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Stereoselective Synthesis of 2′-Fluoro-6′-methylene Carbocyclic Adenosine via Vince Lactam

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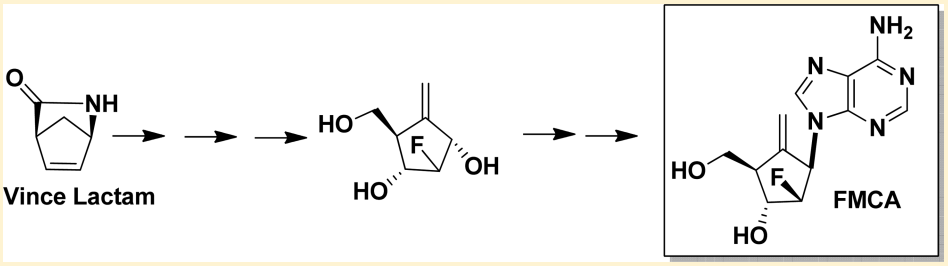
Supporting Information



ABSTRACT: 2′-Fluoro-6′-methylene carbocyclic adenosine (FMCA) is a potent and selective inhibitor of wild type as well as drug-resistant hepatitis B virus (HBV) mutants. FMCA demonstrated excellent anti-HBV activity against both adefovir-resistant and lamivudine-resistant double (rtL180M/rtM204V) mutants as well as in lamivudine/entecavir triple mutants (L180M+S202G +M204V) in vitro. Its monophosphate prodrug (FMCAP) demonstrated a greater than 12-fold increase of anti-HBV activity in comparison to that of the nucleoside without elevation of cellular toxicity. In the preliminary in vivo study in chimeric mice harboring the lamivudine/entecavir triple mutant, FMCAP effectively reduced HBV viral load, while entecavir was not effective. Therefore, it was of great interest to develop an efficient synthetic procedure to support the preclinical investigation. In this article, a new approach for the synthesis of FMCA from a readily available starting material (Vince lactam) in 16 steps is described. An efficient and practical methodology for stereospecific preparation of a versatile carbocyclic key intermediate, D-2′-fluoro-6′-methylene cyclopentanol **14**, has been developed from diazotization, elimination, stereoselective epoxidation, fluorination, and oxidation−reduction sequence of the Vince lactam in 14 steps. The utility of D-2′-fluoro-6′-methylene cyclopentanol **14** is demonstrated in the preparation of FMCA using the Mitsunobu coupling to introduce the adenine base to synthesize the final nucleoside.

INTRODUCTION

According to the World Health Organization (WHO) an estimated 2,000,000,000 people worldwide are infected with the hepatitis B virus (HBV). More than 350,000,000 patients live with chronic infection that results in 600,000 deaths worldwide every year.[1] Currently, there are several nucleos(t)ide analogues such as lamivudine, adefovir, telbivudine, entecavir, clevudine, and tenofovir which have demonstrated clinical efficacy.[2,3]

Currently, entecavir and tenofovir are being prescribed as major anti-HBV agents for drug-naïve patients as well as for those harboring adefovir- and lamivudine-resistant strains. However, the continuous use of entecavir also develops mutation, and particularly, in conjunction with lamivudine-resistant mutation, entecavir becomes clinically ineffective.[4] Therefore, viral mutations limit the use of currently approved anti-HBV drugs.[5] Thus, it is of great interest to discover anti-HBV agents which are effective against drug-resistant HBV mutants.

As part of our continued efforts to identify new and effective agents for HBV therapy, we discovered 2′-β-fluoro-6′-methylene carbocyclic adenosine (FMCA, **1**)[6] and its phosphoramidate prodrug (FMCAP, **2**)[7] (Figure 1) as promising agents. FMCA and FMCAP demonstrated anti-HBV efficacy in both wild type and resistant mutants. FMCA (EC_{50} = 0.67 μM) and FMCAP (EC_{50} = 0.054 μM) maintain their anti-HBV potency in vitro against the entecavir-resistant triple mutant (L180M+M204V+S202G), while entecavir loses its potency by 150-fold against the mutant in comparison to

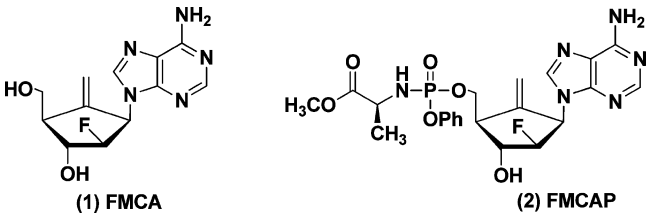


Figure 1. Structures of 2′-fluoro-6′-methylene-carbocyclic adenosine (FMCA) and its monophosphate prodrug (FMCAP).

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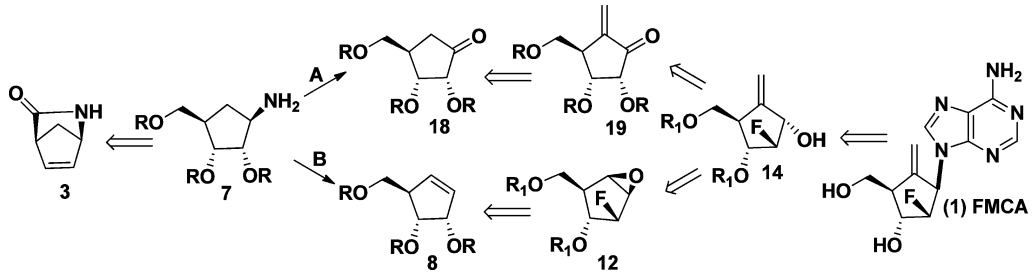
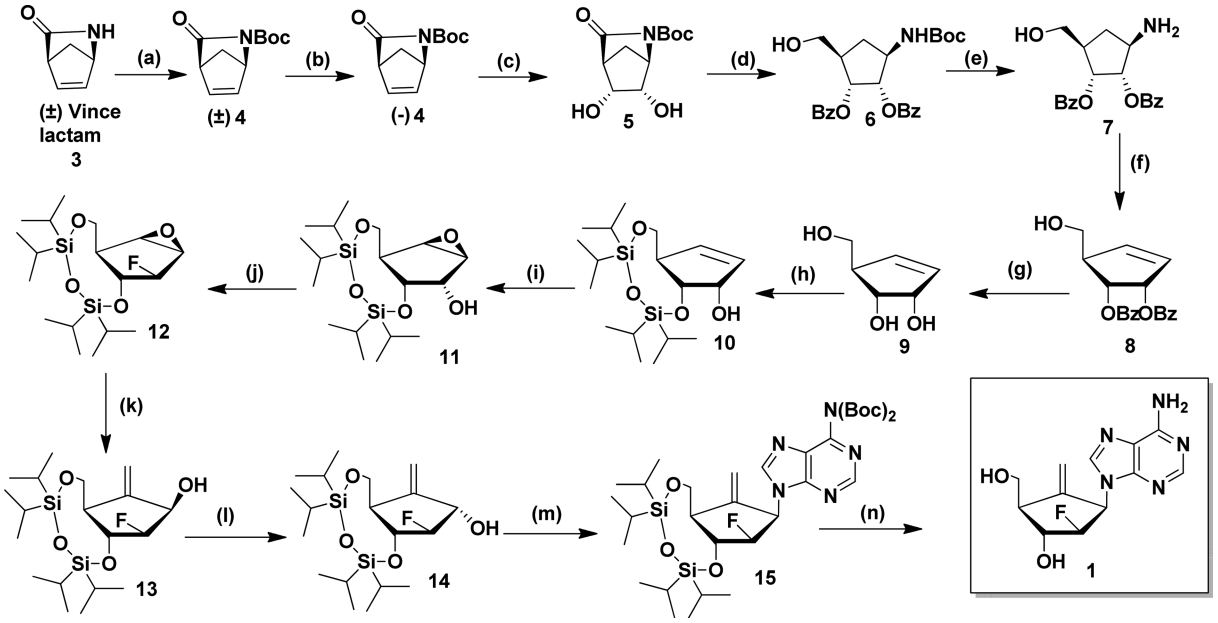
Scheme 1. Retrosynthetic Analysis of FMCA



Scheme 2. Synthesis of FMCA 1 from Vince Lactam 3



Reagents and conditions: (a) $(Boc)_2O$, DMAP, THF; (b) savinase, THF, buffer solution; (c) OsO_4, NMO, acetone; (d) (i) BzCl, DMAP, DCM, (ii) $NaBH_4$, methanol; (e) HCl/ether, methanol; (f) $NaNO_2$, acetic acid, water, acetonitrile; (g) NaOMe, methanol; (h) $TIPDSCl_2$, Imidazole, DMF; (i) *m*-CPBA, DCM; (j) DAST, DCM; (k) *n*-BuLi, trimethylsulfonium iodide, THF; (l) (i) Dess–Martin periodinane, DCM; (ii) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, methanol; (m) diBoc-adenine, DIAD, TPP, THF; (n) TFA, TBAF/THF.

wild type.[8] To support ongoing biological and preclinical development, an efficient scale-up synthesis of FMCA was required.

Herein we report the synthesis of the carbocyclic moiety **14**, which was effectively utilized for the synthesis of FMCA. Previously, we reported the synthesis of FMCA, in which the scheme was long and tedious with an inefficient methodology from ribose for an initial discovery.[6] Although our group has been extensively involved in the synthesis of carbocyclic nucleosides from D-ribose,[9,10] the earlier procedure was not suitable and was hazardous for a large-scale preparation, as an excess of MeI is required,[11] and it also had low overall yield.[6]

For a new methodology, the major problem was to generate the enantiomerically pure carbocyclic intermediate **14** in a shorter step with a fixed stereogenic center via milder reactions, with cost-effective methods that could be amenable to a large-scale synthesis. Therefore, herein we report a full account of a synthetic methodology amenable to a large-scale preparation of D-2′-fluoro-6′-methylene cyclopentenol (**14**) that is significantly improved in comparison to the previously reported method.[6] The newly developed methodology may also be utilized in the synthesis of other carbocyclic nucleosides of therapeutic interest.

RESULTS AND DISCUSSION

The retrosynthetic analysis of FMCA is illustrated in Scheme 1. The strategy was to synthesize the key chiral intermediate, 2′-*β*-fluoro-6′-methylene cyclopentanol **14**, from (±)-2-azabicyclo[2.2.1]hept-5-en-3-one (**3**), commonly known as Vince lactam. The lactam was first introduced by Robert Vince and has been used as a synthetic intermediate for various carbocyclic nucleosides, including puromycin,[12] carbovir,[13] and abacavir.[14]

To explore path A, we tried several oxidative methods for the conversion of amine **7** to the ketone analogue **18**, including $KMnO_4$, CrO_3, and Corey's oxidation of amine to ketone;[15] however, in every case it was unsuccessful. The failure of this crucial conversion led us to path B. Diazotization of the amine followed by an elimination reaction would produce the alkene **8**. Stereoselective epoxidation followed by fluorination of **8** would give **12**. Selective opening of the epoxide would construct the key intermediate **14** for the synthesis of FMCA.

The optically pure *γ*-lactam (−)-(1*R*,4*S*)-*tert*-butyl-3-oxo-2-azabicyclo[2.2.1]hept-5-ene-2-carboxylate ((−)-**4**) was synthesized by the reported procedure.[16] Treatment of the commercially available *γ*-lactam (±)-**3** with di-*tert*-butyl dicarbonate in the presence of a catalytic amount of 4-

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dimethylaminopyridine (DMAP) in THF afforded the *N*-Boc-protected (±)-γ-lactam **4** in 80% yield (Scheme 2). The resolution of the (±)-γ-lactam **4** was carried out with savinase in 50% THF−phosphate buffer solution (pH 8.0) for 2 days, selectively producing only the optically pure γ-lactam (−)-**4** in 84% yield with an enantiomeric excess (ee) of more than 99%. It has been reported that the stereochemistry of OsO_4-catalyzed hydroxylation of (−)-2-azabicyclo[2.2.1]hept-5-en-3-one (γ-lactam **3**) can be controlled through the N−H protecting group of the lactam.[17,18] A large group sterically directs the hydroxylation to the exo face of an olefin, yielding a hydroxylation product that can be converted into an analogue of carbocyclic riboside, as the exo isomer was desired for our synthesis. Thus, a bulkier Boc protecting group would prevent the OsO_4 oxidation from the β-face of the olefin and favor the production of the α-diol. Catalytic cis-hydroxylation of (−)-**4** was then carried out with OsO_4 and 4-methylmorpholine *N*-oxide (NMO) in H_2O/acetone/*tert*-butyl alcohol for 4 h at room temperature, affording a complete conversion of (−)-**4** to a single product **5** in 70% yield.[18] Benzoylation of **5** was performed with benzoyl chloride and DMAP in DCM at 0 °C to room temperature, giving the benzoyl-protected lactam. Opening of the lactam was accomplished by treatment with sodium borohydride ($NaBH_4$) in methanol to provide the alcohol **6** in 83% yield.[18] Deprotection of the NH-Boc group was carried out by using a 2 M solution of HCl/ether in THF for 16 h at room temperature to give the amine **7** in 90% yield.

With the benzoyl-protected amine **7** in hands, our first approach was to oxidize the amine to a ketone that would directly convert to the cyclopentanone **18** (Scheme 1). In our case, the reaction did not proceed satisfactorily. Only 5% of **18** was formed by Corey's oxidation method,[15] while in case of $KMnO_4$ and CrO_3 oxidations the starting material was not consumed. Therefore, we devised an alternative approach to convert the amine **7** to the alkene **8** via a diazotization−elimination reaction. The amine **7** was treated with sodium nitrite ($NaNO_2$) in a 50% acetic acid/50% water mixture for diazotization in acetonitrile, followed by elimination of the diazonium salt in situ at 0 °C to room temperature to give the alkene **8** in 54% yield. To improve this step, a number of variations for the diazotization reaction, including different organic acids, HCl, $HClO_4$, H_2SO_4, etc., were tried; however, no significant improvement in the yield was obtained. In another attempt by a sequential *N*,*N*-dimethylation reaction with formaline−sodium cyanoborohydride, *m*-CPBA oxidation to *N*-oxide and then a thermal Cope elimination[19] in THF gave only 48% yield. The debenzoylation of **8** was carried out by sodium methoxide (NaOMe) in methanol to give the triol **9** in 84% yield.

Our next crucial step was to introduce a fluorine at the 2-position in the carbocyclic moiety (compound **11**). Previoulsy, diethylaminosulfur trifluoride (DAST) fluorination of α/β epoxide with a *cis*/*trans* hydroxyl group was studied by Lakshmipathi et al.,[20] who reported that reaction of the *cis*(α)-epoxide with a hydroxyl group with DAST gave a cyclic ring-expanded product rather than the desired fluorinated compound. On the other hand, the *trans*(β)-epoxide with respect to a hydroxyl group gave the expected fluorinated epoxide in excellent yield. These results encouraged us to prepare the *trans*(β)-epoxide **11** from the allyl alcohol **10**, to give the fluoro epoxide **12**.

To accomplish these reactions, first we attempted the epoxidation on the olefin **9** with *m*-CPBA (77%) in 20% methanol/water, which exclusively resulted in the undesired *cis*(α)-epoxide in 85% yield. Thus, in order to obtain the opposite *trans*(β)-epoxide, silylation of 3′,5′-hydroxyl groups was first carried out using 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TIPDSCl_2$)/imidazole in DMF to give the 3′,5′-silyl-protected alcohol **10** in 82% yield. The epoxidation of **10** with *m*-CPBA in DCM selectively gave the desired *trans*(β)-epoxide **11** in 85% yield. The α-face epoxidation by *m*-CPBA was probably prevented by the bulkier silyl protecting group, resulting in the *trans*(β)-epoxide. The stereochemistry of the α- and β-epoxides was confirmed by $^1H-^1H$ rotating-frame nuclear Overhauser effect correlation spectroscopy (ROESY). Conversion of the *trans*(β)-epoxide **11** to *cis*-fluoro-β-epoxide **12** was accomplished by treating **11** with DAST at −20 °C for 1 h, furnishing *cis*-fluoro-β-epoxide **12** in 53% yield. It was observed that the fluorination with DAST was temperature-sensitive; at higher temperature (>−10 °C) the formation of a variety of side products were observed on TLC. The reaction was quenched with ice at low temperature (<−10 °C), because quenching at >0 °C decreases the yield of the desired product **12**.

The addition of a 6′-methylene group on the cyclopentyl ring was accomplished by a regioselective ring-opening reaction of the epoxide **12** reported by Alcaraz et al.[21] to produce the allylic alcohol **13** with retention of the β-configuration; the β-epoxide **12** was treated with dimethylsulfonium methylide at −10 °C to afford the β-allylic alcohol **13** in 81% yield. It was found that the addition of an exocyclic double bond via an epoxide ring-opening reaction was more convenient than our previously reported method.[11] The configuration of the β-allylic alcohol **13** was validated by ^1H NMR and $^1H-^1H$ ROESY spectroscopy. The ^1H NMR spectrum of compound **13** revealed distinct multiplicities due to H−F couplings: a doublet of triplets for H-2 at δ 4.73 (H-2), a multiplet for the anomeric H-1 proton at δ 4.48 (H-1), a multiplet at δ 4.44 (H-3), and a multiplet at δ 2.58 (H-4). The $^1H-^1H$ ROESY spectra of **13** showed the correlation of the proton H-4 with the anomeric H-1 proton as well as with the H-2 proton (Figure 2), which confirmed that these protons have the same orientation, indicating the β-configuration of the OH group in **13**.

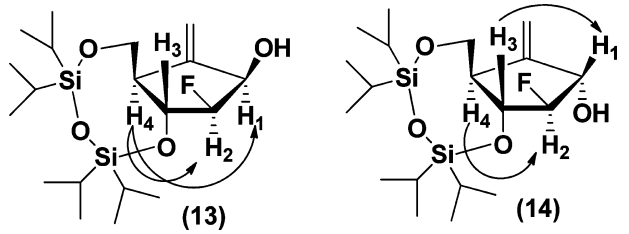

Figure 2. $^1H-^1H$ ROESY correlations of compounds **13** and **14**.

In order to condense the carbocyclic moiety with adenine to synthesize the desired nucleoside, an inversion of the configuration at C-1 of **13** was required. To accomplish this, a Mitsunobu reaction[21] was first tried; coupling of benzoic acid in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine (TPP) gave the α-benzoic ester of **14** via an S_N2 mechanism, which upon hydrolysis usually produced an α-alcohol. However, during hydrolysis of the ester elimination of the fluorine was observed from compound **14**, which was confirmed by ^{19}F NMR spectroscopy. Thus, it was concluded that basic conditions were not suitable for **13**. We searched for

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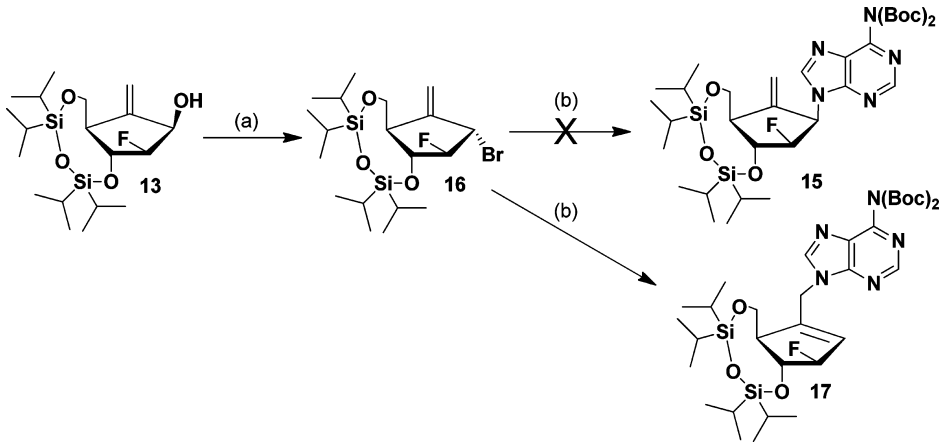
Scheme 3. S_N2' Reaction instead of S_N2 Reaction[a]



[a]Reagents and conditions: (a) CBr_4, TPP, DCM; (b) K_2CO_3, 15-crown-5-ether, DMF.

an alternative inversion method, in which oxidation of **13** with the Dess–Martin periodinane reagent at 0 °C gave the cyclopentenone intermediate in 90% yield that upon Luche reduction[22] with $NaBH_4$ in the presence of cerium chloride heptahydrate ($CeCl_3.7H_2O$) at −78 to 0 °C selectively gave exclusively the desired α-isomer **14** in 86% yield. The anomeric H-1 proton of compound **14** exhibited a doublet of doublets at δ 4.47 (H-1), a doublet of triplets at δ 4.65 (H-2) due to H–F coupling, a multiplet at δ 4.23 (H-3), and a multiplet for H-4 at δ 2.66 ppm in the ^{1}H NMR spectrum. In the ^{1}H–^{1}H ROESY analysis of **14**, H-4 shows correlation with H-2 but not with the anomeric proton H-1, while H-3 shows correlation with H-1, confirming the α-configuration of the alcohol **14** (Figure 2).

Compound **14** served as the key intermediate for the synthesis of FMCA. Coupling of **14** with Boc-protected adenine was accomplished under Mitsunobu coupling conditions using DIAD and TPP in THF to produce **15** in 65% yield. To increase the yield of this coupling reaction, various methods were tried; converting the hydroxyl group of **13** to give the α-bromo derivative **16** by treatment of **13** with carbon tetrabromide (CBr_4) in the presence of TPP in DCM at 0 °C furnished 86% of the α-bromo compound **16** through the S_N2 mechanism (Scheme 3). The α-bromo compound **16** was reacted with the anion of Boc-protected adenine generated by K_2CO_3 in DMF to give compound **15**. From the reaction we obtained the addition product **17** in 80% yield, instead of the S_N2 product (FMCA analogue, **15**), as the adenine anion attacked the terminal methylene carbon of the cyclopentane ring of **16** rather than the (pseudo) anomeric carbon (C1). Consequently, we found that a Mitsunobu coupling reaction is a better method to produce compound **15** in adequate yield. The Boc and silyl protecting groups of **15** were removed by using trifluoroacetic acid (TFA) and tetrabutylammonium fluoride (TBAF, 1 M solution in THF) in THF at room temperature, affording the targeted compound **1** (FMCA) in 85% yield.

CONCLUSION

In summary, we have developed an efficient practical synthetic method for preparation of the key carbocyclic intermediate **14** on a multigram scale from Vince lactam via kinetic resolution of the lactam **4**, diazotization–elimination of the amine derivative **7**, stereoselective epoxidation of **10**, stereoselective fluorination of **11**, epoxide opening through a regioselective introduction of the olefin of **12**, and inversion of the OH group of **13**, followed by the condensation of the key intermediate **14** to complete the synthesis of the final nucleoside (FMCA) in approximately 2.61% yield. It is expected that the new synthetic method may be suitable for the large-scale preparation of FMCA for preclinical studies.

EXPERIMENTAL SECTION

General Analytical Methods. Reagents and anhydrous solvents were purchased and used without further purification. Reactions were monitored by thin-layer chromatography plates (TLC silica gel GF 250 μm) that were visualized using a UV lamp (254 nm) and developed with a 15% solution of sulfuric acid in methanol. Melting points were recorded on a digital melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR with tetramethylsilane as an internal standard. Chemical shifts (δ) are quoted as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets) and dt (doublet of triplets). Optical rotations were measured on a digital polarimeter. ESI high-resolution mass spectra were recorded on a Q-TOF mass spectrometer. Elemental analyses were performed by combustion experiments. Thin- layer chromatography was performed on a glass plate coated with silica gel.

(±)-*tert*-Butyl 3-oxo-2-azabicyclo[2.2.1]hept-5-ene-2-carboxylate (4). A solution of di-*tert*-butyl dicarbonate (500 g, 2.291 mol) in tetrahydrofuran (200 mL) was added slowly to a suspension of racemic **3** (250.0 g, 2.291 mol), and 4-dimethylaminopyridine (2.8 g, 22.91 mmol) in tetrahydrofuran (2000 mL). The brown turbid solution was stirred at 20 °C until the reaction was complete. The solution was concentrated in vacuo to give brown foam. Recrystallization twice from cyclohexane afforded the product **4** (racemic) as pale pink crystals (384 g, 80%): mp 70.5–71.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.5 (s, 9H), 2.15 (d, J = 8.5 Hz, 1H), 2.35 (d, J = 8.5 Hz, 1H), 3.39 (s, 1H), 4.96 (s, 1H), 6.65–6.67 (m, 1H), 6.89 (dd, J = 2.0 and 5.0 Hz, 1H); MS: $(M + H)^+$ 210.

(−)-(1*R*,4*S*)-*tert*-Butyl 3-Oxo-2-azabicyclo(2.2.1)hept-5-ene-2-carboxylate ((−)-4). Savinase (500 mL, 16 U/g) was added to a solution (3000 mL) containing 335 g (1.6 mol) of racemic (±)-**4** in 50% tetrahydrofuran/50% phosphate buffer (50 mM, pH 8.0) at 30 °C. The reaction mixture was stirred at room temperature for 2 days. Upon completion of the reaction, the pH of the reaction mixture was raised to pH 9.0 with a saturated solution of sodium bicarbonate. The mixture was then extracted with cyclohexane (500 mL × 3). The combined organic layers were washed with 700 mL of sodium bicarbonate solution and subsequently washed with 500 mL of brine. Evaporation and drying yielded a brown crude residue, which was purified by silica gel column chromatography (20% EtOAc/80% hexane) to give the optically pure white solid (−)-**4** (140 g, 84%). The

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lactam was identified by ^{1}H NMR as well as by comparison to an authentic sample ($[\alpha]^{24}_D = -194°$ (*c* 2.0, $CHCl_3$)). The enantiomeric excess (ee) was better than 99%, as analyzed by the optical rotation: $[\alpha]^{24}_D = -193°$ (*c* 2.0, $CHCl_3$); mp 88.6 °C ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.5 (s, 9H), 2.15 (d, *J* = 8.5 Hz, 1H), 2.35 (d, *J* = 8.5 Hz, 1H), 3.39 (s, 1H), 4.96 (s, 1H), 6.65−6.67 (m, 1H), 6.89 (dd, *J* = 2.0 and 5.0 Hz, 1H).

(−)-(1*R*,4*S*,5*R*,6*S*)-*tert*-Butyl 5,6-Dihydroxy-3-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate (5).[18] To a solution of *tert*-butyl 3-oxo-2-azabicyclo[2.2.1]hept-5-ene-2-carboxylate ((−)-**4**; 50.0 g, 239.2 mmol) in acetone (200 mL) was added 4-methylmorpholine *N*-oxide (55.9 g, 477.7 mmol) at 0 °C with stirring, followed by addition of a solution of OsO_4 (121 mg, 0.476 mmol) in *tert*-butyl alcohol (2.5 mL), and the mixture was stirred at room temperature for 2 h. The solvent was evaporated in vacuo, and the residue was purified by flash column chromatography on silica gel using 30% EtOAc/70% hexane as the eluent to give a white solid of **5** (41 g, 70%): $[\alpha]^{24}_D = -28.19°$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (s, 9H), 1.99 (d, *J* = 10.5 Hz, 1H), 2.10 (d, *J* = 10.5 Hz, 1H), 2.80−2.81 (m, 1H), 3.44 (bs, 2H), 4.11 (d, *J* = 5.5 Hz, 1H), 4.26 (d, *J* = 5.5 Hz, 1H), 4.35 (s, 1H); HRMS (EI) calcd for $(C_{11}H_{17}NO_5 + H)^+$ 244.1185, found 244.1179.

(−)-(1*R*,2*S*,3*R*,5*R*)-3-((*tert*-Butoxycarbonyl)amino)-5-(hydroxymethyl)cyclopentane-1,2-diyl Dibenzoate (6).[18] Benzoyl chloride (45.8 mL, 395 mmol) was added to a solution of diol **5** (40 g, 164.4 mmol) and DMAP (40.2 g, 329 mmol) in anhydrous dichloromethane (500 mL) at 0 °C. The mixture was then stirred for 1 h, quenched with water, and extracted with DCM (500 mL × 2). The combined organic layers were washed with brine (250 mL) and dried over Na_2SO_4. The solvent was removed, and the residue was purified by silica gel column chromatography (8% EtOAc/92% hexane) to give the benzoylated intermediate (63.9 g, 86%) as a white solid: $[\alpha]^{24}_D = -43.40°$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58 (s, 9H), 2.26 (dt, *J* = 2.0, 10.5 Hz, 1H), 2.43 (d, *J* = 11.0 Hz, 1H), 3.14 (d, *J* = 1.5 Hz, 1H), 4.70 (d, *J* = 1.5 Hz, 1H), 5.48 (d, *J* = 5.5 Hz, 1H), 5.59 (dd, *J* = 1.0, 6.0 Hz, 1H), 7.24−7.31 (m, 4H), 7.48−7.53 (m, 2H),7.82−7.86 (m, 4H). To the benzoylated intermediate (63.8 g, 141 mmol) dissolved in methanol (500 mL) was added sodium borohydride (11.76 g, 311 mmol) at 0 °C. The reaction mixture was warmed to room temperature, and after 1.5 h, the mixture was quenched with 1 N HCl and concentrated in vacuo. The aqueous layer was extracted with ethyl acetate (500 mL × 2), and the combined organic layers were washed with water, dried over Na_2SO_4, and concentrated at reduced pressure. The residue was purified by silica gel column chromatography (50% DCM/50% hexane) to give compound **6** (53.4 g, 83%) as a white solid: mp 78−79 °C; $[\alpha]^{25}_D = -56.2°$ (*c* 2.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.44−2.56 (m, 2H), 3.71 (dd, *J* = 5.5, 11.5 Hz, 1H), 3.87 (dd, *J* = 4.0, 11.5 Hz, 1H), 4.43−4.50 (m, 1H), 5.13 (d, *J* = 8.0 Hz, 1H), 5.32−5.37 (m, 1H), 5.51 (t, *J* = 4.5 Hz, 1H), 7.34−7.39 (m, 4H), 7.51−7.55 (m, 2H), 7.94−8.00 (m, 4H); HRMS (EI) calcd for $(C_{25}H_{29}NO_7 + H)^+$ 456.2022, found 456.2017.

(−)-(1*R*,2*S*,3*R*,5*R*)-3-Amino-5-(hydroxymethyl)cyclopentane-1,2-diyl Dibenzoate Hydrochloride (7). A 2 M solution of HCl in ether (121 mL) was added with stirring to a solution of compound **6** (55.0 g, 121 mmol) in methanol at 0 °C. The mixture was warmed to room temperature gradually, and stirring was continued for 8 h. The solvent was evaporated under reduced pressure, and the residue was treated with anhydrous ether (120 mL) to precipitate the product **7**. The precipitated product was washed with ether (50 mL × 2) to afford the hydrochloride salt of amine **7** as a white solid (42.0 g, 90%): $[\alpha]^{25}_D = -28.19°$ (*c* 1.0, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.60−1.67 (m, 1H), 2.36−2.42 (m, 1H), 2.47−2.49 (m, 1H), 3.52−3.54 (m, 1H), 3.60−3.63 (m, 1H), 3.93−4.00 (m, 1H), 5.05−5.09 (m, 1H), 5.46−5.50 (m, 2H), 7.42−7.49 (m, 4H), 7.63−7.68 (m, 2H), 7.86−7.90 (m, 4H), 8.40 (bs, 2H, D_2O exchange, NH_2); ^{13}C{^{1}H} NMR(125 MHz, DMSO-d_6) δ 27.7, 43.7, 53.0, 61.5, 73.6, 75.2, 128.9, 129.0, 129.1, 129.4, 129.6, 129.8, 134.0, 165.3, 227.7; HRMS (EI) calcd for $(C_{20}H_{21}NO_5 + H)^+$ 356.1498, found 356.1492.

(+)-(1*R*,2*S*,5*R*)-5-(Hydroxymethyl)cyclopent-3-ene-1,2-diyl Dibenzoate (8). To a well-stirred solution of (−)-(1*R*,2*S*,3*R*,5*R*)-3-amino-5-(hydroxymethyl)cyclopentane-1,2-diyl dibenzoate hydrochloride (**7**; 42.0 g, 107.0 mmol) in an acetonitrile/water (1/1) mixture was added sodium nitrite (16.27 g, 236.0 mmol) portionwise at 0 °C. After 15 min, 50% aqueous acetic acid was added dropwise over a period of 0.5 h and the mixture was then vigorously stirred for 2 h. The organic solvent was removed under reduced pressure, and the rest of the mixture was quenched with water. The aqueous phase was extracted with ethyl acetate (100 mL × 3). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography (20% EtOAc/80% hexane) to give compound **8** (21.5 g, 54%) as a viscous oil: $[\alpha]^{24}_D = -156°$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.29 (bs, 1H), 3.27−3.28 (m, 1H), 3.82- 3.88 (m, 2H), 5.54−5.56 (m, 1H), 6.08−6.13 (m, 3H), 7.27−7.30 (m, 2H), 7.36−7.39 (m, 2H), 7.48−7.54 (m, 2H), 7.89−7.91 (m, 2H), 7.98−8.00 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 53.2, 63.1, 74.1, 128.2, 128.4, 129.5, 129.7, 129.8, 129.9, 133.3, 136.9, 150.0, 165.9, 166.6; HRMS (EI) calcd for $(C_{20}H_{18}O_5 + H)^+$ 339.1232, found 339.1226.

(+)-(1*R*,2*S*,5*R*)-5-(Hydroxymethyl)cyclopent-3-ene-1,2-diol (9). To a stirred solution of (1*R*,2*S*,5*R*)-5-(hydroxymethyl)cyclopent-3-ene-1,2-diyl dibenzoate (**8**; 19.2 g, 56.7 mmol) in methanol at room temperature under a nitrogen atmosphere was added sodium methoxide (25 wt % in methanol) (38.9 mL, 170 mmol) dropwise over a period of 20 min. The mixture was stirred at room temperature for 2 h and quenched by dropwise addition of a 1 N HCl solution to neutral pH. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (5% methanol/95% DCM) to give triol **9** (6.1 g, 84%) as an oil: $[\alpha]^{24}_D = +254.04°$ (*c* 1.0, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 2.78 (d, *J* = 5.0 Hz, 1H), 3.55 (dd, *J* = 6.5, 10.5 Hz, 1H), 3.73 (dd, *J* = 5.0, 11.0 Hz, 1H), 3.93 (t, 1H), 4.50 (d, *J* = 6.0 Hz, 1H), 5.87−5.88 (m, 1H), 5.97 (d, *J* = 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, CD_3OD) δ 53.7, 62.2, 73.2, 74.5, 132.0, 135.0; HRMS (EI) calcd for $(C_6H_{10}O_3 - H)^+$ 129.0552, found 129.0553.

(+)-(6a*R*,9*S*,9a*R*)-2,2,4,4-Tetraisopropyl-6,6a,9,9a-tetrahydrocyclopenta[*f*][1,3,5,2,4]trioxadisilocin-9-ol (10). To a stirred mixture of triol **9** (5.8 g, 44.6 mmol) and imidazole (21.2 g, 312.3 mmol) in DMF (300 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (14.7 mL, 46.8 mmol) dropwise at 0 °C under nitrogen. The mixture was stirred at room temperature for 2.5 h, quenched with water (200 mL), and extracted with ethyl acetate (200 mL × 3). The combined organic layers were washed with brine (100 mL × 2), followed by water (100 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (5% EtOAc/95% hexane) to give **10** (13.7 g, 82%) as an oil: $[\alpha]^{24}_D = +45.87°$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93−1.04 (m, 28H), 2.89−2.91 (m, 1H), 3.16 (d, *J* = 2.0 Hz, 1H), 3.48−3.51 (m, 1H), 4.01 (dd, *J* = 3.0, 11.0 Hz, 1H), 4.21 (t, *J* = 5.6 Hz, 1H), 4.45−4.47 (m, 1H), 5.60 (dd, *J* = 1.5, 6.0 Hz, 1H), 5.86 (dd, *J* = 3.0, 6.5 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 12.6, 12.7, 12.9, 13.2, 13.3, 13.4, 17.0, 17.1, 17.2, 17.3, 17.4, 17.6, 54.6, 66.7, 74.7, 76.3, 132.5, 134.4; HRMS (EI) calcd for $(C_{18}H_{36}O_4Si_2 + Na)^+$ 395.2050, found 395.2052.

(+)-(6a*S*,6b*R*,7a*S*,8a*R*)-2,2,4,4-Tetraisopropylhexahydrooxireno[2′,3′:3,4]cyclopenta[1,2-*f*][1,3,5,2,4]trioxadisilocin-8-ol (11). To a stirred solution of compound **10** (13.7 g, 36.8 mmol) in dichloromethane (300 mL) was added *m*-CPBA (15.9 g, 92.0 mmol) portionwise at room temperature. The mixture was stirred at room temperature for 16 h, quenched with a saturated $NaHCO_3$ solution, and extracted with DCM (200 mL × 2). The combined organic layers were washed with brine (100 mL × 2) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (3% EtOAc/97% hexane) to give epoxide **11** (12.2 g, 85%) as an oil: $[\alpha]^{24}_D = +18.25°$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00−1.11 (m, 28H), 2.28−2.32 (m, 1H), 3.05 (s, 1H), 3.37 (s, 1H), 3.56 (d, *J* = 2.5 Hz, 1H), 3.99−4.05 (m, 2H), 4.19 (d, *J* = 5.0 Hz, 1H), 4.26 (dd, *J*

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= 3.0, 11.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 12.6, 13.1, 13.3, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5, 48.2, 55.5, 58.4, 64.7, 70.7, 75.0; HRMS (EI) calcd for $(C_{18}H_{36}O_5Si_2 + H)^+$ 389.2180, found 389.2171.

(+)-(6a*S*,6b*R*,7a*R*,8*R*,8a*R*)-8-Fluoro-2,2,4,4-tetraisopropylhexahydrooxireno[2′,3′:3,4]cyclopenta[1,2-*f*][1,3,5,2,4]trioxadisilocine (12). To a solution of compound **11** (11.5 g, 29.6 mmol) in anhydrous dichloromethane (DCM) was added diethylaminosulfur trifluoride (DAST; 19.0 mL, 118.5 mmol) slowly at −20 °C, and the mixture was warmed to room temperature with stirring for 30 min. The reaction mixture was quenched with ice−water at −20 °C, the organic layer was collected, and the aqueous phase was extracted with DCM (200 mL × 2). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography (1% EtOAc/99% hexane) to give **12** (6.1 g, 53.0%) as an oil: $[\alpha]^{24}_D$ = +3.58° (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.93−1.12 (m, 28H), 2.15−2.19 (m, 1H), 3.39 (s, 1H), 3.56 (dd, *J* = 1.5, 3.0 Hz, 1H), 4.03−4.11 (m, 2H), 4.15−4.18 (m, 1H), 4.86−4.98 (ddd, *J* = 1.5, 5.5, and 52.0 Hz, 1H); ^{19}F NMR (500 MHz, $CDCl_3$) δ −201.73 (dd, *J* = 21.0, 52.5 Hz, 1F); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 12.6, 13.1, 13.3, 16.9, 17.01, 17.06, 17.13, 17.4, 17.6, 29.7, 47.6 (d, *J* = 6.2 Hz), 52.5 (dd, *J* = 7.2, 20.5 Hz), 54.9, 64.2 (d, *J* = 17.6 Hz), 75.5 (d, *J* = 19.5 Hz), 100.4 (dd, *J* = 28.1, 187.8 Hz); HRMS (EI) calcd for $(C_{18}H_{35}FO_4Si_2 + H)^+$ 391.2136, found 391.2131.

(−)-(6a*R*,8*R*,9*R*,9a*R*)-9-Fluoro-2,2,4,4-tetraisopropyl-7-methylenehexahydrocyclopenta[*f*][1,3,5,2,4]trioxadisilocin-8-ol (13). To a suspension of trimethylsulfonium iodide (30.5 g, 138.4 mmol) in THF (150 mL) at −20 °C was added *n*-BuLi (2.5 M solution in hexane; 55.3 mL, 138.4 mmol). After 30 min, the epoxide **12** (6.0 g, 15.5 mmol) in THF (30 mL) was introduced at −20 °C and the reaction mixture was slowly warmed to 0 °C over 1 h. The mixture was then stirred at ambient temperature for 2 h, quenched with water, and then extracted with ethyl acetate (200 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% EtOAc/90% hexane) to give the allylic alcohol **13** (5.1 g, 81%) as an oil: $[\alpha]^{26}_D$ = −0.54° (*c* 0.5, MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.93−1.08 (m, 28H), 2.01 (dd, *J* = 2.0, 5.5 Hz, 1H, OH), 2.54−2.59 (m, 1H), 3.84 (dd, *J* = 9.0, 11.0 Hz, 1H), 4.08 (dd, *J* = 5.0, 12.0 Hz, 1H), 4.43−4.49 (m, 2H), 4.73 (dt, *J* = 9.0, 52.0 Hz, 1H), 5.09 (s, 1H), 5.34−5.35 (m, 1H); ^{19}F NMR (500 MHz, $CDCl_3$) δ −202.9 (ddd, *J* = 14.0, 21.0, and 56.0 Hz, 1F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 12.5, 12.9, 13.4, 13.5, 16.9, 17.0, 17.3, 17.43, 17.47, 17.6, 50.1 (d, *J* = 4.0 Hz), 65.4, 72.5 (d, *J* = 17.4 Hz), 97.3 (d, *J* = 185.0 Hz), 111.9, 146.8; HRMS (EI) calcd for $(C_{19}H_{37}FO_4Si_2 + H)^+$ 405.2293, found 405.2287.

(−)-(6a*R*,8*S*,9*R*,9a*R*)-9-Fluoro-2,2,4,4-tetraisopropyl-7-methylenehexahydrocyclopenta[*f*][1,3,5,2,4]trioxadisilocin-8-ol (14). To a stirred solution of allylic alcohol **13** (5 g, 12.3 mmol) was added the Dess−Martin periodinane reagent (7.8 g, 18.5 mmol) at 0 °C. The mixture was warmed to ambient temperature and stirred for l h. The mixture was then passed through a Celite bed, and the filtrate was concentrated under reduced pressure to give a crude allylic ketone, which was used as such in the next step without further purification. The crude ketone (4.5 g, 11.1 mmol) was dissolved in anhydrous methanol, the solution was cooled to −78 °C, $CeCl_3{\cdot}7H_2O$ (5.5 g, 14.7 mmol) was added at −78 °C, and then after 10 min of stirring, $NaBH_4$ (0.54 g, 14.3 mmol) was added in one portion. After 15 min of stirring at −78 °C, the reaction mixture was warmed to 0 °C, a saturated solution of ammonium chloride (30 mL) and a 10% aqueous solution of acetic acid were added, and then the mixture was allowed to stand for 1 h with stirring. The organic solvent was removed under reduced pressure, and the residue was extracted with DCM (200 mL × 2). The combined DCM extracts were washed with brine (50 mL × 2), dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (5% EtOAc/95% hexane) to give compound **14** (4.3 g, 86%) as an oil: $[\alpha]^{26}_D$ = −88.1° (*c* 0.5, MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.93−1.08 (m, 28H), 2.63−2.69 (m, 1H), 3.89 (dd, *J* = 6.0, 11.5 Hz, 1H), 3.99 (dd, *J* = 4.5, 12.0 Hz, 1H), 4.19−4.26 (m, 1H), 4.47 (dd, *J* = 4.5, 13.5 Hz, 1H), 4.65 (dt, *J* = 8.0, 55.0 Hz, 1H), 5.16 (d, *J* = 2.5 Hz, 1H), 5.35 (s, 1H); ^{19}F NMR (500 MHz, $CDCl_3$) δ −195.8 (dt, *J* = 17.5, 59.5 Hz, 1F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 12.5, 12.7, 13.3, 13.4, 16.88, 16.89, 16.95, 17.06, 17.37, 17.43, 17.54, 49.1 (d, *J* = 6.1 Hz), 63.7, 73.7 (d, *J* = 19.1 Hz), 74.6 (d, *J* = 21.4 Hz), 102.3 (d, *J* = 189.7 Hz), 111.5, 144.9 (d, *J* = 9.1 Hz); HRMS (EI) $(C_{19}H_{37}FO_4Si_2 + H)^+$ 405.2293, found 405.2287.

(+)-9-[(1′*R*,2′*R*,3′*R*,4′*R*)-2′-Fluoro-3′,4′-methyl[1,3,5,2,4]trioxadisilocine-5′-methylenecyclopentan-1′-yl]-6-*N*,*N*-dibocadenine (15). To a stirred solution of triphenylphosphine (1.4 g, 5.56 mmol), in THF (20 mL) at −10 °C, was added DIAD (1.12 mL, 5.56 mmol) dropwise, the reaction mixture was stirred at this temperature for 30 min, and then a solution of *N*,*N*-diBoc-protected adenine (1.5 g, 4.46 mmol) in THF (10 mL) was added; this mixture was stirred for 30 min at 0 °C. Compound **14** (0.75 g, 1.85 mmol) in THF (5 mL) was then added, and the reaction mixture was stirred for 3 h at room temperature. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane 1/20 to 1/10) to give **15** (0.87 g, 65%) as a colorless oil: $[\alpha]^{26}_D$ = +15.6° (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.95−1.06 (m, 28H), 1.36 (s, 18H), 2.61−2.69 (m, 1H), 3.94 (dd, *J* = 7.5, 11.5 Hz, 1H), 4.15 (dd, *J* = 4.5, 11.5 Hz, 1H), 4.47−4.53 (ddd, *J* = 4.0, 6.0, and 20.5 Hz, 1H), 4.81 (s, 1H), 4.93 (t, *J* = 6.0 Hz, 1H), 4.99 (dt, *J* = 4.5, 52.5 Hz, 1H), 5.82 (dd, *J* = 4.5, 19.5 Hz, 1H), 8.07 (d, *J* = 2.0 Hz, 1H), 8.80 (s, 1H); ^{19}F NMR (500 MHz, $CDCl_3$) δ −192.9 (dt, *J* = 21.0, 56.5 Hz, 1F); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 12.4, 13.1, 13.2, 13.4, 16.90, 16.94, 17.0, 17.3, 17.4, 17.6, 21.7, 21.9, 27.7, 50.1, 69.9, 75.1, 84.4, 111.5, 128.2, 143.7, 144.8, 150.0, 153.8; HRMS (EI) calcd for $(C_{34}H_{56}FN_5O_7Si_2 + H)^+$ 722.3781, found 722.3770.

(+)-9-[(1′*R*,2′*R*,3′*R*,4′*R*)-2′-Fluoro-3′-hydroxy-4′-(hydroxymethyl)-5′-methylenecyclopentan-1′-yl]adenine (FMCA, 1). To a solution of compound **15** (1.0 g, 1.38 mmol) in THF was added trifluoroacetic acid (0.10 mL, 1.80 mmol), and the mixture was stirred for 16 h at ambient temperature. To this reaction mixture was added tetrabutylammonium fluoride (TBAF, 1 M solution in THF) (1.3 mL, 1.38 mmol), and this mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure; the residue was dissolved in a mixture of isopropyl alcohol and chloroform (4/1, 200 mL) and washed with water (2 × 50 mL). The organic layer was collected, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (methanol/DCM 0.2/10 to 0.6/10) to give **1** (0.33 g, 85%) as a white solid: mp 215−218 °C; $[\alpha]^{25}_D$ = +152.10° (*c* 0.5, MeOH); UV (H_2O) λ_{max} 259.0 nm (ε 14000, pH 2), 260.0 nm (ε 15600, pH 7), 260.0 nm (ε 15600, pH 11); ^1H NMR (500 MHz, CD_3OD) δ 2.81 (bs, 1H), 38.1−3.91 (m, 2H), 4.44 (dt, *J* = 3.0, 14.0 Hz, 1H), 4.95 (s, 1H), 4.96 (dt, *J* = 2.5, 52.5 Hz, 1H), 5.46. (s, 1H), 5.90 (d, *J* = 25.0 Hz, 1H), 8.10 (d, *J* = 2.5 Hz, 1H), 8.26 (s, 1H); ^{19}F NMR (500 MHz, DMSO-d_6) δ −192.93 (ddd, *J* = 14.0, 28.0, and 56.0 Hz, 1F); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3OD) δ 51.0, 57.5 (d, *J* = 17.4 Hz), 61.7, 72.9 (d, *J* = 23.6 Hz), 95.9 (d, *J* = 184.0 Hz), 111.7, 117.9, 141.1, (d, *J* = 5.3 Hz), 146.0, 149.9, 152.5, 156.0. Anal. Calcd for $C_{12}H_{14}FN_5O_2$: C, 51.61; H, 5.05; N, 25.08; Found: C, 51.74; H, 5.09; N, 24.92.

(−)-(6a*R*,8*S*,9*S*,9a*R*)-8-Bromo-9-fluoro-2,2,4,4-tetraisopropyl-7-methylenehexahydrocyclopenta[*f*][1,3,5,2,4]trioxadisilocine (16). To a stirred solution of compound **13** (0.5 g, 1.23 mmol) in dry DCM was added carbon tetrabromide (1.63 g, 4.9 mmol), followed by the addition of triphenylphosphine (1.29 g, 4.9 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was neutralized with triethylamine and passed through a small bed of silica gel. The filtrate was concentrated under reduced pressure, and the residue was purified by flash silica gel column chromatography (4% EtOAc/96% hexane) to give allyl bromide **16** (0.49 g, 86%) as an oil: ^1H NMR (500 MHz, $CDCl_3$) δ 0.93−1.01 (m, 28H), 2.65−2.63 (m, 1H), 3.87 (dd, *J* = 4.5, 14.0 Hz, 1H), 3.96 (dd, *J* = 4.0, 12.0 Hz, 1H), 4.11−4.07 (m, 1H), 4.60 (ddd, *J* = 2.0, 6.5, and 17.0 Hz, 1H), 4.95 (dt, *J* = 6.5, 54.5 Hz, 1H), 5.22 (d, *J* = 2.0 Hz, 1H), 5.40 (s, 1H); ^{19}F NMR (500 MHz, $CDCl_3$) δ −187.0 (dt, *J* = 17.5, 56.0 Hz, 1F); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 11.50, 11.53, 11.7, 11.8, 12.2, 12.4, 15.8, 15.9, 16.02, 16.05, 16.2, 16.3,

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16.4, 28.6, 47.8, 59.3, 101.7 (d, J = 194.6 Hz), 113.6, 142.4; HRMS (EI) calcd for $(C_{19}H_{36}BrFO_3Si_2 + H)^+$ 467.1449, found 467.1434.

(+)-9-[(2′*R*,3′*R*,4′*R*)-2′-Fluoro-3′,4′-methyl[1,3,5,2,4]trioxadisilocine-5′-methylcyclopentene-6′-yl]-6-*N*,*N*-dibocadenine (17). A mixture of 6-*N*,*N*-diBoc-adenine (0.34 g, 2.5 mmol) and K_2CO_3 (0.17 g, 1.3 mmol) in 10 mL of dry DMF was heated to 60 °C for 1 h. The mixture was cooled to 0 °C, and compound **16** (0.4 g, 0.8 mmol) in dry DMF was added dropwise; after that, 2−3 drops of 15-crown-5-ether were added. Then mixture was again heated to 60 °C for 4 h. The reaction mixture was quenched with water and extracted with ethyl acetate (3 × 100 mL), and the combined organic layers were washed with brine (2 × 50 mL) and finally with water (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (2% MeOH/98% DCM) to give compound **17** (0.49 g, 78%) as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86−1.03 (m, 28H), 1.38 (s, 18H), 2.66−2.64 (m, 1H), 3.79 (dd, J = 7.5, 12.5 Hz, 1H), 4.08 (dd, J = 4.0, 12.0 Hz, 1H), 4.42 (dt, J = 5.0, 24 Hz, 1H), 4.81 (dd, J = 4.5, 16.0 Hz, 1H), 4.90 (dd, J = 3.5, 16.0 Hz, 1H), 5.26 (s, 1H), 5.36 (s, 1H), 8.00 (s, 1H), 8.80 (s, 1H); ^{19}F NMR (500 MHz, $CDCl_3$) δ −174.1 (dd, J = 28.0, 60.0 Hz, 1F); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 12.5, 12.8, 13.35, 13.39, 16.93, 16.99, 17.0, 17.4, 17.5, 27.8, 42.2, 81.3, 83.8, 128.4, 150.0, 152.4; HRMS (EI) calcd for $(C_{34}H_{56}FN_5O_7Si_2 + H)^+$ 722.3781, found 722.3770.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^{1}H NMR, ^{19}F NMR, and ^{13}C NMR spectra of compounds **1** and **6**−**17**. 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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