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

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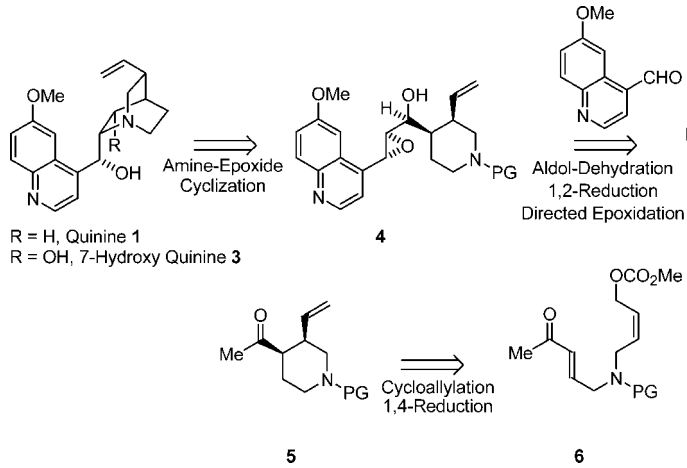

Concise stereoselective syntheses of (±)-quinine and (±)-7-hydroxyquinine are achieved using a catalytic enone cycloallylation that combines the nucleophilic features of the Morita−Baylis−Hillman reaction and the electrophilic features of the Tsuji−Trost reaction. Cyclization of enone−allyl carbonate **11** delivers the product of cycloallylation **13** in 68% yield. Diastereoselective conjugate reduction of the enone **13** (>20:1 dr) followed by exchange of the *N*-protecting group 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. Deoxygenation of the *N*-Cbz-protected allylic acetate **22** provides 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.

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

(1) For an authoritative review on quinine, including previous syntheses, see: Kaufman, T. S.; Rúveda, E. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 854.

(2) For reviews on malaria, see: (a) Greenwood, B.; Mutabingwa, T. *Nature* **2002**, *415*, 670. (b) Wiesner, J.; Ortmann, R.; Jomaa, H.; Schlitzer, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5274.

(3) (a) Pelletier, P. J.; Caventou, J.-B. *Ann. Chim. Phys.* **1820**, *15*, 291. (b) Pelletier, P. J.; Caventou, J.-B. *Ann. Chim. Phys.* **1820**, *15*, 337.

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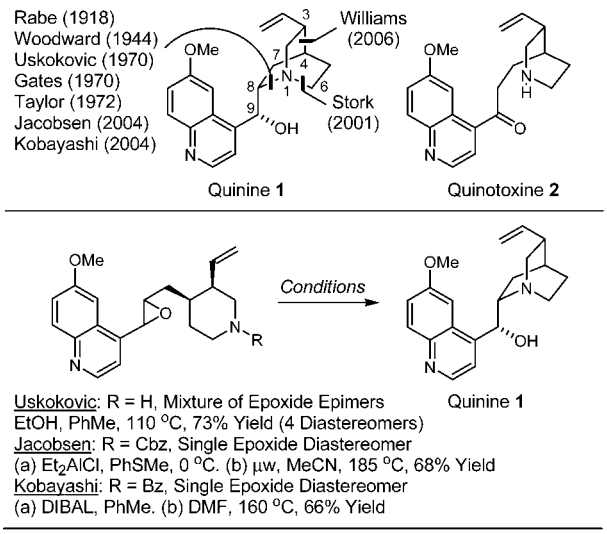
SCHEME 1[a]



[a] (Top) Strategic Bond Constructions in Prior Syntheses and Synthetic Approaches to Quinine. (Bottom) Key Amine−Epoxide Cyclization Developed by Uskoković.

of quinotoxine **2**, a compound that was converted to quinine in three manipulations by Rabe.[4] Recently, Williams and co-workers 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]

Subsequent to Woodward's seminal work, total syntheses of quinine **1** were reported by Uskoković, Gates, Taylor, Stork, Jacobsen, and Kobayashi.[8] Uskokovic 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 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 **1** and quinidine. 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 (±)-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 (±)-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 via aldol 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*-toluenesulfonyl chloride or 2,4,6-trisopropylbenzenesulfonyl chloride provides the crude sulfonamides which under Mitsunobu conditions couple to (*Z*)-4-hydroxy-2-butenyl methyl carbonate[11] 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

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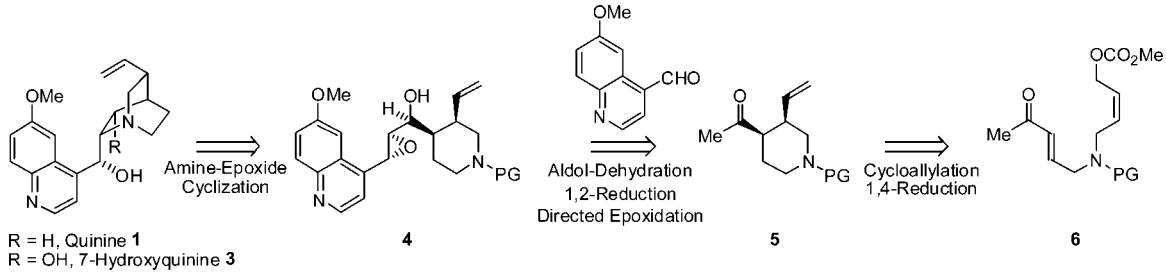
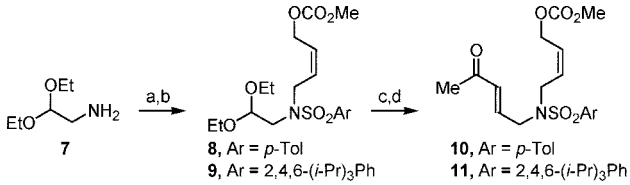
SCHEME 2. Retrosynthetic Analysis of Quinine via Merged Morita−Baylis−Hillman−Tsuji−Trost Cycloallylation



SCHEME 3. Preparation of Enone−Allyl Carbonates 10 and 11

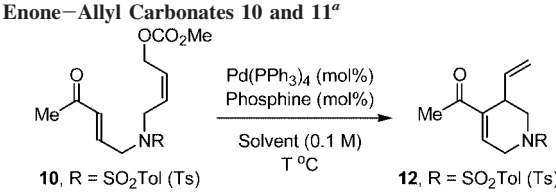


Reagents: (a) $ArSO_2Cl$, Et_3N, DCM, 0 °C. (b) (*Z*)-4-hydroxy-2-butenyl methyl carbonate, DIAD, PPh_3, THF, 0 °C. Ar = *p*-Tol, 86% over two steps. Ar = 2,4,6-(*i*-Pr)$_3$Ph, 99% over two steps. (c) TFA, H_2O, $CHCl_3$, 0 °C. (d) Ph_3P=CHCOMe, DCM, rt. Ar = *p*-Tol, 69% over two steps. Ar = 2,4,6-(*i*-Pr)$_3$Ph, 68% over two steps.

substrate to $Pd(PPh_3)_4$ (1 mol%), PBu_3(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 anionic 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 E_2-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 a 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 ^{1}H NMR analysis. The relative stereochemistry of piperidine **14** was corroborated by 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).

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%)	*t*-BuOH, 0.1 M	60 °C	3%
Ts	5.0 mol%	PBu_3 (100 mol%)	*t*-BuOH, 0.1 M	60 °C	13%
Ts	5.0 mol%	PBu_3 (100 mol%)	*t*-BuOH, 0.1 M	35 °C	46%
Ts	5.0 mol%	PBu_3 (100 mol%)	*t*-AmOH, 0.1 M	25 °C	62%
Ts	5.0 mol%	PBu_3 (100 mol%)	*t*-AmOH, 0.1 M	0 °C	55%
Ts	5.0 mol%	PMe_3 (100 mol%)	*t*-AmOH, 0.1 M	25 °C	39%
Trs	5.0 mol%	PBu_3 (100 mol%)	*t*-AmOH, 0.1 M	25 °C	27%
Trs	5.0 mol%	PMe_3 (100 mol%)	*t*-AmOH, 0.1 M	25 °C	63%
Trs	**5.0 mol%**	**PMe_3 (80 mol%)**	***t*-AmOH, 0.1 M**	**25 °C**	**68%**
Trs	5.0 mol%	PMe_3 (65 mol%)	*t*-AmOH, 0.1 M	25 °C	60%
Trs	2.5 mol%	PMe_3 (80 mol%)	*t*-AmOH, 0.1 M	25 °C	57%
Trs	5.0 mol%	PMe_3 (80 mol%)	*t*-AmOH, 0.05 M	25 °C	27%

[a] Isolated yields of material purified by silica gel chromatography.

In our hands, reductive removal of the *N*-sulfonyl protecting group could not be performed 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 Boc_2O 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 addition-dehydration protocol employing *N*-Boc protected *cis*-piperidine **18** and 6-methoxyquinoline-4-carbaldehyde. To avoid epimerization of the *cis*-piperidine, carefully controlled 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-carbaldehyde[14] 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

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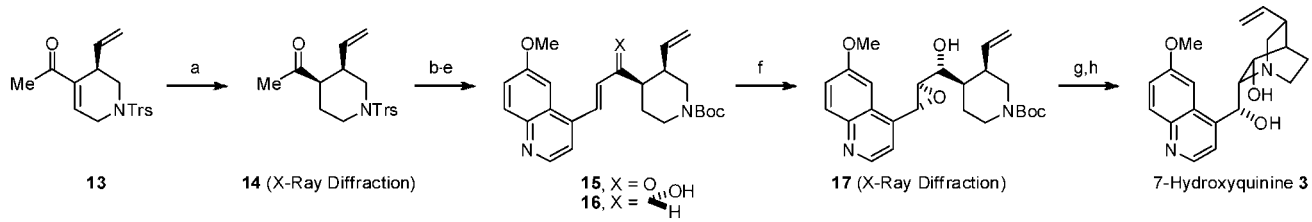
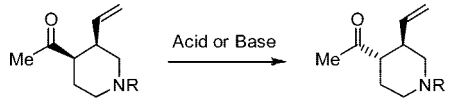
SCHEME 4. Stereoselective Conversion of Cycloallylation Product 13 to (±)-7-Hydroxyquinine Involving a Series of 1,2-Asymmetric Induction Events



Reagents: (a) CuI, MeLi, DIBAL, THF-HMPA, -78 °C. 77% yield, >20:1 dr. (b) Na, naphthalene, DME, -78 °C. (c) Boc_2O, Et_3N, DMAP, DCM, 0 °C. 76% yield over two steps. (d) LHMDS, 6-methoxyquinoline-4-carbaldehyde, THF, -78 °C. Then Ac_2O, DMAP, DBU, -78 °C to -40 °C. 70% yield. (e) L-selectride, THF, -78 °C. 94% yield, >20:1 dr. (f) $VO[tBuCO(MeNO)]_2$, TBHP, DCM, 4 °C. 91% yield, 17:1 dr. (g) TFA, DCM, 0 °C. (h) $Zn(OTf)_2$, Na_2CO_3, MeCN, 80 °C. 70% yield over two steps.

SCHEME 5. Epimerization to Thermodynamically Preferred *trans*-Piperidine 14 and 18



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, the carbon framework of quinine is assembled (Scheme 4).

With clear evidence for the thermodynamic preference of a *trans*-relationship about the piperidine of enone **15**, immediate reduction of the ketone was imperative. 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 ^{1}H NMR analysis (>20:1 dr). This transformation removed the threat of epimerization, while introducing 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 in a 3:1 diastereomeric ratio. Such modest stereoselectivity is presumed to arise 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 $VO[^tBuCO(MeNO)]_2$ (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 $Zn(OTf)_2$ in refluxing MeCN to provide 7-hydroxyquinine **3** in 70% yield. At this point, several different strategies to deoxygenate 7-hydroxyquinine **3** were explored. Selective functionalization of the C-9 hydroxyl is readily achieved, as demonstrated by 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] thioformates[22] 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 ($H_2C{=}SO_2$). 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 a directing group, the reaction of mesylates **26** and **27** with low

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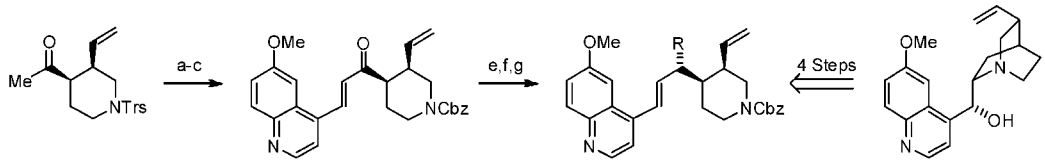
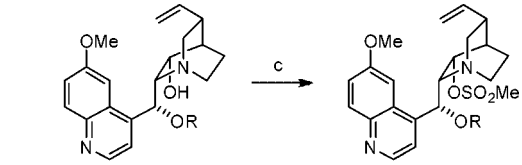
SCHEME 6. Formal Synthesis of (±)-Quinine 1 via Conversion of *cis*-Piperidine 14 to Diene 23



Reagents: (a) Na, naphthalene, DME, -78 °C. (b) CbzCl, Et_3N, DCM, 0 °C. 61% yield over two steps. (c) LHMDS, 6-methoxyquinoline-4-carbaldehyde, THF, -78 °C. Then Ac_2O, DMAP, DBU, -78 °C to -40 °C. 64% yield. (e) L-selectride, THF, -78 °C. 96% yield, >20:1 dr. (f) Ac_2O, Et_3N, DMAP, DCM, 0 °C. 81% yield. (g) $Pd(PPh_3)_4$, PBu_3, HCO_2H, Et_3N, THF, 25 °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.

valent metals was explored. However, the Collman reagent[24] ($Na_2Fe(CO)_4$), Rieke manganese[25] and conditions developed by Yus[26] 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 ^{1}H 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 less manipulations and with complete control of relative stereochemistry.

Summary

Concise stereoselective syntheses of (±)-quinine and (±)-7-hydroxyquinine are reported 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. This route delivers 7-hydroxyquinine in less than half the number of manipulations previously reported.[9]

Among the 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 has been known since the very inception of organic chemistry as a science, may be viewed as a barometer of the state-of-the-art. Hence, it is remarkable that, to date, a highly 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, ^{i}Pr$_2$NH, and HMPA were dried by distillation over CaH_2. Et_2O, 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 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 get plates. 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 (^{1}H NMR) spectra were obtained at either 500, 400, or 300 MHz, as indicated. Chemical shifts are reported in delta (μ) units, parts per million (ppm) downfield from trimethylsilane. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were obtained at either 125, 100, or 75 MHz, as indicated.

(24) Collman, J. P. *Acc. Chem. Res.* **1975**, *8*, 342.
(25) Kim, S.-H.; Rieke, R. D. *Tetrahedron Lett.* **1999**, *40*, 4931.
(26) Radivoy, G.; Alonso, F.; Moglie, Y.; Vitale, C.; Yus, M. *Tetrahedron* **2005**, *61*, 3859.
(27) Hutchins, R. O.; Learn, K.; Fulton, R. P. *Tetrahedron Lett.* **1980**, *21*, 27.

Chemical shifts are reported in delta (μ) units, parts per million (ppm) relative to the residual solvent. ^{13}C NMR spectra were routinely run with broadband decoupling. Vanadium-51 nuclear magnetic resonance (^{51}V NMR) spectra were obtained at 131 MHz. Chemical shifts are reported in delta (μ) units, parts per million (ppm) relative to the singlet at 2.0 ppm for $VOCl_3$. High-resolution mass spectra (HRMS) 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 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 Et_3N (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 h, 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 Cu_2SO_4 (aq.), brine, dried (Na_2SO_4), 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 alcohol[11] (5.72 g, 39.1 mmol, 110 mol%), DIAD (8.32 mL, 42.3 mmol, 120 mol%), and PPh_3 (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 h, at which point the reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2: 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 $CHCl_3$ (74 mL, 0.32 M) and H_2O (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 h, at which point it was quenched with solid $NaHCO_3$, poured into H_2O, and extracted with DCM with the aid of a separatory funnel. The combined organic extracts were washed with saturated $NaHCO_3$ (aq.), brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2: 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, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{15}H_{20}NO_6S$ [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 reagent[28] (0.24 g, 0.75 mmol, 100 mol%). The reaction mixture was allowed to stir for 20 h, at which point the reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2/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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{18}H_{24}NO_6S$ [M + 1]: 382.1324, found: 382.1329.

(28) Kuroda, H.; Hanaki, E.; Izawa, H.; Kano, M.; Itahasi, H. *Tetrahedron* **2004**, *60*, 1913.

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 Et_3N (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 h with stirring, at which point the reaction mixture was poured into H_2O and extracted with DCM with the aid of a separatory funnel. The combined organic extracts were washed with 5% Cu_2SO_4 (aq.), brine, dried (Na_2SO_4), 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 alcohol[11] (17.67 g, 121.1 mmol, 150 mol%), DIAD (25.4 mL, 129.1 mmol, 160 mol%), and PPh_3 (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 h, at which point the reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2/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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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) calcd for $C_{27}H_{44}NO_7S$ [M − 1]: 526.2839, found: 526.2845.

Compound **9** (29.38 g, 55.70 mmol, 100 mol%) was dissolved in $CHCl_3$ (137 mL, 0.4 M) and H_2O (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 h, at which point solid $NaHCO_3$ was added and the reaction mixture was poured into H_2O, and extracted with DCM with the aid of a separatory funnel. The combined organic extracts were washed with saturated $NaHCO_3$ (aq.), brine, dried (Na_2SO_4), 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 reagent[28] (19.73 g, 61.98 mmol, 110 mol%). The reaction mixture was allowed to stir for 18 h, at which point the reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2:/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, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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) calcd for $C_{26}H_{40}NO_6S$ [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 $Pd(PPh_3)_4$ (13 mg, 0.01 mmol, 5 mol%) and freshly distilled PBu_3 (50 μL, 0.2 mmol, 100 mol%). The reaction mixture was allowed to stir at ambient temperature for 20 min, at which point the reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2: 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, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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) calcd for $C_{16}H_{20}NO_3S$ [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 $Pd(PPh_3)_4$ (59 mg, 0.05 mmol, 5 mol%) and PMe_3 (1.0 M in toluene, 0.82 mL, 0.8 mmol, 80 mol%). The reaction mixture was allowed to stir for 30 min, 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 (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2/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. ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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) calcd for $C_{24}H_{36}NO_3S$ [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 Et_2O, 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 h 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 min, 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 H_2O and extracted with Et_2O with the aid of a separatory funnel. The combined organic layers 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, 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; ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{24}H_{38}NO_3S$ [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 h, 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 s, saturated NH_4Cl (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 $CHCl_3$, 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 Et_3N (3.0 mL, 21.52 mmol, 270 mol%), Boc_2O (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 h, at which point the reaction mixture was quenched with saturated NH_4Cl (aq.) 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, 5:1) to provide the title compound (1.52 g, 6.03 mmol) as a colorless oil in 76% yield. ^{1}H NMR (500 MHz, d_6-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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{14}H_{24}NO_3$ [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 h, at which point the quinoline-bearing aldehyde[14] (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 min, at which point Ac_2O (80 μL, 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 min, at which point it was allowed to reach −40 °C (MeCN/solid CO_2) and was allowed to stir for 30 min. 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 min at −40 °C, at which point it was quenched with saturated NH_4Cl (aq.) and 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 (0.13 g, 0.31 mmol) as a yellow foam in 70% yield. ^{1}H NMR (500 MHz, d_6-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 $C_{25}H_{31}N_2O_4$ [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 min, 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.: 148−149 °C; ^{1}H 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 $C_{25}H_{33}N_2O_4$ [M + 1]: 425.2440, found: 425.2441.

VO(hydroxamate)$_2$. To a solution of the known hydroxamic acid[29] (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 $VO(SO)_4\mu H_2O$ (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 min, at which point the reaction mixture was cooled to 0 °C and VO(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.: 134−135 °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 $C_{12}H_{25}N_2O_5V$ [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 VO(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 h, 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. ^{1}H 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 $C_{25}H_{33}N_2O_5$ [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 h, 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 $Zn(OTf)_2$ (65 mg, 0.18 mmol, 150 mol%) were added. The reaction mixture was allowed to stir at 80 °C for 41 h, 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.); ^{1}H 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 $C_{20}H_{25}N_2O_3$ [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 h, 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 s, saturated NH_4Cl (aq.) was added. The crude reaction mixture was filtered through a pipet 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 h, 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. ^{1}H 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 $C_{17}H_{22}NO_3$ [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 °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 °C for 1 h, at which point the quinoline bearing aldehyde[14] (39 mg, 0.21 mmol, 140 mol%) was added. The reaction mixture was allowed to stir at −78 °C for 1 h, 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 °C for an additional 45 min, at which point the reaction mixture was allowed to reach −40 °C (MeCN/solid CO_2) and was allowed to stir for 30 min. DBU (0.11 mL, 0.74 mmol, 500 mol%) was added to the reaction mixture at −40 °C. The reaction mixture was stirred for 15 min at −40 °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. ^{1}H NMR (500 MHz, d_6-DMSO, 90 °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

(29) (a) Lin, X.; Artmant, G. D., III; Stien, D.; Weinreb, S. M. *Tetrahedron* **2001**, *57*, 8779. (b) Grigat, H.; Zinner, G. *Arch. Pharm.* **1986**, 1037.

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 $C_{28}H_{29}N_2O_4$ [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 °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 min 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. ^{1}H NMR (500 MHz, d_6-DMSO, 90 °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 cm^{-1}; HRMS (CI) calcd for $C_{28}H_{31}N_2O_4$ [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 °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 min, 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. ^{1}H NMR (500 MHz, d_6-DMSO, 90 °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 $C_{30}H_{33}N_2O_5$ [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 $Pd(PPh_3)_4$ (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 h, 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. ^{1}H NMR (500 MHz, d_6-DMSO, 90 °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 $C_{28}H_{30}N_2O_3$ [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 °C was added diol **3** (100 mg, 0.30 mmol, 100 mol%). The reaction mixture stirred at 0 °C for 35 min, at which point PMBCl (40 μL, 0.42 mmol, 140 mol%) was added and the mixture was warmed to 4 °C. After 46 h at 4 °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/DCM/MeOH, 40:1 to 30:1) to provide the title compound (0.11 g, 0.23 mmol) as a white foam in 78% yield. ^{1}H 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 $C_{28}H_{33}N_2O_4$ [M + 1]: 461.2440, found: 461.2442.

7-Hydroxy-9-(methoxymethyloxy)-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 °C was added diol **3** (100 mg, 0.30 mmol, 100 mol%). The reaction mixture stirred at 0 °C for 35 min at which time MOMCl (30 μL, 0.39 mmol, 130 mol%) was added and the mixture was warmed to 4 °C. After 45 h at 4 °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/DCM/MeOH, 40:1 to 30:1) to provide the title compound (60 mg, 0.17 mmol) as a colorless oil in 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (125 MHz, d_6-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 $C_{22}H_{29}N_2O_4$ [M + 1]: 385.2127, found: 385.2124.

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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.

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