CHAr) ppm. ^{13}C NMR: δ = 153.3 (C-7), 150.1 (C-4), 143.8 (C-8), 143.1 (TsC-4), 138.2 (TsC-1), 133.2 (C-8a),* 132.9 (C-4a),* 131.1 (CH_3CH=*C*HAr), 129.4 (2 C, TsC-3 and TsC-5), 127.5 (2 C, TsC-2 and TsC-6), 125.8 (CH_3*C*H=CHAr), 119.5 (C-5), 109.8 (C-6), 61.9 (ArNO*C*H$_3$), 60.4 (OCH_3-8), 55.9 (OCH_3-7), 44.8 (C-2), 27.5 (C-3), 21.5 (ArCH_3 of Ts), 18.4 (CH_3CH=CHAr) ppm. HRMS: calcd. for $C_{22}H_{26}N_2NaO_5S$ [M + Na]$^+$ 453.1455; found 453.1447.

8,9-Dimethoxy-5-methyl-1-(4-tolylsulfonyl)-2,3-dihydro-1*H*-1,4-diazaphenalene (29): A degassed solution of **28** (14 mg, 0.03 mmol) in DMA (3 mL) was placed in a microwave oven and irradiated at 140 °C for 20 min. Then, the solvent was removed under vacuum, and the solid residue was purified by chromatography to give **29** (10 mg, 77 %) as a yellowish green solid; m.p. 174–176 °C (EtOAc/EtOH). IR (KBr): $\tilde{\nu}$ 2949, 1624, 1578, 1489, 1404, 1339, 1252, 1157, 769, 658 cm^{-1}. ^{1}H NMR: δ = 7.85 (d, J = 8.5 Hz, 2 H, 2-ArH and 6-ArH of Ts), 7.28 (d, J = 8.5 Hz, 2 H, 3-ArH and 5-ArH of Ts), 7.22 (s, 1 H, 6-H), 6.88 (s, 1 H, 7-H), 4.09 (t, J = 5.8 Hz, 2 H, 2-H), 3.97 (s, 3 H, OCH_3-8), 3.54 (s, 3 H, OCH_3-9), 3.31 (t, J = 5.8 Hz, 2 H, 3-H), 2.60 (s, 3 H, Ar*CH*$_3$-5), 2.42 (s, 3 H, ArCH_3 of Ts) ppm. ^{13}C NMR: δ = 156.5 (C-8), 153.5 (C-3a), 150.7 (C-5), 143.3 (TsC-4), 143.0 (C-9), 138.7 (TsC-1), 134.3 (C-6a), 129.3 (2 C, TsC-3 and TsC-5), 127.2 (C-9a), 127.1 (2 C, TsC-2 and TsC-6), 116.1 (C-6), 115.4 (C-6b), 102.8 (C-7), 60.3 (OCH_3-9), 55.9 (OCH_3-8), 47.2 (C-2), 32.9 (C-3), 24.0 (Ar*CH*$_3$-5), 21.5 (ArCH_3 of Ts) ppm. HRMS: calcd. for $C_{21}H_{23}N_2O_4S$ [M + H]$^+$ 399.1373; found 399.1369.

Preparation of Sodium Naphthalenide:[33e] Sodium (120 mg, 5.2 mmol) and sublimated naphthalene (0.72 g, 5.5 mmol) were successively added to DME (5 mL) under argon, and the mixture was stirred at room temperature for 2 h to afford a dark green solution, which was used without further treatment.

8,9-Dimethoxy-5-methyl-2,3-dihydro-1*H*-1,4-diazaphenalene (31): A vigorously stirred solution of the *N*-tosyl derivative **29** (32 mg, 0.08 mmol) in DME (1 mL) was cooled to –78 °C and treated dropwise with a freshly prepared solution of sodium naphthalenide until the dark green color of the reagent persisted for 5 min. The reaction was quenched with water (1–3 drops), and the reaction was left at –78 °C until the dark green color disappeared. The resulting suspension was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography to afford **31** (16 mg, 81 %) as a yellowish oil. IR (film): $\tilde{\nu}$ = 3600–3040, 2934, 2849, 1626, 1574, 1504, 1387, 1144, 1034 cm^{-1}. ^{1}H NMR: δ = 7.11 (s, 1 H, 6-H), 6.41 (s, 1 H, 7-H), 4.16 (br. s, $w_{1/2}$ = 35.1 Hz, 1 H, NH), 3.95 (s, 3 H, OCH_3-8), 3.84 (s, 3 H, OCH_3-9), 3.60 (t, J = 6.3 Hz, 2 H, 2-H), 3.27 (t, J = 6.3 Hz, 2 H, 3-H), 2.58 (s, 3 H, Ar*CH*$_3$-5) ppm. ^{13}C NMR: δ = 156.6 (C-8), 154.9 (C-3a), 149.9 (C-5), 138.4 (C-9a), 135.1 (C-6a), 131.2 (C-9), 115.8 (C-6), 111.4 (C-6b), 93.8 (C-7), 60.3 (OCH_3-9), 55.6 (OCH_3-8), 41.5 (C-2), 32.4 (C-3), 23.8 (Ar*CH*$_3$-5) ppm. HRMS: calcd. for $C_{14}H_{17}N_2O_2$ [M + H]$^+$ 245.1285; found 245.1293.

8,9-Dimethoxy-5-methyl-1*H*-1,4-diazaphenalene (5-Methyl-aaptamine, 1a): Pd/C (20 mol-% Pd, 14 mg) was added to a stirred solution of **31** (15 mg, 0.06 mmol) in toluene/*n*-butanol (3:1, 1.1 mL). The mixture was heated at 160 °C for 48 h under argon until the starting materials was completely consumed, as confirmed by TLC analysis. After cooling to room temperature, the solids were removed by filtration through a short pad of Celite, and the crude product was purified by column chromatography to give **1a** (12.7 mg, 85 %) as a clear oil. IR (film): $\tilde{\nu}$ = 3700–3100, 2920, 2851, 1643, 1634, 1557, 1470, 1393, 1248, 1121, 1040 cm^{-1}. ^{1}H NMR ([D$_4$]MeOH): 7.75 (d, J = 7.1 Hz, 1 H, 2-H), 6.92 (s, 1 H, 7-H), 6.64 (s, 1 H, 6-H), 6.32 (d, J = 7.1 Hz, 1 H, 3-H), 4.02 (s, 3 H, OCH_3-8), 3.90 (s, 3 H, OCH_3-9), 2.31 (s, 3 H, Ar*CH*$_3$-5) ppm. ^{13}C NMR ([D$_4$]MeOH): 159.1 (C-8), 151.9 (C-3a), 142.4 (C-2), 140.8 (C-5), 135.1 (C-9a and C-6a), 132.7 (C-9), 116.7 (C-6b), 112.3 (C-6), 101.3 (C-7), 98.9 (C-3), 61.2 (OCH_3-9), 56.9 (OCH_3-8), 18.9 (Ar*CH*$_3$-5) ppm. HRMS: calcd. for $C_{14}H_{15}N_2O_2$ [M + H]$^+$ 243.1128; found 243.1137.

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