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Studies toward the Total Synthesis of Dihydrolycolucine. Preparation of AB and CEF Ring Fragments

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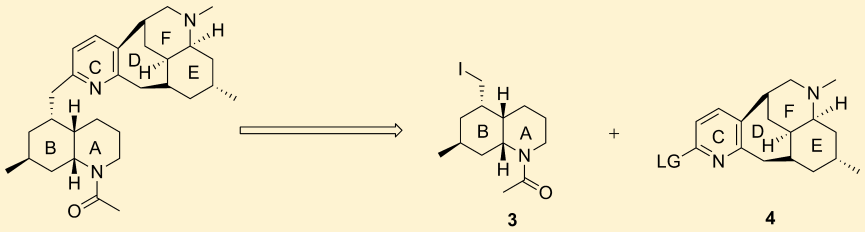
Supporting Information



ABSTRACT: A strategy for the synthesis of the lycopodium alkaloid dihydrolycolucine (**1**) has been investigated. Synthetic routes were developed based on *N*-acylpyridinium salt chemistry to prepare target fragments **3** and **4** that could ultimately converge to the natural product. Key reactions include IMDA cycloadditions and retro-Mannich ring-openings to form both the AB and the EF ring fragments. The ring C precursor was prepared using pyridine substitution and directed lithiation chemistry. A Suzuki cross-coupling of rings C and EF led to the CEF ring fragment. Initial attempts at closure of the seven-membered D ring were unsuccessful.

INTRODUCTION

Extracted from club moss *Lycopodium lucidulum*, the lycopodium alkaloids represent a complex family of heterocyclic natural products with various structural types. These alkaloids have been thoroughly studied over the past 60 years, and more than 200 members of this family have been isolated. Within the *Lycopodium* family, there is an abundant subclass of compounds with the general $C_{30}N_3$ framework, including dihydrolycolucine (**1**) and structurally relevelant lycolucine (**2**) (Figure 1).

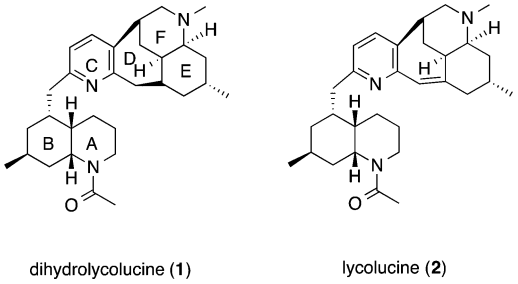


Figure 1. Dihydrolycolucine and lycolucine.

Dihydrolycolucine, isolated in 1979 by Ayer and co-workers, represents one of the more structurally elaborate members of this alkaloid family, and its structure has been fully characterized by crystallographic, spectroscopic, and chemical studies. Embedded within its unique architecture are nine sterogenic centers and a strained seven-membered ring, both of which pose a significant synthetic challenge.[1] To our knowledge, there have been no biological or synthetic studies reported for dihydrolycolucine. Our progress toward its total synthesis is described herein.

RESULTS AND DISCUSSION

Our strategy for preparation of dihydrolycolucine **1** is shown in Scheme 1. It was envisioned that key fragments **3** and **4** would converge via a C−C bond forming reaction to provide alkaloid **1**. Alkyl iodide **3** would be prepared in enantiopure form via a chiral *N*-acylpyridinium salt reaction. Furthermore, the tetracyclic fragment **4** would originate from a Pd^0-mediated ester enolate ring-closure with an appropiately functionalized pyridine. The pyridine motif would be incorporated via a Suzuki cross-coupling reaction with *β*-bromo enecarbamate **7**, furnished by starting from another chiral *N*-acylpyridinium salt reaction.

The synthesis of the AB ring fragment **3** initiated with the in situ generation of the chiral *N*-acylpyridinium salt **5**, from 4-methoxy-3-(triisopropylsilyl)pyridine and (-)-TCC chloroformate, followed by the addition of the enantiopure Grignard **9**,[2c] to yield dihydropyridone **10** upon acidic work up (Scheme 2).[2] The synthesis of compounds **10**−**15** followed our reported procedures for preparing their enantiomers.[2d] Standard one-pot removal of the chiral auxiliary and TIPS group, followed by reprotection of the nitrogen as the benzyl carbamate, produced enantiopure dihydropyridone **11**. The terminal olefin underwent oxidative cleavage, followed by a Horner−Wadsworth−Emmons olefination, to render the *trans* *α*,*β*-unsaturated ester

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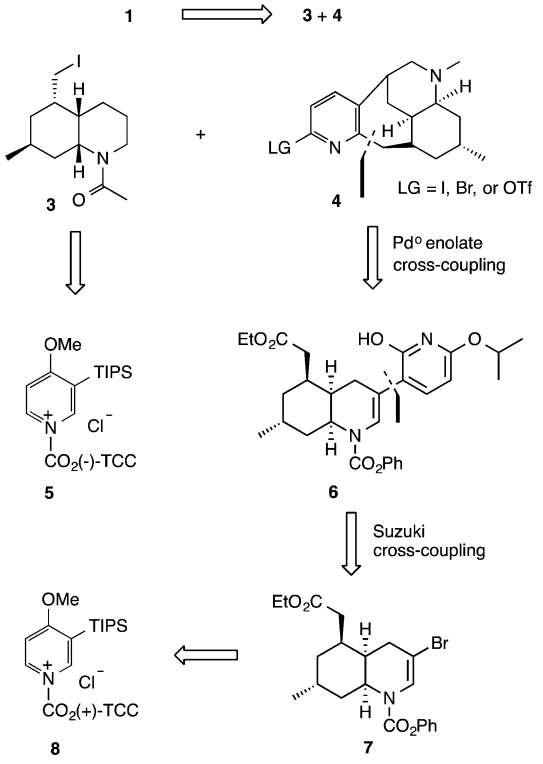
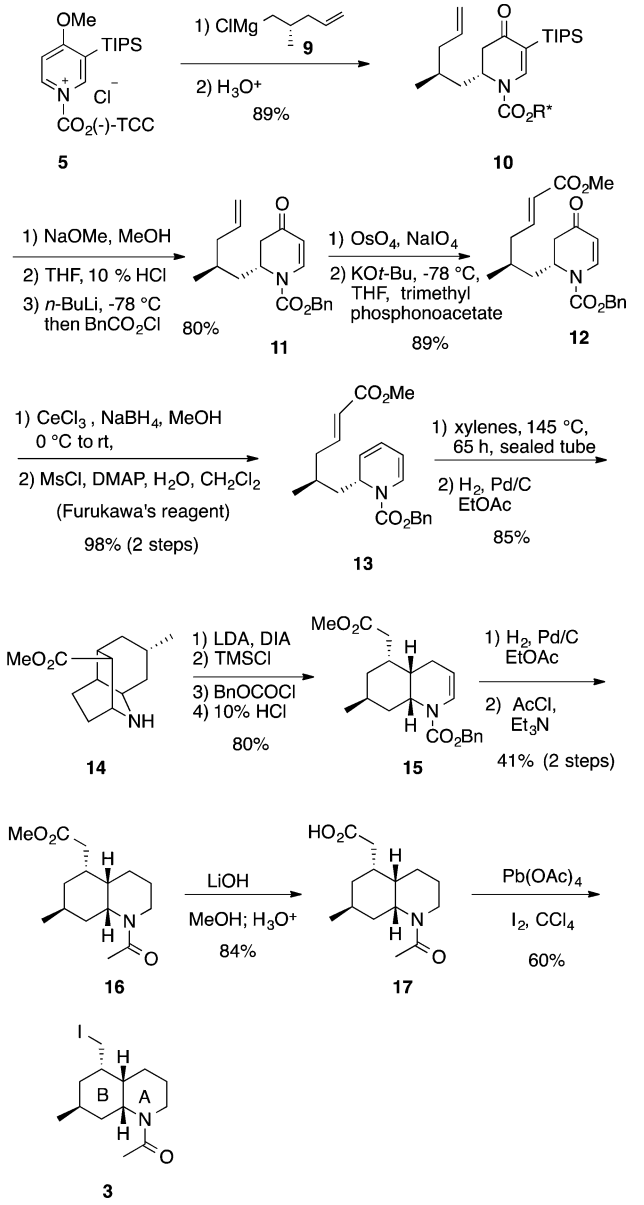
Scheme 1. Retrosynthesis of Dihydrolycolucine 1



Scheme 2. Synthesis of the AB Ring Fragment 3



12. The vinylgous amide carbonyl was reduced under Luche conditions, followed by dehydration of the resulting allylic alcohol with Furukawa's reagent, to smoothly furnish dihydropyridine **13**.[3,4] The triene underwent an intramolecular Diels–Alder (IMDA) cycloaddition, followed by hydrogenation to simultaneously remove the Cbz group and reduce the olefin, revealing amino ester **14**.[5] Bond cleavage was induced through a retro-Mannich ring-opening pathway[5c] that allowed for the formation of bicyclic compound **15**. Concomitant reduction of the enecarbamate and removal of the Cbz group were accomplished under standard hydrogenation procedures utilizing palladium on carbon. The crude amine (88%) was immediately acylated with acetyl chloride to give an unoptimized low yield of amide **16**. Saponification of the methyl ester with LiOH provided the carboxylic acid **17**. Completion of fragment **3** is marked by an iododecarboxylation reaction sequence mediated with $Pb(OAc)_4$ and iodine.[6]

A model study to the northern fragment **4** was initiated with the fundamental *N*-acylpyridinium salt reaction, albeit in a racemic fashion. Nor-methyl intermediates **18**–**21** were prepared as previously reported.[5d] The addition of the Grignard reagent to the *N*-benzyloxy-4-methoxypyridinium salt, followed by mild acid hydrolysis, provided **18** (Scheme 3). Transformation of the terminal olefin to the *trans* α,β-unsaturated ethyl ester was carried out directly via a cross-metathesis reaction using excess ethyl acrylate in the presence of 0.7 mol % of a second-generation Grubbs catalyst,[7] furnishing **19** in 95% yield. With **19** in hand, reduction of the C-4 carbonyl under standard Luche conditions[3] gave the desired alcohol, which was dehydrated with Furukawa's reagent[4] to afford dihydropyridine **20**. The triene underwent our intramolecular Diels–Alder (IMDA) and retro-Mannich ring-opening reaction sequence[5c,d] to provide the *N*-phenoxycarbony intermediate **22**. Through a modification of Overman's protocol,[8] enecarbamate **22** was treated with molecular bromine in the presence of excess 1,2,2′,6,6′-pentamethylpiperidine (PMP) and 4 Å molecular sieves to provide β-bromo enecarbamate **23** in 93% yield.

With the synthetic routes to two of the key fragments established, our attention was directed toward the preparation of the pyridine **28** for an eventual Suzuki coupling. Initially, 2,6-dichloropyridine (**24**) underwent two successive nucleophilic aromatic substitutions to yield the disubstituted pyridine derivative **26** (Scheme 4). Removal of the benzyl group with catalytic hydrogenation provided the pyridone **27**, which was subsequently converted to MOM-protected pyridine **28** in 83% yield. Utilizing the MOM ether as an effective *ortho*-director, pyridyl boronic ester **29** was prepared in high yield by deprotonation of **28** with *n*-BuLi, followed successive treatment with trimethylborate and pinacol.[9]

After establishing practical synthetic routes to β-bromo enecarbamate **23** and pyridine **29**, our attention turned toward their union. A Suzuki cross-coupling reaction mediated by $Pd(t\text{-}Bu_3P)_2$, followed by mild acid hydrolysis of the MOM group of

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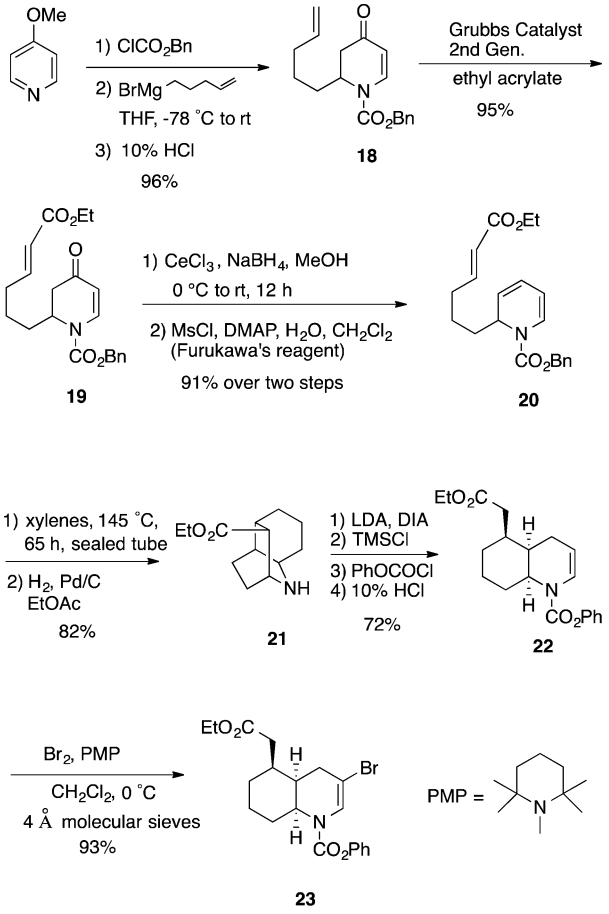
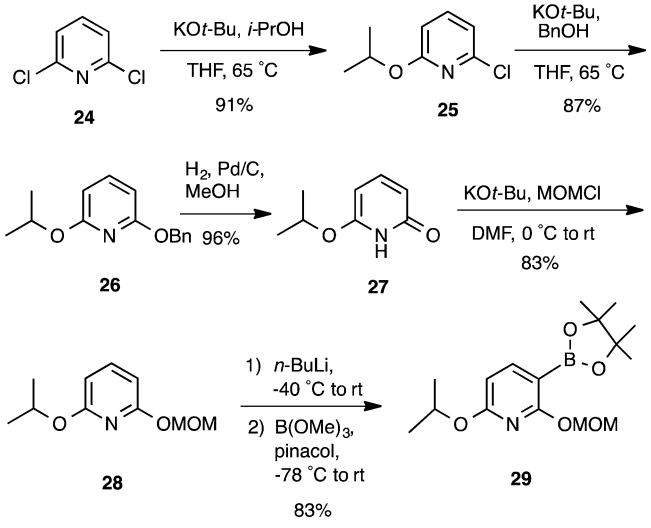
Scheme 3. Synthesis of β-Bromo Enecarbamate 23

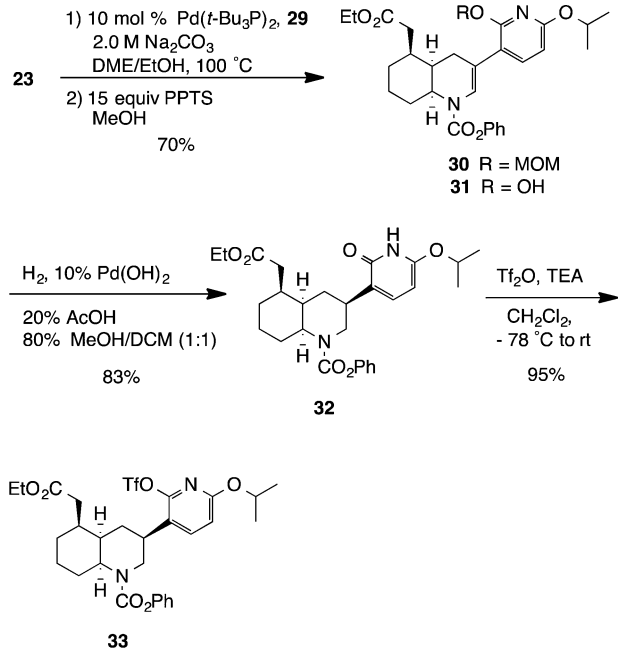


Scheme 4. Synthesis of Pyridyl Boronic Ester 29



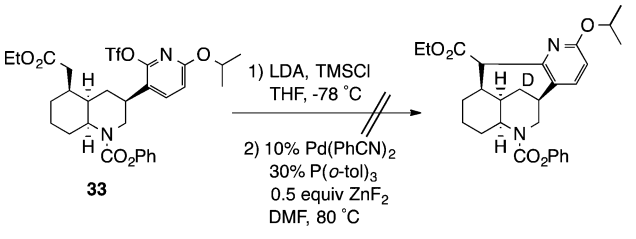
30 with excess pyridinium *p*-toluenesulfonate, afforded the pyridinol **31** over two steps (Scheme 5).[10] After considerable experimentation, reduction of the enecarbamate olefin proceeded smoothly to furnish **32** in high yield as a single diastereomer. Treatment of pyridone **32** with Tf_2O in the presence of TEA afforded pyridyl triflate **33** in 95% yield. It is worth noting that attempted conversions of the pyridone **31** into either the iodo or the bromo derivatives resulted in extensive decomposition.

Scheme 5. Suzuki Cross-Coupling with Pyridyl Boronic Ester 29 and Subsequent Conversions



With pyridyl triflate **33** readily in hand, examination of the crucial seven-membered ring formation was addressed (Scheme 6). Because of the sensitivity and complex nature of the

Scheme 6. Examination of Seven-Membered Ring Formation



substrate, we chose to initially explore the mild Pd-catalyzed arylation conditions as reported by Hartwig.[11a] The silylketene acetal of **33** was prepared in situ by treatment with LDA and TMSCl. The crude silylketene acetal was immediately exposed to cross-coupling conditions mediated by $Pd(PhCN)_2Cl_2$.[11b] Unfortunately, this reaction sequence proved ineffective and only starting material was isolated. Variations of this reaction also resulted in recovered starting material or pyridone **32**. To the best of our knowledge, this is the first attempt to couple aryl triflates with ester enolates.

In summary, a detailed account of our progress toward lycopodium alkaloid dihydrolycolucine is reported utilizing an *N*-acyl-2,3-dihydropyridone as a building block. In particular, the synthesis of two major fragments was accomplished, leading to the examination of the tetracylic core formation. Unfortunately, initial attempts at closing the seven-membered D ring by way of a palladium-catalyzed ester−enolate cross-coupling proved unfruitful. Further studies are needed to accomplish this pivotal ring-closure.

EXPERIMENTAL SECTION

Methyl 2-((4*aS*,5*R*,7*S*,8*aR*)-1-Acetyl-7-methyldecahydroquinolin-5-yl)acetate (16). A solution of **15** (50.5 mg, 0.141

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mmol) in 2 mL of ethyl acetate was hydrogenated for 4 h at rt under balloon pressure in the presence of 5% Pd/C (23 mg). Filtration over Celite and removal of solvent in vacuo resulted in 28.1 mg (88%) of the amine as a yellow oil. The crude amine was dissolved in 1 mL of CH_2Cl_2, followed by the addition of triethylamine (25.1 μL, 0.178 mmol) and freshly distilled acetyl chloride (11.3 μL, 0.157 mmol). The resulting mixture was stirred at 0 °C. After 30 min, distilled H_2O (1 mL) was added to the reaction, and the biphasic solution was transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (2 × 5 mL). The organic layers were collected, washed with brine, dried over $MgSO_4$, and filtered through a thin pad of Celite. The volatiles were removed in vacuo, and purification by chromatography (SiO_2, 5−10% MeOH/CH_2Cl_2) afforded 17.3 mg (47%) of pure **16** as a yellow oil. IR (neat) 2926, 2869, 1737, 1644, 1434, 1266, 1172, 1035, 874 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.95−4.89 (m, 1H), 4.49−4.45 (m, 1H), 3.97−3.93 (m, 1H), 3.68−3.66 (pair of s, due to rotamers, 3H), 3.60−3.53 (m, 1H), 3.14−3.08 (m, 1H), 2.63−2.56 (m, 1H), 2.42−2.10 (m, 3H), 2.09 and 2.06 (pair of s, due to rotamers, 3H), 1.98−1.14 (m, 7H), 1.17 and 1.10 (pair of d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (rotamers) 173.3, 173.2, 169.2, 168.9, 51.9, 51.8, 51.7, 46.0, 41.8, 39.7, 38.6, 38.5, 38.2, 36.4, 32.3, 31.9, 31.7, 31.5, 29.6, 28.2, 27.8, 27.4, 26.0, 25.0, 22.3, 21.5, 18.7, 18.5, 17.7, 17.6; HRMS (ESI) calcd for $C_{15}H_{25}NO_3$ 267.1834, found 267.1840; $[\alpha]_D^{23}$ −44.6 (*c* 0.28, $CHCl_3$).

2-((4*aS*,5*R*,7*S*,8*aR*)-1-Acetyl-7-methyldecahydroquinolin-5-yl)acetic acid (17). Compound **16** (17.3 mg, 0.0647 mmol) was dissolved in 80% aqueous MeOH (5 mL), followed by the addition of LiOH·H_2O (51.9 mg, 1.23 mmol). After stirring at rt for 16 h, distilled H_2O (5 mL) was added to the mixture. The mixture was acidified with a solution of 10% HCl and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After filtration through Celite, the volatiles were removed in vacuo, followed by purification (SiO_2, 5% MeOH/CH_2Cl_2) to give 13.8 mg (84%) of **17** as a tacky white oil. IR (neat) 3500, 2926, 2875, 1619, 1561, 1401, 1270, 1174, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.00−8.00 (bs, 1H), 4.95−4.91 (m, 1H), 4.51−4.46 (m, 1H), 3.99−3.96 (m, 1H), 3.60−3.56 (m, 1H), 3.16−3.09 (m, 1H), 2.64−2.58 (m, 1H), 2.42−2.02 (m, 5H), 2.11 and 2.08 (pair of s, due to rotamers, 3H), 1.98−1.16 (m, 5H), 1.11 (appar t, due to rotamers, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (rotamers) 177.5, 177.1, 169.8, 169.4, 52.1, 46.3, 41.9, 39.5, 38.5, 38.4, 38.2, 36.7, 32.3, 31.9, 31.5, 31.4, 29.7, 28.2, 27.8, 27.4, 26.0, 25.0, 22.1, 21.3, 18.7, 18.5, 17.7, 17.6; HRMS (ESI) calcd for $C_{14}H_{23}NO_3$ ($[M + H]^+$) 254.1757, found 254.1756; $[\alpha]_D^{23}$ −86.7 (*c* 0.09, $CHCl_3$).

1-((4*aS*,5*S*,7*S*,8*aR*)-5-(Iodomethyl)-7-methyloctahydroquinolin-1(2*H*)-yl)ethan-1-one (3). An oven-dried flask was charged with **17** (13.8 mg, 0.0545 mmol) and $Pb(OAc)_4$ (31.4 mg, 0.071 mmol) in anhydrous CCl_4 (1.2 mL). The mixture was stirred under N_2 at reflux while being irradiated with a tungsten 350 W lamp. Iodine (15.2 mg, 0.06 mmol) dissolved in anhydrous CCl_4 (0.8 mL) was added to the refluxing mixture. After heating for an additional 2 h, the reaction mixture was allowed to cool to rt, after which a precipitate formed. The precipitate was filtered and washed with CCl_4. The combined filtrates were washed with 10% $Na_2S_2O_3$, water, and sat. $NaHCO_3$. The solution was dried over $MgSO_4$ and filtered, and the volatiles were removed under reduced pressure. Purification of the crude residue by chromatography (SiO_2, 0−5% MeOH/CH_2Cl_2) afforded 11 mg (60%) of iodide **3** as an unstable yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.92−4.85 (m, 1H), 4.52−4.47 (m, 1H), 3.94−3.90 (m, 1H), 3.61−3.56 (m, 1H), 3.17−3.09 (m, 4H), 2.64−2.56 (m, 1H), 2.11 and 2.06 (pair of s, due to rotamers, 3H), 1.98−1.16 (m, 7H), 1.11 (appar t, due to rotamers, 3H). LRMS calcd for $C_{13}H_{22}INO_3$ 335, found 335.

Phenyl (4*aR,5*S**,8*aS**)-5-(2-Ethoxy-2-oxoethyl)-4*a*,5,6,7,8,8*a*-hexahydroquinoline-1(4*H*)-carboxylate (22).** A solution of lithium diisopropylamide (1.50 mmol, prepared from 0.62 mL of 2.4 M *n*-BuLi and 0.218 mL of diisopropylamine) in 5 mL of THF under N_2 was cooled to −78 °C (dry ice/acetone). Tricyclic amine **21** (0.113 g, 0.50 mmol) in THF (4 mL) was then added, and the mixture was stirred at −78 °C for 30 min. Trimethylsilyl chloride (0.223 mL, 1.76 mmol) was added at −78 °C, and the mixture was warmed to rt for 15 min. Dry hexane (10 mL) was added to cause precipitation. The mixture was filtered and concentrated under reduced pressure. This process was repeated again to finally provide 0.190 g (103%) of the crude bis-silyl intermediate as a yellow oil. To a solution of the crude oil (0.60 g, 0.26 mmol) in 5 mL of dry CH_2Cl_2, under N_2 at rt, was added phenyl chloroformate (0.067 mL, 0.52 mmol). The mixture was heated to reflux for 12 h and then cooled to rt. A solution of 10% HCl (4 mL) was added, and the mixture was stirred for 1.5 h. Saturated $NaHCO_3$ solution (5 mL) was added, followed by ether (20 mL). The organic phase was washed with brine (5 mL) and dried (K_2CO_3). The solution was filtered, concentrated, and purified by preparative layer chromatography (silica gel, EtOAc−hexanes, 1:5, three elutions) to give 0.07 g (86% from **21**) of **22** as a light yellow oil. ^1H NMR (300 MHz, $CDCl_3$) 7.3 δ(m, 5H), 6.8 (d, 1H), 4.8 (m, 1H), 4.2 (q, 2H), 3.9 (m, 1H), 2.9 (m, 1H), 2.9 (m, 1H), 2.2−2.5 (m, 2H), 1.1−2.2 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) 173.1 (2C), 129.2 (2C), 125.1, 121.6 (2C), 120, 115.8, 105.2, 60.8, 53.9, 47.2, 38.6 34.5, 34.0, 33.6, 24.1, 15.6, 14.3; IR (neat) 2920, 1750, 1650, 1570 cm^{-1}.

(4*aR,5*S**,8*aS**)-Phenyl-3-bromo-5-(2-ethoxy-2-oxoethyl)-4*a*,5,6,7,8,8*a*-hexahydroquinoline-1(4*H*)-carboxylate (23).** To a solution of **22** (89 mg, 0.259 mmol) in CH_2Cl_2 (5 mL) was added 10 mg of crushed 4 Å molecular sieves, followed by addition of 1,2,2′,6,6′-pentamethylpiperidine (141 mg, 0.906 mmol). The mixture was cooled to 0 °C and bromine (0.518 mL, 0.259 mmol) as a 0.5 M solution in CH_2Cl_2 was added over 1 h via syringe pump. Following completion of bromine addition, the reaction was warmed to rt and stirred for 1 h. The mixture was filtered through a thin pad of Celite, and the volatiles were removed under reduced pressure. Purification by radial PLC (SiO_2, 0−5% EtOAc/hexanes) afforded 101 mg (92%) of pure **23** as a clear oil. IR (neat) 3434, 2933, 2861, 1726, 1660, 1493, 1202 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.09 (m, 6H), 4.21−4.09 (m, 3H), 2.49−2.24 (m, 7H), 1.81−1.72 (m, 2H), 1.53−1.42 (m, 3H), 1.25 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz $CDCl_3$) δ 172.4 and 173.3 (due to rotamers), 151.3 and 151.0 (due to rotamers), 150.5, 129.6, 126.0, and 125.9 (due to rotamers), 124.6 and 124.3 (due to rotamers), 121.8, 102.1, and 101.8 (due to rotamers), 60.7, 54.0, 53.2, 38.5, 36.8, and 36.7 (due to rotamers), 36.4 and 36.1 (due to rotamers), 26.0, 25.4, 24.5, and 24.3 (due to rotamers), 14.4; HRMS (ESI) calcd for $C_{20}H_{24}BrNO_4$ 421.0888, found 421.0905.

2-Chloro-6-isopropoxypyridine (25).[12] Anhydrous isopropanol (0.31 mL, 4.05 mmol) was added to a solution of KO*t*-Bu (417 mg, 3.72 mmol) in THF (3 mL) at rt. After 30 min, 2,6-dichloropyridine (500 mg, 3.38 mmol) was added to the milky solution. The mixture was warmed to 65 °C and stirred for 12 h. The solvent was removed by evaporation, water (5 mL) was added, and the mixture was extracted with methylene chloride. The combined organic layers were dried over K_2CO_3, filtered, and concentrated. The crude product was purified by radial PLC (silica gel, 2% EtOAc/hexanes) to afford 510 mg (91% yield) of **25** as a clear oil. IR (neat) 2980, 2936, 1592, 1559, 1441, 1302, 1159, 1109, 963, 788 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J = 6.8 Hz, J = 8.0 Hz, 1H), 6.82 (d, J = 6.8 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 5.32−5.20 (m, 1H), 1.32 (d, J = 104 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 148.4, 140.6, 115.9, 109.8, 69.1, 22.0.

2-Benzyloxy-6-isopropoxypyridine (26). Benzyl alcohol (0.37 mL, 3.54 mmol) was added to a solution of KO*t*-Bu (397 mg, 3.54 mmol) in THF (5 mL) at rt. After 30 min, 2-chloro-6-isopropoxypyridine (506 mg, 2.95 mmol) was added, and the mixture was stirred at 65 °C for 12 h. The reaction was allowed to cool to rt, the solvent was removed by concentration, and the residue was extracted with methylene chloride. The combined organic layers were dried over K_2CO_3, filtered, and concentrated. The crude product was purified by radial PLC (silica gel, 5% EtOAc/hexanes) to afford 629 mg (87%) of **26** as a clear oil. IR (neat) 3088, 1064, 3033, 2977, 2936, 2876, 1596, 1579, 1444, 1371, 1312, 1237, 1140, 1115, 1041, 989, 788 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50−7.25 (m, 5H), 6.35 (d, J = 7.6 Hz, 1H), 6.27 (d, J = 7.6 Hz, 1H), 5.36 (s, 2H), 5.28−5.18 (m, 1H), 1.34 (d, J = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5,

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162,4, 141.2, 137.9, 128.6, 127.9, 102.4 101.5, 68.3, 67.6, 22.3 (2C); HRMS (ESI) calcd for $C_{15}H_{17}NO_2$ ([M]$^+$) 243.1259, found 243.1263.

6-Isopropoxy-1-*H*-pyridin-2-one (27). A solution of 2-benzyloxy-6-isopropoxypyridine (2.11 g, 8.65 mmol) in MeOH (50 mL) was hydrogenated (balloon pressure) over 10% Pd/C (461 mg) at rt for 12 h. The mixture was filtered through Celite, and the solids were rinsed with methylene chloride. The crude product was purified by radial PLC (silica gel, 50% EtOAc/hexanes) to afford 1.28 g (96%) of **27** as a white solid, mp 106−107 °C; IR (neat) 3500−2500, 1648, 1599, 1453, 1372, 1273, 1109 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J = 8.8, 7.6 Hz, 1H), 6.15 (d, J = 8.8 Hz, 1H), 5.62 (d, J = 7.6 Hz, 1H), 4.66−4.60 (m, 1H), 1.31 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 157.7, 142.9, 108.6, 89.4, 71.8, 21.8; HRMS (ESI) calcd for $C_8H_{11}NO_2$ ([M + H]$^+$) 154.0868, found 154.0869.

6-Isopropoxy-2-(methoxymethoxy)pyridine (28). A solution of **27** (75 mg, 0.489 mmol) in DMF (1 mL) was added to a solution of KO*t*-Bu (60 mg, 0.538 mmol) in DMF (2 mL) at 0 °C. After 20 min at 0 °C, the mixture was warmed to rt and stirred for 2 h. The mixture was then cooled back down to 0 °C, and MOMCl (0.04 mL, 0.59 mmol) was added dropwise. After 5 min at 0 °C, the mixture was warmed to rt and stirred overnight (15 h). The reaction was quenched with water, and the mixture was extracted with methylene chloride. The combined organic layers were dried over K_2CO_3, filtered, and concentrated. The crude product was purified by radial PLC (silica gel, 5% EtOAc/hexanes) to afford 80 mg (83% yield) of **28** as a clear oil. IR (neat) 2978, 2936, 1600, 1580, 1447, 1312, 1236, 1158, 1141, 1114, 1009, 970 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (t, J = 7.9 Hz, 1H), 6.34−6.27 (m, 2H), 5.45 (s, 2H), 5.19 (septet, J = 6.0 Hz, 1H), 3.50 (s, 3H), 1.32 (d, J = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 161.4, 141.4, 103.7, 101.4, 68.3, 57.0, 22.2; HRMS (ESI) calcd for $C_{10}H_{15}NO_3$ ([M + H]$^+$) 198.1130, found 198.1127.

Isopropoxy-2-methoxymethoxy-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine (29). To a solution of pyridine **28** (355 mg, 1.80 mmol) in freshly distilled THF (10 mL) was added *n*-BuLi at −42 °C (2.36 M in hexanes, 1.21 mL, 2.85 mmol), and the mixture was stirred for 30 min at −42 °C. The solution was slowly warmed to rt and stirred for an additional 30 min. After cooling to −78 °C, neat trimethylborate (0.41 mL, 3.60 mmol) was quickly added, and after 15 min, the solution was warmed to rt. Stirring was continued at rt for 1 h, and then pinacol (490 mg, 4.14 mmol) was added in one portion. After 2 h, the reaction mixture was filtered through a thin pad of Celite with a diethyl ether (10 mL) wash. Concentration of the filtrate under reduced pressure provided the crude product. Purification by radial PLC (SiO_2, 2% Et_3N/10−20% EtOAc/hexanes) gave 517 mg (83%) of boronic ester **29** as a pale yellow oil. IR (neat) 2978, 1595, 1566, 1370, 1111, 963 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 8.1 Hz, 1H), 6.28 (d, J = 8.1 Hz, 1H), 5.54 (s, 2H), 5.20 (m, 1H), 3.53 (s, 3H), 1.32 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 165.6, 164.6, 149.1, 103.7, 91.5, 83.5, 68.7, 56.8, 25.0, 22.2; HRMS (ESI) [(M + Na)$^+$] Calcd for $C_{16}H_{26}BNO_5$ 346.1796, found 346.1803.

(4*aR,5*S**,8*aS**)-Phenyl-5-(2-ethoxy-2-oxoethyl)-3-(6-isopropoxy-2-(methoxymethoxy)-pyridin-3-yl)-4*a*,5,6,7,8,8*a*-hexahydroquinoline-1(4*H*)-carboxylate (30).** In a 15 mL round-bottom flask containing boronate ester **29** (44 mg, 0.137 mmol) was added 1 mL of degassed DME:EtOH (20:0.5). The boronate ester solution was added to a 15 mL flask containing vinyl bromide **23** (34 mg, 0.081 mmol), followed by the addition of 1 mL of DME:EtOH (20:1). To the combined solution was added aqueous 2.0 M Na_2CO_3 (0.081 mL, 0.161 mmol). With good stirring, the solution was degassed for 10 min and then Pd(*t*-$Bu_3P)_2$ (2.1 mg, 0.004 mmol) was added in one portion. The flask was quickly fitted with a reflux condenser and purged with N_2 for 2 min. The reaction was heated to 100 °C for 4 h or until disappearance of starting material by TLC. Once complete, the reaction vessel was cooled to rt, and the contents were filtered through Celite with a CH_2Cl_2 wash. The volatiles were removed under reduced pressure. Purification by flash chromatography (Florisil, 0−5% EtOAc/hexanes, 2% Et_3N) afforded 36 mg (80%) of pure **30** as a clear oil. IR (neat) 3403, 2359, 2329, 2090, 1642, 1460, 1308, 1202 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.12 (m, 7H), 6.34−6.28 (m, 1H), 5.59−5.52 (m, 2H), 5.20−5.11 (m, 1H), 4.31−4.10 (m, 3H), 3.54−3.51 (m, 3H), 2.51−2.32 (m, 6H), 1.87−1.50 (m, 6H), 1.37−1.23 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 160.5, 157.6, 151.4, and 151.3 (due to rotamers), 140.2, 129.6, 125.8, 122.9, 122.6, 121.8, 113.5, and 113.1 (due to rotamers), 103.2, 92.2, and 92.0 (due to rotamers), 68.6, 60.6, 57.4, 54.4, 53.7, 38.8, 37.1, and 36.9 (due to rotamers), 35.1 and 34.8 (due to rotamers), 29.9, 26.2, 24.6, and 24.5 (due to rotamers), 22.2, 21.9, and 21.7 (due to rotamers), 14.5; HRMS (ESI) calcd for $C_{30}H_{38}N_2O_7$ 538.2679, found 538.2670.

(4*aR,5*S**,8*aS**)-Phenyl-5-(2-ethoxy-2-oxoethyl)-3-(2-hydroxy-6-isopropoxypyridin-3-yl)-4*a*,5,6,7,8,8*a*-hexahydroquinoline-1(4*H*)-carboxylate (31).** To a stirred solution of **30** (45 mg, 0.083 mmol) in MeOH (5 mL) cooled to 0 °C was added solid pyridinium *para*-toluenesulfonate (1.42 mmol, 357 mg) in portions. After stirring for 15 min at 0 °C, the temperature was raised to rt, and the mixture was stirred for 48 h or until complete by TLC analysis. The MeOH was removed under reduced pressure, and the residue was redissolved in CH_2Cl_2 (5 mL), followed by the addition of deionized H_2O (5 mL). The mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 × 10 mL). Combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and filtered through Celite. The volatiles were removed in vacuo, and purification by flash chromatography (Florisil, 10% EtOAc/hexanes to 50% EtOAc/MeOH) afforded 35 mg (87%) of pure **31** as a clear oil. IR (neat) 3436, 2933, 2866, 1716, 1630, 1605, 1402, 1356, 1274, 1201, 1111 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 and 7.66 (bs, 1H), 7.39 (m, 6H), 5.56 (d, J = 8.40 Hz, 1H), 4.56 (m, 1H), 4.25 (m, 1H), 4.12 (q, J = 7.2 Hz, 2H), 2.32−1.49 (m, 11H), 1.31−1.22 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9 and 172.7 (due to rotamers), 162.3, 154.9, and 154.5 (due to rotamers), 151.7 and 151.5 (due to rotamers), 138.5 and 137.0 (due to rotamers), 129.4, 125.6, 122.6, 122.1, 121.8, 114.2, and 112.8 (due to rotamers), 87.7 and 87.3 (due to rotamers), 72.4, 60.6, 54.4, 53.7, 38.9, 37.0, 35.2, and 34.8 (due to rotamers), 29.9, 26.1, and 25.6 (due to rotamers), 24.6 and 24.4 (due to rotamers), 21.8, 21.0, 14.5; HRMS (ESI) [(M + Na)$^+$] calcd for $C_{28}H_{34}N_2O_6$ 517.2315, found 517.2313.

(3*S,4*aR**,5*S**,8*aS**)-Phenyl-5-(2-ethoxy-2-oxoethyl)-3-(2-hydroxy-6-isopropoxypyridin-3-yl)octahydroquinoline-1(2*H*)-carboxylate (32).** A 15 mL round-bottom flask was charged with pyridinol **31** (21 mg, 0.042 mmol), a mixture of acetic acid:-MeOH:CH_2Cl_2 (1:2:2, 3 mL), and 10 mg of $Pd(OH)_2$. The flask was fitted with a balloon containing hydrogen gas. Using an aspirator, the mixture was purged two times. The heterogeneous mixture was stirred for 3 h or until the disappearance of starting material by TLC. Once complete, the mixture was filtered through Celite and concentrated under reduced pressure. Purification by radial PLC (30−50% EtOAc/hexanes) gave 18 mg (85%) of **32** as a clear oil. IR (neat) 3855, 3423, 1626, 1524, 1025, 696, 460 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.09 (m, 7H), 5.57−5.54 (m, 1H), 4.60 (sep, J = 5.6 Hz, 1H), 4.32−4.08 (m, 4H), 3.25 (t, J 12.4 Hz, 1H), 2.90−2.83 (m, 1H), 2.30−1.46 (m, 12H), 1.34 (d, J = 6.0 Hz, 6H), 1.24 (t, J = 9.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 162.9, 155.7, 154.0, 151.8, 139.8, and 139.6 (due to rotamers), 129.3, 125.2, 122.6, 122.0, 88.0, and 87.8 (due to rotamers), 72.2, 60.5, 54.5, and 53.7 (due to rotamers), 43.7 and 42.9 (due to rotamers), 39.6, 39.1, and 38.8 (due to rotamers), 38.3 and 38.0 (due to rotamers), 37.7 and 37.5 (due to rotamers), 26.5, 25.0, 24.3, 23.7, and 23.4 (due to rotamers), 21.9, 14.4; HRMS (ESI) calcd for $C_{28}H_{36}N_2O_6$ 496.2578, found 496.2576.

(3*S,4*aR**,5*S**,8*aS**)-Phenyl-5-(2-ethoxy-2-oxoethyl)-3-(6-isopropoxy-2-(trifluoromethylsulfonyloxy)pyridin-3-yl)octahydroquinoline-1(2*H*)-carboxylate (33).** To a solution of pyridone **32** (10 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) was added triethylamine (0.026 mmol) from a 1 M stock solution in CH_2Cl_2. The solution was cooled to −78 °C, and to it was added Tf_2O (0.022 mmol) as a 0.5 M stock solution in CH_2Cl_2. Once the addition was complete, the temperature was slowly raised to rt. After 30 min, saturated aqueous $NaHCO_3$ (3 mL) was added, and the biphasic solution was transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the organics were collected, dried over $MgSO_4$, and

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filtered through a thin pad of Celite. The volatiles were removed in vacuo, and purification by radial PLC (SiO_2, 10−30% EtOAc/hexanes) afforded 11.3 mg (90%) of pure **33** as a clear oil. IR (neat) 3436, 3054, 2985, 2935, 2306, 1710, 1625, 1421, 1265, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (m, 1H), 7.40−7.09 (m, 5H), 6.74 (m, 1H), 5.16 (sep, J = 6.0 Hz, 1H), 4.37−4.12 (m, 4H), 3.1−2.93 (m, 2H), 2.24−1.48 (m, 12H), 1.33 (d, J = 6.0 Hz, 6H), 1.25 (t, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 161.2, 153.6, 151.6, 141.2, and 140.8 (due to rotamers), 129.5, 125.5, 122.0, 119.3, 112.1, 70.3, 60.6, 54.2, and 53.3 (due to rotamers), 44.4 and 43.4 (due to rotamers), 39.2 and 38.8 (due to rotamers), 37.3, 32.1, 29.8, 26.4, 25.5, 24.8, 24.1, 23.3, 22.9, 21.8, 14.4; HRMS (ESI) calcd for $C_{29}H_{35}F_3N_2O_8S$ ($[M + H]$)$^+$ 629.2139, found 629.2140.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H NMR spectra for **3** and **22**, and ^1H and ^{13}C NMR spectra for **16**, **17**, **23**, and **26**−**33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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