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Studies toward the Synthesis of Lepadiformine A

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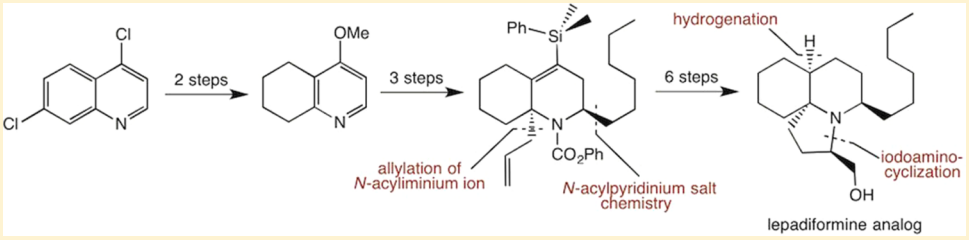
Supporting Information



ABSTRACT: Herein is described an original approach to access a tricyclic framework of the lepadiformine-type alkaloids. A Grignard/*N*-acylpyridinium salt reaction of a 4-methoxytetrahydroquinoline is the key carbon−carbon bond-forming step that was used to establish the desired absolute stereochemistry at the C2 position of the target alkaloid. The synthesis features an allylation reaction with an *N*-acyliminium ion to set the C10 quaternary stereocenter, a mild dissolving-metal cleavage of hindered phenyl carbamates, and an aminoiodocyclization to form the pyrrolidine ring. While this route does not provide the correct C10 stereochemistry, it showcases an efficient method to build analogues with the ring system of this class of alkaloids in 11 steps overall.

INTRODUCTION

A marine tunicate *Clavelina lepadiformis* was collected in the Mediterranean sea by Biard and served as a source of an azatricyclic alkaloid lepadiformine A (**1a**).[1] This alkaloid belongs to a large family of natural products (Figure 1), and since their initial discovery by Blackman[2] in the early 1990s, more than 10 different alkaloids from a variety of tunicates have been isolated and further characterized. The structural features of this class are unique perhydropyrrolo[2,1-*j*]quinoline or perhydropyrido[2,1-*j*]quinoline frameworks.

Initially, it was proposed that lepadiformine A has a zwitterionic structure **1d** similar to that of cylindricine with a *cis* relationship between the A and B rings (Figure 1);[1] however, this structure was proven to be incorrect since in 1999 the Weinreb group prepared this molecule and comparison of spectroscopic data with naturally isolated material revealed distinct discrepancies.[3] In the same year, Pearson and co-workers accomplished the synthesis of three different diastereomers of originally proposed compound **1d**, but none of the prepared compounds fully matched the authentic alkaloid.[4] A year later, the structure of lepadiformine was finally unambiguously established by the Kibayashi group, who furnished the racemic synthesis of **1a** and prepared a sample of its hydrochloride salt for X-ray crystallographic analysis.[5] The most striking structural element of the alkaloid core is an atypical boat conformation of the B ring that forms to avoid an unfavorable $A^{1,3}$ interaction between the pyrrolidine C-ring and hexyl substituent in the rigid *trans*-fused 1-azadecalin system. Taking into consideration this particular structural element during the initial planning steps is crucial for achieving any success in the synthesis of the core.

Challenging structures of this class of alkaloids prompted significant interest from the scientific community.[6] As a consequence, a multitude of successful approaches toward the total syntheses of lepadiformine were developed. These efforts clearly underlined the difficulties in formation of the C5 and the quaternary C10 stereocenters possessing a *trans* stereochemistry. Retrosynthetically, the majority of routes were designed to introduce these key elements initially and then build a B and C ring system later. Thus, commonly utilized strategies for the indolizidine group members of this alkaloid family were not effective despite a presence of an obvious indolizidine motif (B,C rings) in the lepadiformine structure. The most frequent starting point leading to the most straightforward syntheses of the core was utilization of an amino acid derived building block, pyroglutamic acid, or its derivatives. These strategies took advantage of the initial chirality and carbonyl functionality of the amino acid to build a C-10 quaternary center and to form a cyclohexane A ring in a stereoselective fashion. For example, in the work of Kibayashi,[5] Weinreb,[7] and Hsung,[8] protected lactams were used to generate *N*-acyliminium ions which were cyclized to afford the corresponding *trans*-5,10 spirocycles (Scheme 1). Installation of the piperidine B ring and closing of the *trans*-perhydroquinoline subunit were the finishing elements of these syntheses.

Using similar bond disconnections, the Shibasaki[9] and Kim[10] groups utilized a Mannich−aza Michael cascade and a Claisen−Ireland rearrangement, respectfully, to set the *trans*-5,10

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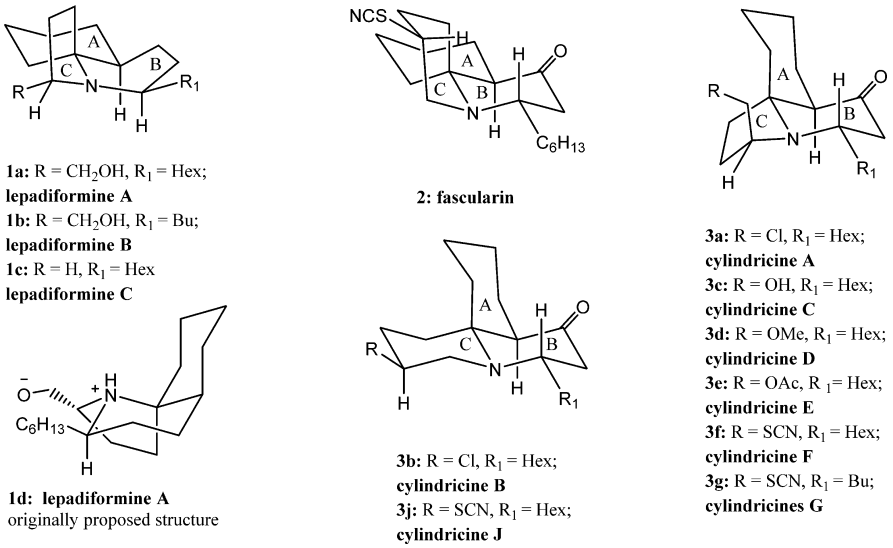
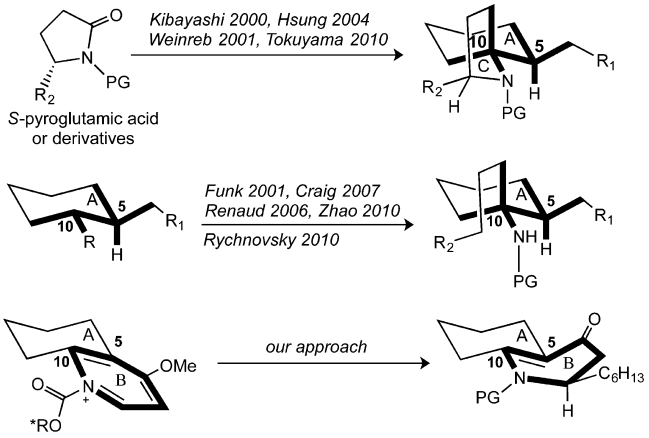


Figure 1. Tricyclic alkaloids isolated from marine tunicates.

Scheme 1. Different Strategies toward the Lepadiformine Skeleton



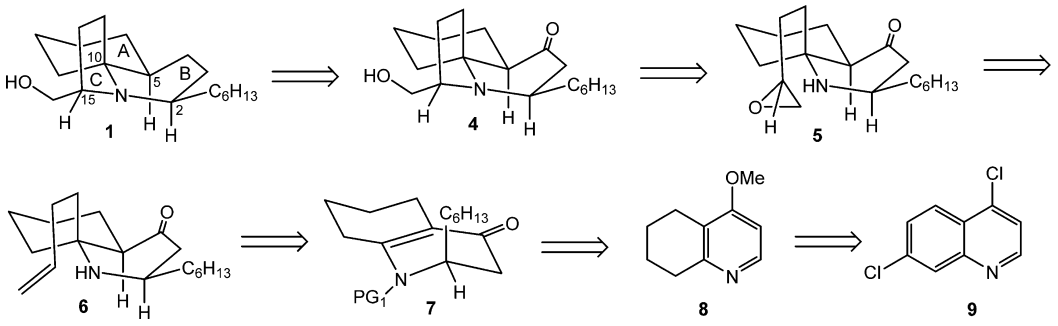
stereocenters. The Tokuyama group[11] accomplished the same goal by application of an unusual 1,5-radical migration translocation−cyclization reaction of an *N*-(2-iodobenzyl)-pyrollidin-2-one.

In another approach, the *trans* relationship between C5 and C10 centers was introduced initially using manipulation of the cyclohexane A ring followed by the formation of the C ring in the later stages of the syntheses (Scheme 1). The Funk[12] and Rychnovsky[13] groups introduced the desired C5/C10 stereochemistry by synthesizing an A ring by using a Diels−Alder strategy with amidoacrolein as a dienophile and a double alkylation of an aminonitrile with a chiral dibromide, respectfully. Craig and co-workers[14] started with an easily accessible cyclohexanone that was converted into a unique spiroaziridine motif and further manipulated to provide the desired pyrrolidine C fragment. The Renaud group[15] developed an inventive radical of exocyclic alkene to introduce the desired functionality. Finally, in the Zhao synthesis,[16] addition of an allylzinc reagent to a chiral *tert*-butanesulfinyl imine was used to set the C10 quaternary center.

Unique strategies to access lepadiformine were recently developed by the Aube group[17] and by Lygo and co-workers.[18] In the first case, a Prins-type reaction of 1-(silyloxy)-1-cyclohexylcyclopropane with an aldehyde furnished a cyclobutanone intermediate, which was subjected to Schmidt rearrangement to forge the desired framework of the natural product. In the second approach, the tricyclic core of lepadiformine was prepared in a one-step protocol using an intramolecular hetero-Diels−Alder reaction.

We envisioned a novel approach for the construction of the lepadiformine core using an alternative disconnection strategy. Herein, we report our attempt at accessing this alkaloid via an unique route from inexpensive 4,7-dichloroquinoline as starting material and using an A/B system as the initial framework to install all stereocenters and the pyrrolidine ring C. Our studies revealed interesting reactivity patterns for nucleophilic

Scheme 2. Retrosynthetic Analysis of Lepadiformine



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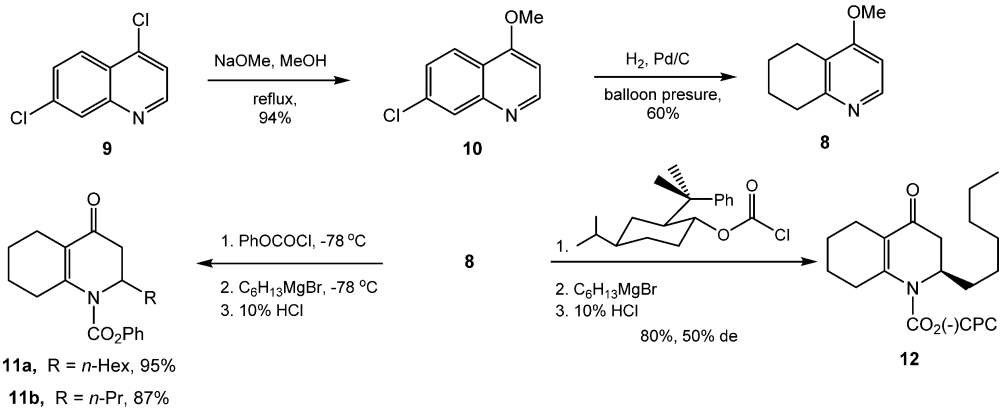
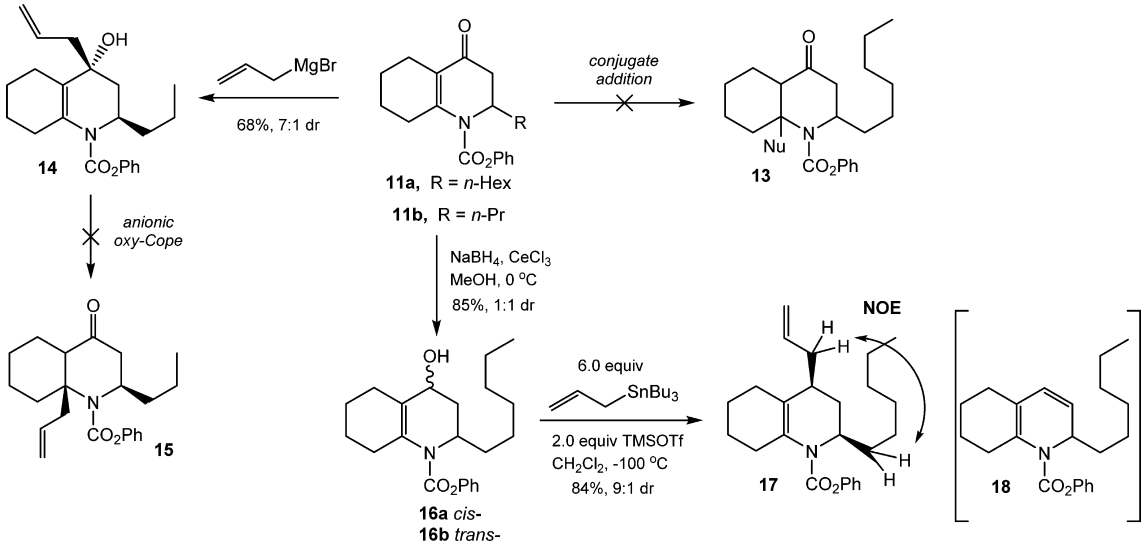
Scheme 3. *N*-Acylpyridinium Salt Reaction of 4-Methoxy-5,6,7,8-tetrahydroquinoline



Scheme 4. Preliminary Attempts at the C10 Quaternary Center Formation



additions of organometallic reagents with hindered bicyclic *N*-acylvinylogous amides. Unexpected stereochemical outcomes of these reactions were observed that differ from anticipated results based on similar transformations of related monocyclic dihydropyridone systems.

RESULTS AND DISCUSSION

1. Retrosynthetic Strategy. A plan was conceived where a simple quinoline would serve as a progenitor for the A and B rings of lepadiformine. Our detailed strategy was based on this idea as shown in Scheme 2. It was envisioned that the initial stereocenter would be installed via an asymmetric *N*-acylpyridinium salt reaction of 4-methoxy-5,6,7,8-tetrahydroquinoline **8** to provide compound **7** having the reactive functionality for introducing the C10 quaternary stereocenter via conjugate addition of an organometallic species. Deprotection of the secondary amine followed by its nucleophilic attack to open a chiral epoxide would form pyrrolidine ring C. Desired epoxide **5** would be prepared using a Sharpless asymmetric dihydroxylation/cyclization sequence starting from the alkene **6**. Finally, the ketone carbonyl would be removed at the end of the synthesis.

2. *N*-Acylpyridinium Salt Reaction of 4-Methoxy-5,6,7,8-tetrahydroquinoline. Commercially available 4,7-dichloroquinoline (**9**) was chosen as a suitable and inexpensive starting material. The synthesis commenced with nucleophilic substitution of the C4 chlorine with a methoxy group upon treatment with NaOMe in refluxing MeOH (Scheme 3). The simultaneous operation of removing the C7 chlorine and reduction of the benzene ring was successfully accomplished using Pd/C and hydrogen at balloon pressure.

Formation of the *N*-acylpyridinium salt with phenyl chloroformate followed by treatment with *n*-hexyl Grignard reagent provided racemic enone **11a** in excellent yield after acidic workup. With compound **11** in hand, the possibility of a corresponding asymmetric synthesis was investigated. The analogous reaction using the chiral chloroformate of (−)-CPC[19] gave octahydroquinolone **12** in an unoptimized but promising 80% yield and 50% de.

3. Introduction of the C10 Quaternary Stereocenter. Our efforts were now directed toward introducing the C10 quaternary center via conjugate addition to **11**. Unfortunately, multiple attempts with a broad range of nucleophiles and Lewis acids did not result in formation of any 1,4-addition product **13** (Scheme 4).

A sigmatropic oxy-Cope rearrangement approach also proved to be unsuccessful. The addition of allyl Grignard to **11b** provided alcohol **14** in 68% yield as a 7:1 mixture favoring the desired diastereomer; however, heating compound **14** in the presence of KH as a base failed to provide the rearrangement

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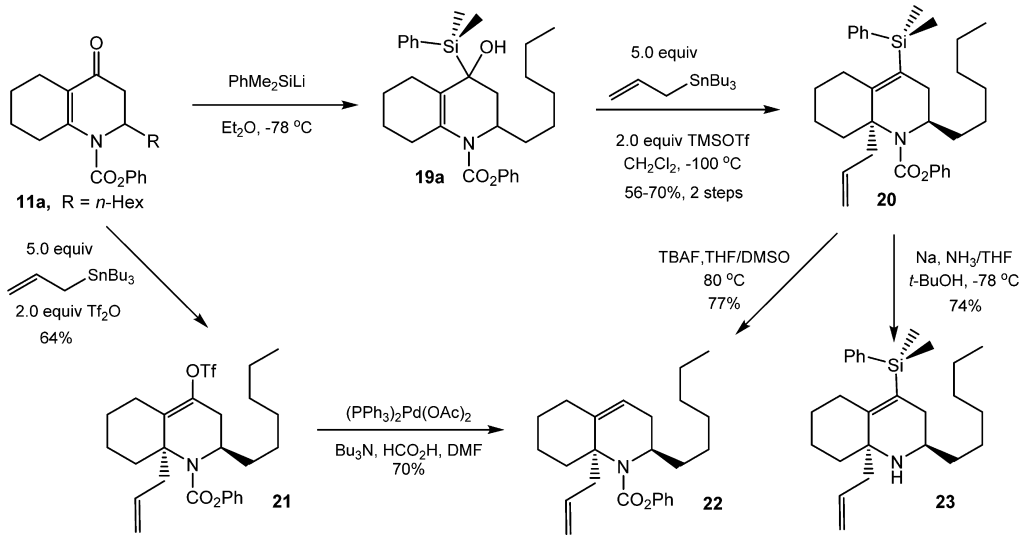
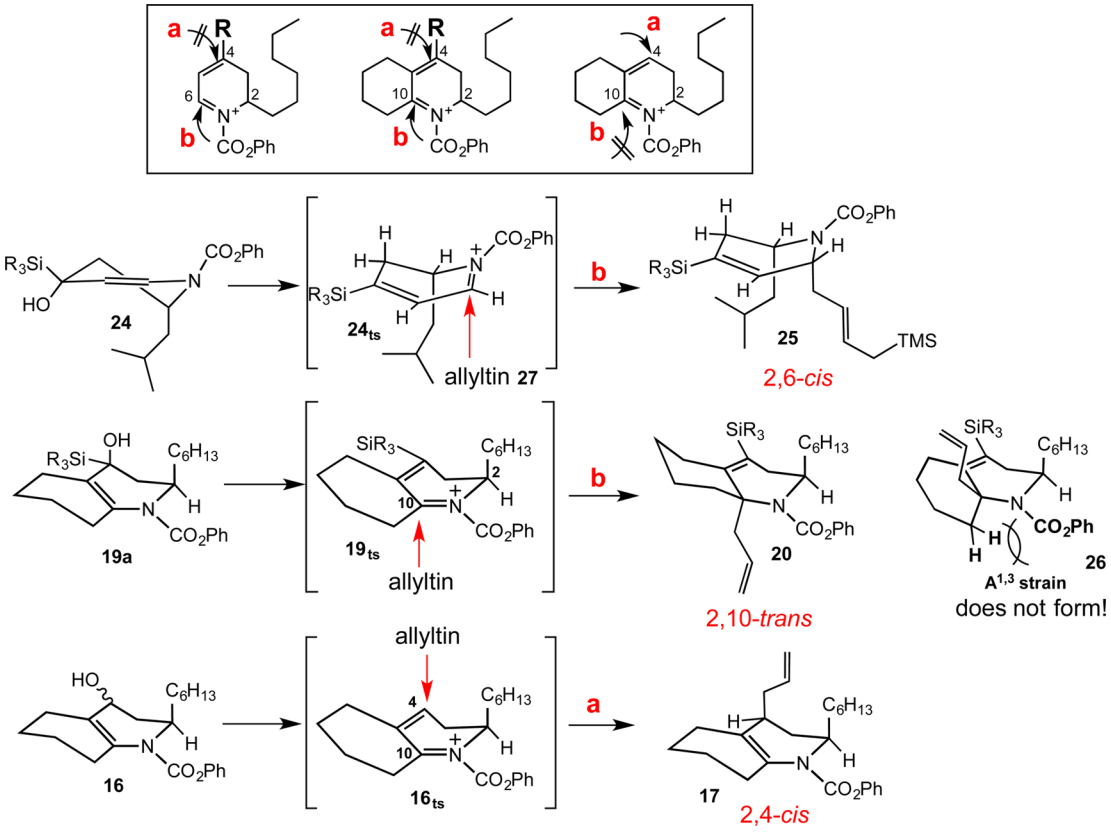
Scheme 5. Allylation of *N*-Acyliminium Ion with a C4 Blocking Group



Scheme 6. Bifurcated Reactivity of *N*-Acyliminium Ion



product, and only unreacted starting material was recovered. The failure is probably due to the inability of this system to reach a transition state with the proper orbital overlap necessary for the sigmatropic rearrangement.

The major barrier to the success of the conjugate addition reactions of **11** was a lack of reactivity of the *N*-acylvinylogous amide system due to steric and stereoelectronic reasons. To obviate this problem, the idea of transforming **11** to a more reactive *N*-acyliminium ion was pursued. To this end, dihydropyridone **11a** was converted into the alcohol **16** (Scheme 4) and then treated with TMSOTf to furnish a highly reactive *N*-acyliminium ion that was intercepted by allyltributyltin[20] at −100 °C. Unfortunately, in this case, the C4-addition product **17** was isolated in a 9:1 diastereomeric ratio. The stereochemistry of the major product was confirmed via NOE studies. Another problem with this transformation was the varying amounts of product **18** generated from the *N*-acyliminium ion through a competitive isomerization. This pathway could be minimized by conducting the reaction at low temperatures and very high concentrations of nucleophile.

With the reactivity problem solved, our experiments focused on finding a solution to the regiochemistry problem. To

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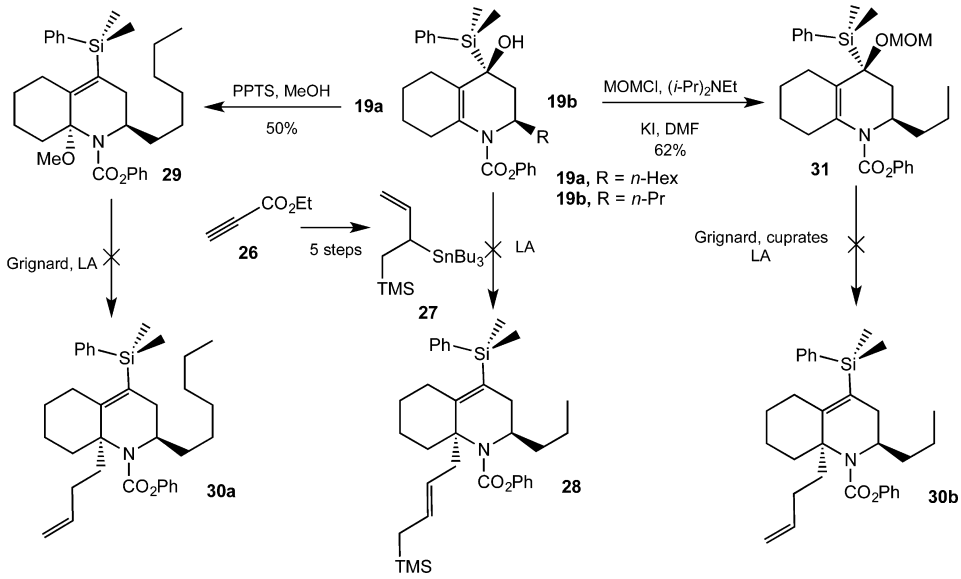
Scheme 7. Attempts at Introduction of Butenyl Side Chain at C10



address this issue, a bulky substituent at the C4 position was introduced. Thus, dihydropyridone **11a** was transformed into allylic alcohol **19a** via addition of dimethylphenylsilyllithium (Scheme 5). Indeed, when the allylic alcohol **19a** was exposed to TMSOTf, the resulting *N*-acyliminium ion reacted with allyltributyltin at the C10 position, forming the desired regioisomer **20** in 56−70% yield; however, at this stage, extensive NMR studies were not able to assign stereochemistry of the newly formed quaternary center.

It was also discovered that under conditions developed by Trauner and co-workers[21] dihydropyridone **11a** would undergo a direct C10 allylation via a similar *N*-acyliminium-type intermediate formed through reaction with triflic anhydride. Furthermore, the synthesis of compound **22** from both vinyl silane **20** and vinyl triflate **21** confirmed that the reaction proceeds in similar manner, providing the same stereochemical outcome. Pd-mediated reduction[22] of **21** was conducted using formic acid and tributylamine, while desilylation[23] of **20** was realized with TBAF in DMSO at 80 °C. Comparison of ^{1}H and ^{13}C NMR spectra of the both products did not show any discrepancies.

The stereochemical assignment of C10 quaternary center was achieved upon removal of carbamate protecting group. Due to steric hindrance of this carbamate, simple cleavage using basic conditions was not a plausible option. Reduction was also a challenge due to a presence of the terminal double bond. As an alternative approach, a milder reduction procedure was developed. Carbamate **20** was exposed to sodium metal in NH_3/THF at −78 °C. In this case, precise control of conditions was key, and the reaction was quenched immediately upon appearance of a blue color in order to avoid over reduction of the phenylsilyl protecting group. Unfortunately, NOE analysis demonstrated that the C10 quaternary center possesses stereochemistry opposite to the one found in lepadiformine A.

It is worth noting that these stereochemical results were unanticipated since prior work with the model system **24** revealed that an allyltin nucleophile attacks the *N*-acyliminium ion mainly from the direction *cis* to the C2 substituent through a boat conformation to generate product **25** (Scheme 6). Moreover, it is known that most conjugate additions of simple dihydropyridones commonly proceed with high stereoselectivity to form *cis*-2,6-disubstituted piperidones to avoid a higher energy twist-boat transition state. Behavior of the *N*-acyliminium intermediate in the bicyclic system $\mathbf{19}_{ts}$ is defined by nonbonding interactions between the C2 and C10 substituents and the carbamate group but differs from the simple dihydropyridone system $\mathbf{24}_{ts}$ due to the presence of the additional fused cyclohexane ring. In addition, in the absence of a blocking substituent at the C4 position of the iminium ion ($\mathbf{16}_{ts}$) there is a significantly higher energy barrier for an attack at the C10 vs C4 positions of the iminium ion. Taking into account stereoelectronic and steric considerations, a reasonable outcome of this reaction is the 2,4-*cis* compound **17** formed via axial attack at C-4 of the iminium ion intermediate ($\mathbf{16}_{ts}$). Steric interactions with the bulky silicon group in $\mathbf{19}_{ts}$ reverse the regioselectivity by forcing nucleophilic attack to occur at the C10 position. Unfortunately, in the transition state, the 1,3-allylic strain interactions of the cyclohexane ring with the phenyl carbamate, ring strain, and stereoelectronic effects combine to force the allyl nucleophile to approach the iminium ion from the opposite face via a twist-boat conformation to generate the 2,10-*trans* compound **20**.

Given the outcome of these experiments, it was decided to investigate further the reactivity of intermediate **19**. It is also important to mention that, despite numerous attempts, the only nucleophile suitable for addition at the C10 position was allyltributytin. To probe reactivity with a more functionallized organotin nucleophile, compound **27**, accessed in five steps starting from ethyl propiolate, was examined as a potential nucleophile in this system (Scheme 7). Nucleophilic addition and TMS cleavage via protonation would provide the four-carbon butenyl side chain required to accomplish formation of the C ring of the lepadiformine system. To our surprise, reaction of allylic alcohol **19b** with **27** resulted only in an elimination product, and no C10 addition was observed. This result is in contrast with the analogous reaction previously carried out with **24** to give **25** (Scheme 6). Allylic alcohol **19** was also successfully transformed into two other *N*-acyliminium ion precursors **29** and **31**; however, all attempts at reacting these compounds with a variety of organometallic reagents failed to provide any evidence of the desired addition products.

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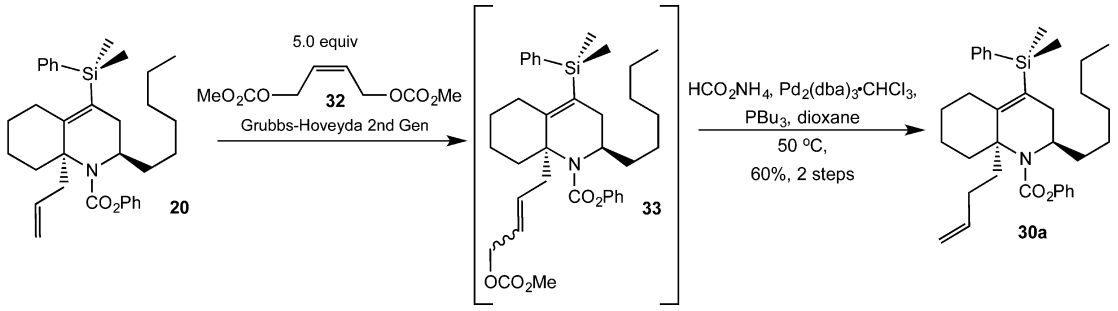
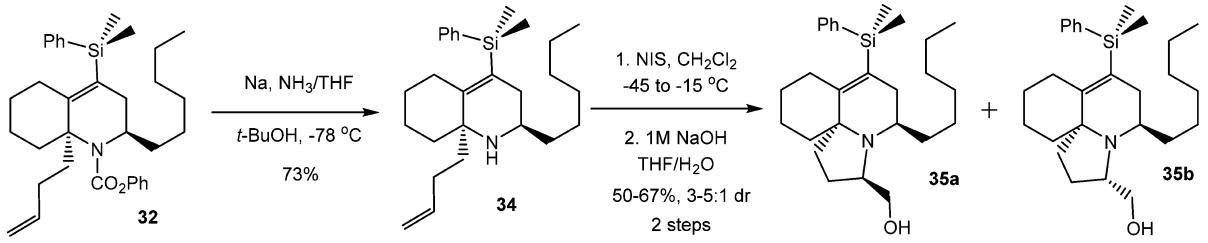
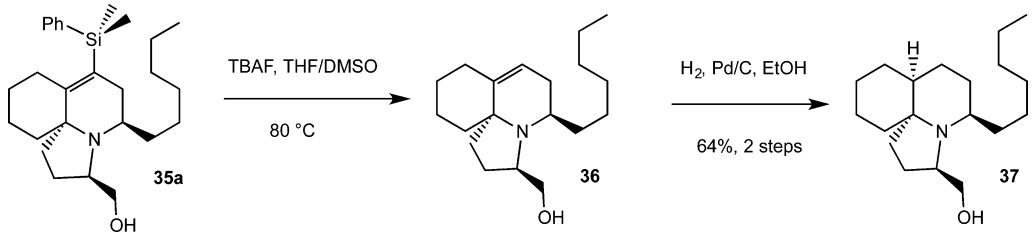
Scheme 8. Synthesis of the Butenyl Side Chain



Scheme 9. Iodoaminocyclization Reaction of 34



Scheme 10. Synthesis of the Lepadiformine C10,15 Epimer



4. Synthesis of the C Ring and a Lepadiformine Analogue. Although an intermediate with the correct configuration at the C10 quaternary center could not be accessed, it was decided to pursue our endgame strategy and attempt to finish the C ring and potentially a diastereomer of the natural product. To accomplish this objective, it was required to add an extra carbon atom by transforming the allyl side chain into a butenyl one. One way to achieve this goal is to perform a three-step protocol including hydroboration, oxidation, and methylenation. Previously, our group developed an efficient one-step procedure[24] that consists of two reactions: metathesis to form an allylic acetate or carbonate followed by a Tsuji–Trost reduction.

Unfortunately, under our original conditions, reaction of alkene **20** with Grubbs' second-generation catalyst and the bis(carbonate) **32**, or the corresponding bis(acetate), provided the required functionalized alkene **33** only in poor yield (Scheme 8). A better result was obtained by switching to Grubbs–Hoveyda second-generation catalyst.[25] In the second step, the Tsuji–Trost reduction with $Pd_2(dba)_3$ chloroform adduct and PPh_3 as a ligand generated an inseparable mixture of the terminal and *Z*,*E*-internal olefins. After some experimentation, it was found that a simple ligand exchange to PBu_3 furnishes the desired terminal alkene **30a** as a single product; however, in this case, the two catalytic systems appeared to be incompatible, and each step had to be conducted separately. Thus, the allyl side chain was converted into a butenyl group in two steps and 50–60% overall yield.

With the side chain in place, our next experiments concentrated on formation of the C ring. Using our previously developed method, the phenyl carbamate group of **30a** was removed under dissolving-metal conditions. In our original plan, a chiral epoxide was to be the electrophile in the cyclization reaction to form the C ring; however, with racemic material in hand, an aminoiodocyclization strategy was pursued based on the precedent from the Funk group[12] (Scheme 9). Under these conditions, the tricyclic products **35** were isolated in 50–67% yield.

Despite extensive efforts to improve on the initial result, diastereoselectivity of the process remained low (2–5:1 dr). After different sources of iodine (I_2, NIS, ICl, $I(col)_2ClO_4$) were screened,[26] *N*-iodosuccinimide showed the best balance of reactivity and the cleanest reaction profile. Solvents and temperature had limited influence on the overall outcome of this process. Cooling of the reaction during the first step led to a slight improvement in diastereoselectivity. The highest yield of the product was obtained using 1.1 equiv of NIS in methylene chloride with slow warming of reaction mixture from −45 to 0 °C.[27] Careful analysis of the reaction mixtures led to the conclusion that low yields of the product could be the result of competing pathways. Under similar reaction conditions, cleavage of a dimethylphenylsilyl protecting group has been reported.[28] In the presence of base, the labile primary iodide can also undergo elimination. Variable amounts of these alkenes were present in the crude reaction mixtures, but their isolation was not pursued.

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In order to complete the analogue synthesis, the dimethylphenylsilyl protecting group of **35a** was removed with TBAF, following the previously reported method by the Feringa group, to provide alkene **36** (Scheme 10).[23] The resulting alkene was reduced using H_2 and Pd/C. Hydrogenation proceeded selectively from the β face, resulting in the *cis*-fused ring system found in the previously synthesized double epimer of lepadiformine (**37**). This confirmed the stereochemistry of the iodoaminocyclization step. The spectral characteristics for the prepared material were in accordance with the data previously reported by Weinreb.[3]

CONCLUSIONS

In summary, we have investigated a new strategy toward the synthesis of the tricyclic alkaloid lepadiformine starting from 4,7-dichloroquinoline. This approach demonstrates the power and versatility of *N*-acylpyridinium salt chemistry, which can be successfully translated to quinoline derivatives. This work also includes a detailed study of vinylogous amide reactivity. We were able to show the unique nature and high reactivity of *N*-acyliminium intermediates formed from the bicyclic dihydropyridones, which allowed the introduction of the hindered C-10 quaternary center using allytributyltin as a nucleophile. Alternatively, the same reaction could provide a 1,4-addition product exclusively and stereoselectively simply by removing any blocking group at C4. Also developed was a very mild dissolving-metal reduction procedure to cleave hindered phenylcarbamate groups. Despite the fact that the constructed quaternary center had the opposite stereochemistry of the alkaloid lepadiformine A, our approach showcases a distinct, original, and effective approach for the preparation of similar tricyclic systems. Finally, our pursuit of the endgame strategy gave some additional insight in the area of iodoaminocyclizations and efficiency of this reaction based on the substrate and also provided us an opportunity to prepare the double-epimer analogue **37** of the natural product with high stereoselectivity in 11 steps overall.

EXPERIMENTAL SECTION

7-Chloro-4-methoxyquinoline (10).[29] Sodium metal (2.38 g, 103 mmol) was slowly added to methanol (50 mL) at −30 °C with stirring. The reaction was stirred at room temperature for 18 h. A solution of 4,7-dichloroquinoline (4.04 g, 20.4 mmol) in 5 mL of methanol was added to the sodium methoxide solution, and the mixture was heated to reflux for 24 h. The excess methanol was removed via distillation or rotary evaporation. To the crude material were added EtOAc (50 mL) and deionized water (50 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), filtered, and concentrated to afford 3.71 g (94%) of 7-chloro-4-methoxyquinoline: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.75−8.73 (d, 1H, J = 5.6 Hz), 8.13−8.11 (d, 1H, J = 8.8 Hz), 8.02−8.01 (d, 1H, J = 2.4 Hz), 7.45−7.42 (dd, 1H, J = 9.2, 2.0 Hz). 6.73−6.72 (d, 1H, J = 5.2 Hz), 4.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.5, 125.7, 149.9, 135.9, 128.1, 126.7, 123.6, 120.0, 100.5, 56.0.

4-Methoxy-5,6,7,8-tetrahydroquinoline (8).[30] In a 1-L flask were added 7-chloro-4-methoxyquinoline (19.8 g, 102 mmol), lithium carbonate (9.23 g, 125 mmol), 10% palladium on carbon (13.3 g), and 500 mL of EtOH. The reaction was charged with hydrogen gas at balloon pressure and stirred. After 5 days, the reaction mixture was filtered through Celite with hot methanol. The solvent was removed via rotary evaporation. The oil was purified by column chromatography (silica gel, 5% MeOH/CH_2Cl_2) to afford 10.2 g (60%) of compound **8**: IR (neat) 2935, 1578, 1475, 1439, 1336, 1289, 1160, 1109, 1089, 1057, 997, 879, 808 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25, (d, 1H, J = 5.6 Hz), 6.57, (d, 1H, J = 5.6 Hz), 3.84 (s, 3H), 2.87 (t, 2H, J = 6.0 Hz), 2.62 (t, 2H, J = 6.4 Hz), 1.80 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.7, 158.0, 148.0, 121.3, 103.3, 55.3, 32.6, 22.9, 22.4, 22.3; HRMS calcd for $C_{10}H_{14}NO$ ([M + H]$^+$) 164.1075, found 164.1064.

***rac*-Phenyl 2-*n*-Hexyl-4-oxo-3,4,5,6,7,8-hexahydroquinoline-1(2*H*)-carboxylate (11a).** To a solution of 4-methoxy-5,6,7,8-tetrahydroquinoline **8** (638 mg, 3.91 mmol) in 10 mL of anhydrous THF was added dropwise phenyl chloroformate (0.54 mL, 4.32 mmol) at −42 °C. The reaction mixture was stirred at −42 °C for 30 min and then cooled to −78 °C. The solution of *n*-hexylmagnesium bromide (0.78 M in THF, 10 mL, 7.8 mmol) was transferred dropwise to the flask containing the newly formed *N*-acylpyridinium salt, and stirring was continued at −78 °C for 3 h. The reaction mixture was quenched with 10% HCl (10 mL), warmed to rt, and stirred for an additional 1 h. The aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by radial PLC (SiO_2, 4−8% EtOAc/hexanes) to yield 1.2 g (87%) of the hexahydroquinolone **11a** as a clear oil: IR (neat) 3044, 2930, 2858, 1725, 1666, 1609, 1495, 1384, 1338, 1164, 1137, 737 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41 (m, 2H), 7.26 (m, 1H), 7.14 (m, 2H), 4.87 (m, 1H), 3.16 (m, 1H), 2.96 (dd, 1H, J = 5.9, 17.1 Hz), 2.47 (m, 2H), 2.26 (m, 2H), 1.82 (m, 3H), 1.57−1.28 (m, 11H), 0.88 (t, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.5, 152.3, 150.6, 150.4, 129.5, 125.9, 121.4, 121.3, 55.9, 42.1, 31.6, 30.8, 30.6, 28.9, 26.2, 22.6, 22.5, 21.6, 21.4, 14.0; HRMS calcd for $C_{22}H_{30}NO_3$ [(M + H)$^+$] 356.2220, found 356.2227.

4-Oxo-2-*n*-propyl-3,4,5,6,7,8-hexahydro-2*H*-quinoline-1-carboxylic Acid Phenyl Ester (11b). To a solution of 4-methoxy-5,6,7,8-tetrahydroquinoline **8** (12 mg, 70 μmol) in 3 mL of THF at −50 °C was added phenyl chloroformate (10 μL, 80 μmol). After 30 min, the mixture was cooled to −78 °C, and a 2.0 M solution of *n*-propylmagnesium bromide (70 μL, 140 μmol) in THF was added dropwise. After 18 h at −55 °C, 0.5 mL of 10% HCl was added, and the reaction was warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL). The solution was dried with magnesium sulfate, filtered through Celite, and concentrated in vacuo. The crude product was purified by radial PLC (silica gel, gradient 10−30% EtOAc/hexanes) to yield 20 mg (87%) of compound **11b** as an oil: IR (neat) 2934, 2864, 1736, 1667, 1655, 1607, 1495, 1385, 1337, 1287, 1256, 1203, 1137 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (t, 2H, J = 8.4 Hz), 7.24 (t, 1H, J = 7.5 Hz), 7.13 (d, 2H, J = 7.2 Hz), 4.87 (m, 1H), 3.14 (m, 1H), 2.93 (dd, 1H, J = 6.0 Hz, 17.4 Hz), 2.48 (m, 2H), 2.25 (m, 2H), 1.74−1.87 (m, 3H), 1.55−1.35 (m, 5H), 0.96 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.7, 152.5, 150.9, 150.6, 129.7, 126.1, 121.7, 121.6, 55.9, 42.4, 33.2, 30.8, 22.8, 21.9, 21.7, 19.8, 14.1; HRMS calcd for $C_{19}H_{24}NO_3$ ([M + H]$^+$) 314.1756, found 314.1767.

(2*R*)-2-Hexyl-4-oxo-3,4,5,6,7,8-hexahydro-2*H*-quinoline-1-carboxylic acid (1*R*,2*S*,4*R*)-4-isopropyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (12). To a solution of 4-methoxy-5,6,7,8-tetrahydroquinoline (1.34 g, 8.2 mmol) in 3.5 mL of THF and 10.5 mL of toluene at −30 °C was added the chloroformate of (−)-(1*R*,2*S*,4*R*)-2-(1-methyl-1-phenylethyl)-4-(2-propyl)cyclohexanol (2.74 g, 8.5 mmol) in 3.5 mL of THF and 10.5 mL of toluene. After 4 h, the reaction was cooled to −78 °C, and *n*-hexylmagnesium bromide (THF, 9 mL, 16 mmol) was added dropwise over 1 h. After the reaction was stirred for 4.5 h, 10 mL of 10% aqueous HCl was added, and the reaction was warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The organic layers were combined, washed with water (50 mL) and brine (30 mL), dried over magnesium sulfate, and filtered. The solvent was removed in vacuo. The crude oil was purified via column chromatography (1% EtOAc/hexanes) to yield 2.57 g (60%) of the major diastereomer and 0.86 g (20%) of the minor diastereomer (50% de) as clear oils. Major isomer: IR (neat) 2931, 2860, 1709, 1665, 1605, 1497, 1467, 1399, 1368, 1337, 1258, 1169, 1148, 1106, 1077,

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1034, 989, 861, 766 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33−7.24 (m, 4H), 7.12−7.07 (t, 1H, J = 6.9 Hz), 4.79−4.73 (m, 1H), 3.14- 3.06 (m, 2H), 2.43−2.24 (m, 3H), 2.16−1.67 (m, 8H), 1.47−0.85 (m, 33H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.9, 152.8, 152.6, 151.9, 128.5, 125.3, 125.2, 119.4, 53.6, 50.0, 43.7, 42.5, 39.8, 33.4, 32.7, 31.7, 30.6, 30.5, 30.2, 29.1, 27.4, 26.2, 23.2, 22.9, 22.8, 21.8, 21.6, 20.3, 19.7, 14.3; HRMS calcd for $C_{34}H_{52}NO_3$ [(M + H)$^+$] 522.3947, found 522.3950; $[\alpha]^{31}_D$ −102 (c 1.79, MeOH).

Minor isomer: IR (neat) 2930, 2859, 1696, 1665, 1605, 1386, 1325, 1303, 1168, 1146, 1029, 761, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.26−7.21 (t, 2H, J = 7.5, 6 Hz), 7.14−7.09 (t, 2H, J = 7.5 Hz), 7.00−6.95 (t, 1H, J = 6.9 Hz), 4.84−4.76 (dt, 1H, J = 10.8, 4.5 Hz), 4.60−4.54 (q, 1H, J = 6.6 Hz), 2.73−2.65 (dd, 1H, J = 17.4, 6.0 Hz), 2.38−2.27 (m, 3H), 2.20−1.84 (m, 4H), 1.76−1.60 (m, 4H), 1.50−0.98 (m, 23H), 0.94−0.82 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.1, 153.5, 152.2, 150.7, 128.0, 125.2, 125.0, 119.8, 55.2, 52.1, 43.7, 42.1, 39.7, 33.2, 32.7, 31.8, 31.3, 30.8, 30.5, 29.8, 29.1, 27.3, 26.3, 23.0, 22.7, 22.7, 21.6, 21.5, 20.4, 19.7, 14.2; HRMS calcd for $C_{34}H_{52}NO_3$ [(M + H)$^+$] 522.3947, found 522.3947; $[\alpha]^{31}_D$ +99 (c 1.25, MeOH).

***rac*-4-Allyl-4-hydroxy-2-*n*-propyl-3,4,5,6,7,8-hexahydro-2*H*-quinoline-1-carboxylic Acid Phenyl Ester (14).** To a solution of hexahydroquinolone **11b** (79 mg, 250 μmol) in 2 mL of Et_2O at −78 °C was added dropwise a solution of 1.35 M 1-propenylmagnesium chloride (200 μL, 270 μmol) in THF. After 3 h at −78 °C, 2 mL of ammonium chloride was added, and the mixture was warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL) and dried over magnesium sulfate. The mixture was filtered through Celite and concentrated via rotary evaporation. The crude product was purified by radial PLC (silica gel, 10% EtOAc/hexanes) to afford 61 mg (68%) of the major diastereomer **14** as a light yellow oil: IR (neat) 3491, 2932, 2860, 1738, 1732,1699, 1686, 1681, 1595, 1506, 1495, 1394, 1327, 1204, 1162, 999, 912, 751, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36 (t, 2H, J = 7.8 Hz), 7.19 (t, 1H, J = 7.2 Hz) 7.09 (d, 2H, J = 7.5 Hz), 5.66−5.80 (m, 1H), 5.18 (s, 1H), 5.14 (d, 1H, J = 5.7 Hz), 4.90−4.35 (m, 1H), 2.98−2.93 (m, 1H), 2.42−2.23 (m, 4H), 2.14 (d, 1H, J = 17.4 Hz), 1.98 (d, 1H, J = 16.5 Hz), 1.83−1.68 (m, 5H), 1.67−1.54 (m, 2H), 1.52−1.33 (m, 3H), 0.95 (t, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.2, 151.4, 133.5, 130.5, 129.5, 128.3, 125.5, 121.8, 119.5, 70.6, 51.8, 44.8, 42.4, 35.4, 29.5, 23.2, 23.2, 22.8, 20.0, 14.2; HRMS calcd for $C_{22}H_{29}NO_3$ 355.2147, found 355.2122.

***rac*-Phenyl 2-*n*-Hexyl-4-hydroxy-3,4,5,6,7,8-hexahydroquinoline-1(2*H*)-carboxylate (16).** To a stirred solution of **11a** (465 mg, 1.31 mmol) in MeOH (7 mL) at rt was added cerium chloride heptahydrate (512 mg, 1.38 mmol), and the mixture was cooled to 0 °C. Sodium borohydride (98 mg, 2.62 mmol) was added, and the reaction mixture was stirred for 30 min at 0 °C. The reaction was quenched with 5 mL of water. The resulting mixture was diluted with Et_2O, and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 × 10 mL). The organic layers were combined, washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The product was purified by radial PLC (SiO_2, 5−7.5% EtOAc/hexanes) to yield 196 and 200 mg of *cis*/*trans* diastereomeric alcohols **16** (85% overall) as clear oils.

2,4-cis-Alcohol: IR (neat) 3468, 2927, 2857, 1698, 1493, 1396, 1327, 1207, 1129, 1041, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.36 (m, 2H), 7.19 (m, 1H), 7.10 (m, 2H), 4.48 (m, 1H), 3.98 (bs, 1H), 2.97 (m, 1H), 2.49 (m, 1H), 2.23 (dt, 1H, J = 5.8, 14.5 Hz), 2.2 (m, 2H), 1.91−1.26 (m, 16H), 0.88 (t, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.8, 151.2, 130.1, 129.2, 125.2, 123.9, 121.5, 65.2, 51.8, 37.2, 31.8, 31.7, 29.4, 29.0, 26.8, 25.9, 23.4, 22.5, 22.4, 14.0; HRMS calcd for $C_{22}H_{31}NO_3Na$ [(M + Na)$^+$] 380.2196, found 380.2203.

2,4-trans-Alcohol: IR (neat) 3415, 3045, 2930, 2857, 1713, 1495, 1393, 1326, 1206, 1143, 1016, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36 (m, 2H), 7.20 (m, 1H), 7.11 (m, 2H), 4.53 (m, 1H), 4.10 (m, 1H), 2.91 (m, 1H), 2.49 (m, 1H), 2.20 (ddd, 1H, J = 2.8, 7.4, 13.2 Hz), 2.06−1.26 (m, 18H), 0.88 (t, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.9, 151.2, 131.5, 129.3, 125.3, 123.1, 121.5, 66.7, 55.1, 37.7, 31.7, 30.8, 29.7, 29.0, 26.4, 25.9, 23.2, 22.5, 22.3, 14.0; HRMS calcd for $C_{22}H_{31}NO_3Na$ [(M + Na)$^+$] 380.2196, found 380.2203.

***rac*-Phenyl 4-Allyl-2-*n*-hexyl-3,4,5,6,7,8-hexahydroquinoline-1(2*H*)-carboxylate (17).** To a solution of diastereomeric alcohols **16** (100 mg, 280 μmol) in CH_2Cl_2 (1 mL) at −100 °C was added allyltributylstannane (5.0 equiv, 430 μL, 1.40 mmol) followed by dropwise addition of trimethylsilyl triflate (2.0 equiv, 100 μL, 560 μmol). The reaction was stirred for 1 h at −100 °C, and then 1 M NaOH was added (5 mL). The reaction mixture was warmed to rt and stirred for an additional 1 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The residue was purified by radial PLC (SiO_2, 1−2% EtOAc/hexanes) to afford 90 mg (84%, 9:1 mixture of diastereomers) of allyl product **17** as a clear oil: IR (neat) 3074, 2928, 2857, 1715, 1596, 1495, 1456, 1392, 1324, 1205, 1143, 993, 912 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35 (m, 2H), 7.18 (m, 1H), 7.11 (m, 2H), 5.72 (m, 1H), 5.05 (m, 2H), 4.43 (m, 1H), 2.92 (m, 1H), 2.31 (m, 2H), 2.18−1.45 (m, 10H), 1.43−1.20 (m, 10H), 0.88 (t, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.2, 151.4, 136.1, 129.5, 129.2, 125.1, 121.9, 121.6, 116.6, 53.2, 37.1, 35.0, 34.1, 31.7, 31.2, 29.6, 29.2, 27.8, 26.4, 23.2, 22.8, 22.6, 14.1; HRMS calcd for $C_{25}H_{35}NO_2Na$ [(M + Na)$^+$] 404.2560, found 404.2562.

***rac*-(2*R**)-4-(Dimethylphenylsilanyl)-4-hydroxy-2-propyl-3,4,5,6,7,8-hexahydro-2*H*quinoline-1-carboxylic Acid Phenyl Ester (19b).** To a mixture of lithium wire (94 mg, 13.5 mmol) in 5.0 mL of THF was added chlorodimethylphenylsilane (240 μL, 1.43 mmol) all at once. The reaction was stirred at rt for 4 h. In a separate flask were added hexahydroquinolone **11b** (206 mg, 657 μmol) and 5.0 mL of ether. The mixture was cooled to −78 °C, and the dimethylphenylsilyllithium was added dropwise with a syringe pump over 1 h. After 18 h at −78 °C, 5 mL of saturated sodium bicarbonate was added, and the reaction was warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over magnesium sulfate, and filtered through Celite. The solvent was removed via rotary evaporation, and the crude material was purified by radial PLC (silica gel, 10% EtOAc/hexanes) to afford 177 mg (59%) of compound **19b** as a clear oil and 41 mg (20%) of recovered starting material: IR (neat) 3467, 2933, 2857, 2361, 1699, 1685, 1681, 1652, 1495, 1428, 1394, 1325, 1248, 1204, 1162, 1114, 1024, 817, 775, 737, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.60−7.57 (m, 2H), 7.38−7.38 (m, 5H), 7.19 (t, 1H, J = 7.5 Hz), 7.12 (d, 2H, J = 7.5 Hz), 4.32−4.24 (p, 1H), 3.03−2.97 (m, 1H), 2.47−2.40 (dd, 1H, J = 13.8, 7.2 Hz), 2.22−2.16 (m, 1H), 1.96 (d, 1H, J = 16.8 Hz), 1.81−1.60 (m, 5H), 1.57−1.28 (m, 7H), 0.91 (t, 3H, J = 7.2 Hz) 0.40 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.4, 136.4, 134.6, 129.8, 129.5, 129.4, 128.1, 125.5, 121.9, 66.9, 50.8, 42.7, 36.2, 29.7, 25.3, 23.4, 22.9, 19.8, 15.9, 14.2, −4.6, −5.1; HRMS calcd for $C_{27}H_{36}NO_3Si$ [(M + H)$^+$] 449.2386, found 449.2378.

***rac*-Phenyl 8a-Allyl-4-(dimethyl(phenyl)silyl)-2-*n*-hexyl-2,3,6,7,8,8a-hexahydro-quinoline-1(5*H*)-carboxylate (20).** To a solution of hexahydroquinolone **11a** (115 mg, 323 μmol) in dry ether (2.5 mL) at −78 °C was added a freshly prepared solution of dimethylphenylsilyllithium (0.215 M in THF, 3 mL, 646 μmol) dropwise over a period of 10 min. The reaction mixture was stirred for an additional 40 min, quenched with saturated $NaHCO_3$ (5 mL), and warmed to rt. The biphasic solution was transferred to a separatory funnel. The aqueous layer was extracted with Et_2O (2 × 10 mL), and the combined organic layers were washed with aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$ and filtered through Celite. The volatiles were removed in vacuo, and the crude product was purified by radial PLC (SiO_2, 7% EtOAc/3% Et_3N/hexanes) to remove $PhMe_2SiH$. The resulting product **19a** was immediately used in the second step without additional purification due to its low stability.

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To a solution of allylic alcohol **19a** in CH_2Cl_2 (1 mL) at −100 °C was added allyltributylstannane (5.0 equiv, 500 μL, 1.62 mmol) followed by a very slow dropwise addition of trimethylsilyl triflate (2.0 equiv, 120 μL, 646 μmol) over a period of 10−15 min. The reaction was stirred for 1 h at −100 °C, and then 1 M NaOH was added (5 mL). The reaction mixture was warmed to rt and stirred for an additional 1 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The residue was purified by radial PLC (SiO_2, 1−6% EtOAc/hexanes) to afford 93 mg (56%, two steps) of alkene **20** as a clear oil: IR (neat) 3068, 2930, 2856, 1714, 1614, 1495, 1389, 1355, 1298, 1250, 1209, 1179, 1110, 813 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.54 (m, 2H), 7.36 (m, 5H), 7.19 (m, 1H), 7.08 (m, 2H), 5.73 (m, 1H), 5.08 (m, 2H), 4.49 (m, 1H), 3.53 (m, 1H), 2.89 (m, 1H), 2.58 (m, 1H), 2.50 (m, 1H), 2.34 (m, 1H), 2.16 (m, 2H), 1.65−1.28 (m, 15H), 0.88 (t, 3H, *J* = 6.2 Hz), 0.40 (s, 3H), 0.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.6, 151.4, 149.0, 139.5, 134.3, 133.5, 129.1, 128.8, 127.7, 124.9, 121.9, 116.9, 63.0, 51.4, 37.1, 36.0, 33.7, 33.0, 31.7, 31.5, 29.2, 26.8, 22.8, 22.6, 14.0, −1.0, −1.1; HRMS calcd for $C_{33}H_{46}NO_2Si$ [(M + H)$^+$] 516.3292, found 516.3291.

***rac*-Phenyl 8a-Allyl-2-*n*-hexyl-4-(trifluoromethylsulfonyloxy)-2,3,6,7,8,8a-hexahydroquinoline-1(5*H*)-carboxylate (21).** To a solution of enone **11** (68 mg, 191 μmol) in CH_2Cl_2 (2 mL) at −78 °C was added allyltributylstannane (5.0 equiv, 290 μL, 956 μmol) followed by dropwise addition of trifluoromethanesulfonic anhydride (2.0 equiv, 60.0 μL, 382 μmol). The reaction was stirred for 1 h at −78 °C, and then 1 M NaOH was added (5 mL). The reaction mixture was warmed to rt and stirred for an additional 1 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The residue was purified by radial PLC (SiO_2, 1−2% EtOAc/hexanes) to afford 65 mg (64%) of allyl product **21** as clear oil: IR (neat) 3077, 2932, 2859, 1720, 1594, 1495, 1417, 1364, 1299, 1208, 1142, 1007, 961, 901 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37 (m, 2H), 7.20, (m, 1H), 7.06 (m, 2H), 5.69 (m, 1H), 5.12 (m, 2H), 4.69 (m, 1H), 3.49 (m, 1H), 2.90 (m, 3H), 2.61 (m, 1H), 2.23 (dd, 1H, *J* = 1.3, 16.5 Hz), 2.12 (tt, 1H, *J* = 4.7, 14.6 Hz), 1.86 (m, 1H), 1.80−1.26 (m, 14H), 0.87 (t, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 22.4, 22.5, 24.3, 25.4, 26.8, 29.0, 31.5, 31.6, 34.2, 35.8, 37.6, 52.6, 63.1, 118.2, 118.3 (q, CF_3), 118.5, 121.8, 125.3, 129.3, 130.0, 132.5, 139.1, 151.0, 152.6; HRMS calcd for $C_{26}H_{35}F_3NO_5S$ [(M + H)$^+$] 530.2183, found 530.2172.

***rac*-Phenyl 8a-Allyl-2-*n*-hexyl-2,3,6,7,8,8a-hexahydroquinoline-1(5*H*)-carboxylate (22).** *Method I.* To a solution of vinyl silane **20** (35 mg, 68 μmol) in anhydrous DMSO (2 mL) at rt was added TBAF (1 M in THF, 1.0 mL, 1.0 mmol), and the reaction mixture was heated at 80 °C for 1 h. The mixture was cooled to rt, diluted with Et_2O (10 mL), washed with water (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The residue was purified by radial PLC (SiO_2, 2% EtOAc/hexanes) to afford 20 mg (77%) of alkene **22** as a clear oil.

Method II. To a degassed solution of triflate **21** (40 mg, 76 μmol) in anhydrous DMF (2 mL) at rt were added tributylamine (5.0 equiv, 90.0 μL, 377 μmol), formic acid (4.0 equiv, 10.0 μL, 304 μmol), and $Pd(PPh_3)_2(OAc)_2$ (0.1 equiv, 6.0 mg, 8.0 μmol), and the reaction mixture was stirred at rt for 5 h. The reaction mixture was diluted with Et_2O (10 mL). The resulting mixture was washed with 1% HCl (10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The residue was purified by radial PLC (SiO_2, 2% EtOAc/hexanes) to afford 20 mg (70%) of alkene **22** as a clear oil: IR (neat) 3073, 2930, 2856, 1717, 1596, 1495, 1455, 1389, 1350, 1297, 1207, 1168, 1207, 1114, 989, 912 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38 (m, 2H), 7.18 (m, 1H), 7.07 (m, 2H), 5.69 (m, 1H), 5.58 (d, 1H, *J* = 7.4 Hz), 5.03 (m, 2H), 4.51 (q, 1H, *J* = 6.1 Hz), 3.43 (bs, 1H), 2.85 (m, 1H), 2.59 (m, 1H), 2.97 (m, 3H), 1.97 (dd, 1H, *J* = 7.7, 17.1 Hz), 1.78 (d, 1H, *J* = 13.5 Hz), 1.65−1.25 (m, 14H), 0.87 (t, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.6, 151.4, 138.4, 134.4, 129.2, 124.9, 122.0, 117.7, 116.7, 62.5, 52.0, 36.7, 35.9, 34.5, 33.1, 31.8, 29.7, 29.3, 27.2, 27.0, 23.2, 22.6, 14.1; HRMS calcd for $C_{25}H_{36}NO_2$ [(M + H)$^+$] 382.2741, found 382.2742.

***rac*-8a-Allyl-4-(dimethyl(phenyl)silyl)-2-*n*-hexyl-1,2,3,5,6,7,8,8a-octahydroquinoline (23).** Phenyl carbamate **20** (50 mg, 96.9 μmol) was dissolved in a mixture of anhydrous THF (1.5 mL) and freshly distilled liquid ammonia (5.5 mL) at −78 °C. Anhydrous *tert*-butyl alcohol (5 μL) was added followed by a slow addition of sodium (7.0 equiv, 16 mg, 0.68 mmol) in small portions until a deep blue color persisted. The reaction was immediately quenched with solid NH_4Cl and then warmed to rt. The resulting solution was filtered through Celite and concentrated in vacuo. The crude product was purified by radial PLC (SiO_2 1−12% EtOAc/hexanes) to yield 28.5 mg (74%) of the free amine **23** as a clear oil: IR (neat) 3068, 2925, 2856, 1636, 1607, 1454, 1428, 1247, 1110, 912, 814 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51 (m, 2H), 7.32 (m, 3H), 5.80 (m, 1H), 5.13 (m, 2H), 2.83 (m, 1H), 2.57 (dd, 1H, *J* = 6.6, 14.0 Hz), 2.42 (dd, 1H, *J* = 8.5, 14.3 Hz), 2.30 (m, 1H), 2.09 (m, 1H), 1.96−1.83 (m, 2H), 1.76 (dq, 1H, *J* = 2.3, 13.1 Hz), 1.57−1.05 (m, 15H), 0.88 (t, 3H, *J* = 6.6 Hz), 0.35 (s, 3H), 033 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.6, 140.2, 133.8, 133.6, 128.6, 127.6, 124.6, 118.5, 57.4, 46.9, 38.2, 37.7, 37.6, 37.1, 32.0, 29.6, 27.2, 26.0, 22.6, 22.2, 14.1, −0.7, −1.1; HRMS calcd for $C_{26}H_{42}NSi$ [(M + H)$^+$] 396.3081, found 396.3085.

***rac*-4-(Dimethylphenylsilanyl)-4-hydroxy-2-isobutyl-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Phenyl Ester (24).** To a solution of lithium wire (50 mg, 9.8 mmol) in 5.0 mL of THF was added chlorodimethylphenylsilane (180 μL, 1.07 mmol) all at once. The reaction was stirred at rt for 4 h. In a separate flask was added dihydropyridone (201 mg, 730 μmol) in 1.5 mL of THF and 9.0 mL of ether. The mixture was cooled to −78 °C, and the dimethylphenylsilyllithium was added dropwise via a syringe pump over 1 h. After 8 h at −78 °C, 2 mL of saturated aqueous sodium bicarbonate was added, and the reaction was warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over K_2CO_3, and filtered through Celite. The solvent was removed by rotary evaporation, and the crude material was purified by radial PLC (silica gel, 10% EtOAc/hexanes) to afford 162 mg (54%) of compound **24** as a clear oil and 40 mg (20%) of recovered starting material: IR (neat) 3436, 2855, 2927, 2856, 1688, 1453, 1427, 1404, 1366, 1329, 1250, 1171, 1135, 1113, 1020, 832, 816, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.62−7.60 (m, 2H), 7.40−7.35 (m, 5H), 7.25−7.22 (d, 1H *J* = 9.9 Hz), 7.19−7.14 (d, 2H, *J* = 16.5 Hz), 6.96−6.93 (d, 1H, *J* = 7.2 Hz), 5.17−5.08 (dd, 1H, *J* = 17.4, 8.1 Hz), 4.46 (m, 1H), 2.1−1.95 (m, 2H), 1.70−1.55 (m, 4H), 1.27−1.18 (m, 2H), 0.91 (br s, 6H), 0.38 (s, 6H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.8, 151.2, 135.6, 134.9, 129.8, 129.6, 128.1, 125.8, 125.2, 124.5, 121.8, 121.7, 111.8, 110.5, 61.5, 48.0, 40.4, 34.9, 25.6, 23.2, 22.5, −5.8, −6.1; HRMS calcd for $C_{24}H_{32}NO_3Si$ [(M + H)$^+$] 410.2151, found 410.2142.

***rac*-4-(Dimethylphenylsilanyl)-2-isobutyl-6-(4-trimethylsilanyl-but-2-enyl)-3,6-dihydro 2*H*-pyridine-1-carboxylic Acid Phenyl Ester (25).** To a solution of silyl alcohol **24** (75 mg, 183 μmol) in 5 mL of CH_2Cl_2 at −78 °C was added compound **27** (135 mg, 323 μmol). After 10 min, $BF_3{\cdot}OEt_2$ (50.0 μL, 0.405 μmol) was added dropwise. After 2.5 h, the reaction was quenched with saturated $NaHCO_3$ (2 mL) and warmed to room temperature. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (10 mL) and dried over K_2CO_3. Filtration and concentration afforded the crude product which was purified by radial PLC (silica gel, 1% TEA, 5% EtOAc/hexanes) to give 59 mg (63%) of compound **25** as a light yellow oil: IR (neat) 2954, 2360, 2340, 1715, 1494, 1406, 1389, 1360, 1333, 1300, 1248, 1207, 1162, 958, 835, 773, 733, 687 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52−7.51 (m, 2H), 7.38−7.33 (m, 5H), 7.21−7.08 (m, 3H), 6.30−6.16 (m, 2H), 5.62−5.55 (m, 1H), 5.16−4.98 (m, 2H), 4.19 (br s, 2H), 3.16 (br s, 1H), 2.33−2.07 (m, 2H), 1.43−1.26 (m, 4H), 0.88−0.81 (m, 4H), 0.72−0.54 (m, 5H), 0.39 (s, 6H), −0.03 (s, 9H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.6, 151.8, 141.8, 137.7,

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136.6, 134.2, 129.5, 128.1, 126.2, 122.0, 116.8, 60.1, 53.5, 50.4, 47.3, 43.1, 31.2, 28.8, 26.4, 25.7, 24.1, 24.0, 23.6, 23.2, 21.4, 20.0, 19.1, −0.48, −1.7, −3.7; HRMS calcd for $C_{31}H_{46}NO_2Si_2$ $[(M + H)^+]$ 520.3067, found 520.3066.

***rac*-Phenyl 4-(Dimethyl(phenyl)silyl)-2-*n*-hexyl-8a-methoxy-2,3,6,7,8,8a-hexahydroquinoline-1(5*H*)-carboxylate (29).** To a solution of allylic alcohol **19a** (55.0 mg, 112 μmol) in MeOH (dry, 1 mL) at rt was added PPTS (1.0 equiv, 29.0 mg, 112 μmol), and the mixture was stirred for 10−15 min. The reaction was quenched with saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The residue was purified by radial PLC (SiO_2, 1% EtOAc/1% Et_3N/hexanes) to afford 20 mg (35%) of ether **29** as a clear oil: IR (neat) 2929, 2856, 1732, 1703, 1495, 1389, 1335, 1209, 1163, 1109, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52 (m, 2H), 7.36 (m, 5H), 7.17 (m, 1H), 7.11 (m, 2H), 4.54 (m, 1H), 3.13 (s, 3H), 2.98 (m, 1H), 2.40 (m, 2H), 2.23 (dd, 1H, *J* = 1.7, 17.1 Hz), 2.03 (tt, 1H, *J* = 4.1, 13.8 Hz), 1.78−1.53 (m, 6H), 1.30−1.12 (m, 9H), 0.88 (t, 3H, *J* = 6.6 Hz) 0.44 (s, 3H), 0.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.3, 145.2, 139.0, 133.5, 129.1, 129.0, 127.9, 125.0, 121.8, 87.4, 52.6, 48.3, 33.2, 32.3, 31.8, 31.1, 29.3, 27.0, 22.6, 22.4, 14.1, −1.1, −1.3; HRMS calcd for $C_{31}H_{43}NO_3SiNa$ $[(M + Na)^+]$ 528.2904, found 528.2897.

***rac*-Phenyl 8a-(But-3-enyl)-4-(dimethyl(phenyl)silyl)-2-*n*-hexyl-2,3,6,7,8,8a-hexahydroquinoline-1(5*H*)-carboxylate (30a).** To a degassed solution of **20** (157 mg, 304 μmol) in 5 mL of anhydrous methylene chloride was added (*Z*)-but-2-ene-1,4-diyl diacetate (314 mg, 1.83 mmol) followed by addition of Grubbs−Hoveyda second-generation catalyst (9.50 mg, 15 μmol). The mixture was heated at reflux for 2 h, cooled, and filtered through a silica gel pad with a methylene chloride wash. After concentration under reduced pressure, the crude product **33** was used in the next step without additional purification.

To a degassed solution of crude **33** in dioxane were added ammonium formate (193 mg, 3.06 mmol) and tributyl phosphine (15 μL, 60 μmol) followed by the addition of $Pd_2(dba)_3{\cdot}CHCl_3$ (16 mg, 15 μmol). The mixture was heated to 50 °C and stirred for 1 h. The reaction mixture was cooled to rt, diluted with Et_2O (10 mL), washed with water (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The product was purified by radial PLC (SiO_2, 1−3% EtOAc/hexanes) to give 97 mg (60% over two steps) of **30a** as a clear oil: IR (neat) 2929, 2856, 1716, 1495, 1390, 1353, 1296, 1209, 1180, 1111, 997, 813 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52 (m, 2H), 7.35 (m, 5H), 7.17 (m, 1H), 7.08 (m, 2H), 5.84 (m, 1H), 4.98 (m, 2H), 4.51 (m, 1H), 2.87 (bs, 1H), 2.46 (m, 1H), 2.39−1.46 (m, 14H), 1.30−1.13 (m, 8H), 0.87 (t, 3H, *J* = 6.6 Hz), 0.41 (s, 3H), 0.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.6, 151.4, 149.7, 139.5, 139.1, 133.4, 129.2, 128.8, 127.8, 124.9, 121.9, 114.2, 63.1, 51.4, 36.2, 33.7, 33.1, 32.6, 31.7, 31.5, 29.3, 28.4, 27.0, 26.9, 22.7, 22.6, 14.0, −1.0, −1.2; HRMS calcd for $C_{34}H_{48}NO_2Si$ $[(M + H)^+]$ 530.3449, found 530.3445.

***rac*-4-(Dimethylphenylsilanyl)-4-(methoxymethoxy)-2-*n*-propyl-3,4,5,6,7,8-hexahydro-2*H*-quinoline-1-carboxylic Acid Phenyl Ester (31).** To a solution of silyl alcohol **19b** (44 mg, 98 μmol) in 1 mL of DMF was added potassium iodide (~2 mg). The reaction was cooled to −20 °C, and diisopropylethylamine (180 μL, 1.03 mmol) was added followed by chloromethyl methyl ether (100 μL, 1.32 mmol). The reaction was warmed to room temperature and stirred for 18 h. The excess chloromethyl methyl ether was removed via rotary evaporation. The DMF was removed by Kugelrhor distillation (60 °C, 0.25 mmHg). The crude product was purified by radial PLC (silica gel, 10% EtOAc/hexanes) to afford 30 mg (62%) of **31** as an oil: IR (neat) 3074, 2955, 2933, 2855, 1739, 1733, 1717, 1701, 1697, 1597, 1508, 1496, 1394, 1317, 1206, 1121, 1021, 833, 819 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.62 (dd, 2H, *J* = 7.2 and 1.6 Hz), 7.38−7.31 (m, 5H), 7.19 (t, 1H, *J* = 7.6 Hz), 7.11 (d, 2H, *J* = 7.6 Hz), 4.67 (d, 1H, *J* = 6.8 Hz), 4.58 (d, 1H, *J* = 7.2 Hz), 4.35−4.30 (m, 1H), 3.33 (s, 3H), 3.03 (t, 1H, *J* = 6.8), 2.65 (dd, 1H, *J* = 15.6 and 8 Hz), 2.31 (dd, 1H, *J* = 15.6 and 1.6 Hz), 1.93−1.75 (m, 4H), 1.63−1.23 (m, 7H), 0.92 (t, 3H, *J* = 7.2 Hz), 0.38 (d, 6H, *J* = 2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.4, 137.0, 135.0, 129.4, 128.5, 127.7, 125.4, 121.9, 94.6, 73.3, 55.6, 49.5, 37.6, 36.0, 29.8, 25.9, 23.4, 23.0, 20.3, 14.2, −4.8, −5.2.

***rac*-(But-3-enyl)-4-(dimethyl(phenyl)silyl)-2-*n*-hexyl-1,2,3,5,6,7,8,8a-octahydroquinoline (34).** Phenyl carbamate **30a** (194 mg, 367 μmol) was dissolved in a mixture of anhydrous THF (2.5 mL) and freshly distilled liquid ammonia (7.5 mL) at −78 °C. *tert*-Butyl alcohol was added (10 μL) followed by a slow addition of sodium (5.0 equiv, 42 mg, 1.83 mmol) in small portions until a deep blue color persisted. The reaction was immediately quenched with solid NH_4Cl and warmed to rt. The resulting solution was filtered through Celite and concentrated in vacuo. The crude product was purified by radial PLC (SiO_2 1−12% EtOAc/hexanes) to yield 110 mg (73%) of the free amine **34** as a clear oil: IR (neat) 2926, 2855, 1639, 1456, 1249, 1110, 907, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50 (m, 2H), 7.32 (m, 3H), 5.86 (ddt, 1H, *J* = 6.6, 10.2, 17.1 Hz), 2.77 (m, 1H), 5.05 (ddd, 1H, *J* = 1.3, 3.4, 17.1 Hz), 4.96 (dt, 1H, *J* = 1.1, 10.2 Hz), 2.27 (m, 1H), 0.34 (s, 3H), 0.88 (t, 3H, *J* = 6.6 Hz), 2.12−1.02 (m, 22H), 0.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.1, 140.3, 139.4, 133.6, 128.5, 127.6, 124.1, 114.2, 57.1, 47.1, 37.8, 37.7, 37.2, 32.7, 32.1, 31.8, 29.5, 27.3, 27.2, 26.1, 22.6, 22.3, 14.1, −0.6, −1.1; HRMS calcd for $C_{27}H_{44}NSi$ $[(M + H)^+]$ 410.3238, found 410.3239.

***rac*-7-(Dimethyl(phenyl)silyl)-5-*n*-hexyl-2,3,5,6,8,9,10,11-octahydro-1*H*-pyrrolo[1,2-*j*]quinolin-3-yl)methanol (35a).** To a solution of amine **34** (31 mg, 76 μmol) in CH_2Cl_2 (2 mL) at −45 °C was added *N*-iodosuccinimide (1.1 equiv, 19 mg, 84 μmol). The reaction was slowly warmed to 0 °C over a period of 1.5 h. The solvent was removed in vacuo, and the residue was redissolved in THF (2 mL). A solution of NaOH (4 M, 3 mL) was added, and the reaction mixture was stirred at rt overnight. After that period, the reaction mixture was diluted with Et_2O (10 mL), and the organic layer was separated, washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The residue was purified by radial PLC (SiO_2, 1−12% EtOAc/hexanes) to afford 22 mg (67%, 5:1 mixture of diastereomers) of tricyclic product **35a** as a clear oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50 (m, 2H), 7.33 (m, 3H), 3.57 (dd, 1H, *J* = 3.6, 10.4 Hz), 3.37 (d, 1H, *J* = 10.5 Hz), 3.01 (m, 1H), 2.71 (m, 1H), 2.44 (m, 1H), 2.24 (dt, 1H, *J* = 4.7, 16.0 Hz), 2.15 (dd, 1H, *J* = 5.6, 12.2 Hz), 1.94 (d, 1H, *J* = 16.5 Hz), 1.88−1.04 (m, 20H), 0.88 (t, 3H, 6.6 Hz), 0.36 (s, 3H), 0.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.3, 140.4, 133.5, 128.6, 127.7, 119.9, 77.2, 64.0, 63.4, 59.6, 52.8, 40.3, 36.7, 34.2, 34.0, 31.8, 29.7, 29.4, 27.3, 27.1, 26.5, 25.3, 24.7, 22.7, 14.1, −0.7, −0.9; HRMS calcd for $C_{27}H_{44}NOSi$ $[(M + H)^+]$ 426.3187, found 426.3186.

***rac*-((3*R*,5*R*,11a*R*)-5-Hexyl-2,3,5,6,8,9,10,11-octahydro-1*H*-pyrrolo[2,1-*j*]quinolin-3-yl)methanol (36).** To a solution of vinyl silane **35a** (29 mg, 70 μmol) in anhydrous DMSO (2 mL) at rt was added TBAF (1 M in THF, 1.0 mL, 1.0 mmol), and then the reaction mixture was heated at 80 °C for 1 h. The reaction mixture was cooled to rt, diluted with ether (10 mL), and transferred to a separatory funnel. The resulting mixture was washed with water (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The residue was purified by radial PLC (SiO_2, 2% EtOAc/1% Et_3N/hexanes) to afford 15 mg (75%) of alkene **36** as a clear oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.31 (d, 1H, *J* = 6.1 Hz), 3.57 (dd, 1H, *J* = 3.6, 10.5 Hz), 3.35 (dd, 1H, *J* = 1.9, 10.5 Hz), 3.00 (m, 1H), 2.74 (m, 1H), 2.30−2.15 (m, 2H), 2.07 (m, 2H), 1.82−1.15 (m, 20H), 0.88 (t, 3H, *J* = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.6, 113.8, 63.7, 62.8, 60.1, 52.9, 40.0, 36.3, 34.6, 34.3, 31.9, 29.4, 27.4, 27.0, 25.4, 25.0, 23.8, 22.7, 14.1; HRMS calcd for $C_{19}H_{34}NO$ $[(M + H)^+]$ 292.2635, found 292.2632.

***rac*-((3*R*,5*R*,11a*R*)-5-Hexyl-2,3,5,6,8,9,10,11-octahydro-1*H*-pyrrolo[2,1-*j*]quinolin-3-yl)methanol (37).** A 25 mL round-bottom flask was charged with alkene **36** (15 mg, 51 μL) in EtOH (5 mL) and 15 mg of Pd/C. The flask was fitted with a balloon containing hydrogen gas. The mixture was purged two times using reduced pressure. The heterogeneous mixture was stirred at rt for 16 h. The mixture was filtered through Celite and concentrated under reduced pressure. Purification by radial PLC (SiO_2, 2% EtOAc/1%

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Et_3N/hexanes) gave 13 mg (85%) of **37** as a clear oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 3.48 (dd, 1H, J = 3.0, 10.2 Hz), 3.26 (d, 1H, J = 10.2 Hz), 3.13 (m, 1H), 2.64 (m, 1H), 2.14−1.15 (m, 27H), 0.88 (t, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 64.1, 63.5, 63.2, 54.2, 37.1, 35.9, 35.8, 31.9, 30.2, 29.5, 28.1, 26.1, 25.1, 25.0, 22.7, 21.8, 21.0, 14.1; HRMS calcd for $C_{19}H_{36}NO$ [$(M + H)^+$] 294.2791, found 294.2791.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01514.

^1H and ^{13}C NMR spectra; comparison table of spectroscopic data for synthesized natural product analogue **37** (PDF)

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Notes

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