



Published in final edited form as:

J Org Chem. 2008 December 5; 73(23): 9379–9387. doi:10.1021/jo802165k.

Concise Stereocontrolled Formal Synthesis of (±)-Quinine and Total Synthesis of (±)-7-Hydroxyquinine via Merged Morita-Baylis-Hillman-Tsuji-Trost Cyclization

Peter Webber and Michael J. Krische*

University of Texas at Austin, Department of Chemistry and Biochemistry, Austin, TX 78712, USA

Abstract

Concise stereoselective syntheses of (±)-quinine and (±)-7-hydroxyquinine are achieved using a catalytic enone cycloallylation that combines the nucleophilic features of the Morita-Baylis-Hillman reaction and the electrophilic features of the Tsuji-Trost reaction. Cyclization of enone-allyl carbonate **11** delivers the product of cycloallylation **13** in 68% yield. Diastereoselective conjugate reduction of the enone **13** (>20:1 dr) followed by exchange of *N*-protecting groups provides the saturated *N*-Boc-protected methyl ketone **19**, which upon aldol dehydration provides quinoline containing enone **15**, possessing all carbon atoms of quinine. Exposure of ketone **15** to L-selectride enables diastereoselective carbonyl reduction (>20:1 dr) to furnish the allylic alcohol **16**. Stereoselective hydroxyl-directed epoxidation using an oxovanadium catalyst modified by *N*-hydroxy-*N*-Me-pivalamide delivers epoxide **17** (17:1 dr). Cyclization of the resulting amine-epoxide **17** provides (±)-7-hydroxyquinine in 13 steps and 11% overall yield from aminoacetaldehyde diethyl acetal. Notably, highly stereoselective formation of five contiguous stereocenters is achieved through a series of 1,2-asymmetric induction events. A formal synthesis of (±)-quinine is achieved upon deoxygenation of the *N*-Cbz-protected allylic acetate **22** to provide olefin **23**, which previously has been converted to quinine. Thus, (±)-quinine is accessible in 16 steps and 4% overall yield from commercial aminoacetaldehyde diethyl acetal, making this route the most concise approach to quinine, to date.

Introduction

Over three centuries ago, Jesuit monks found the essence of cinchona bark to be a powerful therapeutic agent in the treatment of malaria,¹ which remains the foremost cause of death among human beings since recorded history.² Nearly two centuries have elapsed since the active constituent of cinchona bark, quinine **1**, was isolated in 1820 by Pelletier and Caventou.³ The proper connectivity of quinine was proposed in 1908 by Rabe, who in 1918 reconstructed quinine *via* degradation, thereby establishing the veracity of his structural assignment.⁴ The first total synthesis of quinine was reported by Woodward in 1944.⁵ A “formal total synthesis,” Woodward’s approach is based on the interception of quinotoxine, a compound that was converted to quinine in three manipulations by Rabe.⁴ Recently, Williams and coworkers validated the three-step “Rabe protocol” for the conversion of quinotoxine **2** to quinine **1**,⁶ and in doing so ended the controversy surrounding the Woodward-Doering claim of the first “total synthesis” of quinine (Scheme 1, Top).⁷

mkrische@mail.utexas.edu.

Supporting Information Available: Spectral data for all new compounds. Single crystal X-ray diffraction data for piperidine **14** and glycidic alcohol **17**. This material is available free of charge *via* the internet at <http://pubs.acs.org>.

Subsequent to Woodward's seminal work, total syntheses of quinine **1** were reported by Uskoković, Gates, Taylor, Stork, Jacobsen, and Kobayashi.⁸ Uskoković and co-workers at Hoffman-La Roche developed four different routes to quinine. Although the group at Hoffman-La Roche was unable to develop a highly stereoselective approach, many of their discoveries, especially the N-1 to C-8 amine-epoxide cyclization strategy and the diastereoselective C-9 hydroxylation, have been utilized frequently in subsequent syntheses. In 2001, Stork reported the first stereoselective synthesis of quinine **1** in 20 steps from *trans*-butene-1,4-diol employing a novel N-1 to C-6 disconnection strategy. Completion of this synthesis resulted in optimization of the Hoffman-La Roche C-9 hydroxylation. In 2004, Jacobsen and Kobayashi published synthetic approaches relying on the N-1 to C-8 amine-epoxide cyclization initially reported by Hoffman-La Roche. These syntheses cleverly provide access to both quinine and quinidine **1**. Jacobsen's catalytic asymmetric synthesis of quinine **1** is achieved in 17 steps from *N*-(chloroacetyl)-benzamide but is not fully stereocontrolled. The C-3 stereocenter is obtained in a 3:1 epimeric ratio after epimerization of an initially formed 1:1.7 mixture favoring the undesired isomer. Finally, in a recent effort to prepare quinine, Williams disclosed the synthesis of 7-hydroxyquinine in 27 steps which took advantage of a unique C-3 to C-4 bond construction.⁹ Despite these enormous advances, a concise route to quinine that addresses both relative and absolute stereocontrol remains absent (Scheme 1, Bottom).

Here, we report a highly stereoselective formal synthesis of (\pm)-quinine in 16 steps and 4% overall yield from aminoacetaldehyde diethyl acetal employing a novel cycloallylation methodology developed in our laboratory, wherein the nucleophilic features of the Morita-Baylis-Hillman reaction and the electrophilic features of the Tsuji-Trost reaction are combined.¹⁰ To our knowledge, this route represents the most concise synthetic approach to quinine reported, to date. Additionally, we report a stereoselective route to (\pm)-7-hydroxyquinine in 13 steps and 11% overall yield from aminoacetaldehyde diethyl acetal, wherein highly stereoselective formation of five contiguous stereocenters is achieved through a series of 1,2-asymmetric induction events.

Results and Discussion

Quinine can be envisioned to arise by way of compound **4** *via* amine-glycidic epoxide cyclization. Cyclization would furnish 7-hydroxyquinine **3**, which upon C-7 deoxygenation would deliver quinine. The *N*-protected glycidic epoxide **4** may be obtained by way of aldol coupling-dehydration of piperidine **5** and 6-methoxyquinoline-4-carbaldehyde, followed by diastereoselective 1,2-reduction and hydroxy-directed epoxidation of the resulting allylic alcohol. Finally, the requisite *cis*-1,2-disubstituted piperidine **5** is potentially accessible through merged Morita-Baylis-Hillman-Tsuji-Trost reaction of enone-allyl carbonate **6** followed by diastereoselective conjugate reduction. In accordance with this approach, all five stereocenters of glycidic epoxide **4**, 7-hydroxyquinine **3** and, ultimately, the relative stereochemistry embodied by quinine itself, would be controlled through a series of 1,2-asymmetric induction events, relayed from the initially formed stereocenter bearing the vinyl moiety, which arises at the stage of cycloallylation (Scheme 2).

Efforts toward quinine began with the preparation of enone-allyl carbonate **6**, the substrate for merged Morita-Baylis-Hillman-Tsuji-Trost cycloallylation. Sulfonylation of commercially available aminoacetaldehyde diethyl acetal **7** with either *p*-toluene sulfonyl chloride or 2,4,6-trisopropylbenzene sulfonyl chloride provides the crude sulfonamides which under Mitsunobu conditions couple to (*Z*)-4-hydroxy-2-butenyl methyl carbonate¹¹ to furnish the products of *N*-allylation **8** and **9** in excellent yields over two steps. Hydrolysis of acetal **8** and **9** mediated by trifluoroacetic acid followed by Wittig olefination of the resulting aldehyde delivers enone-allyl carbonates **10** and **11** in 69% and 68% yields over two steps, respectively (Scheme 3).

With the requisite cycloallylation substrate in hand, the merged Morita-Baylis-Hillman-Tsuji-Trost cycloallylation of the *N*-Ts protected enone-allyl carbonate **10** was explored. Applying standard conditions,¹⁰ which involve exposure of substrate to Pd(PPh₃)₄ (1 mol%), PBu₃ (100 mol%) in *tert*-butanol (0.1 M) at 60 °C, only a 3% isolated yield of cyclization product **12** was obtained. This result is attributed to the sulfonamide moiety, which enhances the electrophilicity of the enone such that anion polymerization becomes problematic.

Intramolecular capture of the phosphonio-enolate is facilitated by increasing the loading of palladium (5 mol%) and by conducting the reaction at ambient temperature. Under these conditions, the *N*-Ts protected substrate **10** undergoes cyclization to furnish **12** in 62% isolated yield. A major side-product in the cyclization of **10** is the β,γ -unsaturated piperidine. This material is not produced upon reexposure of piperidine **12** to the reaction conditions, suggesting it is formed upon E₂-elimination of the β -phosphonium intermediate. The corresponding *N*-Trs (Trs = 2,4,6-trisopropylphenyl sulfonyl) derivative **11**, should be resistant to deprotonation at the γ -position after cyclization. Further, the *N*-Trs moiety of **11** may facilitate cyclization through the Thorpe-Ingold effect.¹² In practice, the steric demand of the *N*-Trs moiety mandated use of smaller phosphine, trimethylphosphine, which upon substoichiometric loading (80 mol%) provided the *N*-Trs protected piperidine **13** in 68% isolated yield (Table 1).

Elaboration of the cyclization product **13** to quinine requires diastereoselective conjugate reduction to establish appropriate relative stereochemistry at C-3 and C-4. Using a modification of the copper-hydride mediated 1,4-reduction developed by Tsuda and Saegusa,¹³ the *cis*-piperidine **14** was formed as a single diastereomer, as established ¹H NMR analysis. The relative stereochemistry of piperidine **14** was corroborated through single crystal X-ray diffraction analysis. Interestingly, the corresponding *N*-Ts derivative **12** forms an equimolar mixture of diastereomers upon exposure to identical conjugate reduction conditions. *cis*-Piperidine **14** requires careful handling, as rapid isomerization to *trans*-piperidine *epi*-**14** occurs upon exposure to acid or base (Scheme 5).

In our hands, the *N*-sulfonyl protecting group could not be removed under reductive conditions in the presence of the quinoline. Hence, *N*-Trs protected *cis*-piperidine **14** was converted to the corresponding *N*-Boc derivative **18**. Exposure of **14** to sodium naphthalenide in DME at -78 °C resulted in cleavage of the sulfonyl moiety. However, to avoid epimerization to the *trans*-piperidine, quenching of the reaction mixture at -78 °C using saturated aqueous ammonium chloride was required. Treatment of the crude amine with Boc₂O delivers the *N*-Boc protected *cis*-piperidine **18** in 76% isolated yield over these two manipulations (Scheme 4).

Introduction of the quinoline moiety was accomplished using an aldol coupling-dehydration protocol involving *N*-Boc protected *cis*-piperidine **18** and 6-methoxyquinoline-4-carbaldehyde. To circumvent epimerization of the *cis*-piperidine, carefully tailored conditions were required. Regioselective deprotonation at the methyl group of the acetyl moiety is accomplished by treating *cis*-piperidine **18** with one equivalent of LHMDS at -78 °C in THF solvent. After stirring for one hour, 6-methoxyquinoline-4-carbaldehyde¹⁴ was added. The reaction mixture was quenched at -78 °C with acetic anhydride and warmed to -40 °C, at which point DBU was added. Quenching of the reaction mixture at -40 °C using saturated aqueous ammonium chloride was required to avoid epimerization. Using this procedure, the *N*-Boc protected aldol adduct **15**, which retains the *cis*-piperidine, is obtained in 70% isolated yield. Thus, in eight manipulations from commercially available aminoacetaldehyde diethyl acetal, all carbon atoms of quinine are assembled (Scheme 4).

With clear evidence for the thermodynamic preference of a *trans*-relationship about the piperidine of enone **15**, it was imperative to immediately reduce the ketone functional group. Upon exposure of enone **15** to L-selectride at -78 °C in THF, allylic alcohol **16** is formed as a single stereoisomer, as determined by ¹H NMR analysis (>20:1 dr). This transformation

removed the threat of epimerization, while introducing the functionality required for hydroxyl-directed diastereoselective epoxidation. However, under standard conditions developed by Sharpless employing VO(acac)₂ (5 mol%) as precatalyst and TBHP as terminal oxidant in toluene at 50 °C,¹⁵ the glycidic alcohol **17** is formed in 98% yield as a 3:1 ratio of diastereomers. This modest level of stereoselectivity presumably arises in response to the relatively low levels of allylic strain embodied by the *trans*-1,2-disubstituted olefin of **16**.¹⁶

Hydroxamates are effective ligands in asymmetric oxovanadium catalyzed epoxidations of allylic alcohols.¹⁷ Upon screening a number of achiral hydroxamic acids, that derived from *N*-methyl hydroxylamine and pivaloyl chloride, when complexed to VO(acac)₂ *in situ*, promoted greater levels of diastereoselection (6:1 dr). It was found that preformation of the oxovanadium *bis*(hydroxamate) complex was required to suppress a less selective background reaction promoted by VO(acac)₂.¹⁸ After extensive optimization, it was found that exposure of **16** to VO[*t*-BuCO(MeNO)]₂ (5 mol%) and TBHP (1000 mol%) in dichloromethane at 4 °C promotes formation of epoxide **17** in 91% isolated yield as a 17:1 ratio of diastereomers. In this way, highly stereoselective formation of five contiguous stereocenters is achieved through a series of 1,2-asymmetric induction events. Validating the superiority of the *bis*(hydroxamate) catalyst, epoxidation of allylic alcohol **16** under identical conditions employing VO(acac)₂ as catalyst results in a substantial decline in stereoselectivity (6:1 dr). The stereochemical assignment of glycidic alcohol **17** was confirmed by single crystal X-ray diffraction analysis.

Removal of the *N*-protecting group of glycidic alcohol **17** was accomplished upon treatment of **17** with trifluoroacetic acid in dichloromethane. The resulting crude amine underwent intramolecular cyclization when exposed to Zn(OTf)₂ and in refluxing MeCN to provide 7-hydroxyquinine **3** in 70% yield.

Several different strategies to deoxygenate 7-hydroxyquinine **3** were explored. Selective functionalization of the C-9 hydroxyl is readily achieved, as demonstrated by the formation of the *p*-methoxybenzyl ether **24** and methoxymethyl ether **25** (Scheme 7). Having differentiated the alcohol functionalities, the Barton-McCombie deoxygenation was first investigated.¹⁹ This strategy appeared quite attractive, as deoxygenation of the epimeric C-7 hydroxyl had been accomplished in a quinine model study.²⁰ The C-7 hydroxyl of **24** and **25**, however, proved to be especially resistant to the action of external reagents. Treatment of **24** and **25** with thiocarbonyldiimidazole under a range of conditions provided none of the desired thiocarbamate. Attempted xanthate formation also failed. Protocols for the radical deoxygenation of tertiary alcohols and hindered secondary alcohols are reported by Barton, which involve formation of mixed oxalates,²¹ thioformates²² and phenylselenocarbonates.²³ These too were ineffective.

The remarkable resistance of alcohols **24** and **25** toward derivatization is underscored by their reluctance to react with ketene, neat acetic anhydride or acetyl chloride. The singular method identified for derivation of alcohols **24** and **25** involves mesylation, which likely occurs through the intervention of sulfene (H₂C=SO₂). Mesylates **26** and **27** were treated with a range of hydride sources, molten thiolate, various iodide sources and hydrazines, however, mesylates **26** and **27** proved to be quite impervious. Presumably, an appropriate trajectory for S_N² displacement cannot be attained due to the position of the C-3 vinyl moiety. In the hope of exploiting the C-3 vinyl moiety as an active volume, the reaction of mesylates **26** and **27** with low valent metals was explored. However, the Collman reagent²⁴ (Na₂Fe(CO)₄), Rieke manganese²⁵ and conditions developed by Yus²⁶ for the deoxygenation of hindered sulfonates also were ineffective.

Given the difficulties encountered in the deoxygenation of 7-hydroxyquinine, an alternate strategy was pursued involving C-7 deoxygenation in advance of amine-epoxide cyclization.

Thus, in analogy to the preparation of the corresponding *N*-Boc protected allylic alcohol **16**, *cis*-piperidine **14** was converted to the *N*-Cbz derivative **19**, which was transformed to the quinoline containing enone **20** via aldol coupling-dehydration to 6-methoxyquinoline-4-carbaldehyde. Exposure of enone **20** to L-selectride in THF solvent at -78 °C resulted in 1,2-reduction to furnish allylic alcohol **21** as a single diastereomer, as determined by ^1H NMR analysis ($>20:1$ dr). Conversion of allylic alcohol **21** to the corresponding acetate **22** followed by palladium-catalyzed, formate-mediated reduction delivers the product of C-7 deoxygenation **23** as a single alkene regio- and stereoisomer (Scheme 6).²⁷

Diene **23** is an intermediate in Jacobsen's synthesis of quinine **1**. Although Jacobsen's approach provides diene **23** in optically enriched form, the C-3 stereocenter is initially formed as a 1:1.7 mixture favoring the undesired isomer, which after epimerization is converted to a 3:1 mixture favoring the desired isomer. Our route to racemic diene **23** is accomplished in two fewer manipulations and with complete control of relative stereochemistry.

Summary

We report concise stereoselective syntheses of quinine and 7-hydroxyquinine using a catalytic enone cycloallylation that combines the nucleophilic features of the Morita-Baylis-Hillman reaction and the electrophilic features of the Tsuji-Trost reaction. In accordance with this strategy, quinine is accessible in 16 steps and 4% overall yield from commercial aminoacetaldehyde diethyl acetal, making it the most concise approach to quinine, to date. Additionally, 7-hydroxyquinine is prepared in 13 steps and 11% overall yield from aminoacetaldehyde diethyl acetal through a sequence wherein five contiguous stereocenters are formed with high levels of relative stereocontrol through a series of 1,2-asymmetric induction events. Our route delivers 7-hydroxyquinine in less than half the number of manipulations previously reported.⁹

Among the many challenges that remain, control of absolute stereochemistry and the identification of an effective method for C-7 deoxygenation of 7-hydroxyquinine figure prominently. With regard to the former issue, it is interesting to note that the *N*-2,4,6-triisopropylbenzenesulfinyl derivative of compound **6** engages in cyclization with only modest levels of diastereoselection (2:1), presumably as highly diastereoselective cyclization requires high levels of diastereofacial selectivity at the stage of phosphine conjugate addition and enolate allylation.

Quinine, which was present at the very inception of organic chemistry as a field, may be viewed as a barometer of the state-of-the-art. Hence, it is remarkable that to this day, a step-economic route to quinine that completely addresses both relative and absolute stereochemistry remains absent. The present study has evoked effective new strategies for controlling the relative stereochemistry of quinine via substrate direction. However, it is but one of many small steps toward the distant goal of devising an ideal synthesis.

Experimental Section

General

All reactions were run under an atmosphere of argon when exclusion of water or oxygen was deemed appropriate. Anhydrous solvents were transferred by an oven-dried syringe. Dichloromethane (DCM), t BuOH, t AmOH, MeCN, t Pr₂NH, and HMPA were dried by distillation over CaH₂. Et₂O, DME, THF, and toluene were dried by distillation over sodium benzophenone. DMF and pyridine were stored over molecular sieves and KOH respectively. Chemical reagents were purchased from Aldrich, Fischer, and Strem Chemicals and used as received without further purification unless otherwise stated. Flasks were flame-dried and

cooled under a stream of argon. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F₂₅₄). Flash chromatography was performed on silica gel 60 (200 – 400 mesh) according to the method of Still. Solvents for chromatography are listed as volume:volume ratios.

Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a Varian Inora 500, Varian Mercury 400, or Varian UNITY + 300 spectrometer. ¹H NMR spectra were obtained at either 500, 400, or 300 MHz, as indicated. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from trimethylsilane. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded on a Varian Inora 500, Varian Mercury 400, or Varian UNITY + 300 spectrometer. ¹³C NMR spectra were obtained at either 125, 100, or 75 MHz, as indicated. Chemical shifts are reported in delta (δ) units, parts per million (ppm) relative to the residual solvent. ¹³C NMR spectra were routinely run with broadband decoupling. Vanadium-51 nuclear magnetic resonance (⁵¹V NMR) spectra were recorded on a Varian Inora 500. ⁵¹V NMR spectra were obtained at 131 MHz. Chemical shifts are reported in delta (δ) units, parts per million (ppm) relative to the singlet at 2.0 ppm for VOCl₃. FT-IR spectra were obtained using a Nicolet Impact 410 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Micromass ZAB-E spectrometer and are reported m/z (relative intensity). Accurate masses are reported for the molecular ion (M + 1) or a suitable fragment ion. Melting points were obtained on a Thomas-Hoover Unimelt apparatus in open capillaries and are uncorrected.

Conversion of aminoacetaldehyde diethyl acetal 7 to enone 10—To a solution of aminoacetaldehyde diethyl acetal **7** (5.07 mL, 34.9 mmol, 100 mol%) in DCM (55.8 mL, 0.63 M) at 0 °C was added Et₃N (6.46 mL, 46.4 mmol, 133 mol%) and tosyl chloride (8.85 g, 46.4 mmol, 133 mol%). The reaction mixture was allowed to slowly warm to room temperature with stirring over 20 hours, at which point the reaction mixture was quenched with water and extracted with DCM with the aid of a separatory funnel. The combined organic layers were washed with saturated Cu₂SO₄ (aq.), brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to furnish the crude sulfonamide.

The crude sulfonamide (10.76 g) was dissolved in THF (116 mL, 0.3 M) and the solution was cooled to 0 °C with stirring. The known allylic alcohol¹¹ (5.72 g, 39.1 mmol, 110 mol%), DIAD (8.32 mL, 42.3 mmol, 120 mol%), and PPh₃ (11.1 g, 42.3 mmol, 120 mol%) were added to the reaction vessel. The reaction mixture was allowed to slowly warm to room temperature with stirring over 20 hours, at which point the reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO₂: hexanes:EtOAc, 10:1 to 2:1) to provide **8** (12.47 g) as a thick yellow oil.

Compound **8** (12.47 g) was dissolved in CHCl₃ (74 mL, 0.32 M) and H₂O (36 mL) at 0 °C. Trifluoroacetic acid (36 mL, 492 mmol, 1410 mol%) was added and the reaction mixture was allowed to slowly warm to room temperature with stirring over 20 hours, at which point it was quenched with solid NaHCO₃, poured into H₂O, and extracted with DCM with the aid of a separatory funnel. The combined organic extracts were washed with saturated NaHCO₃ (aq.), brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO₂: hexanes:EtOAc, 5:1 to 1:1) to provide the aldehyde (8.07 g, 23.7 mmol) as a yellow oil in 68% over 3 steps. ¹H NMR (300 MHz, CDCl₃): δ 9.56 (s, 1 H), 7.69 (d, 2 H, *J* = 8.2 Hz), 7.33 (d, 2 H, *J* = 8.2 Hz), 5.78-5.70 (m, 1 H), 5.61-5.53 (m, 1 H), 4.55 (d, 2 H, *J* = 6.7 Hz), 3.94 (d, 2 H, *J* = 6.9 Hz), 3.86 (s, 2 H), 3.74 (s, 3 H), 2.43 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃): δ 197.7, 155.5, 144.1, 135.5, 129.9, 128.9, 128.5, 127.3, 62.3, 56.1, 54.9, 45.8, 21.5; IR (film): 2958, 1598, 1445, 1345, 1267, 1161, 763 cm⁻¹; HRMS (CI) calcd. for C₁₅H₂₀NO₆S [M + 1]: 342.1011, found: 342.1011

To a solution of the aldehyde (0.26 g, 0.75 mmol, 100 mol%) in DCM (7.5 mL, 0.1 M) at ambient temperature was added the known Wittig reagent²⁸ (0.24 g, 0.75 mmol, 100 mol%). The reaction mixture was allowed to stir for 20 hours, at which point the reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO₂: hexanes:EtOAc, 5:1 to 2:1) to provide **10** (0.20 g, 0.52 mmol) as a yellow oil in 69% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.64 (d, 2 H, *J* = 8.2 Hz), 7.27 (d, 2 H, *J* = 7.9 Hz), 6.51 (dt, 1 H, *J* = 16.1 Hz), 6.06 (dt, 1 H, *J* = 16.4, 1.4 Hz), 5.66-5.60 (m, 1 H), 5.49-5.42 (m, 1 H), 4.51 (dd, 2 H, *J* = 6.8, 1.0 Hz), 3.86 (m, 4 H), 3.69 (s, 3 H), 2.37 (s, 3 H), 2.14 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 197.4, 155.2, 143.7, 141.1, 136.2, 132.4, 129.7, 129.1, 127.2, 127.0, 62.3, 54.6, 48.2, 44.6, 26.9, 21.2; IR (film): 3055, 2985, 1599, 1422, 1265, 741, 706 cm⁻¹; HRMS (CI) calcd. for C₁₈H₂₄NO₆S [M + 1]: 382.1324, found: 382.1329.

Conversion of aminoacetaldehyde diethyl acetal 7 to enone 11—To a solution of aminoacetaldehyde diethyl acetal **7** (11.7 mL, 80.7 mmol, 100 mol%) in DCM (129 mL, 0.63 M) at 0 °C was added Et₃N (13.8 mL, 99.0 mmol, 120 mol%) and 2,4,6-triisopropylbenzenesulfonyl chloride (25 g, 82.6 mmol, 102 mol%). The reaction mixture was allowed to slowly warm to room temperature over 22 hours with stirring, at which point the reaction mixture was poured into H₂O and extracted with DCM with the aid of a separatory funnel. The combined organic extracts were washed with 5% Cu₂SO₄ (aq.), brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to furnish the crude sulfonamide.

The crude sulfonamide (32.25 g) was dissolved in THF (269 mL, 0.3 M) and the solution was cooled to 0 °C with stirring. The known allylic alcohol¹¹ (17.67 g, 121.1 mmol, 150 mol%), DIAD (25.4 mL, 129.1 mmol, 160 mol%), and PPh₃ (34.04 g, 121.1 mmol, 160 mol%) were added to the reaction vessel. The reaction mixture was allowed to slowly warm to room temperature with stirring over 20 hours, at which point the reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO₂: hexanes:EtOAc, 15:1 to 3:1) to provide compound **9** (42.59 g, 26.9 mmol) as a thick yellow oil in 100% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.16 (s, 2 H), 5.78-5.72 (m, 1 H), 5.63-5.56 (m, 1 H), 4.66 (dd, 2 H, *J* = 6.8, 1.0 Hz), 4.53 (t, 1 H, *J* = 5.3 Hz), 4.15-4.07 (m, 2 H), 4.04 (d, 2 H, *J* = 7.2 Hz), 3.76 (s, 3 H), 3.68-3.60 (m, 2 H), 3.52-3.44 (m, 2 H), 3.26 (d, 2 H, *J* = 5.5 Hz), 2.89 (hp, 1 H, *J* = 6.8 Hz), 1.25 (dd, 18 H, *J* = 6.9, 1.1 Hz), 1.18 (t, 6 H, *J* = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 155.4, 153.1, 151.2, 131.2, 129.5, 127.5, 123.8, 102.3, 63.0, 63.0, 54.6, 47.1, 43.6, 34.0, 29.1, 24.6, 23.4, 15.1; IR (film): 2962, 2872, 1752, 1601, 1445, 1425, 1365, 1012, 940 cm⁻¹; HRMS (CI) calc. for C₂₇H₄₄NO₇S [M - 1]: 526.2839, found: 526.2845.

Compound **9** (29.38 g, 55.70 mmol, 100 mol%) was dissolved in CHCl₃ (137 mL, 0.4 M) and H₂O (68 mL) at 0 °C. Trifluoroacetic acid (68 mL, 915 mmol, 1640 mol%) was added and the reaction mixture was allowed to slowly warm to ambient temperature with stirring over 20 hours, at which point solid NaHCO₃ was added and the reaction mixture was poured into H₂O, and extracted with DCM with the aid of a separatory funnel. The combined organic extracts were washed with saturated NaHCO₃ (aq.), brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to provide the crude aldehyde (24.01 g) as a yellow oil.

To a solution of the crude aldehyde in DCM (520 mL, 0.1 M) at ambient temperature was added the known Wittig reagent²⁸ (19.73 g, 61.98 mmol, 110 mol%). The reaction mixture was allowed to stir for 18 hours, at which point the reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO₂: hexanes:EtOAc, 5:1 to 3:1) to provide compound **11** (18.70 g, 37.88 mmol, 68%) as a white solid. M.P.: 42 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.18 (s, 2 H), 6.65 (dt, 1 H, *J* = 16.1, 6.4 Hz), 6.14 (d, 1 H, *J* = 16.1 Hz), 5.79-5.73 (m, 1 H), 5.68-5.62 (m, 1 H), 4.56 (d, 2 H, *J* = 6.8 Hz), 4.10 (hp, 2 H, *J* = 6.8 Hz), 3.97 (dd, 2 H, *J* = 5.2, 1.0 Hz), 3.89 (d, 2 H, *J* = 7.2 Hz), 3.77 (s, 3 H), 2.90 (hp, 1 H, *J* = 6.8 Hz), 2.23 (s, 3 H), 1.26 (dd, 18 H, *J* = 6.8, 1.4 Hz); ¹³C NMR

(75 MHz, CDCl₃): δ 197.5, 155.3, 153.5, 151.4, 141.0, 133.3, 130.3, 129.1, 127.6, 124.0, 70.9, 62.4, 54.8, 46.6, 42.8, 36.2, 34.0, 29.2, 28.5, 26.9, 24.7, 23.4; IR (film): 2960, 2931, 2871, 1601, 1384, 1107, 1072, 1060, 703 cm⁻¹; HRMS (CI) calc. for C₂₆H₄₀NO₆S [M + 1]: 494.2576, found: 494.2579.

1-[1-(Toluene-4-sulfonyl)-3-vinyl-1,2,3,6-tetrahydro-pyridin-4-yl]-ethanone (12)

—To a degassed solution of enone **10** (83 mg, 0.20 mmol, 100 mol%) in *t*AmOH (2.0 mL, 0.1 M) at ambient temperature was added Pd(PPh₃)₄ (13 mg, 0.01 mmol, 5 mol%) and freshly distilled PBu₃ (50 μ L, 0.2 mmol, 100 mol%). The reaction mixture was allowed to stir at ambient temperature for 20 minutes, at which point the reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO₂: hexanes:EtOAc, 5:1 to 2:1) to provide the title compound (42 mg, 0.12 mmol) as a yellow oil in 62% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.66 (d, 2 H, *J* = 8.2 Hz), 7.32 (d, 2 H, *J* = 8.2 Hz), 6.72 (t, 1 H, *J* = 3.5 Hz), 5.83 (ddd, 1 H, *J* = 17.1, 10.3, 6.8 Hz), 5.12–5.07 (m, 2 H), 4.20 (dd, 1 H, *J* = 19.0, 3.8 Hz), 3.74 (dd, 1 H, *J* = 11.6, 2.1 Hz), 3.51 (br s, 1 H), 3.36 (dt, 1 H, *J* = 19.1, 2.4 Hz), 2.54 (dd, 1 H, *J* = 11.5, 3.8 Hz), 2.42 (s, 3 H), 2.26 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 196.4, 143.9, 139.2, 136.6, 134.0, 132.8, 129.7, 127.6, 116.9, 47.2, 44.8, 36.8, 25.6, 21.5; IR (film): 2924, 2854, 1674, 1597, 1354, 1166, 1093, 668 cm⁻¹; HRMS (CI) calc. for C₁₆H₂₀NO₃S [M + 1]: 306.1164, found: 306.1173.

1-[1-(2,4,6-Triisopropyl-benzenesulfonyl)-3-vinyl-1,2,3,6-tetrahydro-pyridin-4-yl]-ethanone (13)

—To a degassed solution of enone **11** (0.50 g, 1.0 mmol, 100 mol%) in *t*AmOH (10.0 mL, 0.1 M) at ambient temperature was added Pd(PPh₃)₄ (59 mg, 0.05 mmol, 5 mol%) and PMe₃ (1.0 M in toluene, 0.82 mL, 0.8 mmol, 80 mol%). The reaction mixture was allowed to stir for 30 minutes, at which point the reaction mixture was poured into water and extracted with DCM with the aid of a separatory funnel. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO₂: hexanes:EtOAc, 10:1 to 5:1) to provide the title compound (0.29 g, 0.68 mmol) as a yellow oil in 68% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.18 (s, 2 H), 6.80 (t, 1 H, *J* = 3.6 Hz), 5.70 (ddd, 1 H, *J* = 17.1, 10.3, 6.8 Hz), 5.03–4.96 (m, 2 H), 4.12 (hp, 2 H, *J* = 6.8 Hz), 3.93 (dd, 1 H, *J* = 18.7, 4.0 Hz), 3.80 (dt, 1 H, *J* = 18.7, 2.6 Hz), 3.68 (dd, 1 H, *J* = 12.2, 2.6 Hz), 3.55 (br s, 1 H), 3.04 (dd, 1 H, *J* = 12.0, 3.8 Hz), 2.90 (hp, 1 H, *J* = 6.8 Hz), 2.29 (s, 3 H), 1.26–1.23 (m, 18 H); ¹³C NMR (100 MHz, CDCl₃): δ 196.5, 153.5, 151.8, 139.3, 136.9, 134.4, 129.4, 123.9, 116.7, 45.6, 43.8, 36.8, 34.1, 29.4, 28.5, 25.6, 25.0, 24.7, 23.4, 23.4; IR (film): 3068, 2962, 2870, 2823, 2255, 1674, 1601, 1562, 1462, 1385, 1152, 918 cm⁻¹; HRMS (CI) calc. for C₂₄H₃₆NO₃S [M + 1]: 418.2410, found: 418.2407.

cis-1-[1-(2,4,6-Triisopropyl-benzenesulfonyl)-3-vinyl-piperidin-4-yl]-ethanone (14)

—To a solution of CuI (2.92 g, 15.37 mmol, 110 mol%) in THF (480 mL) at –60 °C was added MeLi (1.6 M in Et₂O, 10.8 mL, 17.3 mmol, 125 mol%), HMPA (59.3 mL, 340.8 mmol, 2500 mol%), and DIBAL (1.0 M in cyclohexane, 69 mL, 69 mmol, 500 mol%). The resulting mixture was allowed to stir between –60 °C and –55 °C for 1.5 hours and was then cooled to –78 °C. Enone **13** (5.74 g, 13.76 mmol, 100 mol%) in THF (19 mL, 0.72 M) was added to the reaction mixture at –78 °C. The reaction mixture was allowed to stir for 10 minutes, at which point the reaction mixture was quenched with 2 M HCl (aq.) at –78 °C and the cooling bath was removed. The reaction mixture was allowed to reach room temperature, at which point the reaction mixture was poured into H₂O and extracted with Et₂O with the aid of a separatory funnel. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO₂: hexanes:EtOAc, 5:1 to 4:1) to provide the title compound (4.47 g, 10.60 mmol) as a white solid in 77% yield exclusively as the *cis*-diastereomer. M.P.: 112–113 °C; ¹H NMR (400

MHz, CDCl₃): δ 7.16 (s, 2 H), 5.83 (ddd, 1 H, $J = 17.2, 10.5, 8.7$ Hz), 5.30-5.06 (m, 2 H), 4.16-4.07 (m, 2 H), 3.78-3.73 (m, 1 H), 3.44-3.40 (m, 1 H), 3.12 (dd, 1 H, $J = 11.8, 3.3$ Hz), 2.94-2.84 (m, 3 H), 2.66 (dt, 1 H, $J = 10.3, 4.4$ Hz), 2.12 (s, 3 H), 1.88-1.79 (m, 2 H), 1.24 (dt, 18 H, $J = 6.9, 1.5$ Hz); ¹³C NMR (100 MHz, CDCl₃): δ 208.5, 153.4, 151.8, 135.0, 129.6, 123.9, 117.7, 51.6, 48.4, 43.9, 40.4, 34.1, 31.6, 29.4, 28.6, 25.1, 24.7, 23.5, 22.6, 22.6, 14.1; IR (film): 2959, 2929, 2869, 1711, 1601, 1276, 1261, 1151, 764, 750 cm⁻¹; HRMS (CI) calcd. for C₂₄H₃₈NO₃S [M + 1]: 420.2572, found: 420.2585.

cis-4-Acetyl-3-vinyl-piperidine-1-carboxylic acid tert-butyl ester (18)—To a solution of naphthalene (9.57 g, 74.64 mmol, 940 mol%) in DME (22.8 mL) at room temperature was added freshly cut sodium (1.42 g, 61.72 mmol, 780 mol%). The resulting green solution of the anion radical was stirred for 2 hours, at which point it was added dropwise to a solution of *N*-trisyl piperidine **14** (3.33 g, 7.94 mmol, 100 mol%) in DME (50 mL, 0.16 M) at -78 °C. Once the green color of the anion radical persisted for 10 seconds, saturated NH₄Cl (aq.) was added immediately. The crude reaction mixture was allowed to reach ambient temperature, at which point the reaction mixture was filtered with the aid of CHCl₃, and concentrated *in vacuo*.

The crude amine was dissolved in DCM (79 mL, 0.1 M), and the solution was cooled to 0 °C. To the stirred solution was added Et₃N (3.0 mL, 21.52 mmol, 270 mol%), Boc₂O (8.66 g, 39.68 mmol, 500 mol%), and DMAP (0.98 g, 8.02 mmol, 101 mol%). The reaction mixture was allowed to slowly warm to ambient temperature with stirring over 18 hours, at which point the reaction mixture was quenched with saturated NH₄Cl (aq.) and extracted with DCM with the aid of a separatory funnel. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO₂: hexanes:EtOAc, 5:1) to provide the title compound (1.52 g, 6.03 mmol) as a colorless oil in 76% yield. ¹H NMR (500 MHz, d₆-DMSO, 90 °C): δ 5.65 (ddd, 1 H, $J = 17.3, 10.5, 2.8$ Hz), 5.11 (ddd, 1 H, $J = 17.3$ Hz, 1.8 Hz, 1.2 Hz), 5.03 (ddd, 1 H, $J = 10.6, 1.7, 1.0$ Hz), 3.93 (ddd, 1 H, $J = 13.2$ Hz, 3.5 Hz, 1.6 Hz), 3.95-3.88 (m, 1 H), 3.11 (dd, 1 H, $J = 13.2$ Hz, 3.3 Hz), 2.85-2.80 (m, 2 H), 2.77 (dt, 1 H, $J = 10.7$ Hz, 4.2 Hz), 2.07 (s, 3 H), 1.62-1.59 (m, 1 H), 1.58-1.52 (m, 1 H), 1.39 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃): δ 208.8, 154.7, 134.8, 117.2, 79.4, 79.3, 52.3, 40.6, 28.4, 28.2, 28.1, 22.5; IR (neat): 2976, 2930, 2854, 1478, 1464, 1423, 1366, 1241, 1164, 1119 cm⁻¹; HRMS (CI) calcd for C₁₄H₂₄NO₃ [M + 1]: 254.1756, found: 254.1757.

4-[3-(6-Methoxy-quinolin-4-yl)-acryloyl]-3-vinyl-piperidine-1-carboxylic acid tert-butyl ester (15)—To a solution of methyl ketone **14** (0.11 g, 0.44 mmol, 100 mol%) in THF (1.4 mL, 0.3 M) at -78 °C was rapidly added LHMDS (1.0 M in THF, 0.53 mL, 0.53 mmol, 120 mol%). The reaction mixture was stirred at -78 °C for 1 hour, at which point the quinoline-bearing aldehyde¹⁴ (0.11 g, 0.57 mmol, 130 mol%) was added as a solution in THF (0.3 mL). The reaction mixture was allowed to stir at -78 °C for 45 minutes, at which point Ac₂O (80 μ L, 0.89 mmol, 200 mol%) and DMAP (54 mg, 0.44 mmol, 100 mol%) were added. The reaction was allowed to stir at -78 °C for an additional 45 minutes, at which point it was allowed to reach -40 °C (MeCN/solid CO₂) and was allowed to stir for 30 minutes. To the reaction mixture was added DBU (0.34 mL, 2.27 mmol, 520 mol%) at -40 °C. The reaction mixture was allowed to stir for 15 minutes at -40 °C, at which point it was quenched with saturated NH₄Cl (aq.) and was extracted with Et₂O with the aid of a separatory funnel. The combined ethereal extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO₂: hexanes:EtOAc, 1:1 to 1:3) to provide the title compound (0.13 g, 0.31 mmol) as a yellow foam in 70% yield. ¹H NMR (500 MHz, d₆-DMSO, 90 °C): δ 8.76 (d, 1 H, $J = 4.5$ Hz), 8.18 (d, 1 H, $J = 15.8$ Hz), 7.99 (dd, 1 H, $J = 6.8$ Hz, 3.1 Hz), 7.74 (d, 1 H, $J = 4.5$ Hz), 7.48-7.45 (m, 2 H), 7.23 (d, 1 H, $J = 15.8$ Hz), 5.72 (ddd, 1 H, $J = 17.3, 10.6, 2.8$ Hz), 5.11-5.07 (m, 1 H),

5.05-5.02 (m, 1 H), 3.98-3.92 (m, 2 H), 3.97 (s, 3 H), 3.31-3.24 (m, 2 H), 2.98-2.95 (m, 2 H), 1.84-1.76 (m, 1 H), 1.71-1.66 (m, 1 H), 1.41 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3): δ 199.0, 170.6, 158.0, 154.5, 146.9, 144.5, 138.1, 136.6, 134.6, 131.3, 128.7, 127.1, 122.1, 117.9, 117.1, 100.6, 79.3, 55.3, 55.3, 51.0, 40.5, 28.0, 22.6; IR (film): 2974, 1690, 1619, 1506, 1472, 1429, 1366, 1318, 1227, 1165 cm^{-1} ; HRMS (CI) calcd for $\text{C}_{25}\text{H}_{31}\text{N}_2\text{O}_4$ [$M + 1$]: 423.2284, found: 423.2284.

4-[1-Hydroxy-3-(6-methoxy-quinolin-4-yl)-allyl]-3-vinyl-piperidine-1-carboxylic acid tert-butyl ester (16)—To a solution of enone **15** (0.98 g, 2.33 mmol, 100 mol%) in THF (65.8 mL, 0.04 M) at -78°C was added dropwise L-Selectride (1.0 M in THF, 3.1 mL, 3.07 mmol, 130 mol%). The reaction mixture was allowed to stir for 5 minutes, at which point saturated NH_4Cl (aq.) was added and the reaction mixture was extracted with Et_2O with the aid of a separatory funnel. The combined ethereal extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2 : hexanes:EtOAc, 1:1 to 1:3) to provide the title compound (0.93 g, 2.19 mmol) as a white solid in 94% yield as a single diastereomer. M.P.: $148\text{--}149^\circ\text{C}$; ^1H NMR (500 MHz, d_6 -DMSO, 90°C): δ 8.66 (d, 1 H, $J = 4.5$ Hz), 7.92 (d, 1 H, $J = 9.2$ Hz), 7.51 (d, 1 H, $J = 4.7$ Hz), 7.48 (d, 1 H, $J = 2.7$ Hz), 7.40 (dd, 1 H, $J = 9.2, 2.8$ Hz), 7.24 (d, 1 H, $J = 15.3$ Hz), 6.49 (dd, 1 H, $J = 15.8, 7.0$ Hz), 5.93 (ddd, 1 H, $J = 17.4, 10.5, 2.3$ Hz), 5.22 (ddd, 1 H, $J = 17.4, 2.4, 1.1$ Hz), 5.16 (dd, 1 H, $J = 10.9, 1.9$ Hz), 4.73 (brs, 1 H), 4.08-4.02 (m, 3 H), 3.94 (s, 3 H), 2.90 (dd, 1 H, $J = 13.2, 3.0$ Hz), 2.79 (brs, 1 H), 2.70 (td, 1 H, $J = 12.4, 3.0$ Hz), 1.77-1.71 (m, 1 H), 1.45-1.41 (m, 1 H), 1.40 (s, 9 H), 1.36-1.33 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 157.5, 154.9, 147.0, 144.0, 141.2, 138.4, 135.4, 130.8, 126.9, 125.6, 121.7, 117.5, 101.2, 79.3, 73.5, 65.7, 55.3, 55.3, 45.2, 39.1, 28.2, 23.8, 15.1; IR (film): 3630, 3264, 2359, 2341, 2018, 1693, 1620, 1392, 1366, 1230, 1164, 1138, 1034 cm^{-1} ; HRMS (CI) calcd for $\text{C}_{25}\text{H}_{33}\text{N}_2\text{O}_4$ [$M + 1$]: 425.2440, found: 425.2441.

VO(hydroxamate) $_2$ —To a solution of the known hydroxamic acid²⁹ (1.00 g, 7.64 mmol, 160 mol%) in H_2O (12 mL) at ambient temperature was added Na_2CO_3 (0.80 g, 7.52 mmol, 150 mol%) and $\text{VO}(\text{SO}_4)_4 \cdot \text{H}_2\text{O}$ (0.80 g, 4.89 mmol, 100 mol%) in H_2O (12 mL, 0.4 M). The reaction mixture, which immediately turned purple, was allowed to stir for 5 minutes, at which point the reaction mixture was cooled to 0°C and $\text{VO}(\text{hydroxamate})_2$ (0.32 g, 1.27 mmol) was collected by filtration with the aid of a Hirsch funnel, washed with cold H_2O and dried *in vacuo* to provide the title compound as a light purple solid in 26% yield. M.P.: $134\text{--}135^\circ\text{C}$; ^{51}V NMR (130 MHz, C_6D_6): δ $-375.3, -412.7, -492.4, -552.0$; IR (film): 2978, 2939, 2361, 1572, 1483, 1422, 1368, 1111, 983, 956, 718, 606 cm^{-1} ; HRMS (CI) calcd for $\text{C}_{12}\text{H}_{25}\text{N}_2\text{O}_5\text{V}$ [$M + 1$]: 328.1203, found: 328.1206.

4-{Hydroxy-[3-(6-methoxy-quinolin-4-yl)-oxiranyl]-methyl}-3-vinyl-piperidine-1-carboxylic acid tert-butyl ester (17)—To a solution of allylic alcohol **16** (1.00 g, 2.27 mmol, 100 mol%) in DCM (22.3 mL, 0.1 M) at 4°C was added $\text{VO}(\text{hydroxamate})_2$ (38 mg, 0.11 mmol, 5 mol%) and TBHP (5.0 M in decane, 4.4 mL, 22.2 mmol, 980 mol%). The reaction mixture was allowed to stir at 4°C for 71 hours, at which point the reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2 : hexanes:EtOAc, 1:1 to 1:2) to provide the title compound (0.91 g, 2.07 mmol) as a white foam in 91% yield as a 17:1 ratio of separable diastereomers. ^1H NMR (500 MHz, d_6 -DMSO, 90°C): δ 8.69 (d, 1 H, $J = 4.4$ Hz), 7.96 (d, 1 H, $J = 2.7$ Hz), 7.44 (dd, 1 H, $J = 9.2, 2.8$ Hz), 7.28 (d, 1 H, $J = 4.4$ Hz), 5.88 (ddd, 1 H, $J = 17.4, 10.5, 2.3$ Hz), 5.25 (ddd, 1 H, $J = 17.4, 2.3, 1.1$ Hz), 5.15 (dd, 1 H, $J = 10.5, 2.3$ Hz), 4.96 (dd, 1 H, $J = 6.2, 2.1$ Hz), 4.42 (d, 1 H, $J = 2.0$ Hz), 4.10-4.05 (m, 2 H), 3.95 (s, 3 H), 3.23 (ddd, 1 H, $J = 12.6, 9.5, 6.4$ Hz), 3.01-2.99 (m, 1 H), 2.91 (dd, 1 H, $J = 13.0, 2.8$ Hz), 2.75-2.70 (m, 2 H), 1.91-1.85 (m, 1 H), 1.65 (dd, 1 H, $J = 13.6, 2.9$ Hz), 1.40 (s, 9 H), 1.39-1.34 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.1, 154.9,

147.4, 143.3, 141.6, 135.1, 131.2, 127.2, 122.0, 118.1, 116.8, 109.7, 100.9, 79.6, 70.5, 63.3, 55.7, 52.1, 44.7, 39.4, 29.7, 28.3, 22.9; IR (film): 2975, 2932, 2858, 2358, 2338, 2029, 1689, 1621, 1429, 1238, 1167, 1147, 853 cm^{-1} ; HRMS (CI) calcd for $\text{C}_{25}\text{H}_{33}\text{N}_2\text{O}_5$ [$M + 1$]: 441.2389, found: 441.2383.

7-Hydroxy-quinine (3)—To a solution of epoxide **17** (53 mg, 0.12 mmol, 100 mol%) in DCM (1.2 mL, 0.1 M) at 0 °C was added trifluoroacetic acid (0.30 mL, 3.90 mmol, 3300 mol %). The reaction mixture was allowed to stir at 0 °C for 1 hour, at which point the reaction mixture was concentrated *in vacuo*. Toluene (2 mL) was then added to the flask and the mixture was concentrated again *in vacuo*. The yellow residue was dissolved in MeCN (3 mL, 0.04 M) and Na_2CO_3 (64 mg, 0.60 mmol, 500 mol%) and $\text{Zn}(\text{OTf})_2$ (65 mg, 0.18 mmol, 150 mol%) were added. The reaction mixture was allowed to stir at 80 °C for 41 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was poured into H_2O and was extracted with DCM with the aid of a separatory funnel. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2 : DCM:MeOH, 20:1 to 15:1) to provide the title compound (28 mg, 0.084 mmol) as a white solid in 70% yield. M.P.: 196 °C (decomp.); ^1H NMR (400 MHz, d_6 -DMSO): δ 8.69 (d, 1 H, $J = 4.8$ Hz), 7.91 (d, 1 H, $J = 9.2$ Hz), 7.59 (d, 1 H, $J = 2.7$ Hz), 7.51 (d, 1 H, $J = 4.4$ Hz), 7.37 (dd, 1 H, $J = 9.2, 2.7$ Hz), 5.99-5.90 (m, 1 H), 5.60 (dd, 1 H, $J = 9.4, 4.3$ Hz), 5.46 (d, 1 H, $J = 4.1$ Hz), 5.07-5.01 (m, 2 H), 4.81 (d, 1 H, $J = 2.4$ Hz), 4.26-4.23 (m, 1 H), 3.89 (s, 3 H), 3.14-3.02 (m, 2 H), 2.65 (dd, 1 H, $J = 13.2, 10.1$ Hz), 2.49-2.24 (m, 3 H), 2.08-1.99 (m, 2 H), 1.18-1.11 (m, 1 H); ^{13}C NMR (100 MHz, d_6 -DMSO): δ 156.6, 148.9, 147.5, 144.0, 142.0, 131.0, 127.8, 120.9, 120.0, 114.5, 102.8, 66.9, 64.9, 63.8, 55.4, 54.5, 48.6, 41.4, 34.3, 20.0; IR (film): 3310, 2918, 2868, 2216, 2159, 2035, 1622, 1509, 1476, 1275, 1261, 1242, 1094, 1025, 750 cm^{-1} ; HRMS (CI) calcd for $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_3$ [$M + 1$]: 341.1865, found: 341.1863.

cis-4-Acetyl-3-vinyl-piperidine-1-carboxylic acid benzyl ester (19)—To a solution of naphthalene (0.57 g, 4.45 mmol, 1850 mol%) in DME (1.35 mL) at ambient temperature was added freshly cut sodium (0.90 g, 3.8 mmol, 1580 mol%). The resulting green solution of anion radical was allowed to stir for 2 hours, at which point it was added dropwise to a solution of *N*-trisyl piperidine **14** (0.10 g, 0.24 mmol, 100 mol%) in DME (1.42 mL, 0.17 M) at -78 °C. Once the green color of the anion radical persisted for 10 seconds, saturated NH_4Cl (aq.) was added. The crude reaction mixture was filtered through a pipette packed with Na_2SO_4 with the aid of CHCl_3 and the filtrate was concentrated. The residue was dissolved in DCM (2.4 mL, 0.1 M) and the solution was cooled to 0 °C, at which point Et_3N (0.20 mL, 1.43 mmol, 600 mol%) and CbzCl (0.11 mL, 0.78 mmol, 330 mol%) were added. The reaction mixture was allowed to slowly warm to ambient temperature with stirring over 18 hours, at which point saturated NH_4Cl (aq.) was added and the reaction mixture was extracted with DCM with the aid of a separatory funnel. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2 : hexanes:EtOAc, 3:1) to provide the title compound (41 mg, 0.15 mmol) as a colorless oil in 61% yield. ^1H NMR (500 MHz, d_6 -DMSO, 90 °C): δ 7.37-7.28 (m 5 H), 5.65 (ddd, 1 H, $J = 17.3, 10.5, 2.7$ Hz), 5.12-4.99 (m, 4 H), 4.01-3.94 (m, 2 H), 3.21 (dd, 1 H, $J = 13.3, 3.5$ Hz), 2.97-2.91 (m, 1 H), 2.85-2.83 (m, 1 H), 2.80 (dt, 1 H, $J = 10.6, 4.2$ Hz), 2.08 (s, 3 H), 1.71-1.58 (m, 2 H); ^{13}C NMR (125 MHz, d_6 -DMSO): δ 208.5, 154.5, 136.9, 135.6, 128.3, 128.3, 127.7, 127.6, 127.4, 117.0, 66.1, 51.0, 47.6, 42.6, 28.1, 22.0; IR (film): 2923, 2361, 2340, 1717, 1700, 1696, 1684, 1653, 1559, 1437, 1233, 668 cm^{-1} ; HRMS (CI) calcd for $\text{C}_{17}\text{H}_{22}\text{NO}_3$ [$M + 1$]: 288.1600, found: 288.1599.

4-[3-(6-Methoxy-quinolin-4-yl)-acryloyl]-3-vinyl-piperidine-1-carboxylic acid benzyl ester (20)—To a stirred solution of methyl ketone **19** (42 mg, 0.15 mmol, 100 mol

%) in THF (0.54 mL, 0.28 M) at $-78\text{ }^{\circ}\text{C}$ was rapidly added LHMDs (0.9 M in methylcyclohexane, 0.19 mL, 0.17 mmol, 110 mol%). The reaction mixture was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 1 hour, at which point the quinoline bearing aldehyde¹⁴ (39 mg, 0.21 mmol, 140 mol%) was added. The reaction mixture was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 1 hour, at which point Ac_2O (30 μL , 0.32 mmol, 210 mol%) and DMAP (18 mg, 0.14 mmol, 90 mol%) were added. The reaction was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for an additional 45 minutes, at which point the reaction mixture was allowed to reach $-40\text{ }^{\circ}\text{C}$ (MeCN/solid CO_2) and was allowed to stir for 30 minutes. DBU (0.11 mL, 0.74 mmol, 500 mol%) was added to the reaction mixture at $-40\text{ }^{\circ}\text{C}$. The reaction mixture was stirred for 15 minutes at $-40\text{ }^{\circ}\text{C}$, at which point it was quenched with saturated NH_4Cl (aq.) and extracted with Et_2O with the aid of a separatory funnel. The combined ethereal extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2 ; hexanes: EtOAc , 1:1 to 1:3) to afford **20** (43 mg, 0.10 mmol, 64%) as a yellow oil. ^1H NMR (500 MHz, d_6 -DMSO, $90\text{ }^{\circ}\text{C}$): δ 8.78 (d, 1 H, $J = 4.6$ Hz), 8.19 (d, 1 H, $J = 15.9$ Hz), 8.02-8.00 (m, 1 H), 7.78 (d, 1 H, $J = 4.4$ Hz), 7.50-7.47 (m, 2 H), 7.38-7.29 (m, 5 H), 7.24 (d, 1 H, $J = 15.9$ Hz), 5.71 (ddd, 1 H, $J = 17.3, 10.5, 2.7$ Hz), 5.13-5.00 (m, 4 H), 4.04-3.98 (m, 2 H), 3.97 (s, 3 H), 3.38-3.31 (m, 2 H), 3.12-3.07 (m, 1 H), 3.02-2.99 (m, 1 H), 1.88-1.80 (m, 1 H), 1.75-1.70 (m, 1 H); ^{13}C NMR (125 MHz, d_6 -DMSO): δ 199.8, 157.8, 154.5, 147.5, 144.4, 138.2, 137.0, 135.8, 135.3, 131.3, 130.4, 128.3, 127.8, 127.4, 126.8, 122.1, 118.7, 117.0, 66.1, 55.6, 49.4, 42.4, 30.4; IR (film): 2960, 2360, 2340, 1700, 1695, 1684, 1617, 1506, 1436, 1227, 668 cm^{-1} ; HRMS (CI) calcd for $\text{C}_{28}\text{H}_{29}\text{N}_2\text{O}_4$ [$M + 1$]: 457.2122, found: 457.2128.

4-[1-Hydroxy-3-(6-methoxy-quinolin-4-yl)-allyl]-3-vinyl-piperidine-1-carboxylic acid benzyl ester (21)—To a solution of enone **20** (27 mg, 0.065 mmol, 100 mol%) in THF (1.8 mL, 0.04 M) at $-78\text{ }^{\circ}\text{C}$ was added dropwise L-Selectride (1.0 M in THF, 70 μL , 0.070 mmol, 110 mol%). The reaction mixture was stirred for 5 minutes at which time it was quenched with saturated NH_4Cl (aq.) and extracted with Et_2O with the aid of a separatory funnel. The combined ethereal extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2 ; hexanes: EtOAc , 1:2 to 1:3) to provide the title compound (29 mg, 0.062 mmol) as a clear oil in 96% yield as a single diastereomer. ^1H NMR (500 MHz, d_6 -DMSO, $90\text{ }^{\circ}\text{C}$): δ 8.66 (d, 1 H, $J = 4.6$ Hz), 7.93 (d, 1 H, $J = 9.3$ Hz), 7.51 (d, 1 H, $J = 4.4$ Hz), 7.48 (d, 1 H, $J = 2.7$ Hz), 7.40 (dd, 1 H, $J = 9.1, 2.8$ Hz), 7.37-7.28 (m, 5 H), 7.25 (d, 1 H, $J = 15.6$ Hz), 6.49 (dd, 1 H, $J = 15.7, 7.0$ Hz), 5.92 (ddd, 1 H, $J = 17.3, 10.5, 2.2$ Hz), 5.28-5.24 (m, 1 H), 5.14 (dd, 1 H, $J = 10.6, 2.3$ Hz), 5.10 (d, 1 H, $J = 12.9$ Hz), 5.06 (d, 1 H, $J = 12.9$ Hz), 4.76 (brs, 1 H), 4.15-4.12 (m, 2 H), 4.06-4.03 (m, 1 H), 3.93 (s, 3 H), 3.00 (dd, 1 H, $J = 13.2, 2.9$ Hz), 2.84-2.78 (m, 2 H), 1.80-1.74 (m, 1 H), 1.50-1.40 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3): δ 157.3, 154.6, 147.5, 144.2, 140.8, 139.6, 137.0, 135.7, 130.9, 128.3, 127.7, 127.4, 126.7, 124.7, 121.6, 117.4, 117.1, 101.9, 79.1, 72.3, 66.0, 55.6, 44.6, 43.6, 38.1, 30.4; IR (film): 2927, 2360, 2340, 1700, 1695, 1684, 1507, 1472, 1436, 1231, $668, 417\text{ cm}^{-1}$; HRMS (CI) calcd for $\text{C}_{28}\text{H}_{31}\text{N}_2\text{O}_4$ [$M + 1$]: 459.2284, found: 459.2280.

4-[1-Acetoxy-3-(6-methoxy-quinolin-4-yl)-allyl]-3-vinyl-piperidine-1-carboxylic acid benzyl ester (22)—To a solution of allylic alcohol **21** (22 mg, 0.052 mmol, 100 mol %) in DCM (0.87 mL, 0.6 M) at $0\text{ }^{\circ}\text{C}$ was added Et_3N (40 μL , 0.29 mmol, 560 mol%), Ac_2O (30 μL , 0.32 mmol, 620 mol%), and DMAP (1.2 mg, 0.01 mmol, 20 mol%). The reaction mixture was stirred for 45 minutes, at which point it was poured into H_2O and extracted with DCM with the aid of a separatory funnel. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2 ; hexanes: EtOAc , 1:1 to 1:2) to provide the title compound (21 mg, 0.042 mmol) as a white foam in 81% yield. ^1H NMR (500 MHz, d_6 -DMSO, $90\text{ }^{\circ}\text{C}$): δ 8.70 (d, 1 H, $J = 4.4$ Hz), 7.97 (d, 1 H, $J = 8.0$ Hz), 7.56 (d, 1 H, $J = 4.6$ Hz), 7.46-7.42 (m,

2 H), 7.37-7.28 (m, 6 H), 6.41 (dd, 1 H, $J = 15.6, 7.6$ Hz), 5.89 (ddd, 1 H, $J = 17.1, 10.5, 1.5$ Hz), 5.19-5.05 (m, 5 H), 4.17-4.14 (m, 1 H), 4.10-4.07 (m, 1 H), 3.94 (s, 3 H), 3.08 (dd, 1 H, $J = 13.4, 2.9$ Hz), 2.89-2.83 (m, 1 H), 2.69-2.66 (m, 1 H), 2.16-2.09 (m, 1 H), 2.08 (s, 3 H), 1.56-1.48 (m, 2 H); ^{13}C NMR (125 MHz, d_6 -DMSO): δ 169.5, 157.6, 154.5, 146.8, 143.1, 140.9, 137.0, 135.1, 133.8, 130.2, 128.3, 128.3, 127.7, 127.4, 126.7, 122.2, 117.7, 117.5, 102.0, 79.1, 75.5, 66.1, 55.6, 43.3, 41.8, 40.1, 38.9, 20.8; IR (film): 3009, 2931, 2863, 2360, 2340, 1734, 1700, 1696, 1685, 1617, 1507, 1231, 1027 cm^{-1} ; HRMS (CI) calcd for $\text{C}_{30}\text{H}_{33}\text{N}_2\text{O}_5$ [$M + 1$]: 501.2389, found: 501.2391.

4-[3-(6-Methoxy-quinolin-4-yl)-allyl]-3-vinyl-piperidine-1-carboxylic acid benzyl ester (23)—To a solution of allylic acetate **22** (50 mg, 0.13 mmol, 100 mol%) in THF (1.0 mL, 0.13 M) at ambient temperature was added $\text{Pd}(\text{PPh}_3)_4$ (3 mg, 0.003 mmol, 2.5 mol%), freshly distilled PBU_3 (20 μL , 0.08 mmol, 60 mol%), Et_3N (90 μL , 0.65 mmol, 500 mol%), and formic acid (88% in H_2O , 20 μL , 0.53 mmol, 400 mol%). The reaction mixture was stirred for 4 hours, at which point it was poured into H_2O and extracted with Et_2O with the aid of a separatory funnel. The combined ethereal extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2 : hexanes: EtOAc , 1:1 to 1:2) to provide the title compound (42 mg, 0.10 mmol) as a colorless oil in 78% yield. ^1H NMR (500 MHz, d_6 -DMSO, 90 $^\circ\text{C}$): δ 8.65 (d, 1 H, $J = 4.6$ Hz), 7.92 (d, 1 H, $J = 9.3$ Hz), 7.51 (d, 1 H, $J = 4.6$ Hz), 7.46 (d, 1 H, $J = 2.7$ Hz), 7.40 (dd, 1 H, $J = 9.1, 2.8$ Hz), 7.39-7.28 (m, 5 H), 7.16 (d, 1 H, $J = 15.6$ Hz), 6.56-6.50 (m, 1 H), 5.87 (ddd, 1 H, $J = 17.3, 10.4, 2.1$ Hz), 5.20-5.05 (m, 4 H), 4.02-3.98 (m, 1 H), 3.93 (s, 3 H), 3.17 (dd, 1 H, $J = 13.2, 3.2$ Hz), 3.02-2.97 (m, 1 H), 2.48-2.45 (m, 1 H), 2.37-2.24 (m, 2 H), 1.97-1.91 (m, 1 H), 1.60 (dd, 1 H, $J = 13.4, 3.7$ Hz), 1.50-1.42 (m, 1 H), 1.26 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3): δ 157.6, 155.4, 147.3, 144.3, 142.0, 136.8, 135.4, 131.1, 128.3, 127.8, 127.7, 127.0, 126.6, 121.7, 117.5, 117.4, 101.4, 66.9, 55.4, 49.0, 48.5, 43.9, 42.5, 38.9, 37.3, 27.2; IR (film): 2928, 2360, 2340, 1695, 1619, 1506, 1470, 1432, 1365, 1229 cm^{-1} ; HRMS (CI) calcd for $\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_3$ [$M + 1$]: 443.2335, found: 443.2332.

7-Hydroxy-9-(4-methoxybenzyloxy)-quinine (24)—To a solution of KH (30% in oil, 47 mg, 0.35 mmol, 120 mol%) in DMF (2.9 mL, 0.1 M) at 0 $^\circ\text{C}$ was added diol **3** (100 mg, 0.30 mmol, 100 mol%). The reaction mixture stirred at 0 $^\circ\text{C}$ for 35 minutes, at which point PMBCl (40 μL , 0.42 mmol, 140 mol%) was added and the mixture was warmed to 4 $^\circ\text{C}$. After 46 hours at 4 $^\circ\text{C}$, the reaction mixture was poured into H_2O and extracted with Et_2O with the aid of a separatory funnel. The combined ethereal extracts were washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2 : $\text{DCM}:\text{MeOH}$, 40:1 to 30:1) to provide the title compound (0.11 g, 0.23 mmol) as a white foam in 78% yield. ^1H NMR (400 MHz, d_6 -DMSO): δ 8.71 (d, 1 H, $J = 4.4$ Hz), 7.95 (d, 1 H, $J = 8.9$ Hz), 7.55 (m, 1 H), 7.49 (d, 1 H, $J = 4.4$ Hz), 7.41 (dd, 1 H, $J = 9.2, 2.7$ Hz), 7.18 (d, 2 H, $J = 8.5$ Hz), 6.88 (d, 2 H, $J = 8.5$ Hz), 5.91-5.82 (m, 1 H), 5.13 (brs, 1 H), 4.98-4.91 (m, 2 H), 4.30 (d, 1 H, $J = 10.9$ Hz), 4.20 (d, 1 H, $J = 10.9$ Hz), 3.86 (s, 3 H), 3.72 (s, 3 H), 3.13 (m, 2 H), 2.88-2.72 (m, 1 H), 2.42-2.32 (m, 2 H), 2.17 (m, 1 H), 1.83 (m, 1 H), 1.72 (m, 1 H), 1.60-1.59 (m, 2 H), 1.42 (m, 1 H); ^{13}C NMR (100 MHz, d_6 -DMSO): δ 158.6, 156.4, 147.5, 142.2, 141.9, 131.2, 131.0, 130.9, 130.3, 130.1, 129.4, 129.2, 129.0, 121.0, 114.4, 113.6, 71.5, 70.8, 70.1, 63.0, 55.3, 55.0, 54.4, 34.6, 30.5; IR (film): 2931, 2360, 2340, 1684, 1618, 1518, 1543, 1363, 1240, 1036 cm^{-1} ; HRMS (CI) calcd for $\text{C}_{28}\text{H}_{33}\text{N}_2\text{O}_4$ [$M + 1$]: 461.2440, found: 461.2442.

7-Hydroxy-9-(methoxymethoxy)-quinine (25)—To a solution of KH (30% in oil, 47 mg, 0.35 mmol, 120 mol%) in DMF (2.9 mL, 0.1 M) at 0 $^\circ\text{C}$ was added diol **3** (100 mg, 0.30 mmol, 100 mol%). The reaction mixture stirred at 0 $^\circ\text{C}$ for 35 minutes at which time MOMCl (30 μL , 0.39 mmol, 130 mol%) was added and the mixture was warmed to 4 $^\circ\text{C}$. After 45 hours

at 4 °C, the reaction mixture was poured into H₂O, and extracted with Et₂O with the aid of a separatory funnel. The combined ethereal extracts were washed with water, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO₂: DCM:MeOH, 40:1 to 30:1) to provide the title compound (60 mg, 0.17 mmol) as a colorless oil in 58% yield. ¹H NMR (400 MHz, CDCl₃): δ 8.74 (brs, 1 H), 8.02 (d, 1 H, *J* = 9.2 Hz), 7.46 (brs, 1 H), 7.38-7.35 (m, 2 H), 5.92-5.79 (m, 1 H), 5.07-5.04 (m, 2 H), 4.57 (d, 1 H, *J* = 5.8 Hz), 4.40 (m, 1 H), 3.94 (s, 3 H), 3.68-3.52 (m, 1 H), 3.36 (s, 3 H), 3.30-3.16 (m, 1 H), 2.79 (m, 1 H), 2.52-2.43 (m, 3 H), 2.23-2.19 (m, 3 H), 1.28-1.17 (m, 3 H); ¹³C NMR (125 MHz, d₆-DMSO): δ 156.6, 156.5, 147.5, 142.2, 131.1, 131.0, 120.8, 120.7, 114.7, 114.4, 102.8, 95.9, 79.1, 55.4, 55.3, 54.3, 41.7, 34.6, 32.6, 30.4, 29.0, 20.4; IR (film): 3246 (br), 2929, 2361, 2340, 1622, 1508, 1473, 1244, 1101, 1032, 668 cm⁻¹; HRMS (CI) calcd for C₂₂H₂₉N₂O₄ [M + 1]: 385.2127, found: 385.2124.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

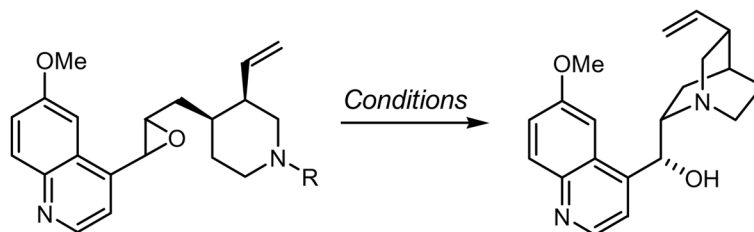
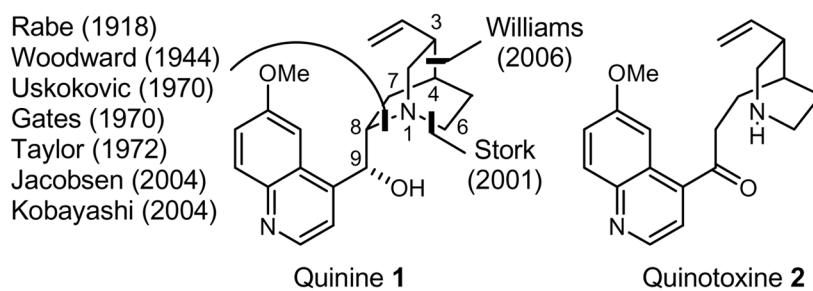
Acknowledgments

Acknowledgment is made to the Research Corporation Cottrell Scholar Program, the Sloan Foundation, the Dreyfus Foundation, Eli Lilly, Johnson & Johnson, the Robert A. Welch Foundation and the NSF (CHE-0749016) for partial support of this research.

References

1. For a authoritative review on quinine, including previous syntheses, see: Kaufman TS, Rúveda EA. *Angew Chem Int Ed* 2005;44:854.
2. For reviews on malaria, see: (a) Greenwood B, Mutabingwa T. *Nature* 2002;415:670. [PubMed: 11832954] (b) Wiesner J, Ortmann R, Jomaa H, Schlitzer M. *Angew Chem Int Ed* 2003;42:5274.
3. (a) Pelletier PJ, Caventou JB. *Ann Chim Phys* 1820;15:291. (b) Pelletier PJ, Caventou JB. *Ann Chim Phys* 1820;15:337.
4. Rabe P, Kindler K. *Ber Dtsch Chem Ges* 1918;51:466.
5. (a) Woodward RB, Doering WE. *J Am Chem Soc* 1944;66:849. (b) Woodward RB, Doering WE. *J Am Chem Soc* 1945;67:860.
6. Smith AC, Williams RM. *Angew Chem Int Ed* 2008;47:1736.
7. Seeman JJ. *Angew Chem Int Ed* 2007;46:1378.
8. (a) Uskoković M, Gutzwiller J, Henderson T. *J Am Chem Soc* 1970;92:203. [PubMed: 5410107] (b) Gutzwiller J, Uskoković M. *J Am Chem Soc* 1970;92:204. [PubMed: 5410108] (c) Gutzwiller J, Uskoković MR. *J Am Chem Soc* 1978;100:576. (d) Grethe G, Lee HL, Mitt T, Uskoković MR. *J Am Chem Soc* 1978;100:581. (e) Grethe G, Lee HL, Mitt T, Uskoković MR. *J Am Chem Soc* 1978;100:589. (f) Gates M, Sugavanam B, Schreiber WL. *J Am Chem Soc* 1970;92:205. [PubMed: 5410109] (g) Taylor EC, Martin SF. *J Am Chem Soc* 1972;94:6218. [PubMed: 5054415] (h) Stork G, Niu D, Fujimoto A, Koft ER, Balkovec JM, Tata JR, Dake GR. *J Am Chem Soc* 2001;123:3239. [PubMed: 11457058] (i) Raheem IT, Goodman SN, Jacobsen EN. *J Am Chem Soc* 2004;126:706. [PubMed: 14733531] (j) Igarashi J, Katsukawa M, Wang YG, Acharaya HP, Kobayashi Y. *Tetrahedron Lett* 2004;45:3783. (k) Igarashi J, Kobayashi Y. *Tetrahedron Lett* 2005;46:6381.
9. Johns DM, Mori M, Williams RM. *Org Lett* 2006;8:4051. [PubMed: 16928071]
10. Jellerichs BG, Kong J-R, Krische MJ. *J Am Chem Soc* 2003;125:7758. [PubMed: 12822967] For a related cycloallylation methodology see, Krafft ME, Haxell TFN. *J Am Chem Soc* 2005;127:10168. [PubMed: 16028918]
11. Oppolzer W, Fürstner A. *Helv Chim Acta* 1993;76:2329.
12. Jung ME, Piizzi G. *Chem Rev* 2005;105:1735. [PubMed: 15884788]
13. Tsuda T, Hayashi T, Satomi H, Kawamoto T, Saegusa T. *J Org Chem* 1986;51:537.

14. (a) Estévez C, Venemalm L, Alvarez M, Joule J. *Tetrahedron* 1994;50:7879. (b) Theeraladanon C, Arisawa M, Nishida A, Nakagawa M. *Tetrahedron* 2004;60:3017. (c) Biot C, Delhaes L, Maciejewski LA, Mortuaire M, Campus D, Dive D, Brocard JS. *Eur J Med Chem* 2000;35:707. [PubMed: 10960186]
15. Sharpless KB, Michaelson RC. *J Am Chem Soc* 1973;95:6136.
16. Hoveyda AH, Evans DA, Fu GC. *Chem Rev* 1993;93:1307.
17. (a) Michaelson RC, Palermo RE, Sharpless KB. *J Am Chem Soc* 1977;99:1990. (b) Hoshino Y, Yamamoto H. *J Am Chem Soc* 2000;122:10452. (c) Zhang W, Basak A, Kosugi Y, Hoshino Y, Yamamoto H. *Angew Chem Int Ed* 2005;44:4389.
18. Berrisford DJ, Bolm C, Sharpless KB. *Angew Chem Int Ed Engl* 1995;34:1059.
19. Barton DHR, McCombie SW. *J Chem Soc, Perkin Trans 1* 1975:1574.
20. Stotter PL, Friedman MD, Minter DE. *J Org Chem* 1985;50:29.
21. (a) Barton DHR, Crich D. *J Chem Soc, Chem Commun* 1984:774. (b) Barton DHR, Crich D. *J Chem Soc Perkin Trans 1* 1986:1603.
22. (a) Barton DHR, McCombie SW. *J Chem Soc Perkin Trans 1* 1975:1574. (b) Barton DHR, Hartwig W, Motherwell RSH, Motherwell WB, Stange A. *Tetrahedron Lett* 1982;23:2019.
23. Pfenninger J, Heuberger C, Graf W. *Helv Chim Acta* 1980;63:2328.
24. Collman JP. *Acc Chem Res* 1975;8:342.
25. Kim SH, Rieke RD. *Tetrahedron Lett* 1999;40:4931.
26. Radivoy G, Alonso F, Moglie Y, Vitale C, Yus M. *Tetrahedron* 2005;61:3859.
27. Hutchins RO, Learn K, Fulton RP. *Tetrahedron Lett* 1980;21:27.
28. Kuroda H, Hanaki E, Izawa H, Kano M, Itahasi H. *Tetrahedron* 2004;60:1913.
29. (a) Lin X, Artmant GD III, Stien D, Weinreb SM. *Tetrahedron* 2001;57:8779. (b) Grigat H, Zinner G. *Arch Pharm* 1986:1037.

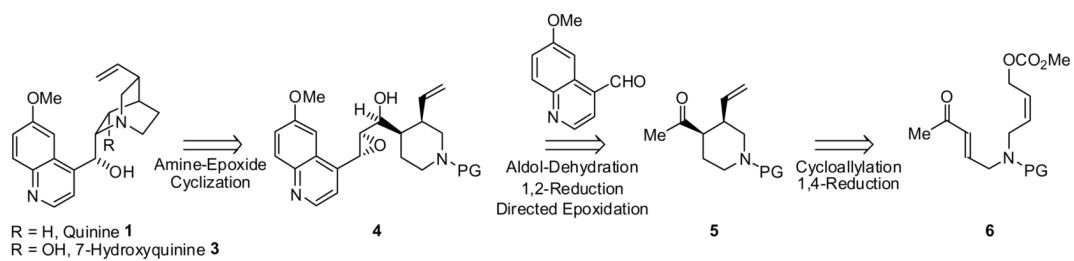


Uskokovic: R = H, Mixture of Epoxide Epimers
 EtOH, PhMe, 110 °C, 73% Yield (4 Diastereomers)
Jacobsen: R = Cbz, Single Epoxide Diastereomer
 (a) Et₂AlCl, PhSMe, 0 °C. (b) μw, MeCN, 185 °C, 68% Yield
Kobayashi: R = Bz, Single Epoxide Diastereomer
 (a) DIBAL, PhMe. (b) DMF, 160 °C, 66% Yield

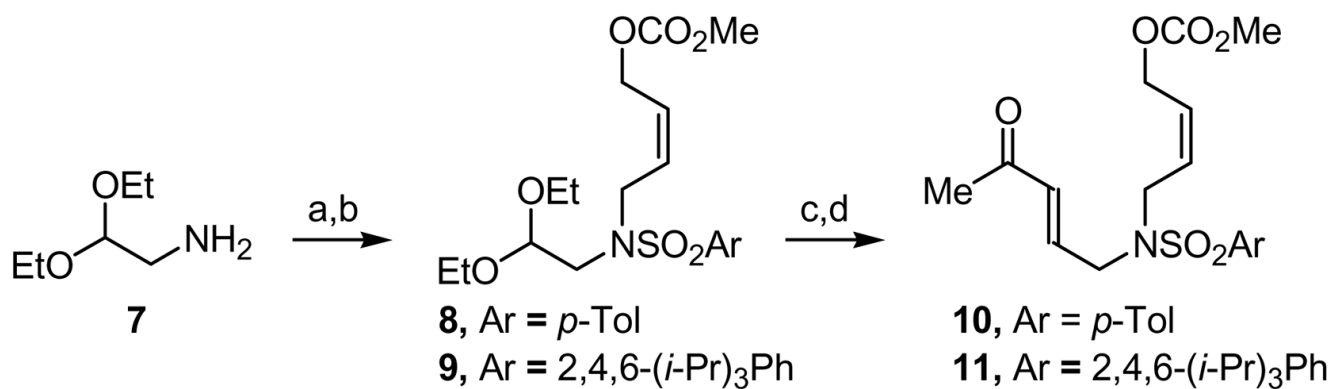
Scheme 1.

Top: Strategic bond constructions in prior syntheses and synthetic approaches to quinine.

Bottom: Key amine-epoxide cyclization developed by Uskoković.

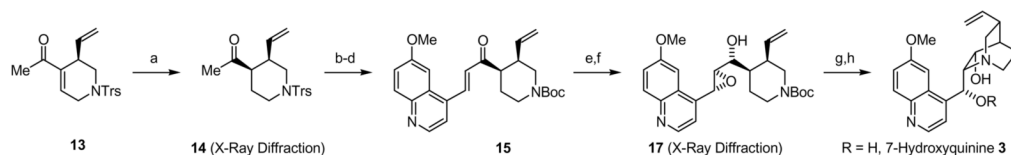
**Scheme 2.**

Retrosynthetic analysis of quinine *via* merged Morita-Baylis-Hillman-Tsuji-Trost cycloallylation.

**Scheme 3.**

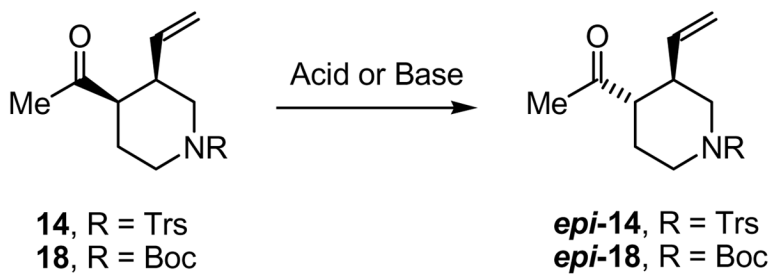
Preparation of enone-allyl carbonates **10** and **11**.

Reagents: (a) ArSO₂Cl, Et₃N, DCM, 0 °C. (b) (*Z*)-4-hydroxy-2-butenyl methyl carbonate, DIAD, PPh₃, THF, 0 °C. Ar = *p*-Tol, 86% over two steps. Ar = 2,4,6-*i*-Pr₃Ph, 99% over two steps. (c) TFA, H₂O, CHCl₃, 0 °C. (d) Ph₃P=CHCOMe, DCM, rt. Ar = *p*-Tol, 69% over two steps. Ar = 2,4,6-*i*-Pr₃Ph, 68% over two steps.

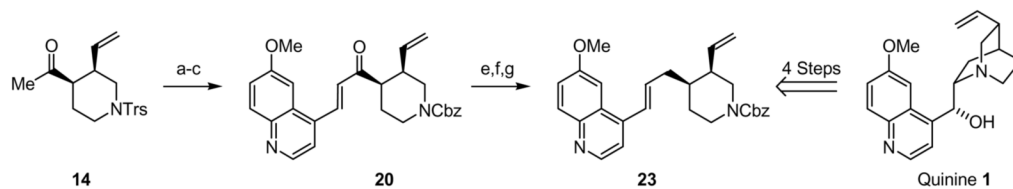
**Scheme 4.**

Stereoselective conversion of cycloallylation product **13** to (±)-7-hydroxyquinine employing a series of 1,2-asymmetric induction events.

Reagents: (a) CuI, MeLi, DIBAL, THF-HMPA, $-78\text{ }^{\circ}\text{C}$. 77% yield, >20:1 dr. (b) Na, naphthalene, DME, $-78\text{ }^{\circ}\text{C}$. (c) Boc_2O , Et_3N , DMAP, DCM, $0\text{ }^{\circ}\text{C}$. 76% yield over two steps. (d) LHMDS, 6-methoxyquinoline-4-carbaldehyde, THF, $-78\text{ }^{\circ}\text{C}$. Then Ac_2O , DMAP, DBU, $-78\text{ }^{\circ}\text{C}$ to $-40\text{ }^{\circ}\text{C}$. 70% yield. (e) L-selectride, THF, $-78\text{ }^{\circ}\text{C}$. 94% yield, >20:1 dr. (f) VO [tBuCO(MeNO)]₂, TBHP, DCM, $4\text{ }^{\circ}\text{C}$. 91% yield, 17:1 dr. (g) TFA, DCM, $0\text{ }^{\circ}\text{C}$. (h) Zn (OTf)₂, Na_2CO_3 , MeCN, $80\text{ }^{\circ}\text{C}$. 70% yield over two steps.

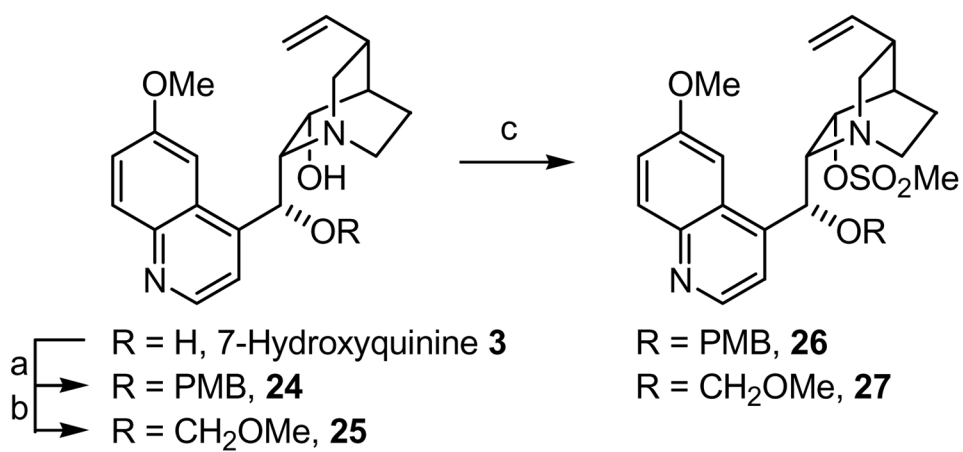
**Scheme 5.**

Epimerization to thermodynamically preferred *trans*-piperidine **14** and **18**.

**Scheme 6.**

Formal synthesis of (±)-quinine **1** via conversion of *cis*-piperidine **14** to diene **23**.

Reagents: (a) Na, naphthalene, DME, $-78\text{ }^{\circ}\text{C}$. (b) CbzCl, Et_3N , DCM, $0\text{ }^{\circ}\text{C}$. 61% yield over two steps. (c) LHMDS, 6-methoxyquinoline-4-carbaldehyde, THF, $-78\text{ }^{\circ}\text{C}$. Then Ac_2O , DMAP, DBU, $-78\text{ }^{\circ}\text{C}$ to $-40\text{ }^{\circ}\text{C}$. 64% yield. (e) L-selectride, THF, $-78\text{ }^{\circ}\text{C}$. 96% yield, >20:1 dr. (f) Ac_2O , Et_3N , DMAP, DCM, $0\text{ }^{\circ}\text{C}$. 81% yield. (g) $\text{Pd}(\text{PPh}_3)_4$, PBU_3 , HCO_2H , Et_3N , THF, $25\text{ }^{\circ}\text{C}$. 78% yield.

**Scheme 7.**

Selective functionalization of 7-hydroxyquinine **3**.

Reagents: (a) KH, DMF, PMBCl, 4 °C. 78% yield. (b) KH, DMF, MOMCl, 4 °C. 58% yield. (c) MsCl, pyr.

Table 1

Selected experiments in the optimization of the merged Morita-Baylis-Hillman-Tsuji-Trost reaction of enone-allyl carbonates **10** and **11**.^a

R	Pd(PPh ₃) ₄	Phosphine	Solvent	T °C	Yield
Ts	1.0 mol%	PBu ₃ (100 mol%)	<i>t</i> -BuOH, 0.1 M	60 °C	3%
Ts	5.0 mol%	PBu ₃ (100 mol%)	<i>t</i> -BuOH, 0.1 M	60 °C	13%
Ts	5.0 mol%	PBu ₃ (100 mol%)	<i>t</i> -BuOH, 0.1 M	35 °C	46%
Ts	5.0 mol%	PBu ₃ (100 mol%)	<i>t</i> -AmOH, 0.1 M	25 °C	62%
Ts	5.0 mol%	PBu ₃ (100 mol%)	<i>t</i> -AmOH, 0.1 M	0 °C	55%
Ts	5.0 mol%	PMe ₃ (100 mol%)	<i>t</i> -AmOH, 0.1 M	25 °C	39%
Ts	5.0 mol%	PBu ₃ (100 mol%)	<i>t</i> -AmOH, 0.1 M	25 °C	27%
Ts	5.0 mol%	PMe ₃ (100 mol%)	<i>t</i> -AmOH, 0.1 M	25 °C	63%
Trs	5.0 mol%	PMe₃ (80 mol%)	<i>t</i>-AmOH, 0.1 M	25 °C	68%
Trs	5.0 mol%	PMe ₃ (65 mol%)	<i>t</i> -AmOH, 0.1 M	25 °C	60%
Trs	2.5 mol%	PMe ₃ (80 mol%)	<i>t</i> -AmOH, 0.1 M	25 °C	57%
Trs	5.0 mol%	PMe ₃ (80 mol%)	<i>t</i> -AmOH, 0.05 M	25 °C	27%

^aIsolated yields of material purified by silica gel chromatography.